Jose Pablo Díaz-Jimenez
Alicia N. Rodriguez
Editors

Interventions in Pulmonary Medicine

Second Edition

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Alicia
To Manuel and Francisco, of course. To my sisters Maria, Fatima, Elsa and Adriana. To Pablo, friend and teacher.

Pablo
To my wife Mercedes, to whom I owe so much, and who is by my side on the way of life. To my father my best friend. To my sisters Yolanda, Delia and Dolores with love. To my children Arturo, Cristián, Carlos and Pablo. To my grandchildren Elia, Lluc, Quim, Ferran and Bruna, from whom I am learning to live. To Alicia Rodriguez, my dearest friend and superb pulmonologist, the true architect of this book.

To my mentors: Dr. D. Cortese, Dr. UBS Prakash and especially to Dr. JF Dumon who directed my first steps in interventional pulmonology.

Foreword

The demand for a second edition of this fine textbook after only 3 years shows the increasing importance of interventional bronchology in pulmonary medicine. For 70 years after its invention by Killian in 1897, rigid bronchoscopy remained restricted to a limited number of specialized hospitals. Only after the introduction of the flexible bronchoscope by Ikeda in 1966 did bronchoscopy became widely applied. This was promoted by the early work of pioneers, by a European group, including J. P. Diaz-Jimenez in Spain, J. F. Dumon in France, and S. Cavliere in Italy. The preservation of skills in rigid bronchoscopy in combination with the flexible instrument proved ideal, especially in developing treatment of the central airways such as mechanical resection, using lasers, stents, etc. As Freiburg in former times, Marseille, Barcelona, and, briefly afterward, also Heidelberg, Germany, became European training Meccas for physicians from all over the world. I am calling myself fortunate for experiencing such exciting times and counting these pioneers among my friends, apart from having been able to contribute (e.g., EBUS, SEMS, and EMN).

Due to exponential development in imaging and instrumentation technology during the last three decades, bronchology has developed into an important specialty in its own right within pulmonary medicine. The champions have become numerous worldwide as is reflected by the list of contributors in this book. Many associations for bronchology and interventional pulmonology have been founded on all continents and are connected under the umbrella of the World Association for Bronchology and Interventional Pulmonology (WABIP). Training centers have been established worldwide, where structured courses are offered and formalized tests provide credentials of proficiency. For those unable to attend on site, a digital training module is offered on the Internet.

All topics are covered within this concise textbook by renowned authors. The chapters cover the anatomical and technical basics as well as quality management. All current technologies for treatment of central airway obstruction are discussed. As especially in the diagnosis and treatment of lung cancer bronchoscopy is playing a major role, the concepts of screening, early detection, and staging for making sound decisions for therapy are described in extenso. This includes also the pleural space as far as is relevant for the pulmonologist. The final chapters deal with recent developments for intervention in benign diseases such as asthma and emphysema and in special indications.

The conclusion describing the history and the outlook into the future should encourage the next generation to carry the torch onward.

The book is not only a must for all physicians who take up the path to become interventional pulmonologists but also for every pulmonologist as interventional bronchoscopy has become such an important integrated part in pulmonary medicine. Knowledge of its indications and limitations is essential for intelligent decision-making. The authors can only be congratulated on their remarkable effort.

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Preface to the First Edition

Nothing beats the pleasure of seeing a finished work.

This book is a reflection of what we do every day in the endoscopy room, and it would not have been possible without the collaboration of the colleagues who have participated, sharing their knowledge and expertise to clearly set out the fundamental concepts of this wonderful interventional pulmonology world.

I have been working in the interventional area for more than 30 years, and one of the main concepts that I have learned is that success in daily work does not rely on one individual, but it is only achievable when everybody works with the conviction of being part of a team.

It would not be possible to perform a complex treatment such as releasing the airway from an obstructive malignant tumor without each and every team member's participation, applying their knowledge and abilities in a coordinated and complementary fashion. As team members, we all share responsibilities. I believe one of the main ones is to make the whole team function based on these three mainstays: coordination, communication, and complement, since they are the keys of a successful work.

Since the advent of bronchoscopy in 1887, the field of bronchology and interventional pulmonology has demonstrated its clinical value with amazingly rapid developments. The last three decades have brought to us spectacular advances in technology and their clinical applications, which have led to lifesaving therapies. We can predict that we will see newer clinical applications and improvement in established techniques in the near future. These dynamic changes will bring together the scientists and clinicians interested in our specialty and further expand the field.

It is our duty to keep updating the state of the art and maintain a continuous progress. The scientific and clinical training of the respiratory endoscopist must rest on solid principles and remain in constant forward motion, and therefore, constant teaching and learning become our obligations.

During all these years, we have received pulmonary fellows from all continents who have spent long periods of time with us or have attended our courses or conferences, teaching them interventions and also learning from them. We have also learned from very respected physicians of the interventional pulmonology field who have honored us with their presence, sharing their experiences and making this learning process extremely easy, as if we were in a family reunion listening and exchanging everyday experiences. At

the end of the day, we were all enriched, and I believe all our patients benefited from our sessions and discussions.

Experience does not come only as a consequence of performing many procedures but also from having an open mind and listening to the advice and suggestions from other colleagues. The learning process takes a lifetime. At the beginning, we are all learners, and as time goes by, it becomes our turn to take the position of the teacher and to contribute to the growing number of fellows and residents interested in endoscopic procedures. What would have occurred if retired from daily practice Killian, Jackson, Andersen, Ikeda, Zavala, Hayata, Kato, Cortese, or Dumon had not transmitted their experiences to the rest of the scientific community? It would have been much more difficult for us to arrive to our present state of knowledge. However, the generosity of all of them made our way much easier.

Bertrand Russell said it is good from time to time to think on the present as if it were the past and consider which of the elements of our time will enrich the permanent deposit of the universe and which ones will live and give life when our generation has disappeared. Having this contemplation, the human experience transforms, and the personal experience vanishes.

With this in mind, I believe the teaching and learning process is crucial, and they both have to be taken with humility. To our teachers, we always owe gratitude and respect, and when we become teachers, it is important to be generous, recognize limitations, and transmit what is worth, keeping always as a goal to benefit our patients in every possible way.

Following this line, Alicia and I would like to take this opportunity to thank the many teachers and colleagues around the world who helped us along the way, with their advice and continuous support:

- Dr. Udaya Prakash and Eric Edell form Mayo Clinic
- The coworkers from the Bronchoscopy Department at Bellvitge University Hospital in Barcelona, A. Rosell, R. Lopez, and N. Cubero, and from the MD Anderson Cancer Center Team in Houston, R. Morice, G. Eapen, C. Jimenez, D. Ost, and B. F. Dickey
- The Pulmonary Department Team at Lahey Clinic in Massachusetts
- The Pulmonary Department Team at Clinica Colon in Mar del Plata: L. Araya, N. Baillieau, S. Ruiz, C. Materazzi, M. Rocha, and B. Nuñez

And finally, our especial thanks go to all the colleagues who participated in this work, generously sharing their wisdom and making possible this small addition to the art of respiratory endoscopy. It is our hope that this book will contribute to improve our daily interventional pulmonology practice.

Barcelona, Spain Jose Pablo Díaz-Jimenez

Preface to the Second Edition

The future belongs to those who learn more skills and combine them in creative ways. —Robert Greene, Mastery

When we presented the first edition of *Interventions in Pulmonary Medicine*, both Pablo and I thought it was a great honor to include in our book the most prominent colleagues in the area, updating the state of the art in their field of expertise.

Incredible to us, we now have a second opportunity to review the topics, and we are deeply grateful to have many great professionals who generously shared their knowledge with all of us improving our medical practice and, most importantly, improving the lives of people who consult us looking for help.

It is a great privilege to practice medicine. It is in our hands to do the best continuously updating what we know. That goes hand in hand with the warm touch, empathy, and compassionate conversation with the fellow suffering human being who is in front of us. Undoubtedly, this part of medicine is the most satisfactory feature in the life of a doctor and what patients value the most since it helps them to better endure their moments of illness.

We therefore want to dedicate this book to our patients and thank them for being our daily reason to be better at what we do.

Medical knowledge is crucial in our service path, and with this idea, we present this new edition, as a growth tool for all those who perform interventions in pulmonary medicine.

We also owe our thanks to our work teams, who support and share our ideals, contribute daily to solve issues, and pay attention to details making harmonious and effective functioning at the workplace. A doctor cannot be good without a support system, and in that sense, the work team is a family where each one brings a different and necessary quality.

We also want to mention and honor our teachers, those of whom we learned both what to do and what not to do. Undoubtedly, their contribution of knowledge, work ethic, and human qualities have had a great impact in the way we practice every day at the consultation and in the operating room.

Finally, we also dedicate this edition to physicians in training, hoping that what has been turned into these pages become an important contribution coming from experienced professionals with decades of medical practice. Their advice and reflections will undoubtedly modify some practices, they certainly have improved Pablo's and mine. We wish that the medical practice

of those who are beginning this path will be as satisfactory as ours and that we will all have the main objective to benefit our patients in every possible way. We also encourage younger doctors to develop new ideas and perfection techniques, so that the area of interventionism continues to grow with the younger generation.

We hope the reading of this edition will be enjoyable and useful for everyone. It was an honor to us to have well-known colleagues who are the true protagonists of this book and once again to make a small contribution to the art and science of interventional pulmonary medicine.

Mar del Plata, Argentina — Alicia N. Rodriguez
June 2017

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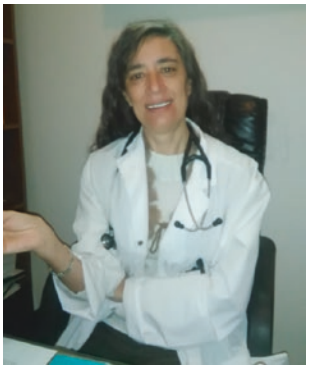
Jose Pablo Diaz-Jimenez is head of the Pulmonary Department at Clinic Corachan, Barcelona, and Adjunct Professor in the Pulmonary Department at MD Anderson Cancer Center. He is also former Chairman of the World Association for Bronchology and Interventional Pulmonology (WABIP) and former President of the World Bronchology Foundation (WBF).



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Part VIII Interventions in Pulmonary Medicine: History and Future Perspectives

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Part I

Basic Endoscopy

Tracheobronchial Anatomy

1

Juan Antonio Moya Amorós
and Anna Ureña Lluveras

Trachea

Introduction

The trachea or windpipe is a tube of approximately 12 cm in length. Viewed laterally, it assumes an oblique course, running from superoanterior to inferoposterior, from 23° to 34° related to the body's major axis. It ends up by dividing into two bronchial tubes at the level of the tracheobronchial bifurcation, which usually has an angle of 60°. Changes in the degree of angulation can orient to diagnose some conditions located distally to the bifurcation such as enlarged lymph nodes or left atrium dilatation in mitral stenosis. The tracheal tube extends from C6 to C7 (limited by the cricoid cartilage superiorly) to D4–D5, approximately at 1 or 2 cm below a horizontal plane passing through the Louis sternal angle. Topographically its average length (12 cm as stated) is equally divided between the cervical and mediastinal region.

External Morphology

The external tracheal configuration is characterized by the presence of roughness due to incomplete cartilage rings that are staggered, horizontally and segmentally distributed. Usually 20 rings are identified in the trachea.

In the cervical region, the tube has a flattened shape posteriorly, due to the absence of cartilage, so that the predominant diameter is the sagittal or anteroposterior (approximately 16 mm), but inside the chest it predominates the transverse diameter (approximately 16 mm).

In the external tracheal wall, narrowing or depressions can be seen, produced by the imprint of organs in close proximity contacting to the tracheal wall. In the left side, two of them are visible: one due to the left thyroid gland lobe (neck) and the other one due to the aortic arch (mediastinum).

The posterior membrane closing the entire tracheal canal is flat, soft, and depressible; it is known as the *membranous pars* (Fig. 1.1).

The especial tracheal configuration and its elastic structure make it capable to elongate up to one third of its length. This fact is of particular interest for tracheal reconstruction surgeries.

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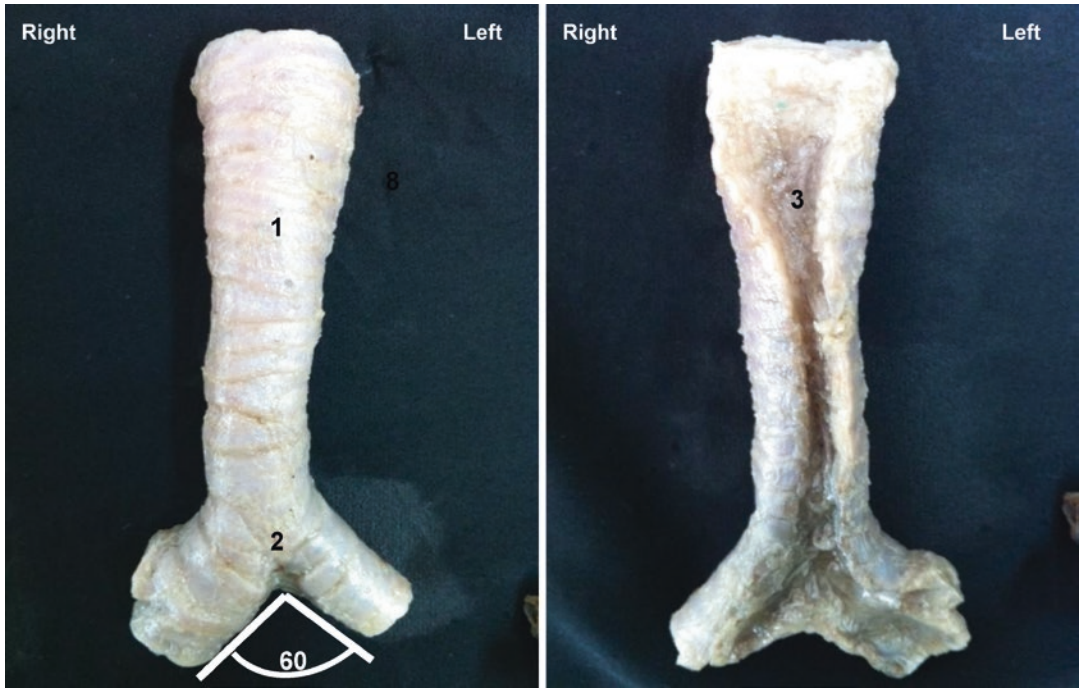
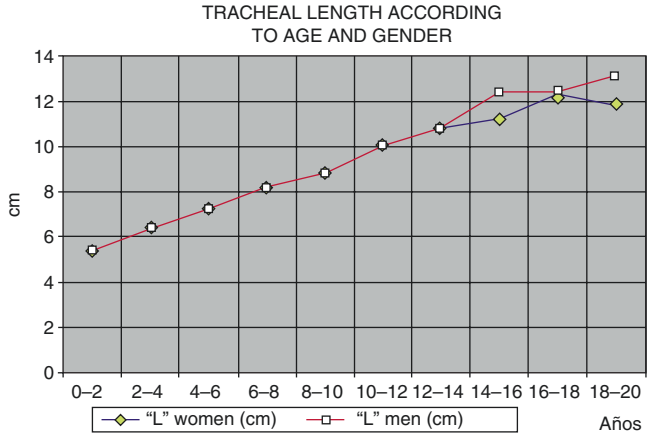


Fig. 1.1 Anterior view of the dissected trachea. Note the tracheal bifurcation angle of 60°, (*1*) anterior view: trachea and tracheal cartilage. (*2*) Tracheobronchial bifurcation. (*3*) Membranous pars or tracheal muscle. Unit of Human Anatomy and Embryology. Department of Pathology and Experimental Therapeutics. Universitat de Barcelona



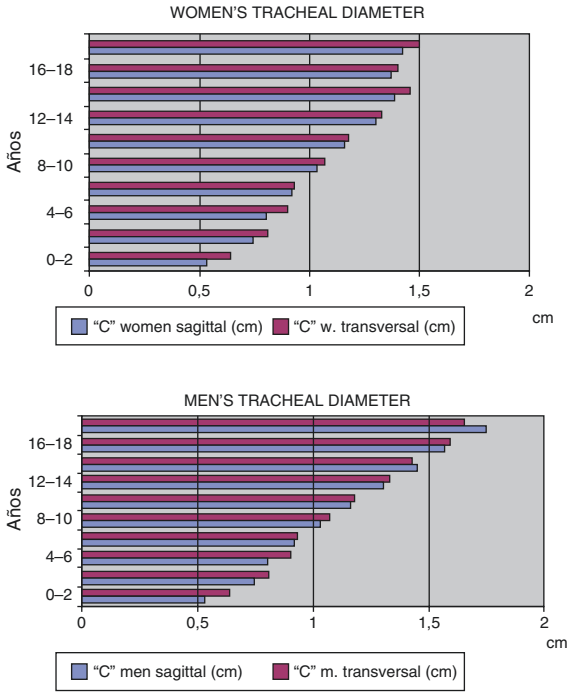
	"L" women (cm)	"L" men (cm)
0–2	5.4	5.4
2–4	6.4	6.4
4–6	7.2	7.2
6–8	8.2	8.2
8–10	8.8	8.8
10–12	10	10
12–14	10.8	10.8
14–16	11,2	12,4
16–18	12,2	12,4
18–20	11,8	13,1

Medium length of the trachea increases similarly in both genders until the age of 14. After that it only increases in men.

Fig. 1.2 Medium length of the trachea increases similarly in both genders until the age of 14. After that it only increases in men

Dimensions of the trachea vary primarily according to age and less so with gender. Figures 1.2, 1.3, 1.4, and 1.5 present the normal size variations in all three axes, internal size, area, and volume.

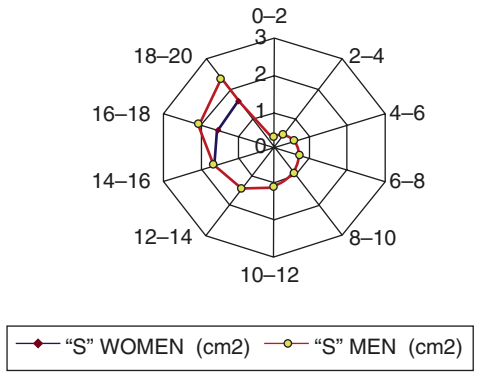
Among both genders, there are also differences in tracheal size especially in the sagittal and transverse axes, which are evident in tomographies and 3D reconstructions (Figs. 1.6 and 1.7).



AGE in years	*"C"* sagittal women (cm)	*"C"* transv. women (cm)	*"C"* sagittal men (cm)	*"C"* transv. men (cm)
0–2	0.53	0.64	0.53	0.64
2–4	0.74	0.81	0.74	0.81
4–6	0.8	0.9	0.8	0.9
6–8	0.92	0.93	0.92	0.93
8–10	1.03	1.07	1.03	1.07
10–12	1.16	1.18	1.16	1.18
12–14	1.3	1.33	1.3	1.33
14–16	1,39	1,46	1,45	1,43
16–18	1,37	1,4	1,57	1,59
18–20	1,42	1,49	1,75	1,66

Medium tracheal diameter increases similarly in both genders until the age of 14. After that it only increases in men.

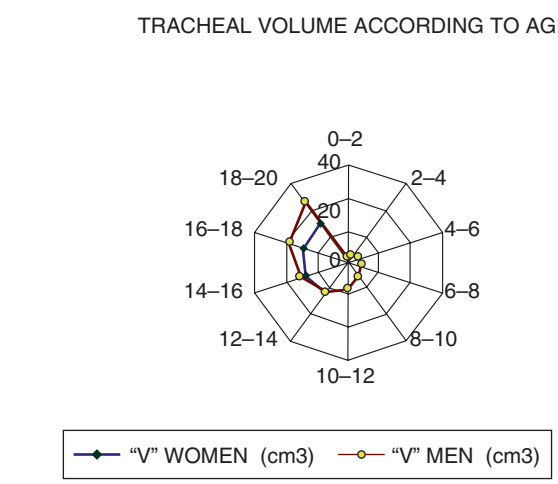
Fig. 1.3 Medium tracheal diameter increases similarly in both genders until the age of 14. After that it only increases in men



AGE	*"S"* WOMEN *(cm^2)*	*"S"* MEN *(cm^2)*
0–2	0.28	0.28
2–4	0.48	0.48
4–6	0.58	0.58
6–8	0.69	0.69
8–10	0.89	0.89
10–12	1.1	1.1
12–14	1.39	1.39
14–16	1.62	1.62
16–18	1,54	2,01
18–20	1,59	2,3

- Medium tracheal area increases similarly in both genders until the age of 14.
- At age 20, tracheal area is 44.6% larger in men than in women.

Fig. 1.4 Medium tracheal area increases similarly in both genders until the age of 14. At age 20, tracheal area is 44.6% larger in men than in women



AGE	*"V"* WOMEN *(cm^3)*	*"V"* MEN *(cm^3)*
0–2	1.57	1.57
2–4	3.11	3.11
4–6	4.16	4.16
6–8	5.67	5.67
8–10	7.87	7.87
10–12	11.1	11.1
12–14	15.4	15.4
14–16	18,2	20,2
16–18	18,8	25,1
18–20	18,9	30,3

* Medium tracheal volumen increases similarly in both genders until the age of 14

* By age 20, men's tracheal volume is 60% larger than women's.

Fig. 1.5 Medium tracheal volume increases similarly in both genders until the age of 14. By age 20, men's tracheal volume is 60% larger than women's

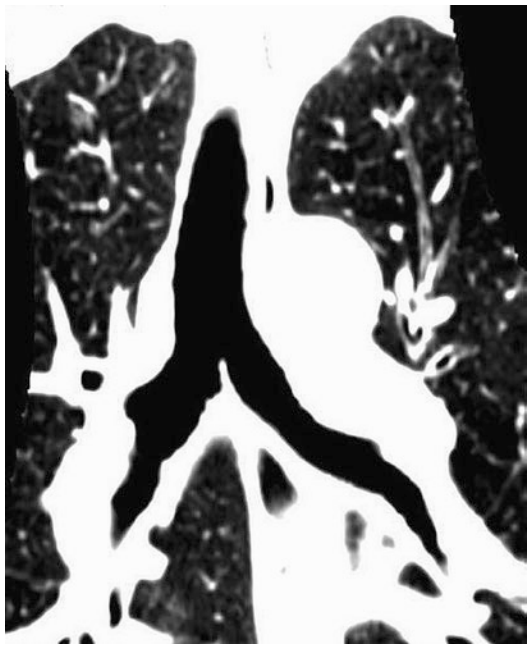


Fig. 1.6 : At age 20, men's sagittal and transverse tracheal axes are 23% and 11.4% larger than women's, respectively. Coronal computerized tomography: view of mediastinal trachea, tracheobronchial bifurcation, and main bronchi

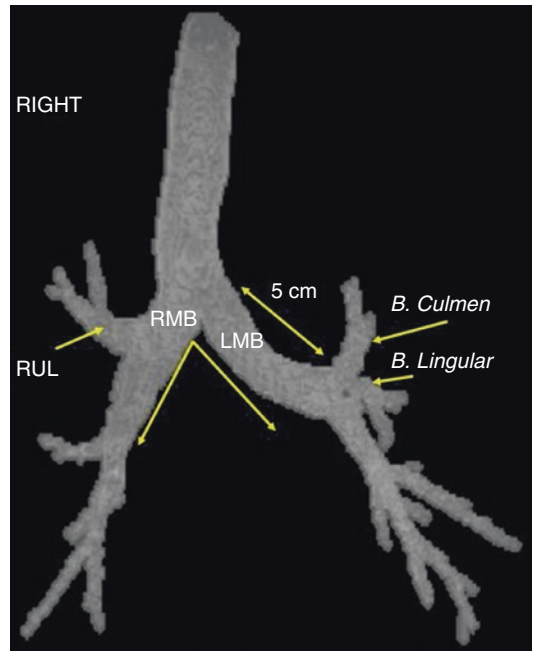


Fig. 1.7 Medium tracheal diameter is 1.5 mm larger in men than in women. Medium bronchial diameter is 1 mm larger in men. 2D tomographic reconstruction of the tracheobronchial tree. Note that the intracarinal angle is 60°. Lengths are 5 cm for the left main bronchus and 2.5 cm for the right main bronchus

Internal Morphology

The tracheal tube has two covers or layers.

Fibro-Chondro-Elastic Layer

It is a completely circular, soft, and elastic connective tissue fundamental matrix. It affects the entire circumference of the windpipe. It presents tiny holes that represent the point of vascular entrance or exit to and from inside the trachea.

Enclosed to this layer, there are bands of incomplete hyaline cartilage rings, horseshoe shaped. The cartilage forms about four fifths of the circumference of the trachea. Given that the posterior border of the trachea is formed by a fibromuscular membrane, tracheal cross-sectional shape is similar to a letter D, with the flat side located posteriorly. The tracheal muscles cross transversely and obliquely, forming a continuum of entangled fibers which constitute a large muscle: the common tracheal muscle. Contraction of this muscle produces adduction of the free cartilage edges, thus modulating the internal tracheal caliber. Wrapping the outer tracheal tube, we found the adventitia, a membrane that acts as a false pretracheal fascia. Between the adventitia and the tracheal wall, vascular and nervous branches are located, and they incorporate to the tracheal tube wall at the level of the interchondral spaces.

Mucous Layer

The trachea is lined by pseudostratified columnar epithelium that sits in an elastic *lamina propria* and covers the inside of the tracheal tube. Goblet mucous cells and small subepithelial glands that secrete into the luminal surface are interspersed among the ciliated columnar cells. The produced mucus adheres to inhaled foreign particles, which are then expelled by the action of cilia propelling the mucus lining upward towards the pharynx from which they can be coughed and sneezed out of the airway. At the end of the tracheal duct, when it is divided into the main bronchi, the mucosa presents a middle line elevation known as carina, similar to a medial ridge. The tracheal carina indicates the entrance to the right and left main bronchus (Fig. 1.8a–c).

Blood Supply

Arterial—it is established by two arterial systems on each side of the trachea, communicating the aorta artery with the subclavian artery:

- From the aorta, the left paratracheal ascending artery (Demel arteries) and the tracheobronchial esophageal artery. Of the latter, the right bronchial artery, the esophageal artery, and the right paratracheal ascending artery are born.
- From both subclavian arteries and inferior thyroid arteries and from these in turn emerge the right and left paratracheal descending arteries (Haller arteries).

Each paratracheal descending artery anastomoses with the paratracheal ascending artery of the corresponding side, closing the vascular circuit at the back of the tracheal wall and along its side edges. From these two vascular axes, tracheal perforating arteries are born that supply tracheal layers entering through the interchondral spaces.

Anatomo-Clinical Relationships

The trachea is related to their surroundings through the peritracheal fascia, as if it were a hanger between the neck and the mediastinum. Vascular and nerve structures hung from or are in contact with it.

Regardless of the anatomical details, the tracheal relationships from inside out are:

Fig. 1.8 (**a**) Cross section, trachea. (*1*) Respiratory cylindric epithelium and mucous glands. (*2*) Horseshoe-shaped cartilage, with a posterior opening. (*3*) Main layer, connective tissue fundamental matrix, surrounded by the adventitia. (**b**) Schematic illustration of the elements of the tracheal wall. (*1*) Poli-pseudostratified columnar epithelium, (*2*) gland drainage orifice, (*3*) gland duct, (*4*) submucous, (*5*) vagus nerve, (*6*) venules and arterioles. (**c**) Tracheal mucous gland. (*1*) Arteriole, (*2*) erythrocyte, (*3*) endothelial cell, (*4*) basement membrane, (*5*) Golgi apparatus of a goblet cell, (*6*) endoplasmic reticulum, (*7*) vacuole, and (*8*) mucus secretion

- Posterior: recurrent nerve, esophagus, and vertebral bodies covered by the deep cervical aponeurosis
- Anterior: thyroid gland, medium cervical aponeurosis, anterior jugular veins, and superficial cervical aponeurosis
- Lateral: thyroid gland, vessels and nerves, deep cervical aponeurosis, and superficial cervical aponeurosis (involving the sternocleidomastoid and trapezius muscles) (Fig. 1.9a, b)

The tracheobronchial bifurcation has similar topographical relationships in both genders, and it is located at 7 cm depth from the skin of the anterior midline chest (Figs. 1.10 and 1.11).

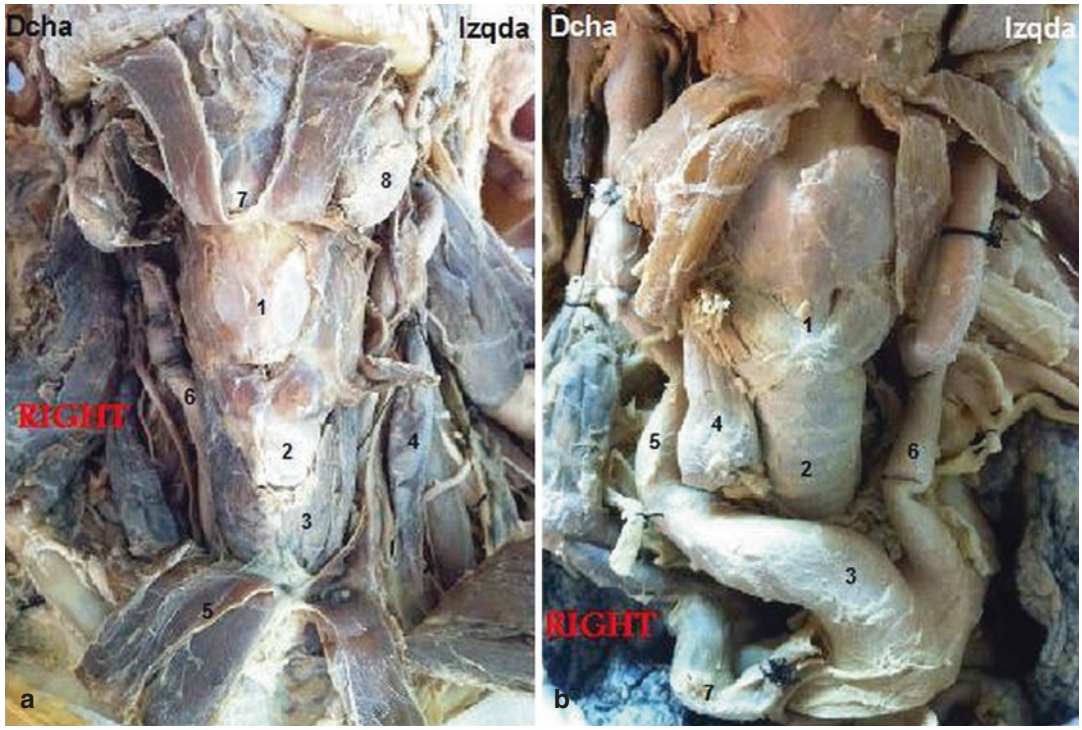


Fig. 1.9 (**a**) Dissection of the cervical trachea. (*1*) Larynx, (*2*) trachea, (*3*) left thyroid lobe, (*4*) left internal jugular vein, (*5*) right infrahyoid muscles, (*6*) right common carotid artery, (*7*) hyoid bone, and (*8*) left submandibular gland. (**b**) Dissection of the cervical trachea. (*1*) Larynx, (*2*) trachea, (*3*) brachiocephalic arterial trunk, (*4*) right internal jugular vein, (*5*) right common carotid artery, (*6*) left common carotid artery, and (*7*) left venous brachiocephalic trunk or innominate trunk. Unit of Human Anatomy and Embryology. Department of Pathology and Experimental Therapeutics. Universitat de Barcelona

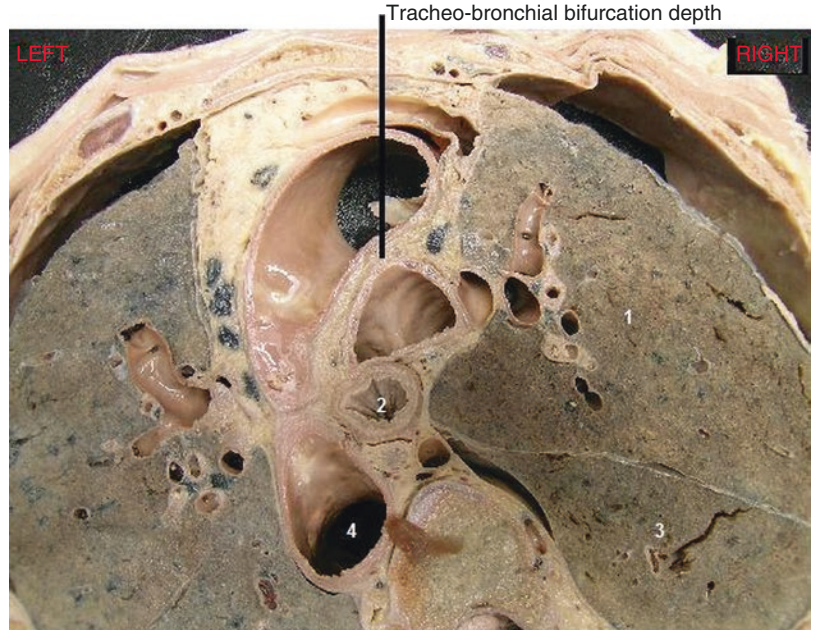


Fig. 1.10 Cranial view of thoracic cross section at the level of D4. Note the location of the tracheobronchial bifurcation at a depth of 7 cm from the surface. (*1*) Right upper lobe, (*2*) thoracic esophagus, (*3*) right lower lobe, 4: Descending thoracic aorta. Unit of Human Anatomy and Embryology. Department of Pathology and Experimental Therapeutics. Universitat de Barcelona

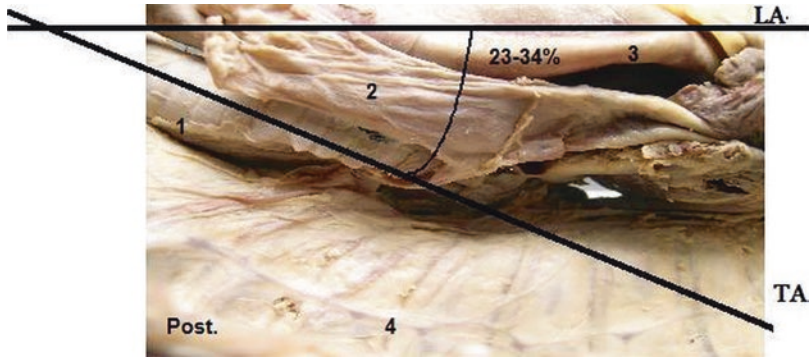


Fig. 1.11 Right lateral view of mediastinum: *TA* tracheal axis, *LA* long axis of the body. (*1*) Trachea, (*2*) superior vena cava, (*3*) ascending aorta, (*4*) dorsal spine. Unit of Human Anatomy and Embryology. Department of Pathology and Experimental Therapeutics. Universitat de Barcelona

Bronchi

Main Bronchi

Main bronchi are located in a compartment known as the mediastinum. The mediastinum is delimited by the pleural cavity. This space does not have a regular shape (mediastinum = "servant" or "heart and major vessels service area").

There are two main bronchi, left and right. Each main bronchus is related to some elements of the mediastinum, and they are not equal in length or size.

Left main bronchus: it is 5 cm in length. It is longer than the right main bronchus, passing beneath the aortic arch and the left pulmonary artery.

Right main bronchus: it is 2.5 cm in length. It presents more vertical than the left bronchus and has a bigger diameter.

Inside the lung parenchyma, both bronchi will continue dividing into branches to the 24th order (Fig. 1.12).

Bronchial Division

Left Main Bronchus (LMB)

- *Left upper lobe bronchus*—it divides into:
  - Apicoposterior segmental bronchus (B1 + 2), from where B1 (apical) and B2 (dorsal or posterior) bronchi are born
  - Anterior or ventral segmental bronchus (B3)
  - Lingular bronchus, divided into superior lingular segmental bronchus (B4) and inferior lingular segmental bronchus (B5)
- *Left lower lobe bronchus*—it divides into:
  - Apical segmental bronchus form the left lower lobe or Nelson's bronchus (B6).
  - Posterior or dorsal bronchus (B10).
  - Lateral bronchus (B9).
  - Trunk (B7 + 8) or ventromedial bronchus, from which B7 (medial) and B8 (ventral) originate.

Right Main Bronchus (RMB)

- *Right upper lobe bronchus*—it divides into:
  - Apical segmental bronchus (B1)
  - Anterior o ventral segmental bronchus (B3)
  - Dorsal segmental bronchus (B2)
- *Right middle lobe bronchus*—it divides into:
  - Medial segmental bronchus (B5)
  - Lateral segmental bronchus (B4)
- *Right lower lobe bronchus*—it divides into:
  - Apical bronchus of the right lower lobe (Nelson's bronchus) (B6)
  - Posterior or dorsal bronchus (B10)
  - Lateral bronchus (B9)
  - Anterior bronchus (B8)
  - Paramediastinic bronchus (B7)

The right main bronchus, after the superior lobe bronchus departure, is called *intermedius bronchus*.

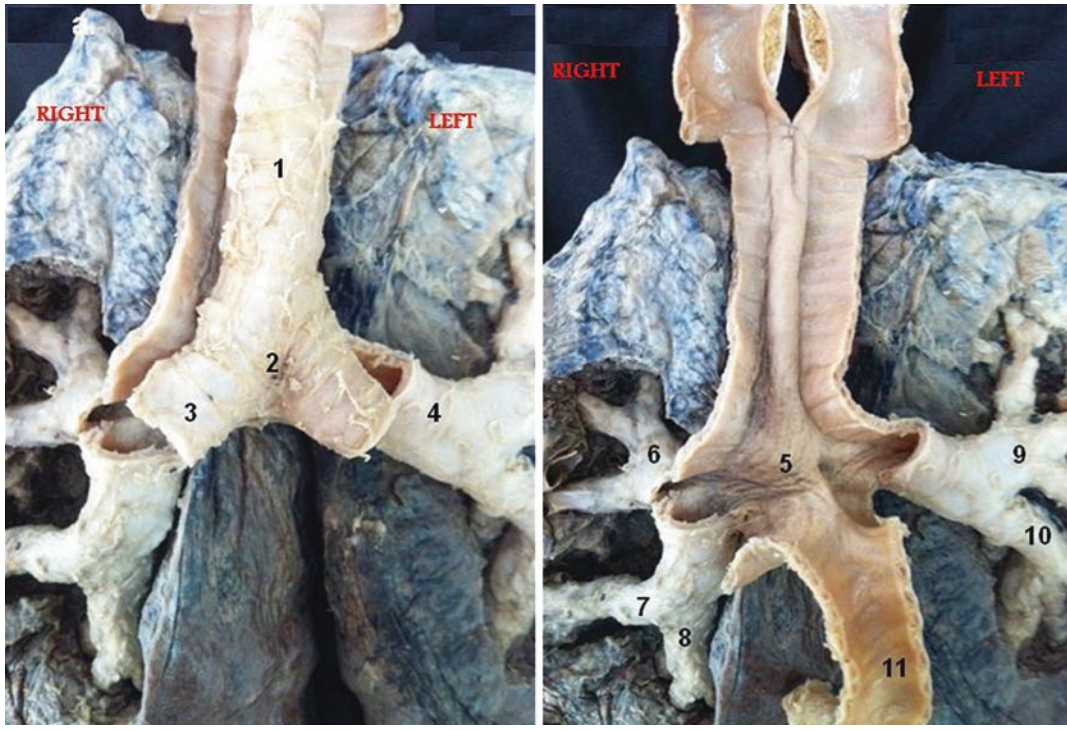


Fig. 1.12 Tracheobronchial bifurcation. Notice in the image on the right a tracheal cross section with anterior inclination of its ventral side. (*1*) Trachea, (*2*) tracheobronchial bifurcation, (*3*) right main bronchus, (*4*) left main bronchus, (*5*) bronchial carina, (*6*) right upper lobe bronchus, (*7*) right middle lobe bronchus, (*8*) right lower lobe bronchus, (*9*) left upper lobe bronchus, (*10*) left lower lobe bronchus, (*11*) inner wall of the anterior trachea. Unit of Human Anatomy and Embryology. Department of Pathology and Experimental Therapeutics. Universitat de Barcelona

The intermedius bronchus after approximately 15 mm originates the right middle lobe bronchus. From that on it is called *right lower lobe bronchus*.

Each bronchial division is accompanied by the corresponding segmental pulmonary artery, giving place to the different bronchopulmonary segments.

Endoscopic Vision of the Bronchial Tree and Anatomical Relationships

It is very important to learn the normal endoscopic view of the airways and keep in mind the anatomical relationships. Figure 1.13 depicts the tracheobronchial tree when inspected with a bronchoscope, with the patient in the supine position and the endoscopist located posteriorly. The camera is moving down from head to feet.

The most important anatomic relationships we have to consider are:

– Cervical trachea: anteriorly, the thyroid gland is located at the level of the second, third, and fourth tracheal rings. Thyroid lobes are in contact with the side walls of the cervical trachea. The veins that drain the thyroid gland are located at the bottom and head to the left innominate vein. In general these veins are arranged along the tracheal wall and do not constitute a serious hazard. The same occurs for the left innominate vein, which is located in front of the trachea behind the sternal manubrium. Bifurcation of arterial brachiocephalic trunk is in close contact with the windpipe at the base of the neck, and the main right carotid artery is located right in front of cervical trachea. From behind, the cervical trachea is in close contact with the esophagus, which is slightly more to the left. The right recurrent nerve meets the sixth level windpipe cartilage ring, running parallel to its rear edge. The left

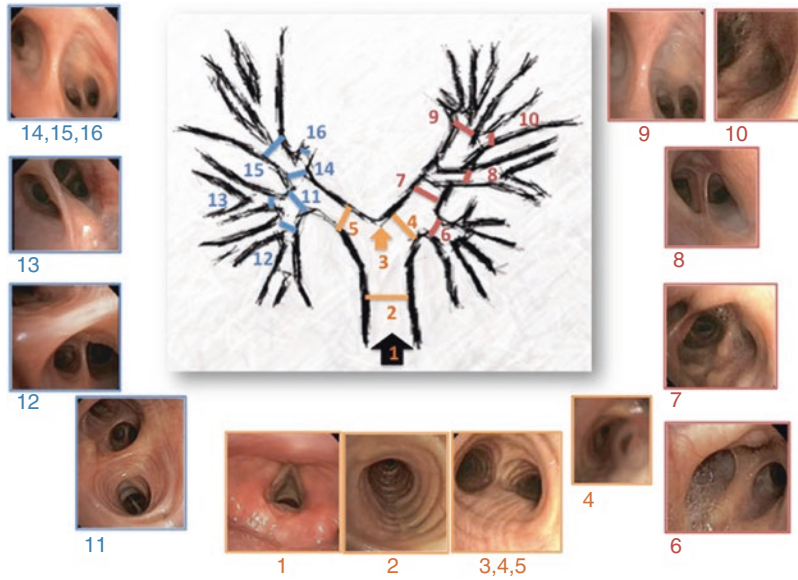


Fig. 1.13 Endoscopic vision of the bronchial tree: (*1*) vocal cords, (*2*) trachea, (*3*) carina, (*4*) right main bronchus, (*5*) left main bronchus. *Right*: (*6*) right upper lobe bronchus, three apical segments; (*7*) intermediate bronchus; (*8*) middle lobe bronchus; (*9*) basal pyramid bronchus; (*10*) six right segment bronchus. *Left*: (*11*) left upper lobe bronchus, (*12*) culmen bronchus, (*13*) lingular bronchus, (*14*) left lower lobe bronchus, (*15*) basal pyramid and (*16*) six left segment bronchus

recurrent nerve, coming from below the aortic arch, runs along the posterior tracheal wall in front of the esophagus. Laterally, apart from the thyroid gland, cervical trachea is close to the neurovascular structures of the neck (common carotid artery, internal jugular vein, vagus nerve). From the base of the neck, these structures deviate from the windpipe. Only the common carotid artery is in virtual contact with the outer edge of the trachea. The internal jugular vein and vagus nerve are more superficial.

– Thoracic trachea: as already explained, the thoracic trachea is a bit longer than the cervical trachea and has close contacts with the large vessels of the mediastinum. The danger of massive bleeding at this level is very high. The most important anterior anatomical relationships are vascular. The venous system: left innominate vein, right innominate vein, and superior vena cava (which is located below and to the right of the windpipe). The azygos vein is located at the level of the right edge of the windpipe. Important arterial structures are in close contact with the trachea: the aortic arch passes directly from front to back and right to left along the left edge of the trachea, generating a mark on it and deviating it to the right. Then the aorta is curved on the left main bronchus and descends along the column. The arterial brachiocephalic trunk is born in front of the windpipe and crosses obliquely to stand on its right edge. The left common carotid artery relates to the left edge of the windpipe but is farther away, like the left subclavian artery, so they do not constitute a danger. The left vagus nerve descends along with the common carotid artery, crossing the left side of the aortic arch, generating the left recurrent nerve that ascends along the left edge of the trachea and the esophagus. On the back, the thoracic trachea continues in close contact with the esophagus, which descends to the stomach and moves away to the left.
– Carina: at its inferior part, the trachea is divided into right and left main bronchi, looking like an inverted Y. The divergence angle

thus formed is 70°.The carina has important neurovascular connections. Anteriorly to it, the pulmonary artery divides into right and left branches. Also anteriorly and to the right, we find the union of the azygos vein and the superior vena cava. Anteriorly and to the left, the carina is in contact with the aortic arch and the left recurrent nerve. Posteriorly, the carina also remains in contact with the esophagus.

– Main right bronchus: the most important vascular connection of the main right bronchus is the right pulmonary artery, which crosses horizontally and anteriorly of the ascending aorta and the superior vena cava, before passing in front of right main bronchus. The pulmonary vein is located slightly below the artery, but not in direct contact with the bronchi. This is very important to know because the use of laser, for instance, is less dangerous when applied in the main right bronchus than in the left. For the rest, vascular distribution is practically superimposed on the bronchial tree, being parallel to the bronchial walls. Veins are more remote from the walls than the arteries, except in the inner edge of the middle and lower lobe, where they constitute a real danger during invasive procedures.
– Main left bronchus: the left main bronchus has a more horizontal path than the main right bronchus and is also longer and thinner. It has important vascular relations: the aortic arch is in contact with the superior and posterior aspects of it. Anteriorly, the aorta is separated from the bronchus by the main pulmonary artery.
– The left pulmonary artery is short and its path is oblique, upward, and backward to the origin of the left upper lobar bronchus. It depicts an "S" curve that wraps around the left main bronchus and then around the left upper lobe bronchus. The superior pulmonary veins cross the main left bronchus at the level of the origin of the upper lobe bronchus. The esophagus is posterior, in contact with the first few centimeters of the left main bronchus.
– At the level of the main left bronchus, dangers are more numerous than the main right one, mainly due to the proximity of the aortic arch and pulmonary artery and veins. In the rest of the left bronchial tree, arteries are parallel to the bronchial walls.

Blood Supply

Bronchial arterial supply depends upon the bronchial arteries, which are aortic branches. These bronchial arteries are small in size and are located at the posterior wall of the bronchus following the first bronchial divisions. Bronchial arteries can be divided into:

– Right bronchial artery
– Left superior bronchial artery
– Left inferior bronchial artery

We can also see the *Demel artery* and the *Tracheobroncho-esophageal artery*, both aortic branches. The latter will divide into three more branches:

- *Ascending tracheal artery*.
- *Esophageal artery*.
- *Right bronchial artery*: it is a single artery located at the posterior bronchial wall that will be divided into two bronchial branches each time it finds a bronchial division.

There are anastomoses between arteries on each side, which close the territory between the left and right bronchial arteries. These interbronchial anastomoses are called *Juttin asa*.

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Flexible Bronchoscopy

2

Tarek Dammad and Bilal A. Jalil

Introduction

Flexible bronchoscopy (FB) is the term that describes invasive, direct visualization of the airways via the flexible bronchoscope for diagnostic and therapeutic purposes.

Flexible bronchoscopy is a safe procedure that is usually performed by pulmonologists and thoracic surgeons to inspect the proximal and distal airways, reaching the lung parenchyma. It is easy to use; it has minimal sedation requirement and a great safety profile, facts that account for its popularity [1, 2].

The uses and applications of FB have evolved over the last 50 years to a variety of diagnostic and therapeutic modalities. This chapter will review the history of FB and its indications and contraindications and describe the procedure and its basic and advanced diagnostic and therapeutic techniques.

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History

The history of exploring human airways dates back to Hippocrates. Hippocrates mentioned "Cannulas should be carried into the throat along the jaws so that air may be drawn into the lungs."

However, it was not until 1897, when Gustav Killian in Freiburg, Germany, performed the first rigid bronchoscopy, investigating the larynx and trachea to extract a pork bone from the right main stem bronchus of a farmer. He then presented his experience in Heidelberg, Germany, branding it "direct bronchoscopy." Gustav Killian is regarded today as the father of bronchoscopy [3].

Rigid bronchoscopy remained the standard practice for the next 70 years, until Shigeto Ikeda, a thoracic surgeon from Tokyo, Japan, introduced the first prototype of the flexible fiber-optic bronchoscope in Copenhagen in 1966 [4] (Fig. 2.1).

The first commercially available flexible bronchoscope was manufactured by Machida in 1968 and comprised of over 15,000 glass fibers. Further revisions and improvements by Machida and Olympus allowed an enhanced working channel, image quality, and maneuverability.

The invention of the flexible bronchoscope represented a paradigm shift in the world of bronchoscopy. It was an easier procedure to perform than rigid bronchoscopy and allowed superior visualization of the distal airways. It continued to evolve with extensive technical and clinical

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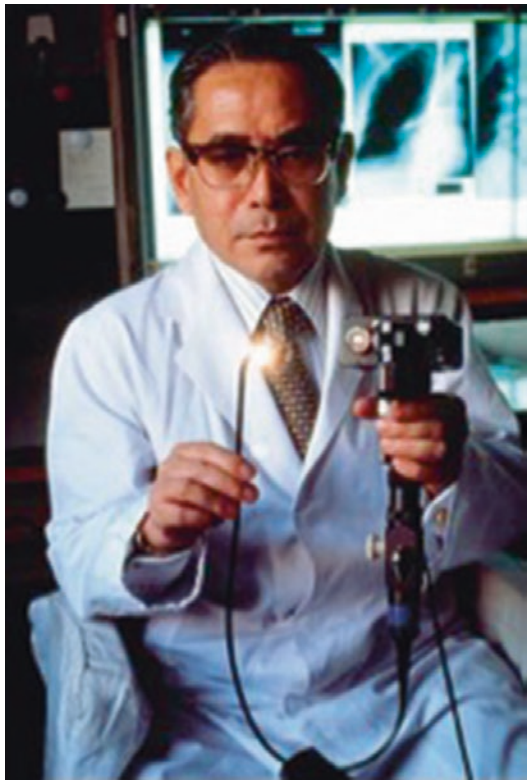

Fig. 2.1 Dr. Shigeto Ikeda, surgeon at the National Cancer Center, Japan, 1977 (Photography: Burt Glinn Magnum Photos)

applications. With Ikeda's contribution, Pentax produced the first flexible video bronchoscope in 1987, where a miniature video camera at the tip of the bronchoscope replaced the fiber-optic bundle, allowing for the bronchoscopy team to watch the procedure on a screen with tremendous definition and record it for documentation and educational purposes [5].

A second paradigm shift occurred with the introduction of endobronchial ultrasound (EBUS) bronchoscopy, another form of flexible bronchoscopy.

The usefulness of radial probe EBUS was first reported by Hurter and Hanrath in 1992. They studied 74 patients with central tumors and 26 patients with peripheral carcinomas [6]. In 1996, Heinrich Becker demonstrated the great potential of EBUS in assessing tumor infiltration of the bronchial wall and parabronchial structures, including lymph nodes [7].

In the early 2000s, Yasufuku and colleagues were the first to describe the high diagnostic yield of convex probe EBUS, enabling real-time visualization and sampling of the mediastinal, hilar adenopathy and central lesions, changing the way we diagnose and stage lung cancer forever [8, 9].

Significant technological innovations over the last few decades such as *laser* therapy, argon plasma coagulation (APC), transbronchial cryobiopsy, and electromagnetic navigational bronchoscopy were specifically developed and designed to use with the flexible bronchoscope [10].

Description

The flexible bronchoscope constitutes a flexible hollow vinyl tube called the "insertion tube" that contains optical fibers and a longitudinal working channel for suction and ancillary instruments.

The proximal handle contains a control lever to maneuver the distal end of the scope and control buttons for the camera and suction (Fig. 2.2).

There are two light transmitting bundles and one viewing bundle. Each bundle contains up to 30,000 ultrafine glass fibers (8–15 μm). In the fiber-optic bronchoscope, the light entering to the system is internally reflected and emitted at the opposite end.

However, in the video bronchoscope, a charge-coupled device (CCD) has replaced the viewing bundle. The CCD converts energy from light photons into digital information allowing excellent quality image capturing.

Fig. 2.2 The bronchoscope handle with the control lever at the proximal end and working channel insertion point at the distal end

The current flexible video bronchoscope's outer diameter ranges from 2.8 mm for the ultrathin scope to 6.9 mm for convex probe EBUS.

The working channel ranges from 1.2 mm for the ultrathin bronchoscope to 3.0 mm for the therapeutic bronchoscope (Fig. 2.3).

The length of the insertion tube ranges from 400 to 600 mm and the distal-end flexion angulation ranges from 120 to 210° in the latest generation bronchoscopes [11]. On the other hand, the distal-end extension angle ranges from 60 to 130° on the flexible bronchoscope (Fig. 2.4a, b). Of note, the flexible bronchoscope was designed to hold with the left hand since Dr. Ikeda was left-handed.

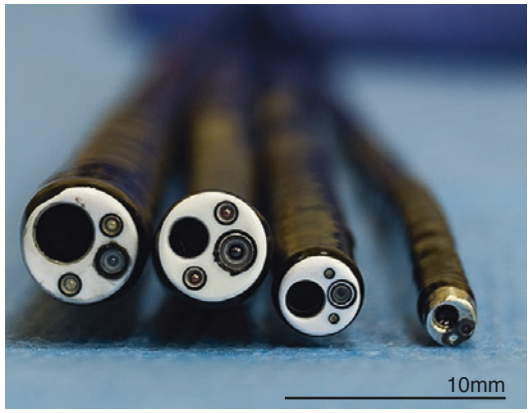

Fig. 2.3 Distal ends of different bronchoscopes ranging from the therapeutic bronchoscope with a 3 mm working channel on left to the thin bronchoscope with a 1.2 mm working channel on the right

Indications and Contraindications

Indications for flexible bronchoscopy are divided into diagnostic and therapeutic (Tables 2.1 and 2.2).

It is not uncommon that a diagnostic flexible bronchoscopy becomes both diagnostic and therapeutic at the same session, depending on unexpected findings that go undetected with pre-procedure imaging modalities or a change in the patient's condition.

Increasingly, therapeutic flexible bronchoscopic interventions are being performed by pulmonologists. In our opinion, it is due to increased number of dedicated interventional pulmonology training programs and the more recent innovations in this field.

Flexible bronchoscopy, in general, has a great safety profile [1, 2]. Major complications such as bleeding, respiratory depression, cardiorespiratory arrest, arrhythmia, and pneumothorax occur in less than 1% of cases. Mortality is rare, with a reported death rate of 0–0.04% in more than 68,000 procedures [12]. Most contraindications are relative rather than absolute [12–14].

Absolute Contraindications

- Life-threatening arrhythmia and/or hemodynamic collapse
- Profound refractory hypoxemia/inability to oxygenate patient during the procedure
- Lack of informed consent

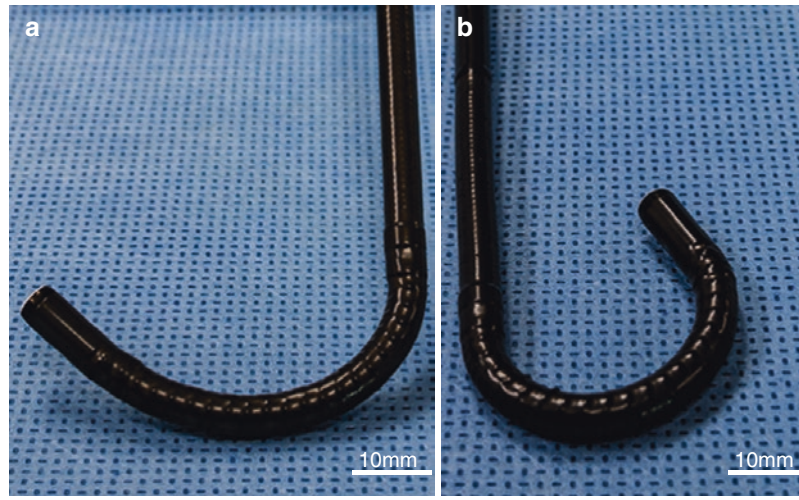

Fig. 2.4 (**a**) Distal end of the bronchoscope maximally extended at 130°. (**b**) Flexion of distal end of bronchoscope to 210°

Table 2.1 Indications for diagnostic flexible bronchoscopy

Suspected malignancy	Lung nodule/mass, airway lesion, hilar or mediastinal mass/adenopathy, lung cancer staging
Pulmonary infections	Pneumonia in immunocompromised host, cavitary lesions, non-resolving pneumonia, recurrent pulmonary infections
Diffuse lung disease	Interstitial lung disease, pulmonary toxicity, suspected diffuse alveolar hemorrhage, inhalation lung injury
Symptoms and signs	Hemoptysis, stridor, persistent cough, unexplained dyspnea, unilateral wheezing
Abnormal chest imaging	Persistent lobar collapse, localized bronchiectasis, suspected airway obstruction/narrowing, suspected excessive expiratory airway collapse, tracheobronchomalacia
Miscellaneous	Suspected aerodigestive fistula, bronchopleural fistula, chest trauma with suspected airway tear/injury, perioperative thoracic surgery, chemical and thermal burns of the airway, suspected foreign body aspiration, evaluation of posttransplant patients, endotracheal tube positioning

- Lack of capable bronchoscopist
- Lack of adequate facility

Relative Contraindications (Risk-Benefit Assessment)

- Bleeding diathesis: Platelet count less than 50,000/mm^3, uremic platelet dysfunction, and INR > 1.5 are relevant when brushing or biopsies are considered [15, 16]. Papin and colleagues demonstrated significant incidence of bleeding in 24 patients who underwent transbronchial lung biopsy (TBLB) with mean platelet count of 30,000/mm^3 [17]. Ernest and colleagues concluded that Clopidogrel use greatly increases the risk of bleeding after TBLB in humans and therefore should be discontinued 5 days before bronchoscopy with planned biopsies [18]. On the other hand, Herth et al. found that aspirin does not increase bleeding complications after TBLB [19]. A small case series by Stather concluded that proceeding to EBUS-TBNA without first withdrawing clopidogrel should only be performed in situations where the risk of short-term thrombosis is believed to outweigh the (theoretical) risk of bleeding [20].
- Recent myocardial infarction or unstable angina: Most experts will postpone elective bronchoscopies for 6 weeks post-acute coronary syndrome [21].
- Lack of patient cooperation.
- Pregnancy.
- Asthma attack.
- Increased intracranial pressure.
- Inability to sedate.

Table 2.2 Indications for therapeutic flexible bronchoscopy

Central airway obstruction (CAO)	Benign disease: *laser* coagulation, radial cuts, electrocautery, balloon dilatation of stenosis/stricture
	Malignant disease: tumor debulking/resection, *laser* coagulation/ablation, argon plasma coagulation (APC), cryotherapy, photodynamic therapy, stenting (self-expandable stents)
Foreign body removal	Removal of aspirated foreign body or broncholith extraction
Fiducial marker placement	Assisting in tumor localization for tumor resection or stereotactic body radiation therapy
Hemoptysis	Coagulation via LASER/ APC or electrocautery of visible tumor/lesion, placement of airway blocker
Tracheobronchial toilet	Therapeutic lavage in necrotizing pulmonary infections
Bronchopleural fistula closure	Spigots, endobronchial vale placement, sealant placement
Aspiration of cyst, drainage of abscess	EBUS-guided drainage of cysts and abscesses
Difficult airway intubation	Awake intubation for difficult airway and guidance in percutaneous dilatational tracheostomy
Bronchial thermoplasty	Treatment option in select asthmatics
Endoscopic lung volume reduction	Endobronchial one-way valve placement in select patients with emphysema

Procedure Preparation

Flexible bronchoscopy can be performed in the endoscopy suite, operating room, intensive care unit, or even emergency room:

1. Equipment
   The basic equipment needed is a bronchoscope and its accessories: light source and preferably a video monitor if available, BAL container, cytology brushes, biopsy forceps, needle aspiration catheters, syringes, normal saline aliquots, specimen containers, bronchoscope lubricant, bite block, suction apparatus, supplemental oxygen, continuous pulse oximetry, hemodynamic monitoring, and equipment for resuscitation including an endotracheal tube, laryngoscope, and chest tube insertion kit. Fluoroscopy can be valuable when performing TBLB and advanced diagnostic or therapeutic FB.
2. Personnel
   The bronchoscopist, registered nurse, endoscopy technician or respiratory therapist (RT), and the anesthesiologist or certified registered nurse anesthetist should all be familiar with the patient's condition and the procedure being performed as well as appropriate handling of the specimens. This will maximize patient experience and outcome (Fig. 2.5).
3. Patient Preparation
   A consent form must be obtained after explaining the procedure, its indication, risks, and benefits.

   The bronchoscopist must perform a thorough history and physical exam prior to proceeding. Chest imaging and diagnostic tests should be reviewed carefully.

   A few important concerns to mention:
   - Nil per os (NPO): Indicated for 2 h for clear liquids and 6–8 h for solids prior to FB [22].
   - Electrocardiograms are generally indicated for patients with suspected or known cardiac history.
   - Spirometry is not indicated prior to proceeding with bronchoscopy [23].

Fig. 2.5 The bronchoscopy team in the procedure suite

   - Premedication with atropine or glycopyrrolate is not beneficial in reducing bronchoscopy-related cough or secretions [12, 13].
   - Prophylactic antibiotics: FB is a rare cause of bacteremia and endocarditis [24]. Prophylactic antibiotics are indicated in patients with mechanical valves and history of endocarditis.
   - Chest X-ray is indicated 1 h post-transbronchial lung biopsy (TBLB) to rule out pneumothorax [25]. Alternatively, a thoracic ultrasound exam, documenting sliding lung sign, will rule out pneumothorax post-TBLB. Kumar and colleagues performed a total of 379 FB and 113 TBLB. Chest US exam detected all cases of PTX, whereas CXR missed 1 PTX. The sensitivity, specificity, and overall accuracy for US were 100% as compared with the sensitivity of 87.5% and accuracy of 99.6% for the CXR group [26].
4. Anesthesia and Monitoring
   The current guidelines do not address the type of anesthesia needed for each procedure, but

Fig. 2.6 A bronchoscopy procedure in progress using ENB and radial EBUS through a laryngeal mask airway with general anesthesia

suggest that simple diagnostic FB procedures can be performed under local anesthesia or moderate conscious sedation. On the other hand, complex diagnostic and therapeutic bronchoscopy usually requires general anesthesia like total intravenous anesthesia (TIVA) [27].

The most used local/topical anesthetic for FB is lidocaine. Its plasma level of 5 μg/mL or dose greater than 8.2 mg/kg instilled in the airways can result with CNS toxicity (restlessness, slurred speech, seizure), cardiovascular toxicity (atrioventricular block, hypotension), and methemoglobinemia.

Common sedative and opioid combinations used during conscious sedation are midazolam and fentanyl. Propofol or, to a less extent, ketamine or dexmedetomidine coupled with fentanyl or remifentanil is used in TIVA (Fig. 2.6).

After FB procedure, patients are observed in the recovery unit until they meet discharge criteria. Written discharge instructions and contact information are provided to the patient.

Technique of FB Procedure

- Insertion route: According to an ACCP survey done in 1991, 33.8% of the total 871 responders/bronchoscopists preferred the nasal FB route, compared to 6.4% preferred oral route only and 42.6% had no preference [15]. Choi and colleagues in 2005 randomly assigned 307 patients to nasal vs. oral insertion route. They concluded that oral insertion of a flexible bronchoscope was associated with less discomfort for patients than nasal insertion, although the route of insertion had no significant effect on outcome [28]. Beaudoin and colleagues assessed the feasibility of using nasal route for linear endobronchial ultrasound performed on 196 patients where in 73.5% of patients, nasal insertion was possible. The author concluded that linear EBUS can be performed safely and with high accuracy via the nasal route [29].
- When ready to proceed with FB, the patient should be placed in either a semirecumbent or supine position after IV access has been obtained. A topical anesthetic should be applied to the nasal passages and pharynx in case of nasal route insertion and only pharynx if oral route is chosen. Then, the bronchoscope is introduced either through the nose or mouth with a bite block in place to protect the bronchoscope. The oropharynx is examined, reaching the vocal cords, which are re-anesthetized topically. The vocal cords are examined for

abduction and adduction. The bronchoscope is passed through the vocal cords to examine the tracheobronchial tree. We prefer to start with inspection of the normal airways, leaving the diseased area of interest to the end. A thorough, systematic approach to examine the airways is recommended. Description of airway configuration, mucosal membranes, secretions, location, extent, and size of the abnormality is very valuable. Luminal narrowing/obstruction whether intrinsic, extrinsic, combined, or dynamic should be described; its length and distance from the closest carina should be documented in the report since it is very valuable if surgical intervention may become an option.

- Both diagnostic and therapeutic bronchoscopic procedures can be performed during flexible bronchoscopy. Lengthy, complex diagnostic and therapeutic procedures are better performed under IV general anesthesia.
- Depending on the indication, the following diagnostic procedures can be performed: BAL, endobronchial or transbronchial biopsies, cytological washes or brushings, conventional TBNA, endobronchial ultrasound (EBUS) TBNA, radial probe EBUS, cryobiopsy, navigational bronchoscopy, and narrow-band imaging (NBI) bronchoscopy. Therapeutic procedures such as balloon dilatation, endobronchial laser ablation/coagulation, electrocautery, photodynamic therapy, brachytherapy, self-expandable stent placement, and endobronchial valve placement can all be accomplished through flexible bronchoscopy [12, 14].

Complications of FB Procedure

Flexible bronchoscopy, in general, has a great safety profile [1, 2, 30]. Major complications such as bleeding, respiratory depression, cardiorespiratory arrest, arrhythmia, and pneumothorax occur in less than 1% of cases [15]. Mortality is rare, with a reported death rate of 0–0.04% in more than 68,000 procedures [12].

It is important to mention that transient hypoxemia during and after bronchoscopy is the most common complication, especially when performing BAL in a patient with borderline cardiopulmonary reserve [2, 31]. Cardiac arrhythmia and risk of myocardial infarction are increased in elderly patients with cardiovascular comorbidities [32, 33].

Other complications of FB are adverse events of sedatives and narcotics, hypercapnia, hypotension, bronchospasm and laryngospasm, pneumothorax, and bleeding. Gas embolism has been reported with using argon plasma coagulation [34].

Basic Diagnostic Procedures

1. Bronchoalveolar Lavage (BAL)

   The bronchoalveolar lavage was first introduced to clinical practice by Reynolds in 1974 [35].

   Standardization of BAL was addressed in a report by the European Respiratory Society task force in 1999. The report considers in detail the four main problems that prevent accurate quantification of components in alveolar epithelial lining fluid (ELF) using BAL:

   (a) Unknown amount of dilution during lavage.
   (b) Contamination of the ELF sample with material from the bronchi.
   (c) Inadequate sampling due to incomplete mixing.
   (d) Lung permeability varies allowing loss of introduced lavage fluid into the tissues and increased leakage of soluble components from the blood capillaries and tissues into the ELF [36].

To perform a BAL, the bronchoscope is wedged in the target bronchus, while keeping the working channel in the lumen of the bronchus. A total of four aliquots (30–60 mL each) are instilled in the alveoli for a total of at least 100 mL and a maximum of 240 mL of sterile normal saline. Subsequently, the fluid is suctioned into a trap with a pressure below 100 mmHg adjusted to avoid visible airway collapse. In a healthy nonsmoking subject, the BAL cellular composition is macrophages (80–90%), lymphocytes (5–15%)

with CD4/CD8 ratio of 1.5:1.8, neutrophils (1–3%), and eosinophils and mast cells <1% [37].Cell counts on BAL can have nonspecific results in many conditions such as cryptogenic organizing pneumonia and usual interstitial pneumonia, making its utility, to some extent, controversial [38, 39]. On the other hand, BAL plays an important role in the diagnosis of pulmonary infections, especially in immunocompromised hosts and mycobacterial infections, as well as in eosinophilic pneumonia [40, 41]. Higher yield can be achieved by adding TBLB [42]. It is important to mention that the presence of more than 5% squamous or epithelial cells represents contamination of the sample with bronchial secretions, rendering it a nonrepresentative sample of alveolar cells [36].

2. Transbronchial Lung Biopsy (TBLB)
   TBLB refers to sampling the lung parenchyma via flexible biopsy forceps. Anderson and colleagues first describe the method and results in 1960s and early 1970s [43, 44] (Fig. 2.7).

   It is usually performed by first, wedging the bronchoscope in the bronchus. The forceps are then advanced in the closed position through the working channel of the bronchoscope, reaching the lung parenchyma where resistance is felt. The forceps are pulled back about 1 cm to open, readvanced until the desired tissue is in contact with the forceps, and closed again to obtain a biopsy.

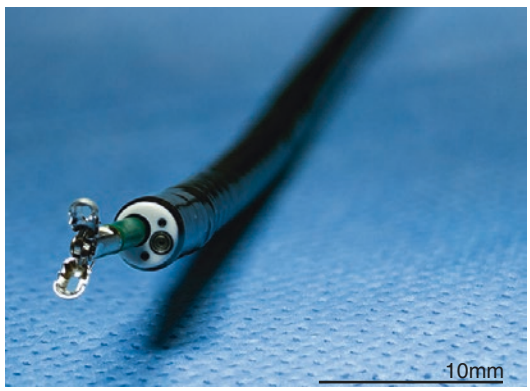

Fig. 2.7 Biopsy forceps used with the flexible bronchoscope

The wedging position of the bronchoscope will facilitate further biopsies without the need to reposition the scope. It will also help isolate and tamponade any significant bleeding from the biopsy site.

The yield of TBLB increases with the number of biopsies taken. Descombes and colleagues showed that TBLB yield is increased from 38 to 69% when six or more biopsies are performed [45]. The yield is also dependent on the pulmonary disease being investigated. The yield in usual interstitial pneumonitis (UIP) is only 30%, whereas higher yield of 70% or more is seen in pulmonary diseases with:

- Centrilobular distribution such as granulomatous lung diseases (hypersensitivity pneumonia and sarcoidosis), eosinophilic pneumonia, and lymphangitic carcinomatosis [46, 47]
- Pulmonary infection in immunocompromised host and mycobacterial infections [41, 42]
- Lung transplant patients with acute rejection or infection [48]

TBLB has a low complication rate with major bleeding (greater than 50 mL) averaging 1% and risk of pneumothorax between 1 and 4% [2, 49, 50].

3. Transbronchial Needle Aspiration
   TBNA refers to sampling through the tracheal or bronchial wall. The mediastinal and hilar lymph nodes and lung and mediastinal masses can be sampled via this method. A thorough review of the patient's chest CT and knowledge of thoracic anatomy is essential prior to proceeding. A retractable hollow cytology needle (21 or 22 gauge) or histology needle (19 gauge) is used, with suction applied to the proximal end of the needle. Fluoroscopy should be used when performing TBNA of peripheral lung lesions.

   Wang and colleagues in 1978 performed the first successful TBNA of a paratracheal tumor via the flexible bronchoscope. They later published their experience with TBNA for hilar and mediastinal adenopathy [51, 52].

Blind TBNA is the term used for standard TBNA with no EBUS guidance. The sensitivity of blind TBNA varies according to size, location, number of aspirates per lymph node's station, and the bronchoscopist experience. A sensitivity of 78% and specificity of 99% have been reported for blind TBNA in patients with lung cancer [53, 54]. Baaklini and coworkers found a yield of 64% for pulmonary lesions located in the inner third of the lungs vs. 35% for lesions located in the outer two thirds of the lungs. They also showed a lower yield for smaller lesions (<2 cm) [55].

Blind TBNA also has a role in the diagnosis of peripheral lung mass and nodules as Katis and colleagues first showed in 1995 [56].

Despite its great diagnostic utility, both ACCP and UK surveys have shown low routine use of blind TBNA in malignant and nonmalignant diseases with 11.8% and 2.3%, respectively, in the ACCP survey [15] and 10% use in the UK survey [2].

The overall complication rate for blind TBNA is quite low 0.8% [54]. The most common is damage to the bronchoscope working channel [15].

The introduction of EBUS-TBNA for mediastinal and hilar adenopathy and central tumors has replaced blind TBNA to a great extent. More guidance tools to reach peripheral lung nodules, like radial probe EBUS and virtual bronchoscopy have changed the way pulmonologists perform TBNA.

A brief review of advanced diagnostic bronchoscopy is to follow.

4. Bronchial Brushings

Bronchial brushings involves the introduction of a small-protected brush via the flexible bronchoscope to the visible endoluminal lesion or peripheral pulmonary nodule with assistance via fluoroscopy or guidance tools of bronchoscopy (radial EBUS or virtual bronchoscopy techniques).

It is a useful tool to obtain both microbiological and cytological samples.

Protected brushings have shown to increase the diagnostic yield in peripheral lung nodules [57].

A review of 30 studies published in 2003 assessed the performance characteristics of different modalities for suspected lung cancer. They found that the diagnostic yield of all modalities combined for central endobronchial disease is 88%. The highest sensitivity is for endobronchial biopsy 74%, followed by cytobrushing 59% and washings 48%. For peripheral lung lesions, cytobrushing demonstrated the highest sensitivity (52%) followed by transbronchial biopsy (46%) and BAL/washings (43%). The overall sensitivity for all modalities was 69%. Peripheral lesions <2 cm or >2 cm in diameter showed sensitivities of 33% and 62%, respectively [58].

Advanced Diagnostic Bronchoscopy

1. EBUS-TBNA

EBUS-TBNA refers to the technique of obtaining needle aspiration biopsies under direct sonographic visualization using the EBUS bronchoscope (Fig. 2.8).

The special flexible bronchoscope incorporates an ultrasound transducer at its distal end allowing real-time visualization and characterization of mediastinal and parabronchial structures and real-time needle aspiration of lymph nodes and lesions. The procedure is usually performed under moderate sedation. No advantage has been demonstrated by performing EBUS-TBNA under general anesthesia [59]. The reported safety profile is

Fig. 2.8 An endobronchial ultrasound bronchoscope

excellent. In their meta-analysis, Gu et al. reported only two complications in 1299 patients (0.15%) [60].

The current available needle sizes for EBUS-TBNA are 22G, 21G, and most recently 19G needle.

Nakajima and colleagues demonstrated no differences in the diagnostic yield between the 21G and 22G needles during EBUS-TBNA, though more blood contamination was present in the 21G needle TBNA biopsies. The preserved histological structure of the samples obtained by the 21G needle may be useful for the diagnosis of mediastinal and hilar adenopathy of unknown etiology which may be a challenge with the 22G needle [61].

Yarmus and colleagues retrospectively evaluated the results of 1299 patients from six centers who underwent EBUS-TBNA. No difference in diagnostic yield or sample adequacy was found when comparing 22G and 21G needles. However, EBUS-TBNA in conjunction with rapid onsite cytological evaluation and a 21G needle was associated with fewer needle passes compared with a 22G needle [62]. Jeyabalan and coworkers have recently confirmed the high clinical utility of EBUS-TBNA samples processed as histopathological specimens for EGFR and ALK genotyping in primary lung adenocarcinoma. The needle gauge did not affect genotyping efficacy [63].

In 2009, two meta-analyses and one systematic review reported the sensitivity and specificity of EBUS-TBNA. Adams et al. and Gu et al. reported that the pooled sensitivity for EBUS-TBNA was 88% and 93% respectively [60, 64]. In their systematic review, Varela-Lema et al. reported that sensitivity for the diagnosis of malignancy ranged from 85 to 100% [65].

Therefore, the most recent ACCP guidelines in 2013 on the diagnosis and management of lung cancer recommend EBUS-TBNA over surgical staging as the best first invasive test in patients with intermediate or high suspicion of N2 or N3 involvement (Grade 1B) [66].

In a recent meta-analysis by Ge and colleagues comparing video-assisted mediastinoscopy (VAM) and EBUS-TBNA for staging of lung cancer, a total of ten studies with 999 EBUS-TBNA patients and seven studies with 915 VAM patients were included. The pooled sensitivities for EBUS-TBNA and VAM were 0.84 (95% CI 0.79–0.88) and 0.86 (95% CI 0.82–0.90), respectively. The conclusion of the analysis was: VAM and EBUS exhibited equally high diagnostic accuracy for mediastinal staging of lung cancer [67].

The role of EBUS-TBNA is less established for the diagnosis and subtyping of lymphoma. In a recent study by Grosu and colleagues, EBUS-TBNA was able to establish a diagnosis and subtype the lymphoma in 67% (95% CI, 0.45–0.88) of patients with de novo lymphoma and 81% (95% CI, 0.70–0.91) of patients with relapsed lymphoma [68]. EBUS-TBNA plays an important role in the diagnosis of Sarcoidosis. The diagnostic yield ranges from 88 to 93% [69–72]. It is equally effective in identifying noncaseating granulomas when compared with transbronchial/endobronchial lung biopsies combined with bronchoalveolar lavage [73].

2. Radial Probe Endobronchial Ultrasound (RP-EBUS)

   RP-EBUS utilizes a miniature ultrasound probe with a diameter of 1.4–1.7 mm and provides a circumferential radial ultrasound image. It is inserted through the working channel of the scope with or without a guidance sheath (GS). The characteristic "snowstorm-like" appearance represents normal lung. The high resolution provided by 20 MHz US probe allows detailed imaging of the peripheral lung lesion. Solid tumor will appear dark, homogenous, and well differentiated from normal lung with bright border (Fig. 2.9a–c).

   Once the target lesion is reached, the GS is left in place as an extending working channel of the bronchoscope. The US probe is removed and sampling tools, like biopsy forceps, protected brushes, and aspiration needles can be introduced to obtain samples with or without fluoroscopic guidance.

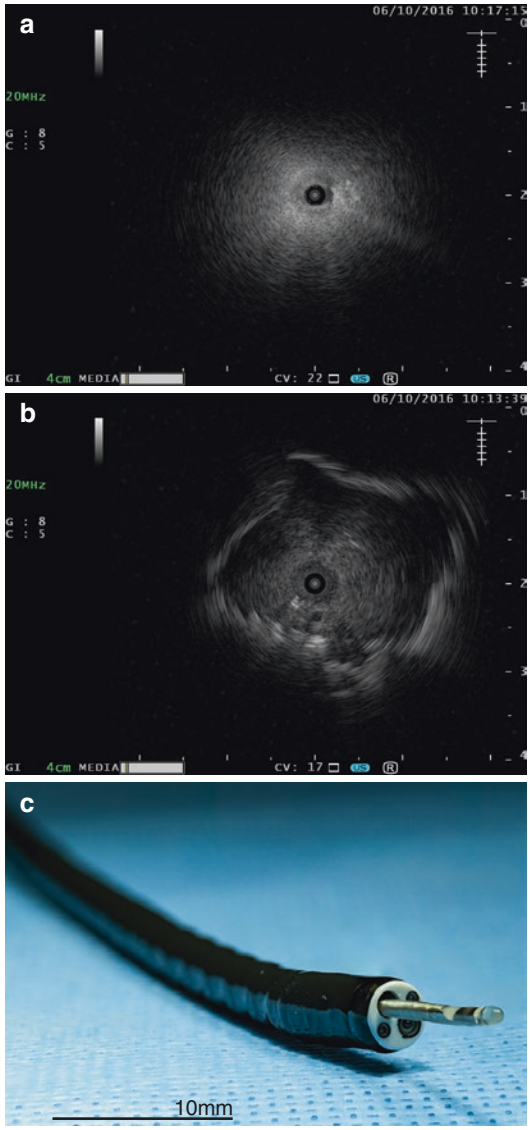

Fig. 2.9 (**a**) Radial ultrasound of the lung, showing normal "snowstorm-like" appearance. (**b**) Radial ultrasound of a malignant lung mass. (**c**) Radial EBUS probe seen through the working channel of a bronchoscope

RP-EBUS has increased the yield of FB in the diagnosis of peripheral lung lesions. Chen and colleagues, showed that of all 467 nodules, 96% were successfully identified using radial probe EBUS. When the radial probe position was within the target lesion, the diagnostic yield was 84% compared with 48% when the probe was positioned adjacent to the lesion [74].

A systematic review and meta-analysis with 1420 patients revealed significant inter-study variations in the RP-EBUS technique; however, the overall pooled sensitivity of RP-EBUS for detection of lung cancer in peripheral pulmonary lesions was 73% [75]. In a prospective randomized trial, Steinfort and colleagues demonstrated that the diagnostic accuracy of RP-EBUS transbronchial biopsy is not inferior to that of CT-guided transthoracic needle aspiration, but with a significantly lower complication rate [76].

The size of the lesion, position of the probe within the lesion, and number of biopsies taken all are important factors that affect the diagnostic yield [77, 78]. Utilizing combined modalities like RP-EBUS and ENB has pushed the diagnostic yield to 88% for the diagnosis of peripheral lung nodules, compared to EBUS (69% yield) and ENB (59% yield) utilized alone [79]. In a multicenter randomized trial, Ishida et al. demonstrated virtual bronchoscopic navigation VBN-assisted RP-EBUS significantly improved the diagnostic yield of small (<30 mm) peripheral pulmonary nodules to 80.4%; 13% higher than the non-VBN-assisted group [80].

3. Ultrathin Bronchoscopy

Peripheral pulmonary lesions are commonly encountered by the pulmonologist and require pathologic analysis to determine treatment options. Transbronchial biopsy has a low diagnostic yield for peripheral lesions <20 mm [81]. Thus, bronchoscopy is currently not recommended as a diagnostic technique for peripheral lesions <20 mm [82]. Transbronchial biopsy is limited by the difficulty in guiding the bronchoscope and biopsy instrument to the peripheral lesion. Navigational bronchoscopy as well as radial probe EBUS with guidance sheath has been used to overcome this issue.

The ultrathin bronchoscope with a working channel has an external diameter of approximately 2.8 mm and is commercially available. It is used in the diagnosis of peripheral pulmonary lesions and can be advanced to more peripheral bronchi than conventional bronchoscopes under

direct observation. Ultrathin bronchoscopes have been reported to be advanced to sixth-generation bronchi and to be valuable in patients where diagnosis is difficult using conventional bronchoscopy [83]. Oki et al. conducted a randomized controlled trial comparing ultrathin (3 mm) and thin bronchoscopy with guidance sheath (4 mm) bronchoscopy for peripheral lesions and found ultrathin bronchoscopy to be superior [83]. The combination of navigational bronchoscopy with ultrathin bronchoscopes was recently studied by Asano et al. and did not show a statistically significant difference [84].

4. Transbronchial Lung Cryobiopsy (TBLC)
   Cryobiopsy is the term used to describe utilization of cryoprobes to obtain lung tissue. The cryosurgical equipment operates by the Joule–Thomson effect, which dictates that a compressed gas in liquid state, released at high flow, rapidly expands and creates a very low temperature. The most commonly used cryogenic agents are carbon dioxide (CO_2) or nitrous oxide. The gas at the tip expands due to the sudden difference in pressure relative to the atmospheric pressure, resulting in a drop in temperature at the tip of the probe (around minus 80 °C). The size of cryobiopsies correlates positively with longer activation time and larger diameters of the cryoprobe.

   The technique is simple. The cryoprobe (diameter of 1.9 or 2.4 mm) is introduced into the selected area under fluoroscopic guidance via flexible bronchoscope. A distance of approximately 10–20 mm from the thoracic wall and a perpendicular relation between the thoracic wall and the probe are considered optimal. Once the tip of the probe is at the target area, the probe is activated for approximately 3–6 s. The frozen tissue attached to the probe's tip is removed by pulling both the bronchoscope and cryoprobe together.

   The advantage of TBLC over TBLB has been highlighted in several publications [85, 86].

   Ravaglia and colleagues compared the diagnostic yield and safety of TBLC and surgical lung biopsy (SLB) in a large cohort of patients with ILD. The diagnostic yield of TBLC was 82.8% compared to 98.7% in SLB with less median hospitalization time (2.6 days) in TBLC vs. (6.1 days) for SLB. Mortality due to adverse events was observed in 2.7% (SLB) and 0.3% (TBLC) of the patients. Pneumothorax was the most common complication after TBLC (20.2%). No severe bleeding was observed [87]. A meta-analysis of 15 investigations including 781 patients revealed an overall diagnostic yield of 81%. The overall pooled probability of developing a pneumothorax, as retrieved from 15 studies including 994 patients, was 6% [87].

   It is important to recognize the higher rate of potential complications when using TBLC, like pneumothorax and bleeding. Therefore, TBLC should be performed by interventional pulmonologists who are trained to manage potential complications.

Therapeutic Procedures via FB

Therapeutic bronchoscopy refers mainly to the management of central airway obstruction (CAO), intrinsic, extrinsic, or combined. This entitles mechanical and nonmechanical tumor debulking in malignant and benign diseases, tracheobronchial dilatation of stenosis, deployment of airway stents, extraction and removal of foreign bodies, and management of hemoptysis. It also includes newer therapeutic applications like endobronchial valve placement for prolonged air leak post-lobectomy or endoscopic lung volume reduction interventions in selected emphysema patients.

Therapeutic bronchoscopic interventions, to a certain degree, can be accomplished via the flexible bronchoscope. However, the bronchoscopist must be competent and experienced with the use of rigid bronchoscopy and ready to use it when intervening on a complex central airway obstruction. The rigid bronchoscope remains the tool of choice recommended by most experts in the field when treating CAO [14, 88].

In this chapter, we will outline a brief summary of some available interventional therapeutic modalities that can be implemented for use with flexible bronchoscopy.

LASER Bronchoscopy

The majority of publications on LASER bronchoscopy report the use of Nd:YAG laser [89, 90]. Other lasers like CO_2, Nd:YAP, Holmium:YAG, and diode lasers are utilized in bronchoscopic interventions.

In laser therapy, the heat energy from laser light is used to coagulate and vaporize the endobronchial lesion.

It is recommended to set laser at low power (40 W) to coagulate the target lesion in anticipation to prevent bleeding.

The laser fiber is introduced through the working channel of the FB. The tip of the laser fiber should be at least 4 mm away from both the target lesion and the bronchoscope distal end. The inspired FiO_2 should be lowered to 40% or less, and frequent suctioning should be used to minimize the risk of endobronchial fire [91].

Then coagulation followed by mechanical resection with the flexible forceps can occur. In general, laser treatments performed using a flexible bronchoscope are long and require a significant amount of patience. The flexible bronchoscope is not useful in severe obstruction or critical situations; they are better handled with the rigid bronchoscope [16]. Small lesions such as granulomas are easily treated with laser application via flexible bronchoscopy.

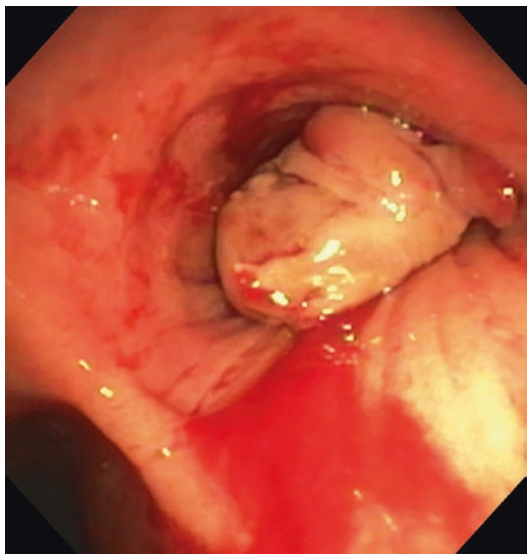

Fig. 2.10 Endobronchial lesion at the level of the right main bronchus

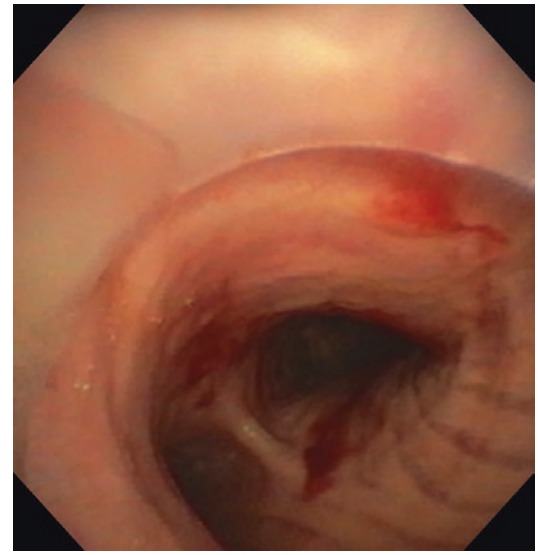

Fig. 2.11 Endoscopic view after resection

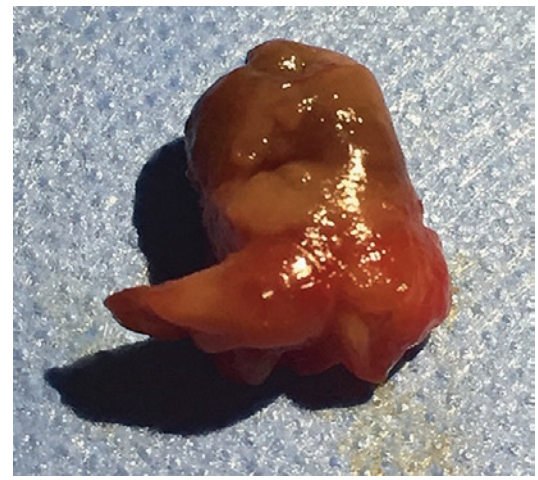

Fig. 2.12 Tumor resected

Laser is very effective in restoring airway patency, with symptomatic improvement in around 70–80% of patients [89, 90, 92]. Complications related to laser application include massive hemoptysis (1%), pneumothorax (0.4%), pneumomediastinum (0.2%), and endobronchial fire and periprocedural death of (2–3%) [90, 92, 93] (Figs. 2.10, 2.11, and 2.12).

Electrocautery

Electrocautery is used to treat central airway obstructions from benign or malignant tumors of

the airway [94]. It also acts through coagulation and vaporization. The electrical probe can be used to treat superficial lesions, while the snare can be applied to polypoid tumors protruding into the airway lumen. Similar to LASER, electrocautery is contraindicated when the obstruction arises from extrinsic compression without an intraluminal component [95].

Palliation of malignant obstructions using electrocautery is effective, with a rate of restoration of airway patency and symptomatic relief similar to LASER debulking (69–94%) [96–98].

Complications are similar to those of LASER application, with massive hemoptysis being the most concerning. Suggested settings to avoid fire during the procedure are a FiO_2 equal or less than 40% and low power (20–30 W).

Argon Plasma Coagulation

APC is a noncontact mode of electrocautery that causes coagulation and vaporization. It is performed to treat exophytic endobronchial tumors and has good results treating bleeding tumors. APC can also be applied to other benign lesions compromising the airway, such as granulomas resulting from airway stents.

APC shows good results in central airway obstruction, with a partial or complete restoration of airway patency in 66% of patients. It has a reported success rate of 99% when treating hemoptysis [99].

Complications related to APC are airway perforation and gas embolism [34].

Cryotherapy

Cryotherapy refers to the use of extreme cold to destroy abnormal or diseased tissue. The cryoprobe is inserted through the working channel of the flexible bronchoscope, and cycles of freezing and thawing are applied to the target, causing delayed necrosis. A repeat bronchoscopy is performed 3–7 days after the application to remove necrotic tissue. Cryotherapy does not open the airway rapidly and it is not utilized in critical airway obstruction since its application generates edema that may worsen the degree of the obstruction.

Conventional cryotherapy is indicated in malignant airway obstruction as a palliative method. A success rate of 61% has been reported in airway restoration and significant improvement of symptoms such as hemoptysis, cough, and dyspnea [100, 101]. Complications related to cryotherapy are hemoptysis, bronchospasm, cardiac arrhythmia, and death [102].

A newer modality of cryotherapy called cryoextraction or cryorecanalization can be considered a rapid airway restoration method since tumor pieces attached to the cryoprobe are removed immediately [13].

Photodynamic Therapy

It involves the administration of a photosensitizer substance (most commonly porfimer sodium) followed by its activation with a laser light of a given wavelength. This generates a photodynamic reaction that produces oxygen radicals that are very damaging for tumor cells, ultimately resulting in cellular death. Photodynamic therapy can be applied to both early and advanced malignant lesions with good results [103].

Complications related to this procedure are photosensitivity (can last up to 6 weeks) and hemoptysis.

Airway Stent Placement

The flexible bronchoscope can be used to deploy self-expandable metallic stents (SEMS) in the airway. Both bare and fully covered SEMS are commercially available.

The bare SEMS application is limited to malignant conditions since long-term permanence inside the airway has been linked to severe complications such as erosion and perforation of the airway wall, excessive granulation tissue, bacterial colonization, stent disruption, and fracture [104].

The FDA released very clear recommendations regarding the use of metallic airway stents in 2005 [105]. Recommendations from experts are to avoid bare metallic stents and consider other therapeutic strategies. Placement of a sili-

con stent can be performed in the majority of patients via rigid bronchoscopy and represents a safer alternative [106].

However, postsurgical stenosis that follows lung transplant or tracheal resection can be an indication for metallic stents. Bronchial dehiscence after lung transplantation can present as a life-threatening respiratory insufficiency, and deployment of a metallic stent can be not only lifesaving but also can favor healing taking advantage of the granulation tissue formation secondary to the stent placement [107]. This indication is left to the team of experts managing lung-transplanted patients, not applicable to the general interventional bronchoscopy practice.

It is crucial to note that when bronchoscopists deploy a stent via flexible bronchoscopy approach, they must be skilled and ready to perform rigid bronchoscopy if needed.

Conclusion

The evolution of flexible bronchoscopy over the last 50 years has changed the field of diagnostic and therapeutic bronchoscopy. It started with basic diagnostic procedures that we must, as trainees and teachers, master and not forget. It continued to evolve with sophisticated, novel modalities that have proven to advance the care of our patients with thoracic and pulmonary diseases.

It is important for today's pulmonologist to understand and learn some of the advanced techniques in flexible bronchoscopy. It is also vital for our interventional pulmonology trainees to utilize the current and future techniques in order to achieve the best possible outcomes for our patients.

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Ultrathin Bronchoscopy: Indications and Technique

3

Marta Diez-Ferrer and Antoni Rosell Gratacos

Introduction and Definition of the Procedure

Standard flexible bronchoscopes may enter up to third- to fifth-generation bronchi and allow visualization of one to two further generations in adult patient airways, while the category of "ultrathin bronchoscope" can reach small peripheral airways up to 9th to 12th generation. Although no formal definition of "ultrathin bronchoscope" has been established, the term ultrathin has been widely used when referring to bronchoscopes with an outer diameter of 3 mm or less that are used for the exploration of peripheral airways in adult patients. In Fig. 3.1 you can compare the size of different bronchoscopes.

In this chapter we will review the technique and applications of the ultrathin bronchoscope.

Fig. 3.1 Comparison of different bronchoscopes: 2.8, 4.9, and 6.0 mm external diameter

History and Historical Perspective

The first ultrathin fiber-optic bronchoscope (FOB) was used through the working channel of a conventional bronchoscope. Developed by Tanaka et al. [1] in 1984, the model Olympus BF-1.8T was composed of fine optical glass fibers and had a tip diameter of 1.8 mm that could go up to 180 mm past the tip of a conventional fiber-optic bronchoscope. It had no working channel and could be bent passively only. Attachment to a special camera allowed for the first photographs of peripheral airways of 2 mm or less [2] and their

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first endoscopic classification [3]. By the same time, Prakash was using a regular pediatric fiberoptic bronchoscope (Olympus BF-3C4) with an external diameter of 3.5 mm to explore and sample with a cell brush the abnormalities present in more distal airways of adult patients [4]. In 1990 Tanaka et al. developed a second model of ultrathin with an outer diameter of 2.2 mm and distal tip that could be bent 120° upward and downward (Olympus BF-2.2T) [5]. Later in 1994 a new bronchoscope (Olympus BF-2.7T) was released by the same authors with a tip diameter of 2.7 mm and the novelty of incorporating a 0.8 mm working channel that allowed small airways sampling under direct vision with a cell brush (Olympus BC-0.7T) [6]. Since then, newer ultrathin fiber bronchoscopes and video bronchoscopes with working channels up to 1.2 mm have been developed as well as various types of brushes and biopsy forceps. Most recently, a new prototype of ultrathin hybrid bronchoscope with a working channel of 1.7 mm has been used that allows for radial probe EBUS performance [7]. A summary of the evolution of ultrathin bronchoscopes found in medical literature can be seen in Table 3.1. Pediatric bronchoscopes from other brands have also been used for exploring the peripheral airways of adult patients.

In essence, ultrathin bronchoscopes are thinner versions of the standard bronchoscopes. Although they can be used either in pediatric patients or in peripheral airways of adults, they are provided with longer insertion tubes than pediatric bronchoscopes.

Indications and Contraindications

Unlike standard flexible bronchoscopy which is divided into diagnostic and therapeutic categories, the use of ultrathin bronchoscopy is mainly diagnostic. As will be discussed later, its main limitation when sampling is the small working channel which limits both the suctioning capability and the use of instruments. In terms of contraindications, however, the same may apply.

Indications

The study of the peripheral pulmonary nodule is the main indication for ultrathin bronchoscopy.

Table 3.1 Evolution of ultrathin bronchoscopes

Image[a]	Year	Type	Working length (mm)	External diameter (mm)	Internal diameter (mm)	Tip angulation (up/down)	Additional imaging techniques	Instruments
nF	1984	Olympus BF-1.8T	950	1.8	–	–	–	–
F	1990	Olympus BF-2.2T	1150	2.2	–	120°/120°	–	–
F	1994	Olympus BF-2.7T	1200	2.7	0.8	120°/120°	–	Brush
F	1999	Olympus BF-XP40	600	2.8	1.2	180°/130°	–	
F	2004	Olympus BF-XP60	600	2.8	1.2	180°/130°	–	Brush and forceps
H	2004	Olympus BF-XP160F	600	2.8	1.2	180°/130°	–	
V	2014	Olympus BF-XP190	600	3.1	1.2	210°/130°	NBI	
H	2015	Olympus Y-0025[b]	600	3.0	1.7	180°/130°	–	Brush, forceps, and radial EBUS probe

[a]*F* fiber-optic bronchoscope, *H* hybrid bronchoscope, *V* video bronchoscope
[b]Prototype

In the review by Rivera et al. for the third edition of the ACCP guidelines, the overall sensitivity of flexible bronchoscopy for diagnosing central lesions was 88% while for peripheral lesions was 78% [8]. This is partly due to direct visualization of the lesion while sampling areas that the bronchoscope does not reach. The importance of the ultrathin bronchoscope relies therefore in the ability to reach and directly visualize the abnormalities of the peripheral airways, primarily peripheral pulmonary nodules, and its capability of sampling the periphery of the lung under direct visualization.

Although no specific guidelines regarding ultrathin bronchoscopy have been developed, its use is not limited to the study of the peripheral pulmonary nodule. Other uses may include the exploration of cavitated nodules if aspergilloma formation is suspected, the study of critical stenosis (Fig. 3.2) (where the use of the ultrathin may avoid the presence of asphyxia and even barotrauma due to its small diameter), or the study of postoperative scars. Asai et al. used an ultrathin bronchoscope to apply suction in a giant bulla, observing radiologic and functional improvement after 2 months [9]. Also, peripheral nodule marking with barium prior to surgery has been described [10].

Contraindications

The same contraindications as for standard bronchoscopy may apply. It has to be noted though that the ultrathin bronchoscope is a very fragile instrument, and therefore careful manipulation is imperative.

Description of the Equipment Needed

Ultrathin bronchoscopy may be performed in a bronchoscopy suit with the patient awake or in mild sedation or in the operating room under general anesthesia and endotracheal intubation.

The equipment needed includes:

- Trained staff: a skilled operator and two assistants (at least one of them should be a qualified nurse).
- Ultrathin bronchoscope and its accessories.
- Light source and video processor.

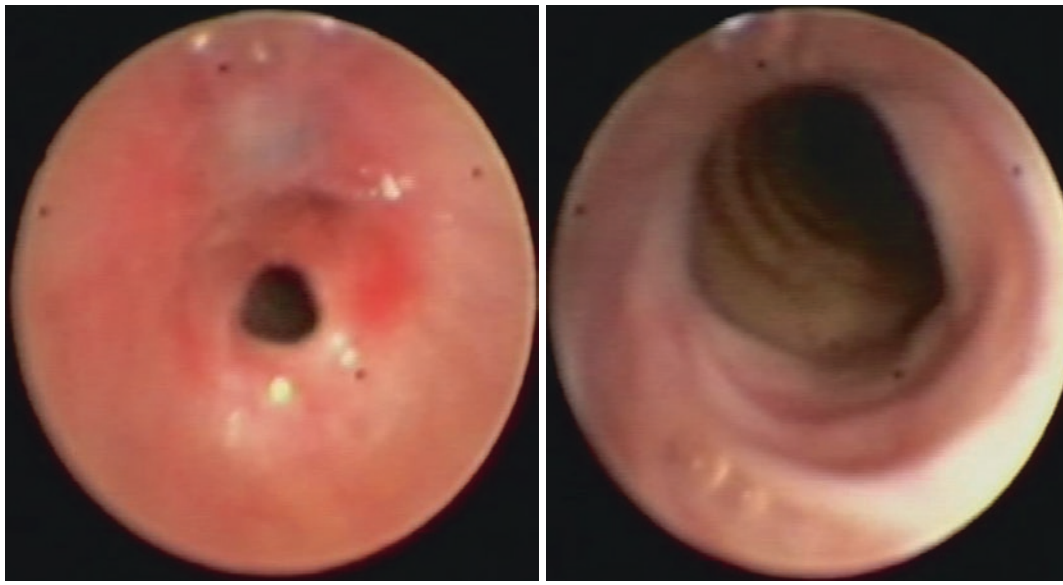

Fig. 3.2 Examination of critical stenosis with the ultrathin bronchoscope: view of the severe stenosis and distal trachea

- 50 mL syringes.
- Topical anesthesia: 2.5% lidocaine.
- Room temperature saline.
- Mini biopsy forceps and/or mini cytological brush (1 mm diameter).
- Specimen collection devices (bronchial washing receptacle, 95% alcohol and CytoLyt® solution).
- Cold saline should be ready to use in case of bleeding.
- Chest tube placement kit should be ready to use in case of pneumothorax.
- C-arm fluoroscopy or computed tomography (CT) should be available for guidance of the bronchoscope or sampling instruments, to verify their position and to confirm that no pneumothorax is present right after sampling.

Optional equipment:

- Virtual bronchoscopy or virtual bronchoscopic navigation for aiding in procedure planning and guiding.

In Fig. 3.3 you can see the operating room with the necessary equipment for ultrathin bronchoscopy with virtual bronchoscopic navigation performance in a patient under general anesthesia.

Procedure Description

The authors of the present text prefer performing ultrathin bronchoscopy under general anesthesia since it allows greater technical precision and better patient and operator comfort. Exploration of the peripheral airways can be a long procedure, and it is technically more challenging to manipulate the ultrathin through smaller bifurcations if the patient is not under a controlled respiration and in the absence of any movements or cough. Even more, having the patient under general anesthesia, it allows for a short controlled apnea application when sampling thus aiding in operator control of the instruments in the still peripheral lung. As in any case of general anesthesia, an anesthesiologist and qualified assistant as well as the necessary material for intravenous access, assisted ventilation, cardiorespiratory monitoring, and resuscitation equipment have to be available in the procedure room. While the diameter of the orotracheal tub is not relevant as ultrathin bronchoscope minimally compromises its lumen, its length needs sometimes to be shortened.

In those relatively tall patients with peripheral pulmonary lesions, the 600 mm working length of the ultrathin bronchoscope is not sufficient to

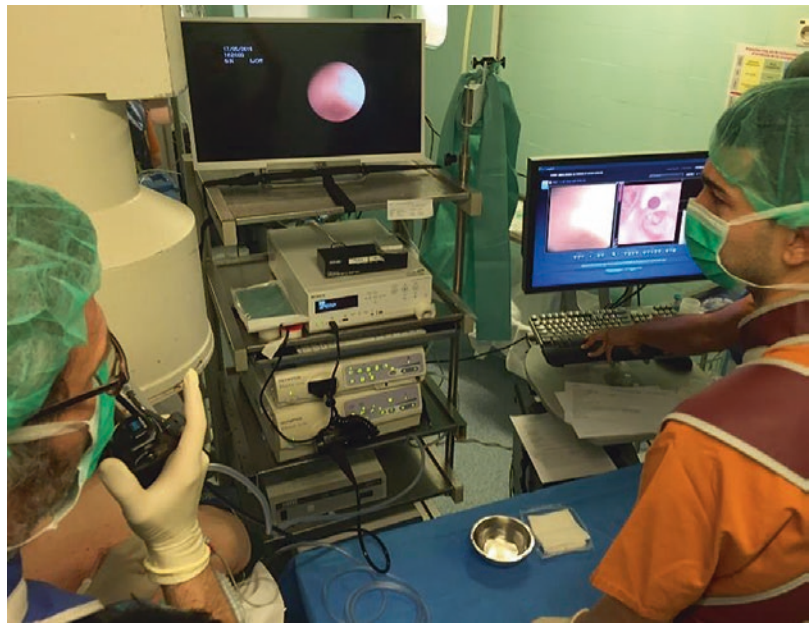

Fig. 3.3 Operating room: two bronchoscopists and one trained nurse performing ultrathin bronchoscopy with virtual bronchoscopic navigation (LungPoint®)

reach the target. In these cases, cutting some centimeters of the orotracheal tube proximal end might be helpful in order to further insert the ultrathin bronchoscope.

Planning a procedure in advance is a must when performing any technique, but this becomes especially relevant when concerning ultrathin bronchoscopy. A deep understanding of the anatomy of the airways is fundamental for the interpretation of the CT as well as for a meticulous three-dimensional reconstruction of the route through bronchial bifurcations to the peripheral pulmonary nodule. Although highly trained bronchoscopists have the ability to memorize the route, complementary technologies have been used since the beginning for assisting the bronchoscopist in this process of orientation throughout the bronchial tree. These assisting tools are mainly image based. Electromagnetic navigation is not feasible with the ultrathin scopes. Therefore, when talking about ultrathin bronchoscopy, it is understood that an image-based technique will complement the procedure either while planning or to verify the position of the ultrathin bronchoscope at any time during the procedure. Different image-based techniques can be used alone or in combination, and these include virtual bronchoscopy, virtual bronchoscopic navigation, fluoroscopy, and computed tomography. Radial EBUS has also been used in the diagnosis of the peripheral pulmonary nodules. A meta-analysis by Wang et al. [11] comparing diagnostic yields of different navigational techniques, including radial EBUS, ultrathin bronchoscopy, and the use of a guide sheath, showed a benefit for using guided bronchoscopy although no method proved being superior. Recently, a randomized, multicenter trial by Oki et al. [7] combined virtual bronchoscopic navigation, radial EBUS, and fluoroscopy with either a thin or a novel prototype of ultrathin bronchoscope. A total of 305 patients were randomized, and results showed a higher diagnostic yield with the ultrathin bronchoscope than with a guide sheath method (74% vs. 59%). It has to be noted that this novel prototype ultrathin bronchoscope had a 1.7 mm working channel that allowed the use of a radial probe EBUS and sampling with a 1.5 mm biopsy forceps.

In conclusion, to take most advantage of ultrathin bronchoscopy, it is important to consider combination with image-based techniques. The following paragraphs provide a detailed description of the procedure and complementary image-based techniques.

Planning the Procedure

One of the most relevant points to consider when planning the procedure on a CT image is the presence of a bronchus or artery afferent or within the nodule, the so-called bronchus sign [12] and artery sign [13]. When present, the sensitivity of ultrathin bronchoscopy is higher. A positive bronchus and artery sign are shown in Fig. 3.4.

Image-based techniques used for aiding in procedure planning include virtual bronchoscopy (VB) and virtual bronchoscopic navigation (VBN).

VB is based on multiplanar reconstruction and segmentation of the airways. Through dedicated software in the CT working station, it allows performing a virtual bronchoscopy through the segmented airways.

More recently, VBN software has been developed that allows the bronchoscopist to perform virtual bronchoscopy in the bronchoscopy suite. This provides the bronchoscopist with an on-site route map that can be followed while performing the procedure. However, VBN requires assis-

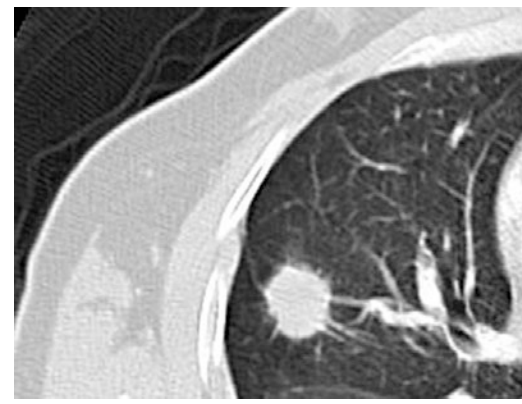

Fig. 3.4 Bronchus sign and artery sign

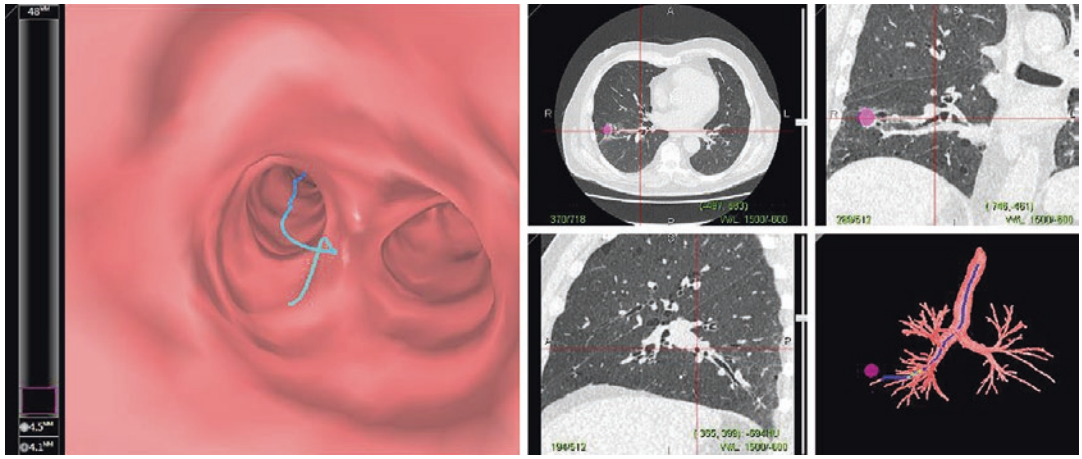

Fig. 3.5 A view of the LungPoint® planning system

tance by a trained bronchoscopist who performs the virtual bronchoscopy, while the operator follows the indications in each encountered bifurcation. A view of the LungPoint® planning system is shown in Fig. 3.5. VBN not only adds information to the path to be followed but also serves as an approximation of the position of the bronchoscope. However, VBN does not permit real-time tracking, and therefore a method for verifying the actual position of the bronchoscope is always necessary at this point.

Reaching the Target with the Ultrathin Bronchoscope

In our institution, the ultrathin bronchoscope is inserted through the endotracheal tube. This allows for a better path selection and maneuverability and better patient comfort as the procedure is usually long, and also it avoids damaging the scope. In Fig. 3.6 you can see black dots on the bronchoscopic image corresponding to broken fibers after the ultrathin fibrobronchoscope was accidentally bitten by a patient.

Due to the small diameter of the working channel, it becomes very difficult to carefully aspirate tracheobronchial secretions. If abundant secretions are present, performance of a bronchoscopy with a wider bronchoscope for secretion aspiration prior to examination with the ultrathin bronchoscope should be considered. In rare occasions, two instruments are used simultaneously (as seen in Fig. 3.7). When working at a subsegmental level besides the range of a bronchoscope, it is recommended that secretions are not aspirated and saline be continuously instilled instead. A 50 mL syringe is connected to the working channel and the assistant instills saline as requested. This allows for a better view of the airways since secretions are bypassed and lumen diameter widens. A view of ultrathin bronchoscopy in peripheral airways under saline infusion is shown in Fig. 3.8. When accessing the right upper lobe, it is recommended to leave the biopsy

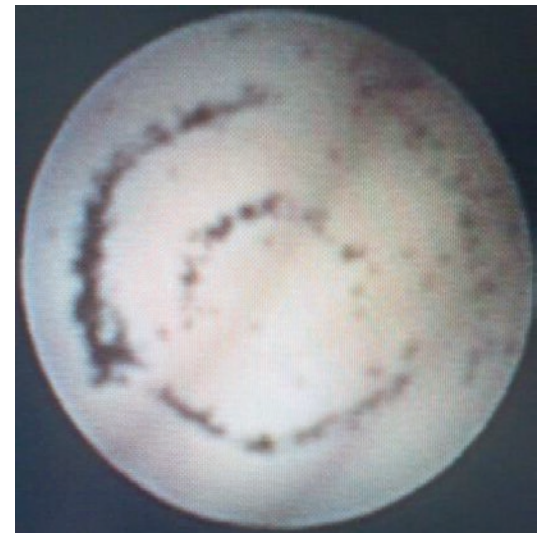

Fig. 3.6 *Black dots* corresponding to broken fibers after the ultrathin fibrobronchoscope was accidentally bitten by a patient

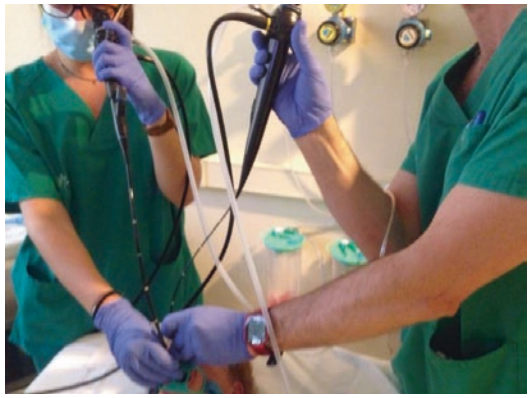

Fig. 3.7 Dual examination with an ultrathin bronchoscope and a standard bronchoscope to better suction secretions

forceps inside the working channel to gain stiffness and avoid bending backward 180°.

Fluoroscopy can be used to approximate visible lesions. It is not a guidance tool, but it can serve as a trial-and-error tracking tool since it gives information about target approximation accuracy.

VBN can also be used for aiding in target achievement. As previously noted, this method does not allow for real-time tracking of the ultrathin bronchoscope, but it can assist in pathway choice and faster nodule achievement. When using VBN systems, a trained bronchoscopist is needed to perform the virtual bronchoscopy through the previously selected path.

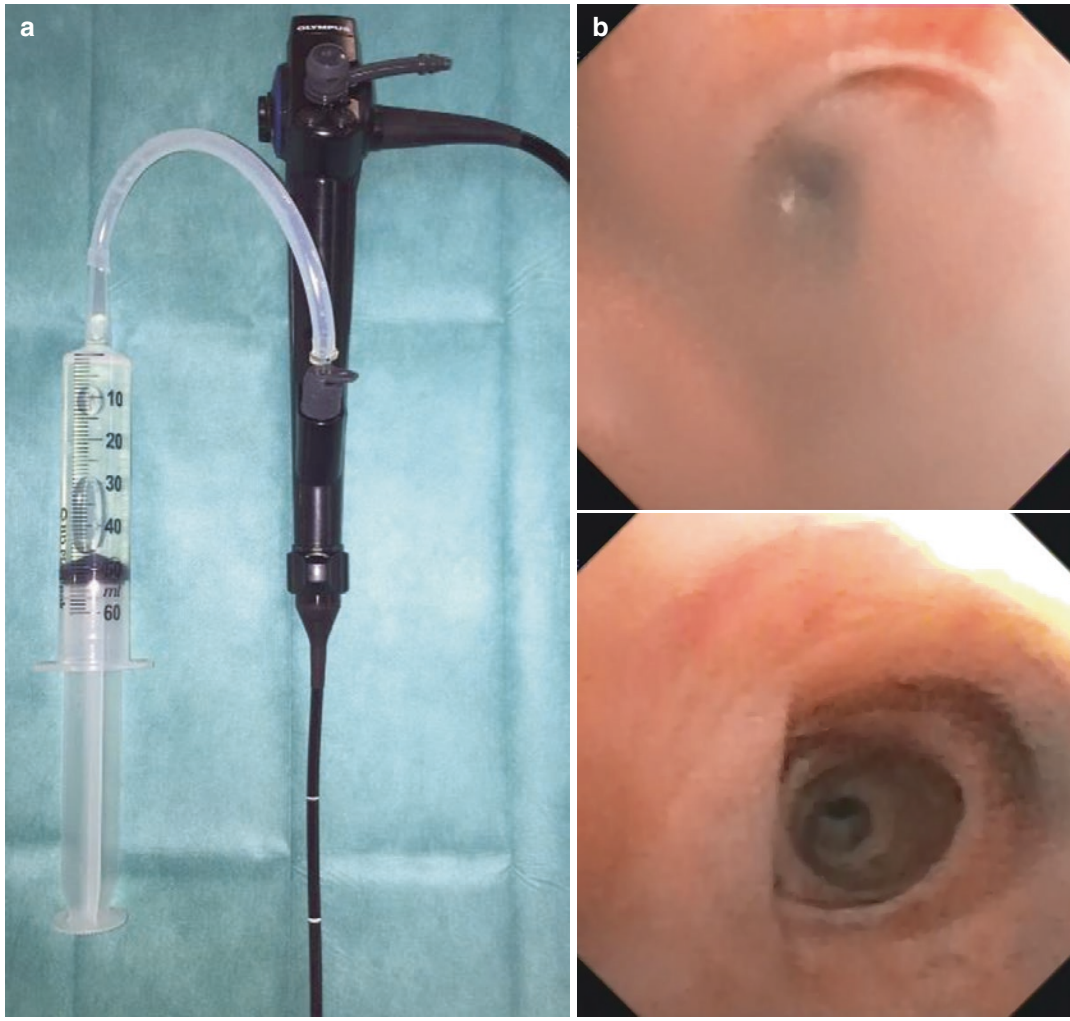

Fig. 3.8 Ultrathin bronchoscopy in peripheral airways: (**a**) 50 mL aliquot with saline connected to the working channel. (**b**) Views before and after saline infusion

This will guide the operator through the airways and assist in choosing the right direction in each encountered bifurcation. Therefore, when using a VBN system, two trained bronchoscopists will be needed: one to perform the virtual bronchoscopy and a second to advance the ultrathin the same path that the first is following. To date, there is only one large randomized trial comparing ultrathin bronchoscopy with and without the use of virtual bronchoscopic navigation. This study by Asano et al. showed no significant differences in diagnostic yield on both groups (67.1% vs. 59.9%, $p = 0.173$) in 350 patients with peripheral nodules ≤3 cm. However, subgroup analysis of these data showed that the navigation system could be helpful for achieving nodules located in the peripheral third of the lung, those invisible in the posteroanterior radiographs and when located in the upper right lobe. Fluoroscopy was used in both groups to ensure location of the ultrathin bronchoscope and sampling of the desired location [14]. At this point, several limitations encountered when performing ultrathin bronchoscopy need to be clarified.

The first concerns lung periphery. It is easy to understand that chances of getting lost in the peripheral third of the lung are greater since more bifurcations need to be overcome. The second concerns the probability of approximating a target that is not seen on plain chest X-ray. In fact, Kaneko et al. reported 73% negative chest radiography in 15 patients with CT-detected small peripheral lung cancers out of 1369 individuals at high risk screened for small peripheral lung cancer detection [15]. In these cases, only CT guidance will allow verifying that the ultrathin bronchoscope is approximating the nodule. The third critical consideration relies on the fact that only endobronchial nodules can be seen with a bronchoscope. A graphic explanation can be seen in Fig. 3.9, which shows Tsuboi's classification of the relationship between the nodule and the bronchus [16]. Therefore, achieving the target with a bronchoscope is sometimes simply impossible.

Finally, it has to be noted that width is not the only mechanical restriction to bronchoscopes but also angulation. This point becomes especially challenging in the upper lobes where the anatomical disposition of the airways may contain angulations that are challenging or even impossible to perform with the ultrathin bronchoscope. As commented before, by leaving the biopsy forceps inside the working channel, the instrument gains stiffness and avoids bending backward 180°.

Therefore, although virtual bronchoscopic navigation may be a useful image-based technique for aiding in ultrathin bronchoscopy performance in selected cases, sometimes this is simply not enough.

Verifying the Position of the Ultrathin Bronchoscope

When the peripheral pulmonary nodule has been approximated and if no endobronchial abnormality is visualized, fluoroscopy or CT can be used to verify the position of the ultrathin bronchoscope relative to the lesion. Fluoroscopy was the first imaging technique used for guiding the ultrathin bronchoscope to the nodule [2]. Biplanar fluoroscopy is desirable but, when not accessible, the C-arm must be rotated adequately. If the lesion is not fluoroscopically visible, the use of a VBN system is recommended. CT has also been used for verifying the position of the ultrathin bronchoscope [17, 18]. It allows for nodule detection independent of size, localization, and characteristics. However, in most centers it is not possible to perform bronchoscopy in the CT room, and it is also important to point out that irradiation is higher than with fluoroscopy.

Sampling with the Ultrathin Bronchoscope

Through the working channel, two instruments of 1 mm diameter can be used: mini cytology brush (Olympus BC-201C-1006) and reusable mini biopsy forceps (Olympus FB-56D-1). Caution must be taken to manipulate the forceps as they can break and their cost is relatively high (around 1000€).

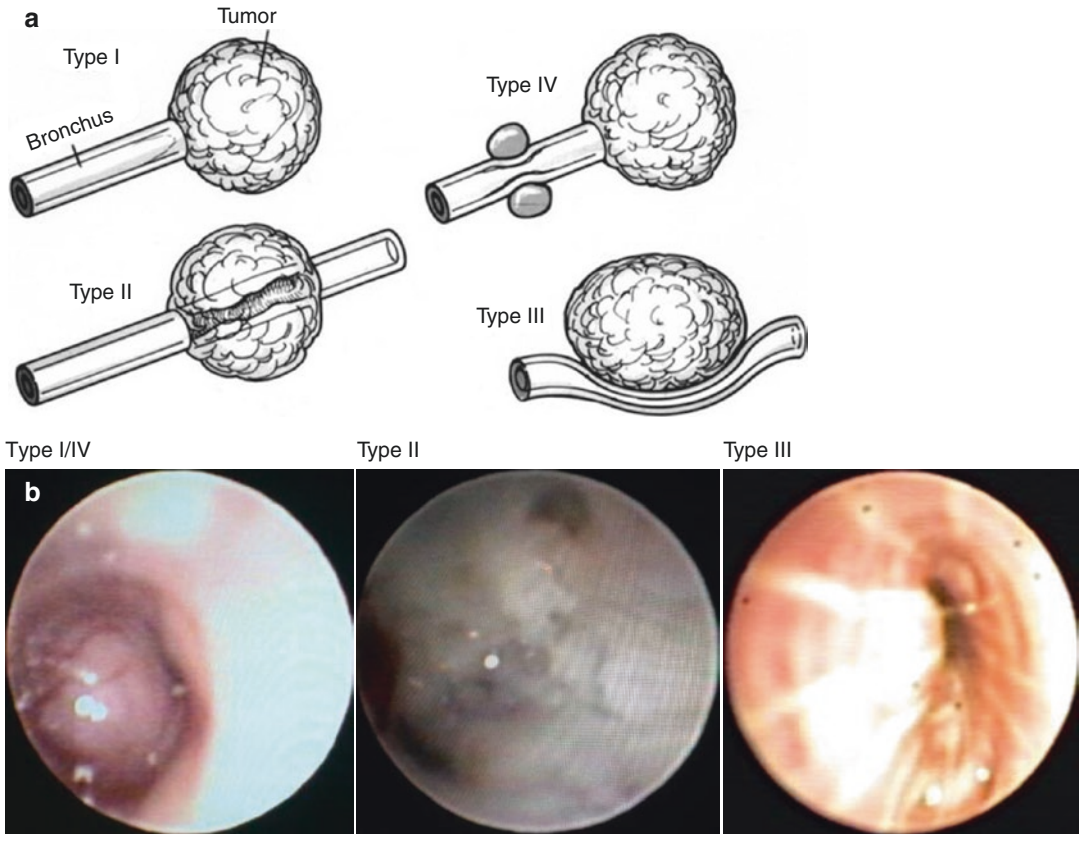

Fig. 3.9 (**a**) Tsuboi's classification of the relationship between the bronchus and the nodule. Type I: bronchus leads to the nodule. Type II: the bronchus is completely surrounded by the nodule. Type III: extrinsic compression without bronchial mucosal invasion. Type IV: the bronchus is proximally obstructed either by the peribronchiolar disease or by lymphadenopathy and then continues on to communicate with the tumor distally. Picture from reference [20]. (**b**) Examples of each type

Recent studies in animals have used mini cryoprobes that may allow for sampling of extrabronchial lesions and may therefore improve the quality and quantity of tissue obtained [19].

In the future, the development of thin needles for transbronchial needle aspiration (TBNA) would be desirable.

Once the peripheral nodule has been approximated, several points have to be considered:

1. Position of the lesion relative to the bronchus
   When an endobronchial lesion is reached (types I and II from Tsuboi's classification), sampling with forceps or brush under direct visualization is possible and rather simple. However, when there's only external compression or no alteration is directly visualized, even though the ultrathin bronchoscope has apparently reached the lesion after radiologic verification, the probability of obtaining a diagnosis diminishes significantly.

2. Sampling instruments are small
   This represents a major limitation in the era of molecular diagnosis. Therefore, it is important to take multiple samples with brushes and forceps. In our institution, four different biopsy and brushing samples are performed.

Complications

Although not frequent, several complications may occur during ultrathin bronchoscopy and these include:

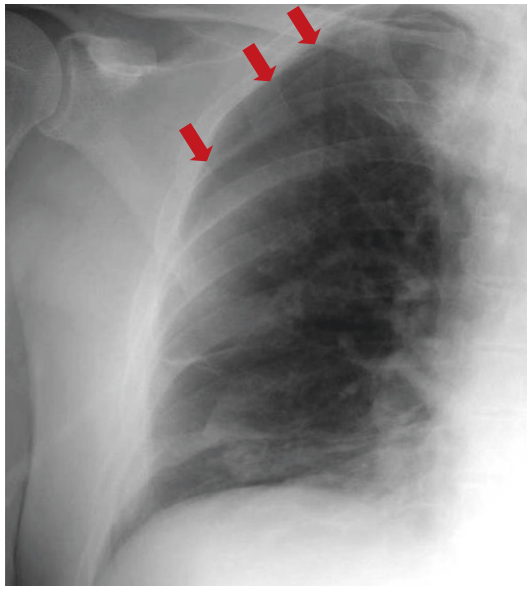

Fig. 3.10 Apical laminar pneumothorax after sampling a peripheral pulmonary nodule in the right lower lobe with an ultrathin bronchoscope

- Transient fever and pneumonia, especially if a relatively high amount of saline is retained and in those with purulent secretions. In our institution, prophylactic antibiotic with 2 g of amoxicillin/clavulanate is administered during the procedure.
- Pneumothorax can occur during or after sampling. Performance of a chest X-ray is recommended when biopsies are performed without endoscopic control. An example of a pneumothorax is seen in Fig. 3.10.

Summary and Recommendations

The ultrathin bronchoscope is a versatile instrument that is mainly used for studying peripheral pulmonary nodules but also for examination of cavitated nodules, critical stenosis, postoperative scars, barium marking prior to surgery, and giant bulla treatment.

When used for diagnosing a peripheral pulmonary lesion, it should be combined with image-guiding techniques in order to overcome the complex anatomy of the peripheral airways. Alone or in combination, these include (1) CT and/or virtual bronchoscopy for procedure planning; (2) fluoroscopy, CT, or virtual bronchoscopic navigation for orienting the bronchoscopist through the airways; and (3) fluoroscopy or CT for verifying the position of the ultrathin bronchoscope relative to the nodule, guiding the instruments during sampling and confirming that no pneumothorax has been produced right after sampling.

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Rigid Bronchoscopy

4

Jose Pablo Diaz-Jimenez and Alicia N. Rodriguez

Introduction and History

Bronchoscopy is the invasive procedure most commonly indicated to diagnose and treat pulmonary problems. There are two kinds of bronchoscopes: the flexible bronchoscope (FB) and the rigid bronchoscope (RB). The first one is the most utilized in clinical practice. However, the rigid bronchoscope is a very important instrument for the diagnosis and treatment of many pulmonary disorders and has been applied to the airway for many decades.

The interest on reviewing the airway goes back to 1823, when Horace Green introduced first a sponge and then a rubber catheter into the bronchi, applying silver nitrate to burn lesions located at the level of the larynx and trachea. Later, Joseph O'Dwyer introduced a tube to release adhesions of the lower airways caused by diphtheria, and he also constructed a thin-walled tube to assist in the removal of foreign bodies.

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The rigid bronchoscope was introduced by Gustav Killian (Germany) in 1897, for the extraction of a foreign object (a small piece of a pig bone) from a 63-year old man, becoming the father of bronchoscopy. For the procedure, Killian used an esophagoscope and rigid forceps [1]. Chevalier Jackson, from Philadelphia, Pennsylvania (USA), made popular this new bronchoscopic technique and developed the most commonly used rigid bronchoscope. His idea of placing a small light in the distal part of the endoscope revolutionized the endoscopist's ability to examine the airways. In 1916 he established bronchoesophagology departments in five hospitals in Philadelphia, training many well-known bronchoesophagology professionals [2, 3].

During more than 70 years, the rigid bronchoscope or open tube was the only available instrument to review the airway. At first, it was mainly used to remove foreign bodies or dilate strictures, but later new applications were described: aspiration of secretions, hemoptysis treatment, biopsies, etc.

Shigeto Ikeda's flexible bronchoscope (FB) development in the 1960s [4] has been the most significant advance in the area of bronchoscopy and has changed the practice to our days, allowing the pulmonology physicians to develop ability in performing flexible bronchoscopy and also gave place to the introduction of new technologies specifically designed to apply with FB.

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Shortly after its invention, the FB almost replaced the RB in the clinical practice. However, the rigid bronchoscope is still a very important instrument in the study and treatment of airway disorders.

RB and flexible bronchoscope complement each other in many indications, and there is no reason to see their application in opposite terms, since each instrument has strengths and limitations. In this chapter, we will review our experience on RB, along with a complete discussion on indications and contraindications.

Overview of RB

The RB is a stainless steel open tube with variable lengths and widths. It has a distal end, beveled and smooth, and a proximal end that can be adapted to a metallic universal head with several side ports. The distal end is used to lift the epiglottis during intubation and is also very useful to dilate strictures and to "core" tumors. Lateral openings or fenestrations are present to allow contralateral lung ventilation while working.

The RB is the preferred instrument for endoscopic resections. The rigid tube is the only device that allows a complete control on the airway, assuring proper oxygenation and ventilation while performing, for instance, a laser resection. Aspiration of blood, secretions, and smokes can be easily achieved at the same time that an excellent view of the central airway is depicted.

One of its main strengths is the ability to confront serious hemorrhagic accidents or airway obstruction from various etiologies: benign or malignant conditions, foreign bodies, mucus plugs, etc. Although unusual, massive hemorrhages can occur even in routine fibrobronchoscopies. The RB allows the application of pressure on the hemorrhagic area until hemostasis occurs, giving sufficient time to apply other therapeutic modalities, which can bring a definitive solution to the problem. It is also particularly useful in the pediatric population. Children airway diameter is very small, and it is preferable to use a hollow tube in order to allow spontaneous breathing or assisted ventilation. The FB blocks the airway, and the patient has to breathe around it, increasing significantly the airway resistance and work of breathing, difficulting procedures. The RB, in turn, allows the patient to breathe through it, favoring spontaneous breathing and mechanical ventilation while performing the procedure.

The rigid bronchoscope has undergone modifications over time, particularly after laser resection and stent placement became regular indications for different airway conditions. The most used brand names today are Efer(R), Storz(R), and Wolf (R).

Innovations

The first rigid bronchoscope for laser application was designed by Jean François Dumon (Fig. 4.1), from Marseille, France, for the brand Wolf. In contrast to other rigid bronchoscopes, the Wolf system has two lateral ports (one for the laser fiber and the other one for the suction catheter) and a rotating ventilation connector that allows assisted ventilation without interrupting the treatment. All ports can be occluded to allow closed

Fig. 4.1 Dr. JF Dumon

circuit ventilation. Based on this experience, the Dumon-Harrell (Efer) universal rigid bronchoscope was later developed; it associated modifications already present in the Wolf system with other advantages, such as the possibility of using a series of 11 interchangeable tubes with increasing diameters available in two different lengths: the short tubes (Fig. 4.2) for endotracheal treatments, with no side orifices (diminishing the air lost in the trachea), and the long tubes for endobronchial treatments, with lateral orifices that allow an adequate ventilation even when the bronchoscope is placed in a peripheral bronchus. Internal and external diameters are color coded on each tube (from 3.5 to 10 mm internal diameter and from 4 to 12 mm external diameter). Available tubes for pediatric use have an internal diameter from 3 to 5 mm and 20 cm in length.

The head of the rigid bronchoscope can be adapted to the desired tube, according to the different needs (Figs. 4.3 and 4.4).

The Dumon-Harrell rigid bronchoscope comes with a separate deployment system for the silicon (Dumon) prosthesis.

Another Dumon-Harrell system innovation is the fact that it is possible to lift the superior part of the lateral door, allowing the aspiration of large tumor fragments without modifying the position of the suction catheter. The securing caps are made of Silastic, with one or several

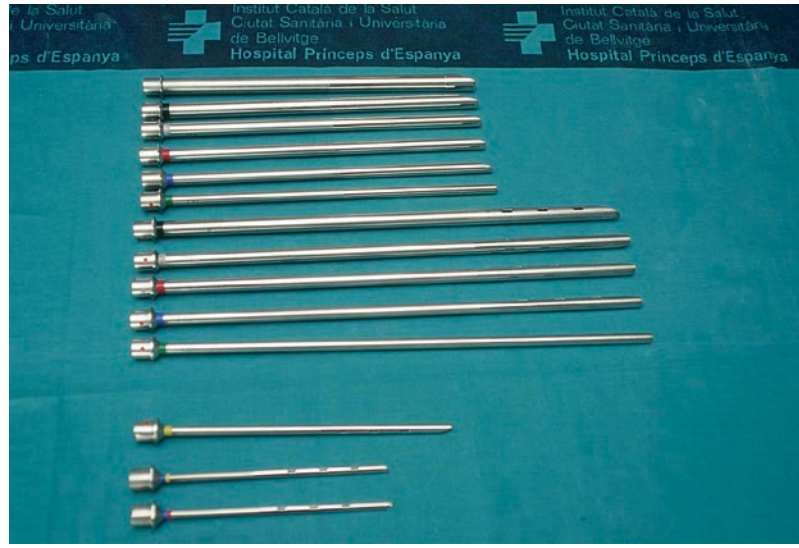

Fig. 4.2 Dumon's rigid bronchoscope

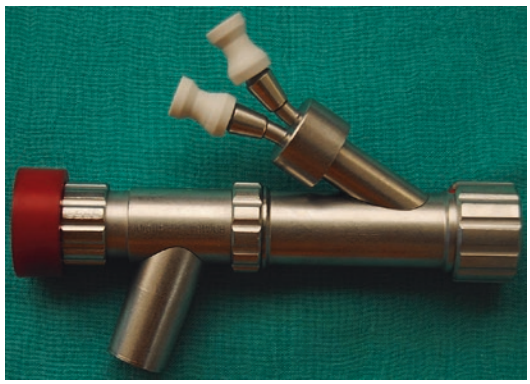

Fig. 4.3 Universal head of the rigid bronchoscope

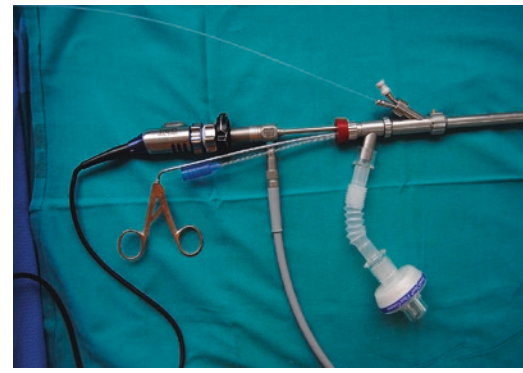

Fig. 4.4 Rigid bronchoscope with ancillary tools and connection for ventilation

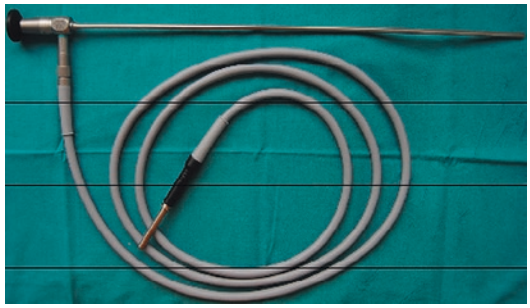

Fig. 4.5 Rigid telescope (optic)

orifices of different sizes. These caps are much more solid than the usual rubber ones, allowing a more hermetic closure, optimizing ventilation.

The rigid optics offer direct 0° vision (Fig. 4.5); they come in three diameters, 3.5, 5.5, and 7 mm; and they are not fixed. There is also a smaller optics for pediatric use. These instruments easily slide through the Silastic caps and can be moved back and forth according to need. It is a very useful feature to avoid sudden movements that can injure the airway. The rigid optic can be pulled back to avoid midst or loss of visualization due to blood or detritus. The rigid optic, suction catheter, and laser fiber are independent inside the rigid tube, making handling easier.

The most comfortable position when applying laser is placing the tip of the laser fiber advanced within the airway, the suction catheter located slightly back to the laser tip, and the rigid optic further back from the working field (Fig. 4.6). The independence of these elements allows modifying at any time their position according to the intervention needs.

The RB has been designed to present a universal character; in other words, to adapt to multiple endoscopic situations. In addition to laser application settings described above, this instrument can take other configurations: all or some of the entrance ports can be used (from one to three), open or closed ventilation circuit (for "jet ventilation," manually assisted ventilation, or spontaneous ventilation), and use of short or long tubes and adult or pediatric tubes, allowing diagnostic and/or therapeutic procedures on practically any group of patients.

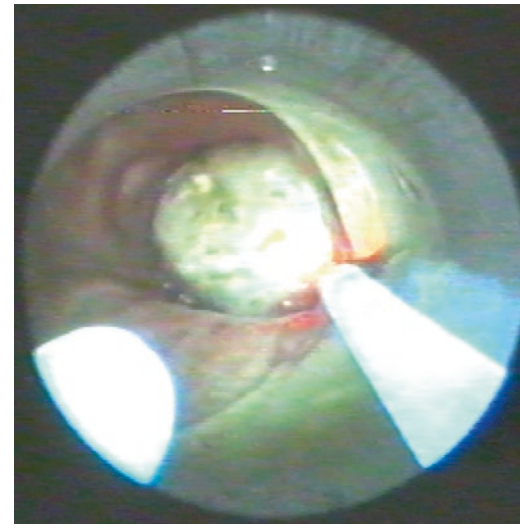

Fig. 4.6 Correct position of the suction catheter and laser fiber into the RB. It is important to always see the tip of the bronchoscope during the procedure

The Storz rigid bronchoscope was designed by Shapshay from Boston, USA. It is specially manufactured for jet ventilation, and for this reason it has a fixed port designed to serve this purpose. It is available in 10 mm internal diameter size (12 mm external diameter), presenting also a connection for ventilation and two additional ports [5].

A recently introduced rigid bronchoscope, called rigid integrated bronchoscope developed by Wolf, presents separate channels for optics and instruments and integrates the operator head with the camera. It has also an irrigation port to wash the distal lens. It has the advantage of increasing the working space and thus improves manipulation within the bronchoscope. However, the vision is limited since the camera does not go further distal to the end of the rigid bronchoscope.

It is clear that the RB, although keeping its original basic shape, has suffered several modifications to adapt to specialized procedures, like laser application, prosthesis placements, and dilatation of tracheobronchial strictures. The RB allows flexible bronchoscopes to get through it, taking advantage of both instruments at the same time.

Ancillary Equipment

Suction catheters: they play a very important role during procedures. In addition to suction of blood, smokes, and debris, they are useful in palpating lesions to give an idea on consistency. They are also used to instill medications such as saline, epinephrine, and lidocaine. It is recommended that they do not exceed 3 mm in diameter and are made of rigid transparent material. In that way the laser beam will not burn them, and they will not collapse during suction.

Other ancillary instruments that should be available are foreign body rigid forceps (used to retrieve different elements from the airway and to adjust position of silicone stents), scissors, scalpel, balloons, mechanical dilators, endoscopic resectors, prostheses, and laser equipment, most of them designed by Dumon (Fig. 4.7).

The capability of project images is very important as well. That serves various purposes: it allows all the team to follow the procedure in detail and anticipate steps. It also permits recording the procedure, for both educational and documentation purposes.

Applications and Contraindications

RB's most important applications are therapeutic and include laser application, electrocautery, argon plasma coagulation or cryotherapy, dilatation of tracheobronchial stenosis using balloon dilatation or directly with the rigid tube, airway stent placement, and foreign body removal, particularly in children. Massive hemoptysis is also another therapeutic indication. Diagnostic applications are hemoptysis and the need for deep

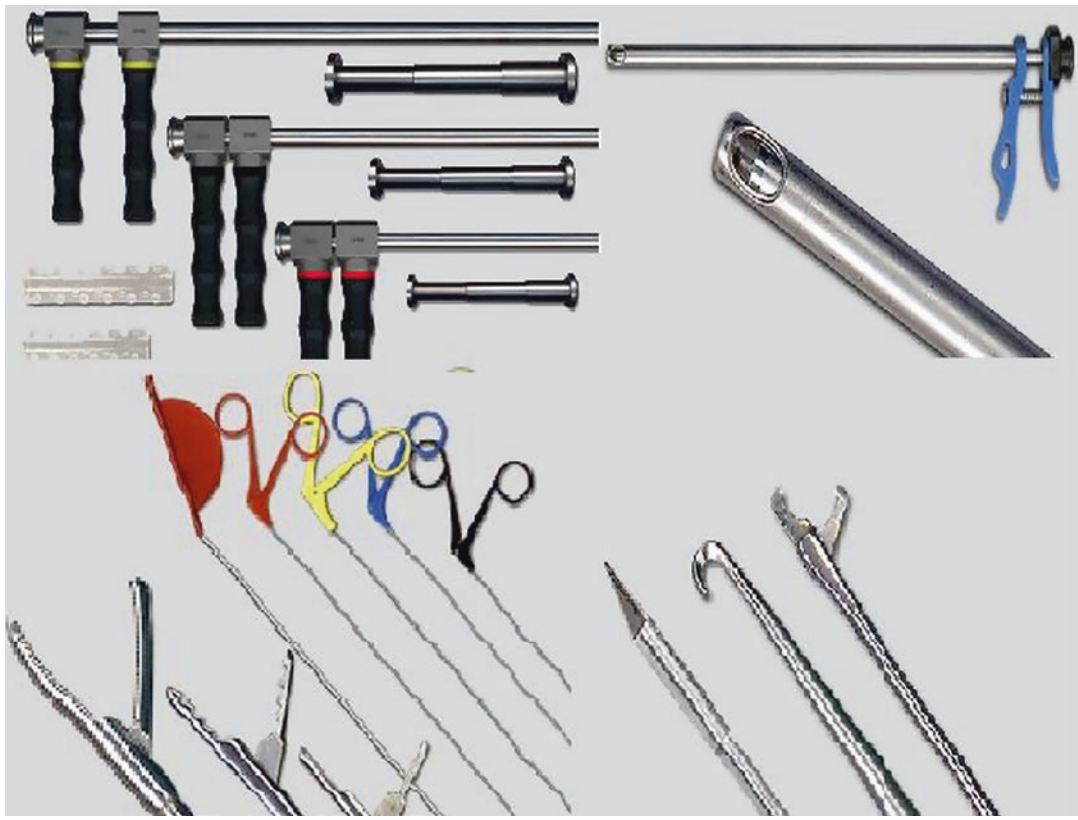

Fig. 4.7 Ancillary equipment designed by Dr. Dumon

Table 4.1 Indications for rigid bronchoscopy

– Foreign body removal
– Hemoptysis
– Tracheobronchial stenosis
– Tracheobronchiomalacia
– Central airway obstruction
– Extrinsic compression
– Therapeutic procedures:
Stents
Laser
Electrocautery
Cryotherapy
Argon plasma coagulation
Dilatational balloons

Modified from Lamb and Beamis [6]

biopsies, better obtained with the rigid biopsy forceps (Table 4.1) [6].

There are not many absolute contraindications for the use of the rigid bronchoscope: unstable cardiovascular state, significant cardiac arrhythmias, severe hypoxemia that will not improve with the procedure, and cervical spine instability. The most important contraindication is lack of appropriately trained personnel [7].

Some clinical situations, however, must be considered as relative contraindications for RB: an unstable neck that makes unsafe the excessive mobilization during the bronchoscopy, microstomy, maxillofacial trauma, or other oral lesions that prevent an appropriate mouth opening to introduce the rigid tube and technical difficulties related with cervical ankylosis and severe kyphoscoliosis, among the most important ones.

Rigid Bronchoscopy Applications

Laser Bronchoscopy

Laser bronchoscopy application has diminished in the last years. Reasons include high cost of the equipment, lack of adequate training, need for RB in most of the cases, long procedure time, the absence of improvement in mortality when applied to malignant conditions (even though quality of life and survival definitely get better), and the insufficient number of patients in some centers. In addition to this, other therapeutic modalities such as electrocautery and argon plasma coagulation have become more popular given their availability, low cost, and similar good results.

However, the application of laser therapy through the RB has not been replaced in some indications, and it is still the technique offering the best results. RB laser resection is an important tool in treating central airway obstructions (benign or malignant) and provides an immediate reopening of the trachea or bronchus when stenotic lesions are found. Most of the treatments are performed with Nd-YAG laser (neodymium-doped yttrium alulminum garnet) or Nd-YAP laser (neodymium-doped yttrium aluminum phosphate). Diode laser is also equally useful and has become more popular given its lower cost.

In a published series about laser applications in malignant lesions, 1585 patients were treated with 2253 therapy sessions of Nd-YAG laser during a period of 11 years. More than 93% showed immediate good results. Complications included 18 hemorrhages, 6 pneumothoraxes, and 10 deaths [8].

Similar results have been published on low-grade malignant tumors that are unresectable or present in nonsurgical candidates for advanced age or severe cardiorespiratory insufficiency. In a prospective study of 19 patients that presented with carcinoid tumor and cylindroma with inoperability criteria, the use of laser was associated with an immediate symptomatic improvement following the treatment in 100% of the cases. Fifteen patients were free from disease during a follow-up time of average 20 months (from 6 to 50 months), and two patients died of unrelated causes at 21 and 6 months of treatment. Although low-grade malignant tumor recurrence is hard to predict, the use of laser is an excellent way to keep inoperable patients free from symptoms [9].

In a retrospective review on laser bronchoscopy application, laser resection was offered to 17 patients with inoperable lung carcinoma requiring mechanical ventilation secondary to acute respiratory failure. All of them received Nd-YAG laser treatment through a RB, with respiratory assistance (jet ventilation) at the

operating room. A subgroup of seven patients could be weaned from mechanical ventilation and were able to receive other therapies showing an improved survival. The rest of the patients had tumoral extrinsic compression of the airway or submucosal growing of the tumor and had almost no benefit from laser application. They died on mechanical ventilation or after been extubated when the order "comfort measures only" was established. Survival improvement seen in the first group of patients ($p = 0.0038$) was associated with the presence of obstructive endobronchial tumor as the cause of respiratory insufficiency [10]. These results show that even those patients with acute respiratory failure due to obstructive lesions can be treated with laser bronchoscopy with good results.

Tracheobronchial Prosthesis

On the last years, tracheobronchial stenosis has received much interest from bronchoscopists due to the several available techniques to treat this problem. Endoscopic treatment of tracheobronchial stenosis can be achieved through balloon dilatation, stent placements, laser resection, and even with dilatation with the rigid bronchoscope.

Balloon dilatation can be done through a RB or through a fibrobronchoscope with a wide working channel. The balloons are designed for esophagus dilatation but are also used in the airway; angioplasty balloons can be used as well.

RB dilatation is performed by applying a smooth rotation to the rigid tube, simultaneously advancing, and passing through the stenotic area several times until a safe airway diameter is achieved. Laser resection can be applied before this dilatation if needed. All fibrous stenoses treated by mechanical dilatation have the tendency to recur, and repeated procedures are needed to keep the airway open. In addition, sometimes forceful maneuvers cause mucosal damage with more scar formation, and in the long term, they can worsen the stenosis. Thus, mechanical dilatation is only recommended to solve an acute situation and as a bridge to a more definitive treatment. Benign airway stenosis is discussed in detail in a dedicated chapter of this book.

Tracheobronchial prostheses can be indicated in benign or malignant airway stenosis [11].

Several types of prosthesis are available to use with both the RB and the flexible bronchoscope. Many of the autoexpandable metallic prostheses have been designed specially to allow placement with the flexible bronchoscope under fluoroscopic control. Airway prosthesis is discussed in detail someplace else in this book. However, we have to say that the RB is the only instrument suited for silicon prosthesis placement. We recommend the use of silicon prosthesis to treat most of the airway lesions, particularly benign conditions since metallic stents are associated with significant complications that have been recognized for many experts and made clear by the FDA during 2005, when it recommended against metallic stent application to airway benign conditions. (Available at www.fda.gov/cdrh/safety/072905-tracheal.html.)

Results on the application of the RB are presented in a study where this instrument was used under general anesthesia to insert silicone prostheses (Dumon) in 31 adult patients with more than 50% malignant airway obstruction. After laser resection, a stent was placed, and all patients presented immediate improvement in respiratory symptoms. All patients but three tolerated well the prostheses. Stents were placed in the trachea in 14 cases, right main bronchus 13, left main bronchus 8, and intermedius bronchus 3. Complications included migration in five patients, mucous obstruction in two patients, and hemoptysis in one patient [12].

We consider training in RB use crucial to any interventional pulmonologist. Regardless of the type of stent selected for a given treatment, expertise working with the RB will be needed at some point during the course of therapy. For instance, when a complication arises (i.e., migration, stent disruption) and the prosthesis needs to be removed or replaced, the best instrument to retrieve it is the RB. In addition, most of the prostheses placed via FB are very difficult to remove with fibrobronchoscope, requiring the

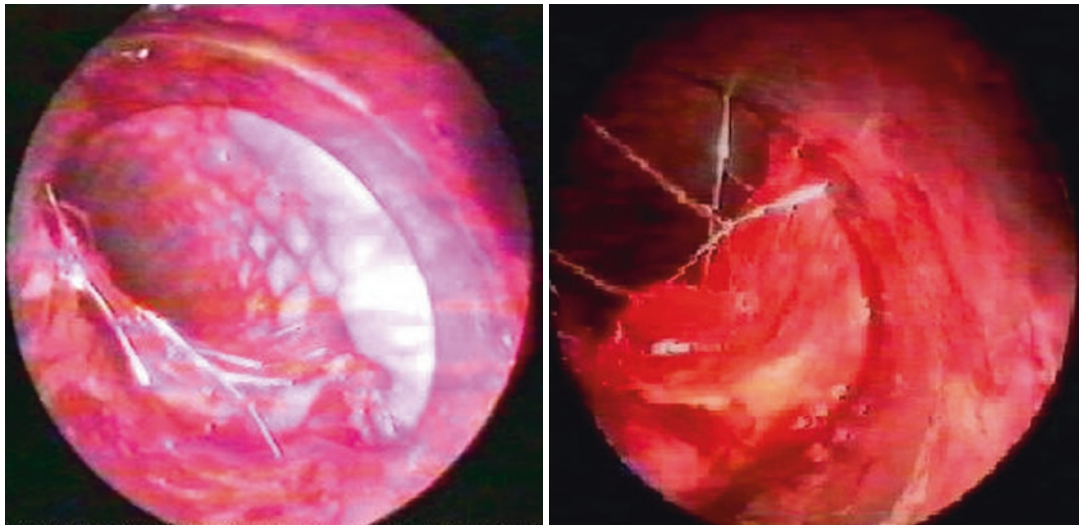

Fig. 4.8 Metallic prosthesis removal with the rigid bronchoscope

application of the RB to extract or adjust them. When metallic uncovered stents stay for a given period of time within the airway, they became embedded to the mucosa. In order to remove them, the beveled end of the RB should be placed between the metallic stent wall and the tracheal mucosa, and with soft rotating movements, the RB is advanced distally "dissecting" the stent from the airway wall until it is totally detached. Then it can be removed with a forceps (Fig. 4.8).

Likewise, the growth of tumor tissue through uncovered metallic stents requires RB and laser to relieve the obstruction, remove the prosthesis, and replace it in case of need. Training in RB is one of the most important skills that an interventionist has to learn and be proficient at and is a requisite when placing silicon (Dumon) prosthesis [12, 13]. Such training also involves the staff assisting and collaborating during the procedure: assisting nurse or scrub nurse, anesthesiologist, circulating assistant, etc.

Transbronchial Needle Aspiration

Transbronchial needle aspiration (TBNA) of subcarinal and paratracheal nodules was described in 1950. Wang, in 1978, reported a diagnostic sensibility of 90% for this technique when applied with the RB [14]. After the introduction of the FB during the 1960s, most of the bronchoscopists have been using this instrument to perform TBNA in lymph nodes located subcarinal and parahilar. Diagnostic sensibility for TBNA when performed with the FB has been reported as 80–89%, especially when the 19-gauge needle is used [15, 16].

The appearance of EBUS (endobronchial ultrasound) has completely changed the approach to lymph node sampling, and this technique has virtually replaced all blind procedures given the high diagnostic yield, particularly in mediastinal sampling [17]. However, in spite of EBUS generalized use, it can still be a place for blind TBNA applied both with the RB and the FB, particularly where EBUS is not available given its high cost.

A study published in 1996 described results on needle aspiration through the RB. Twenty-four procedures were performed in 24 patients using RB and a 2-cm long rigid needle, under general anesthesia and guided with computerized tomography. Samples taken were the tracheal wall (n = 11), main carina (n = 3), right secondary carina (n = 3), left principal bronchus (n = 2), and right principal bronchus (n = 3). The average amount of samples was 6 (from 1 to 19). An in situ cytopathologist

immediately reviewed the samples to determine the number of samples needed. Diagnostic sensibility and specificity were 88% and 100%, respectively. TBNA resulted diagnostic in 18 patients. Findings helped in therapeutic decisions in 21 patients. There were no false positives during a follow-up period of 6 months. Three false negatives were present, and follow-up showed that these three patients ultimately had malignant lesions. There were no complications [18]. Those findings suggest that even though the technique has been improved by using EBUS or blind TBNA with the FB, the RB can have a role in the diagnostic of intrathoracic lymphadenopathies if no other method is available.

Rigid Bronchoscope in Other Treatments for Bronchial Obstruction

Laser treatments in tracheobronchial obstructions are effective but expensive. As a result, other therapeutic options have been developed and applied with good results. Electrocautery is broadly available, and results in airway resections are comparable to laser. Also, cryotherapy and argon plasma coagulation can be applied with RB.

Results on electrocautery application with the RB are depicted in a study that performed this procedure under general anesthesia in 29 patients with tracheobronchial obstruction, 24 of which had malignant conditions. In nine patients, stents were placed immediately after electrocoagulation. All patients but one presented immediate improvement of the symptoms, and an objective improvement in the pulmonary function was also observed in eight patients who had been tested with spirometry before surgery. There were neither intraoperative deaths nor complications [19]. Electrocautery can be also applied through the FB, but similar to laser applications, procedures are more time-consuming since the RB allows better vision, optimal suction, and the possibility to remove large tumoral pieces. Cryotherapy has been presented as an alternative therapy for obstructions. However, it is called a "slow" opening method since it lacks immediate effects. Initially, all treatments with cryotherapy were performed with RB, but more recently, the cryotherapy probes have been designed for application with the FB, and new modalities of cryotherapy are available, such as cryoextraction or cryoresection and also cryospray, that make this technique more versatile and can be applied as a fast method to open the airway.

Balloon dilatation can be applied both with the RB or FB.

Mechanical Debridement

Even though laser, electrocautery, cryotherapy, and argon plasma coagulation are useful coagulating during debridement of airway lesions, most of the obstructive tumors are generally extracted in a mechanical mode. In fact, all opening procedures involve the use of forceps. When performed with a FB, this procedure is invariably long and tedious, especially if large tumors are involved. The removal of big tumor pieces through the narrow channel of FB is very complicated, since the biggest pieces that can be extracted fits in a small biopsy forceps. It is obvious that a bigger channel such as the one of the RB will accomplish the same task in a much short period of time.

Most of the experienced bronchoscopists use laser only to coagulate the tumor, and when that is accomplished, dissect large tumoral pieces with the beveled rigid tube, (Figs. 4.9 and 4.10) obtaining a much efficient procedure [20]. Grillo et al. [21] affirm that the use of auxiliary methods like laser is not necessary to reopen the airway and only adds costs and risks to the procedure. However, their study on 56 patients whose tumors were removed only by mechanical means showed a 7% mortality associated to the treatment; considerately higher than when other methods are applied, including laser.

The RB itself acts as an airway dilatator and can achieve reopening of an obstruction in a shorter time than required by the FB. There is an important

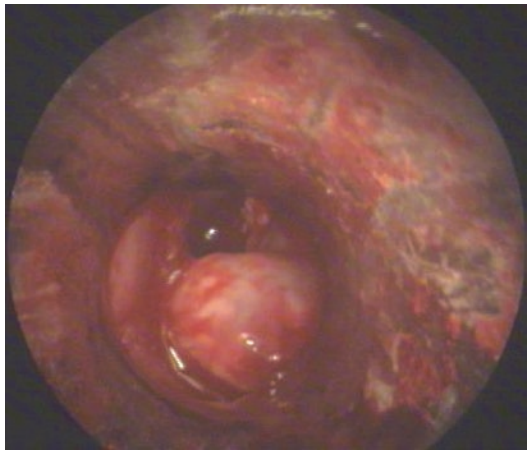

Fig. 4.9 Resection of a tumor with the beveled end of the rigid bronchoscope

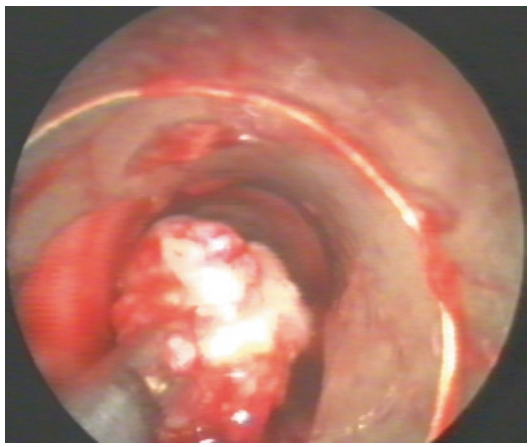

Fig. 4.10 Aspiration of a tumor piece with the rigid aspiration catheter

and statistically significant difference in the total number of sessions needed to permeabilize the airway with RB and FB; the RB requires only one session and the FB an average of two [22]. In fact, bronchoscopists who use only FB to extract tumors usually require several sessions. The theoretical advantage of the FB in opening peripheral airway obstructions is rarely needed, since these cases are infrequent and the need of reopening a distal airway as a palliative measure is questionable, unless postobstructive infection is present. In case of need, the FB can be more easily introduced through the RB (Fig. 4.11) and thus take advantage of the strengths of both instruments [23].

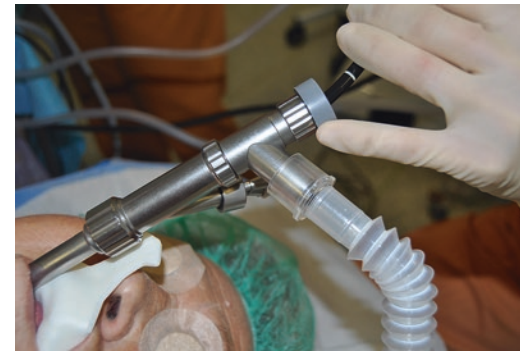

Fig. 4.11 Use of the flexible bronchoscope through the RB

Pediatric Rigid Bronchoscopy

In 1997 the Pediatric Bronchoscopy Group of the European Respiratory Society (ERS) presented the current pediatric bronchoscopy state in Europe. From the 125 contacted centers, it was informed that during the 12 months previous to the survey, 7446 bronchoscopies had been done on pediatric patients. About 4587 (61.6%) of these bronchoscopies were completed with FB and 2859 with RB. While 29 centers were utilizing both techniques, 17 centers were using only FB, and 5 centers just RB. Twenty-three centers were applying RB in the operating room, 7 centers in the intensive care unit, and 15 centers in a specially equipped room.

The most frequent indications included the following: persistent/recurrent pneumonia, wheezing refractory to medical treatment, persistent atelectasis, stridor, chronic cough, interstitial pneumonia, pulmonary tuberculosis, suspected foreign body, hemoptysis, and suspicion of pulmonary malformation, among others. The RB was completed under general anesthesia in 31 centers and under local anesthesia and intravenous sedation in 2. A bronchoalveolar lavage (BAL) was performed in 2231 children; 812 of them were immunodepressed. The utility of the diagnostic varied with the type of procedure. For centers using only FB, only RB, and the combination of both (FB + RB), diagnostic application was almost invariably superior when the use of FB and RB were combined, except for persistent/recurrent pneumonia [24].

Advantages of the RB in the pediatric population are mainly due to the fact that, in a small diameter airway, it is safer to use an instrument that does not produce increased resistance in the airway. The rigid scope provides complete airway control and, at the same time, the possibility of applying diagnostic or therapeutic interventions.

Tracheobronchial Dilatation

The RB has been used to perform tracheobronchial stenosis dilatation in children. The dilatation technique with an angioplasty catheter can be performed as follows: the catheter (6F, 8 mm diameter) is placed under direct vision with the RB, and balloon inflation is controlled with a manometer. Children so treated showed a significant improvement in the size of the intraoperatory lumen and an important postoperative clinical improvement, confirmed with endoscopies and radiographies. Recurrence of stenosis many times requires a repeated procedure until a more definitive therapy can be offered, or the natural increment of the airway diameter as the child grows up relieves the stenosis without the need of further procedures [25].

Other therapeutic options include the progressive dilatation using the rigid bronchoscope.

Foreign Body Removal

The RB is the instrument of choice to extract foreign objects in pediatric patients. It is a safe, effective, and lifesaving technique. The number of ancillary instruments such as forceps, baskets, etc. to use with the RB is important; almost every type of foreign body can be extracted. However, the flexible 1 mm channel bronchoscope can also be utilized for the same purpose [26]. Urologic instruments (like ureteral baskets and forceps) can go easily through this narrow 1-mm channel and capture big foreign bodies.

Nevertheless, it is recognized that the BR is still the best instrument to extract foreign bodies from the pediatric airway, and it is also preferred in adults. In a retrospective study in 60 adults presenting foreign body aspiration, the FB was successful in removal in 61% of cases, while the RB had a success rate of 96% [27]. In adults, however, the FB is frequently applied first to inspect and to try removal, and if it is not possible, then RB is considered [28].

Opinions about RB use on children, though, are divided. A prospective study evaluating the role of both instruments (rigid and flexible) showed that the predictive value of clinical and the radiologic findings in 83 children with foreign bodies in the airway were useful in deciding selection of RB or FB. The study concluded that the rigid bronchoscope must be used if any of the following clinical signs were present: asphyxia, a radiopaque foreign body present in the radiography, and the association of decreased air sounds along with obstructive overinflation in the chest radiograph. The FB can be used in the rest of the cases, and if during the procedure a foreign body is identified, RB must be utilized for its extraction. Application of the RB was always successful, except in one child who required a second session for the extraction of the foreign body. Postsurgical complications included laryngospasm ($n = 1$) and laryngeal edema ($n = 6$), and two of them required brief intubation. The extracted foreign bodies comprised of peanuts, vegetables, inert metals, bones and teeth, plastic pieces, and other inorganic objects [29]. The authors conclude that following this protocol was cost-effective, limiting the number of unsuccessful procedures and the use of RB. Many of the recommendations and conclusions of this study have been questioned, however. The study implies that the RB cannot examine the distal airway as good as the flexible bronchoscope. However, with the rigid bronchoscopes and smaller optics, the presence of foreign bodies can be detected as much as with a flexible bronchoscope. Procedures performed with the RB versus the FB are not more time-consuming at all; on the contrary, general anesthesia for RB can be completed with intravenous sedation, and the required time is comparable to the fibrobronchoscopy time. In addition to this, most of the foreign body removal performed with FB are also under general anesthesia, introducing the FB through an

endotracheal tube, making manipulation cumbersome. Besides, children who were treated with RB did not have longer hospitalizations than children treated with FB [30]. In conclusion, we prefer the RB for foreign body retrieval in the pediatric population since it is safer and easier to do and the number of ancillary elements is such that virtually all foreign bodies can be removed in one session.

Rigid Bronchoscopy in Intensive Care Units

RB indications in the intensive care units (ICU) are limited. The most common are massive hemoptysis, large foreign bodies, obstructive lesions of the central airway, laser treatments, and prosthesis placement. All of these cases constitute relative indications, and the RB is, in practice, used only when the FB cannot fix the problem.

In the event of lung cancer patients ventilated for tumoral airway obstruction, the application of rigid laser bronchoscopy and airway stent according to need can result in a change of level of care allowing immediate discontinuation of mechanical ventilation as was published by Colt et al. [31].

Two important inconveniences in applying the RB in an ICU are the need of the bronchoscopist to be situated behind the patient and the difficulty of positioning the patient to easily insert the device. If the RB is indicated, it may be better to transfer the patient to the operating room to proceed.

Other Indications

The RB can be a lifesaving instrument in situations other than massive hemoptysis and foreign body removal.

In difficult tracheal intubations, the FB is used to guide the endotracheal tube to the trachea. Occasionally, when this technique fails, the RB may act as endotracheal tube.

Impacted mucus plugs, difficult to aspirate with the FB, can be easily extracted with the RB. This is especially useful in pediatric patients with cystic fibrosis, asthma, and post-operatory atelectasis.

Complications

Most of the complications arise from a poor RB insertion technique: laryngeal or vocal cord trauma, hypercapnia, hypoxemia, or hemodynamic instability. The bronchoscopist must not forget that he/she shares the airway control with the anesthetists and that oxygenation and ventilation have priority.

Complications associated to the use of RB include teeth, lips, gums, and throat lesions. Moderate laryngeal edema is very common but rarely produces relevant problems. Post-procedure throat and neck pain are frequent and usually last from 24 to 36 h. Vocal cord lesion is inversely related to the ability of the operator: on trained hands, it hardly occurs. Luxation of arytenoids may be also seen when a bad technique is used during intubation or when the procedure is executed with a poor local anesthesia or with an awake patient. A very infrequent and severe complication is rupture of the posterior tracheal wall. This requires surgical repair. Minimum or massive bleeding may occur during tumor resections. Most of the complications diminish as the bronchoscopist ability increases. Lack of training of the endoscopist or his/her assistants must be considered an absolute contraindication for the use of the RB [6, 32] (Table 4.2).

Drummond et al. published their 8 years of experience using the RB in a university hospital [33]. During this time 775 procedures were performed. The authors found that 13.4% of the patients experienced an associated complication. Most of them were minor complications. Patients presenting abnormal pulmonary function or basal hypoxemia and known cardiac disease and those with coagulation abnormalities (prolonged prothrombin time or thrombocytopenia) were more susceptible to complications than those without comorbid conditions. Preoperative risk increased when the following parameters were present:

Table 4.2 Complications

Hypoxemia
Cardiovascular instability
Tracheobronchial perforation
Esophageal perforation
Laryngeal edema
Vocal cord damage
Dental trauma
Pneumothorax
Severe bleeding
Mediastinal emphysema
Laryngospasm
Bronchospasm

- $PaO_2 < 55$ mmHg
- FEV1 < 50% of the predicted value
- Unstable angina or cardiac failure
- Severe arrhythmia
- Heart attack during the 6 months prior to the procedure
- Thrombocytopenia < to 50 × 10 [9]
- Abnormal prothrombin time

Patient presenting with any of these risk factors had a 37% rate of complication during rigid bronchoscopy. The group of patients with more complications presented malignant conditions involving the main carina. Also, those undergoing RB for airway obstruction had more chance to complicate. Only three deaths resulted from RB application. The cause of death was bleeding in two of the patients and respiratory insufficiency in the remaining one.

Complications were also frequent in the group of patients receiving RB to remove foreign bodies. The least complicated group was the one presenting benign conditions (benign tumor removal or benign stenosis treatment). In general, these patients showed less comorbidities.

One patient presented pneumothorax associated to the use of laser for airway resection. Other complications were those associated with anesthesia (hypoxemia, arrhythmia) and a dental piece rupture.

The experience published by this group reinforces the notion that patients must be carefully selected according to risk before performing RB. It also reminds us that the RB is a powerful therapeutic tool that can also cause damage.

The Procedure

When rigid bronchoscopy was introduced, it used to be performed in awake patients. Nowadays it would be an exception to proceed under those conditions. All patients we treat with RB are under general anesthesia, and they are carefully evaluated just as we do for any other surgical procedure. History taken should be detailed, noting all comorbid conditions and medications in use. Physical exam should focus on temporomandibular disorders, cervical spine mobility, and spine abnormalities. Minimum laboratory values must be obtained: coagulation profile, blood count, chemistry profile, acid-base status, and electrocardiogram. Usually patients already have images of the pulmonary lesions: chest radiograph and thoracic computerized tomography, which must be carefully reviewed before the procedure.

The patient and his/her family must receive a clear explanation about what will be done and sign informed consent.

The procedure can be performed in the bronchoscopy suite or the operating room, and a minimum of four persons are needed: bronchoscopist, anesthesiologist, assistant nurse, and a circulating assistant.

Preparation involves positioning the patient in a supine position, with a little pillow under the head, and application of topical anesthesia, lidocaine or tetracaine. Dental prosthesis should be removed and proceed to the inspection of teeth and gums. Additional local anesthesia is also flushed on the chords and high trachea with a syringe, under direct view via laryngoscopy. Then, an oxygen mask is placed for preoxygenation, and anesthetic induction and muscle relaxant medications are administered according to the usual practice.

A protection for the superior teeth is placed; it can be made of plastic or simply be a thick folded gauze that works as the rigid tube support and protects teeth and gums (Table 4.3).

Table 4.3 Requirements to perform RB

• Rigid bronchoscope and tracheoscope
• Light source
• Video monitor if available
• Rigid optic 0° angulation
• Ancillary equipment (alligator forceps, scissors, foreign body retrieval elements)
• Rigid suction catheter
• Ventilation system (jet ventilation, ventilation bag)
• Eye protection
• Mouth protection
• Flexible bronchoscope with additional light source and suction port
• Interventional application: stents and deployment systems, laser, electrocautery, dilatational balloons, etc., according to the procedure taking place

RB procedures have become a common practice, and the anesthetic techniques have evolved. All procedures are performed under general intravenous anesthesia. Muscular relaxation and paralysis can be avoided by administering appropriate sedation. This technique shortens the recovery period. We do not apply muscle relaxants since we have found that with appropriate sedation there is no need for administration of these agents. Many centers apply jet ventilation, but we prefer to perform all rigid procedures with manually assisted spontaneous ventilation. There is a special chapter in this book discussing in detail anesthesia in interventional procedures.

Once the equipment is prepared and the video camera system is connected, the conditions are given to initiate the procedure. The classic intubation technique requires considerable experience. It is performed with the RB and the rigid optic connected to the video system if available. The steps are the following (Fig. 4.12a–i):

1. The RB is held with a hand, adjusting the optic a little retracted in a way that the distal end of the RB is interiorly visible. The other hand is used to open the patient's mouth, advance the RB, and adjust the tongue. Then, with the index finger and thumb, the tip of the RB is held to direct it and to keep it in the middle line at the same time. When initiating the maneuvers, the instrument edge must be looking forward, and an appropriated protection for the teeth must be observed.
2. Keeping the instrument in the middle line, it is advanced slowly. Soft back-and-forth movements are simultaneously performed, in order to position it properly without causing any mouth injury and to get a better vision. The advance direction must be perpendicular to the operating table.
3. The RB should be thus advanced until the uvula is visible in the 6 o'clock position.
4. From there on, the advance angle is changed approximately 45° to the procedure table, and with soft rotation movements, the RB is introduced until the epiglottis is visible in the 12 o'clock position.
5. The RB tip is used then to softly lift the epiglottis, using the same rotation movements, and it is carefully crossed through until the vocal chords are visible.
6. Moving forward to immediately above the vocal chords, the RB is given a 90° clockwise turn, so the beveled edge is softly leaned on a vocal cord while turning and simultaneous advancing through the chords.
7. Once this is done, the trachea will be intubated, and the RB is again rotated 90° counterclockwise. The rigid tube is then introduced further. Then, the universal head is disconnected and reconnected to a bronchial tube, which is then inserted through the tracheal tube (Figs. 4.13 and 4.14).
8. Ventilation is connected and the therapeutic procedure can start. It is very important that the operator works in a comfortable position (Fig. 4.15).

It takes time and experience to be able to perform rigid intubation as described above. There are other techniques to place a rigid bronchoscope that are very useful during the training period. The first of them implies to intubate the patient with a conventional endotracheal tube and as a second step execute the intubation with the rigid tube, along the side of the ETT. This method has the advantage of giving the operator all the time needed to maneuver, since it does not require the patient to be in apnea like during the conventional

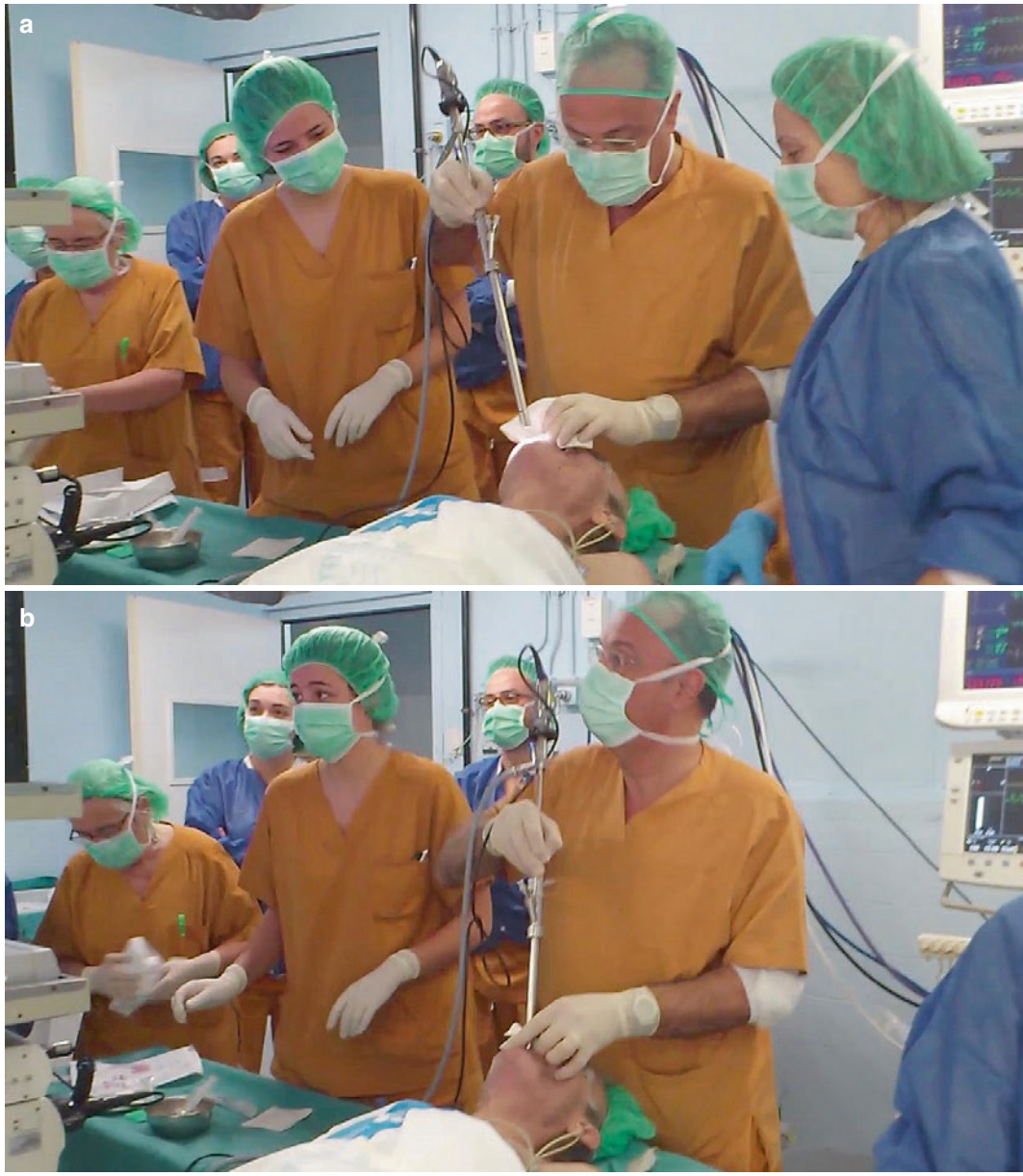

Fig. 4.12 Sequence of RB intubation. (**a**) Initial positioning, protection for teeth and tongue. (**b**) Slowly advancing with the RB perpendicular to the operation table until the uvula is in view. (**c**) Uvula. (**d**) Advancing from uvula, changing the angle to 45° until the epiglottis is in view. (**e**) Epiglottis. (**f**) The epiglottis is lifted changing to a more acute angle, until the arytenoid cartilages can be seen. (**g**) Once the arytenoids are in view, the RB should be positioned more horizontally until the chords are visible. (**h**) When vocal cords are in view, the RB is rotated 90° clockwise to place the beveled end leaning on the right vocal cord to protect it, while simultaneously advancing. Once in the trachea, the RB is rotated counterclockwise and advanced further. (**i**) Finally, ventilation is connected to oxygenate the patient for a while

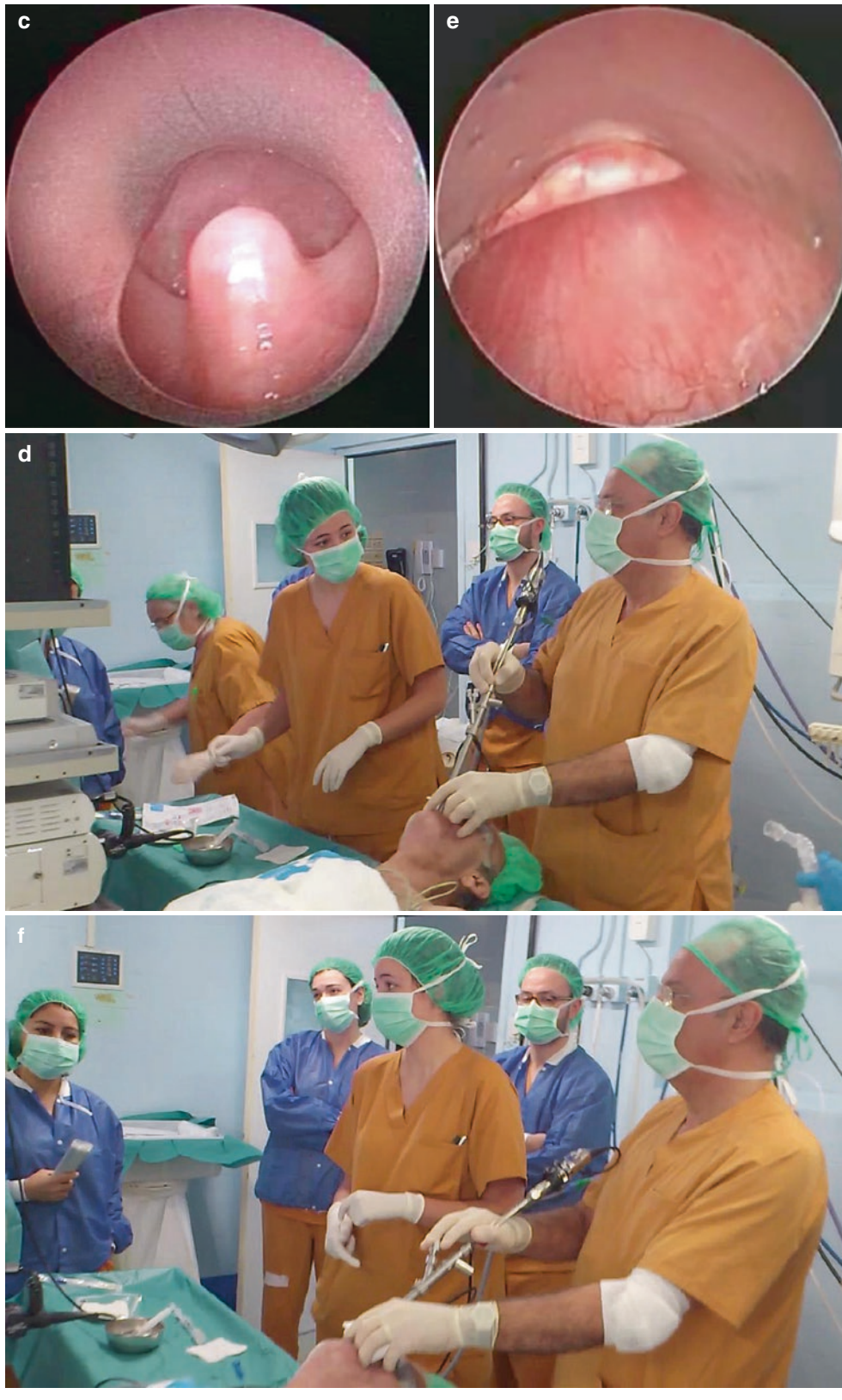

Fig. 4.12 (continued)

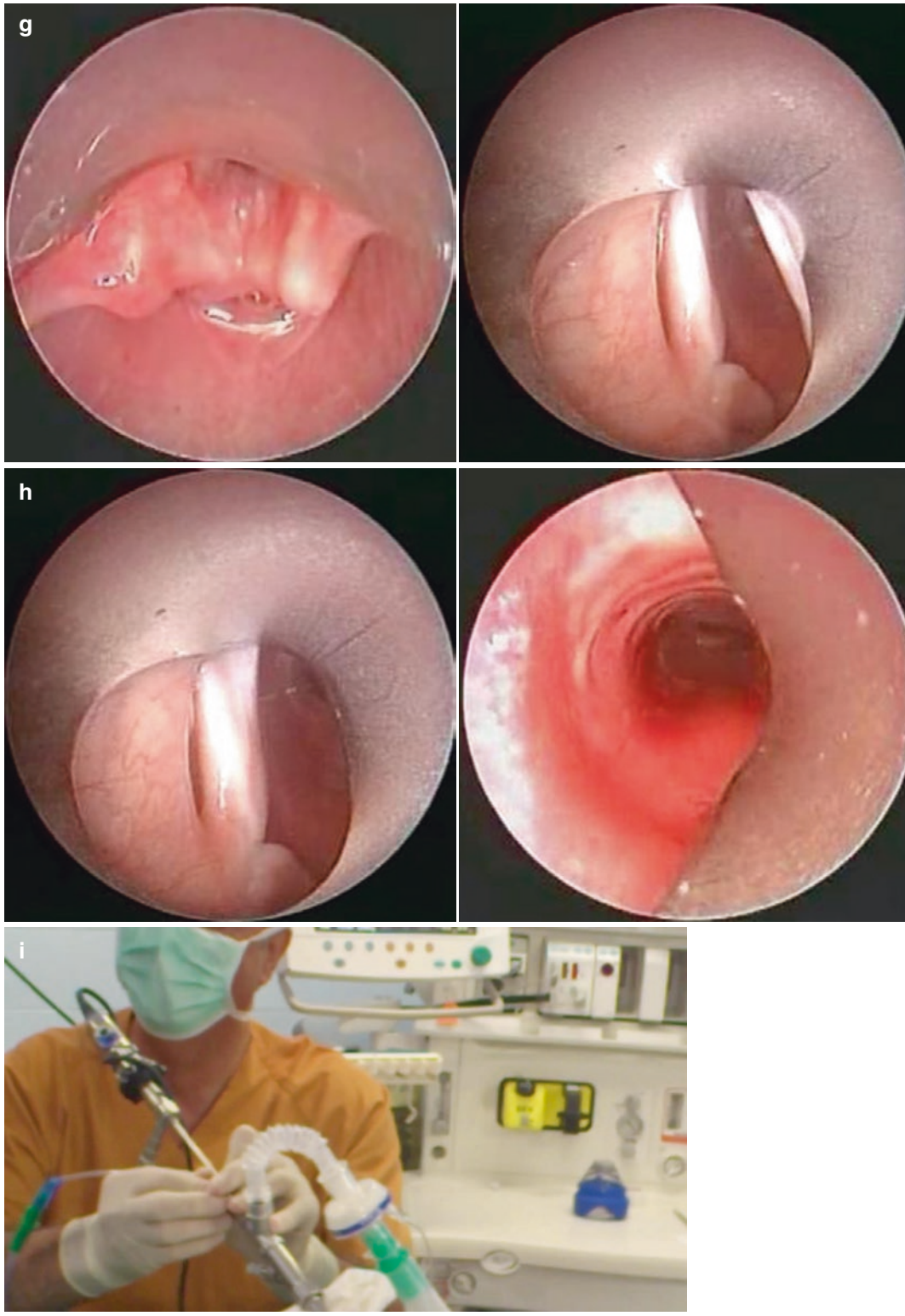

Fig. 4.12 (continued)

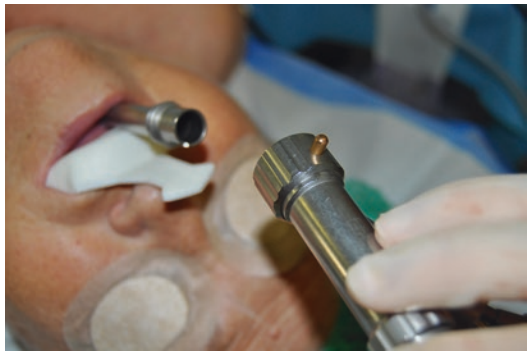

Fig. 4.13 Once the rigid tracheoscope is in the airway, the head of the RB is removed

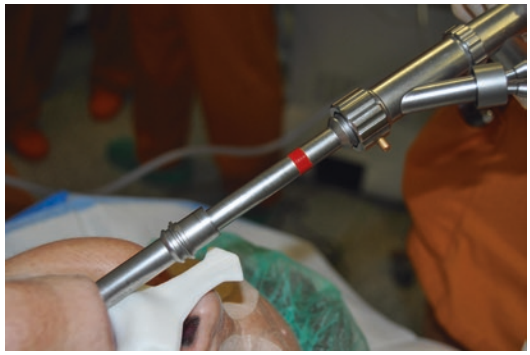

Fig. 4.14 Head of the RB connected to a bronchial rigid tube. They are then introduced through the tracheal tube, and the procedure can start

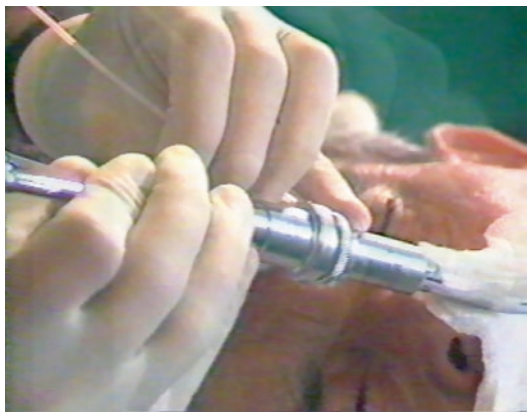

Fig. 4.15 Comfortable position of the hands for manipulation of ancillary tools

technique but ventilated until the tubes are changed. The other alternative is to complete the intubation with the help of a laryngoscope.

This intubation is achieved observing the chords with a conventional laryngoscope. After lifting the epiglottis with it, the RB is inserted by the side of the mouth, directing it toward the larynx. Then, it is introduced between the vocal chords and softly rotated to keep it on the middle line without injuring the subglottic area. At this moment, the laryngoscope is removed, and the rigid optic is placed through the RB and advanced within the trachea under direct vision.

Intubation with RB through a tracheotomy is also possible. For this method, the rigid tube is introduced obliquely through the tracheotomy, previously numbed with local anesthetics. This maneuver must be carefully performed to avoid lesion of the posterior tracheal wall.

Some Conclusions

Before the FB introduction, the use of RB was almost limited to surgeons. During a British study, it was observed that, even though only 2% of the 39,564 bronchoscopies completed between 1974 and 1986 used RB, more than 90% were performed by surgeons. This work also noted that 81% of the bronchoscopists used FB, 9% of them were using both techniques, and an 8% used the FB through the RB [34].

In a review made by the American College of Chest Physicians, only 8% of the responding endoscopists were using RB [20]. The reasons are multiple, but some of the most important ones are that the FB is more available and easier to use than the RB that requires special training not given routinely during training programs.

This data ratifies a known fact: obtaining training on the RB technique is difficult, for several reasons. The first one is that its teaching is not part of the pulmonary specialist training as we discuss, while FB training is included. Besides, its use is generally associated with therapeutic procedures such as laser, stent placement, etc., and that requires specific technology not always available. Another inconvenience is that the technique is indeed difficult and requires full dedication to learn it. The number of procedures to become proficient varies from person to

person. In addition, when proficiency is obtained, a number of regular procedures are required in order to maintain the ability and to get the interest of the involved team: nurses and anesthesiologists. In general, it is advisable that the person who is interested in learning interventionism follows a formal training with an expert, in a place where an adequate number of procedures are performed per year. Many experts agree that expertise on RB takes years and that courses and seminars (although indispensable to a complete learning) are not enough to initiate the individual practice without supervision. The ACCP guidelines published in 2003 recommended that a trainee should perform at least 20 procedures in a supervised setting to establish basic competency in patients with normal airways, and then he/she should perform ten procedures per year in order to maintain competency. They also recommended that program directors should decide whether or not the candidate is able to perform RB procedures without supervision. [35].

The ideal bronchoscopist should be able to perform both FB and RB, on pediatric and adult population. Given that lung cancer incidence continues rising and today the multimodality approach to treatment includes a pulmonary physician able to perform palliative procedures according to need, the RB will continue to be indicated. This instrument has unique features that make it irreplaceable, and it is also complementary to many other tools, particularly when treating central airway diseases. Though still RB is performed by a minority of physicians, there is an increased interest to train and maintain proficiency in rigid bronchoscopy, and we are sure that it will be more so in the future.

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Anesthesia for Interventional Bronchoscopic Procedures

5

Mona Sarkiss

Introduction and Definition of Anesthesia for Interventional Bronchoscopy

Introducing the bronchoscope into the airway has proved to be a challenge since the invention of the first bronchoscope. Airway reflexes, such as the gag reflex, cough, laryngospasm, hemodynamic alteration, and the associated anxiety stimulated by the passage of the bronchoscope into the airway, forced the bronchoscopist to be skilled and quick to perform the procedure [1]. As a result interest emerged in using anesthesia to ameliorate the airway reflexes and patient's anxiety associated with bronchoscopy. A wide range of anesthesia techniques were developed to accommodate a variety of interventional bronchoscopic procedures such as simple diagnostic bronchoscopy, advanced diagnostic bronchoscopy, therapeutic bronchoscopic interventions, and pleural procedures. Anesthesia for interventional bronchoscopy varies from local anesthesia as the sole anesthetic modality to moderate sedation/analgesia ("conscious sedation") with or without local anesthesia to general anesthesia [2]. Moderate sedation/analgesia ("conscious sedation") is defined by the American Society of Anesthesiologist (ASA) as "a drug-induced depression of consciousness during which patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually maintained" [3]. Moderate sedation may progress to deep sedation/analgesia or even general anesthesia during the same procedure. Once under deep sedation, "the patients cannot be easily aroused but respond purposefully following repeated or painful stimulation. The ability to independently maintain ventilatory function may be impaired. Patients may require assistance in maintaining a patent airway, and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained" [3]. At the other end of the spectrum is general anesthesia, where "patients are not arousable, even by painful stimulation." The ability to independently maintain ventilatory function is often impaired. Patients often require assistance in maintaining a patent airway, and positive pressure ventilation may be required because of depressed spontaneous ventilation or drug-induced depression of neuromuscular function. Cardiovascular function may be impaired [3].

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Although the current guidelines do not define which anesthesia technique to use for each procedure, it is generally accepted that simple diagnostic and interventional airway procedures of short duration are well tolerated by the patient when performed under local anesthesia and/or moderate sedation, whereas more complex interventional bronchoscopic procedures that require a still field have a longer duration and entail more risk to the patient due to comorbidities or a compromised airway are best performed under general anesthesia. General anesthesia has the added advantage of the availability of special modes of ventilation and monitoring that can be provided and managed by anesthesia providers. This chapter will first provide a brief historical perspective. Then, the indications and contraindications for different levels of anesthesia are described. Next, the equipment required and the application of the techniques are discussed. Finally, a summary and recommendations are presented.

History and Historical Perspective

When Dr. Killian invented the rigid bronchoscope in 1865, anesthesia had not been discovered, and the procedure was performed in conscious patients. "In order to desensitize the airway reflexes, patients were advised to repeatedly touch their pharynx and vocal cords for several weeks before the procedure." According to early reports, "the physicians performing the procedures were trained by practicing on an excised head that had been severed from a corpse and hung from a hook or by practicing on healthy volunteers." This practice allowed the bronchoscopists to become extremely skilled and swift as operations had to be performed within seconds before the view disappeared [1]. Multiple attempts to anesthetize the airway with ammonia, iodine, belladonna, or potassium bromide had failed. In 1884 Jellinek introduced cocaine, the first local anesthetic, for airway exam and reported its benefits by stating that "by eliminating the reflexes of the pharynx and the larynx it was possible to perform some of the operations in which even the most skillful artists in surgery had failed. The procedure completely changed. Virtuosity gave way to careful methodology, skill to exactness and the former almost endless preparation that so often tried the patience of the physician as well as of the patient could be almost completely abandoned" [1]. Similarly, Killian emphasized the advantages of using cocaine during bronchoscopy by saying that "whether one stops inspection with the rigid tube at the bifurcation or passes on for some distance into a major bronchus does not matter for the patient. If he is sufficiently cocainized he does not even realize it" [1].

In 1968, the flexible bronchoscope was invented by Ikeda and gradually replaced the rigid bronchoscope. Compared to the rigid bronchoscope, the flexible bronchoscope is well tolerated by the patient, even without anesthesia due to its small diameter and plasticity. Flexible bronchoscopy was initially used for simple diagnostic bronchoscopic procedures of short duration making local anesthetics an ideal technique for anesthesia. However, subsets of anxious patients remained unable to tolerate the procedure. As a result, conscious sedation with anxiolytics and opioids, to ameliorate anxiety and cough, respectively, in addition to local anesthetics became common practice for airway procedures. As the field of interventional bronchoscopy expanded, a growing number of lengthy and technically demanding procedures especially in patients with severe comorbidities and compromised central airway emerged. As a result the use of the rigid bronchoscope was revived to aid in the management of large airway tumors and procedure-related complications and to allow for ventilation during lengthy procedures. Accordingly, a renewed interest in monitored anesthesia care (MAC) or general anesthesia has emerged. Currently, some centers in the United States and Europe made it its standard practice to have an anesthesiologist provide either sedation or general anesthesia to selected patients undergoing interventional bronchoscopic procedures. This arrangement allows the interventionalist to direct his or her full attention to the procedure, the patient to undergo the procedure with minimal or no discomfort, and the anesthesiologist to

vigilantly manage the patient's airway, medical condition, and the anesthesia.

Indications and Contraindications

In its 2003 guidelines for interventional pulmonary procedures, the American College of Chest Physicians (ACCP) left the choice of anesthesia to the interventionalist, depending on the guidelines and resources available at their practice. This was due to the lack of evidence and consensus on what are the indications for different types of anesthesia. However general anesthesia was recommended for rigid bronchoscopy and for pediatric bronchoscopic procedures [4]. More specific guidelines on anesthesia for interventional pulmonology, published by the European Respiratory Society and the American Thoracic Society (ERS/ATS) in 2002, alerted the interventional bronchoscopists "to be prepared to convert to general anesthesia, if the situation requires (page 358)" and recommended that "the design of the bronchoscopy suite should account for the presence of anesthesia equipment" [5]. It is important to note that the availability of anesthesia support in different practices, especially in nonacademic settings, remains limited. Some facilities have anesthesia support only when procedures are performed in the operating room, and others have anesthesia support in the bronchoscopy suite and/or the operating room, but some practices remain with no access to anesthesia support. Under all circumstances pre-procedural evaluation of the patient along with the nature of the procedure and consideration of the available resources should direct the interventionalist to determine the most appropriate form and location of anesthesia needed for a particular procedure.

Pre-procedural Evaluation and Preparation

Medical history should be elicited with particular interest in respiratory and cardiovascular diseases, exercise tolerance, and performance status. In addition, history of stridor, snoring and sleep apnea, drug allergy, current medication, tobacco, alcohol, or drug used should be documented. Complications related to previous sedation and anesthesia such as prolonged sedation unplanned hospital admission or intubation should be sought. The American Society of Anesthesiologist (ASA) score is commonly assigned to the patient to assess the patient physical status and severity of illness; however, the ASA status is not intended to predict anesthesia or procedure-related risk (Table 5.1). Women of childbearing age should be questioned about possibility of pregnancy and counseled regarding effect of anesthesia and the procedure on pregnancy [6].

Table 5.1 ASA physical status

ASA physical status 1—A normal healthy patient
ASA physical status 2—A patient with mild systemic disease
ASA physical status 3—A patient with severe systemic disease
ASA physical status 4—A patient with severe systemic disease that is a constant threat to life
ASA physical status 5—A moribund patient who is not expected to survive without the operation
ASA physical status 6—A declared brain-dead patient whose organs are being removed for donor purposes

Physical Examination

Airway should be assessed to determine difficulty of intubation in case of airway compromise or if rigid bronchoscopy is planned. Direct inspection of pharyngeal structure when the mouth is wide open and the tongue is protruding as far as possible is used to assess difficulty of intubation by direct laryngoscopy according to the Mallampati classification (Fig. 5.1). Other parameters that predict difficult intubation are decreased extension of the atlanto-occipital joint (normally 35° from neutral midline position) by more than two-thirds, decreased mouth opening below the normal range of 50–60 cm, and thyromental distance measured in an extended neck from the mentum to the notch of the thyroid cartilage ≤6 cm in adults, short muscular neck, and receding mandible.

Dental inspection is necessary to identify the presence of loose teeth; dental prosthesis;

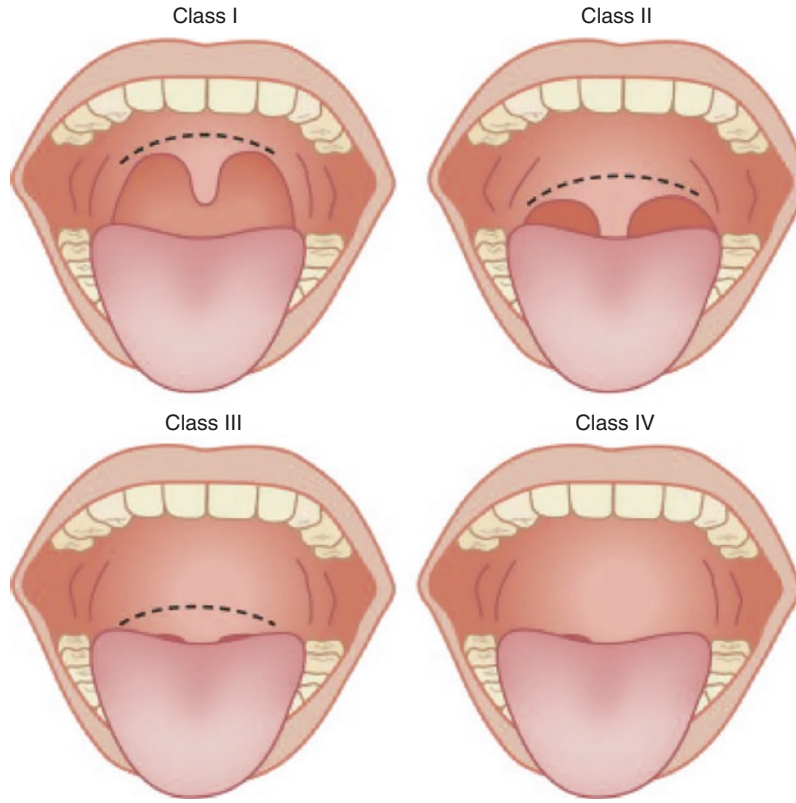

Fig. 5.1 The Mallampati classification

chipped, missing teeth; bridges; crowns; or denture. The presence of prominent or protruding maxillary incisors may alert the bronchoscopist to the possibility of difficult intubation and/or damage to the teeth during direct laryngoscopy or rigid bronchoscopy.

Respiratory system assessment should be performed with emphasis on baseline saturation, requirement of supplemental oxygen, and the use of accessory respiratory muscle.

Cardiovascular system exam focused on baseline vital signs and signs of cardiovascular compromise due to intrathoracic disease, e.g., superior vena cava syndrome and pericardial effusion.

Laboratory testing should be performed based on the baseline comorbidities and nature of the procedure (e.g., complete blood count, electrolytes, coagulation profile).

Radiographic studies, e.g., chest x-ray, computed tomography (CT), and electrocardiogram, are recommended.

Pulmonary function tests and assessment of arterial blood gases may be required depending on the nature of the procedure [5].

Informed consent should be obtained from the patient after detailed explanation of the risks, benefits, and possible alternatives of the procedure and sedation or anesthesia.

Nothing per os (NPO) is indicated for 2 h for clear liquids and 6–8 h for solids before the procedure according to the current ASA guidelines. Patients with history of uncontrolled or untreated acid reflux, post-esophagectomy, or gastroparesis should be instructed to take the anti-reflux medication on the day of the procedure and can benefit from airway protection by endotracheal intubation.

Procedure-Related Indications

Despite few reports of rigid bronchoscopy performed under local anesthesia [7] or general anesthesia with spontaneous ventilation [8], the

most common practice is to perform rigid bronchoscopy under general anesthesia with muscle relaxation [4]. The rationale for utilizing general anesthesia for rigid bronchoscopy is the lengthy nature of the procedures and the resulting occurrence of hypoxemia and hypercapnia [8]. Spontaneous, assisted, mechanical, or jet ventilation can be used during rigid bronchoscopy to overcome such occurrences [9].

Great controversy exists over performing EBUS under moderate sedation or general anesthesia. The EBUS bronchoscope has a larger external diameter of 6.9 mm and is more tolerated when inserted through the mouth compared the nose. Therefore, some practitioners prefer to perform all EBUS procedures or only the lengthy staging EBUS procedures under general anesthesia. Recent study showed that more lymph nodes per patient and smaller lymph nodes were sampled more often when EBUS was performed under deep sedation or general anesthesia. In addition on-site cytology evaluation was used more frequently when general anesthesia was used [10]. However, several reports indicated no difference in patient satisfaction, yield, sensitivity, or specificity of the EBUS procedure when performed under moderate sedation versus general anesthesia [11, 12].

Application of the Technique

Topical Anesthesia

Local anesthetics cause reversible block of the conduction of nerve impulses with subsequent sensory, motor, and autonomic blockade. Cocaine was the first topical anesthetic discovered, but it was soon found to cause topical irritation and psychological dependence. Subsequently, synthetic local anesthetics lacking such side effects were discovered. Procaine, the first synthetic local anesthetic, was introduced by Einhorn in 1905 and was followed by lidocaine, which was synthesized in 1943 by Löfgren. Synthetic local anesthetics have a lipophilic benzine ring linked via an amide or an ester bond to a hydrocarbon chain that is attached to a hydrophilic tertiary amine structure. Local anesthetics are classified according to the type of their linking bond to ester or amide local anesthetics. The nature of the linking bond affects the metabolism of the local anesthetic as well as its potential to produce an allergic reaction. Amide local anesthetics, which are commonly used in bronchoscopy, are metabolized by the liver microsomal enzymes and are also extracted through the lungs. The addition of epinephrine at 1:200,0000 (5 μg/mL) concentration or 0.25% phenylephrine causes local vasoconstriction, which slows down the absorption of the local anesthetic, prolongs its duration of action, and decreases its systemic toxicity.

Side Effects of Local Anesthetics

Absorption of large amounts of local anesthetics from the application site or direct accidental intravascular injection of large dose can result in systemic toxicity, e.g., lidocaine plasma level of 5 μg/mL or greater than 8.2 mg/kg of lidocaine instilled in the airway can result in systemic toxicity [13]. The toxic dose of benzocaine is 100 mg, and the toxic dose of tetracaine is 100 mg (but toxicity has been reported at 40 mg).

Central nervous system (CNS) toxicity initially presents with symptoms of CNS excitation such as restlessness, vertigo, tinnitus, and slurred speech. The symptoms may progress to tonic–clonic seizure followed by CNS depression in the form of coma and possibly death. Seizures should be immediately treated with small doses of intravenous benzodiazepine (diazepam or midazolam), intravenous thiopental, or propofol. Hypoxemia should be treated with supplemental oxygen. Additionally hyperventilation with subsequent respiratory alkalosis causes hyperpolarization of the nerve membrane, increases the threshold for seizure, and increases the amount of local anesthetic bound to protein thus decreases the delivery of free drug to the brain. If seizures continue despite treatment, intubation is warranted to protect the airway.

Cardiovascular toxicity due to blockade of the cardiac sodium channels can result in hypotension, long PR interval, and widening of the QRS complex. More severe cardiotoxicity can present with severe hypotension, cardiac arrhythmias, and atrioventricular heart block.

Methemoglobinemia occurs when local anesthetic oxidize the iron molecule in the hemoglobin from the ferrous to ferric state. Hemoglobin with iron molecule in the ferric state is called methemoglobin and is characterized by its inability to release bound oxygen to tissue. Patients with methemoglobinemia present with cyanosis, chocolate-colored blood, stupor, coma, and death. Methemoglobinemia is easily treated by the administration of 1–2 mg/kg of methylene blue intravenously.

Allergic reactions to local anesthetics are rare but are more common with ester local anesthetic metabolite para-aminobenzoic acid (PAPA). In addition, the preservatives used with either ester or amide local anesthetics (e.g., methylparaben) can be a source of allergic reaction. It is noteworthy that cross sensitivity does not exist between ester and amide local anesthetics.

Anesthesia of the Nasal Mucosa and Nasopharynx

Sensation to the nasal mucosa is provided by the middle division (V2) of the trigeminal nerve (CN V), the sphenopalatine ganglion, and the ethmoid nerve. The nasal mucosa and the nasopharynx can be topicalized using a cotton-tipped applicators or pledgets soaked in the 1, 2, or 4% lidocaine solution with or without a vasoconstricting agent. The applicators are placed sequentially along the inferior turbinate, the middle turbinate, and the superior turbinate. Each applicator should be left in place for 5 min.

Anesthesia of the Mouth and Oropharynx

Sensation of the mouth and oropharynx is supplied by branches of the glossopharyngeal, vagus, and facial nerves. The lingual branch of the glossopharyngeal nerve provides sensation to the posterior third of the tongue, the vallecula, and the anterior surface of the epiglottis. The pharyngeal branch provides sensation to the posterior and lateral walls of the pharynx, and the tonsillar branch supplies the tonsillar pillars. The tongue can be anesthetized by placing a tongue blade coated with lidocaine gel on the tongue for several minutes. Oral and pharyngeal mucosa are anesthetized by inhalation of nebulized 4% lidocaine or 0.5% tetracaine or by using an Cetacaine atomizer spray (tetracaine and benzocaine combination). Gargle with 2–4 mL of viscous lidocaine for 30 s can provide additional anesthesia to the posterior pharyngeal wall.

Superior Laryngeal Nerve Block

The superior laryngeal nerve (SLN) is a branch of the vagus nerve that divides lateral to the cornu of the hyoid bone into internal and external branches. The internal branch passes under the greater cornu of the hyoid bone before piercing the thyrohyoid membrane and entering the pyriform recess where it provides sensory innervation to the base of the tongue, the superior epiglottis, the aryepiglottic folds, the arytenoids, and the laryngeal mucosa above the vocal cords. The external branch supplies motor innervation to the cricothyroid muscle.

To perform SLN block, the patient should be placed in a supine position with the head slightly extended, and the greater horn of the hyoid bone is palpated above the thyroid cartilage. The needle (size 22 or 23 gauge) is inserted toward the greater horn of the hyoid bone and then moved caudally until a pop is felt when the thyroid ligament is pierced at a depth of about 1–2 cm. Negative aspiration is then followed by injecting 2–3 mL of 2% lidocaine with epinephrine. Bilateral blocks should be performed (Fig. 5.2).

Recurrent Laryngeal Nerve (RLN) Block

The recurrent laryngeal provides motor innervation to the vocal cords and sensory innervation to both the trachea and vocal cords. In a supine patient with hyperextended neck, the skin over the cricothyroid membrane is anesthetized with lidocaine 1–2% with a 22-gauge needle. A 22-gauge IV catheter is

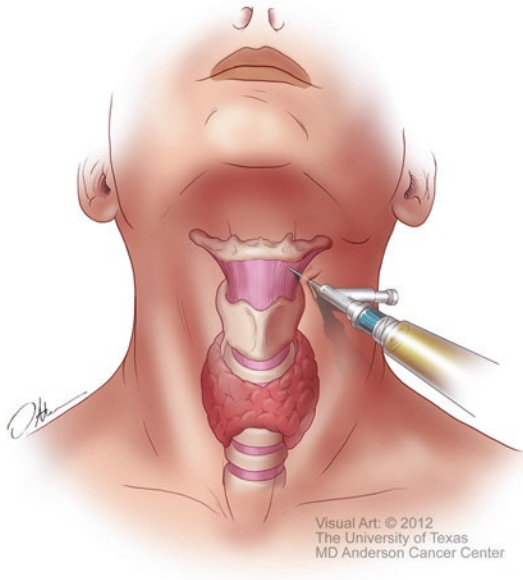

Fig. 5.2 Superior laryngeal nerve block

then inserted through the cricothyroid membrane into the tracheal lumen at an angle of 45° caudally. Air should be aspirated to confirm intratracheal position. The needle should then be removed leaving the plastic catheter in the tracheal lumen. The patient is asked to take a deep breath followed by forced exhalation while 3–4 cc of 1–2 or 4% lidocaine is injected through the catheter. This maneuver commonly result in cough that aids in spreading the local anesthetic over the vocal cords and the trachea.

Conscious Sedation

The American College of Chest Physicians has suggested in its consensus statement in 2011 that all physicians performing bronchoscopy should consider using topical anesthesia, analgesic, and sedative agents, when feasible [14]. The advantages of conscious sedation are the reduction of patient anxiety, pain, airway reflexes such as cough and gag, and the dyspnea associated with the insertion of the bronchoscope. Amnesia from the procedure also increases patient satisfaction and willingness to undergo another bronchoscopic procedure. In addition, the ability of the bronchoscopist to adequately perform advanced diagnostic and therapeutic procedures in shorter duration improves with sedation.

Different drug regimens have been used, and they vary depending on the bronchoscopist's preference and experience. The most commonly used classes of drugs are benzodiazepines for anxiolysis and amnesia in combination with opioids for suppression of cough and pain. The combination of narcotics and benzodiazepines has an additive effect on the suppression of the respiratory drive and cardiovascular hemodynamics thus increasing the likelihood of apnea, desaturation, and hypotension. Therefore, these drugs should be titrated gradually to achieve the desired effect and avoid undesired side effects.

Benzodiazepines act primarily by enhancing the action of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) causing increased resistance of neuronal excitation. This translates clinically to anxiolysis, sedation, anterograde amnesia, centrally mediated muscle relaxation, and minimal depression of ventilation or of the cardiovascular system. When compared with no sedation for bronchoscopy, benzodiazepine, as a single sedating agent, was associated with increased patient satisfaction and willingness to undergo another bronchoscopy. However, the post-procedure recovery time was longer in the benzodiazepine-treated patients without an increase in complication rates [15].

The three commonly used benzodiazepines for procedural sedation are midazolam, diazepam, and lorazepam. Midazolam is the most preferred benzodiazepine because of its water solubility, absence of pain with injection, rapid onset, short duration of action, and rapid clearance. The average dose of midazolam is 0.06–0.07 mg/kg with special consideration to use lower doses in elderly patients. Diazepam is a water-insoluble drug that is dissolved in the organic solvent propylene glycol that causes pain on intravenous or intramuscular injection. Diazepam is metabolized into two active metabolites desmethyldiazepam and oxazepam by the liver. The activity of these metabolites may cause prolonged sedation for 2–4 days in elderly patients and in those with impaired liver function. Lorazepam is an intermediate-acting benzodiazepine with a stronger

amnestic effect and a delayed peak effect, making it the least favored benzodiazepine for procedural sedation (Table 5.2).

Flumazenil is the only known benzodiazepine antagonist. A dose of 0.2 mg IV every 1 min to a total dose of 1–3 mg per 1 h is commonly used. The onset of action is at 1–3 min, the peak is at 10 min, and the duration of action is 20 min. Additional doses may be required to maintain antagonism and prevent the recurrence of sedation by longer-acting benzodiazepines. Side effects of flumazenil include nausea, vomiting, tachycardia, hypertension, headache, and rarely seizures.

Opioids are natural and synthetic substances that bind opioid receptors in the central nervous system and peripheral tissue, causing presynaptic inhibition of release of neurotransmitters (e.g., acetylcholine, dopamine, norepinephrine, and substance P). Activation of the opioid receptors mu, kappa, and delta results in varying degrees of analgesia and side effects such as depression of ventilation, urinary retention, constipation, miosis, and physical dependence. The naturally occurring opioid morphine and the synthetic opioids meperidine, fentanyl, sufentanil, alfentanil, and remifentanil have been used for bronchoscopic procedural sedation. Fentanyl is the most commonly used opioid for bronchoscopy sedation due to its rapid onset of action and short half-life. Although therapeutic bronchoscopy is not associated with significant somatic pain, opioids were found to cause suppression of airway reflexes in particular cough, tachycardia, and hypertension associated with bronchoscopy [16]. See Table 5.3 for a comparison between the pharmacodynamics of different opioids. Noteworthy is that the combination of an opioids and a benzodiazepine is associated with better patient's tolerance of bronchoscopy when compared to each agent alone [17] (Table 5.3).

Table 5.2 Pharmacodynamics of benzodiazepines

Drug	Dose (mg/kg)	Elimination half-life (h)
Midazolam	0.3–0.5	1–4
Lorazepam	0.05	10–20
Diazepam	0.15–0.3	21–37

Monitored Anesthesia Care (MAC)

MAC is defined as a specific anesthesia service in which an anesthesiologist has been requested to participate in the care of a patient undergoing a diagnostic or therapeutic procedure. However, MAC does not describe the depth of sedation. Under MAC, the anesthesiologist can either provide sedation or general anesthesia and the post-procedure recovery care. Situations where MAC is valuable are as follows: when variable levels of sedation are needed to meet changes in the patient and the bronchoscopist needs during a procedure, patients who are sensitive to small doses of sedatives where respiratory or hemodynamic complications can occur and resuscitation will be required, and patients who need transient period of general anesthesia. Therefore, the drugs of choice for MAC should be the ultrashort-acting anesthetics that are easily titrated to match the patient tolerance to the procedure with rapid return to baseline status at the end of the procedure, e.g., remifentanil, alfentanil, propofol, dexmedetomidine and fospropofol. In addition, midazolam, fentanyl, and morphine can also be acceptable choices [18].

Table 5.3 Pharmacodynamics of commonly used opioids

	Onset (min)	Peak (min)	Duration (h)	Elimination (h)	Context-sensitive half-life (min)	potency
Morphine	2–3	15–30	3	2–3		1
Meperidine	5	5–7	3	3–5		0.1
Fentanyl	1–2	3–5	0.5–1	3–6	260	75–125
Sufentanil	1–2	3–5	0.3	2–4	30	500–1000
Alfentanil	1–2	1.5–2	0.2–0.3	1.4–1.5	60	10–25
Remifentanil	1–2	1.5–2	0.1–0.2	0.17–0.33	4	250

General Anesthesia

If general anesthesia is the chosen anesthesia technique for an interventional bronchoscopic procedure, an open discussion between the anesthesiologist and the bronchoscopist should take place before and throughout the procedure. The discussion should include procedure location (e.g., trachea vs. bronchi), degree of airway obstruction (e.g., complete vs. partial obstruction), depth of anesthesia needed (e.g., general vs. sedation), airway device options (e.g., none, endotracheal tube, laryngeal mask airway, or rigid bronchoscope), and the most suitable mode of ventilation (e.g., spontaneous ventilation, noninvasive positive pressure, assisted ventilation, mechanical ventilation, or jet ventilation). In addition, the anesthesiologist should be familiar with the step-by-step plan the bronchoscopist has to manage the airway pathology and possible complications.

Total intravenous anesthesia (TIVA) is the anesthetic technique of choice for interventional bronchoscopic procedures when compared to inhalation anesthesia [12]. Inhalational anesthetics have multiple disadvantages, including the variable levels of anesthetic gas delivered because of frequent suctioning during the procedure and the contamination of the operating room air by inhalation agents. However, it is important to emphasize that inhalation agents can be a better choice in cases of bronchospasm. The following medications are commonly used for TIVA.

Propofol, similar to benzodiazepines, acts to facilitate the inhibitory effect of GABA. When used for sedation for airway procedures, propofol has been shown to be superior to midazolam due to its short onset time of 30 s, metabolism independent of organ function, and rapid recovery time of 15 min after a 2 h infusion. In addition, propofol has been shown to result in significantly better neuropsychometric recovery than midazolam [19]. When compared to inhalation anesthetics, propofol has been shown to reduce coughing and the depression in ciliary function [20] as well as the release of cytokines and the stress hormone response [21, 22].

Propofol infusion rates of 100–150 μg/kg/min can be used for anesthesia induction while maintaining spontaneous ventilation. The bi-spectral index monitor (BIS) can be used to titrate the propofol infusion rates to achieve and sustain an appropriate depth of anesthesia.

Remifentanil is the shortest-acting narcotic available, with duration of action of 3–10 min and a rapid onset of action at 1 min. After interventional bronchoscopic procedures, patients do not suffer from post-procedure pain thus eliminating the need for the use of long-acting narcotics. Remifentanil is ideal for blunting airway reflexes during the procedure with no residual effect in the recovery room [23].

Ketamine is a general anesthetic that induces a dissociative state in which sensory stimuli are blocked from reaching the cerebral cortex, causing amnesia and analgesia. Although ketamine is an old drug, its use has been revived because of its profound analgesic property. Ketamine-induced analgesia makes it a good adjunct to propofol that lacks any analgesic properties [24]. Ketamine is particularly valuable for bronchoscopic procedures because of its bronchodilating properties and absence of respiratory depressant effect.

Dexmedetomidine is an α-2 agonist that inhibits norepinephrine release causing its unique ability to provide sedation and analgesia without respiratory depression [25]. Dexmedetomidine has also been found to offer cardioprotective benefits during surgery by lowering perioperative oxygen consumption and the stress response [26].

Muscle relaxants, such as succinylcholine, rocuronium, or cisatracurium, can be used safely during general anesthesia to prevent laryngospasm and coughing associated with the insertion of the bronchoscope in the airway. The use of muscle relaxation for therapeutic bronchoscopic procedures has many advantages. These include facilitating the insertion of airway devices (e.g., LMA, endotracheal tube, and the rigid bronchoscope), better lung compliance during positive pressure ventilation or jet ventilation, providing the bronchoscopist with a still field when precise targeting of lesions adjacent to major vessels and the heart is needed, and maintaining the glottis aperture open during multiple insertion and

removal of the bronchoscope and other instruments thus minimizing trauma to the vocal cord.

On the other hand, the indiscriminate use of muscle relaxant in interventional bronchoscopy can be associated with severe complications. For example, there are several reports of loss of the airway patency after muscle relaxant was given in patients with large anterior mediastinal mass. Pneumothorax and/or pneumomediastinum can develop in patients with tracheoesophageal fistulas, bronco-esophageal fistulas, or airway tears when muscle relaxant is given and positive pressure ventilation is used. In addition, prolonged unwanted muscle relaxation has been reported in patients with lung cancer associated with paraneoplastic Lambert–Eaton myasthenic syndrome.

In the event that muscle relaxation is deemed unsuitable, instillation of lidocaine on the vocal cord and the proximal airway is a better alternative to the use of muscle relaxation prior to insertion of the rigid bronchoscope or other airway devices.

Fraction of inspired oxygen (FiO_2) should be continuously adjusted to maintain patient oxygen saturation >90% during interventional bronchoscopic procedure. FiO_2 of 100% is commonly needed during an advanced bronchoscopic procedure especially in patients with advanced lung pathology, poor baseline oxygen saturation, and/or the use of supplemental oxygen. In addition, FiO_2 of 100% is valuable when periods of complete airway occlusion and/or inability to provide mechanical ventilation are anticipated, e.g., during deployment or extraction of stents, balloon dilation of the airway, removal of a tumor mass where positive pressure ventilation can force the excised tumor down the airway causing acute obstruction, or during exchange of one rigid bronchoscope to a different type or size rigid bronchoscope.

It is important to note that low FiO_2 of less than 40% is required during electrocautery, laser, and argon plasma coagulation (APC) in order to avoid airway fire.

Monitoring the Depth of Anesthesia

Processed electroencephalograms can be used to monitor the depth of anesthesia and in combination with the patient's clinical signs can guide the titration of intravenous anesthetics to achieve adequate depth of anesthesia [19]. Consequently, adequate sedation without undesired side effects, such as respiratory failure or cardiovascular instability associated with increased depth of anesthesia, is more likely to be attained [27].

Description of the Equipment Needed

Interventional Bronchoscopy Suites

Interventional bronchoscopic procedures are commonly performed in an interventional bronchoscopy suite or the operating room. In most centers, the choice of the location of the procedure depends on the available resources and the anesthesia technique required. Interventional bronchoscopic procedures requiring local anesthesia and/or conscious sedation are usually performed in an interventional bronchoscopy suite where a trained bronchoscopy nurse under the supervision of the bronchoscopist administers conscious sedation. Meanwhile, rigid bronchoscopy or procedures that require general anesthesia are commonly performed in the operating room [28]. In recent years, interventional bronchoscopy departments that perform a large number of procedures on a daily basis have resorted to designing interventional bronchoscopy suites in collaboration with the anesthesia department at their practice. These specialized bronchoscopy suites are designed to be a replica of an operating room allowing the bronchoscopists to perform more procedures under MAC or general anesthesia in the bronchoscopy suites. Interventional bronchoscopy suites have been operational for several years with great success in several centers in the United States and Europe [29].

Airway Devices

Procedures performed under conscious sedation or MAC require no invasive airway devices. Meanwhile, the patient's oxygenation should be

monitored by pulse oximetry, and supplemental oxygen should be delivered to maintain patient saturation above 90% during the procedure and in the recovery area [13].

- Laryngeal mask airway (LMA)
  The LMA was first introduced more than 20 years ago and is still used today, with a consistently low incidence of complications. The LMA is an ideal airway device for advanced bronchoscopic procedures. The large diameter of the shaft of the LMA makes it easy to insert large therapeutic bronchoscopes without compromise to the ventilation. The LMA also allows the bronchoscopist to inspect the entire length of the airway from the vocal cords to the distal large bronchi. Additionally, the LMA allows free mobility of the bronchoscope in the airway when compared to an ETT. A bite block needs to be inserted around the LMA. Alternatively, the I-gel version of the LMA has a built in bite block. The disadvantages of the LMA are the lack of protection against aspiration and the inability to obtain adequate seal during positive pressure ventilation particularly in patients with oral, pharyngeal, or laryngeal deformity secondary to airway pathology or radiotherapy. It is important to note that the LMA was originally designed for spontaneously ventilating patients; however, positive pressure ventilation can be performed, with a limitation on the maximum peak airway pressure of 20 cm H_2O in order not to overcome the tone of the lower esophageal sphincter and insufflate the stomach with oxygen [30, 31] (Fig. 5.3).
- Endotracheal tube (ETT)
  Although an ETT is the most definitive and most reliable airway devices in patients undergoing general anesthesia, an ETT has challenges when inserted in a patient with central airway obstruction undergoing a therapeutic bronchoscopic procedure. Insertion of the ETT does not allow the bronchoscopist to examine the vocal cords and the upper part of the trachea for pathology. The large external diameter of the therapeutic flexible bronchoscope requires the insertion of an ETT with an internal diameter of 8.5 or 9 mm in order to deliver adequate ventilation around the bronchoscope. The length of the ETT projecting from the patient's mouth limits the length of the flexible bronchoscope available for insertion into the airway, and the proximal end of the ETT is commonly cut off. Insertion of an ETT in a patient with pre-existing tracheal or bronchial stents carries a risk of dislodging or deforming the stents, which can potentially result in airway compromise [32] (Fig. 5.4).
- Rigid bronchoscope
  The rigid bronchoscope is an ideal airway device in complicated interventional bronchoscopic procedures where instruments and stents are inserted in the airway. The distal end of the rigid bronchoscope is beveled to allow for lifting of the epiglottis and safer insertion through the vocal cords. The proximal end of the rigid bronchoscope can remain open to air to allow for simultaneous insertion of multiple instruments. Leak of the ventilating gas through the open end of the rigid bronchoscope makes jet ventilation or spontaneous

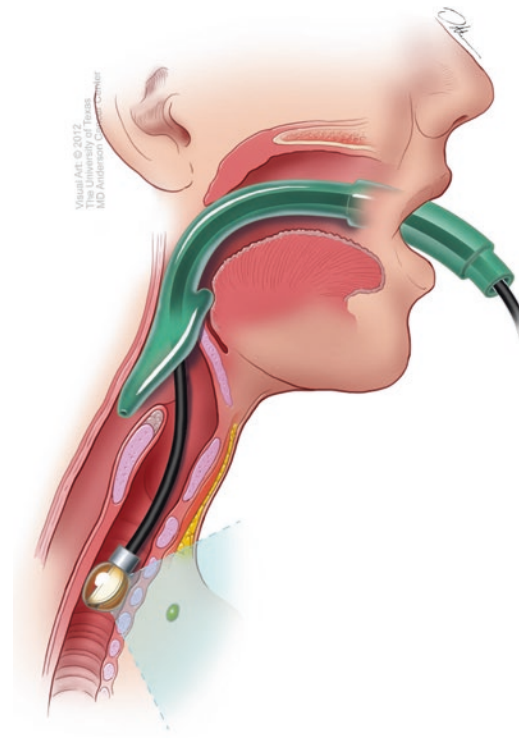

Fig. 5.3 EBUS bronchoscope introduced through LMA

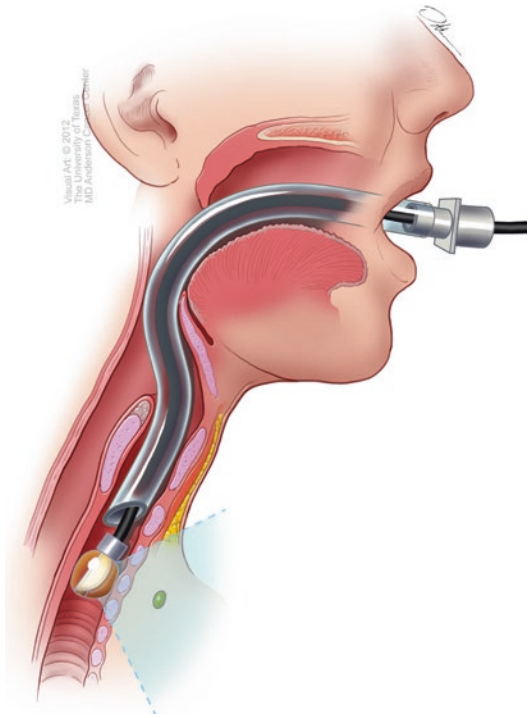

Fig. 5.4 EBUS bronchoscope introduced through ETT

ventilation the only possible mode of ventilation. Alternatively, when a cap is placed to seal the proximal end of the rigid bronchoscope, positive pressure ventilation from anesthesia ventilator can be used. Leak is overcome by inserting a throat pack and Vaseline gauze to occlude the nostrils. A short stainless steel cylinder attached to the proximal end of the rigid bronchoscope has multiple side ports to accommodate a jet ventilator, an anesthesia circuit, and bronchoscopic instruments [33].

The rigid bronchoscope has many advantages over the flexible bronchoscope. These include the ability to provide positive pressure ventilation during lengthy airway procedures and the ability to insert instruments with a large diameter into the airway such as the microdebrider, large suction catheter, and the deployment device for silicone stents. The rigid bronchoscope can also be used as a coring device to debulk airway tumors, dilate stenotic areas, stent the airway open in the case of external airway compression by an anterior mediastinal mass, and tamponade airway bleeding [34].

Modes of Ventilation

- Spontaneous ventilation
  Spontaneous ventilation is necessary in cases when the integrity of the airway is compromised, such as tracheoesophageal fistulas, broncho-esophageal fistulas, and iatrogenic tears in the airway. In such cases, positive pressure ventilation can result in leakage of the ventilating gas (oxygen and/or air) to the mediastinum, the thoracic cavity, and possibly the peritoneum. Anterior mediastinum mass is another indication for spontaneous ventilation because of multiple reports of worsening of the compressive obstruction of the central airway by the mass after a muscle relaxant was given. In addition, spontaneous ventilation is valuable during pleuroscopy, when collapse of the lung on the side of the procedure is essential for visualization.
  Spontaneous ventilation can be easily achieved under conscious sedation, MAC, or general anesthesia. Inhalation anesthetics or intravenous anesthetics with adequate topical anesthesia can be used, without the muscle relaxant, for the insertion of the rigid bronchoscope, LMA, or the ETT. Alternatively, a small dose of the short-acting muscle relaxant succinylcholine can be used for the intubation with rapid regain of spontaneous ventilation.
- Assisted ventilation
  In a patient with an airway device in place, ventilation can be assisted by multiple modalities to overcome hypoxia and/or hypercapnia associated with spontaneous ventilation under general anesthesia. For example, intermittent hand-bag ventilation with a large tidal volume, pressure support, or synchronized intermittent mandatory ventilation can be used to overcome atelectasis and improve saturation and CO_2 elimination during bronchoscopic procedures.
- Noninvasive positive pressure ventilation (NIV)
  NIV, commonly used for patients with sleep apnea, has been described as beneficial in hypoxemic patients undergoing bronchoscopy with anesthesia. Modified nasal or fullface

masks, with a special adaptor to allow for the insertion of the bronchoscope, can be used. NIV should be considered when endotracheal intubation and mechanical ventilation is suspected to carry an increased risk to the patient undergoing bronchoscopy. The use of NIV ventilation was shown to improve oxygenation and reduce the risk of acute respiratory failure after bronchoscopy in patients with impaired baseline oxygenation, such as chronic obstructive pulmonary disease (COPD) patients with pneumonia or immunocompromised patients [35, 36].

- Positive pressure controlled mechanical ventilation
  Patients undergoing interventional bronchoscopic procedure that require muscle relaxation need mechanical ventilation. Mechanical ventilation can be delivered through the LMA, ETT, or rigid bronchoscope. When the LMA is the airway device of choice, the peak airway pressure should be kept below 20 Cm H_2O to avoid opening the lower esophageal sphincter and inflating the stomach. Mechanical ventilation through the rigid bronchoscope is associated with leak around and through the rigid bronchoscope. To overcome such leak, insertion of a throat pack, occlusion of the nostrils with Vaseline gauze, capping of the rigid bronchoscope ports, and high oxygen flow rates with high tidal volumes are needed.
- Jet ventilation
  Jet ventilation can be performed using a handheld device through which 100% oxygen is injected into a port at the proximal end of the rigid bronchoscope. The pressure of the injected oxygen can be adjusted with a dial; the frequency of ventilation is left to the operator to select and frequently ranges from 8 to 20 breaths per minute. Jet ventilation should be performed only when the proximal end of the rigid bronchoscope is open to air, to avoid barotrauma [37]. Air is entrained at the open proximal end of the rigid bronchoscope, causing variation in the delivered FiO_2.
- Electronic mechanical jet ventilation
  The mechanical jet ventilator (Acutronic Medical Systems, Hirzel, Switzerland) has many advantages over the simple handheld jet ventilators [38]. The user can control the FiO_2, the frequency of ventilation (up to 150 breaths per minute), and the driving pressure of ventilation (up to 40 mmHg). The inspired oxygen can be humidified up to 100%, enabling prolonged jet ventilation without the risks of airway mucosal dryness and necrosis or damage to ciliary function [38]. In addition, the mechanical jet ventilator has two alarms to protect against barotrauma and will discontinue ventilation if the set maximum airway pressure limit is reached.

Post-procedure Care

After interventional bronchoscopic procedures, patients should be transported to a standard designated recovery area with well-trained nursing staff. The recovery unit is generally equipped with wall oxygen, vital signs monitors, crash carts, and emergency intubation equipments. In patients who have undergone general anesthesia or who remain deeply sedated at the end of the procedure, supplemental oxygen should be continued via a face mask or a nasal cannula and weaned off gradually. Patients should be observed until they meet discharge criteria (i.e., for 30–45 min). Residual muscle relaxation or post-procedure respiratory failures for a variety of reasons are possible complications that may require intubation, unplanned hospital stay, and/or likely ICU admission.

Upon discharge, all patients should be advised in writing and verbally not to drive, sign legally binding documents, or operate machinery for 24 h after the procedure. A responsible adult should accompany the patient home.

Conclusion

The field of interventional bronchoscopy has been evolving and becoming more sophisticated, as has the field of anesthesiology. As a result, the older techniques of local anesthesia may not be as well suited for new, complex, prolonged bronchoscopic procedures. Communication between interventional

bronchoscopy departments and anesthesiology departments is necessary to delineate when anesthesia services are needed and where certain bronchoscopic procedures should be performed. Recent advances in the field of anesthesiology render both conscious sedation and general anesthesia for interventional bronchoscopy safe, and the use of these advances is invaluable for the continued growth of the field of interventional bronchoscopy.

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Evaluation of Outcomes After Interventional Procedures

6

Teruomi Miyazawa and Hiroki Nishine

Interventional Procedure

Inoperable central airway stenosis due to a malignant tumor is a relatively common condition and may be life threatening. Because of the poor prognosis, palliative methods are needed to maintain airway patency. In patients with severe malignant airway stenosis, interventional bronchoscopy is considered as a method of maintaining airway patency [1].

Flow limitation during forced expiration is affected by the relationship between transmural pressure (P_{tm}) and the cross-sectional area (A) of the airway. The wave speed is dependent on the stiffness of the airway wall, i.e., dP_{tm}/dA, and on the cross-sectional airway itself [2, 3]. The flow-limiting segment (FLS) occurs originally where the cross-sectional area of the airway is the narrowest. On the basis of wave-speed concepts of maximal expiratory flow limitation, stenting at the FLS improved expiratory flow limitation by increasing the cross-sectional area, supporting the weakened airway wall and relieving dyspnea [4, 5].

Assessment of Flow–Volume Curve

The location of the FLS is assessed using flow–volume curves. Analysis of the flow–volume curve can be used to define the nature of the stenosis and provide reliable information on the efficacy of stenting [5–10]. In patients with tracheal stenosis, the flow–volume curve shows a marked reduction of the expiratory flow (fixed narrowing patterns) with a plateau. In patients with bronchial stenosis, the flow–volume curve shows decreased flow with expiratory choking (initial transient peak flow followed by acute flow deterioration and consecutive low flow and dynamic collapse patterns). In patients with carinal stenosis, the flow–volume curve shows a descending expiratory limb with a plateau and choking (combined fixed and dynamic patterns). In patients with extensive stenosis from the trachea and carina, extending to the bronchi due to tumor and/or mediastinal lymphadenopathy, the flow–volume curve shows severe reduction of the expiratory flow (complex patterns containing elements of all the former).

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Dyspnea

The degree of dyspnea depends on the degree of airway obstruction and becomes severe when well over 70% of the tracheal lumen is obstructed [11]. In cases with 50% *tracheal obstruction*, the highest velocities are in the jet, which is generated by glottic constriction. In cases with over 70% *tracheal obstruction*, peak velocities are generated at the stenosis and exceed velocities in the glottic area. Pressure differences changed dramatically from 70% *tracheal obstruction*.

The relation between the baseline degree of *tracheal obstruction* and the changes in MMRC (ΔMMRC) is shown in Table 6.1. Any patient with an improvement in the MMRC scale of 2 or more was considered to be a clinical responder. The clinical responder rate was 84.6% for obstructions above 80 and 58.8% for obstructions between 50 and 80%. Preoperation measures by the baseline degree of *tracheal obstruction* could be used to predict the postoperation impact on dyspnea [12].

Assessment of Lateral Airway Pressure

Analysis of the flow–volume curve could be used in defining the nature of the stenosis. However, flow–volume curves cannot identify the precise location of the lesion where airway resistance increases, nor can it immediately define the outcome of stenting.

With the use of airway catheters in dogs [13–15] and in human subjects [16–18], the FLS could be located by measuring lateral airway pressure (P_{lat}) during induced flow limitation generated by either an increase in pleural pressure or a decrease in downstream pressure. Healthy subjects have relatively uniform pressure drop down of the bronchial tree during expiration. In patients with airway stenosis, the major pressure drop occurs across the stenosis. By measuring P_{lat} on each side of the stenosis, we could detect the pressure difference between two sites (proximal and distal) of the stenotic segment [12].

After intubation, a double lumen airway catheter was inserted into the trachea during bronchoscopy. P_{lat} was measured simultaneously at two points during spontaneous breathing with light general anesthesia before and after intervention. P_{lat} at the two points was plotted on an oscilloscope (pressure–pressure (P–P) curve). The angle of the P–P curve was defined as the angle between the peak inspiratory and expiratory pressure points and the baseline of the angle. If the cross-sectional area (CSA) was small, then the angle was close to 0°; however, after intervention, the CSA significantly increased and the angle was close to 45°.

In healthy subjects, no pressure difference between the carina and trachea was observed (0.10 ± 0.22 cm H_2O) during tidal breathing (Fig. 6.1a). The P–P curves were linear and the angle of the P–P curve was close to 45° (44.6 ± 0.98) (Fig. 6.1b).

In patients with *tracheal obstruction*, dyspnea scale, pressure difference, and the angle changed significantly beyond 50% obstruction (Fig. 6.2a, b). After stenting, the pressure difference disappeared and the angle was close to 45°. The degree of *tracheal obstruction* was significantly correlated with the pressure difference and the angle ($r = 0.83$, $p < 0.0001$, and $r = -0.84$, $p < 0.0001$, respectively) [12].

Table 6.1 Relation between the baseline degree of *tracheal obstruction* and the change in MMRC after interventional bronchoscopy

Degree of tracheal obstruction (%)	ΔMMRC[a]		Responders[b] (%)
	≦1	≧2	
51–60		2	
61–70	2	2	10/17 (58.8%)
71–80	5	6	
81–90	2	9	11/13 (8406%)
91–100		2	

[a]ΔMMRC = change in MMRC scale
[b]ΔMMRC responder = improvement in MMRC scale of 2 or more

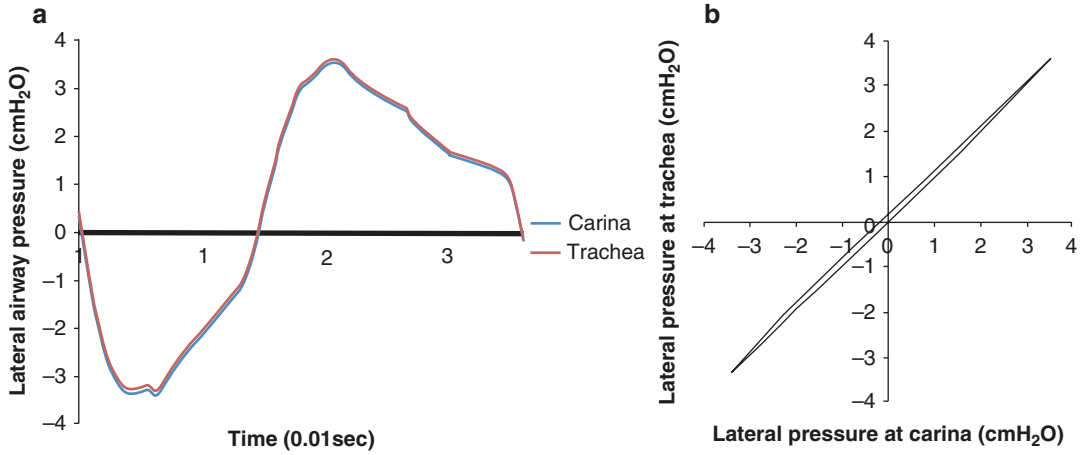

Fig. 6.1 Typical patterns of lateral airway pressure (P_{lat}) measurements during tidal breathing in a *healthy subject*. P_{lat} is measured simultaneously at two points (upper trachea and carina). There are no pressure differences between the carina and upper trachea (**a**). (*Blue*, carina; *red*, upper trachea.) The angle of pressure–pressure (P–P) curve is defined as the angle between peak inspiratory and expiratory pressure points and the baseline of the angle. The P–P curves are linear and the angle of P–P curve is close to 45° (**b**)

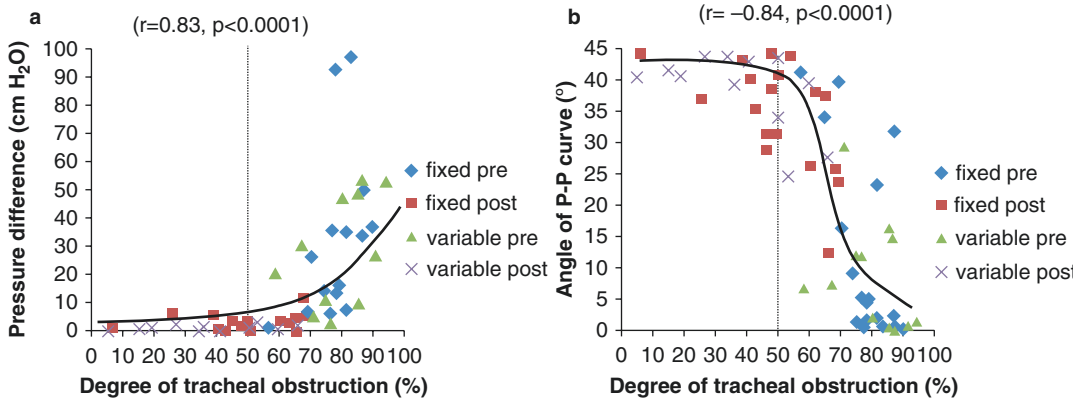

Fig. 6.2 Scatter plot of pressure difference and the angle of the pressure–pressure (P–P) curve versus the degree of *tracheal obstruction*. *Blue diamonds* show before intervention and *red squares* indicate after intervention in cases with *fixed stenosis*. *Green triangles* show before intervention and *purple Xs* indicate after intervention in cases with *variable stenosis*. *Dotted line* shows the threshold for 50% *tracheal obstruction*. The pressure difference (**a**) and the angle of P–P curves (**b**) are significantly correlated with the degree of *tracheal obstruction*. The pressure difference increased significantly above 50% obstruction (**a**). When the cross-sectional area was small, the angle of the P–P curve was close to 0°. After interventional bronchoscopy, the cross-sectional area increased and the angle of the P–P curve was close to 45° (**b**)

This approach identified a need for additional treatment during interventional bronchoscopy. In a patient with *fixed intrathoracic stenosis* due to tracheal tuberculosis, CT showed a tracheal stenosis at the middle trachea (Fig 6.3a). Before treatment, a considerable pressure difference between the upper trachea and carina was noted (Fig. 6.3d), and the angle of the P–P curve was 0.3° (Fig. 6.3i). The flow–volume curve shows marked reduction of the expiratory and inspiratory

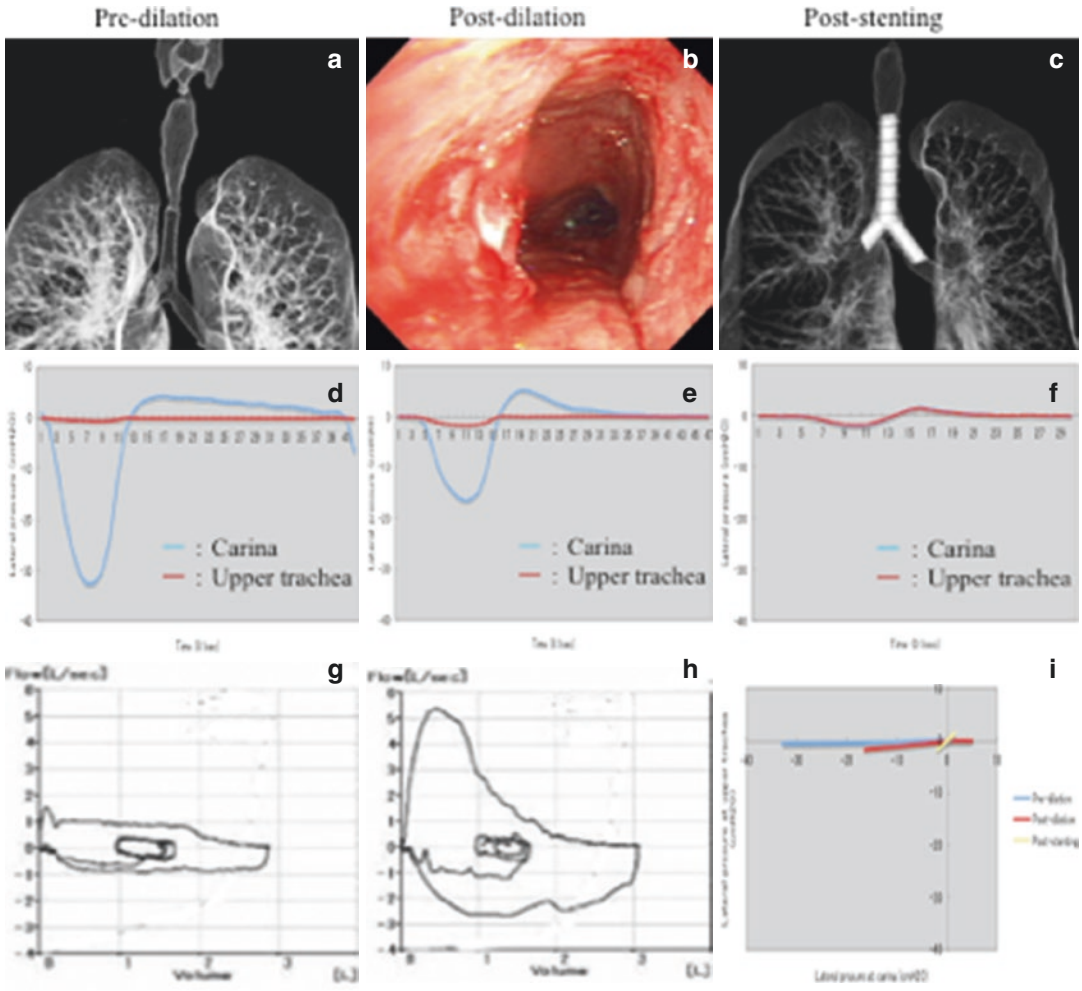

Fig. 6.3 Lateral airway pressure (P_{lat}) measurements during interventional bronchoscopy with balloon dilation and silicone Y stent implantation in *fixed intrathoracic stenosis* due to tracheal tuberculosis (before treatment, *panels* (**a**, **d**, and **g**); after balloon dilation, *panels* (**b** and **e**); after stenting, *panels* (**c**, **f,** and **h**)). P_{lat} was measured simultaneously at two points (the upper trachea and carina). *Blue line* shows P_{lat} at carina and the *red line* indicates P_{lat} at upper trachea (**d–f**). After each treatment, the angle of P–P curve showed a stepwise improvement over the interventional procedures (**i**). See text for further explanation

flow (Fig. 6.3g). After balloon dilation, bronchoscopic imaging revealed greater patency for the trachea (Fig. 6.3b). However, the pressure difference only decreased from 36.6 to 20.1 cmH_2O (Fig. 6.3e), and the angle of the P–P curve only increased from 0.3° to 5.0° (Fig. 6.3i). Subsequently, a silicone Y stent was implanted from the upper trachea to the both main stem bronchi. After stenting (Fig. 6.3c), pressure differences disappeared (Fig. 6.3f), and the angle of the P–P curve increased from 5.0° to 35.8° (Fig. 6.3i). The MMRC scale decreased from 2 to 0 and flow–volume curve returned to a near-normal pattern (Fig. 6.3h). Measuring P_{lat} could estimate the need for additional procedures better than bronchoscopy alone. The direct measurement of the pressure difference and the angle of pressure–pressure curve is a new assessment modality for the success of interventional bronchoscopy.

Analysis of Pressure–Pressure Curve

Central airway stenosis can be divided into four major types: *fixed*, *variable*, *extrathoracic*, and *intrathoracic stenosis*. In *fixed stenosis*, the CSA at the site of the lesion does not change during the respiratory cycle, and the P–P curve was linear. In *variable stenosis*, the configuration of the stenotic lesion changes between phases of respiration. Airway narrowing occurs during expiration in *intrathoracic stenosis*, whereas airway narrowing occurs during inspiration in *extrathoracic stenosis*. In *variable extrathoracic stenosis*, the angle of the P–P curve during inspiration is smaller than during expiration, and in *variable intrathoracic stenosis*, the angle of the P–P curve during expiration is smaller than during inspiration.

Conclusions

Placement of the stent at the flow-limiting segment (FLS) provided the greatest functional benefit to patients with central airway stenosis [4, 5]. Although bronchoscopic imaging showed that tracheal patency was restored after procedures, the angle of P–P curve did not always improve. It is difficult to estimate the outcome of interventional procedures by bronchoscopy alone. When the location of the FLS is assessed using flow–volume curves, the pressure difference and the angle of pressure–pressure curve are able to immediately estimate the outcomes of interventional bronchoscopy in real time.

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Bronchoscopy Education: New Insights

7

Henri G. Colt

"Tell me and I'll forget; show me and I may remember; involve me and I'll understand."
Chinese proverb

Background

I have always been amazed that medical education involved learning "on" patients as well as from them. Many years ago, surrounded by other medical students, I positioned myself so as to stand directly beside my senior resident as he prepared to perform a lumbar puncture. Erect in our long white coats, leaning inward with anticipatory curiosity and awe, we marveled at the way he told the patient what he was going to do before ordering her to turn onto her side. After prepping the skin, he inserted the spinal needle effortlessly. We cringed collectively, however, as it was repositioned, causing the patient to cry out in pain. We sighed with relief when a clear fluid suddenly appeared, and the procedure finished; we admired the authoritative tone with which our resident informed this small, frail, and frightened 18-year-old girl with sweat-drenched hair and a poorly fitting hospital gown that uncovered her bare buttocks and lower back that she must lay quietly for several hours and that everything was going to be fine. As we followed the resident out of the room (the ward had several patients, all of whom had been watching us), we felt important in our white coats. Like a swarm of flies around a picnic table covered with food, we excitedly spoke about how cool the resident had been and how easy the procedure seemed. Later that afternoon, I recalled that we had never been told the patient's name nor been introduced to her as she lay passively on her bed. We were not given much of an explanation about the procedure either, and I had not yet had the opportunity to watch others before I was told the very next morning to "go tap that patient in bed 3."

Until very recently, medical training has followed guidelines established by Flexner and Halsted in the early twentieth century [1]: A stepwise postgraduate training program is designed within a "see one, do one, teach one" paradigm, with patients serving as teaching material. Trainees gradually achieve independence from faculty supervision as they progress through their years of apprenticeship. Competency is often presumed based on numbers of procedures performed, and objective measures of knowledge (high-stakes tests) are used for licensure and certification purposes [2].

Today, "see one, do one, teach one" is no longer an acceptable paradigm of procedure-related medical instruction, so patients need no longer suffer the burden of procedure-related training. Furthermore, teachers need no longer devote hours to enumerating facts and figures related to medical illnesses because educational media are increasingly accessible, with information at the fingertips and on the computer screens of

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health-care providers and patients alike [3]. Using inanimate and computer-based platforms, technical skills can be practiced independently or under supervision; structured curricula help assure a foundation of knowledge regardless of the diversity and variability of the clinical setting, and new norms and expectations governing professionalism help guide physician behaviors that promote respect for patient autonomy and shared decision making.

These early twenty-first century learning environments empower both teacher and learner. Benefitting from a bidirectional learning process, they are able to explore together many new and exciting roles. Digital simulation allows students to practice procedures before ever going to the patient's bedside, and, as new delivery systems for instructional materials replace conventional textbooks, enhancing the portability, access, and design of information, both learners and teachers can devote more time to learning *how to think* or *how to teach*, rather than on rote memorization and content development [4]. The availability of web-based instruction, use of interactive case-based exercises, role-playing sessions, opportunities for individualized instruction, and an open forum where teachers serve more as coaches or wise elders free teachers from their podiums. Low-stakes assessment tools and self-assessments can be used to identify areas that warrant remedial training, as well as to document one's progress toward competency and proficiency because at the bedside and in the classroom, the implementation of new models of instruction allows educators more time to build personal relationships with learners. Learners benefit from this because face time with instructors can be used to encourage learning through positive reinforcement, provide key insights into a procedure or management decision, enhance intrinsic motivation, and discover fun in learning. Learning curves may thus be climbed with greater confidence and comfort in a truly caring education environment.

Taking the liberty to depart from a conventional chapter devoted to science and literature review, my objectives in the following paragraphs are instead to (1) address major elements of curricular structure and delivery, (2) provide an example of how a structured curricular approach using a combination of onsite and online materials such as those provided in the Bronchoscopy Education Project might facilitate learning, (3) describe how assessment tools might help guide the educational process and assure procedure-related competency, and (4) discuss how an ethics of teaching underlies and justifies the paradigm shift occurring in today's world of medical procedural education. While flexible bronchoscopy and airway procedures are used as models for discussion, much of what I write is applicable to other areas of procedure-related medicine.

Curricular Structure and Delivery

Bronchoscopy is performed by a variety of medical and surgical specialists including pulmonologists; thoracic surgeons; ear, nose, and throat specialists; anesthesiologists; and intensivists. Indications vary from simple inspection to diagnosis of lung and airway disorders, assistance with intubation, and therapeutic procedures to remove foreign bodies, restore airway patency, and treat emphysema, asthma, or cancer, to name but a few. There does not appear to be a universally accepted convention by which to teach the technical skills required to perform this procedure, nor to introduce learners to the complexities of a bronchoscopy-related consultation.

In many institutions, the bronchoscopy learning experience is variable, in part because of diverse practice patterns and patient referrals but also because of different teaching interests, methodologies, and time committed to the educational process [5]. In fact, despite its existence since the late 1960s, many questions remain regarding the clinical practice of flexible bronchoscopy. The variability of equipment used and resources available for teaching further complicates matters when contemplating a global approach to the educational process. Videobronchoscopes, for example, are used in most prosperous areas of North America, Europe, and the Middle East, whereas flexible fiberoptic bronchoscopes are still the workhorses of South Americans and many developing

countries in Asia. Techniques are also controversial: Should the scope be held in the left of the right hand? Where should assistants stand? Should the procedure be performed from the head or from in front of the patient? Should the patient be supine or semi-erect? What kind of sedation, if any, should be used? Are universal precautions, including gown, gloves, and protective eyewear, always necessary, and how should equipment be cleaned? Finally, who should be considered able and competent to perform the procedure? Could it be performed by nonphysician providers in specific settings such as an intensive care unit or as part of a lung donor eligibility assessment, or should bronchoscopy remain a physician-only performed procedure? Should training and certification processes be different depending on medical specialty? Should bronchoscopy privileges extend to all types of procedures, or should only certain specialists perform certain types of procedures? How many procedures should one perform to be deemed competent, and if numbers are used as a metric, how many must be performed each year to maintain competency? If they are not used as a metric, what assessment and testing tools might be employed to assure that procedures are performed safely and competently?

Table 7.1 What we know about bronchoscopy education today

• Various learning and teaching modalities are and can be complementary
• Didactic lectures can be conveniently accessed off-site though the use of the Internet
• Well-edited videos can replace watching cases performed in real time, without jeopardizing patient care or programmatic structure
• A learner's active engagement time is maximized if less time is devoted to hands-off demonstrations, and more time is spent assisting learners with clearly identified hands-on skill sets and exercises
• Participation in problem-solving and critical thinking (practical approach, case-based) exercises helps assure procedural safety, effectiveness, efficiency, and systems-based practice and tells instructors "how" learners think and process information
• The sacrifice of live animals for practice purposes has been rendered unnecessary because cadavers, inanimate models, and computer-based simulation are excellent, proven, and cost-efficient alternatives
• Assessments and outcome metrics help identify a learner's position along the experience curve, ascertain knowledge, and measure technical skill acquisition. Insights are provided regarding a program overall effectiveness, and assessments identify weaknesses that can be corrected through remedial, individualized training
• A "Bronchoscopy university at your fingertips" is possible using portable tablets and mobile devices. This increases access to learning materials and helps achieve a democratization of knowledge, whereby bronchoscopy training is more uniformly achievable regardless of one's place of work or practice

What Is a Bronchoscopy Curriculum?

In most countries, there is no fixed curriculum pertaining to bronchoscopy education (Table 7.1). It is assumed that physicians in various specialties become competent in the procedure as a result of their subspecialty training. In the United States, where more than 500,000 bronchoscopies are performed each year, there is no uniform structure for bronchoscopy training other than learning during residency or fellowship [6]. Nor is there a standardized method by which technical skills and procedure-related knowledge are assessed. In fact, very few questions (usually less than five) are devoted to bronchoscopy on subspecialty board examinations, even though it is the major minimally invasive procedure performed by chest physicians.

Surveys pertaining to flexible bronchoscopy in countries as diverse as Singapore, Great Britain, India, Poland, Egypt, and the United States consistently identify variations in practice and training [7–9]. This diversity derives from a lack of uniform requirements, paucity of structured curricula, absence of validated measures of competency and proficiency, unequal access to learning materials, variability of patient-based learning experiences, and differences in skill, interest, and teaching abilities of medical practitioners designated as bronchoscopy instructors. Furthermore, the lack of a uniform competency-based framework for bronchoscopy education makes it difficult for physicians already in practice to acquire new skills.

A curriculum (noun, plural of which is cur-ric-u-la or cur-ric-u-lums) can be defined as a group of related courses, often in a special field of study [10]. As such, it pertains to the purpose, content, activities, and organization inherent to an educational program [11]. There are many challenges that must be overcome, however, as one contemplates curricular structure [12]. Some of these are related to conceptualizing the instructional process and defining meaningful learning experiences. Others relate to tradition, availability of resources, variability of deeply held beliefs and teaching styles, and the paucity of bronchoscopy education-related research.

Instructional Process and Defining Meaningful Learning Experiences

John Dewey (born 1859–1952), probably one of America's most influential philosophers, wrote "the belief that all genuine education comes about through experience does not mean that all experiences are genuinely or equally educative" [13]. For health-care providers, being obliged to perform what might be for the first time, albeit with guidance, a procedure in a patient is both discomforting and anxiety-provoking. A social mandate for accountability and truly informed consent will make it increasingly difficult for practitioners to learn by doing. In addition, such a learning environment creates an ethical dilemma for the competent instructor being asked to advocate for efficient, evidence-based, cost-effective quality of care and who knows that he or she can perform the procedure more quickly and more efficiently and with greater patient comfort than the learner. These arguments justify, whenever possible, a more widespread use of simulation-based bronchoscopy training.

Changes in the perception of the educational process have resulted from modifications of medical education systems. In the United States, for example, the Accreditation Council of Graduate Medical Education currently advocates a competency-based training model that replaces one based on process and number of cases performed [14]. Great emphasis is placed on objective measurements of competency, including elements of professionalism, systems analysis, and health-care team development. In designing a bronchoscopy curriculum, therefore, one must consider how learning processes reach beyond technical skill development to involve the cognitive, affective, and experiential forms of knowledge, as well as how knowledge acquisition and retention might be assessed both during and after training [15]. In my opinion, these arguments, particularly in view of the expansion of bronchoscopic practice,[1] give good reason for a more structured approach to bronchoscopy training. One such approach might include a curriculum that includes recommended reading assignments, case-based and problem-based learning exercises [16], hands-on simulation and real patient-based procedure performance, low-stakes assessments to document progress along the learning curve [17], individual learner-centric training opportunities, and outcome metrics [18] to identify strengths and weaknesses of continued medical education programs as well as the effectiveness of courses and seminars on both individuals and groups.

From a learner-centric perspective, therefore, bronchoscopy education should entail elements of critical thinking, problem-solving, ethical values and behaviors, mastery of critical facts and figures, mastery of certain technical skills unique to each type of procedure being performed, self-realization, self-esteem and emotional stability, safety, and an ability to effectively and efficiently integrate procedural practice into one's institution-based medical practice. While much of this is presumed to be learned during traditional apprenticeship-style training, various components are often not documented, and in most

[1] Bronchoscopy is increasingly used to diagnose and treat patients with a variety of lung and airway disorders. Therapeutic procedures such as bronchial thermoplasty, endobronchial valve insertion, and airway stent placement have been added to the traditional interventional pulmonology armamentarium. Additionally, evolving acoustic and optical technologies augment diagnostic capabilities, and the need for greater amounts of tissue for tumor markers and other lung cancer-related analyses is expanding the role of bronchoscopists in the area of cancer management.

institutions, from what I have been told by many bronchoscopy experts, no precise written curricular structure is in place.

Despite increasing patient care responsibilities and the stress of providing cost and time-effective quality care, many bronchoscopists create time in their busy schedules in order to devote themselves to the educational process. From a teacher's perspective, such unselfish involvement might be enhanced if curricular elements were developed in a manner that is time and cost-efficient, nonalienating, and conducive to individualized and collective learning. Some educational methodologies and curricular content, for example, could be standardized to the extent that a generally accepted or more uniform foundation of facts and philosophies becomes available and can be integrated into various individual and group educational venues (i.e., clinical settings, online or computer-based programs, postgraduate seminars, online and onsite courses).

All of us, regardless of our experience and level of competence or expertise, can benefit from pedagogical technical assistance. As new concepts, learning materials, and techniques are introduced into practice, faculty development programs could be used to enhance teaching skills, assure continuity and growth, and develop educational resources. During these venues, experiences could be shared regarding the advantages and challenges of moderating small group interactive learning sessions, using presentations and audience participation software, and integrating video, other media, real-time decision trees, instant messaging, Twitter, tablet PCs, or writing boards into educational programs (Figs. 7.1 and 7.2).

While a mentor's behaviors might readily be emulated after observation, it is unrealistic to expect that the ability to teach effectively comes naturally to everyone. Of course, many physicians are excellent teachers, but the assumption that a medical doctor is a natural-born instructor represents, in my opinion, a significant shortcoming of our academic philosophy and runs contrary to assumptions in other professions such as public education and sports, where particular emphasis is placed on learning how to teach. The purpose of faculty development programs, often referred to as train-the-trainer seminars, therefore, is to help motivate, stimulate, inspire, and train professionals interested in serving as role models, mentors, and instructors in the use of diverse educational techniques and methodologies and to develop, provide, and study resources that are incorporated in whole or in part into various learning curricula.

Fig. 7.1 Example of instructor-led small group discussion in Peru. Participants are debating the advantages of using bronchoscopy skills and task assessment tool (BSTAT) in background quiz to develop a common language for airway secretions and mucosal abnormalities

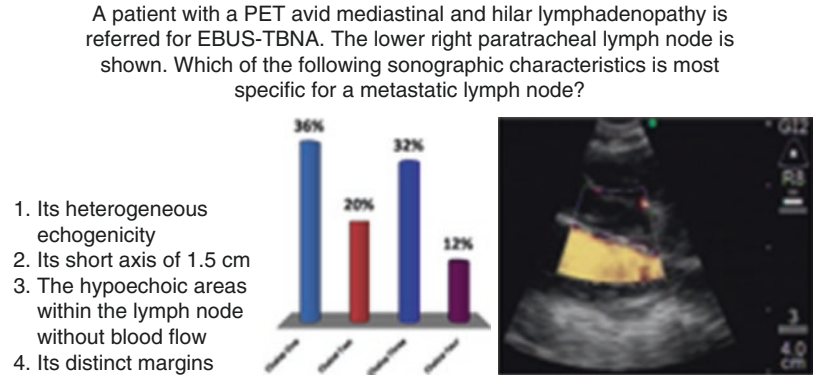


Fig. 7.2 Example of using audience participation software during an interactive question/answer session. In view of the wide variety of responses shown on the graph, the instructor will provide insight regarding each of the possible answers

Tradition, Teaching Styles, and Beliefs

There is a grand tradition in bronchoscopy education. This tradition is twofold. In the first instance, we assume that learners will learn bronchoscopy during the course of their specialty training [19] and that learning will be satisfactory because learners are exposed to different faculty members who might each perform bronchoscopy in a different way (setup, positioning, sedation and medication use, techniques, etc.). Accompanying this is the idea that the complexities of a bronchoscopy-related consultation are always learned while rotating on a specialty consultation service and that all of the items pertinent to such a consultation are satisfactorily addressed, even if they are not explicitly reviewed with the attending faculty (i.e., indications and informed consent, procedure-related strategy and planning, technique and expected results, response to complications, post-procedure management, and follow-up).

The second tradition pertains to the popularity of 1- and 2-day postgraduate courses, devoted until recently and for the most part to physicians already in practice. We have always trusted that these courses were effective and met particular training objectives. For bronchoscopists, the tradition comes from decades of hands-on learning that began with the admired and effective patient-based rigid bronchoscopy instruction programs conducted by Gustav Killian and Chevalier Jackson. In such a program, the expert speaker lectures on a topic, while the learner group listens dutifully. Often, individual experts prepare their lectures with little information or fixed-in-advance knowledge regarding common purpose that might integrate their lectures with content from other talks given during the course. Popular hands-on sessions are organized using animal models and equipment loaned from equipment manufacturers. More recently, computer-based simulation and inanimate models have been introduced. Learners rotate from station to station, listening to experts tell them about a procedure or technique, then watch as he (until recently, most bronchoscopy experts have been male) demonstrates the technique. Then one after another, learners take the scope in hand and do something, some less well than others. Sometimes, live transmissions of cases are included in the program, with either the operator or other faculty member interacting with the audience to discuss indications and procedural techniques.[2]

During these programs, we had always assumed learners would learn by simply being present: preliminary or postcourse assessments are rarely performed and little time is devoted to truly individualizing the learning process. An

[2]Live transmissions carry many challenges not the least of which are that cases may be selected based on the expectant participants, intraoperative decisions might be made solely on the basis of educational or theatrical need, and the operator may be distracted by questions or other interactions with the audience.

objective commentary about these programs, however, might include the following:

1. The complexities of bronchoscopy-related instruction and consultation are increasing in view of the rapid expansion of interventional pulmonology.
2. Time constraints, accountability, concerns for cost-effectiveness, and a mandate for enhanced patient safety and respect make patient-based instruction increasingly problematic, so complementary venues for learning are necessary.
3. Passive learning from listening to a speaker giving a lecture is not as effective as when learners are actively engaged.
4. Critical thinking and problem-solving are rarely addressed, yet these are major components of achieving procedure-related competency.
5. Educational content and the effectiveness of its delivery depend on who prepares the lecture and how it is delivered.
6. Active engagement time (the time the learner is actually devoting to learning by doing) is minimal, consisting of, for example, only 3–5 min per person for a group of five people during a 30-min station session.
7. Specific tasks and learning objectives are often not made explicit at each hands-on station, decreasing the likelihood that a specific skill will actually be enhanced or acquired at the skill station.
8. Substantial time is spent listening to lecturers during didactic as well as hands-on sessions.
9. Baseline knowledge and skill levels of course participants are rarely assessed, making targeted individualized or problem-focused instruction difficult.
10. After they return to their clinical practices, few resources are available to help participants apply and master what they have experienced.

A paucity of studies pertaining to the effectiveness, or lack thereof, of these traditional methods of bronchoscopy education makes it challenging to step out of the box in order to view the abovementioned traditional educational processes differently. It is equally challenging to introduce and potentially justify changing a well-entrenched educational system. The reality is, however, that an older paradigm frequently provides a dynamic vision for what is to come after it. Today, we know that:

1. Different learning and teaching modalities are and can be complementary.
2. Many lectures could be accessed off-site through the use of the Internet.
3. Well-edited videos could replace long periods of watching a transmitted “live” case, without jeopardizing patient care.
4. Not all bronchoscopists, especially myself, are as good at teaching as they could be.
5. Not all lectures provide a foundation of knowledge considered useful or required by learners.
6. Active engagement time can be maximized if less time is devoted to demonstrations. and more time is spent assisting learners as they perform specific skill sets or exercises.
7. Problem-solving and critical thinking needs to become a standard part of bronchoscopy courses because they are essential to the safety, effectiveness, and efficiency of bronchoscopic practice.
8. Animals, veterinary services, cadavers, and animal laboratories are costly and regulated, also prohibiting instructional programs in hotels or congress halls.
9. (9) The unnecessary sacrifice of live animals can almost always be avoided by using inanimate models and computer-based simulation.
10. (10) Metrics are needed to help ascertain knowledge and skill acquisition as well as program effectiveness as part of a competency-oriented program of procedure-related learning.

This list is obviously not exclusive, and many other elements are important in rethinking traditional methods of bronchoscopy

education. Agents of change are necessary to develop and implement different teaching strategies and methodologies across the globe. Industry support is essential to educational programs, and professional societies may need to work together, rather than compete, in order to foster a foundation of information and assure a greater democratization of knowledge. Finally, either/or debates and opposing points of view can be synthesized in a manner that promotes learning and choice, acknowledging both points of view in the context of a broadened educational perspective [20] (Fig. 7.3).

Bronchoscopy Education-Related Research

The bronchoscopy-related literature is gradually supporting the paradigm shift, whereby patients will no longer bear the burden of procedure-related training. In a review pertaining to the use of simulation for bronchoscopy education [21], we noted that simulation helps learners improve procedural efficiency and economy of movement, thoroughness, and accuracy of airway examination and decreases airway wall trauma [22]. In addition to increasing learner satisfaction

EITHER	OR	BOTH-AND SYNTHESIS
Scope handling with the left hand.	Scope handling with the right hand.	Both are correct and impact positioning of bronchoscopy assistants and handling of ancillary equipment. Operator comfort and theching traditions with influence choice.
Operator position from the head of the patient.	Operator position from in front of the patient.	Both are correct and should be learned because either may be necessary depending on procedural setting and indication.
Tests	Assessments	Both are important in improving learning. How should competency be ascertained? Is there a role for Mastery learning? What kind of remedial training may be warranted? How can both be used in the setting of physicians-in-training as well as for physicians already in practice?
Teacher-centered instruction	Learner-centered learning	Teacher-learner relationships are important and allow teachers to assume various roles. New technological platforms create greater opportunities for independent study, collaboration, and long distance learning.
Apprenticeship-style learning	Competency-oriented learning	Both are important as learners take on greater responsibilities. Using new technologies and educational methodologies are likely to help accelerate quality patient care and safety, and allow a more rapid introduction of new procedures and techniques into the patient care arena.
Face-to-face instruction	Online learning	Both are important. Face-to-face instruction and active engagement time, especially during hands on training, takes on even greater value when learners learn using online resources. Face-to-face time can occur though videoconferencing as well as during onsite seminars, and of course at the patient's bedside or in the simulation center.
Learning on patients	Learning using simulation	Both are important. All facets of bronchoscopic knowledge and skill, including elements of professionalism, physician behaviors, procedural techniques, response to complications, and management decision making can be improved upon using inanimate models, computer-based simulation, and by helping learners work through the decision-making process during individual or group learning sessions. These can occur prior to or concurrent with patient-based experiences.
Reading conventional textbooks and articles	Media and technology	Both are important. Reading conventional textbooks may still be helpful, but media and technology are changing the way learners can interact with reading, both online and in print. Videos and interac tive images and text (such as patient-centered exercises and clinical pathways) enliven the learning process and help learners analyze their performance. Articles are easily retrieved today using online informational databases and can be used to justify decision-making and enhance evidence-based quality care practice.
Competency determined based on single institution subspecialty training	Competency determined based on completing a core curriculum that maight be applicable in part or in whole in many	Both are necessary. For example, a curriculum similar to one proposed in the Bronchoscopy Education Project and modified based on institutional needs or medical practice setting (see Figure 4) assures objective monitoring of trainees who attend onsite learning programs, clinical pathways, experience the advantages of simulation, and demonstrate skills using checklists and assessment tools in both the simulation and patient-care environment.

*Inspired from reference #20: Chen M, Education Nation pg 23-24.

Fig. 7.3 Examples of turning either/or debates into both/and syntheses

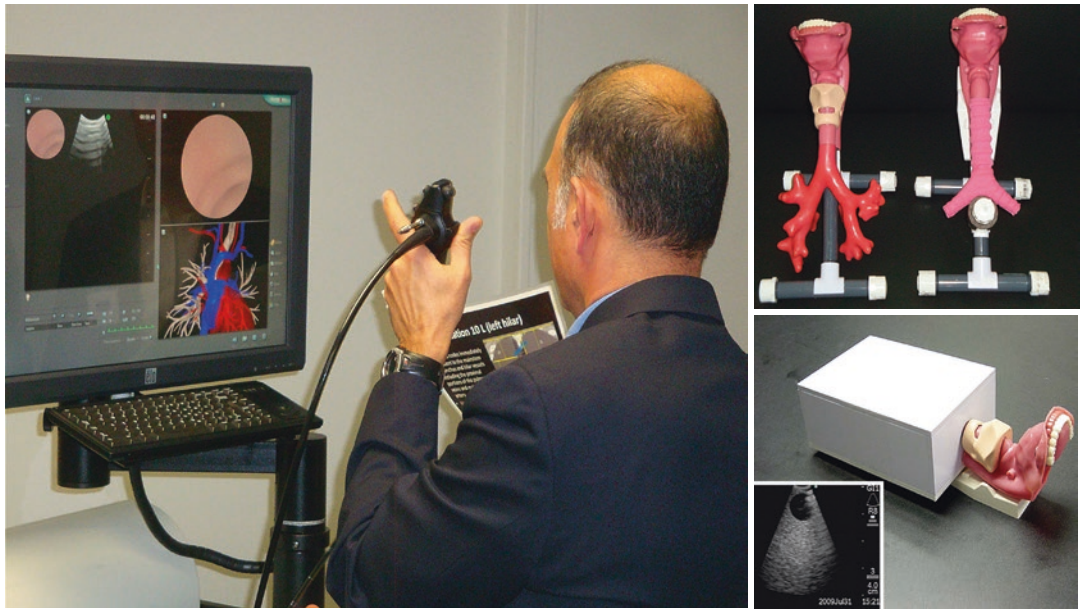


Fig. 7.4 Examples of inanimate and computer-based simulation platforms for learning bronchoscopy. Shown are the Simbionix Bronch Mentor (EBUS module) and inanimate models assembled by Bronchoscopy International: bronchoscopy airway inspection model using bifurcated normal airway from CLA, Germany; transbronchial needle aspiration model using silicone airway from Sawbones Seattle, WA, USA; and inanimate EBUS model using Laerdal Laryngeal structure and ATS Laboratories ultrasound phantom with bifurcated airway and simulated lymph nodes at levels 2, 4, and 7 (ATS Laboratories, Bridgeport, CT)

and interest, simulation allows tasks to be practiced repeatedly without jeopardizing patient safety, and training scenarios can be individualized. Both low- and high-fidelity simulation have been shown to enhance competency in procedural skills while saving time and improving the learning curve [23, 24]. Furthermore, skills acquired through practice on simulators are transferable to the clinical setting [25]. Objective assessment identifies errors and provides opportunities for remedial training [26, 27].

High-fidelity simulation platforms using three-dimensional virtual anatomy and force feedback technology can be used to teach conventional and EBUS-guided transbronchial needle aspiration (TBNA) although less expensive, low-fidelity models comprised of molded silicone excised animal airways and ultrasound phantoms are also effective [28]. The efficacy of a low-fidelity hybrid airway model made of a porcine trachea and a plastic upper airway was demonstrated for learning transcarinal and transbronchial needle aspiration [29]. This model gave learners an opportunity to practice needle insertion, positioning, safety measures, and communication with ancillary personnel. It has since been modified so that a plastic airway is used, obviating the need for discarded animal parts and making the use of such training materials possible in hotel conference centers and nonhospital facilities. Models can also be used to teach scope manipulation and airway anatomy, foreign body removal, bronchoscopic intubation, EBUS-guided TBNA, and other interventional techniques, some of which can also be practiced using high-fidelity computer-based simulation[3] (Fig. 7.4). New, portable computer-based bronchoscopy simulation is becoming available using laptop computers and proxy bronchoscopes.[4]

Demonstrating improvements in technical skill complete only part of the picture [30]. The increasing emphasis on competency-oriented education

[3] See, for example, http://simbionix.com/.

[4] See, for example, http://www.orsim.co.nz/ and http://www.anesthesia.utoronto.ca/edu/cme/bronch.htm.

warrants that bronchoscopy courses also use competency-based measures to assess the efficacy of course curricula and training modalities [31]. Outcome measures might take the form of high- or low-stakes testing in the various cognitive, technical, affective, and experiential elements of procedure-related knowledge [32–34]. Using quasi-experimental study design and a series of pretest/posttest assessments with calculations of absolute, relative, and class-average normalized gain, we have demonstrated the efficacy of a 1-day structured curriculum including a uniform set of didactic lectures, interactive sessions, workshops, and hands-on simulation-based training in flexible bronchoscopy and thoracoscopy [35, 36].

Assessment tools that objectively measure skill and knowledge acquisition will also need to be designed and validated in various learning settings and medical environments [37]. Ideally, their design should be flexible so that instructors with different habits or biases can still incorporate them into their programs without feeling compelled to radically modify their own way of performing procedures. As faculty development programs are integrated into curricular structures, it may become helpful to study their value and contributions to enhanced teaching and learning. Finally, research targeting curricular platforms and the results of educational interventions will contribute to the elaboration of new bronchoscopy instruction-related theories and processes.

The Bronchoscopy Education Project

Developed by Bronchoscopy International[5] in collaboration with many experts from all over the world, the Bronchoscopy Education Project (BEP)[6] has been officially endorsed by several international bronchology and interventional pulmonology societies. Its aim is to complement and hopefully enhance existing educational programs by providing bronchoscopy instructors and training program directors with competency-oriented tools and materials. These may be used to help train bronchoscopists and assess progress along the learning curve from novice to competent practitioner. The curriculum includes *The Essential Bronchoscopist*™ series of books and e-books [38, 39]; a series of training manuals [40]; an encyclopedia of *Practical Approach*© patient-centered exercises that integrate cognitive, affective, and experiential knowledge pertinent to bronchoscopy-related consultation; *Bronchoscopy Step-by-Step*© lessons; a problem-oriented BronchAtlas™ video series[7]; a compilation of PowerPoint-based lecture programs called Fundamentals of Bronchoscopy©; and a set of *Bronchoscopy Assessment Tools*© and Checklists. Material can be integrated in whole or in part, as needed by each program. Learning is based on individual and group study of training manuals, participating in didactic and interactive lecture programs delivered onsite and online, viewing instructional videos on social media sites such as YouTube and Facebook, and participating in deliberate hands-on practice sessions during postgraduate programs and in the course of subspecialty training. Officially supported by and in collaboration with professional medical societies, faculty development programs are being conducted across the globe to help an international group of bronchoscopists, early adopters, and agents of change use these learning materials, improve their presentation skills, create personalized curricula specific to the needs and medical culture of their region, and develop concepts that will strengthen future educational programs. Specific criteria exist by which instructors become certified. A brief description of some of the BEP resources built on the philosophy of using frequent, repeated group and individual exposures to multimedia

[5]Bronchoscopy International is a transnational group of educators and agents of change devoted to the development of educational resources and to the dissemination of bronchoscopy-related knowledge.

[6]The BEP is a work in progress with materials constantly being added. For more information, visit HONcode certified website at www.Bronchoscopy.org and the BronchOrg page on YouTube.

[7]For example, video found at http://www.youtube.com/watch?v=-MP-WdVcCxY

rather than single-medium instruction [41] is found below:

- As part of the *Essential Bronchoscopist*™ series of e-books, *The Essential Flexible Bronchoscopist*© and *The Essential EBUS Bronchoscopist*© are comprised of specific reading materials, learning objectives, and posttests. Each module contains thirty question/answer sets with information about major topics relating to bronchoscopic procedures. The aim of these modules is not to replace the apprenticeship model but to complement in-hospital subspecialty training and to encourage open dialogue between learners and faculty.
- A *Bronchoscopy Step-by-Step*© and *EBUS Step-by-Step*© series of graded exercises help learners acquire technical skills necessary to perform these procedures.[8] Instructional videos are readily viewable on desktop computers as well as handheld devices, IPADs, or cell phones. Specific training maneuvers help the learner practice incrementally difficult steps of bronchoscopy and EBUS-guided TBNA.[9] Steps are designed to enhance the development of "muscle memory" by breaking down complex moves into constituent elements and practicing the separate elements repeatedly before gradually combining them into more complex maneuvers.
- *The Fundamentals of Bronchoscopy*© lecture series includes a compilation of PowerPoint lectures and interactive slide presentations that can be delivered as part of online or onsite courses. Material has been developed with input from many generous experts worldwide and constitutes a uniform collection of learning resources that can be presented by speakers as part of local, regional, or international training programs.
- *The Introduction to Flexible Bronchoscopy* and *The Endobronchial Ultrasound and EBUS-Guided TBNA* are specific training manuals that are available in hard copy as well as in the form of e-books. Each contains program materials, model schedules of 1-day seminars, suggestions for elements of a program completion checklist, specific simulation scenarios, recommended reading assignments, patient-centered practical approach exercises, checklists, and procedure-specific assessment tools. Volumes pertaining to other aspects of bronchoscopic practice are being developed.
- An encyclopedia of *Practical Approach Patient-Centered Exercises* using a four-box approach to bronchoscopy-related consultation (includes elements from the initial evaluation, procedural strategies, techniques and results, and long-term management). Specific scenarios and case resolutions can be used for purposes of individual and group study, assessment, or as content for didactic or interactive lecture sessions.
- *BronchAtlas*™ includes a series of PowerPoint presentations and the BronchAtlas™ video series, a group of concise problem-oriented text files and short, hyperlinked videos designed to address specific issues encountered in daily bronchoscopic practice. Each text (PDF) file enunciates the problem (e.g., bronchoscopy in patients with obstructive sleep apnea) and uses bullet lists to describe the problem with greater detail before providing solutions, a video, and a handful of relevant references. Files can be downloaded onto IPADs and mobile devices for easy review.
- A series of *Bronchoscopy Assessment Tools*© designed as learning instruments provide objective measures of knowledge acquisition. Fixed numeric scores are attributed to learners based on performance of technical skills that include dexterity, accuracy, anatomic recognition, navigation, posture and position, economy of movement, atraumatic instrument manipulation, pattern recognition, and image analysis (Fig. 7.5).

[8] Colt HG. *Bronchoscopy Lessons.* Instructional video pertaining to various aspects of bronchoscopy You Tube (posted 2010): http://www.youtube.com/watch?v=phRv73Ik7fI&feature=related

[9] For example, video found at http://www.youtube.com/watch?v=Z9FdgVx_xrM

EBUS-STAT 10 Point Assessment Tool

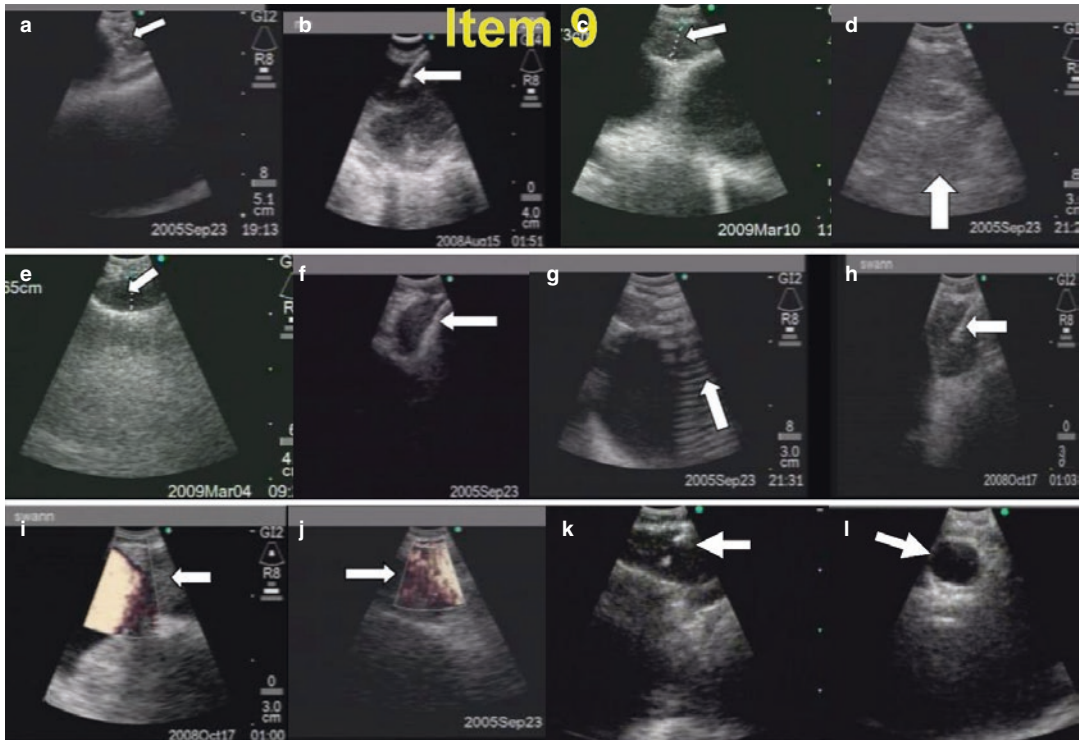
Learner: _____ Year of Training _____
Faculty _____ Date _____

Educational Item* Items 1-10 each scored separately	Satisfactory Yes/No
1. Able to maneuver the scope through upper airway into trachea, without trauma or difficulty (5 points for single item tested) ☐ Mouth and Vocal cords ☐ ET Tube ☐ Laryngeal mask airway	Yes / No Score ____/5
2. Able to maneuver scope using white light bronchoscopy within tracheobronchial tree without trauma (4 points, no partial points) ☐ Scope centered in airway lumen avoiding airway wall trauma	Yes / No Score ____/4
3. Ultrasound image obtained without artifacts (5 points, no partial points) ☐ Absence of artifacts on image, any target	Yes / No Score ____/5
4. Identify major mediastinal vascular structures (4 points per item) ☐ Aorta ☐ Pulmonary artery ☐ Superior vena cava ☐ Azygos vein ☐ Left atrium	Yes / No Score ____/20
5. Identify lymph node station (Select 3 targets, 5 points each) ☐ 2R ☐ 2L ☐ 4R ☐ 10R ☐ 7 ☐ 4L ☐ 10L ☐ 11L ☐ 11Rs ☐ 11Ri	Yes / No Score ____/15
6. Able to operate EBUS processor (2 points each item) ☐ Gain ☐ Depth ☐ Doppler	Yes / No Score ____/6
7. Performance of EBUS-TBNA (1 point each, target 15 points) ☐ Advance needle through working channel (neutral position) ☐ Secure needle housing by sliding the flange ☐ Release sheath screw ☐ Advance and lock sheath when it touches wall ☐ Release needle screw ☐ Advance needle using jab technique ☐ Visualize needle entering target node ☐ Move stylet in and out a few times ☐ Remove stylet ☐ Attach syringe ☐ Apply suction ☐ Pass needle in and out of node 10-15 times ☐ Release suction ☐ Retract needle into sheath ☐ Unlock and remove needle and sheath	Yes / No Score ____/15
8. Image analysis: CT scans (1 point each, target 10 points) ☐ Image 1 ☐ Image 2 ☐ Image 3 ☐ Image 4 ☐ Image 5 ☐ Image 6 ☐ Image 7 ☐ Image 8 ☐ Image 9 ☐ Image 10	Yes / No Score ____/10
9. Image analysis: EBUS views (1 point each, target 10 points) ☐ Image 1 ☐ Image 2 ☐ Image 3 ☐ Image 4 ☐ Image 5 ☐ Image 6 ☐ Image 7 ☐ Image 8 ☐ Image 9 ☐ Image 10	Yes / No Score ____/10
10. Decision-making tasks: (2 points each, target 10 points) ☐ Image 1 ☐ Image 2 ☐ Image 3 ☐ Image 4 ☐ Image 5	Yes / No Score ____/10

* The combined use of the 10 items tests competencies needed to climb the learning curve from novice to advanced beginner to intermediate to competent bronchoscopist able to independently perform EBUS-TBNA.

FINAL GRADE PASS FAIL **SCORE** _____/100

Fig. 7.5 Example of EBUS-STAT (checklist and one component of the EBUS-STAT image quiz), an assessment tool for endobronchial ultrasound, and EBUS-guided transbronchial needle aspiration (*STAT* Skills and Tasks Assessment Tool)



ITEM 9: Match the photo (A-L) to the corresponding 10 EBUS views (Only one response per description)			
____ Station 4R adjacent to pulmonary artery superior vena cava and ascending aorta	____ Needle penetrating through and through	____ Needle missing target node	____ Station 4L adjacent to aorta and pulmonary artery
____ Station 4L adjacent to pulmonary artery	____ Needle within lymph node	____ Normal lung	____ Reverberation artifact
____ Station 7 adjacent to left atrium	____ Hilar node adjacent to normal lung	NO RESPONSE	

Fig. 7.5 (continued)

Using Assessment Tools to Guide the Educational Process

Whether learning to play a musical instrument, participate in a sporting activity, or perform a medical procedure, learning requires acquisition of technical skill, facts (cognition), experience, and an understanding about how we relate emotionally to what we are doing (affect). The effectiveness of the learning process depends, in part, on the frequency, variety, quality, and intensity of the learning encounter, as well as on the presence, quality, interest, skill, and demeanor of the teacher. One's natural talents and predisposition, motivation, and

personality come into play, as do the various written, passive, visual, aural, interactive ways that are used to present learning materials.

Just as tasting is a prerequisite to good cooking, assessments are a fundamental part of learning. In health professions education, written tests, performance tests, clinical observation, and other methods of evaluation such as chart reviews and oral examinations are used as in high-stakes tests for certification[10] or licensure but are also valuable as low-stakes assessments[11] that are part of the learning process during a learner's quest for competency.[12] In this case, they help document progress along the learning curve,[13] identify gaps in knowledge warranting remedial or individualized training, uncover strengths and weaknesses of an educational program, may help identify different knowledge levels among a group of trainees or course participants in order to design a more individualized sequence of training, and help determine congruence with self-assessments performed by learners as part of a feedback or debriefing session [42].

When cognitive knowledge is assessed using standardized tests with written multiple-choice questions or oral interviews, questions should ideally be validated using specific criteria that include testing for difficulty and internal reliability. This may not be absolutely necessary when designing assessment tools where learning is the major objective. Assessments, contrary to tests, have the primary purpose of giving feedback to both teachers and learners about gaps in knowledge and how to improve learning. Technical skill assessments, however, to be of value across a broad range of learners, should probably use measures that are validated in various learning settings, be reliable,[14] and have a strong correlation to the procedure being taught. Checklists can be used to ascertain progress toward competency in various components of a procedure such as ability to obtain informed consent or safe use of fluoroscopy. Checklists also democratize knowledge and have the potential to improve safety and quality of care [43].

It is noteworthy that validity evidence refers to the data and information collected in order to assign meaningful interpretation to assessment scores or outcomes designed for a specific purpose and at one specific point in time [44]. Hence, validity refers to score interpretations and not to the assessment itself [45]. While validity has been traditionally divided into *construct*, *content*, *criterion*, and *face*

[10] *Certification* is defined as a process that provides assurance to the public that a medical specialist has successfully completed an educational program and undergone some type of evaluation, which almost always includes a high-stakes written examination that is designed to test the knowledge, experience, and skills requisite to the provision of high-quality care in that specialty (see ACGME—Accreditation Council for Graduate Medical Education).

[11] *Low-stakes* testing usually does not have pass/fail thresholds or carry significant consequences. Such assessment would be consistent with an educational process that emphasizes a quest toward professionalism and competency (progress along the learning curve) but does not measure skill or knowledge with significant consequences. A *high-stakes* assessment, on the other hand, usually carries significant consequences, such as licensure or pass/fail certification.

[12] *Competency* is the ability gained from knowledge and skills, which forms a basis for performance. To be competent means having the ability to activate and utilize specific knowledge when faced with a problem.

[13] In medicine, a learning curve, also called an *experience curve*, applies to a process where performance improves as a function of practice. This curve may be more or less steep depending on the learner's skill and knowledge, circumstances, and experience and on whether the procedure being learned is new or established. We increasingly tend to differentiate learners into novices, beginners, intermediate learners (also referred to by some as advanced beginners), experienced, and experts, but simpler delineations of beginner, intermediate, and competent practitioner might also be used. Progress along the learning curve usually occurs in steps, with learners remaining or choosing to remain on a particular plateau that itself may have its occasional dips and peaks.

[14] Reliability is defined as the proportion of reproducible data to random noise recorded by the assessment instrument. Using criterion-referenced testing, concrete criteria are established and the individual is challenged to meet them. This explores what proportion of specific content of knowledge and skills the learners know or are able to perform, as opposed to norm-referenced tests that compare an individual's performance to the performances of a group (see http://www.valparint.com/CRITERIO.HTMreference downloaded May 25, 2012).

Introduction to Flexible Bronchoscopy Program
Program Completion Checklist

Educational Item*	Completed Yes/No	Assessment Item	Pass/Fail/Incomplete
1. Participation in regional introductory course	Yes / No	Post-test scores Target 12/20 (60% correct) Score _____%	Pass / Fail / Incomplete
2. Assigned reading: *The Essential Flexible Bronchoscopist*	Yes / No	Post-test scores Target 7/10 (70% correct)	Pass / Fail / Incomplete
Module 1	Yes / No	Score _____	Pass / Fail / Incomplete
Module 2	Yes / No	Score _____	Pass / Fail / Incomplete
Module 3	Yes / No	Score _____	Pass / Fail / Incomplete
Module 4	Yes / No	Score _____	Pass / Fail / Incomplete
Module 5	Yes / No	Score _____	Pass / Fail / Incomplete
Module 6	Yes / No	Score _____	Pass / Fail / Incomplete
3.*Sedation module*	Yes/No	Score _____	Pass / Fail / Incomplete
4. *Fluoroscopy Module*	Yes/No	Score _____	Pass / Fail / Incomplete
5. Informed consent, patient safety, and procedural pause simulation workshops	Yes / No Yes / No Yes / No	IC 10-pt Checklist Target 100% Score _____% on each	Pass / Fail / Incomplete
6. Informed consent, patient safety, and procedural pause patient-based scenarios	Yes / No Yes / No Yes / No	IC 10-pt Checklist Target 100% Score _____% on each	Pass / Fail / Incomplete
7. Practical Approach interactive workshop	Yes / No	Subjective scores Target Pass	Pass / Fail / Incomplete
8. Flexible bronchoscopy simulation workshop	Yes / No	Target scores 100% BSTAT _____% TBLB/TBNA ____%	Pass / Fail / Incomplete
9. Flexible bronchoscopy patient-based scenario	Yes / No	Target scores 100% BSTAT _____% TBLB/TBNA ____%	Pass / Fail / Incomplete
10. Proctored case bronchoscopy checklist	Yes / No	FB 10-pt Checklist Target 100% Score _____%	Pass / Fail / Incomplete

*When completed, learners are assumed to be able to perform flexible bronchoscopy independently. Programs may still require observation and faculty presence based on training regulations and preferences.

Fig. 7.6 Program completion checklist from the Bronchoscopy Education Project's Introduction to Flexible Bronchoscopy curriculum

validity, Downing and others consider construct validity (a test measuring what it is supposed to measure) as the whole of validity and validity evidence as both case and time specific.[15]

The Bronchoscopy Education Project stresses the importance of using a mastery training paradigm, whereby the eventual expected score on an assessment reflects 100% correct responses because operators should ideally be able to master each of the constituent elements of a safe and effective procedure in order to achieve and document competency. The main variable that distinguishes different learners is the slope of the curve, i.e., the time each learner requires to reach a particular educational objective [46]. Different facets of the project, including introduction to bronchoscopy, endobronchial ultrasound, bronchoscopy in the intensive care unit, and interventional bronchoscopy curricula, can be integrated in part or in whole into ongoing training programs. A program completion checklist helps document a learner's participation as shown in

[15] In other words, the evidence presented to support or refute the interpretation assigned to assessment that can be used for one test administration and is not necessarily applicable to a different test administration (see Downing [45, page 22–23]).

this example pulled from the Introduction to Flexible Bronchoscopy Program (Fig. 7.6).[16]

The Ethics of Teaching

"We're Doctors" proclaims actor Harry Connick Jr. portraying Dr. Dennis Slamon[17] in his plea for continued research funding in the Lifetime television movie *Living Proof* (Dan Ireland, 2008), about the discovery of epidermal growth factor Her2 and subsequent development by Genentech of the antibreast cancer drug Herceptin. Perhaps this simple statement, more than any other, justifies taking a new look at how bronchoscopy is both taught and learned.

As medical practitioners dedicated to the health and well-being of our patients, it is paradoxical that for the past 40 years, patients have suffered the burden of bronchoscopy-related training. As availability to technology and computer-based learning increases around the world and the cost of using alternative learning materials such as instructional videos, training models, and simulation decreases, however, educational processes and philosophies inevitably change. Learners are already less dependent on rote memorization, referring frequently to web-based instruction, digital textbooks, electronic information delivery systems, and social communication media available through their computers and handheld mobile devices.

Those interested in the advantages of "scaffolding," a process by which instructional techniques, materials, and other resources are used to structure programs that are conducive to a learner's more rapid ascent of the experience curve, can excitedly revisit ways to package and deliver educational materials. The world is rapidly becoming a global village. By altering our views and practices, health-care education can better reflect society's adoption of new technologies and fulfill an increasingly verbalized directive for provider competency, accountability, professionalism, and expert medical procedural practice.

Much of the intrinsic value physicians accord to medical education is derived from knowing that jobs are well done and that patients are well served. In this sense, both consequentialist (to reduce suffering and avoid retribution) and nonconsequentialist ethical arguments (duty, obligation, and the respect of principles such as beneficence or justice) enhance intrinsic motivation and prompt learners freed from the classroom and the patient's bedside, to improve their skills and knowledge by accessing educational resources using new technologies. Resistance to this shifting paradigm is futile in light of the increasing availability of learning materials on the Internet. Learners cannot be denied access, nor be restrained from obtaining varying points of view regarding a certain procedure or technique. Because access is often free, teachers, rather than being fearful of their loss of power and control, should view them as shortcuts to the learning process. Embracing the digital age and encouraging learners to access these resources fosters dialogue and debate.[18] Faculty can thus use face time with learners, whether online or onsite, more productively to enhance understanding, rectify erroneous interpretations, and teach how to *think* and *process* information.

Curiously, doctors are unfairly expected to be good mentors and effective instructors without ever having learned to teach. As mentioned earlier, this presumption is, for the most part, absent in other areas such as public school, sports, or music education and represents, in my opinion, a significant shortcoming of our academic institutions and profession. Very few bronchoscopists have been offered seminars specifically designed

[16] While user instructions, checklists, and assessment tools are provided in the Bronchoscopy Education Project Faculty Development Training Manual, they can also be obtained from various professional societies (such as the ASER and WABIP) and at www.Bronchoscopy.org.

[17] Currently director of clinical/translational research, UCLA Jonsson Comprehensive Cancer Center

[18] Tinsley and Lebak expanded on Vygotsky's contructivist theories, describing a zone of reflective capacity in which adults increased their ability for critical reflection through feedback, analyses, and evaluation of one another's work in a collaborative environment (see Lebak, K. & Tinsley, R. Can inquiry and reflection be contagious? Science teachers, students, and action research. Journal of Science Teacher Education;2010:21;953–970).

to teach educational methodologies [47], team dynamics, communication techniques, leadership, presentation skills, or conflict resolution. Even fewer have received formal instruction in behavioral psychology or learned to evaluate and relate to students with different individual propensities for learning.[19]

When learners teach: the journey from novice to mastery and back again.

For those interested in teaching, a fascinating yet challenging journey lies ahead. Physicians already adept at bronchoscopic interventions but less knowledgeable about education can experience the thrill and insecurity of becoming novices again. In addition to renewing interests in bronchoscopy-related knowledge and techniques, teachers can find out more about how social media facilitates communication with a new generation of learners at a time that is most convenient for both. We can become skillful using programs and devices for editing audio and video files, creating e-books, constructing learning platforms, and delivering educational materials. We might also explore websites like Coolmath, SuccessMaker, and Khan Academy to experience how interactive online programs effectively encourage learning.[20] During our quest we will learn more about ourselves, and while not quite identical to Dorothy's journey along the yellow brick road to Oz, we will also become increasingly knowledgeable of five structural elements crucial to the educational process: curricular design, content development, instructional methodology, teaching techniques, and flexible assessment tools that accurately measure what is learned and identify what remains to be taught.

> "In learning you will teach, and in teaching, you will learn"
> From *Son of Man* (1999), lyrics by Phil Collins

The Future Is Now

In this chapter, I provided a brief overview of curricular structure and delivery; described an example of a structured instructional program, that is, the WABIP-endorsed Bronchoscopy Education Project; explained how assessment tools and checklists are used to help guide the educational process; and argued that an ethics of teaching justifies the paradigm shift from a "see one, do one, teach one" bronchoscopy education model to one where learner-centric behaviors are the focus and target of a laddered learning philosophy. By freely using footnotes and supplemental tables, I tried to clarify terminologies and help enhance the reader's knowledge and understanding of educational processes (Fig. 7.7).

Change is a slow process and, by definition, incites resistance. During the last few years, however, and even since the last edition of this textbook, we have witnessed the enthusiastic adoption of new educational philosophies and innovative teaching modalities. Assessment tools and checklists are increasingly advocated, and physician-educators, recognizing that wearing a white coat in and of itself does not make one an "educator," are obtaining advanced degrees in education. Programs are being designed and implemented to help bring a more uniform approach to the bronchoscopy educational process, including translations of key texts and videos (Fig. 7.8), official endorsements of structured training modalities by national and international bronchology organizations, and introduction of new assessment tools in other fields of interventional pulmonology (such as the UGSTAT developed and officially endorsed by the TSANZ [48]). Consistent with the move toward increasing use of artificial

[19] Fenstermacher and Soltis describe a humanistic teaching approach, whereby teachers strive to impart knowledge within an environment in which learning has personal meaning for the learner. By adopting various teaching techniques, facilitator (*coaching*), executive (*modifying the curriculum based on review of assessment results*), or liberationist (*fostering discovery and creativity*), for example, liberationist educators, might alter their teaching methods on the spot according to the medical learning environment and to fit the many different ways individual learners learn (italics are mine).

[20] David Ausubel (1918–2008) in his meaningful reception theory where, contrary to rote memorization or discovery learning based on problem-solving, one's knowledge of new material is enhanced if the material is related to relevant ideas within the learner's existing cognitive structure (http://tip.psychology.org/ausubel.html, downloaded December 27, 2010)

Fig. 7.7 Examples of translations of *The Flexible Essential Bronchoscopist* in Italian and Romanian

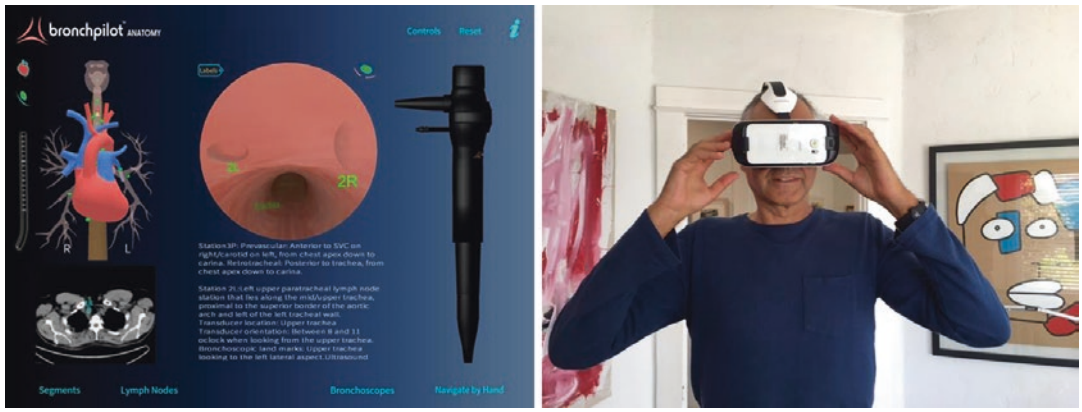


Fig. 7.8 Example of the *Sharp Visions Software* iPad-based BronchPilot Anatomy and Samsung-based BronchPilot Virtual programs help bring individualized learning to the forefront of the educational process

intelligence, long-distance learning, inverted classroom teaching modalities, and advancing technology, educators are also working toward greater democratization, making learning materials globally available and accessible regardless of one's place of work or practice. An example of using these new technologies is the WABIP-endorsed BronchPilot Anatomy program that is an iPad-based learning modality, whereby learners can drive a flexible bronchoscope through the airways while simultaneously accessing 3D reconstructions of airway and mediastinal anatomy. The Samsung-based platform used for the new BronchPilot Virtual program is another step forward, using fully immersive virtual reality that allows the learner to virtually "be the bronchoscope" examining the airways through a self-guided tour (Fig. 7.8). These new teaching modalities, accompanied by more accepted and conventional (how times change, for just a few years ago these modalities were considered to be innovative and new) methods providing access to Internet-based learning materials and interactive presentation-like programs, provide learners of the future with a veritable *Bronchoscopy University* at

their fingertips. That future, most excitingly, is already upon us, beckoning teachers and learners alike to become agents of change in a world where step-by-step, one person at a time, can indeed change the world.

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Part II

Tracheobronchial Obstructions

Reopening the Airway: Fast Methods

8

Michela Bezzi and Marco Trigiani

Introduction

Central airway obstruction can occur secondary to a number of lung primary or secondary malignancy and benign processes. These may cause vegetation, infiltration, or compression.

Interventional options for central airway obstruction are subject to the availability of experienced personnel and equipment. Also, the degree of obstruction and severity of symptoms, the nature of the disease, and the patient's overall prognosis and quality of life impact the choice of intervention [1–5].

Lung cancer is the leading cause of cancer-related deaths in both men and women. Approximately 30% of lung cancer patients will develop central airway obstruction, making palliative airway treatments essential to improve quality and length of life [6].

Control of ventilation and hemorrhage is paramount in the management of central airway obstruction, and rigid bronchoscopy has proven to be an excellent tool to provide airway access and control for these therapies [7].

The main indication for rigid bronchoscopy in interventional pulmonology in adult patients remains central airway obstruction due to malignant or benign tumors. Negative pressure ventilation (NPV) with general anesthesia is used to prevent intraoperative apnea and respiratory acidosis [8]. This technique allows opioid sparing and a shorter recovery time and avoids manually assisted ventilation, thereby reducing the amount of oxygen needed while maintaining free access to the airways with optimal surgical conditions. The major indication for NPV rigid bronchoscopy is airway obstruction by neoplastic tracheobronchial tissue, mainly treated by laser-assisted mechanical resection (LAMR). NPV rigid bronchoscopy is an excellent tool for the endoscopic treatment of locally advanced tumors of the lung, especially when conventional therapeutic resources have been ruled out or are not temporarily feasible. LAMR and stent placement are the most effective procedures for preserving quality of life in patients with advanced stage cancer.

Endobronchial therapy for malignant tumors is purely palliative and should only be performed in nonsurgical cases. Surgical resection is feasible only in about 25% of patients with lung cancer, and less than 30% of these survive longer than 5 years. Thus, more than 90% of these patients require palliative treatment. Thirty percent of lung cancers cause obstructions of the trachea and main bronchi [9] with consequent respiratory distress, bleeding, and infection. The technique of endobronchial coagulation and

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disobstruction plays a pivotal role in all these situations, since conventional treatment with chemo- and radiotherapy is often performed with unsatisfactory results with regard to the endobronchial component of the tumor [10, 11]. In symptomatic patients with inoperable obstructive central tumors, endoscopic coagulation and debulking allow restoring of airway patency, palliation of symptoms, and improvement of quality of life.

Though, strictures and critical airway stenoses may also result from benign conditions involving the central airways. For patients amenable to surgery, resection and reconstruction are the best therapeutic options. However, whenever surgery is not feasible or non-indicated, endoscopic therapies are essential [12] since airway obstruction due to benign endobronchial obstruction may also be amenable to laser resection. Such lesions include benign tumors, inhaled foreign bodies, stenoses due to granulation tissue, intubation injuries, postradiation strictures, complications of tracheal or bronchial resection and anastomosis, or weblike strictures from inhalation injury and also benign exophytic disease with either mucosal infiltration or circumferential narrowing due to granulomatosis with polyangiitis, amyloidosis, or tuberculosis.

Endoscopic laser resection (LAMR) should be the first therapeutic choice for exclusively endoluminal central benign tumors. Surgery should be limited to those cases with partial or exclusive extra bronchial growth.

The advent of endoscopic therapies has also deeply modified the approach to the management of *inflammatory*, *iatrogenic tracheobronchial strictures.* Candidates for bronchoscopic laser resection include those who are not eligible for open resection (because of age, overall medical status, fear of surgery, severity of other underlying diseases, or the extent, location, and degree of the stricture) but also severe dreadfully symptomatic stenoses. Interestingly, most simple stenoses (e.g., weblike stenoses or stenoses without cartilage involvement) can be successfully dilated through LAMR and after this surgery could no longer be necessary [13].

Clinical Presentation

Central airway obstruction may cause a variety of symptoms, from shortness of breath to respiratory failure and death. The hallmark of the severely compromised airway is impairment of oxygenation and ventilation. Patients may develop symptoms suddenly or more gradually; the onset and progression of symptoms depend upon the nature of the disease (acute with foreign bodies, slowly progressive with an expansive goiter) and the location of the lesion (tracheal vs. bronchial).

Symptoms and signs develop when airflow impairment reaches a critical threshold. Patients complain of shortness of breath, which is often constant and unresponsive to bronchodilators. Monophonic wheezing may be present and can be unilateral if the lesion is distal to the carina. Stridor is a sign of severe subglottic or tracheal obstruction. Breathing becomes labored in advanced phases and heralds impending respiratory failure. In the decompensated patient, immediate restoration of ventilation and oxygenation is of vital importance.

Patients with minor obstruction are often asymptomatic, since airflow limitation is mild. However, rapid deterioration may occur if swelling or secretions increase the degree of luminal impingement during a respiratory tract infection.

It is not uncommon for patients with subcritical lesions to be misdiagnosed as suffering from an exacerbation of asthma or chronic obstructive pulmonary disease (COPD) while the true etiology is anatomic airway obstruction. Patients with airway obstruction also frequently present with pneumonia; if symptoms and/or radiographic infiltrates do not resolve within 4–6 weeks, or recur after therapy, bronchoscopy should be considered.

Imaging techniques can be employed to confirm the presence of central airway obstruction and estimate its magnitude: plain chest radiographs are rarely diagnostic. If an airway lesion is suspected and time permits, a high-resolution chest computed tomography (CT) could prove helpful [1]. In a stable patient, spirometry can also show the characteristic changes of airway

obstruction on flow volume loops, frequently before abnormalities in the spirometric volumes are noted. Direct bronchoscopic visualization is the gold standard though for confirming the presence of airway obstruction, and also it aids in discerning its etiology. Often the differentiation of endobronchial or extrinsic lesions can be accomplished only at bronchoscopy (Fig. 8.1a–d).

Management of critical central airway obstruction requires initial stabilization of the patient with secure access to the airways to permit ventilation. Further interventions can then be considered. In a stable patient, imaging studies and pulmonary function tests should be obtained as mentioned above. In patients with severe tracheal or bronchial obstruction and limited lung function, flexible bronchoscopy can be performed only after the airway has been secured (orotracheal tube/deep sedation or general anesthesia) and appropriate gas exchange documented. During the bronchoscopic examination, the airway is inspected, lesions are assessed, distal secretions are suctioned, and diagnostic samples are obtained if needed. This information is used to plan further interventions aimed at opening the airways and maintaining patency. After the

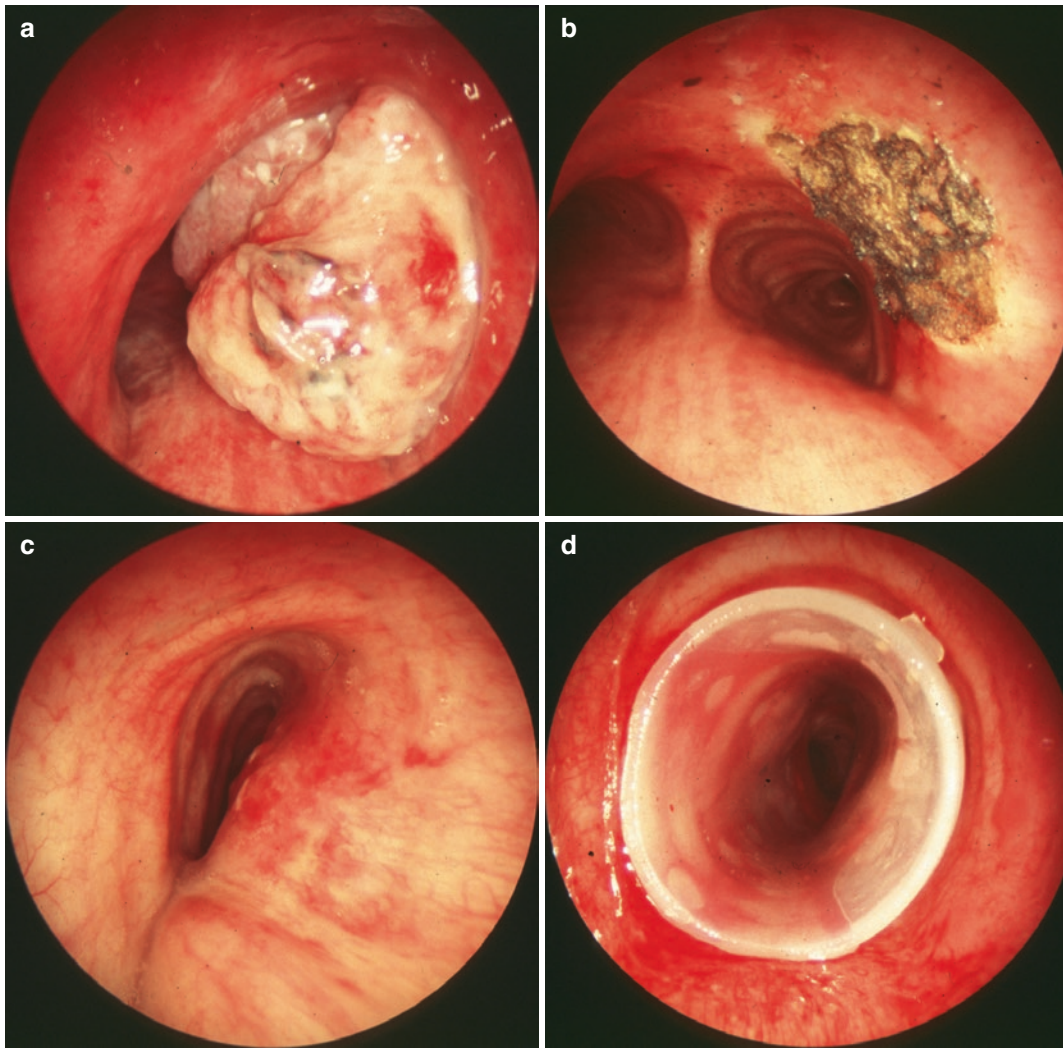

Fig. 8.1 (**a–d**) Extrinsic/intrinsic stenosis before and after treatment

patient has been stabilized, he should be transferred to an interventional pulmonary department where a dedicated team is available.

In case of severe tracheal obstruction, the use of the open ventilating rigid bronchoscope is the preferred method of airway control. The rigid bronchoscope not only provides a secure airway during visualization but is also a therapeutic tool. It is the preferred instrument for unstable patients especially when significant bleeding can be expected. The airway can be dilated with the barrel of the scope [2]. During this procedure, the patient is intubated with the instrument under general anesthesia. The optical telescope is advanced through the stenotic airway opening and the barrel then pushed through the obstruction in a rotating motion. Bleeding is usually minimal due to compression of the lesion by the rigid scope (Fig. 8.2). In one session, using the rigid bronchoscope under general anesthesia, immediate good results can be achieved: bronchial recanalization with improvement of ventilation and drainage of post-stenotic secretions. Dilation is immediately effective for intrinsic and extrinsic lesions, but the results are usually not lasting. For this reason, multimodality approaches featuring a combination of several interventions are preferred for their mucosal sparing effects and long-term success over dilation alone [1–3]. The number and scope of therapeutic options

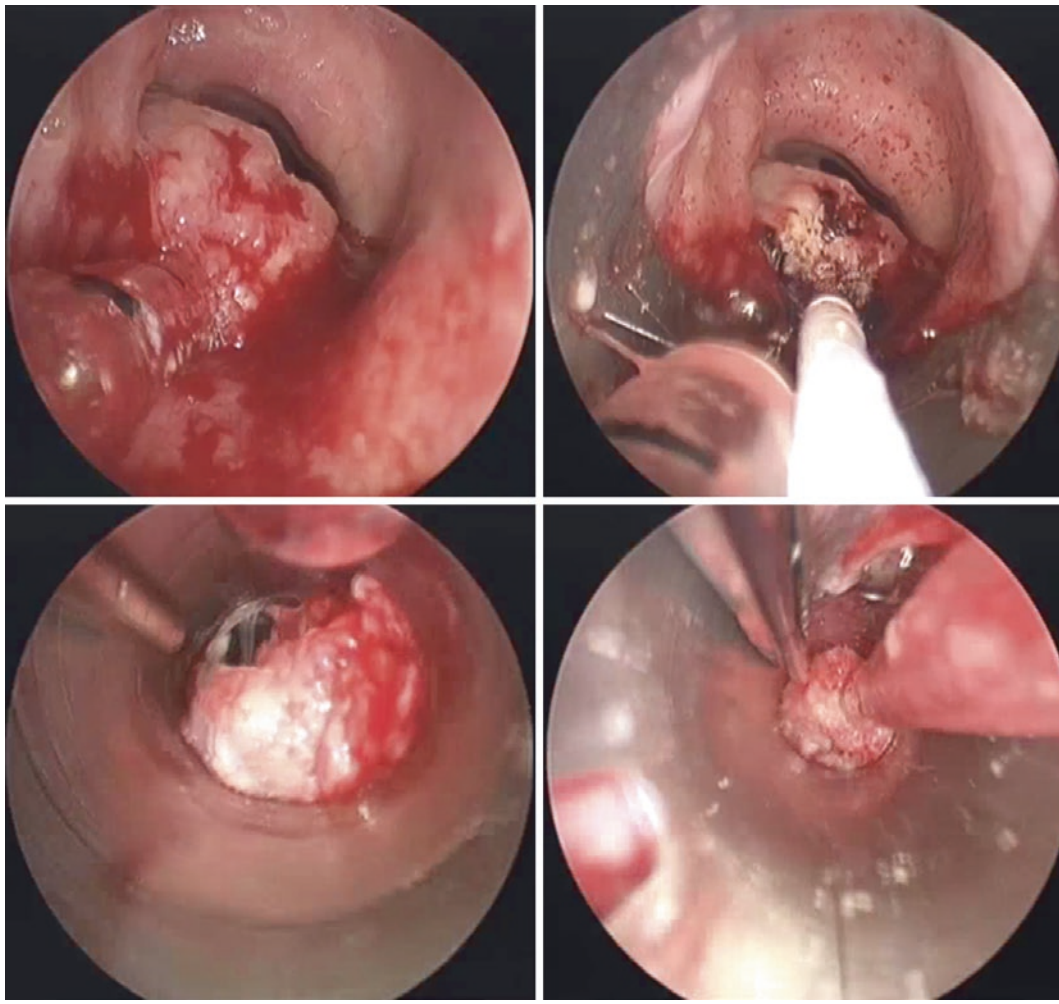

Fig. 8.2 Tumor resection with the rigid bronchoscope

have increased dramatically, and a given intervention must be chosen carefully in the context of an individual patient's situation. They can be divided into "slow methods" such as photodynamic therapy, cryotherapy, and brachytherapy or fast methods: laser, argon plasma coagulation (APC), and electrocautery (EC). Fast methods will be the topic of this chapter whereas slow methods are described elsewhere in this book. Laser therapy more often integrates rigid bronchoscopic resection; this procedure is worldwide known as laser-assisted mechanical resection (LAMR) and represents the safest and more effective way to obtain all potential effects of laser in bronchoscopy. Some authors use laser with the flexible bronchoscope with limited safety and efficacy if compared to LAMR [14]. Different operating modalities allow tissue-light interaction with diverse thermal tissue modifications such as vaporization, coagulation, resection, or incision of obstructing lesions [15]. Laser therapy was originally indicated for short endobronchial central airway lesions with a visible distal lumen. Bronchoscopists who become familiar with the technique will use it even in complete stenoses where the distal bronchial tree can only be reached using the suction tube and the rigid bronchoscope basing upon precise knowledge of the anatomy and preferably with support from CT scan images. In these cases the combination of rigid bronchoscopy and laser firing is crucial. The technique is most commonly applied in cases of malignant intrinsic airway obstruction or in post-intubation tracheal stenosis. The effects upon airway lumen size are usually immediate and accompanied by excellent control of bleeding.

EC and APC also rely on thermal tissue destruction. With EC, a high-frequency current is applied to the lesion with bipolar probes. When the current is directly applied to the tissue, heat develops and leads to tissue necrosis. EC is traditionally defined "the poor man's laser" since it can mimic the effects of laser firing when vaporization and resection are needed with a less expensive equipment. APC is a related therapeutic intervention. Argon gas is emitted through a flexible Teflon tube. This gas is ionized because of exposure to high-frequency current and an electric arc is formed which allows for desiccation and tissue destruction. It is a valuable tool in treating superficial bleeding and debulking granulation tissue and tumors. Indications, equipment, application, and outcomes of these techniques will be extensively discussed hereafter.

Laser-Assisted Mechanical Resection

History and Historical Perspectives

1897—Gustav Killian performed the first rigid bronchoscopy to remove a pork bone from the right main bronchus of a young man [16].

1907—Few years later, in the USA, Chevalier Jackson published his landmark book *Tracheobronchoscopy, Esophagology and Bronchoscopy* [17].

1987—Dumon designed a flexible, multisized, studded silicone stent that gained worldwide popularity in the field of operative rigid bronchoscopy [18].

Nonetheless, until the early 1980s, the endoscopic treatment of central airway obstructions was hazardous and often inadequate. Mechanical resection was performed using the rigid bronchoscope and rigid biopsy forceps with high risk of bleeding. Even when successfully managed, it provided only short-term results. Endoscopic electrosurgery and cryotherapy were then introduced to reduce the risk of bleeding and prolong palliation. These methods though provided only delayed recanalization also carrying an unpredictable risk of damage to the adjacent healthy tissue.

1982—The advent of laser immediately proved very useful in reducing hemorrhages. Once an appropriate technique for the treatment of the implantation base was developed, laser coagulation in depth proved also quite effective in prolonging palliation in central airway obstruction due to lung cancer.

Bronchoscopic mechanical resection turned then into laser-assisted mechanical resection

(LAMR). Nowadays, LAMR through rigid bronchoscopy remains the best tool for the safest management of airway obstructions.

Indications and Contraindications

Bronchoscopic laser resection (LAMR) can relieve malignant and benign intraluminal tumors, particularly exophytic proximal airway lesions, but it has no role when the obstruction is caused by pure extrinsic compression [19, 20]. Laser is also useful in the treatment of benign diseases such as cicatricial tracheobronchial stenoses.

Malignant and Benign Tumors

Airway obstruction from bronchogenic carcinoma is the most frequent indication for laser resection. It is typically employed in patients who have exhausted their therapeutic options, although some may be eligible for salvage chemotherapy, brachytherapy, or surgical resection [2, 3, 21].

Other malignant causes of central airway obstruction that have been managed by laser resection include the so-called low-grade malignancy such as adenoid cystic carcinoma, mucoepidermoid carcinoma, and bronchial carcinoids. Finally, common indications for LAMR are endobronchial metastases from melanoma, colon, kidney, and breast cancer [22, 23].

The major aim of laser therapy in malignant central airway obstruction is to recanalize the tracheobronchial tree and restore adequate ventilation with subsequent drainage of post-stenotic secretions. It is the location and macroscopic appearance of a tumor, rather than its histological type, which determine whether or not laser therapy can be useful. Because of their immediate accessibility and severe impact on ventilation, the best results are obtained in tumors located in the trachea or main bronchi, which is in fact where obstruction causes the greatest respiratory distress. On the contrary, tumors obstructing segmental bronchi do not impair ventilation to the degree that severe symptoms are produced. Furthermore reduced accessibility with the laser fiber and the thin walls of these bronchi increases the difficulty of laser delivery and the risk of perforation. The sole indications for laser disobstruction of segmental bronchi are prevention of bleeding in case of highly vascularized lesions, drainage of distal purulent secretions (postobstructive pneumonia), and cure of benign tumors.

It is very important for the endoscopist to identify the base of the obstructing endobronchial tumor. Polypoid tumors are easy to remove and often completely resectable (Fig. 8.3a, b).

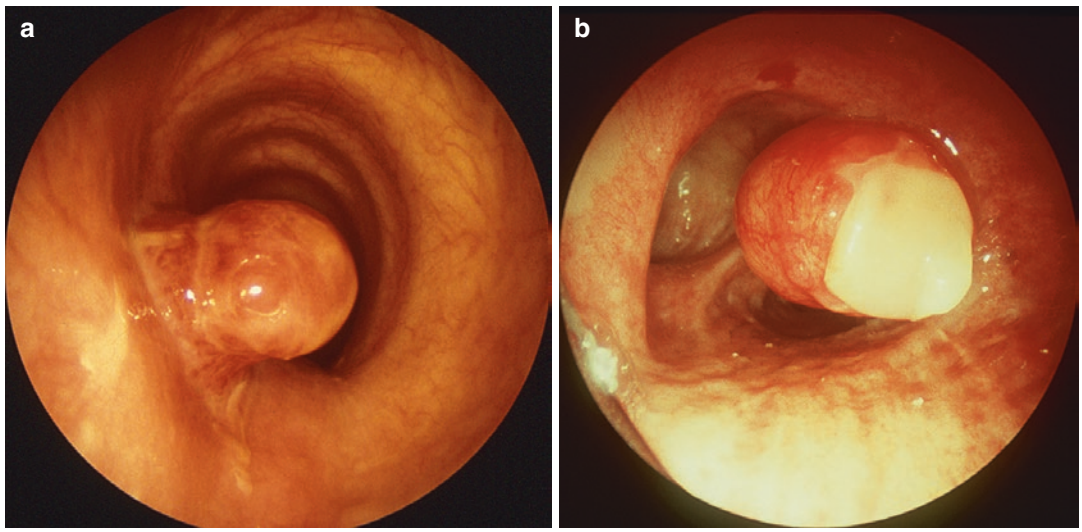

Fig. 8.3 (**a**, **b**) Polypoid lesions

Intraluminal tumors with infiltration of the airway wall cannot be treated completely. Though, if the airway lumen is not seriously reduced by tumor infiltration, ventilation is usually not impaired appreciably, and laser resection may not be necessary.

For occluding endobronchial tumors with significant extraluminal (even mediastinal) growth, laser treatment alone is frequently unsuccessful. Although the endoluminal component may be initially successfully removed, the airway is quickly re-obstructed as a result of further growth, extrinsic compression, and/or endobronchial migration of the tumor. In these cases, laser treatment is to be considered as preliminary to stenting, or, if the extraluminal component is only limited in depth and not compressing, brachytherapy might prove useful. Pure extrinsic compression is a major contraindication for endoscopic laser treatment, being it amenable to immediate stenting.

Regardless of impact on ventilation, location, or macroscopic appearance, vascular tumors producing hemoptysis represent a good indication for laser bronchoscopy. Although the tumor is often not completely resected, short-term reduction or ceasing of bleeding occurs systematically after laser coagulation.

In all of the previous conditions, endoscopic resection allows a precise assessment of the extent of the tumor, shifting to surgery patients originally considered to have inoperable disease or allowing lung-sparing resections [24].

The combination of endobronchial laser therapy with other palliative therapies is possible and can be extremely advantageous. The addition of radiotherapy is particular useful either by external beam radiation or endobronchial brachytherapy, with extension of the palliation. When indicated, laser resection will be performed before radiotherapy, because preventive laser recanalization of obstructed airways allows improved functional status. Furthermore, it is well known that radiotherapy and chemotherapy are poorly effective on the endoluminal component of the tumor [7, 8]. Similar therapeutic algorithms for the management of central airway neoplastic obstructions have been described by different authors [25, 26]. Figure 8.4 is an example [27].

Tumors with Uncertain Prognosis

Tumors with uncertain prognosis lump together several tumors characterized by slow growth and rare tendency to metastasize; among these, carcinoid tumors, adenoid cystic carcinomas, and mucoepidermoid carcinomas are the most

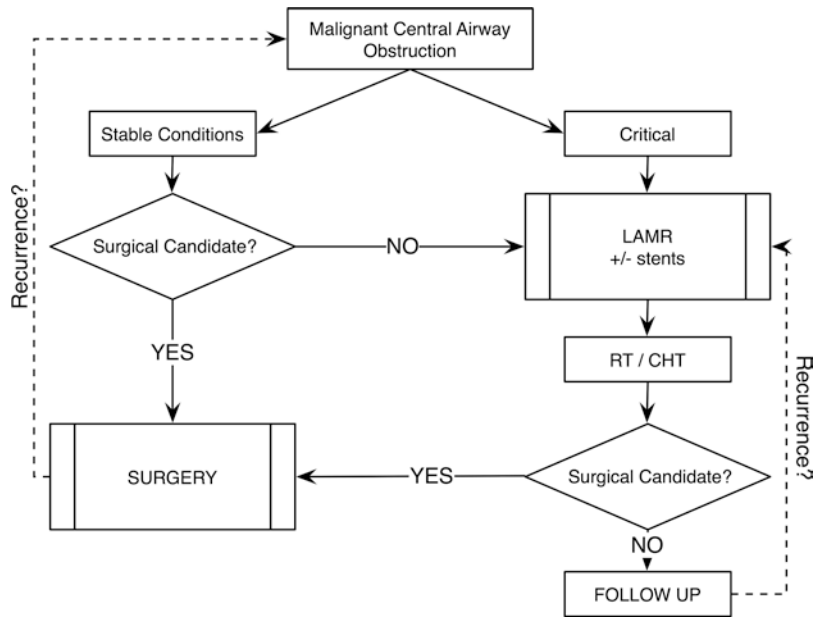

Fig. 8.4 Algorithm for the management of malignant central airway obstruction

common in the airways. The same histological type can present with different grades of malignancy. As for malignant tumors, laser therapy is mainly palliative or in some cases useful for a better surgical assessment.

Local cure may exceptionally be achieved when the tumor has a small and localized base and a low-grade malignancy. This different therapeutic approach in relation to the different tumoral characteristics is to be considered only for typical carcinoid tumors. Atypical carcinoids, i.e., well-differentiated neuroendocrine carcinomas, can deeply infiltrate the bronchial wall and produce an appearance similar to the bronchogenic carcinoma. In most cases the tumor cannot be removed completely and recurrence after laser resection is expected. On the contrary, typical carcinoids can be considered as more benign lesions; their macroscopic and microscopic aspect is similar to benign neoplasms. They are defined as well-differentiated neuroendocrine tumors, normally growing exclusively inside the bronchial lumen as polyps with a narrow base. In these cases, laser-assisted mechanical resection (see further) can be curative [28, 29] (Fig. 8.5).

Although rare, benign tumors are the best indication for laser therapy. If exclusively endoluminal, endoscopic laser resection should be the first therapeutic choice for such tumors, as they are usually polypoid and rarely recur if the tumor base can be well photocoagulated with the laser. Surgery should be limited to those cases with partial or exclusive extra bronchial growth.

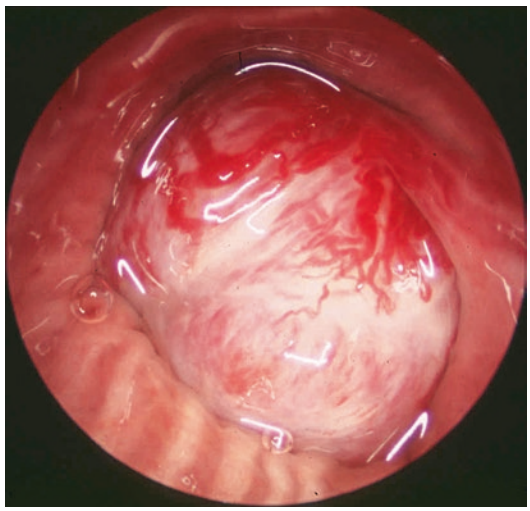

Fig. 8.5 Carcinoid tumor

Benign Conditions

Airway obstruction due to benign conditions may also be amenable to LAMR. Such lesions include inhaled foreign bodies, stenoses due to granulation tissue, intubation injuries, postradiation strictures, lung transplantation, tracheal or bronchial resection and anastomosis, or web-like strictures from inhalation injury; other possible conditions affecting the airway lumen are represented by benign exophytic disease with either mucosal infiltration or circumferential narrowing due to granulomatosis with polyangiitis (formerly called Wegener's granulomatosis), amyloidosis, tuberculosis, or endometriosis [30].

Generally speaking, patients who have benign airway strictures due to causes other than infection should always be considered for open surgical resection [2, 3].

Candidates for bronchoscopic LAMR include those who are not candidates for open resection because of age, overall medical status, fear of surgery, severity of other underlying disease, or the extent, location, and degree of the stricture.

The advent of endoscopic therapy has deeply modified the approach to the management of iatrogenic tracheobronchial strictures [31, 32].

In particular immediate laser recanalization must be considered as the first choice treatment in severely symptomatic and progressive stenoses, putting the patient at risk of death. In such conditions, bronchoscopic recanalization could avoid urgent tracheotomy, which could be responsible for further damage to the trachea. It is almost always possible to obtain rapid and immediate good results, independently of the type of stenosis. Once the emergency has been handled, there will be more time to consider the best treatment strategy (Fig. 8.6a, b). In case of relatively indolent stenoses without severe ventilation impairment,

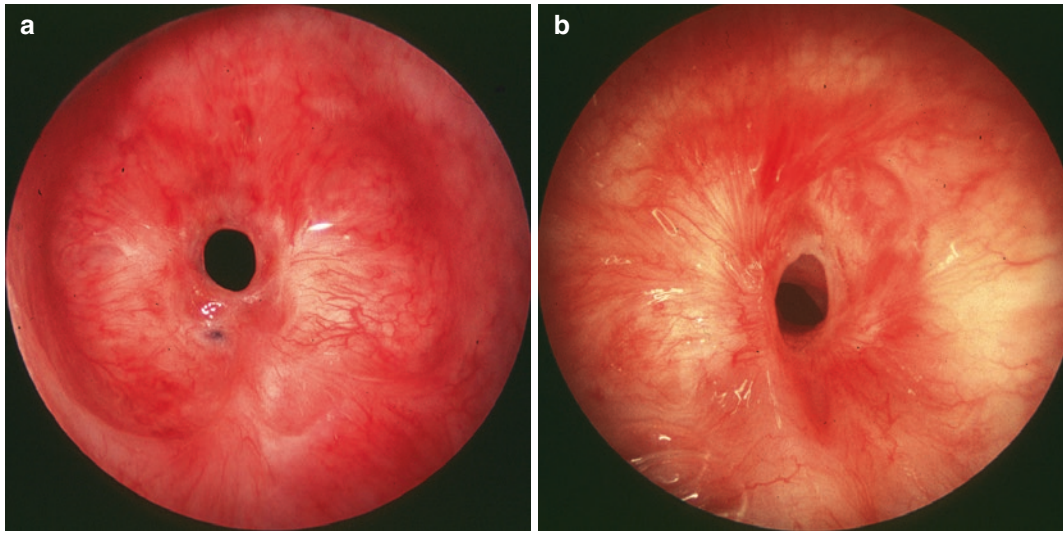

Fig. 8.6 (**a**, **b**) Severe tracheal stenosis

endoscopic therapy should be considered as an alternative to open surgery when the latter is temporarily nonfeasible or contraindicated. Even, patients eligible for resection could benefit from a preliminary endoscopic treatment to allow stenosis stabilization and precise delimitation. Complications to open surgery such as granulomas or restenosis can be effectively treated endoscopically. In some selected simple stenoses (e.g., weblike stenoses or stenoses without cartilage involvement), stable good results can be achieved after laser-assisted mechanical resection, and surgery could no longer be necessary [33–38].

For the treatment of inflammatory strictures of the trachea, it has been recently proposed a combined technique using real-time bronchial endosonography to evaluate and limit the possible laser-induced damage during resection, but this procedure is affected by elevated costs and unavailability in most endoscopic centers [39, 40].

Also, cold instruments such as hand scissors have been proposed occasionally as an alternative to laser for cutting the stenosis radially. Compared with laser, the main advantages are the user-(more)friendly technology and low costs and the absence of thermal damage.

This method is apparently easy to perform and safe and facilitates the resection of simple stenotic scars. It should be considered cautiously though considering the small number of cases reported and should be corroborated by larger studies [41].

Description of the Equipment Needed

The word LASER is the acronym of light amplification by stimulated emission of radiation. The main components of a laser are the laser cavity, the pumped material, and the pumping system. The cavity is a reflecting cylindrical camera with mirrors at each extremity, one of which is partially reflective. When, inside the camera, an active substance is electrically or optically stimulated, it spontaneously emits photons, which are reflected by the mirrors through the active substance itself producing new photons with the same wavelength (and energy) and direction. The result of this stimulated radiation is a laser beam. The wavelength depends on the nature of the active material that is stimulated. For example, Nd:YAG laser emits in the infrared range at 1.064 nm.

The main characteristics of a laser beam are:

- Coherence (the waves emitted are in phase)
- Collimation (the waves are parallel to each other)
- Monochromaticity (the waves are all of the same length)

These properties allow concentration, without loss of power, of the laser beam on a small target. When using laser, one should always have a precise knowledge of a few physical aspects:

- *Laser power* is the power erogated by the laser and can be exclusively regulated through the leaser equipment. It is measured in watts (W).
- *Laser energy* is affected by the time of exposition in a physically determined manner:
  Laser Energy (Joule) = Power (Watt) × time (s)
- *Laser power density* is strongly dependent on the extension of the impact surface:
  Power Density (Watt/cm^2)
  = Laser Power (Watt)/surface (cm^2)

Releasing high power density can cut and vaporize living tissue. A lower power density laser can rather coagulate tissue determining necrosis or hemostasis without loss of substance.

The interaction between laser and living tissues also depends on many other factors, such as wavelength, distance from fiber to target, angle of incidence, color of impact surface, exposure time, absorption, and penetration in depth of the radiation. The thermal effects are the best known and the most used.

With regard to temperature, below 50 °C, we obtain tissue necrosis and inflammation, at a higher temperature vaporization is observed. Power density is inversely proportional to square distance. Penetration, which is inversely proportional to absorption, depends on the frequency of the radiation, tissue color, and its vascularization.

There are many types of biomedical lasers, including the carbon dioxide (CO_2) laser, the neodymium-yttrium-aluminum-garnet (Nd:YAG) laser, neodymium-yttrium-aluminum-perovskite (Nd:YAP) laser, argon ion laser, excimer laser, potassium titanyl phosphate (KTP) laser, alexandrite laser, diode lasers, pulse dye lasers, and the most recent thulium laser.

CO_2 laser was the first laser used in bronchoscopy. It is invisible (10,600 nm in infrared range) and is transmitted to the tissue through an articulate arm composed of mirrors. These characteristics limit its application in bronchial endoscopy. Biologically, tissue vaporization is precise and efficient because of low penetration in depth; yet low penetration determines poor hemostasis.

The laser that is most commonly used for bronchoscopic laser resection is the Nd:YAG laser. Its energy is delivered through flexible quartz fibers that are inserted through either a rigid or flexible bronchoscope. The wavelength of this laser (1064 nm) is invisible; thus, a red helium-neon beam is used to indicate where the laser energy will be applied.

It delivers sufficient power to vaporize tissue, also producing a good coagulating effect. The active substance is a crystal of yttrium-aluminum-garnet doped with neodymium.

A 1320 nm Nd:YAG laser is also available with greater cutting and vaporization effects, especially in low vascularized tissues with high water content.

Coagulation and vaporization are produced by a thermal effect, which is not limited to tissue surface: the laser beam can be transmitted as deep as 1 cm. Tissues, depending on the color of the surface and laser power density, differently absorb this radiation. The beam can pass through a pale and low vascularized tissue without a visible effect, but it will be absorbed by a dark surface limiting penetration in depth.

Diode laser is a differently conceived laser exploiting a semiconductor diode technology. When electric current passes through a diode, it emits a laser radiation. Diode technology reduces problems related to the laser cavity complexity, allowing the design of portable, compact, and high-power air-cooled lasers. It is available in different wavelengths (808, 940, 980, and 1470 nm). The 808 and 940 nm is exclusively absorbed by hemoglobin, making this laser very useful for treating highly vascularized tissues,

but absolutely indolent if fired on a white surface. The 980 and 1470 nm is also well absorbed by water and so very effective when treating white tissues too.

In Nd:YAP laser, the active substance is yttrium-aluminum-perovskite, with a wavelength of 1.340 nm, which is absorbed by water 20 times more than the 1.064 nm of the Nd:YAG, thus providing a better effectiveness-power ratio. Coagulation is particularly good.

Thulium laser has more recently been considered for endobronchial application. The 2-μm wavelength emitted by Cyber TM (thulium) laser is strongly absorbed by water resulting in an outstanding coagulation and aero-hemostatic effects with preservation of the surrounding tissue. Since 2-μm laser wavelength is strongly absorbed by water, which is ubiquitous in all tissues, the speed of cutting and vaporizing will remain relatively constant regardless of tissue vascularization. Energy from the thulium laser penetrates only fraction of millimeter in the tissue, with a high degree of control and substantially reduced risk of inadvertent injury.

In practice, the ideal laser in bronchoscopy should be transmissible by fiber, safe, easy to set up and use, cheap, and portable. It should produce many and sometimes opposite specific effects: excellent coagulation so as to control bleeding and different resecting modes according to clinical occurrence. For cicatricial stenosis, mainly post-intubation tracheal stenosis, lasers should be as precise as a scalpel to spare the surrounding tissues; on the contrary, for endoluminal neoplastic masses, a vaporizing effect on large volumes is needed. More importantly, high penetration of energy without loss of substance, producing deep thermal damage and consequently a cytocidal effect, is required to treat the tumor base in depth and delay (malignant tumors) or even prevent recurrences. This is the principle for cure in benign, strictly endoluminal tumors, typical carcinoids, carcinoma in situ, and early cancers. All these characteristics do not perfectly coexist in the same laser, so the interventional pulmonologist has to choose the best compromise or use more than one tool.

Rigid Bronchoscopy

The rigid bronchoscope is a straight hollow stainless steel tube ~40–45 cm long. Its caliber varies from 6.5 to 13.5 mm. The distal end of the rigid bronchoscope is beveled, allowing mechanical resection of obstructing lesions. The proximal end is conceived with several side ports where instruments can be placed or ventilation tubes can be connected. Zero-degree telescopes are the devices most commonly used to visualize the airway through the rigid scope. Angled telescopes are uncommon; more frequently a flexible bronchoscope can be used in combination with the rigid scope for lobar and segmental bronchi visualization.

The Efer-Dumon bronchoscope consists of a "universal head" to which multiple bronchoscope barrels of varying lengths and diameters can be attached (Fig. 8.7a). This bronchoscope is also designed to deploy endoluminal silicone stents using custom-made stent introducers (Fig. 8.7b).

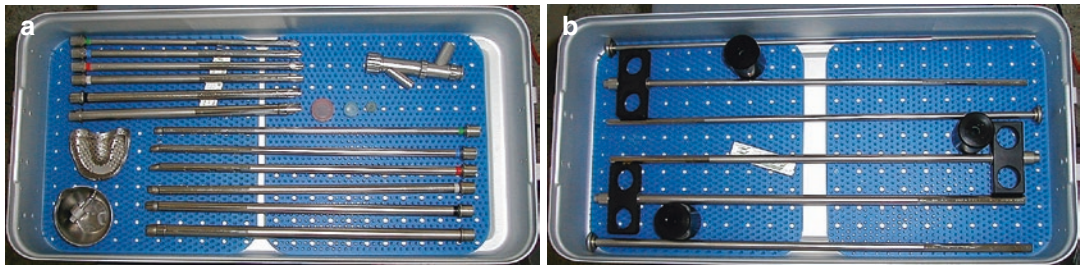

Fig. 8.7 (**a**) An Efer-Dumon rigid bronchoscope set with the "universal head," several bronchoscope barrels of varying lengths and diameters, a rigid 0° telescope, a pair of optic forceps, and a light wire. (**b**) A set of silicone stent delivery systems of different diameters

Application of the Technique

Most bronchoscopic laser resection will be performed via rigid bronchoscopy in the operating room with general anesthesia [28–30]. In fact laser therapy normally integrates rigid bronchoscopic resection; this procedure is worldwide known as laser-assisted mechanical resection (LAMR) and represents the safest and more effective way to obtain all potential effects of laser in bronchoscopy. Some authors use laser with the flexible bronchoscope with limited safety and efficacy if compared to LAMR. It is performed in a specially equipped bronchoscopy suite with topical anesthesia and conscious sedation [14]. During LAMR patient's oxygenation and ventilation can be supported through the rigid bronchoscope by spontaneous-assisted ventilation or jet ventilation. Intermittent negative pressure ventilation (poncho) is another ventilation modality associated with lower incidence of complications such as acidosis due to hypercapnia [8]. Muscle relaxants and paralytic agents can be helpful during general anesthesia because they prevent the patient from coughing during the endoscopic maneuvers and they facilitate insertion of the rigid bronchoscope.

Ventilation System and Anesthesia

Originally, rigid bronchoscopy was performed during spontaneous-assisted ventilation with general intravenous anesthesia, which maintains spontaneous breathing [7]. Low levels of respiratory acidosis are virtually unavoidable with this method particularly during complex long-lasting procedures [8].

Positive pressure ventilation and jet ventilation are popular ventilation modalities but neither guarantees effective ventilation and safety, and both can limit surgical options. In addition, they carry the risk of intraoperative pneumothorax or pneumomediastinum [42].

Negative pressure ventilation (NPV) can safely be used as an alternative [43]. This procedure allows opioid sparing and a shorter recovery time, prevents respiratory acidosis, and avoids manually assisted ventilation while maintaining optimal surgical conditions [44] (Fig. 8.8).

Both external high-frequency oscillation (EHFO) and NPV ensure effective ventilation and comfortable operating conditions in the majority of patients. Some patients may receive inadequate ventilation with EHFO, developing respiratory acidosis and requiring manually assisted ventilation. In comparison with NPV, EHFO requires a higher fraction of inspired oxygen [8].

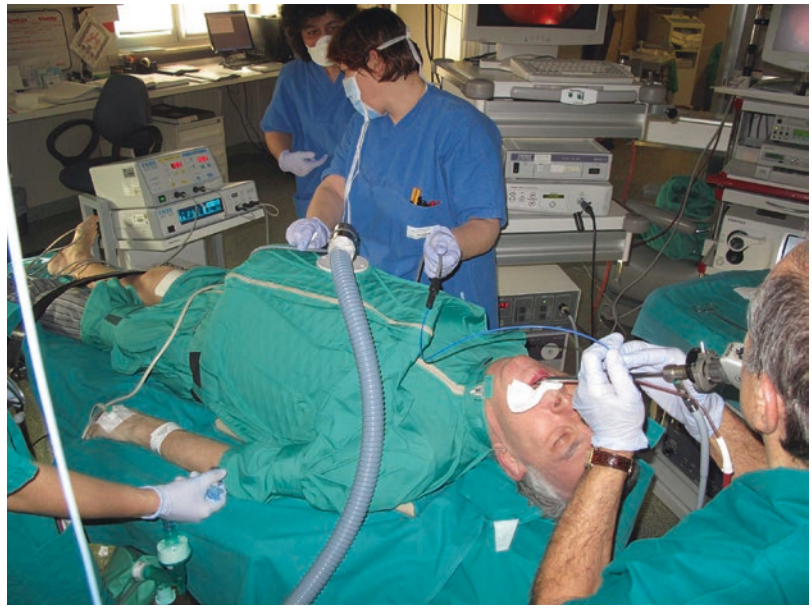

Fig. 8.8 Intermittent negative-pressure ventilation (poncho)

Effects of Laser and Laser-Assisted Mechanical Resection

The four main effects laser can provide are coagulation and resection, vaporization, and incision (Table 8.1).

Laser resection is generally facilitated by the use of the rigid scope in the so-called laser-assisted mechanical resection already mentioned before.

Laser coagulation involves directing the laser at the target lesion, devitalizing the lesion via photocoagulation of the feeding blood vessels, so that the devitalized tissue can be more easily removed with the beveled edge of the bronchoscope, forceps, or suction minimizing the risk of bleeding. Coagulation is possible because the laser penetrates tissue to a depth of up to 10 mm in an inverted cone fashion and provides reliable photocoagulation at this depth. Moving the laser closer to or farther from the target tissue can alter its power density.

Vaporization is possible because energy from the laser is relatively well absorbed by water. It involves aligning the laser parallel to the bronchial wall and aiming at the edge of the intraluminal lesion (the laser should never be discharged perpendicular to the airway wall because of an increased risk of perforation). It can also be performed through the flexible scope; in this setting laser pulses of only 1 s or less are used to vaporize the tissue to prevent thermal injury to the scope and airways. On the contrary, when performed in rigid bronchoscopy, laser can be used for longer periods of time reaching higher temperatures with higher power densities. This is possible because the suction tube inserted through the scope minimizing the risk of injury can effectively suction laser debris and smokes.

Laser vaporization applied using a fiber-optic bronchoscope should be limited to small non-bleeding lesions, to refine and complete treatments previously performed with the rigid scope and, through a tracheal tube, for treating neoplasms in the upper lobe bronchi, in distal locations, and for distal tracheobronchial toilette.

The channel of the rigid bronchoscope is wide enough to ensure ventilation and passage of telescopes, suction tubes, and the laser fiber. Simultaneous laser coagulation of a bleeding site and suction of blood and clots is very important when dealing with airway hemorrhages. In addition, the rigid bronchoscope allows mechanical resection of polypoid tumors, previously coagulated with laser, which saves considerable time over laser vaporization. For all these reasons, most bronchoscopists prefer rigid bronchoscopy, although a flexible bronchoscope is to be available if the airway abnormality is within a distal segmental bronchus and also to remove the blood and debris from the distal airways.

A proposed technique [24] for laser treatment of endobronchial tumors consists of initial low power Nd:YAG laser firing (<30 W) to coagulate the tumor (Fig. 8.9a) followed by removal of the endoluminal portion of the lesion with the tip of the rigid bronchoscope, the biopsy forceps, and the suction tube (Fig. 8.9b).

High power settings (50–60 W) are then employed to vaporize the residual endoluminal tumor. At the end of the procedure, the base of the lesion is exposed to low power settings with long pulses (20–30 W for 4–5 s; 2000 J/cm^2) to obtain a cytocidal effect deeply within the airway

Table 8.1 Laser techniques

Techniques		
Laser vaporization	Flexible bronchoscope	Up to 90% of cases. Time consuming but can be effective
	Rigid bronchoscope	Rare; for control of bleeding and vaporization of tumor remnants after mechanical resection
Laser resection	Rigid bronchoscope (LAMR)	To reduce risk of bleeding during tumor debulking
Laser coagulation	Rigid bronchoscope	To prevent bleeding before mechanical resection
		To treat implant base in depth (up to 5 mm) and delay recurrence
Radial incision	Flexible/rigid	Performed to reduce tension of cicatricial stenoses (before dilation if rigid scope is used)

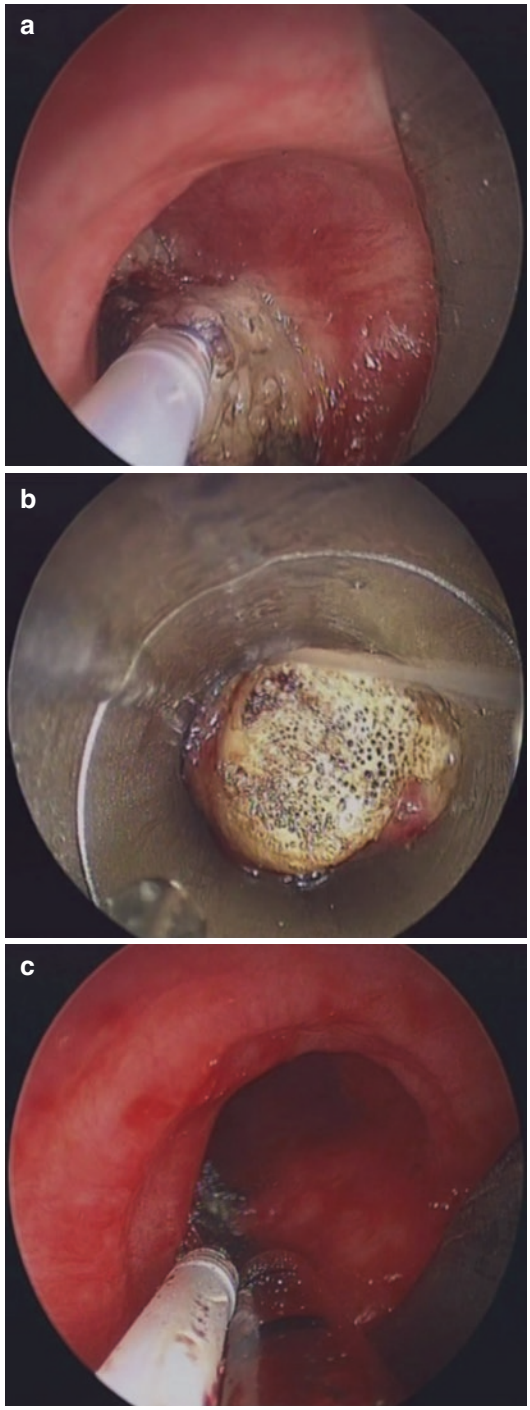

Fig. 8.9 (**a**) Laser coagulation. (**b**) Mechanical resection. (**c**) Treatment of the implantation base

wall. To avoid perforation and explosion, the light is directed tangentially to the wall of the airway and moved continuously (Fig. 8.9c).

Dark colored tissues (e.g., charred or hemorrhagic tissue) and large lesions require special consideration. With respect to dark tissues, laser coagulation in depth is limited because the dark color enhances tissue absorption, limits deep tissue penetration, and reduces deep photocoagulation, leading to poor devascularization of the target lesion. With respect to large lesions, firing with laser in full tumor is not advisable. It is time-consuming and uselessly risky to reduce the whole endoluminal mass by charring and vaporizing it with laser. The laser must be used exploiting its various characteristics in association with the mechanical resection in the so-called laser-assisted mechanical resection. To avoid charring and vaporization due to radiation absorption on the surface and to obtain coagulation in depth, the laser fiber must be kept at a sufficient distance from the tumor surface and directed a little bit more tangentially to the bronchial wall, thus obtaining, because of the divergence of the beam, an increase of the diameter of the spot and therefore a reduction of the power density [45–47].

In the treatment of cicatricial tracheal stenosis (e.g., post-intubation weblike stenoses), laser is used in contact mode to perform radial incisions before a mechanical dilation is obtained with rigid bronchoscopes of progressive caliber. The radial incisions permit to reduce tension with minimum heating of the adjoining tissue thus limiting recurrence [48–50].

Other authors [39] described a different technique with repeated small radial incisions in contact mode through the flexible bronchoscope.

The Setting

Most interventional pulmonary teams include a bronchoscopist, an anesthesiologist experienced with interventional pulmonology techniques and airway management, an endoscopy nurse familiar with the equipment, and a second endoscopy nurse who assists the bronchoscopist and controls the laser settings.

General anesthesia is usually more comfortable for both the patient and the operator; it allows maximal control of ventilation and immediate management of complications.

Anesthetic agents that are rapidly eliminated or readily reversed should be used so that the patient can be rapidly reawakened and

postoperative mechanical ventilation can be avoided. Regardless of the type of anesthesia, the laser endoscopist and the anesthesiologist need to work in close agreement throughout the procedure, adapting to mutual needs.

For endobronchial tumors, which represent the most common indication for laser treatments, the use of a rigid bronchoscope is determining since the most evident part of the maneuver, i.e., the removal of the obstructing mass, is mechanically performed. Laser is more efficiently used to coagulate the endoluminal mass before the mechanical resection to avoid or reduce bleeding and to treat in depth the implantation base of the tumor as discussed before.

Bronchoscopists who have advanced training and experience should only perform bronchoscopic laser resection. Bronchoscopists and team members should remain familiar with the technique and be aware of its potential complications and necessary precautions [40].

To minimize the risk of combustion:

- The fraction of inspired oxygen should be kept below 40% during laser firing [51].
- Power settings should not exceed the maximum recommended for the laser being used (e.g., 60 W for the Nd:YAG laser).
- Flammable materials (including silicone stents) should be kept far away from the operating field [52].
- Adequate suction must be available to remove the combustible laser plume (the smoke caused by vaporization of tissues).
- If a flexible bronchoscope is employed, the laser must be kept a sufficient distance beyond the tip of the bronchoscope.

Video systems allow all personnel to observe the procedure, which makes it easier for assistants to anticipate the needs of the bronchoscopist and patient. Most bronchoscopic laser resection procedures are performed in less than 1 h.

Evidence-Based Review

Outcome data regarding bronchoscopic laser resection are sparse. However, it appears to be a rapid and safe method to relieve airway obstruction. In 1988, a first series of patients treated with Nd:YAG laser was published [53]. Another case series from the same authors that included 2610 laser resections in 2008 patients with malignant airway obstruction proved that airway patency was restored and symptoms were palliated in over 90% of patients [24]. In this series the rigid bronchoscope was used in 92% of the treatments that were performed almost always under general anesthesia. The fiber-optic bronchoscope—alone—was used in less than 10%. In 93% of the patients with endobronchial malignant obstruction, Nd:YAG laser therapy allowed the patency of the central airways and avoided the most distressing symptoms of the disease, enhancing the patient quality of life. According to the authors, the location and macroscopic appearance of the lesion play the greatest role in determining the success of the procedure: for tumors involving the trachea and main bronchi, immediate results were almost always excellent (>95%). The median time between the first and second palliative treatment was 102 days. Mortality was less than 1% within 7 days of the procedure. Smaller series have reported similar results [11], while a larger series reported that death occurred in only 15 out of 5049 patients (0.3%) and serious complications occurred in only 119 out of 5049 patients (2.4%). In 38 typical carcinoids and in more than 150 benign tumors, in which the base of the lesion was reached, laser therapy was curative. These results were achieved in exclusively endoluminal polypoid tumors in which coagulation of the lesion and mechanical resection were followed by a systematic treatment of the base of the tumor with low power setting and long exposure time, avoiding tissue loss while still obtaining a cytocidal effect in depth. Overall mortality rate was 0.25% [42]. In benign stenoses and particularly in post-intubation tracheal stenoses, laser-assisted mechanical dilation can guarantee cure in up to 66% of cases and 100% when only cicatricial weblike stenoses are considered [9]. A more recent report of a series of 124 patients confirms that operative rigid bronchoscopy represents an excellent tool for the endoscopic treatment of locally advanced lung tumors, especially when patients have exhausted the conventional therapeutic resources [54].

Complications of bronchoscopic laser resection are infrequent. They include hypoxia, hemorrhage, airway wall perforation, airway wall necrosis, and fistula formation. Hypoxia, whether due to general anesthetic or to major bleeding, may lead to irreversible cardiovascular complications and thus must be corrected promptly by bleeding suction and ventilation control. Adequate control of hemorrhage and ventilation can only be assured with the rigid bronchoscope. Other possible complications include perforation of the airway with resulting mediastinal emphysema, pneumothorax, or infection. Perforation is unlikely if the procedure is performed by experienced endoscopists familiar with rigid bronchoscopy. Airway fires have been reported, particularly when flexible fiber-optic instruments are used. Fortunately this complication is quite rare. Arterial air embolism has been anedoctically reported as a complication of bronchoscopic laser resection. Studies of laser procedures performed during continuous transesophageal echocardiographic monitoring suggest that air emboli may be caused by coolant gas (which exits the bronchoscope under high flow and pressure conditions to cool the laser probe) entering the pulmonary venules and gaining access to the systemic circulation [55]. Maintaining the laser fiber coolant airflow at the minimum level and avoiding direct contact between the laser probe and tissue may reduce the frequency of this complication.

Summary and Recommendations

- Bronchoscopic laser resection is used to relieve malignant or benign intraluminal airway obstruction. It has no role when the obstruction is caused by sole extrinsic compression.
- Bronchoscopic laser resection has to be considered as a part of a more complete treatment called "laser-assisted mechanical resection/dilation—LAMR/LAMD). It is rapid, effective, and repeatable and may be complementary to other therapies.
- In malignant stenoses, LAMR consists of firstly laser coagulation and then mechanical resection and finally low-power laser treatment in depth of the implantation base.
- The type of laser that is most commonly used for LAMR is the neodymium-yttrium-aluminum-garnet (Nd:YAG) laser. It relieves airway obstruction by either resecting or vaporizing the obstructing lesion.
- Bronchoscopic laser resection should only be performed by bronchoscopists who have advanced training and experience.
- Complications are infrequent but they include hemorrhage, airway wall perforation, airway wall necrosis, fistula formation, and air embolism.

Endobronchial Electrocautery and Argon Plasma Coagulation

Introduction and Definition of the Procedure

Several techniques are available for the bronchoscopic treatment of obstructing tissue in the tracheobronchial tree. Of these options, only laser-assisted mechanical resection (LAMR, already discussed above), argon plasma coagulation (APC), and electrocautery produce rapid tissue destruction in a single session and are therefore appropriate to treat lesions that are producing acute respiratory distress or hemoptysis. The neodymium-yttrium-aluminum-garnet (Nd:YAG) laser is commonly used in this situation, but expense limits the availability of laser equipment in many parts of the world. Endobronchial electrocautery(EC) and argon plasma coagulation (APC) are alternative modes of thermal tissue destruction that may be used via the flexible or rigid bronchoscope [56, 57].

Due to a voltage difference between probe and target tissues, electrons will flow, and current density can be controlled using probes that conduct the electrons toward the target [58].

Electrocautery could be called "the poor man's laser," because it also produces rapid thermal destruction of tissue but does so relatively inexpensively by means of electric current rather than laser light [59, 60].

Electrons will generate heat for tissue coagulation due to the higher resistance of the target

tissue. Argon plasma coagulation (APC) uses ionized argon gas jet flow (5plasma) to conduct electrons allowing a noncontact mode of treatment (lightning effect) [61].

Argon plasma coagulation (APC) is also an electrosurgical technique used to resect an obstructing lesion and/or to achieve hemostasis [62, 63]. The history, principles, equipments, and techniques of endobronchial electrocautery (also referred to as electrofulguration, diathermy, electrocoagulation, thermocoagulation, or electrosurgery) and argon plasma coagulation (APC) will be reviewed here. In addition, their indications, contraindications, and complications are presented.

History and Historical Perspective

Electrocautery was first used in the 1930s to treat rectal cancer [64]. Endoscopic electrocautery subsequently has found wide use in the treatment of gastrointestinal lesions, such as colonic polyps, bleeding vessels, and biliary stenoses. Initial reports of the potential utility of electrocautery in the treatment of tracheal and bronchial tumors also appeared in the 1930s [65–67], but complications such as burns, tracheal perforation, and fatal hemoptysis dampened enthusiasm for the technique [68]. Refinements of the electrodes and other hardware and the use of more sophisticated generators of high-frequency current have improved the efficacy and safety of bronchoscopic electrocautery and have led to a renewed interest in the technique. Nonetheless, the literature describing palliative electroresection is limited, and most pulmonologists remain unfamiliar with its use. A relatively new development is the noncontact mode of argon beam coagulation or argon plasma coagulation (Fig. 8.8). It was meant to improve surgical hemostasis. Its use gradually expanded in the early 1990s when a flexible probe was introduced that could be used via a flexible scope. Since then, APC has been used during bronchoscopic procedures to debulk malignant airway tumors, control hemoptysis, remove granulation tissue from stents or anastomoses, and treat a variety of other benign disorders [59–66].

Indications and Contraindications

Electrocautery and APC are used to treat central endobronchial benign or malignant airway lesions [62, 63, 69–72]. The most common indication for these techniques is resection of an obstructing airway lesion that is associated with dyspnea, hemoptysis, cough, or postobstructive pneumonia. Treatment may be curative or palliative. Characteristics of lesions that are associated with improvement of a patient's quality of life following palliative resection include polypoid shape, large endobronchial component, location in the trachea or main stem bronchus, and a short length. It is also favorable if the airway lumen can be visualized beyond the lesion and the distal lung is still functional. Malignant tumors—Symptomatic airway obstruction caused by bronchogenic carcinoma is the most common indication for endobronchial electrocautery and APC in patients who are not operative candidates [73–76]. Endobronchial electrocautery has been used to treat other causes of malignant airway obstruction as well, including endobronchial metastases [77, 78].

APC and EC can be also used for the treatment of the endoluminal carcinoid, with less complication and bleeding compared with other treatments or lung surgery [79, 80].

Such resections are only palliative if the lesion is malignant. Indolent malignant tumors such as bronchial carcinoids are less common but may also be treated effectively with endobronchial electrocautery [70–73] as well as radiographically occult intraluminal microinvasive lung cancer. Whether APC can cure early lung cancer is not fully established. The fact that endobronchial electrocautery has been shown to cure early lung cancer suggests that APC may do the same.

Benign lesions—Endobronchial electrocautery can be used to treat benign obstructing lesions of the central airways such as granulation tissue, hamartomas, papillomas, and lipomas. Another setting in which endobronchial electrocautery is used to treat benign disease is when there is granulation tissue obstructing metal or hybrid stents. Indications for APC include benign polyp removal, hemostasis, and debridement of

granulation tissue around endobronchial stents [81–84] and new approach for the treatment of lung infection as abscess and neoplastic or post-surgery fistula [85–87].

The penetration depth of the argon plasma is reliably 2–3 mm, which makes APC a valuable tool in treating superficial bleeding and debulking granulation tissue and tumors such as papillomas (Fig. 8.10). Endobronchial lesions may cause hemoptysis or postobstructive pneumonia, both of which can be successfully treated with endobronchial electrocautery.

APC can be used to the treatment of recurrent or massive bleeding, in combination or not with other methods (as cryotherapy) [88]. Treatment (and prevention) of postobstructive pneumonia requires the restoration of at least partial airway patency. This can be achieved using endobronchial electrocautery.

Extrinsic compression of the airway is a contraindication to electrocautery and APC. In this circumstance, there is no endobronchial tumor to remove, and these techniques can produce a hole in the bronchus. Electrocautery with unipolar electrodes can deprogram cardiac pacemakers or implanted defibrillators and should be undertaken with caution in such patients [74].

Description of the Equipment Needed

Similar to laser tissue destruction, the effect of both endobronchial electrocautery and APC is determined by heat and tissue interaction and is fairly rapid. Heat is created through the application of high-frequency electric currents to coagulate or vaporize tissue.

Various probes are available to perform controlled conductance of electrons; each probe can be chosen to match the personal expertise and needs. Current density is the issue to be considered, as the size of the probe functions as the focusing point for electrons. Therefore, ultimate tissue effect depends on the voltage difference between probe and tissue, the surface area of contact, and the time of application [89].

The difference between the two procedures centers on the fact that APC is a noncontact mode of tissue coagulation. Dedicated operators use argon plasma as the medium to conduct the electric current in APC rather than using the contact probe as a medium to conduct the electric current as electrocautery does. In addition to the equipment needed for the flexible or rigid bronchoscopy, a dedicated operator needs a high-frequency electrical generator in combination with insulated

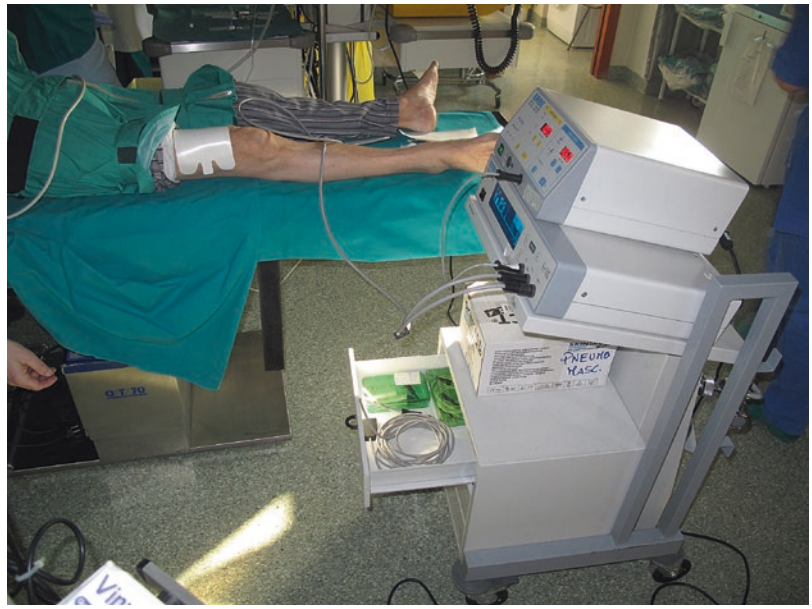

Fig. 8.10 Argon plasma coagulation

probes. Different types of probes in terms of shape as well as polarity (monopolar vs. bipolar) are available. For patient and staff protection, proper insulation precautions need to be observed. Insulated flexible equipment is also available. Electrocautery electrodes—Unipolar electrodes are most commonly used and may be rigid or flexible. The rigid blunt electrode is 70 cm long and 2.5 mm in diameter, while flexible devices are 190 cm long and 2 mm in diameter. Electrodes are available in several configurations: blunt probe, knife, forceps, or wire snare. Rigid probes are more effective for debulking large tumors, while flexible probes permit treatment of small tumors, particularly in the upper lobes. Electric current flows through the desired instrument, tissues, and a grounded neutral plate electrode attached to the patient. The neutral electrode must have a sufficiently large contact surface with the patient to prevent a cutaneous burn at its point of attachment. Endoscope—Rigid electrocautery probes are used with a rigid bronchoscope, while flexible electrodes can be used through the working channel of a fiber-optic bronchoscope. The ability of an electrode to deliver electricity depends in part on its diameter; for this reason, a fiber-optic bronchoscope should be selected with as large an operative lumen as possible. The operative lumen of a rigid bronchoscope must have a diameter large enough for both the electrode and the rigid optic system. Most bronchoscopes in current use are not grounded, and there is a risk of the endoscopist receiving a shock if there is not a suitable low-resistance pathway for current to pass through the patient to the neutral electrode. In addition, burns of the tracheobronchial tree may result if the bronchoscope makes contact with the patient near the point of electrocautery. High-frequency current generator—Most presently available generators are not configured in a manner that permits precise control of the power delivered to a lesion. Standard generators usually have power output settings that are graduated from 1 to 10; estimates about the actual power delivered at a given setting are often inaccurate, and the delivered voltage is variable. In addition, the resistance characteristics of a given tissue change as it is cauterized, and charring can foul the electrode. This promotes adhesion to the tissues, and the charring serves as an insulator that prevents coagulation from progressing. Newer high-frequency generators are regulated with a microprocessor and a voltage stabilizer, which allow precise control of the thermal coagulation process. Most of these generators switch off automatically at 100 °C in order to prevent the production of exploding steam pockets that can cause tissue perforation, rupture, and hemorrhage (the "popcorn effect"). Additional safety features, such as isolated outputs and precise control of delivered power (in watts), are also included. For APC, a dedicated operator needs a special catheter allowing for the argon gas and the electric current flow. This catheter is not used in electrocautery where there is direct tissue contact. The argon gas is emitted through a Teflon tube that can be passed through a flexible bronchoscope. This gas is ionized because of exposure to high-frequency current, and an electric arc is formed which allows for desiccation and tissue destruction without direct contact.

Application of the Technique

Endobronchial electrocautery and APC are thermal tissue-destructive modalities that use electricity to generate heat. They differ in the fact that APC does not make contact with the tissues it destroys and has a penetration depth of just a few millimeters. For these reasons, it is more suitable for the treatment of superficial and spreading lesions. Once gas is released through the catheter tip, it is ignited through electric current; an arc is formed if the probe is close enough to the mucosal surface, causing heat destruction and desiccation of the tissue. The arc can be moved back and forth (painting) and can even be aimed around bends, making it very suitable for hard-to-reach lesions. When electric current flows through human tissue, a *thermal* effect is observed due to the resistance of the tissue to the flow of electric current. The rise in temperature is proportional to the square of the applied electric current times the intrinsic resistance of the tissue; the latter is

largely a function of vascularity and water content, with the bone and fat having a higher resistance than the skin and muscle [90]. Resistance and thermal effects are also increased by reducing the area of contact between the electrical probe and the patient, since the same quantity of current must then flow through less conducting tissue. The temperature rises at different rates in different areas within a given tissue due to inhomogeneity of tissue density and the irregular distribution of electric current. As a rule, the density of the electric current is largest and the rise in temperature greatest, in the contact area between the coagulation electrode and tissue, and decreases with greater distance from this point. Thermal destruction of tissue can be used to effect coagulation or resection. Coagulation—Thermal coagulation (or "white coagulation") is caused by the relatively slow heating of tissue to approximately 70 °C. Above this temperature, the glucose-containing coagulum dehydrates and carbonizes. Three different coagulation modes are differentiated: soft coagulation, forced coagulation, and spray coagulation. Soft coagulation—Soft coagulation is produced when no electric arcs pass between the coagulation electrode and the tissue; this prevents the tissue from becoming carbonized. The unipolar or bipolar electrode is brought into direct contact with the tissue to be coagulated, and <200 V is employed. This mode is used when coagulation is needed solely to stop bleeding. Forced coagulation—Forced coagulation results when electric arcs are generated between the coagulation electrode and the tissue in order to obtain deeper coagulation than is achieved with soft coagulation. The electrode is kept in contact with the tissue, a minimum of 500 V is used, and cutting effects are avoided. This mode is used for vaporization of tissue. Spray coagulation—Spray coagulation is characterized by the intentional generation of long electric arcs between a spray electrode and tissue without any direct contact between electrode and tissue. High voltages are necessary, and tissue destruction and carbonization are readily accomplished. This mode is used when a large area is to be cut and vaporized. Resection—Tissue can only be cut when the voltage between the electrode and the tissue is sufficiently high to produce an electric arc, effectively concentrating the electric current onto specific points of the tissue. The temperature produced at the points at which electric arcs contact the tissue is so high that the tissue is immediately evaporated or burned away. Electric arcs cannot be triggered and tissue cannot be cut if <200 V is used. Higher voltages are sometimes required, depending on the resistance characteristics of the tissue to be resected. General precautions are required to prevent electrical injuries to the patient, clinician, and support staff. The patient should not have any contact with metal from the table, and sheets should be dry. The neutral plate electrode must be placed in its entirety on the patient. If the contact surface is not sufficient, the current will pass from the patient through smaller contact points which, by virtue of their lesser area and consequently higher resistance, may cause burns. At a minimum, cardiac rhythm and oxygen saturation should be continuously monitored and blood pressure frequently assessed during the procedure. Routine intraoperative monitoring protocols are generally used if the electrocautery is performed under general anesthesia. The procedure usually lasts between 20 and 60 min if performed through a rigid bronchoscope and longer if a flexible fiber-optic scope is used. Anesthesia—General anesthesia is usually required if endobronchial electrocautery is performed through a rigid bronchoscope, although dissociative anesthesia with sedatives and neuroleptics is occasionally employed. Local anesthesia and conscious sedation can be used when the procedure is performed through a fiber-optic bronchoscope with flexible electrodes. The fraction of inspired oxygen should be kept at the lowest level required to maintain adequate patient oxygenation in order to reduce the risk of tracheal fires. The maximal fractional concentration of inspired oxygen for use with electrocautery is 0.4. Procedure—The fiber-optic endoscope can be introduced by either the nasal or oral route. The procedure is carried out under direct vision, with the electrode introduced within the tube of the rigid bronchoscope

beside the optical system or in the operating channel of the fiber-optic bronchoscope. The operator assesses the lesions to be treated, noting their position and the extent of stenosis or extrinsic compression, whether they are projecting or infiltrating and whether they are hemorrhagic or bland. The electrode must protrude from the end of the bronchoscope by about 2 cm and is then placed in contact with the lesions to be destroyed. The high-frequency generator is adjusted to automatic control of soft coagulation, with a power setting generally between 40 and 60 W, or is adjusted to the visible coagulative effect if a first-generation machine is used. Other modalities, such as forced or spray coagulation or cutting mode, are used as required, and different electrodes (e.g., blunt electrode, wire snare, forceps, or knife) are selected as needed. It is necessary to clean the tip of the electrode frequently, because buildup may damage the electrode and/or reduce the delivered power. Two main methods of electrocautery are used: debulking of tissue by means of a cutting loop and direct electrodestruction of tissue. Both techniques are effective and provide good results, but smoke needs to be suctioned during resection, and an unpleasant burnt tissue smell is given off. Treatment is continued until sufficient patency of the airway lumen is restored and/or bleeding arrested. Resection of tissue generally is accomplished by the use of a unipolar wire snare apparatus similar to that used to excise colonic polyps. The technique is most suitable for narrow-based lesions causing incomplete bronchial obstruction, such that the instrument can be passed distal to the tumor and the base snared. The device is passed either through the endotracheal tube alongside a fiber-optic bronchoscope or inside the operating channel of the fiber-optic or rigid bronchoscope, looped around the base of the tissue to be resected and then energized [69, 74, 91, 92]. Debrided tissue fragments are often too large to be removed through the flexible bronchoscope and must be grasped and removed in conjunction with it. Tissue can be directly destroyed with electrocautery to achieve an effect similar to that seen with Nd:YAG laser vaporization [91, 92]. A blunt cautery probe is directly applied to burn, desiccate, and vaporize obstructing tissue. Unipolar probes have generally been used for this purpose, but a bipolar flexible electrocautery probe (BICAP) has been adapted for use through the operating channel of a fiber-optic bronchoscope [93–95].

Prior to the procedure, a grounding pad should be placed on the patient's lower back or flank. Once the patient is sufficiently sedated, flexible bronchoscopy is performed and the target lesion is identified. A flexible probe—which is usually 1.5 or 2.3 mm in diameter and 220 cm in length—is then passed through the instrument channel of the bronchoscope and advanced until the location of its tip is several centimeters beyond the bronchoscope's tip. This insures that the bronchoscope will not be burned. The probe tip should be within 1 cm of the target lesion and should not contact it. Argon gas is expelled from the probe, and then a high-voltage electric current is passed along the probe. Reasonable initial settings (Table 8.1) are power of 30 W and argon flow rate of 0.8–1 L/min. The operator may then advance up to an applied power of 80 W with an argon flow rate of 0.3–2 L/min. When the electric current contacts the argon gas, the argon gas becomes ionized and conducts a monopolar current to the target lesion. The application time for each burst is generally <2–3 s. The heat produced denatures protein and evaporates intra- and extracellular water. The net effect is tissue destruction and coagulation. To debulk an obstructing lesion, the eschar is removed with forceps, and then APC is applied to the underlying fresh tissue. This is repeated until the tumor is debulked sufficiently. The depth and volume of tissue impacted depend on the voltage applied to the gas (i.e., the applied power) and the duration (i.e., the application time). As an example, the depth of penetration is <5 mm when the applied power is between 40 and 120 W and the application time is £2 s. When brisk bleeding complicates the procedure, increasing the argon flow rate may blow blood away from the source, thereby providing better visualization of the culprit lesion. An endotracheal tube may sometimes be necessary to provide better airway control for patients who are tenuous or whose procedure may be complicated.

Evidence-Based Review

No controlled trials have been published that compare the various modalities that can perform endobronchial procedures.

As a result, current practice is based upon local influences, available resources and equipment, the bronchoscopist's training and preferences, and uncontrolled studies. Endobronchial electrocautery and APC are frequently seen as a less expensive alternative to laser therapy with similar effects and as such similar indications. These treatment modalities are indicated for any benign or malignant tissue destruction responsive to heat delivery. These indications include endobronchial malignancy, benign tumors, relief of post-intubation stenosis, and, in the case of APC, treatment of stent-induced granuloma. The impact of endobronchial electrocautery on malignant airway obstruction has been illustrated by case series. Generally speaking, in such patients, airway patency is restored in more than 80% of patients, and symptoms are relieved in more than 70% [13].

In one series of 17 patients with locally advanced tracheobronchial malignancies who underwent endobronchial electrocautery, 15 patients had immediate reopening of the airway (89%) [73]. Eleven of those patients had restoration of >75% of the normal airway diameter, although only four patients had objective improvement in their physiological parameters. There were no deaths resulting from treatment, but minor bleeding occurred in one patient, and aspiration pneumonia developed in another.

Three patients required additional therapy. A prospective cohort study of 364 patients who underwent APC (482 procedures) reported a success rate of 67%, defined as hemostasis and/or full or partial airway recanalization [96]. The most common indications were airway obstruction (51%) and hemostasis (33%), of which malignancy was the underlying cause in nearly 90%. Of note, rigid bronchoscopy was used in 90% of the interventions. In a retrospective cohort study of 60 patients who underwent APC (70 procedures), treatment was immediately successful in 59 patients [31]. All of the patients had either hemoptysis or airway obstruction, with treatment success defined as resolution of hemoptysis and/or decreased airway obstruction. Hemoptysis did not recur over a mean follow-up of 97 days, and improved dyspnea persisted over a mean follow-up of 53 days. Malignant disease existed in 95% of patients, and all of the procedures were performed with flexible bronchoscopy. A similar study of 47 patients reported a success rate of 92%, which was maintained over a mean follow-up of 6.7 months [62]. However, an average of more than three sessions per patient was required to achieve this result. Endobronchial electrocautery may also effectively treat indolent malignant tumors [72] as illustrated by a series of 11 patients with intraluminal bronchial carcinoid tumors [70]. Electrocautery eradicated lesions in eight of the patients (73%). The remaining three patients could not be completely treated because the lesions were in the upper lobe bronchi. Treatment of radiographically occult intraluminal microinvasive lung cancer is most likely to be successful in patients who have strict intraluminal disease, visible distal margins (detected using autofluorescence), no invasion of the bronchial wall (identified by bronchoscopy), and no extraluminal growth (determined by high-resolution computed tomography) [97].

Endobronchial electrocautery proved useful in treating benign obstructing lesions of the central airways in a series of 38 patients who underwent endobronchial electrocautery [60]. Twenty-five patients had benign lesions, while 13 patients had malignant tumors. A total of 47 procedures were performed, of which 42 were deemed successful (89%).

Also, APC has successfully treated benign disorders such as granulation tissue due to stents or airway anastomoses [63, 96, 98].

Both postobstructive pneumonia and hemoptysis due to the presence of an endobronchial lesion can be successfully treated with endobronchial electrocautery as well as APC. Treatment (and prevention) of postobstructive pneumonia requires the restoration of at least partial airway patency.

APC is superior to electrocautery and laser photoresection in achieving hemostasis. Effective treatment of hemoptysis requires an accessible,

visible lesion. In such circumstances, immediate hemostatic control is gained in approximately 75% of patients. Adequate visualization of the tumor is essential in this situation, and rigid bronchoscopy may allow more effective suctioning of briskly bleeding structures.

Complications—In addition to the risks associated with the rigid or flexible bronchoscopy, potential complications are similar to other thermal therapies and include airway fires (need to keep oxygen levels as low as possible, preferably <40%), hemorrhage, airway perforation, and stenosis. Endobronchial electrocautery is usually well tolerated, although there have been few large series that documented complication rates. Electrocautery can be performed safely as long as certain precautions are adhered to, including avoiding supplemental oxygenation, avoiding direct applications of energy onto stent covering, and keeping energy applications to a minimum. These precautions are necessary because electrocautery can ignite the lining of covered metal stents as well as break metal stents [99, 100]. A number of complications of endobronchial electrocautery have been described [58, 73, 75, 91–94, 101]:

- Application of deep electrocautery too close to the bronchial wall may result in perforation and pneumothorax. Cartilaginous rings may be destroyed, leading to a loss of structural support, tracheo- or bronchomalacia, and/or secondary stenoses.
- Electrocautery generates electric arcs and can cause tracheal fires or ignition of endotracheal tubes, fiber-optic bronchoscopes, or silicone endoprostheses. The risk of fire is increased if high fractions of inspired oxygen are used. The maximal fractional concentration of inspired oxygen for use with electrocautery (or bronchoscopic laser resection) is 0.4.
- Bleeding can result from penetration of the probe into the tumor but generally stops quickly due to thermocoagulation. Significant bleeding occurs in approximately 2% of cases and may be more common with vascular neoplasms such as carcinoid tumors and hamartomas.
- Aspiration pneumonia has been reported, either as a complication of anesthesia or due to aspiration of postobstructive pus into the contralateral lung immediately after debulking.
- Electrical shock and/or electrical burns to the patient or operator may occur if unipolar leads and a nongrounded apparatus are used.
- Ventricular fibrillation has occurred when electrocautery is used near the heart, and interference with the function of implanted cardiac pacemakers or defibrillators may occur.

Complications of APC are infrequent (<1% of procedures). They include airway burn and airway perforation, which can cause pneumomediastinum, subcutaneous emphysema, and pneumothorax and [96].

APC does not appear to increase the risk of bacteremia compared to airway insertion of the bronchoscope. Although contamination of the APC catheter with oropharyngeal commensal bacteria is common, clinically significant infection following the APC procedure is rare [89].

Gas embolism has also been described in a case series, leading to three cases of cardiovascular collapse and one case of death [73, 102].

In all of the cases, the argon flow rate was within the suggested range, but gas bubbles were seen in the left ventricle during transesophageal echocardiography. Ignition of a nonmetallic stent and electrical shock are theoretical complications of APC. Massive bleeding may occur during tumor resection, although this has not been reported. A burned bronchoscope has also been reported. Limiting the inspired oxygen concentration, the applied power (<80 W), and the application time (<5 s) probably minimizes the risk of airway perforation or fire. Keeping the probe tip several centimeters away from any combustible material and from the bronchoscope tip likely prevents airway fire and similarly the bronchoscope from being burned. Placing a grounding pad on the patient and keeping the probe tip away from the bronchoscope tip may decrease the chance of electrical shock. Finally, maintaining the argon flow rate (<2 L/min) may lessen the chance of gas embolism.

Summary and Recommendations

Electrocautery is an effective and inexpensive technique that is most often used for palliative debulking of endobronchial lesions in the central airways. However, it also has the potential to cure some benign lesions. A common indication for APC is resection of an obstructing airway lesion that is associated with dyspnea, hemoptysis, cough, or postobstructive pneumonia. Alternative indications include benign polyp removal, hemostasis, and debridement of granulation tissue around endobronchial stents.

Endobronchial electrocautery and APC are performed with local anesthesia using a fiber-optic bronchoscope. Advances in the design of electrodes, bronchoscopes, and generators may improve precision and safety. The technique can be very useful, particularly in centers where the cost of bronchoscopic laser equipment is prohibitive. No controlled trials have been published that compare the various modalities that can perform endobronchial procedures. As a result, current practice is based upon local influences, available resources and equipment, the bronchoscopist's training and preferences, and uncontrolled studies.

Complications of endobronchial electrocautery and APC are infrequent, occurring in fewer than 1% of procedures. Strategies exist that may decrease the likelihood of a complication.

New endoscopic techniques are available for the treatment of central airway obstruction, such as bronchoscopic cryotherapy. Currently APC is more efficient to treat bleeding, and 8% of patients who receive resection need APC to control bleeding [103].

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Cryotherapy: Application in the Airways

9

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Introduction and Definition of Procedure

Cryotherapy is a technique that uses very low temperatures, below the freezing point, for a suitable period of time in pathological tissues in order to obtain irreversible damages [1, 2]. The use of low temperature in the treatment of pathological tissues found place originally in neoplastic lesions [1] in several medical fields like neurosurgery, urology, ophthalmology, and dermatology, leading to the use of cryotherapy, also called "cryosurgery." Different body tissues have different "cryosensitivities," mainly depending on their water content and microcirculation: most of neoplastic tissues, granulation tissue, the skin, endothelium, mucous membrane, and nerves are cryosensitive, while connective tissue, nerve sheath, cartilage, fat, and fibrosis are cryo-resistant. For this reason, cryotherapy is effective on highly cellular and well-vascularized tumors such as bronchial carcinomas, carcinoids, or granulomas, while it is not effective for management of paucicellular lesions, such as fibrotic stenosis, cartilaginous, and bony lesions.

The application of cryotherapy in the airways found its main indication in restoring airway patency from endobronchial tumor; other indications are treatment of early stage lung cancer, endobronchial biopsy, and foreign body removal. The main advantage of using cryotherapy over other debulking techniques is its high safety: in fact, the tracheobronchial wall, due to its fibrocartilaginous structure, could not be damaged by low temperatures, even when used for a prolonged period or when used repeated times in the same setting. Therefore, cryotherapy could be used safely to treat small lesions or lesions in small caliber bronchi.

The procedure can be done via rigid or flexible bronchoscope. The most commonly used cooling agent is nitrous oxide (N_2O), which is stored under high pressure in a liquid state. The passage of high-pressured N_2O to atmospheric pressure forces the agent to expand resulting in a temperature of -89°C at the distal probe tip; this thermodynamic effect is called "Joule-Thomson" effect: when a highly compressed gas expands rapidly, a low temperature occurs and rapid control of variations in flow and, therefore, in temperature allows the tip to be cooled. The endobronchial tumor is subjected to repeated freeze-thaw cycles determining a cytotoxic effect: the tissue necrosis

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takes place after few days from the procedure, and a cleanup bronchoscopy can be needed to remove the necrotic tissue several days after; this application of the technique is not suitable for patients with acute symptoms due to airway stenosis. Another application of cryotherapy is called "cryoextraction" or "cryo-recanalization" [3] and consists of freezing the tumor and removing it away: in this case, the removal of the tissue is immediately effective and does not require cleanup bronchoscopy; this application can also be used in patients with acute symptoms.

The maximum yield in endobronchial debulking is reached when cryotherapy is used along with other techniques like photodynamic therapy, neodymium-doped yttrium-aluminum-garnet (Nd:YAG) laser, stents, and electrocautery. However, compared with other techniques (mostly laser procedures), the main advantage of cryotherapy is its better safety profile, with no or few risk of airway perforation; moreover, it is also less expensive, probes are resistant, staff does not require personal protective devices, procedures could be performed using high oxygen flow and in patients with airways stent, and there is no need of special training [4]. In contrast, the most important limitation is the delayed effect of the cryogenic damage and the different response in different tissues; for this reason, cryotherapy could not be useful alone in the management of life-threatening airway obstructions. Therefore, cryotherapy in some cases needs to be integrated with all the other techniques cited above in order to achieve a better therapeutic result and to manage complications. It has to be underlined that cryotherapy alone plays no role when the obstruction is due to external compression.

Samples obtained with cryoextraction are also suitable for molecular analyses [5]: the good quality of specimens obtained and the absence of crush artifacts have led to its use for endobronchial and trans-bronchial lung biopsy in lung diseases [6].

Cryotherapy Damage: Molecular Bases

The destroying of pathological tissue takes place via two mechanisms, an immediate effect that occurs within 1 h from the application of cryotherapy and a delayed effect that occurs later (from several hours to days). Due to the temperature drop at freezing range, crystal ice formation occurs both in intracellular and in extracellular compartments. This leads to (a) intracellular organelles damage, especially mitochondria [5]; (b) intracellular hyperosmolarity followed by cell shrinkage and dehydration; and (c) water that gets into the cells, swelling them and breaking the nuclear and cytoplasmic membranes. Moreover, there is a direct damage of the cellular membrane by the crystal ices. To have a maximum lethal effect, it is necessary to have large ice crystals, especially intracellular: this is achieved with a rapid cooling followed by slow thawing.

The described mechanisms are coupled with vascular injury. Vascular injury happens in the thawing phase: with cooling there is vasoconstriction and a progressive loss of circulation that is restored when the temperature rises above zero. The restoration of circulation is accompanied by a hyperemic response with consequent edema, increasing capillary permeability, platelet aggregation, and micro-thrombi formation. This leads to loss of circulation in 30–40 min. Some cells die by apoptosis some hours later after the application of cryotherapy due to an immunological mechanism. Apoptosis is promoted by DNA fragmentation, cytokine release, inflammation, and ischemic injury. The damaged tissue by cryoprobe corresponds to the frozen tissue: the central part becomes necrotic for the direct damage of the low temperatures and for the ischemic and apoptotic phenomena; the peripheral zone, where the temperature ranged between 0 and -40 °C, is partially destroyed containing a mixture of dead and alive cells [1].

Low-temperature damages depend on several factors, like the cooling rate (faster is more destructive), the minimum temperature reached, the thawing rate (slower is more destructive), and the number of freeze-thaw cycles performed. Moreover, the tissue water content is related to the tissue cryosensitivity: the higher the water content, the more cryosensitive the tissue. Malignant tissue is hypervascularized, and even if this feature could render the tissue more resistant to low temperatures

due to a large warm blood flow that dissipates the thermal effect, the microcirculation is particularly sensitive to cryotherapy, leading to vasoconstriction, endothelial injury, and increased blood viscosity due to the formation of platelet plug and consequent thrombosis with ischemia.

History and Historical Perspectives

The effects of low temperatures on living tissues have been well known for many years [7]. Egyptians and Greeks were aware of the analgesic and anti-inflammatory properties of cold, but only in the nineteenth century, the extreme cold was used for the first time for the local destruction of living tissue: James Arnott used a mixture of salt and crushed ice for tumor palliation with a consequent reduction of pain and local hemorrhage; he then proposed its potential use for cancer, acne, breast and uterine cancer, headaches, and anesthetic purposes. With salt/ice mixture, a temperature of -24°C was reached and this was not enough to treat tumors efficiently: it was only with the introduction of refrigerants that lower temperatures could be reached.

In the late 1800s, there was an increasing interest in liquefying gases: Cailletet first demonstrated that oxygen and carbon monoxide could be liquefied under high pressure; in 1895 there was the first commercial production of liquid air by von Linde, and rapidly there was a large spread of liquefied gases on trade [8].

Exploiting the "Joule-Thomson" effect, liquid gases were proposed as refrigerants in the 1900s, chiefly in dermatologic diseases. Campbell White used for the first time liquid air as refrigerant to treat several kinds of skin conditions, including lupus erythematosus, herpes zoster, nevi, varicose leg ulcers, and cancer like epitheliomas. The use of liquid oxygen was limited at the beginning of the twentieth century, and it was mainly used to treat acne. In the same period, carbon dioxide snow was popularized because it was easily compressed and suitable for local treatments.

In 1950, liquid nitrogen took the place of oxygen due to its similar properties compared to liquid air and to oxygen but with less explosive potential [8]: it was used firstly for skin lesions and then has been used in the following years for cancer therapy in many anatomic areas. In 1913 Cooper, a neurosurgeon, invented a liquid nitrogen probe that reached a temperature of -196°C: he treated Parkinson's disease by freezing the thalamus and also inoperable brain tumors. Amoils introduced the "cryoextraction" technique: it was used in ophthalmology to remove cataract and subsequently was used in neurosurgery and in gynecology. By this time, there were more and more applications of cryotherapy in different diseases, and almost all researches were about liquid nitrogen, which is actually the most common used. Compared to carbon dioxide, liquid nitrogen reaches lower temperature, so it is suitable for both benign and malignant lesions.

In 1968, Gage reported the first endoscopic treatment on a bronchial tumor in the USA. Subsequently, other authors reported their first experience of the application of cryotherapy in the airways for endobronchial tumor debulking: in 1986 Maiwand [9] reported 75 cases of advanced tracheal and bronchial carcinoma (mainly squamocellular carcinoma), in which cryotherapy was used to relieve symptoms. A rigid Storz bronchoscope was used with a rigid cryoprobe, in general anesthesia, using Venturi positive pressure ventilation during the procedure. Endobronchial tissues were frozen with nitrous oxide, at a temperature of -70 °C for 150 s, and afterward thawing was allowed separating the cryoprobe from the tissue. The tumor was then frozen again at the same site for a further 150 s. A second treatment was done after 2, 4, and 8 weeks, depending on the patient's response and on the clinical findings. Symptoms like stridor, dyspnea, and hemoptysis improved in the majority of patients. In 12 cases, the condition of patients did not improve, in 6 patients there was a progressive worsening, and 1 patient died from nonsurgical cause. No cardiovascular complications occurred. Homasson et al. [10] reported the application of cryotherapy for tracheobronchial obstructions with a semirigid cryoprobe through a rigid bronchoscope: out of 21 patients with malignancy, mainly with

squamocellular carcinoma, a good response was achieved in 13 cases. Since then, several studies have investigated the role of cryotherapy in patients with lung cancer, so that cryotherapy was included in international guidelines [1] as one of the available treatments of endobronchial exophytic malignancy and early stage lung cancer.

Despite those promising results, the delayed effect of cryotherapy and the need of further procedures to remove the necrotic tissue led to an increase in the use of other more "immediate" techniques, like Nd:YAG laser, and to a provision of cryosurgery. The advent of flexible cryoprobes, suitable for the flexible bronchoscope, made cryotherapy more widespread than in the past [7]. Moreover, the possibility to extract immediately the tumor with cryoextraction [3] overcame the problem of a delayed effect. The combination of cryotherapy with other therapeutic modalities for lung cancer (chemotherapy, radiation therapy, and other debulking techniques like stent or laser) produced encouraging results [5]. Homasson et al. [11] demonstrated that chemotherapy might be more effective after cryotherapy: the authors explained this effect with the trapping of the anticancer drug in the tumor and immediately the surrounding area due to vascular stasis. Fang et al. analyzed 59 patients with malignant endobronchial masses removed with cryotherapy before chemotherapy [12]: cryotherapy was found to be effective especially for those who can receive chemotherapy due to improvement of performance status after cryotherapy. The combination of cryotherapy and molecular target therapy (gefitinib) resulted in a better stabilization and progression of disease and a better survival in patients with NSCLC (non-small cell lung cancer) when compared with molecular target therapy alone [13].

Cryotherapy would also increase the radiosensitivity of a tumor [14]: initial cryotherapy followed by irradiation was administrated in 38 patients with NSCLC. A better survival was associated both with the efficiency of the initial debulking by cryotherapy and with the local control induced by the irradiation, suggesting a potentiation of irradiation by cryotherapy.

Finally, a new method of delivering cryotherapy was proposed: the so-called spray cryotherapy, a noncontact system to deliver liquid nitrogen through an endoscopic catheter. Rapid freezing and thawing of the targeted tissues causes cellular death and hemostasis. However, intraoperative complications could be higher compared with the standard application of cryotherapy due to nitrogen retention: it should be avoided with adequate venting of the gas with a rigid bronchoscope or an endotracheal tube, to prevent blood oxygen falls and barotraumas.

Indications and Contraindications

The main indications of cryotherapy are listed below [2]:

- Endobronchial lung cancer
- Early stage lung cancer
- Metastatic disease
- Benign and rare tumor
- Foreign body removal

Endobronchial Lung Cancer

Patients with lung cancer present, in approximately 30% of cases, with obstruction of the central airways; with symptoms like cough, dyspnea, hemoptysis, and recurrent infections [15]; with a consequent decrease in quality of life and survival. According to international guidelines [16], patients with endobronchial tumor are not eligible for surgical treatment alone and should be treated with a debulking endoscopic technique in order to improve symptoms related to airway obstruction, to improve performance status, and to improve survival (grade D): the debulking technique should be chosen between electrocautery/diathermy, argon plasma coagulation, laser, cryotherapy and cryoextraction, photodynamic therapy, brachytherapy, and stent placement [17].

In the 1980s, the introduction of the laser technique implied a temporary provision of cryotherapy, but its utility was later revalued either for endobronchial tumor debulking or for

enhancing the effects of chemotherapy and radiotherapy. Several studies described the yield of cryotherapy in endobronchial tumor debulking: rigid and flexible probes have been used, via a rigid or a flexible bronchoscope; the airway recanalization was obtained subjecting the endobronchial tumor to various freeze-thaw cycles and repeating bronchoscopy a second time if necessary to clean up the airways, or using recanalization with the immediate removal of the frozen tissue.

Different outcomes have been reported for cryotherapy depending on the pattern of tumor growth in the airways: polypoid lesions and small tumors with a depth of penetration <10 mm are particularly suitable for cryotherapy; conversely in cases with deeper penetration in the submucosa or extrinsic diseases, cryotherapy alone is not indicated for restoring the airway patency and other techniques are suggested [9].

Interestingly, in the report of Maiwand [12], a better survival was reported in patients with squamous cell carcinoma and in patients with undifferentiated large cell carcinoma, while a worse survival was reported in patients with undifferentiated small cell carcinoma and in those with adenocarcinoma. Those results are consistent with others reported in the following years, confirming that patients with squamous cell carcinoma benefit from cryotherapy much more than other types of tumor.

Finally, in patients with lung cancer, the application of cryotherapy optimizes the effects of chemo- and radiotherapy, by improving patients' performance status and survival.

Early Stage Lung Cancer

The disease-free survival in patients with early stage lung cancer treated with surgical therapy is around 90%. Endoscopic procedures could be of value instead of surgical procedures because they offer similar disease-free survival with less perioperative mortality, morbidity, and costs [18]. International guidelines [19] suggest that cryotherapy, photodynamic therapy, electrocautery, or brachytherapy should be used as a treatment option in patient with early stage lung cancer (squamocellular type) not eligible for surgical therapy (recommendation 1C). The use of Nd:YAG laser is not recommended in those patients due to the risk of airway perforation. Compared with other methods, cryotherapy achieves tumor destruction without inducing collagen damage or bronchial wall perforation [19].

Metastatic Disease

Endobronchial metastases from extrapulmonary tumors are rare findings, and as primary lung cancer, patients suffer from symptoms related to tracheobronchial tree obstruction [20].

Benign and Rare Tumors

The key role of endoscopic techniques in the management of patients with benign airway obstruction is well known. As each endoscopic technique has its advantages and disadvantages, combining more than one method to treat benign tracheobronchial tumor is advised, in order to remove the tumor completely and reduce the incidence of recurrence as far as possible [21]. Only few case series or case reports investigated the role of cryotherapy in benign tracheobronchial tumor like hamartoma [22] and schwannoma [23], lipoma [24], and tracheobronchial carcinoid tumors [25].

Foreign Body Removal

Beyond its conventional use in patients with lung cancer, cryotherapy was found to be effective in foreign body removal. Its effectiveness depends on the cryo-adherence of the aspirated body. Porous structures, like pills, food, blood clots, or peanuts, are more adherent compared with bones, metal, or teeth [1]. It can be performed at the bedside, also in intensive care unit [26], and in many cases eliminates the need for rigid bronchoscopy. Several reports described various foreign bodies that were successfully

removed with cryotherapy, including chewing gum [27], blood clots [26, 28], mucus plug [28], granulation tissue [29], aspirated food material [1], and also aspergilloma [30].

Contraindications

Contraindications of cryotherapy are mainly extra-luminal airway obstruction and cryo-resistant tissues like collagen tissue, poorly cellular tumors, and fibrous scars: in those cases, cryotherapy alone is not indicated. Cryotherapy is not indicated in benign tracheal or bronchial stenosis caused by fibromas, lipomas, or post-intubation stenosis [3, 22].

Complications

In contrast with other techniques, cryotherapy was proven to be more safe, especially when compared with laser therapy, due to the lack of perforation risk [22]. The most common complications reported [3] are hemoptysis (4–10%), bronchospasm (4.5%), cardiac arrhythmia (11%), and death (1.3%). In a large case series of 521 patients, Maiwand reported an overall postoperative complication rate of 9%, including 21 cases of hemoptysis (4%), 12 cases of postoperative atrial fibrillation (2%), and 16 cases of respiratory failure (3%). Seven patients (1.2%) died due to respiratory failure [14]. In another study by Maiwand et al. [31], out of 153 consecutive patients, complications were seen in 11 (3 bleeding, 1 pneumothorax, 5 respiratory failure, and 2 complications related to anesthesia), with no perioperative mortality. Transient fever was observed in the immediate postoperative period, maybe due to cell necrosis and the release of tumor necrosis factor [22, 32]. Finally, in the review of Lee et al. [18], out of more than 2000 patients, complications like hemorrhage, mediastinal emphysema, atrial fibrillation, and dyspnea occurred in 11.1% of patients. Most of those complications were treated with conservative methods, while mortality occurred in 7.1% of cases within 30 days from the operation, mainly due to respiratory failure following the disease progression. Thus, considering that cryotherapy is a palliative treatment in patients with poor clinical conditions or with reduced life expectancy, the complication rate could be considered acceptable and relatively low, especially when compared with other endobronchial debulking modalities.

Description of the Equipment Needed

The cryotherapy equipment has several advantages like reusable probes, compact design, setup simplicity, and no risk of airway fire. Cryotherapy procedures need to be performed in a bronchoscopy suite, through rigid or flexible scopes, with a special cryotherapy equipment that consists of a cryotherapy unit, a gas tank, and cryoprobes. Cryotherapy unit incorporates a console that regulates the flow of cooling agents, either nitrous oxide (N_2O), carbon dioxide (CO_2), or liquid nitrogen (N_2), via a foot pedal with a manometer showing gas pressure (usually 45–50 bar) and a gas tank (N_2O, CO_2, or N_2 gas tank). Mainly, two different kinds of probes are available for the application of cryotherapy in the airways, rigid and flexible cryoprobes: flexible probes are of 78–90 cm in length and are available in two sizes, 1.9 and 2.4 mm, for use with minimal working channel diameter of 2.0 and 2.8 mm. Rigid probes are larger, 60 cm long and 3 mm in diameter with a cooling tip of 9.2 mm. Rigid probes could be straight or right-angled and have a reheating system that allows the activation of the thawing phase immediately after cooling. In contrast, the thawing phase with flexible probes is passive meaning that each cycle of freezing and thawing lasts double of time compared with a rigid probe.

Different probes are designed for cryo-recanalization [3]: probes are 78 cm in length and 3.2 mm in diameter and have a stable attachment of the central gas channel in the probe tip, resulting in greater stability to traction. The freezing power is greater due to a

larger surface area. About cooling agent, CO_2 and N_2O are the cooling agents most commonly used. The achieved tissue temperature is a key factor to obtain tissue damage. Probes' tip is cooled by gas decompression (N_2O) and reaches a temperature of -89.5 °C, according to the "Joule-Thomson" effect: it dictates that a compressed gas passing from the pressure in which it is stored (in the tank) to the atmospheric pressure rapidly expands and undergoes cooling. Spray cryotherapy is another way to deliver a cooling agent: it uses a 7F catheter delivering in its tip gaseous liquid nitrogen (N_2) and generating a spray with an exit temperature of -196°C.

Application of the Technique

Like other endoscopic procedures, a thorough medical history, including information about current medications, should be collected. Blood tests and imaging studies need to be performed and checked. Informed consent is also needed. A flexible bronchoscopy should be performed before the cryotherapy in order to better visualize the lesion that need to be treated.

Endobronchial Tumors

After inserting the cryoprobe into the bronchoscope, the tip of the probe is placed tangentially or perpendicularly or within the lesion. Generally, three cycles of freezing and thawing are performed in each location, with a freezing time of around 2–3 min. At the end of each freezing cycle, the frozen area (the so-called ice ball) is well visible and becomes less viewable at the end of the thawing phase. After three cycles, the probe tip is moved into an adjacent part of the lesion. Tissue necrosis by cryogenic damage is complete about 8 days after application. Following this period, the necrotic tissue could be eliminated by expectoration or a second bronchoscopy, which is needed in order to mechanically remove the necrotic tissue, especially if cryotherapy is used alone as debulking technique, and to treat the adjacent parts if necessary (Fig. 9.1).

Early Stage Lung Cancer

If autofluorescence endoscopy is available, it could be used to define the lesion limits; other-

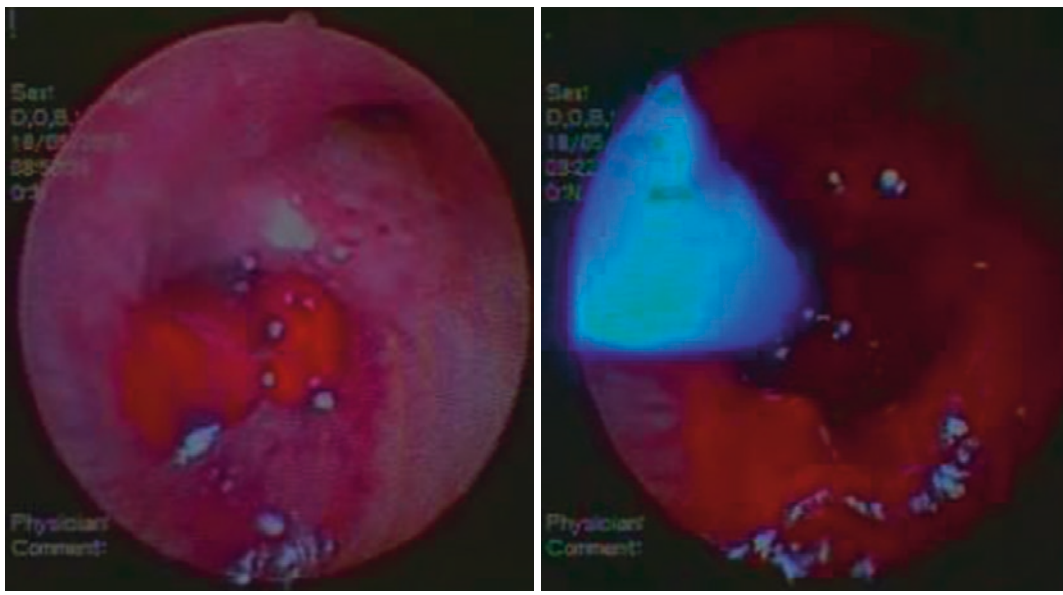

Fig. 9.1 Endobronchial obstruction caused by lung cancer

wise, a margin of 5–10 mm around the visible limits of the tumor should be treated.

Cryo-recanalization

Cryo-recanalization is used for the extraction of benign and malignant tissue. The probe is inserted into the working channel; its tip is placed inside the tumor and then cooled. The destruction due to cryotherapy is visible, allowing the assessment of the local extension of tissue freezing. Together with the bronchoscope, the cooled tissue incorporated at the tip of the probe is pulled out of the respiratory tract. The procedure could be repeated until no relevant stenosis is observed. A newly developed kind of cryoextraction is the lung cryobiopsy technique: with this procedure, trans-bronchial biopsy samples are up to eight times larger than samples taken with forceps, the quality for histological examinations is higher, and additionally no crush artifacts or bleeding is shown [7].

Foreign Body Removal

Foreign body could be cooled and removed with a mechanism similar to cryo-recanalization: a difference in the application of the technique could be the shorter cooling time, for example, clots that could be cooled in 10 s (Fig. 9.2).

Spray Cryotherapy

Spray cryotherapy does not use the "Joule-Thomson" effect, providing a uniform and planar distribution of the liquid nitrogen droplets to the target tissue at a temperature of -196 °C. This allows treating a relatively large area of the central airways despite the irregular surfaces often encountered in endobronchial disease. Understanding the mechanism and potential risks for this new therapy is essential for its safe application to patients. When the liquid nitrogen is delivered to the airway, it undergoes phase transformation and becomes nitrogen gas: it has the potential to displace oxygen and expand

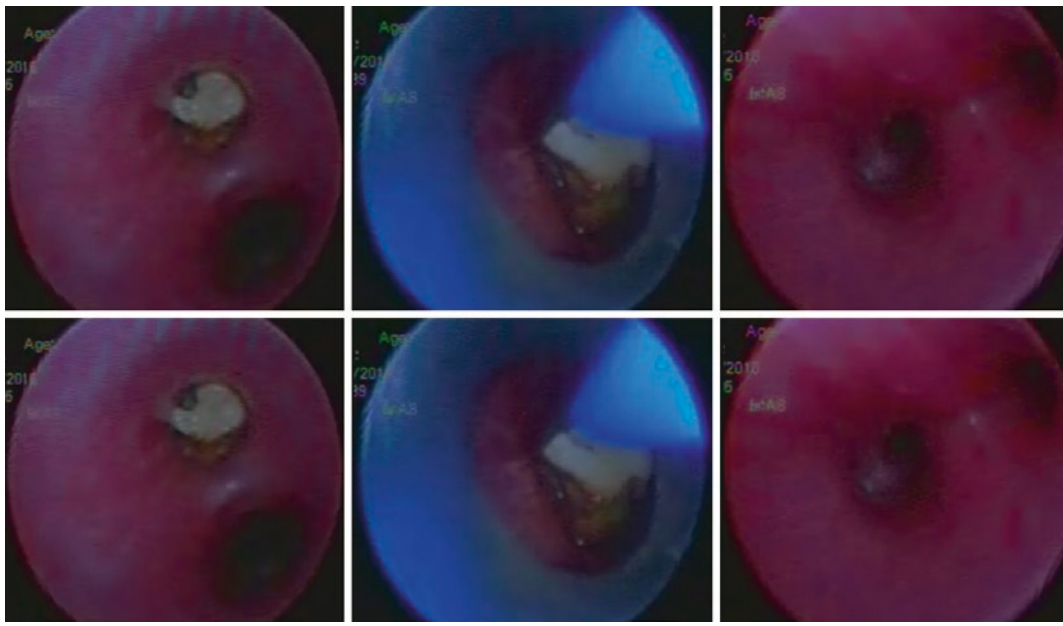

Fig. 9.2 Foreign body in children, a walnut kernel

the lungs to a volume that might exceed their capacity at which point, pneumothorax or barotrauma may occur. So adequate gas ventilation is needed through an endotracheal tube or a rigid bronchoscope.

Evidence-Based Review

Endobronchial Lung Cancer

In endobronchial tumor debulking, the choice of cryotherapy has an evidence level 3 and grade of recommendation D [16]: the same level of recommendation is for electrocautery, argon plasma coagulation, Nd:YAG laser, and stent application, even if each procedure has its safety profile and own indications.

The systematic review by Lee et al. [18] investigated efficacy and safety of endobronchial cryotherapy in lung and bronchial tumor. A total amount of 16 studies were included in the analysis. Patients' population was very diverse, including patients with primary lung cancer, metastatic cancer, benign tumors, and early superficial lung cancer; moreover, due to the variability of methods and the lack of procedure standardization, statistics analyses were not done. Cryotherapy was demonstrated to be effective in approximately 80% of cases and was effective in improving quality of life, symptoms, dyspnea, and pulmonary function especially in inoperable cases.

Maiwand et al. reported 75 cases of advanced tracheobronchial carcinoma (45 squamocellular carcinoma, 7 adenocarcinoma, 18 undifferentiated large cell carcinoma, 5 undifferentiated small cell carcinoma), treated with cryotherapy to relieve symptoms [9]. The majority of patients experienced an improvement of symptoms like stridor, dyspnea, and hemoptysis; 12 patients did not improve, 6 patients worsened, and 1 patient died from nonsurgical cause. Similar results were reported few years later by the same author: in a prospective cohort of 153 consecutive patients, cryotherapy provides effective and rapid control of symptoms caused by tracheobronchial carcinoma and an improved quality of life, with a median survival time of 12.9 months [31]. In this study, a rigid bronchoscope was used except for peripheral smaller tumors that were treated with a flexible bronchoscope.

In an Italian case series, Marasso et al. [33] investigated the therapeutic yield of rigid cryoprobes in 234 patients with malignant and nonmalignant stenosis: 183 patients with malignant tumors (mainly squamocellular carcinoma), 44 nonmalignant stenosis (4 adenoacanthomas, 6 polyps, 16 tracheal granulomas, 12 post-tubercolar heals, 6 leiomyomas and fibroleiomyomas), 4 bronchial carcinoid, and 3 bronchial cylindroma. In patients with malignancy, an improvement of lung atelectasis, hemoptysis, dyspnea, hypoxemia, and sepsis was obtained in 170 cases; in nonmalignant diseases, cryotherapy was also effective, but more settings were necessary to complete the treatment. This study underlined efficacy and safety of cryotherapy compared to other modalities like Nd:YAG laser, limiting its use in nonlife-threatening airway stenosis due to its delayed effect.

Cryotherapy was found to be safe and effective also in a report of 476 consecutive patients with obstructive tracheobronchial tumors [34]: an improvement in hemoptysis, cough, dyspnea, and chest pain was reported and also respiratory function and performance status improved. Survival analysis suggested a possible survival advantage over alternative palliative techniques. Maiwand and Asimakoupoulos [15] reviewed 521 consecutive patients with malignant endobronchial obstruction, not suitable for surgery due to the advanced stage of the disease or the poor clinical condition, which underwent endobronchial cryotherapy for palliation. Rigid probes were used in the trachea and in the main bronchi, and flexible probes were used in peripherally located tumor. There was a symptom improvement in 86% of patients, with a significant improvement in hemoptysis, cough, dyspnea, and chest pain in 76.4%, 69%, 59.25%, and 42.6% of

symptomatic patients, respectively, and there was also a significant improvement in patient's performance status in 63% of cases.

Asimakopoulos et al. [17] investigated the difference in efficacy of cryotherapy in one or two sessions. They reported the data of 329 patients that underwent at least two sessions of endobronchial cryotherapy (group A, $n = 172$) or one session of cryotherapy (group B, $n = 157$) from malignant (primary or metastatic) obstructive lung carcinoma. The most common histologic type of tumor was squamous, followed by adenocarcinoma, small cell carcinoma, and other tumors mainly metastatic. Most of the patients received palliative radiotherapy or chemotherapy, but those treatments were significantly lower in group B. Few patients underwent lung resection, 12 in group A and 8 in group B. About dyspnea, it was improved in both groups: in group A 50.5% of patients improved by at least one NYHA class; less degree of improvement was seen in group B. Similar results in both groups were reported about cough and hemoptysis. About lung function, there was a significant increase in group A in terms of PEF and FVC; the improvement of FEV1 was not significant. An improvement of Karnofsky score was seen in both groups. The mean survival was 15 months in group A and 8.3 months in group B. Patients who had radiotherapy showed longer survival. No particular tumor characteristic was associated with reduction of symptoms. Thus, on the whole, in this study, it was demonstrated that cryotherapy results in symptom relief, respiratory function, and in an improved performance status.

About cryoextraction, Hetzel et al. [3] described a cohort of 60 patients with high-grade airway stenosis from exophytic tumor (51 bronchogenic carcinoma, 4 metastases, 1 carcinoid, 3 granulation tissue and 1 malignant lymphoma). The target tissue was frozen at the tip of the probe and subsequently pooled away with the flexible bronchoscope. The treatment was successful in the 61% of cases, partially successful in the 22% and unsuccessful in the remaining 17% and 14% exhibited local recurrence. About complications, no deaths were recorded, 54 patients had bleeding that was self-limited, and 6 had more intense bleeding (100–300 mL) that was controlled with suction and argon plasma coagulation. In no cases was it necessary to switch to the use of a rigid bronchoscope. More recently, Schumann et al. [35] reported 225 patients with bronchoscopic cryo-recanalization with a flexible cryoprobe. A therapeutic success was achieved in 205 (91.1%) patients. The flexible cryoprobe by means of a flexible scope was used with all patients, and only in 31 cases a rigid bronchoscope was also used. Additional interventional techniques used were endobronchial stents and argon plasma coagulation. Bleeding was the most frequent complication and was mild in 9 patients (treated with ice-cold NaCl or epinephrine solution) and moderate in 18 patients (treated with argon plasma coagulation or bronchus blocker), while severe bleeding never occurred. Finally, Yilmaz and coll. reported similar results [36]: 40 patients with bronchial (primary or metastatic) malignancy were retrospectively included. A successful cryo-recanalization was achieved in 72.5% of patients; authors commented that the success was mainly related to the presence of the distal involvement and the older age of obstruction. Recurrences were observed in 17.2%, with a mean survival of 11 ± 12.7 months. Moderate bleeding occurred in ten patients, which was stopped with an argon plasma coagulator.

Early Stage Lung Cancer

For early stage lung cancer, according to international guidelines [16], the choice of cryotherapy has an evidence level 3 and grade of recommendation D. Only few studies investigated the role of cryotherapy in early stage lung cancer. Deygas and coll. [37] described 35 patients with early superficial bronchogenic carcinoma treated with cryotherapy through a rigid bronchoscope. A therapeutic success was achieved in 91% of cases, local recurrences were observed in ten patients within 4 years, and no complications were observed.

Metastatic Disease

No guidelines state a level of recommendation for metastatic endobronchial tumor. Few report

described this application: [20, 25] reported the first use of cryotherapy in 35 patients with endobronchial metastases from extrapulmonary tumor. The 85% of patients improved their symptoms; in over half of the patients, endoluminal patency improved by ≥50% and survival ranged is from 10 days to 4 years and 8 months, with a median survival of 34 weeks. One-year survival was 37.5%. No complications were observed.

Benign and Rare Tumor

Lipomas: A retrospective multicenter study [26] reviewed the role of bronchoscopic techniques in the management of endobronchial lipomas. Out of 38 patients, 29 underwent laser therapy and mechanical debulking, cryotherapy and mechanical debulking in 7 patients, and mechanical debulking alone in 2 cases.

Hamartoma: Sarioglu et al. [27] reported a case of a man with a polypoid mass arising from the posterior wall of the anterior segment of the right lower lobe. The histopathologic diagnosis was lipomatous hamartoma, and it was resected with an electrosurgical snare, and subsequently cryotherapy was applied to residual lesion on the surface of the bronchus. Ucar [38] reported a case of hamartoma first cauterized using snare electrocautery probe and then removed with cryoextraction. Two other similar cases were reported by Sim et al. [39] using flexible bronchoscopy without complications.

Schwannoma: Le Rouzic et al. [28] reported a case of a patient with a tracheal mass at the CT scan; bronchoscopy revealed an endobronchial multi-lobular tumor with a moderate degree of vascularization. The patient underwent complete resection with a rigid bronchoscope followed by cryotherapy. No relapse was seen during the follow-up period.

Tracheobronchial carcinoid tumors: Dalar et al. [29] investigated the role of endobronchial treatment in patients with tracheobronchial carcinoid tumors. Twenty-nine patients with carcinoid tumor underwent endobronchial endoscopic treatment with diode laser or argon plasma coagulation. Cryotherapy was applied consecutively in patients for whom there were good bronchoscopic visualization of the distal and basal tumor margins and no evidence of bronchial wall involvement. There was no tumor-related death and no recurrence during the following 49 months. There was no difference for survival or recurrence between the surgical and the endobronchial treatment group of patients. Bertoletti et al. [40] studied safety and efficacy of cryotherapy via rigid bronchoscope for the treatment of isolated endoluminal typical carcinoid tumors. Eighteen patients were analyzed: all underwent a complete removal of the tumor and received cryotherapy on the implantation base. Only one patient had a recurrence after 7 years. Thus, cryotherapy was found to be safe and effective in adjunct to endobronchial mechanical resection. Finally, a recent case report by Chawla et al. [41] reported a case of carcinoid tumor successfully biopsied and treated with cryo-recanalization.

Foreign Body Removal

Fruchter et al. [42] investigated the cryo-adherence of various commonly aspirated objects. Organic objects like chicken and fish bones were adherent to cryoprobe, and inorganic objects like safety pin and paper clip were not retrievable by cryo-adhesion. Conversely, several inorganic objects like dental cup despite their low water content were cryo-adhesive. Authors proposed to test the cryo-adherence of the aspirated body before performing the procedure on the patient, if the nature of the aspirated body is not known.

To our knowledge, Sriratanaviriyakul and coworkers [32] described one of the largest case series. They reviewed 38 cases of patients with nonneoplastic tracheobronchial obstruction: the cryoprobe successfully reestablished airway patency in 32 of cases (84%), 24 blood clots, 4 mucous plugs, 2 foreign bodies, and 2 plastic bronchitis. In 68% the procedure resulted in an improvement in oxygenation or ventilation. No complications related to the procedure occurred, only one related to sedation. Lee et al. [31] described a case of a 66-year-old woman admitted

for acute respiratory failure due to an obstruction of the left main bronchus from large blood clots. Flexible bronchoscopy failed to remove the clots, and they were removed using bronchoscopic cryotherapy at bedside in intensive care unit. Grosu et al. [34] reported a case of critical airway obstruction due to pseudomembranous Aspergillus tracheitis: cryotherapy removed successfully a 4 cm piece of tissue and the airway patency was restored. A successful cryoextraction of a chewing gum was reported by Rubio et al. [31]. Maiwand and coworkers [33] described a series of 16 patients with airway complications arising from granulation stenosis after heart-lung transplantation: cryotherapy was an effective treatment for excessive granulation tissue and reduced the need for endobronchial stenting and limited recurrences.

Summary and Recommendations: Highlight of the Development During the Last 3 Years (2013 on)

To date, cryotherapy is an effective and safe technique to treat endobronchial obstruction, both from malignant and nonmalignant diseases. Compared with other treatments, cryotherapy has had a limited role due to its delayed effect and due to the need in some cases to perform a second procedure to achieve an optimal result. Despite this disadvantage, it is safer and cheaper compared to other techniques like Nd:YAG laser, electrocautery, or photodynamic therapy [5]. The introduction of flexible probes that can be used through a flexible scope made the procedure more familiar, and also the access to distal endobronchial lesions was possible. Cryo-recanalization offered a new horizon, allowing the tumor removal immediately without the need of further procedures and with a low complication rate. New devices or new applications of cryotherapy or cryoextraction have been proposed.

Spray cryotherapy consists of a minimally invasive device that delivers extremely cold liquid nitrogen spray through a small catheter to freeze structures inside the airways. Using a flexible bronchoscope, after choosing the target tissue, the operator inserts a special spray cryotherapy 7F catheter through the scope and sprays liquid nitrogen on the diseased or obstructed tissue, with a temperature of -196°C [36]. However, a rigid scope or an endotracheal tube is needed to allow the nitrogen gas to come out. Nitrogen retention is dangerous for two reasons [43]: firstly, it has the potential to displace oxygen, and this could lead to severe desaturation, especially in patients with underlying respiratory failure; secondly, the nitrogen gas expands the lungs to a volume that might exceed their capacity, and this could lead to barotrauma and pneumothorax. The knowledge and the recognition of these side effects are mandatory for the patient's safety. The nitrogen gas during spray cryotherapy is passively removed from the airways: if an endotracheal tube is used, it should always be disconnected from the ventilator and the cuff deflated prior to the procedure, in order to let nitrogen go passively out. A visual assessment should be done, monitoring the chest movements and the frosting mist venting from the mouth or from the endotracheal tube. Browning et al. reported recently [44] 27 patients with malignant airway disease. Eighty procedures were performed in the central airways, with either the truFreeze system or with the G2 CryoSpray Ablation System, alone or in combination (n = 31 procedures) with other therapeutic modalities, also in patients with stent (n = 45 procedures). The truFreeze is an adjustable lower flow setting that allows for a wider margin of safety in the airways by delivering the liquid nitrogen at a slower rate, allowing more time to recognize the buildup of trapped nitrogen gas and make adjustments to the spray and/or the gas ventilation route. Out of 27 patients, 3 complications occurred (transient hypoxemia). The same authors [47] described a case series in which spray cryotherapy with truFreeze was successfully used in malignant and nonmalignant stenosis. Two patients with central tracheobronchial tumor were successfully treated with spray cryotherapy in conjunction with chemotherapy and radiation therapy. In two patients, cryotherapy was used to unblock an airway stent from tumor tissue and from granulation tissue and to prevent

relapses. One patient with cough caused by extensive infiltrating tumor throughout the trachea and the main bronchi was also successfully treated with repeated application of spray cryotherapy. Moreover, spray cryotherapy was also effective in a patient with post-intubation stenosis, in conjunction with balloon dilatation. No complications were reported in all four patients. The only prospective study about cryotherapy, to our knowledge, is still ongoing: the study is performed in the Netherlands [45] and aims to investigate the feasibility, the efficacy, and the safety of spray cryotherapy with the truFreeze system, in malignant and nonmalignant central airway diseases.

Another proposed use of cryoprobes in the airways is in place of endobronchial biopsy to sample exophytic and flat airway lesions. A randomized clinical trial [46] concluded that endobronchial cryobiopsy is a safe technique with superior diagnostic yield in comparison with conventional forceps biopsy: out of 593 patients randomized, in 281 forceps biopsy was done and in 282 cryobiopsies through a flexible bronchoscope. The diagnosis was achieved in 85.1% of patients randomized to conventional forceps biopsy and 95.0% of patients who underwent cryobiopsy and there was no difference in complications (bleeding). Recently, in the study of Rubio et al. [47], cryobiopsy allowed sampling of exophytic and flat lesions located centrally or distally in the airways; specimens were larger when compared with standard forceps biopsy.

Cryotherapy has been shown to have effects also in systemic treatment, such as chemo- and radiation therapy, making the tumor more susceptible to those treatments [19–22].

Finally, an interesting study by Chudasama and coworkers [48] investigated the impact on circulating tumor cell spread after cryotherapy: they enrolled 20 patients scheduled for endobronchial cryotherapy and sampled circulating tumor cells at the baseline and post cryotherapy. An increased level of circulating tumor cells was observed after cryotherapy in the 75% of patients.

In conclusion, the use of new devices and the proposed new applications of cryotherapy make the procedure versatile, and in the near future, there could be the possibility to extend the indications and to minimize the complication rates.

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Endobronchial Brachytherapy

10

Cristina Gutiérrez Miguélez
and Antoni Rosell Gratacos

Introduction

Brachytherapy refers to a radiotherapy method where the source of radiation is inserted into a tumor or in close contact to it. In endobronchial brachytherapy, the applicator is left inside the bronchus or trachea to treat an endobronchial or intratracheal tumor.

The first endobronchial brachytherapy treatment was published in 1922 in the *New York Medicine Journal*, reporting two cases successfully treated.

Since then, there have been great technological advances, such as the introduction of the flexible bronchoscope, the possibility of processing images and planification in 3D with computerized tomography, and also the application of new sources of radiation, that are more active and safer that can be introduced by afterloader devices. As a consequence, treatments are administered by high dose rate (HDR) mainly, while low dose rate treatments (LDR) are no longer applied.

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In consequence, a better local control with amelioration of symptoms has been obtained, as well as a reduction in secondary effects.

Indications

Tumors that benefit the most with brachitherapy are those with an endoluminal component with minimal extraluminal compromise, less than 4 cm in length and less than 1 cm in depth. The endobronchial light should allow passing the treatment catheter. An evaluation bronchoscopy should be performed beforehand, to evaluate the compromized airway, with addition of some other methods such as endobronchial fluorescence, ultrasonography or computerized tomography as consider necessary.

Brachytherapy can be applied with curative or palliative intention, as an only therapeutic method (radical brachytherapy) or after external radiotherapy, when local control has not been achieved. Rarely, it can be indicated to control symptoms such as hemoptysis, or as a bridge to other treatments [1].

Brachytherapy Indications

Curative Intention: Tumors of any histollogy except small cell carcinoma can be treated with brachytherpay. In order to be curative, tumor

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should be limited to the lung, with negative lymph nodes and abscense of distant metastasis. Small tumors benefit the most. This method is selected as an only therapy when patients are not surgical candidates or have very poor lung function to allow external radiation.

A confirmation biopsy is mandatory, as well as a complete staying to rule out secondary compromise.

It can also be indicated when there is a relapse after surgery [2] or radiotherapy, or when positive margins are found after a surgical procedure.

Brachytherapy with palliative intention: In this scenario, the indication is related to symptom control when there is cough, hemoptysis or obstructive pneumonitis. Brachytherapy can be indicated in primary or metastatic endoluminal tumors that do not present esophageal infiltration (to avoid fistula formation). Dosing for all listed situations are smaller than the used for a curative treatment. Brachytherapy can be also associated with other methods such as laser, when the major obstruction has been relieved and there is endoluminal tumor left. Other indication is relapse after surgery or external radiotherapy in advanced lung cancer, to avoid airway obstruction.

Technique

The patient must be fasting and can be premedicated with codeine, benzodiazepines, and bronchodilators. Also local anesthesia with lidocaine can be used.

Under sedation, both the pulmonary physician and the radiation oncologist start the procedure (Figs. 10.1 and 10.2), under fluoroscopy control (Figs. 10.3 and 10.4). It is important that both can see the aspect of the lesion and changes between fractions to evaluate response and possible complications. The bronchoscopist introduces the flexible bronchoscope until reaching the lesion to treat. Site of treatment must be overpassed in at least 2 cm. We check the position of the bronchoscope by fluoroscopy. Then we introduce the treatment catheter (Fig. 10.5)

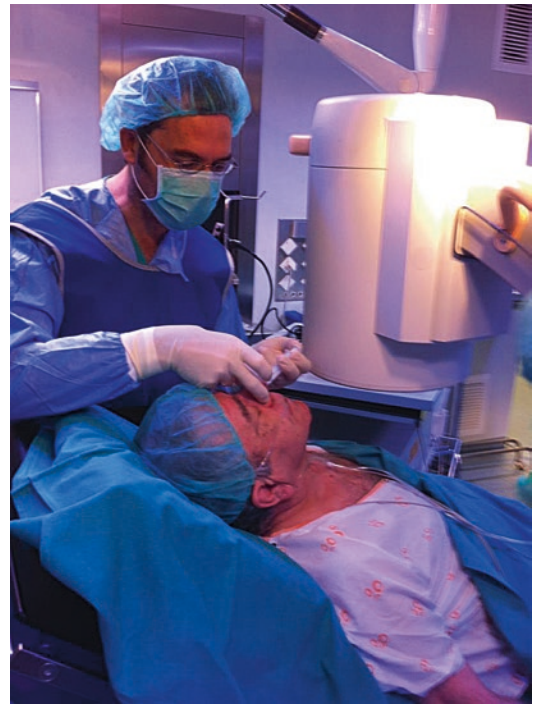

Fig. 10.1 Insertion under fluoroscopy guidance

through the bronchoscope and after that, we withdraw the bronchoscope, leaving the catheter in place, under fluoroscopy control. We attach the connector and inside the catheter a dummy source. Then, we fix the tube to the nostril with tape, and mark the position at the level of the nostril. After that, a CT scan is performed. Images are transferred to the planning system, and both the pneumologist and the radiation oncologist determine the area to treat. A planning target length (PTL) is defined, that must encompass what is called gross tumor volume (GTV). Then, 2 additional centimeters are added: one for the clinical target volume (CTV), and another one to compensate for small movements of the catheter during transferings, changes in patient position, cough, etc.

We must be careful and delineate the possible organs at risk (great vessels, esophagus, etc.) to limit the dose they receive. When we use a simple 5F endoluminal tube, we must be aware that distance to the airway walls is not symmetrical, unless we use a device equipped with a centering

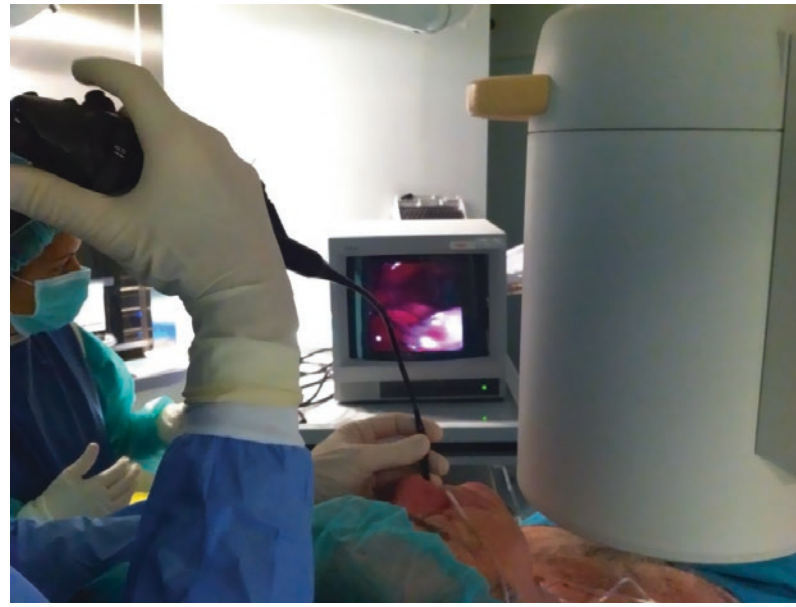

Fig. 10.2 Monitor view

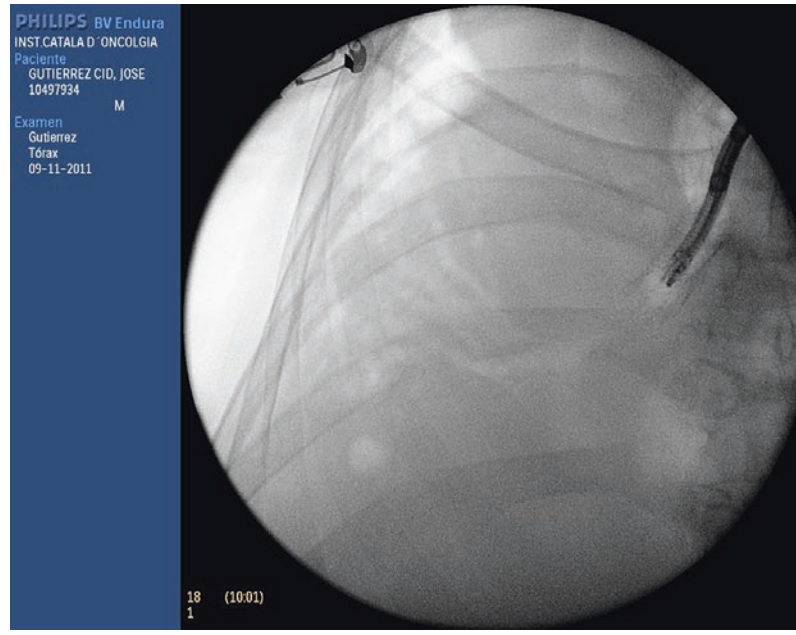

Fig. 10.3 Fluoroscopy before introducing the applicator

method (balloon, protective cover, etc.). With CT planning, GTV is better covered and radiation of critical structures reduced [3].

Usually PTL is between 4 and 6 cm, and the targeted area is at 10 mm from the center of the source. With CT planning, distance to the target zone can be pointed more accurately, ranging between 5 to 10 mm [4] (Figs. 10.6, 10.7, 10.8, and 10.9). When there is an anatomical curve, dose can be increased at the concave

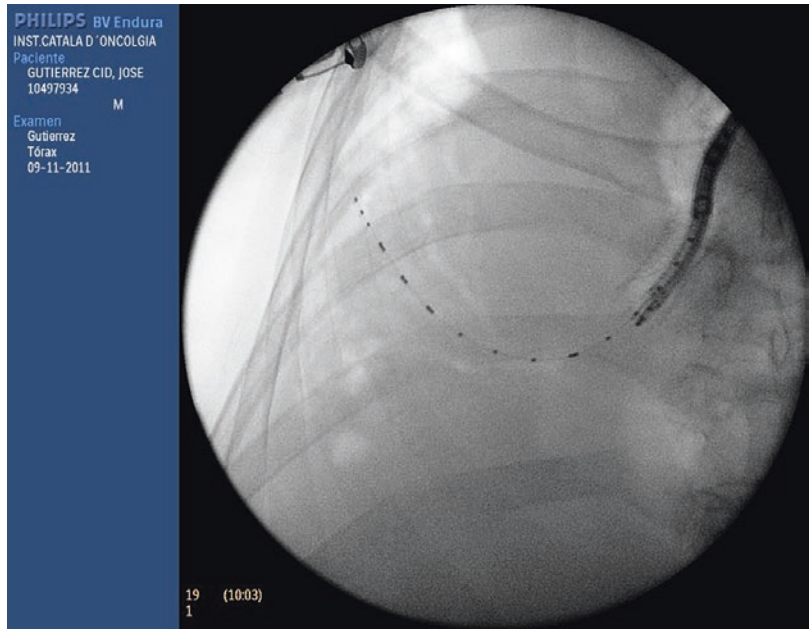

Fig. 10.4 Fluoroscopy with applicator in position

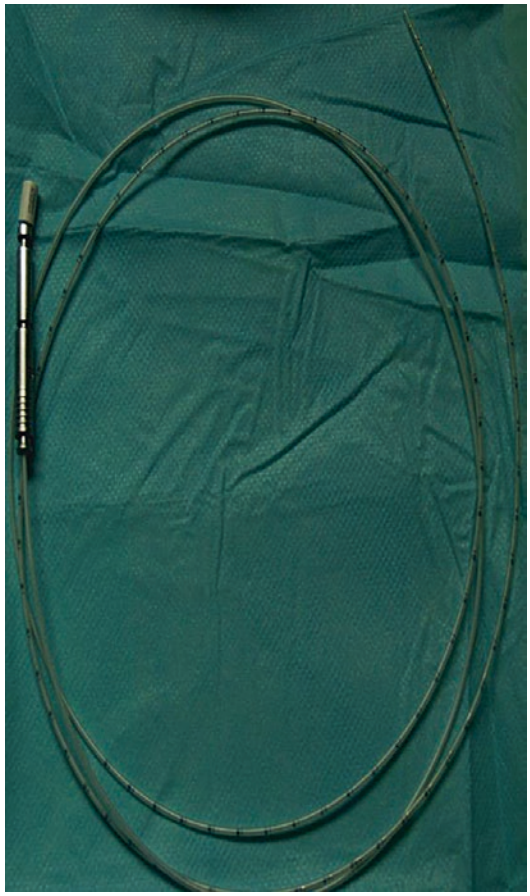

Fig. 10.5 Catheter 5F with dummy source

portion and decreased at the convex part. This correction can be of benefit depending upon tumoral location in the airway [4]. When a metallic stent is in place, we must be aware that the dose can increase in its immediate vicinity.

Before administering the treatment, we must check the ruler mark on the tube at the level of the nostril. We can repeat fluoroscopy to check if the catheter has moved or kinked. Then we connect the tube to the HDR and administer the calculated dose during a short period of time, only few minutes (Figs. 10.10 and 10.11). After the procedure, the tube is easily removed. Patient should be treated maintainig the same body position as the used during CT scanning.

To standardize dose reporting and comparison, we must state not only the target volume but also the dose at 1 cm from the catheter center and the one applied to the sorrounding organs at risk.

The use of appropriate dose reporting, such as the equivalent dose in 2 Gy per fraction (EQD2), should be encouraged when sharing results, particularly when EBRT and brachytherapy are used in combination. This allows more accurate comparison between studies [4].

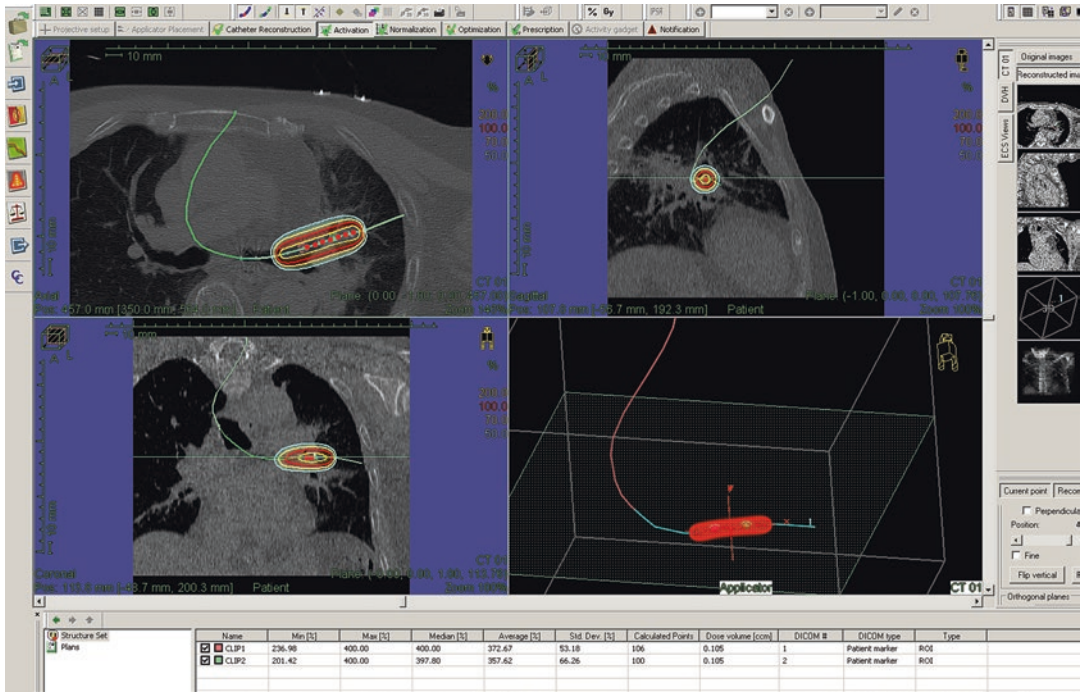

Fig. 10.6 Planning

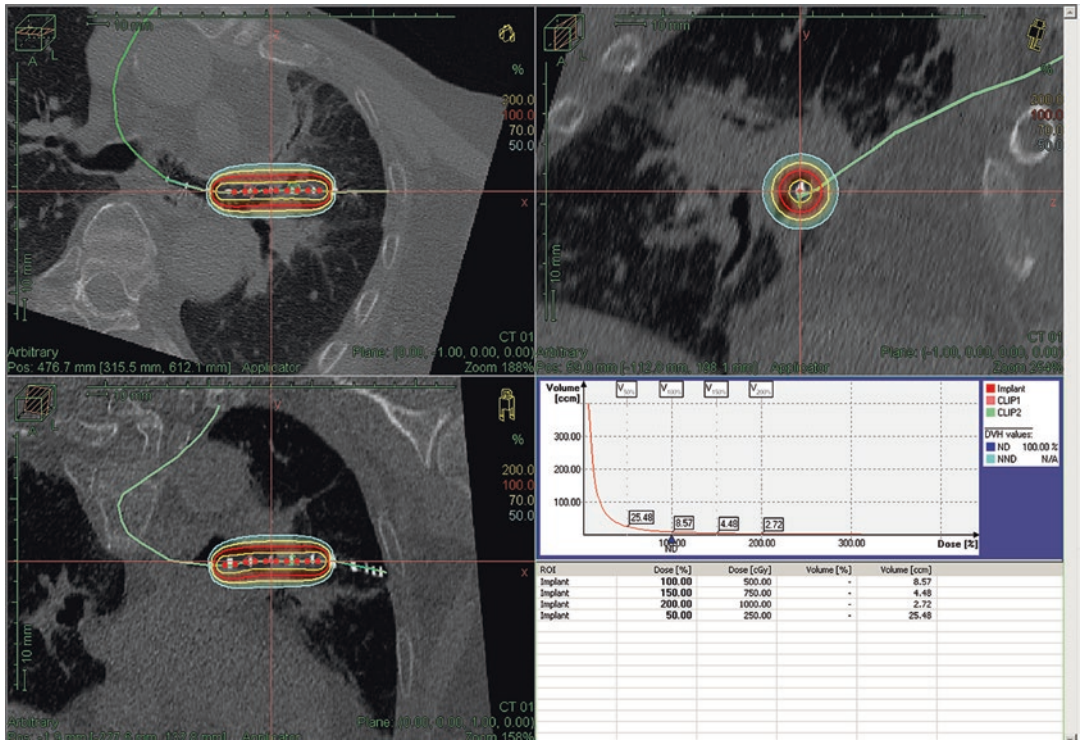

Fig. 10.7 Dose distribution and histogram

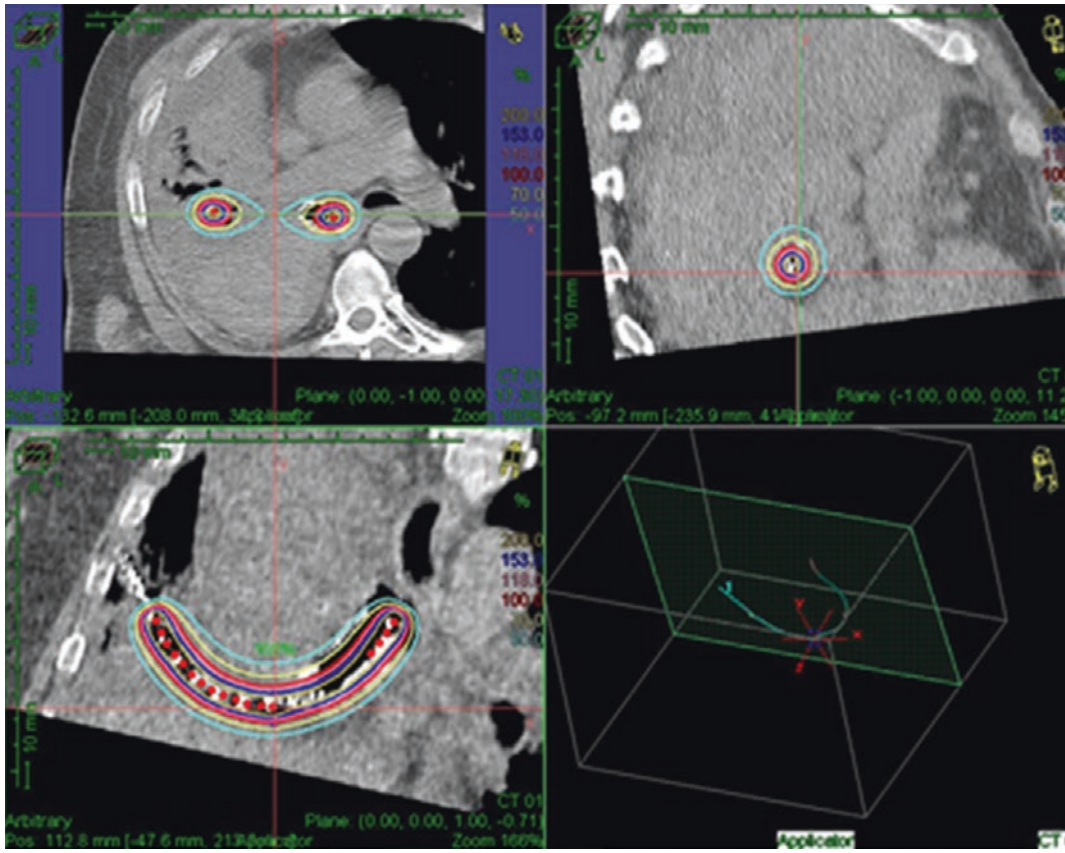

Fig. 10.8 Another case

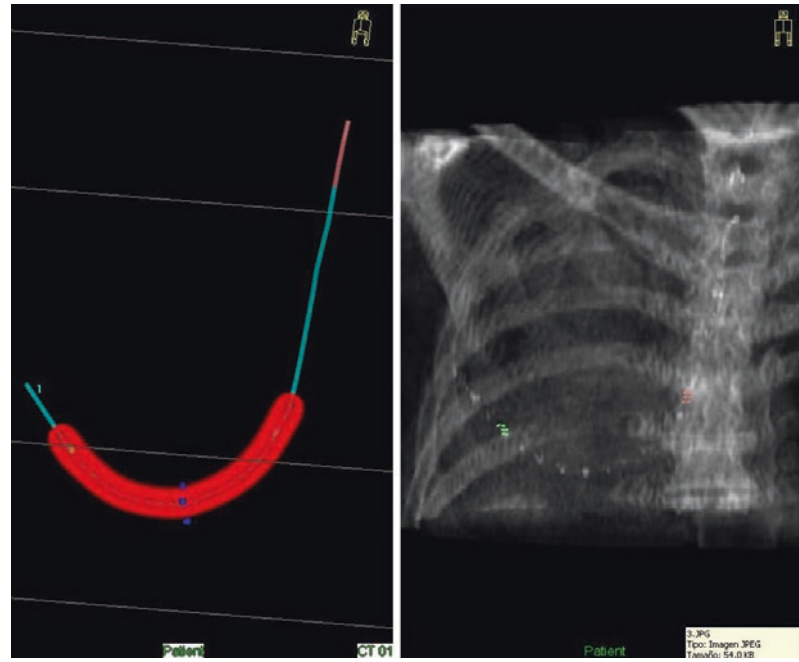

Fig. 10.9 Shape of the 100% isodose

Fig. 10.10 Treatment at the HDR bunker

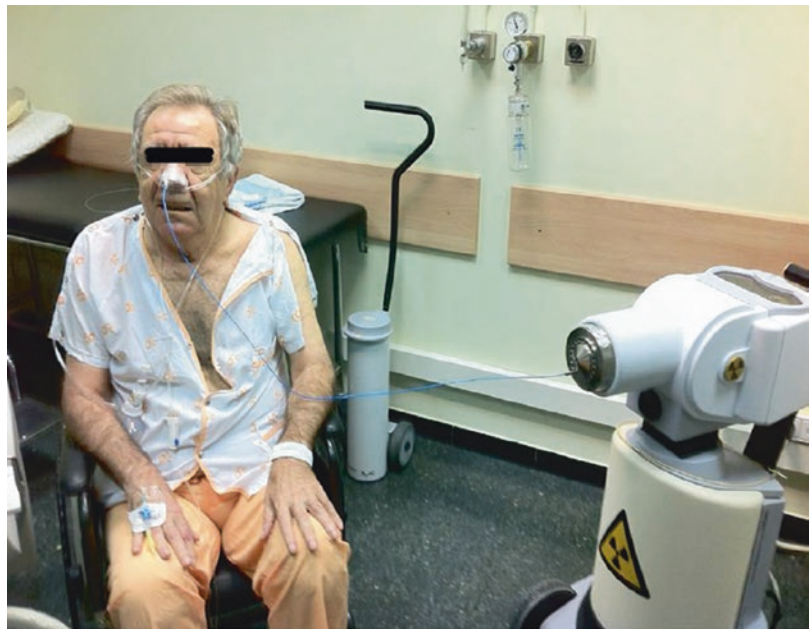

Fig. 10.11 Detail of HDR treatment

Fractionation

The fractionation varies: for curative intent, 6 weekly fractions of 5 Gy is the most commonly used scheme, although there is a great variability ([3–5], see Tables 10.1 and 10.2). When combined with external radiation, one of the most used is 50 Gy plus 3 fractions of 5 Gy [3]. For palliative intention, we tend to administer less fractions and more dose per fraction, in order to diminish patients discomfort [6]. In that case, we would choose 1–2 fractions of 7.5–10 Gy (see Table 10.3).

Table 10.1 Table of fractionations used

First author	Brachytherapy	Distance from source	External beam radiotherapy
Macha	3 × 10.0 Gy	10 mm	–
Speiser (retrospective)	3 × 7.5 Gy	10 mm	–
	3 × 10.0 Gy	10 mm	–
	3 × 10.0 Gy	5 mm	–
Bedwinek	3 × 6.0 Gy	10 mm	–
Mantz (matched pair)	3 × 5.0–7.0 Gy	10 mm	36 × 1.8 Gy (mean)
	–	–	36 × 1.8 Gy (mean)
Huber (randomized)	4 × 3.8 Gy	10 mm	–
	2 × 7.2 Gy	10 mm	–
Mallick (randomized)	2 × 8.0 Gy	10 mm	10 × 3.0 Gy
	1 × 10.0 Gy	10 mm	10 × 3.0 Gy
	1 × 15.0 Gy	10 mm	–
Stout (randomized)	1 × 15.0 Gy	10 mm	–
	–	–	30 × 2.0 Gy
Langendijk (randomized)	2 × 7.5 Gy	10 mm	10 × 3.0 Gy
			30 × 2.0 Gy
	–	–	10 × 3.0 Gy
			30 × 2.0 Gy

Treatment protocols for endoluminal brachytherapy alone and for combined endoluminal and external beam radiotherapy (taken from Lung Cancer. Practical Handbook of Brachytherapy. V. Strnad, R. Potter, G. Kovacs. 1rs edition-Bremen: UNI-MED 2014)

Table 10.2 Brachytherapy: curative intent

First author	Patients	Point of observation (months)	Percentage survival	Percentage of local tumor control
Taulelle	22	30	46%	84%
Perol	19	12	78%	75%
Peiffert	33	14	53%	90%
Marsiglia	34	24	78%	85%
Bleichner	98	24	44.6%	62.5%
Freitag	32	24	100%	81%
Tredanial	29	23	55%	79%
Hennequin	106	24/60	47.4%/24%	60.3%/51.6%

Results of endobronchial brachytherapy with curative intent (taken from Lung Cancer. Practical Handbook of Brachytherapy. V. Strnad, R. Potter, G. Kovacs. 1rs edition-Bremen: UNI-MED 2014)

Table 10.3 Brachytherapy: palliative intent

			Improvement in symptoms			
First author	Patients	1-year survival	Cough (%)	Dyspnea (%)	Hemoptysis (%)	Obstructional pneumonia (%)
Bedwinek	38	n.d.	81	71	81	71
Speiser	362	25	85	86	99	99
Gollins	324	26	62	60	88	46
Muto	280	approx. 45%	82	90	94	90
Mallick	15	n.d.	84.5	90.7	94.1	82.7
Kubaszewska	270	n.d.	77	76	92	82

Results of the clinical studies on endobronchial brachytherapy, palliative intent. (Taken from Lung Cancer. Practical Handbook of Brachytherapy. V. Strnad, R. Potter, G. Kovacs. 1rs edition-Bremen: UNI-MED 2014)

If we combine brachytherapy with external radiotherapy, a good scheme would be 60 Gy plus 3 weekly fractions of 5 Gy each. We must be careful not to administer simultaneously external radiation and brachytherapy in order to decrease toxicity and chronic effects.

Results

Evaluation of treatment must be done at least 3 weeks after last procedure, to let the mucosa recover from acute inflammation. Bronchoscopy is usually indicated then, to assess brachytherapy effects and tumoral response. A 2012 Cochrane meta-analysis [7] examined 14 randomized trials that used endobronchial brachytherapy, either alone or in combination with other therapies, such as EBRT, chemotherapy, or laser therapy. Results showed that a variety of dosing and fractionation schedules used were similar in overall survival. Also, it stated that previous radiation treatment should be taken into consideration when determining the dose and fractionation schedule with HDR endobronchial brachytherapy.

Curative Intent

Complete remission can be obtained in up to 85% of the cases, although very different schemes have been applied, sometimes even during the same study (see Table 10.2). When local control is obtained, survival improves and 40 to 100% of patients are alive after 2 years. Relapses appear usually during the first two years after treatment. Factors associated with local failure are high tumor volume (size greater than 2 cm), the presence of bronchial obstruction greater than 25% of the light, and a tumor that can be visualized on computerized tomography [2]. Having a previous endoscopic treatment is also an indicator of treatment failure. As stated before, the best candidates for brachytherapy with curative intention are those patients with tumors of less than 2 cm in length, not visible on CT scan, occluding less than 25% of the tracheo bronchial lumen.

Palliative Intent

In all series, a relief of symptoms is obtained in most patients (see Table 10.3). Cough, hemoptysis, obstructive pneumonia, and dyspnea, are diminished with brachytherapy, in 85% of patients with no prior radiotherapy and in 70% of the cases that had recurrence after external radiotherapy (see Table 10.4). Quality of life is improved in more than 60% of patients.

Side Effects

Side effects are more frequent when brachytherapy is applied after laser resection or external radiation therapy.

Acute Side Effects

They are very similar to those that can appear after a standard bronchoscopy. Due to inflammatory

Table 10.4 Symptoms Improvement

	Clinical end point			Improvement in symptoms			
First author	Local 1-year control	1-year survival	Remission	Cough	Dyspnea	Hemoptysis	Obstuctional pneumonia
Huber	27%	25%	n.d.	n.d.	n.d.	n.d.	n.d.
Langendijk	57%	25%	n.a.	24%	46%	86%	57%
Sharma	n.d.	n.d.	80%	65%	63%	100%	60%
Mallick	n.d.	n.d.	82.8%	84.5%	90.7%	94.1%	82.7%

Results of clinical studies on combined external beam and endobronchial radiotherapy when used for palliation (in the case of randomised studies, only the results of combined treatment), taken from Lung Cancer. Practical Handbook of Brachytherapy. V. Strnad, R. Potter, G. Kovacs. 1rs edition-Bremen: UNI-MED 2014

changes, the risk of infections is increased. Development of pneumothorax is rare.

Mucosal ulceration can appear if the tube is very close to the wall. CT can help deciding the point of prescription. Distance to the bronchial wall can be adjusted up to 4 to 10 mm in order to avoid this particular side effect. White membranes covering the mucosa are an acute indication of future development of fibrosis or airway stenosis.

Late Side Effects

The most important one is fatal hemoptysis [2, 4] that can occur in up to 32% of cases, depending on the series. It can appear during treatment or few days after the completion of the session. Although it can also be produced by tumor growth in case of progression, it is difficult to distinguish. To avoid this severe side effect, single doses greater than 10 Gy are not recommended [8, 9].

Symptomatic stenosis or necrosis of the bronchial wall in the treated area can also occur [2], as well as the development of tracheobronchialesophageal fistula. The last one is less frequent since treatments are designed by CT and take into consideration the dosing to critical organs such as the esophagous.

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Photodynamic Therapy

11

José Pablo Diaz-Jimenez and Rachid Tazi-Mezalek

Introduction and Principles of Photodynamic Therapy

- Photodynamic therapy (PDT) is a minimally invasive modality used in the treatment of pre-malignant and malignant lung tumor. It's a proven antitumor modality, well tolerated and with few negative effects. PDT uses photosensitizing substance called photosensitizer (PS) that accumulates selectively in tumor tissues leading to harmful reactive oxygen species formation and producing tissue death. In the last years, indications of lung cancer treatment have expanded, and PDT can be used as unique, neoadjuvant, or palliative therapy in the context of a multimodular treatment. It is minimally invasive; it can be applied as outpatient.
- PDT has many advantages:
  - It is selective, damaging tumor tissue and sparing normal cells.
  - It does not compromise additional of future treatments.
  - It does not produce long-term side effects.
  - It can be repeated many times.
  - It has Low systemic toxicity.
  - It is not mutagenic.

Photodynamic reaction is obtained by the association of light and a PS in the presence of oxygen, and produces structural changes that lead to tumor cell-selective killing. Cellular death is obtained by more than one mechanism and mainly involves apoptosis or necrosis, vascular damage, inflammatory reaction, and immune response. The surrounding normal tissue is basically respected, but it can be minimally damaged regenerating afterwards [1, 2].

PDT has been studied from decades; its usefulness has been recognized for a large variety of malignant tumors. However, the photosensitivity phenomenon was already known in the early twentieth century. Several PS are available with different chemical properties and uses in medicine. For more details in research please visit www.clinical trials.gov.

In respiratory diseases, Photofrin® and Npe6 are the most studied PS. FDA (Food and Drug Administration) approved the use of Photofrin® for esophageal cancer in 1995 and early and advanced lung carcinoma treatment in 1998.

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Most of the tumors treated by PDT under protocol are malignant melanoma, angiosarcoma, squamous cell carcinoma, basal cell carcinoma, Kaposi's sarcoma, brain tumors such as glioblastoma, esophageal tumors, retinal tumors including glioblastoma, bladder carcinoma, endometrial and cervix tumors, and tumors of the tongue, larynx, nasopharynx, and vocal cords, among others. The use in low-stage lung tumors had also been supported by several published studies. Cortese et al. in 1997 presented PDT as an alternative treatment method to surgery [3]. The complete response to PDT in low stage depended on tumor size, with a 97.8% success rate in tumors smaller than 1 cm in length.

Principles and Photodynamic Reaction

Three components act simultaneously in PDT: photosensitizer, light source, and oxygen. The principle of PDT is based on the photosensitive molecule activation by a specific wavelength light with the consequent creation of oxygen active forms, being oxygen singlet the main one. This reaction is known as photodynamic reaction (Fig. 11.1).

Singlet oxygen produces in cell membranes, cytoplasm, and organelles peroxidative reactions leading to damage and cell death.

The PS used in clinical and experimental studies accumulate selectively in abnormal or proliferation cells, such as cancer cells or tumor tissues. Its photoactivation produces a specific tissue ablation [4]. After intravenous injection, the photosensitizer can be found in the liver, spleen, kidney, bone marrow, and tumor tissue. Normal organs remove quickly this substance, but in tumoral cells it remains inside for more than 48 h.

The destruction process is quite complex, but basically the damage of a specific subcellular targets depends on the location of the photosensitizer, due to the reduced capacity of migration of oxygen. Photofrin®, for instance, is accumulated in the mitochondria and once activated causes apoptosis. Other PS have empathy for determinate organelles, like lysyl chlorin p6 for lysosomes and porphyrin for membranes. The damage that PDT produces in cell membranes can be observed with in few minutes after light exposure: edema, blistering, ruptured vesicles containing enzymes, reduction of active cell transport, plasmatic membrane depolarization producing more photosensitizer income, increased chromate permeability, and ATPase inhibition [1].

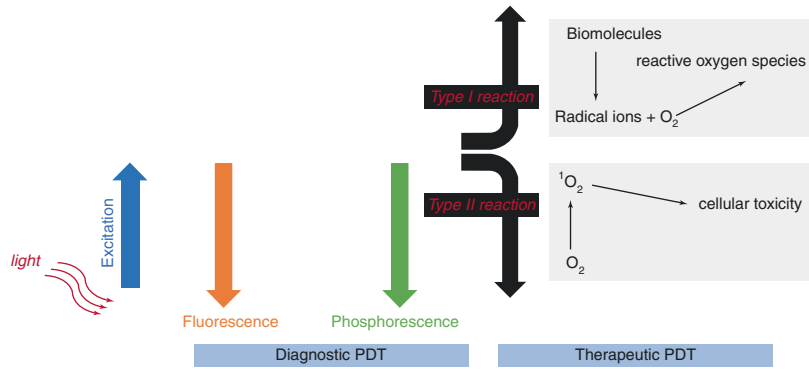

Fig. 11.1 Type I and type II reactions in PDT ("photodynamic reaction"). Schematic Jablonski diagram showing PDT's mechanism of action. Following light absorption, the PS reaches an excited singlet state (PS*). After an intersystem crossing, photosensitizer in a triplet excited state (^{3}PS*) can react in two ways: (1) it reacts with biomolecules through *a hydrogen atom transfer* to form radicals, which react with molecular oxygen to generate ROS (type I reaction); (2) ^{3}PS* can react directly with oxygen through *energy transfer*, generating singlet oxygen ($^1O_2$) (type II reaction). *PS* photosensitizer, *PS** excited singlet, *^{3}PS** excited triplet singlet, *ROS* reactive oxygen species, *$^1O_2$* singlet oxygen, that ultimately produce tissue destruction

Light delivery can be enhanced by using wavelengths from 600 to 800 nm within the optical window [5] to activate PS, which passes from a basal energy level to a "singlet" state. The "singlet PS" can return to its basal state emitting a photon and producing the fluorescence phenomenon or can go to a longer excitement level and more stable state called "triplet PS." To return to its ground state, triplet PS can take two ways reacting with different substances. Triplet PS can react directly with oxygen through energy transfer, generating singlet oxygen with cell toxicity properties through a type II reaction (most common). Or it can react with biomolecules (i.e., lipids, proteins, and nucleic acids) through type I reaction. This reaction transfers hydrogen atoms and generates free radicals and radical ions (radical type depends on the target biomolecule) which along with oxygen result in reactive oxygen species (ROS) generation.

ROS and singlet oxygen have a high reactivity but a short half-life. Due to this, PDT directly affects only those biological substrates that are close to the region where these species are generated, usually within a 20 nm radius [6].

The balance between these two processes (type I and II reaction) depends on the nature of PS being used, the concentrations of oxygen and substrate, and affinity of the PS with the substrate. Both types of reactions result in cell death, but in general, under hypoxic conditions primarily a photodynamic reaction type I occurs, while in oxygenated conditions type II reactions prevail. Schematic Jablonski diagram showing PDT's mechanism of action is represented in Fig. 11.1 [7, 8].

PDT cytotoxic effects on tumor cells can be reached by indirect and direct mechanism. Indirect effect leads to changes in the tumor microenvironment as anti-vascular effect (vasoconstriction, thrombosis, or vessel leakage) and antitumor immune response (release pro-inflammatory cytokines and tumor-associated antigens or fixation of complement). Direct cell killing is due to macromolecule damage with apoptosis and necrosis process. Apoptotic cell death tends to predominate in the most PDT-sensitive cell lines at lower light/photosensitizer doses, and the necrotic mechanism tends to predominate at higher light/photosensitizer doses.

Tumor destruction is based on three steps: (1) PS is distributed in all the cells after the intravenous injection. (2) Because of the differences in the vasculature and lymphatic drainage and the uptake of photosensitizer, PS is selectively retained in tumor cells and interstitial tissue. In a couple of days, PS concentration is higher in the tumor than in the surrounding tissues. (3) The photosensitizing substance absorbs the light energy and produces a photodynamic reaction [9].

Antitumor activity of inflammatory cells and immune reactions are triggered by the sensitized tumor. These two reactions contribute to more complete tumor destruction. But there are some factors that limit it, such as the uneven distribution of the PS agent inside the tumor or oxygen availability.

Likewise, some drugs affect the final result of photodynamic therapy, such as Adriamycin [10] and corticosteroids [11, 12], both enhancing the effects of PDT.

Animal studies by Diaz-Jimenez et al. have shown that the photodynamic reaction, even when it starts almost immediately after exposure to light, continues to act slowly over a rather long time. "In vivo" model showed that tumor cells transplanted immediately after treatment were able to be implanted and to reproduce, while those transplanted 24 h after treatment were not [13].

Technique

Administration of PS can be oral or topical or by a slow intravenous injection (3–5 min), which is the most used modality for lung cancer treatment. Dose and window period until bronchoscopy are variable depending on the PS. The PS should be preferably excited by light of a wavelength included in the therapeutic window between 600 and 800 nm, which has greater capacity for tissue penetration. Photofrin® is used at a dose of 2 mg/kg 48 h before bronchoscopy, and Npe6 is administered at doses of 40 mg/m² 4 h before.

Fig. 11.2 Diode laser of 630 nm

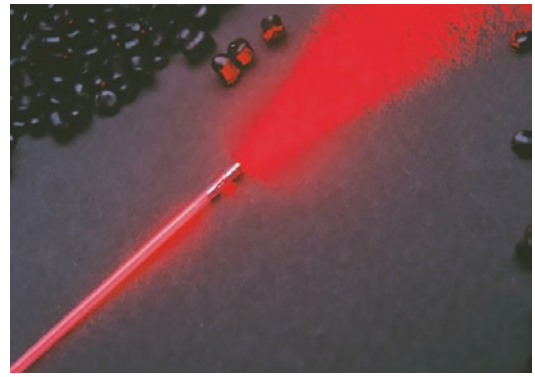

Fig. 11.3 Microlens fiber

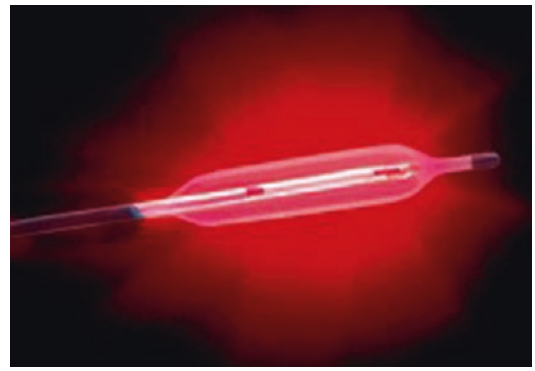

Fig. 11.4 Cylindrical fiber

Bronchoscopy is performed under topical anesthesia or conscious sedation. The tumoral area is illuminated for 500 s with a 630 nm wavelength laser light with nonthermal effect such as the argon-dye laser or diode laser (Fig. 11.2). Forty-eight hours after treatment, one or several clean-up bronchoscopies should be performed to remove viscous debris and detritus from the tumor process destruction to avoid complications such as infection, respiratory distress, or respiratory failure [14].

Two types of light fiber can be used: front light microlens fiber (Fig. 11.3) or 360° diffusing light cylindrical fiber (Fig. 11.4). The microlenses are used for small and superficial tumors such as "in situ" carcinomas. The cylindrical fiber is appropriate for parallel bronchial lumen tumors, tumors that involve small branches of the bronchial tree and in exophytic tumors more than 5 mm in size. It's also useful for large tumors in which the fiber is inserted directly inside the tumor. Current protocols use a power of 200–400 mW/cm² to apply a total light dose of 100–200 J/cm² in a treatment time of 500 s [5]. In addition to argon-dye and diode lasers, other types have been used such as gold vapor laser, copper-dye laser, laser-dye excimer, and yttrium aluminum garnet (YAG) laser with a crystal of potassium titanyl phosphate laser and an optical parametric oscillator [6].

Photosensitizers: Past and Present

The correct choice of PS is important for a successful response to PDT treatment. PS must be nontoxic for the cells in the absence of light exposure and should be selectively retained by

the target (malignant) cells. Ideally, PS should be able to induce an immunogenic response over treated cells such as changes of surface glycoproteins receptors and consequently activate a cascade of immunologic cells response and malignant cells death [15].

Most of PS were first derived from a molecule called hematoporphyrin. Hematoporphyrins are tetrapyrrolic pigments, whose base is the porphyrin molecule, formed by four pyrrolic units linked by four methylic bridges.

Hematoporphyrin is obtained from the blood by two consecutive steps. In a first step, hemin is obtained by treating blood with sulfuric acid, hydrochloric acid, and alcohol. In a second step, the extracted iron is used to obtain crystallized hematoporphyrin. This crystallized form of hematoporphyrin is quite impure.

In 1961 Lipson, Baldes, and Olsen at the Mayo Clinic treated hematoporphyrin by several recrystallization processes, and they obtained a new and pure compound suitable for human use called hematoporphyrin derivative (HpD) [16, 17]. In 1983, Dougherty describes a new component from the HpD called dihematoporphyrin ether or ethyl 8 (DHE), which seemed to have the ability to sensitize tumors [18]. Tetrafenilsulfonato (TPPS) is another well-known PS but not used in clinical practice due to its neurotoxicity and slow serum elimination [19].

At the beginning of the 1980s, PDT was specially used to treat early-stage squamous cell lung cancer, but currently more than 3000 different locations and histological types have been treated in over 32 countries [20]:

(a) *Porfimer Sodium (Photofrin®)*: It is the most extensively studied photosensitizer. In January 1998, the Food and Drug Administration approved in the USA the use of Photofrin® (porfimer sodium) for PDT in patients with microinvasive lung tumor who are ineligible for surgery or radiotherapy [21]. The palliation use of certain tumors was approved in 1997.

Photofrin® and its predecessor, hematoporphyrin derivative, are obtained by complex mixtures of esters from hematoporphyrin. The cytotoxic effect for PDT is limited by the maximum penetration capacity of the laser at 630 nm wavelength light. This wavelength has the highest power to penetrate tissue from 3 to 5 mm.

Following treatment, there is a systemic photosensitivity period that can last up to 6 weeks. Patients should avoid sunlight exposure, artificial light, heat sources, or other strong light sources during the treatment and posttreatment period [4].

(b) *Benzoporphyrin Derivate (BPD)*: It is a second generation PS. Chemically, is a hydrophobic molecule with a maximum absorbing peak at 690 nm, higher than the absorption of the hemoglobin. So it is not attenuated by the blood and has a maximum tissue penetration. Furthermore, BPD is quickly accumulated in the target tissue allowing a PDT treatment from 30 to 150 min after intravenous injection. It is also rapidly cleared from the body. Photosensibility of the skin does not extend more than few days [4].

5-Aminolevulinic Acid (ALA): Endogenous photosensitization induced by ALA is a new approach for photodynamic therapy and tumors detection. It consists in a biosynthetic reaction to produce endogenous porphyrins heme and particularly protoporphyrin IX, which is a very effective photosensitizer that accumulates in mucosal surfaces, such as the skin, conjunctiva, and oral, rectal, vaginal, endometrial, and ureteral mucosa [1]. It has been used with acceptable results to treat superficial tumors of the skin, such as the basal cell carcinoma, squamous cell carcinoma, and adenocarcinoma. Residual photosensitivity after treatment lasts about 48 h.

ALA has been also applied orally and by aerosol inhalation via jet nebulizer, showing that both modalities were well tolerated, allowing tumor visualization, and after oral administration it was possible to perform photodynamic therapy. At 5 and 12 weeks after PDT, marked reduction in tumor volume and recanalization of the bronchus were

observed bronchoscopically, with no associated adverse effects [22].

ALA fluorescence can be used in detection of bladder lesions, early-stage "in situ" lung carcinoma, and malignant gliomas.

N-Aspartyl Chlorin E6 (NPE6): It is a second generation PS that stands out for its excellent antitumor effects and rapid skin clearance in laboratory animals. Npe6 has a longer absorption band (664 nm) than Photofrin®, so it has a slight advantage in deep tumors treatment. The administered dose is 40 mg/m² and laser power density needed is 100 J/cm². Adverse effects are minimal, cutaneous photosensitivity disappears within 2 weeks after administration. It is approved by the Japanese authorities (Japan Ministry of Health, Labor and Welfare) since 2004 for lung cancer treatment. In 2010 it was approved for advanced lung cancer treatment.

Chlorins have been extensively investigated for their potential to treat oral cancer. Extensive cellular damage and complete tumor regression within a week treatment have been reported [23]. Although chlorins exhibit good water solubility and stability, aqueous solutions did not represent the best delivery system in many tumors such as oral cavity or endobronchial tumors. A combination to a mucoadhesive delivery system shows to increase the absorption in the target tissue and improves the overall outcomes [24]. Recently, PS incorporation to nanoparticles prepared from human serum albumin or hyaluronic acid brings new perspectives and challenges to this field [25]. Due to their submicron size, nanoparticles as PS delivery system have numerous advantages such as protection against enzymatic PS degradation, control of PS release allowing a constant and uniform concentration into target cells, and the ability to penetrate target cells [26].

(c) *Others Photosensitizers*: Tin etiopurpurin, SnET2 (Purlytin); lutetium texaphyrin (Lu-Tex); benzoporphyrin derivative monoacid ring A (BPD-MA); mesotetra (hydroxyphenyl) chlorin, mTHPC (Foscan), that are under investigation.

(d) Table 11.1: Summary of main photosensitizers.

Indications and Contraindications

Different tumors treated by PDT include cancers of the digestive tract, lesions of the head and neck, lung cancer, cervix and bladder cancer, and skin cancer, among others. PDT treatment is based on a standard dose of the drug, on a specific light source (nonthermal laser), and on a specific drug-light interval. However, clinical outcomes vary extremely due to many variables: power and duration of light exposure, tissue oxygenation and vascular supply within the tumor; and finally, metabolism of the PS in a particular patient [27]. Summary of curative and palliative indications of photodynamic therapy in the management of patients with non-small cell carcinoma [28] is represented in Table 11.2.

A. Curative PDT Indications

Curative PDT indications are:

1. Carcinoma in situ (this is first-line indication).
2. Microinvasive and limited to the bronchial wall non-small cell lung cancer:
   (a) Early-stage intraluminal and central tumors following definitive surgery or radiation therapy
   (b) Roentgenographically occult central tumors
   (c) Synchronous primary carcinomas
3. Recurrence of operated non-small cell lung carcinoma (stump area) or treated by radiotherapy.
4. Severe dysplasia.

Patient's selection should be cautious taking into account area and depth of tumoral extent. The Japanese Lung Cancer Society defines the criteria of early central lung tumor selection [29]: (1) subsegmentary bronchus location as distal limit, (2) tumor margins must be

Table 11.1 Summary of main photosensitizers

Photosensitizer/generic name	Commercial name	Administration formulation	Approved indications/clinical trials	Skin photosensitivity
Hematoporphyrin derivatives (HpD)/porfimer sodium	Photofrin®	IV/topic/powder for solution Wavelength: 630 nm	Esophageal cancer, high-grade dysplasia in Barrett's esophagus, gastric and cervical dysplasia, bronchial, bladder, and lung cancer	1–3 months
Benzoporphyrin derivative monoacid ring A (BPD-MA)/verteporfin	Visudyne®	IV/liposomes	Age-related macular degeneration	3–5 days
Meso-tetra(hydroxyphenyl)chlorin (mTHPC)/temoporfin	Foscan®	IV/solution in ethanol and propylene glycol Wavelength, 652 nm	Palliative advanced head and neck cancer/squamous cell carcinoma	Up to 6 weeks
Tinethyletiopurpurin (SnET2)/rostaporfin	Purlytin®	IV/lipid emulsion	*Clinical trials*: skin, prostate, and metastatic breast cancer, Kaposi's sarcoma, and age-related macular degeneration	2–3 weeks
Lutetium texaphyrin/motexafin lutetium	Lutrin®	IV/powder for solution	*Clinical trials*: skin and breast cancer	1–2 days
5-Aminolevulinic acid (5-ALA)	Levulan®	Topical/oral/IV/powder for solution/cream	Active keratosis. *Clinical trials*: basal cell carcinoma, esophageal, gastrointestinal, lung, and non-melanoma skin cancer	1–2 days
Methyl aminolevulinate	Metvix®	Topical/cream	Active keratosis, basal cell carcinoma, Bowen's disease. *Clinical trials*: acne	Uncommon
Hexylaminolevulinate (HAL)	Hexvix®	Topical powder for solution/gel	Bladder cancer diagnosis. *Clinical trials*: rectal adenoma and cancer diagnosis, cervical dysplasia	Uncommon

Table 11.2 PDT summary indications—*from J Thorac Dis 2011; 4:63–75* [28]

Summary of curative and palliative indications of photodynamic therapy in the management of patients with non-small cell carcinoma
Definitive therapy for early-stage central endobronchial tumors
Definitive therapy for early-stage locally recurrent central tumors following definitive surgery or radiation therapy
Definitive therapy for roentgenographically occult central tumors
Definitive therapy for synchronous primary carcinomas
Palliation to reduce endobronchial luminal obstruction and tumor stenosis, improve performance status and respiratory function, and resolve acute hemoptysis and poststenotic pneumonia
Neoadjuvant therapy to reduce the extent of surgical resection (pneumonectomy → lobectomy)
Neoadjuvant therapy to convert originally inoperable patients to surgical candidates
Treatment of locally advanced disease as part of multimodality therapy
Treatment of disease with pleural spread as part of multimodality therapy

identified bronchoscopically, (3) tumor size less than 2 cm in its greatest dimension, and (4) squamous cell carcinoma is proven histologically. It also defines three types of lesions according to the endoscopic appearance: flat lesions, nodular lesions, and early polypoid lesions. It has been shown that lesions protruding (nodular or polypoid) tend to invade the bronchial wall in more depth than the flat-type lesions. Flat lesions <1 mm in diameter and visible distal margins were carcinoma in situ in more than 90% of the times, suggesting to be the ideal indication [30, 31].

B. *Curative PDT Contraindications*

Contraindications for curative PDT are:

1. Porphyria or porphyrins allergy
2. Main vessel infiltration (high risk of bleeding)
3. Tracheoesophageal or bronchopleural fistula
4. Carcinoma in situ with lymph node involvement
5. Extrinsic compression or submucosal infiltration

C. *Palliative PDT Indications*

Palliative PDT indications are:

1. To improve endobronchial obstruction caused by any type of tumors: all histological types, primary and metastatic, have responded to treatment [1, 9, 32, 33]. Small cell tumor is not included among the histologic types that can benefit from this treatment mainly because it is known that these tumors respond well to chemotherapy and because they present more as infiltrative tumors than obstructive masses.
2. In order to make tumoral progression as slow as possible and to improve symptoms such as bleeding, secretions, and dyspnea. PDT improves quality of life and survival of patients [1, 9].
3. Some authors have suggested to use PDT for inoperable patients making them candidates for surgical treatment [34] or to reduce tumoral extension in order to perform a less aggressive surgery [35, 36]. Review of available data on this indication, published by four authors [37–40], shows results of 106 responses on 111 patients treated. Recently, PDT has been used at the Tokyo Medical University Hospital as preoperative therapy in 26 patients, reducing the extension of non-small cells tumor and/or converting patients in operable candidates. Four of the 5 patients originally inoperable became operable, and 18 of the 21 patients originally candidates for pneumonectomy were eligible for less invasive surgery such as lobectomy [36].
4. To treat recurrence in the surgical stump. Historically, survival of these patients is around 9 months. McCaughan and Williams have observed 5-year survivals of similar cases treated repeatedly with PDT [9]. Some authors [13] disagree with this view and discourage application of PDT for the treatment of recurrence in the surgical stump, mainly due to the difficulty of managing laser light distally to the surgical suture.

5. PDT causes thrombosis of small vessels and can be used to control bleeding, regardless of location or cause of the bleeding. The amount of bleeding was recorded before, during, and after treatment with PDT, and there was statistically a significant reduction of bleeding during and after treatment [9]. PDT has been described as effective in the palliative treatment of patients with uncontrollable life-threatening hemoptysis [41].
6. In case of non-small cell lung cancer with pleural dissemination, patients can be treated by PDT following a complete surgical resection.
7. As with malignant pleural mesothelioma, PDT may be utilized as part of multimodality management. In fact, PDT can be used for non-small cell lung cancer with pleural spread. In a phase II trial with pleural spread and clinical T4 non-small cell lung cancer, 20 patients underwent surgery that was followed by pleural PDT, and in only 2 patients, PDT was practiced alone. After 6 months of control, the rate of survival was 73.3%, and median overall survival was 21.7 months, compared with 6–9 months for similar patients based on historical controls [42].

D. *Palliative PDT Contraindications*

Palliative PDT contraindications are:

1. Tumoral lesions that obstruct the tracheal lumen in more than 50%, compromize of the main carina or patients with pneumonectomy. PDT causes inflammatory reaction, and airway edema worsens airway obstruction that can go from partial to complete, putting life at risk.
2. Erosion or invasion of vascular structures. When there is infiltration of the tracheobronchial wall or vascular structures, the use of PDT may cause perforation and/or fatal bleeding.
3. Submucosal infiltration or extrinsic compression: PDT is not effective in these cases.
4. Airway acute obstruction. PDT does not relieve airway obstruction immediately, and therefore patients presenting acute obstructive symptoms are not candidates for this treatment and should be treated with Nd-YAG laser or diode laser for rapid desobstruction.
5. Porphyria, allergy, or hypersensitivity to the porphyrin.
6. Leukocyte count less than 2000/mm³, thrombocyte count less than 100,000/mm³, or prothrombin time upper than1.5 normal limit.

PDT Advantages, Disadvantages, and Complications

Advantages of PDT for cancer treatment are:

- Minimally invasive procedure.
- Short treatment time
- Outpatient treatment
- Can be repeated at the same location.
- Little or no scar after healing
- Fewer adverse effects
- Lower cost treatment

Disadvantages of PDT for cancer treatment are:

- Photosensitivity after treatment
- Efficacy of the treatment depending on patient selection, photosensitizer selection and accurate light delivery to the tumoral site.

Complications of PDT for cancer treatment are:

- Fever (approximately 20%).
- Skin and eye photosensitivity (from 4 to 6 weeks). Sun exposure, sources of light, or intense heat (halogen lights, dryers, etc.) should be avoided.
- Adverse reactions to photosensitizing substance.
- Dyspnea due to airway edema and accumulated secretions. Thus, cleanup bronchoscopy is recommended.
- Atelectasis or respiratory failure due to mucus and secretions accumulations.
- Infections: bronchitis and post-obstructive pneumonia.
- Massive hemoptysis.

Applications of PDT in Early-Stage Lung Cancer

The most useful application of PDT is the management of early-stage lung cancer (ESLC) for a curative intent minimizing the loss of lung tissue (Table 11.3). Conventional treatment for patients with ESLC is surgery, and regardless of lesions size, approximately 70% of them require lobectomy. The remaining 30% will require bilobectomy or pneumonectomy [43]. Furthermore, a majority of these patients with lung cancer had a diminished pulmonary function. In addition, the cumulative risk of a second primary cancer in patients with non-small cell lung cancer ranges from 20 to 30% within 6–8 years after initial treatment. Patients successfully treated for small cell lung cancer develop a second primary cancer at an average rate of approximately 6% per year, which increases from 2 to more than 10% per patient per year 10 years after the initial treatment [44, 45].

In Japan, Hayata and colleagues have studied extensively PDT in ESLC, showing that approximately 90% of superficial tumors less than 1 cm of diameter can be completely eradicated with PDT. Patients with nodular tumors less than 0.5 cm diameter showed the same results [46]. Of 81 patients who had complete response to treatment, only 2 died of primary disease during the follow-up period. Fifteen patients were alive and free from disease at 5 years, and three showed similar results at 10 years of follow-up. Complete response (CR) rate was 71%.

In another study, 55 patients with early lung tumors were treated with PDT. Eighty-nine percent of them have a CR, with the best results obtained in those patients with lesions smaller than 1 cm diameter and with visible distal margins under flexible bronchoscopy [13]. Larger tumors tend to penetrate deeper into the bronchial wall with more risk of nodal involvement.

PDT is not useful if there is nodal involvement, so that it is very important to verify absence of nodular compromize before to start treatment. Endobronchial ultrasound has been presented as a useful and complementary method to determine the depth of invasion of small tumors and to detect nodular invasion.

In the series presented by Cortese and colleagues [3], ten patients treated with PDT required a second time surgery, and in 30% of them, N1 nodal staging was found. It is difficult to know if nodal involvement in that series was due to a surgery delay while they were treated with PDT, or was present before treatment. In any case, it shows the need to search aggressively nodal involvement before PDT indication.

Cortese and colleagues present a group of 21 patients with ESLC treated with PDT [3]. Fifty-two percent of them had a CR over 1 year. A total of nine patients, who were followed for an average of 68 months, were able to avoid surgery. Authors concluded that 43% of patients (range 22–66.6%) who are candidates for treatment with PDT could be treated without surgery. Therefore, PDT offers a better quality of life particularly in patients with multiple tumors or elderly ones [20]. The following table (Table 11.3 modified by Sutedja et al.) [47] summarizes the results of early lung cancer treated by PDT with curative intent.

Regarding tumor extension, several studies demonstrated that tumor length on the bronchial surface is strongly related to outcome. Kato and colleagues reported complete remission (CR) in 84.8% (224 of 264 lesions) using Photofrin® for central early-stage lung cancer. Outcome varied according to size of the treated lesions. Four groups were defined as follows: <0.5 cm (56

Table 11.3 PDT in early-stage lung cancer

Reference	Pathology (*n*)	Response	Surviving (months)
Edell et al. [84]	14	CR 14/17 (71%)	7–49 (10 pat.)
Furuse et al. [85]	59	CR 45/59 (83%)	14–32
Imamura et al. [86]	39	CR 25/39 (64%)	4–169 (17 pat.)
Okunaka et al. [87]	10 (sync) 17 (met)	CR 10/10 (100%) CR16/17 (94%)	38 (media)
Sutedja et al. [88]	39	CR 28/39 (72%)	2–95

CR complete response, *Sync* synchronic, *Met.* metachronic, *Pat.* patient

lesions); 0.5–0.9 cm (124 lesions); 1.0–2.0 cm (50 lesions); and >2.0 cm (34 lesions). The CR rates of the first two groups were 94.6% and 93.5%, respectively, while 80 and 44.1% were reported for lesions from 1.0 to 2.0 cm, and for lesions >2.0 cm, respectively [48].

Usuda et al. reported results of 91 consecutive central early-stage lung cancer (CELC) lesions (75 patients) treated with NPe6 at Tokyo Medical University between June 2004 and December 2008. CR was obtained in 85 lesions with a CR rate of 93.4%. Of the 91 lesions examined in this study, 70 had a diameter of ≤1.0 cm and the rest of the 21 cancer lesions were >1.0 cm in size. The CR rate of CELC ≤1.0 cm in diameter was 94% and for those >1.0 cm in diameter 90.4%, respectively [49]. Those studies suggest that central early-stage lung cancer lesion less than 1 cm in diameter showed a favorable cure rate using PDT and that NPe6 has a stronger antitumor effect than Photofrin®.

Regarding treatment of patients with roentgenographically occult carcinoma, surgical resection is the historical indication, but it has significant morbility. PDT a minimally invasive option associated with less side effects and morbility than surgery. Most often, those patients with roentgenographically occult carcinoma present a centrally located early-stage squamous cell carcinoma. Endo et al. [50] treated 48 patients with a follow-up of 12 years. They were all surgical candidates presenting with occult bronchogenic squamous cell tumors of less than 10 mm in lenght. Ninety-four percent of them have a complete response with a survival rate of 81% at 5 years and 71% at 10 years.

Fujimura and colleagues consider PDT as a first-line treatment modality for patients with roentgenographically occult carcinoma of the lung, bronchoscopically visible and less than 1 cm in length, without extracartilaginous invasion or lymphatic node involvement [51].

Finally, in treated patients, a careful monitoring is necessary. Recurrences following PDT can be treated with surgery or radiation therapy.

About synchronous bronchogenic tumors, they present mainly in a central location and they are more often squamous cell tumors [52]. In these cases, PDT should be considered for those patients who are medically or surgically inoperable. Also, it proved benefits in properly selected patients who can be a surgical candidate with a tumor less than 1 cm in diameter. Sokolov and colleagues reported 104 patients with synchronous lung primary tumor treated with PDT that had a significantly correlation between tumor size and regression. A complete regression was observed in tumors less than 1 cm in diameter [53].

Commentary

The average survival of patients with lung cancer is about 13% [54]. One third of these tumors are non-small cell carcinomas. At the moment of diagnosis, approximately one third of patients are stage I or II. Surgery is the standard treatment for patients in stage I, II, or IIIA. The survival for stage I patients has been established from 55 to 75%. For the subgroup of patients with T1N0 disease, survival at 5 years is from 60 to 82 % [55, 56].

In one series, recurrences were about 27%, 60% of them during the first 2 years after resection. Recurrence in the same lung or in the stump area was more common in squamous cell carcinoma. The incidence of a second primary was 34% and was constituted by synchronous (12%) and metachronous (88%) tumors. Therefore, despite surgery, patients with early stage lung cancer have a high rate of tumor recurrence and a high probability of developing a second tumor [38].

Radiation therapy is the standard second-line treatment for patients who are inoperable, with a range of complete responses from 50 to 70% and a median survival of 22 to 48 months for stage I disease. The 5-years survival for patients with T1 tumors who are treated with external radiation varies from 10 to 40% [57].

The best results observed in surgical patients may be due to the fact that patients are less compromized and the extent of the condition is more carefully staged. Patients who are inoperable due to a poor pulmonary reserve will suffer further deterioration after radiation, due to pneumonitis

and fibrosis. Patients who received surgery or maximum radiation doses cannot be retreated in most cases, which is a great disadvantage in a disease with a high recurrence rate.

Therefore, there is a need for therapeutic modalities that can be applied at multiple occasions, if necessary, and do not exclude the use of other methods in case of need. So far, treatment modalities that produce local damage to the tumor include brachytherapy, cryotherapy, electrocoagulation, laser, and photodynamic therapy. They all, however, are limited to centrally located tumors within the endoscopic view and have a penetration power of millimeters. While most of these treatments cause nonspecific tumor damage, PDT causes selective death of cancer cells with subsequent necrosis of the tumor, without injury of the adjacent healthy tissue.

The curative effect of PDT in early stage and superficial tumors has been studied extensively and has been documented in several studies in phase II and III. Since 1980, more than 800 patients have been treated. Success rate oscillate from 80 to 100% in short-term follow-up and between 50 and 60% in long-term follow-up. The main and influencing factors for survival are tumor size and penetration in depth. It also depends on the ability to visualize the full extent of the tumor during bronchoscopy, and its complete irradiation with laser light. Evaluating the location and tumor size is therefore very important. The use of bronchoscopy and high-resolution computed tomography may improve staging and response assessment. Ultrasound has also been used to estimate the depth of the tumor in patients with roentgenographically occult cancer and determine the presence of nodal compromize.

One of the reasons for long-term photodynamic therapy failure is the high incidence of a second primary. Therefore, patients must be followed with regular bronchoscopies, to control local recurrence and to exclude the presence of metachronous lesions, which can be treated with PDT if present.

Complete and prolonged remissions that have been published are promising, but they do not reach the success of surgery (more than 80%). However, it is essential to consider that the term "early cancer" is generic and includes different histological types, with different biological properties and prognosis.

Carcinoma "in situ" is an indication of PDT first-line treatment. Microinvasive carcinoma, however, is an optional indication to be only used in high risk or inoperable patients. Invasive carcinoma is an indication only in a highly selected group of inoperable patients. Severe dysplasia is not a formal indication of this treatment so far.

Application of PDT in Palliative Lung Cancer Treatment (Past and Present)

A review of lung cancer death showed that 57% of patients with nonsurgical disease die of local complications such as asphyxia, hemoptysis, pneumonia, and empyema [58–60]. Other studies show that 36% die from the same causes, whether or not they had surgery. Similar causes of death were found in 58% of patients with surgery versus 83% without surgery, and they have been published in posterior series [61]. Considering that at most, 20–30% of patients with bronchogenic carcinoma are surgical candidates at the time of diagnosis, it can be assumed that most inoperable patients will require palliative treatment at some point during the course of their disease.

However, the use of PDT as palliation in inoperable obstructive cancer patients should be evaluated in the context of what can be obtained with conventional treatment. By applying Nd-YAG laser, coagulation and vaporization of the tumoral tissue is achieved. Laser therapy is usually performed under general anesthesia and is highly effective for debulking airway, especially in centrally located tumors. Massive hemorrhage, respiratory failure, or cardiac arrests are possible severe complications of laser photoresection, but their incidence is quite low (1.5%). Patients can also experience a minor complication in the order of 0.5% of cases [13].

PDT has proven to be an effective palliative treatment. The first treatment with PDT was performed in the 1980s, and since then the number of patients who have benefited from it is increasing day by day. The best results are obtained when the tumor is in early stage (carcinoma "in situ") as shown by several publications [38, 62–66]. When results are depicted according to the stage, I tumors responded with complete response in 80% of cases. Patients who presented in stages II, III, and IV did not obtain complete response except in one patient in 24 cases. Some studies have reported a longer duration response and lower risk of local recurrence when PDT is applied.

Photosensitivity is still a problem. However, it is expected that the second generation of photosensitizers will decrease it significantly. The photosensitizing agent used in most clinical trials is Photofrin® and produces photosensitivity for approximately 6 weeks. This agent is retained in higher concentrations in tumor tissue. The skin, liver, kidneys, and spleen also retain more than the rest of the organs. Skin protection is essential, and patients must be protected from sunlight for a period of 4–6 weeks; otherwise severe retinal and skin damage can occur [67, 68]. No benefit was found in sunscreen creams for the skin, so its use is not recommended.

PDT vs. Nd-YAG Laser Therapy for Advanced-Stage Non-small Cell Lung Cancer

PDT as palliation method was compared to Nd-YAG laser, which has been used for palliation since the 1970s. Photoresection using Nd-YAG laser is considered, by many experts, as the "gold standard" for central airway partial or complete tumor obstruction which is due to nonsurgical malignant primary or metastatic disease. There are enough publications supporting this statement [69, 70]. However, the PDT is a useful palliative method with some advantages over laser therapy, particularly in peripheral tumor localization. In fact, PDT produces more complete tumor destruction, and a better survival rate as been objectified as shown in many studies comparing laser versus photodynamic therapy:

1. In a 1998 prospective randomized study comparing PDT versus Nd-YAG laser in partial obstruction of lung cancer, data of 15 centers in Europe and 20 in the USA and Canada were compared. In the European study, only 40% of patients had prior treatment, while in the American group, all patients had some type of treatment. Results showed that tumor response was similar for the two therapies in the first week, but within a month, 61% and 42% of patients treated with PDT in Europe and the USA/Canada, respectively, had a response, while patients treated with Nd-YAG, 36% and 19%, respectively, were responding in the two work groups (Europe and USA/Canada). Twelve percent and 6% of patients treated with PDT versus 3% and 5% of patients treated with Nd-YAG experienced complete response, with biopsy proven in Europe and the USA/Canada, respectively. The improvement in dyspnea and cough was higher in patients treated with PDT in Europe and was similar in both treatments in the USA/Canada group. The study conclusion was that PDT is superior to Nd-YAG laser to improve dyspnea, cough, and hemoptysis. The incidence of adverse events was similar in both groups, and 20% of patients treated with PDT showed photosensitivity reactions. Those events were due to failure to comply with the precautions suggested [1].
2. Another study from 1997 shows a 14-year prospective experience in 175 patients treated with PDT for squamous cell tumor, endobronchial adenocarcinoma, and tracheal adenocarcinoma [9]. It Included patients that had failed or refused conventional treatment or were ineligible for it. Results showed that survival was affected mainly by the stage of cancer. Compared results with other treatment regimens (surgery or radiotherapy) are presented in Table 11.4 (modified by McCaughan and Williams) [9].

Table 11.4 Comparative analysis of methods of treatment and survival by stage lung cancer TNM (sixth edition TNM classification) (modified by McCaughan and Williams) [9]

TNM stage (sixth edition)	Survival surgery (months)	Survival radiation (months)	Survival PDT (KPS/50)	Survival PDT (KPS.50)
I	42	19	Not reached	Not applicable
II	17.5	18	22.5	Not applicable
IIIA	12	12	8	2
IIIB	7.5	10	7	4
IV	5	–	7	3

KPS Karnofsky performance status, *NA* not applicable, *PDT* photodynamic therapy

Analysis of the period of time after treatment until re-obstruction in patients treated by Nd-YAG laser or PDT showed that immediate results were better in patients treated by Nd-YAG laser bronchoscopy. Airway re-obstruction was faster in patients treated by Nd-YAG laser than PDT (2 weeks with Nd-YAG versus 4 weeks with PDT).

3. A randomized study conducted in the USA, which compared the efficacy and safety of PDT versus Nd-YAG laser, showed that both treatments are equally effective in relieving tumor endobronchial obstruction. The time to treatment failure was slightly longer in the group treated with PDT, and the risk of local recurrence after PDT was lower than after Nd-YAG laser treatment [32].
4. In a prospective study of 41 patients, combination of PDT and radiotherapy and radiotherapy alone were compared. Results showed airway obstruction completely opened in 10% of patients treated with radiation therapy, versus 70% of patients treated with the combination of PDT and radiotherapy. Twenty percent of patients did not have any response to either treatment [33].
5. A group of ten patients with inoperable non-small cell carcinoma and a different degree of tracheobronchial obstruction (86 ± 2%) showed a response of 50% or more in four patients and 50% or less in six patients. However, all patients improved their symptoms, especially cough. Adverse effects included burns in two patients and one moderate anasarca [37].
6. In one of our studies [71], we found similar facts in 31 patients with inoperable non-small cell lung cancer and variable degrees of obstruction. These patients were prospectively randomized to PDT or Nd-YAG laser. The immediate initial response was better in the group treated with Nd-YAG laser, but the duration of response was longer in the PDT group, with a better survival rate. The number of complete responses with biopsy proven was very low and of short duration. Palliation of symptoms as for Karnofsky index was similar in both groups. PDT group had higher incidence of adverse effects, and these were more severe than in the group treated with Nd-YAG laser. Photosensitivity was the most important one.

PDT in Combination with Other Techniques for Advanced-Stage Non-small Cell Lung Cancer

A both Nd-YAG laser application and PDT are useful in centrally located, obstructive malignant lesions of the airways. The choice of one method over the other depends upon many factors, such as patient's preferences, his/her general health status, and physician's experience.

Historically, it had been accepted the combination of chemotherapy and radiotherapy in lung cancer treatment. However, new combinations are accepted as a valid therapy in the palliative management of non-small cell carcinoma. PDT treatment associated with external radiotherapy seems less harmful than the combination of radiotherapy and brachytherapy. It is reasonable to assume that PDT produces less toxicity and it can be a valid option in the multidisciplinary palliative treatment. We compared a group of patients with central airway obstruction due to non-small cell carcinoma treated with only

external radiotherapy (30 Gy in ten sessions) with patients treated with radiotherapy and PDT. Results revealed a better symptom control with radiological and functional improvement when both methods were combined [72].

Prospective studies of Freitag and colleagues have suggested combining PDT and brachytherapy for palliative control of endobronchial non-small cell carcinomas according to the principle of synergistic action. Control at 24 months was successful and without complications such as hemoptysis, obstructive pneumonitis, or bronchial fistula [73].

However, it is not well defined the sequence of the treatment combination of PDT and radiotherapy or brachytherapy (PDT before or after the associated treatment).

Endoscopic techniques could be helpful in choosing the best sequence of application. AFB can evaluate superficial tumor extension along the bronchial mucosa and detects early lesions or local recurrence. EBUS can evaluate the real tumor extension in bronchial wall and allows a better selection of patients.

Commentary

As a palliative treatment, PDT can be used as a single method or in a combined therapy. The excellent work published by McCaughan and Williams is very convincing in the sense that patients with endobronchial obstruction caused by advanced cancer still have a median survival of 7 months and then aggressive palliation seems to be indicated. The correct treatment is something that physicians evaluate considering patient characteristics, availability of the different methods, technique costs, and finally, his or her own personal experience.

Nd-YAG laser and PDT are effective in improving airway obstruction caused by intraluminal tumors. Resection with Nd-YAG laser seems to be the best method in centrally located tumors, which are easily reached with the rigid bronchoscope, coagulated, and then resected. PDT, on the other hand, applied with flexible bronchoscope can treat more peripheral lesion and does not require mechanical removal after irradiation. However, a cleaning bronchoscopy after PDT to remove debris is needed.

PDT cannot be used in patients with tracheal lesions extended to both main bronchi and extensive carina involvement or in patient with pneumonectomy. This is because the inflammatory reaction following the treatment generates edema that can be severe, worsening obstruction and putting at risk the lives of patients.

When the tumor has infiltrated the tracheobronchial wall or vascular structures, the use of PDT may cause perforation and/or fatal bleeding. Another disadvantage is that PDT does not relieve the obstruction immediately, and patients who present acute obstructive symptoms are not candidates for this treatment and should be treated with Nd-YAG or diode laser.

Photoresection with Nd-YAG laser and PDT are both ineffective when there is submucosal infiltration or extrinsic compression. In this case, patients can benefit from radiation therapy, and if necessary, placement of prosthesis [13]. Since most patients have a combination of intraluminal, submucosal, and peribronchial tumor involvement, it seems reasonable to use a combination of PDT and external radiation [33]. PDT can also be used as palliation for debulking an obstructed or a stenotic bronchus before surgery [34, 74].

PDT is recognized worldwide as a palliative option for advanced non-small cell lung cancer. In fact, many studies report a poor quality of life with a shorted life in patients with metastatic non-small lung cancer [75, 76]. PDT can be a palliative option for patients with locally advanced or metastatic non-small cell lung cancer, decreasing dyspnea, and airway obstruction [77], improving respiratory function and quality of life.

Complementary Endoscopic Methods for PDT Applications:

In the evaluation of early-stage lung cancer, EBUS can determine the real depth of “in situ” diseases, because in many cases, the mucosa appears macroscopically intact or has only minimal changes. With EBUS submucosa invasion or peribronchial extension can be detected more accurately. The absence of invasion confirmed by

the EBUS suggests localized tumor and can be treated endoscopically with curative intent [78]. Other authors suggest that the absence of tracheobronchial wall invasion assessed by EBUS defines injury as "early disease" and therefore should be considered an indication for the successful use of PDT [79].

Kurimoto et al. demonstrated the usefulness of EBUS in evaluating the depth of bronchial tumor and its accuracy. EBUS was in accordance with histopathological findings in 95.8% of the cases. Five layers of the bronchial wall in ultrasound images are defined. From the third to the fifth layer, it corresponds to the cartilage. Phototherapeutic treatment response is complete in lesions whose third (sonographically defined) layer is intact [80].

Takahashi et al. performed EBUS to evaluate the degree of carcinoma invasion into the bronchial wall in 22 lesions suspected of central early lung cancer before treatment. Fourteen lesions were diagnosed to be intracartilaginous lesions, and ten of them were treated by PDT. A complete remission was obtained in nine patients [81].

In fact, the endoscopic view is limited to the surface of the airway. Ultrasound can evaluate structures in depth. Processes located on the wall or outside the lumen can only be suspected by indirect signs such as discoloration, edema of the wall, changes in the vasculature, elevation of the mucosa, and distortion of the bronchial wall. Many abnormalities involving the peribronchial structures have no visible signs. Advanced imaging techniques such as computerized axial tomography or magnetic resonance imaging can be useful, but they are limited in detecting carcinomatous spread in peribronchial areas.

Optical coherence tomography (OCT) examination of the airways provides high-resolution images of the bronchial surface, making possible a detailed examination of intraepithelial lesions. Tissue layers between epithelium and basement membrane are clearly demonstrated, which is helpful to evaluate the depth of invasion of bronchial tumors [82, 83].

EBUS evaluation helps to determine the extent and depth of tumor invasion and to select the optimal treatment modality. In a near future, OCT will be widely applied and may prove to be a better complementary method for PDT treatment.

Conclusions

PDT represents a promising but currently underused alternative treatment modality for lung cancer treatment. For patients with early-stage non-small cell lung cancer, PDT is primarily employed as an endobronchial therapy for a definite treatment of endobronchial, roentgenographically occult, or synchronous primary carcinomas. PDT appears to be effective as definitive monotherapy in treating bronchoscopically visible lung cancers $\leq$1 cm extension and without extracartilaginous invasion. Finally, for patients with locally advanced-stage non-small cell lung cancer, PDT can be used to palliate obstructing endobronchial lesions as a neoadjuvant component of multimodality therapy, to reduce the extent of operation required, to palliate symptoms, and to increase operability.

Finally, newer and potentially improved photosensitizers and newer images and endoscopic techniques may expand the clinical indications of PDT in the future.

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Benign Airways Stenosis

12

Jose Pablo Diaz-Jimenez and Rosa López Lisbona

Introduction and Definition

Tracheal or laryngotracheal stenosis and bronchial stenosis are non-specific terms implying the presence of airway compromise involving the larynx, trachea, laryngotracheal, or bronchi. It is the consequence of progressive reduction of the tracheal lumen, with multiple mechanisms depending on their etiology.

In general, there is an alteration of normal epithelium after an inflammatory reaction leading to an abnormal repair and a structural problem.

Scar formation is associated with different degrees of morbidity depending upon the location, extent, and degree of airway obstruction. The sequence of events that leads to tracheal stenosis in adults involves inflammatory reactions with associated granulation tissue, ulceration of the mucosa and cartilage, fibrous tissue formation, and contraction of fibrous scar tissue.

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Clinically, tracheal or bronchial stenosis result in difficulty in breathing and is characterized by the progressive reduction of the airway diameter. Acute clinical situations can be handle by laser treatment, that solves the immediate problem in almost all cases. Although relapses are frequent, a percentage between 70 and 80% present definitive cure with the support of the endotracheal prosthesis. In our opinion, surgery must be addressed when cartilage destruction is diagnosed with rigid bronchoscopy inspection. Such compromize will not benefit from endoscopic approach.

Other causes of tracheobronchial stenosis are idiopathic, infectious, chemical damage (such as gastroesophageal reflux or toxic inhalation), radiotherapy, and associated to systemic diseases (e.g., Wegener's granulomatosis, amyloidosis).

Patients can present with variable symptoms, depending upon the severity of the stenosis and to his/her cardiorespiratory reserve: from no symptoms at all to dyspnea on exertion, progressive dyspnea, dyspnea at rest, wheezing, stridor, and a life-threatening situation such as respiratory failure or respiratory arrest.

Management of this condition is still not standardized or unified around the world, but it is well established that treatment of benign tracheal stenosis requires a multidisciplinary approach by a team of dedicated and experienced physicians.

The initial intervention and the type of treatment depend upon location of the stenosis, wall

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integrity, length and severity, as well as to the presence of comorbidities and overall health status of the patient.

Traditionally, surgery has been the mainstay of treatment, with excellent results in 90% of cases [1–3]. However, surgery is not always definitive, and there is a percentage of recurrence that can reach 10% in some series [4]. Surgery involves some risks, and associated complications have been reported to be greater than 8–12% with a mortality rate of 5% [1, 5, 6]. Moreover, many patients are unable to undergo a surgical procedure because of underlying cardiopulmonary limitations.

Endoscopic management of tracheal stenosis provides a safe and efficient therapeutic option and is often the first-line therapy in patients who are not appropriate surgical candidates or who have failure after airway resection. Several modalities have been used to relieve endoluminal obstructions, including mechanical approaches such as dilatation with a rigid bronchoscope or with balloon; heat-related modalities such as laser, electrocautery, and argon plasma coagulation; contact probe cryotherapy; and a variety of airway stents [7, 8].

Drug therapy combined with endoscopic treatment (intralesional injection of corticosteroids or more recently topical application of mitomycin-C) is another option in the treatment of this pathology, but experience is very limited and results are variable [9, 10]. So far none of these last treatments are curative.

Etiology

Congenital Tracheal Stenosis

Congenital tracheal stenosis is a rare but underdiagnosed anomaly which can present as life-threatening respiratory insufficiency in neonates and infants. Congenital anomalies are the most common cause of airway narrowing in the pediatric population. They are rare malformation, produced by the absence of most of the membranous portion of the trachea in the affected segment, and the cartilaginous rings extend along the entire circumference of the tracheal wall. There have been described three anatomical types:

(a) Generalized stenosis, from the cricoid to the carina with possible bronchial involvement
(b) Infundibular stenosis, where part of the trachea, proximal or distal, has a normal caliber
(c) Segmental stenosis, with involvement of a short portion of the trachea

These malformations can appear alone or, very often, associated with other abnormalities of the bronchovascular tree and other organ malformations, of which the most frequently seen is esophageal atresia [11, 12].

Cardiac anomalies are frequently associated and may be addressed at the time of tracheal surgery.

Management of congenital stenosis is very challenging. Children can present stridor, recurrent pneumonia, cyanosis, wheezing, and sometimes respiratory failure.

Corrective surgery is the treatment of choice; in short stenosis, resection of the compromised segment and anastomosis is the best option. When the stenosis affects long segments of the trachea, anastomosis becomes difficult for excessive pressure on the suture line, and the endoscopic approach can be an effective alternative to help these patients.

Iatrogenic

Iatrogenic airway injury after endotracheal intubation and tracheotomy continues to be a serious clinical problem. The causes of post-intubation and post tracheotomy tracheal stenosis are well established. Endotracheal tube causes pressure injury to the glottis, subglottis, and tracheal mucosa and may result in severe scarring.

Physiologically, the healing of the ulcer formed by the cuff pressure in the mucosa involves regenerating epithelium (primary healing) and repair (secondary recovery), but sometimes the regeneration of the epithelium does not occur and leads to an overgrowth of granulation

tissue. Eventually, the tissue subsequently becomes avascular resulting in a fibrous scar stricture.

Post-intubation tracheal stenosis was recognized for the first time as an entity in 1880, after MacEwen instituted prolonged endotracheal intubation as a therapy in four patients with main airway obstruction [13].

Since then, many reports have been published on serious complications resulting from post-intubation stenosis (PIS) or post tracheostomy stenosis (PTS). The rate of presentation varies: among all intubated patients, 0.6–21% will develop tracheal stenosis. PTS, in turn, can present from 6 to 21% of all patients that have undergone tracheostomy [6, 14]. Only a minority of them (1–2%) will present with symptoms or severe stenosis [15].

Currently, the calculated incidence of moderate or severe stenosis resulting from endotracheal intubation or tracheostomy is estimated on 4.9 cases per million per year in the general population [16].

Prolonged tracheal intubation can produce tracheal stenosis at many tracheal levels [17], from the tip of the endotracheal tube to the glottic and subglottic area, but the most affected places are at the level of the endotracheal tube (ETT) cuff and around the stoma in tracheostomized patients.

The development of the stenosis has many stages; at the beginning there is mucosal ulceration due to decreased blood flow at the level of contact with the ETT cuff. Then, cartilages exposure and perichondritis develop, followed by granulation tissue formation, which over time becomes an established fibrous stenosis that can be more or less fixed. In the worst cases, cartilage destruction occurs, and the airway wall loses its support.

PTS usually affects the area of the stoma, where the tracheostomy tube curves down, following the same sequence mentioned above. Sometimes granulation tissue is formed above the bend of the tube and progresses toward fibrosis [18, 19]. The presence of infection, very common in ventilated patients (tracheitis, mucositis), is a contributing factor for the development of airway stenosis [20]. A common finding in post tracheostomy patients is retraction of the tracheal cartilage at the area of the tracheostomy, producing different degrees of stenosis (Fig. 12.1). Surgery is the treatment of choice in these situations. When the patient is not a surgical candidate, an airway stent may be beneficial.

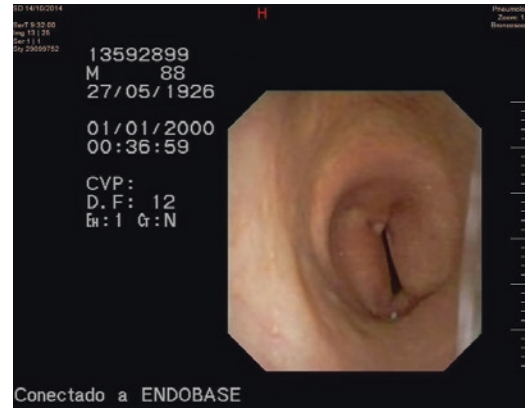

Fig. 12.1 Postracheostomy tracheal stenosis

Percutaneous tracheostomy is a procedure that is increasingly indicated in the critically ill patient, and it is associated to the development of tracheal stenosis as well.

A publication on 100 patients that underwent percutaneous tracheostomy revealed that major postoperative complications presented in 2.4% of cases, and these included death, cardiac arrest, loss of the airway, pneumothorax, tracheoesophageal fistula, and injury to the posterior wall of the trachea (mucosal tear). The rate of minor complications such as bleeding or cellulitis is presented in 1.8% of cases. Tracheal stenosis was reported in 31% of patients, 20% of which were symptomatic [21].

Long-term complications of percutaneous tracheostomy are infrequently mentioned in the literature; however some published data suggests that the rate of tracheal stenosis is significantly higher than reported [22].

VanHearn et al. showed that of 80 decannulated patients after percutaneous tracheostomy, an index of stenosis greater than 10% was found in 26% of them, being moderate in 4% of the cases and severe in 2% [23].

Another study evaluating 214 of 356 patients with percutaneous tracheostomies revealed that 8 of them (3.7%) developed symptomatic tracheal stenosis [24].

Infectious

Many airway infections can cause damage to the tracheal mucosa, resulting in stenosis. Tuberculosis (TB), fungal infections, bacterial tracheitis, histoplasmosis, and diphtheria are some of them, with TB being the most frequently seen.

Tuberculosis is the most common infectious cause of airway stenosis. It usually produces distal stenosis (at the level of the bronchi), but central airway stenosis can also occur. This complication can present at the time of the active infection or long after that, up to 30 years [25]. The most important risk factor for developing airway stenosis is the presence of tuberculous bronchitis, which is found in 10–37% of patients with pulmonary tuberculosis when bronchoscopy is performed [25, 26]. In those cases, over 90% of patients will develop tracheobronchial stenosis in spite of correct TB treatment [27].

Infectious stenosis is more prevalent in underdeveloped countries, particularly in Asia and Africa. Active infection produces necrosis and ulceration of the bronchial mucosa, giving rise to granulation tissue and subsequent fibrous stenosis.

During fibrous, established stenosis, dilatation of the lesion is an option. When the stenosis occurs at bronchial level, balloon dilatation can be offered. At tracheal level, rigid bronchoscope dilatation is useful as well. Repeated dilatations or stent placement are often required, since recurrence rate is very high.

Idiopathic Tracheal Stenosis

The term idiopathic tracheal stenosis (ITS) is used to include patients with tracheal stenosis when all other etiologies have been investigated and ruled out. It is thought to be a result of an inflammatory process of unknown etiology. Since location and general characteristics are similar to inflammatory or cicatricial tracheal stenosis, the investigation of potential causes has to be exhaustive before this term is applied.

ITS is a rare condition, characterized by circumferential fibrous stenosis beginning at the subglottic area and compromising the proximal segment of the trachea. It typically affects women on their third to fifth decade and presents with months to years of symptoms such as progressive dyspnea, wheezing, stridor, or a combination of all of them. In many cases patients are misdiagnosed as difficult to treat asthmatics [28].

Grillo et al. [28] presented 49 patients with tracheal stenosis where no etiology was found after extensive evaluation. A retrospective review of records showed that radiologic studies were still available in only 15 of the 49 patients with ITS. All 15 patients had radiographs and plain tomographies, and one patient had a computerized tomography scan of the neck.

Review of the available information showed that idiopathic laryngotracheal stenosis produced focal, 2–3 cm long stenosis at the cervical trachea. The lumen was severely compromised, measuring no more than 5 mm in diameter at its narrowest portion. The stenosis was concentric or eccentric, presenting either smooth or lobulated margins.

Grillo's report highlighted the need to pay special attention to the airway in chest radiographs or computerized tomographies when evaluating a patient with a history of prolonged dyspnea and wheezing. It is also important to consider ITS in the differential diagnosis of patients with focal narrowing of the airway.

A recent multicenter study described 23 patients, 96% of which were women aged 45 ± 16 years, endoscopically treated for ITS. Time between first symptoms and diagnosis was 19 ± 18 months. Bronchoscopy showed web-like (61%) or complex (39%) stenosis, located at the upper part of the trachea, mainly at the cricoid cartilage area.

Endoscopic treatment included mechanical dilation only (52%) or associated with laser or electrocoagulation (30%) and stent placement (18%). All procedures were efficient. Follow-up after endoscopic therapy was 41 ± 34 months, showing recurrence of ITS in 30% of patients at 6 months, 59% at 2 years, and 87% at 5 years. Treatment of recurrences ($n = 13$) included endoscopic management in 12 cases [29].

Bronchial Stenosis Post Lung Transplantation

Since the first lung transplant in 1963, technical advances in thoracic surgery along with new immunosuppressive agents have made lung transplantation a more common indication for those patients with terminal lung disease. However, one of the main problems of this surgical procedure is the development of stenosis at the level of the suture.

Perianastomotic stenosis occurs in 12–40% of patients and nonanastomotic distal bronchial stenosis in 2–4% of all lung transplants [30, 31].

Bronchial stenosis is related to airway inflammation, with mononuclear cell injury to the epithelium and mesenchyme that is further complicated by endothelial injury on a poorly vascularized area. The severe blood-flow impairment may lead to bronchial cartilage ossification, calcification, or fragmentation, leading to stenosis [32].

Other risk factors increase the risk for suture stenosis, such as the use of a simple suture and prolonged mechanical ventilation. There is a very high risk of suture infection also due to low blood flow and the presence of inflammation. Infection should be looked for and appropriately treated before performing any endobronchial manipulation, particularly if a stent placement is considered.

Success depends primarily on the experience of the interventional pulmonology team and the medical resources available.

Distal Bronchial Stenosis

As mentioned previously, bronchial stenosis secondary to pulmonary tuberculosis is quite common. Approximately 43% of patients with pulmonary tuberculosis will develop stenosis at the distal bronchi [33, 34] (Fig. 12.2). This number corresponds to approximately 4.1% of all bronchoscopies performed in a hospital.

Another cause for distal stenosis is bronchial anthracosis (called anthracostenosis) [35, 36].

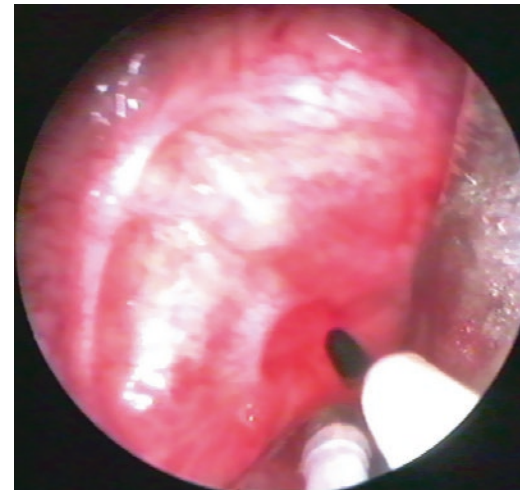

Fig. 12.2 Bronchial stenosis: right upper lobe

As a result of bronchial stenosis, there exists difficult drainage of secretions and recurrent infections distal to the obstruction, with the development of bronchiectasis. In these situations, it is indicated to offer a dilatational therapy that can be performed via balloon dilatation with or without laser application. This treatment is simple to apply and can be easily performed during a short procedure. It has good results, improving secretions clearance which in turn prevents repeated infections. In addition to bronchoscopy, three-dimensional helical tomography of the tracheobronchial tree can be very useful in the evaluation of this condition, since it allows a better distal inspection than bronchoscopy [37].

Another less common cause of airway stenosis is radiation therapy. The incidence of bronchial stenosis has increased following treatment with brachytherapy or external beam radiotherapy of malignant lesions of the airways, with an estimated incidence of 9–12% [38].

Bronchial stenosis is established within an average of 40 weeks after initiation of radiotherapy. Bronchoscopy can show the presence of a whitish-colored membrane covering the mucosa, with important inflammatory response that ultimately results in fibrous stenosis [38]. Radiation therapy rarely compromises the tracheal mucosa.

Diagnosis Methods

Patient History

Due to the broad range of etiologies and the non-specific nature of presentation, the diagnosis of airways stenosis may be delayed in time. A careful medical history should be obtained in patients suspected of airway stenosis, since background data is very important. Prior infectious diseases, history of airway intubation, prolonged mechanical ventilation, timing and severity of dyspnea, presence of dysphonia, etc., should be recorded and evaluated.

Symptoms develop gradually as progressive dyspnea until tracheal stridor appears; this could happen in most of the cases, when the diameter is affected around 70% (diameter around 5 mm in size).

When patients present emergently, it is important to offer a therapeutic procedure to reopen the airway to avoid worsening of symptoms and serious complications such as respiratory failure or respiratory arrest. The goal of treatment is to restore and maintain patency of the airway as soon as possible, and then a multidisciplinary team can decide which is the best long-term solution for a given patient.

In clinical practice, most of the patients present with symptoms of stenosis when they are in the fibrous phase of the stenosis, with minimal evidence of inflammation. They frequently have a history of a prior airway intubation or prolonged mechanical ventilation in the past. Many patients have been diagnosed and treated for difficult to control asthma, with minimal or no response to asthma therapy.

A significantly smaller number of patients will present within days or weeks from extubation, and in those cases an important airway inflammation can be seen.

Onset of symptoms is very variable. In a work of Marquette et al. describing 58 patients with airway stenosis, 5 of them developed symptoms within 5 days, 23 patients presented symptoms from 5 to 30 days of extubation and 19 patients from 30 to 90 days, and 8 patients took more than 90 days in presenting symptoms. Half of them went to the emergency room with acute respiratory failure [39].

The auscultation of wheezes, especially a fixed one, indicates that the passage of airflow through the airway is reduced, but its location does not always correlate with the site of airflow obstruction. That means that when a fixed wheeze is heard over the trachea, it does not necessarily indicate that the source of the obstruction is the trachea [40]. When wheezing is unilateral, it often suggests an obstruction of the airway distal to the carina.

The persistence of a fixed unilateral wheezing should always warrant bronchoscopic examination, paying special attention to the distal airway (segmental or subsegmental bronchi). Stridor is always a sign of severe laryngeal or tracheal obstruction and occasionally main bronchial obstruction.

Imaging Techniques

In the study of tracheobronchial stenosis of the airway, noninvasive imaging techniques have an important role. They help not only in diagnosing but also in deciding the most appropriate treatment and assessing response to therapy during the follow-up period. These techniques have developed significantly in recent years [41] allowing a better approach to airway stenosis.

Simple chest-X rays are rarely diagnostic of central airway obstruction.

Computed tomography (CT) has been the most commonly used imaging test for diagnosis and evaluation of airway stenosis in order to have better information of the length and size of the stricture, degree of destruction of the airway wall, surrouding organ injury and also to have images control after treatments (Fig. 12.3a, b).

Although very useful, CT has some limitations particularly in the evaluation of subtle airway stenosis in axial images, underestimation of the craniocaudal extent of the disease, and generation of a large number of images for review [42].

The introduction of multiplanar reformatting (MPR) CT scans with option to generate three-dimensional (3D) images and virtual endoscopy (VE) provide additional information regarding airway pathology [43] bringing visual data that

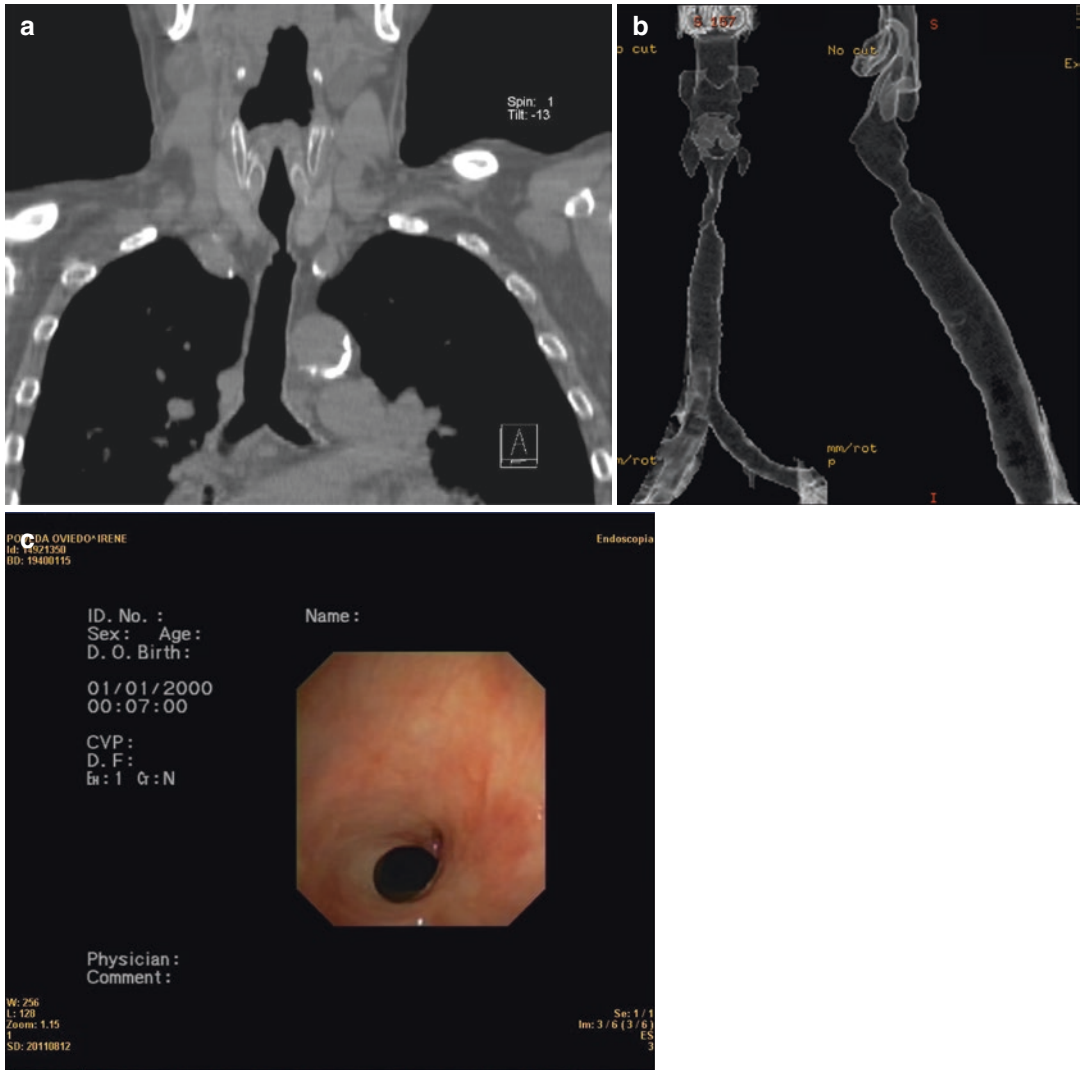

Fig. 12.3 (**a**–**c**) Tracheal stenosis and CT scan with reconstruction in 3D

closely resemble the images obtained from flexible bronchoscopy [44].

MPR CT scan allows the acquisition of thin-slice axial sections of entire body volumes during a single breath-hold, thus eliminating respiratory artifacts [45].

This technique provides information on the length and caliber of the stenosis and the degree of compromise of the laryngotracheal wall. It allows visualizing lesions in depth, showing thickening or thinning of the tracheal wall, fibrous involvement of the submucosa, or disappearance of the tracheal rings. Also, the relationship of the injury to adjacent organs can be better evaluated.

Virtual endoscopy (VE) is a reconstruction technique that exploits the natural contrast between endoluminal air and the surrounding tissue [46], allowing navigation through the tracheobronchial tree with the same endoluminal perspective as an endoscopy [44] (Fig. 12.4).

Several authors have demonstrated the high diagnostic accuracy, sensitivity, and specificity of noninvasive, multirow detector CT virtual endoscopy in evaluating and grading central and segmental airway stenosis and its close correlation

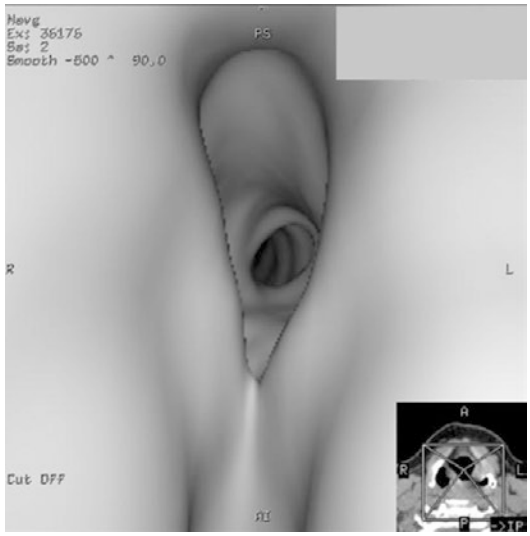

Fig. 12.4 Tracheal stenosis. Virtual bronchoscopy

with flexible bronchoscopy [43, 46–48]. However, it is slightly more accurate at assessing central airway stenosis than segmental airway stenosis [46].

The combination of axial imaging, multiplanar reformatting, and three-dimensional rendering is useful prior to tracheal intervention, especially when there is significant anatomical distortion or airway narrowing [47].

Recently, some authors advocate the use of MRI for diagnosis localization and extension of tracheal stenosis. MRI is a noninvasive procedure without ionizing radiation and can be used to identify the relationship of the trachea to adjacent vascular structures and to determine the degree and length of tracheal stenosis in high-resolution imaging with excellent soft-tissue contrast and without applying ionizing radiation or intravenous contrast medium.

Unfortunately, standard MRI has a limited ability to show dynamic organs.

The use of real-time, dynamic, cine MRI (CMRI) can achieve better results showing the mobility of the organs identified [49].

Bronchoscopy

Flexible bronchoscopy remains the primary diagnostic technique in the study of inflammatory tracheal stenosis and is considered the gold standard procedure for this pathology, allowing direct visualization of the airway lumen and sampling (biopsies). However, when the patient is in acute sever symptoms, flexible bronchoscopy is best avoided due to the risk of precipitating acute or complete airway obstruction. In these cases, the best approach has to be rigid bronchoscopy.

Moreover, bronchoscopy offers information at different levels and can assess the mobility and morphology of the vocal cords and arytenoids in subglottic laryngeal stenosis. In tracheal stenosis, it allows location of the lesion and evaluation of the degree and length of the stenosis and notes characteristics such as the presence or absence of malacia, mucosal involvement in inflammatory disorders, granulomas, ulcerations, or established fibrosis. It also enables obtaining biopsies, a procedure that should always be performed in tracheal stenosis, to rule out other inflammatory conditions. Bronchoscopy is a minimally invasive procedure, with the additional advantage of not exposing the patient to ionizing radiation. One limitation of this technique is the inability to evaluate the distal airways in severe stenosis, since the bronchoscope cannot be further advanced from the stenotic area. In these cases, sedation during the procedures and the use of an ultrathin bronchoscope with external diameter of 2.1 mm help bronchoscopists to explore tracheobronchial tree beyond the stenosis since the bronchoscopy is better tolerated.

Figure 12.5a–c shows how bronchoscopy permits the correct evaluation of the distance from vocal cords to stricture, the length of the stricture, distance from stenosis to main carina, and the degree of compromize of the cricoid cartilage.

New bronchoscopic technologies, however, permit a more accurate assessment of the airway wall structure and characterization of the stricture before, during, and after treatment, since the correct evaluation of tracheal wall structures is necessary for optimal management of tracheal stenosis.

Endobronchial ultrasound (EBUS) has been introduced as an adjunct to diagnostic bronchoscopy. Radial EBUS helps evaluating the different tracheal and bronchial wall layers, as well as

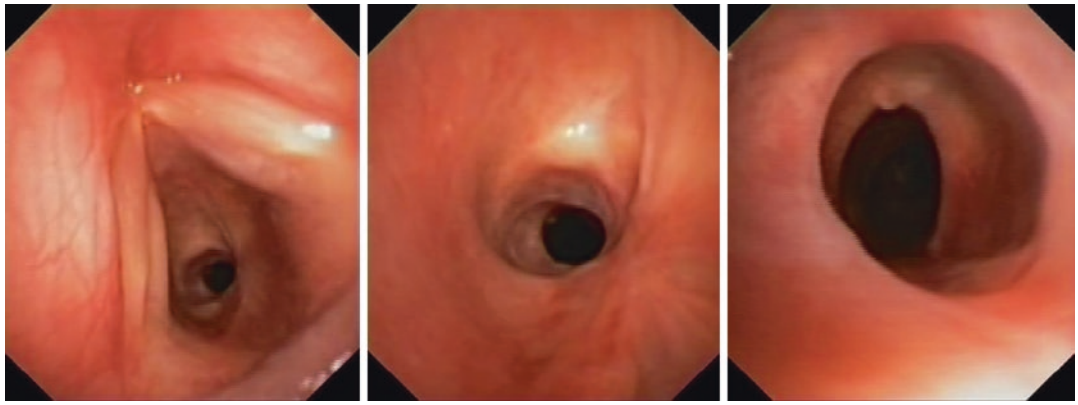

Fig. 12.5 Vision of flexible bronchoscopy permits the correct study of the distance from VC to stricture, length of the stricture, distance from stenosis to main carina, and affectation of the cricoid cartilage

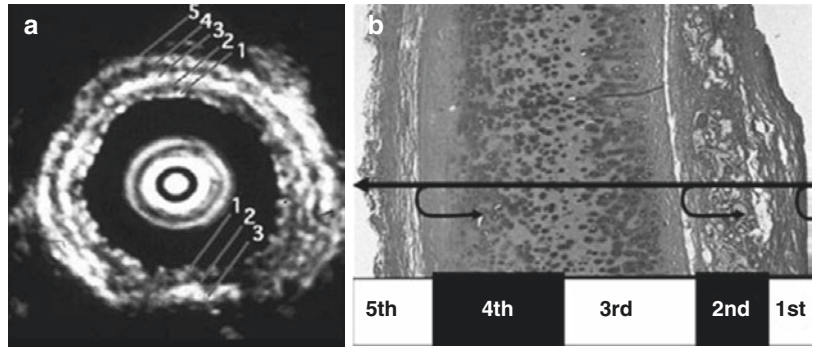

Fig. 12.6 Central airway wall structures: endobronchial ultrasound (EBUS)–histology correlations. (**a**) The five layers of the cartilaginous wall and the three layers of the membranous area of the bronchial wall are revealed by EBUS using a 20 MHz radial probe. (**b**) Laminar structures of the cartilaginous wall as seen on histology and the corresponding hypo- and hyper-echoic layers seen with EBUS. [51] with permission

parabronchial structures. Cartilage damage can be better assessed, influencing the type of treatment that will be offered [50]. Also EBUS could asses differences in central airway wall structure in patients with various forms of expiratory central airway collapse who can be identified by endobronchial ultrasound using a 20 MHz radial probe [51] (Fig. 12.6.).

Optical coherence tomography (OCT) is a new bronchoscopic imaging technique that has generated considerable interest since it has a much better space resolution than computed tomography. It is capable of generating high-resolution cross-sectional images of complex tissue in real time.

Similar to ultrasound, OCT measures backscattered light intensity using coherence interferometry to construct topographical images of complex tissue. It can provide a micron level, real-time image of the airway wall structure with a resolution approaching histology [52]. It offers a unique combination of high-resolution (1–15 mm) and in-depth penetration of 2–3 mm that is adequate for imaging superficial airway anatomy and pathology. OCT has the potential to increase the sensitivity and specificity of biopsies, create 3D images of the airway to guide diagnostic procedures, and may have a future role in different areas such as the study of tracheal stenosis. Some authors hypothesize that this technology may in the future provide a noninvasive "optical biopsy" [53], helping, as we said, in diagnosis and treatment of a number of conditions (Fig. 12.7).

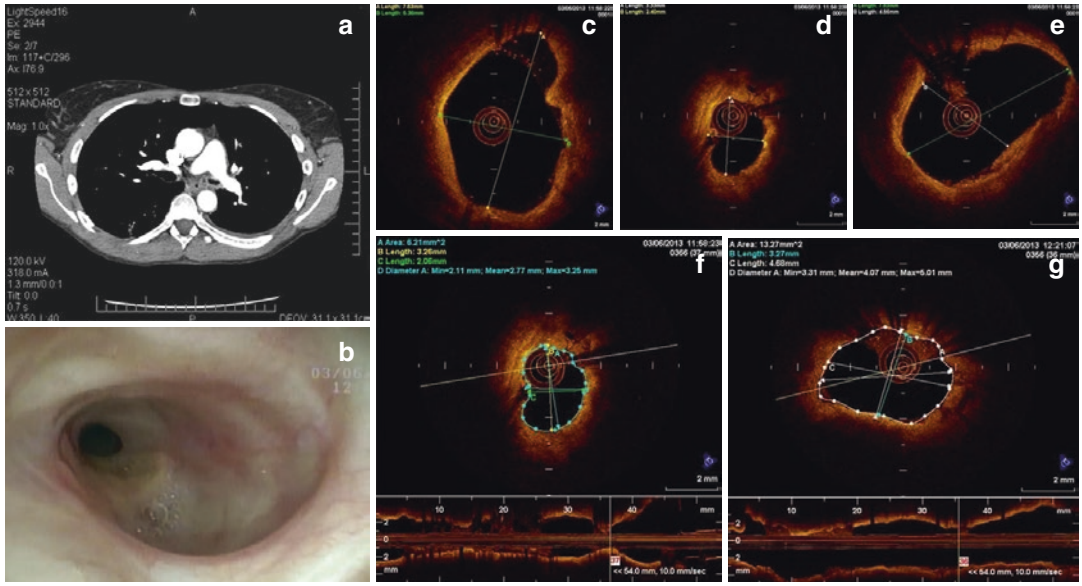

Fig. 12.7 OCT application of OCT image for measurement of tracheobronchial stenosis. CT scan (**a**) and bronchoscopic (**b**) image of LMB (left main bronchus) stenosis. OCT images of normal bronchial lumen before (**c**) and after (**e**) the bronchial stenosis (**d**). OCT allows accurate measurements pre (**f**) and posttreatment (**g**) with balloon dilatation. (Courtesy Dr. Lam and Dr. Shaipanich from BCCA)

Anatomic optical coherence tomography (aOCT), a modification of conventional OCT, is a novel light-based imaging tool with the capacity to measure the diameter and lumen area of the central airways accurately during bronchoscopy. This technique can measure tracheal stenosis dimensions, having good correlation with chest CT scan findings and guiding the selection of a proper-sized airway stent [54]. Standard OCT also could obtain accurate measures of stenosis.

All these new technologies are very promising, and they are currently under active research to define their proper role in the study of airway conditions.

Though flexible bronchoscopy and the different imaging techniques have shown to be useful and reliable in the diagnosis of tracheobronchial strictures, they all have technical limitations that can lead to an inaccurate characterization of airway stenoses [55]. The best way to evaluate these conditions is to combine different diagnostic approaches in order to correctly define the injury and then plan the best procedure, case by case, based on clinical, endoscopic, and radiological findings.

Pulmonary Function Test

Regardless of the cause, tracheal stenosis causes increased airway resistance and decreased flows. A simple test such as spirometry can help in diagnosing and characterizing a central airway stenosis. The shape of the flow-volume curve (*F*/*V*) obtained by spirometry and flow resistance (raw) calculated by plethysmography can give important information. For instance, flattening of the inspiratory loop with preservation of expiratory flow represents variable extrathoracic obstruction of the central airway. In turn, compromise of the expiratory loop with a normal inspiratory limb indicates variable intrathoracic obstruction. In a fixed obstruction (intra- or extrathoracic), both inspiratory and expiratory curves are affected, presenting with a classic flattening in the *F*/*V* loop (Fig. 12.8).

Another important information that can be obtained with spirometry concerns to the functional status, and helps deciding whether or not the patient is a surgical candidate.

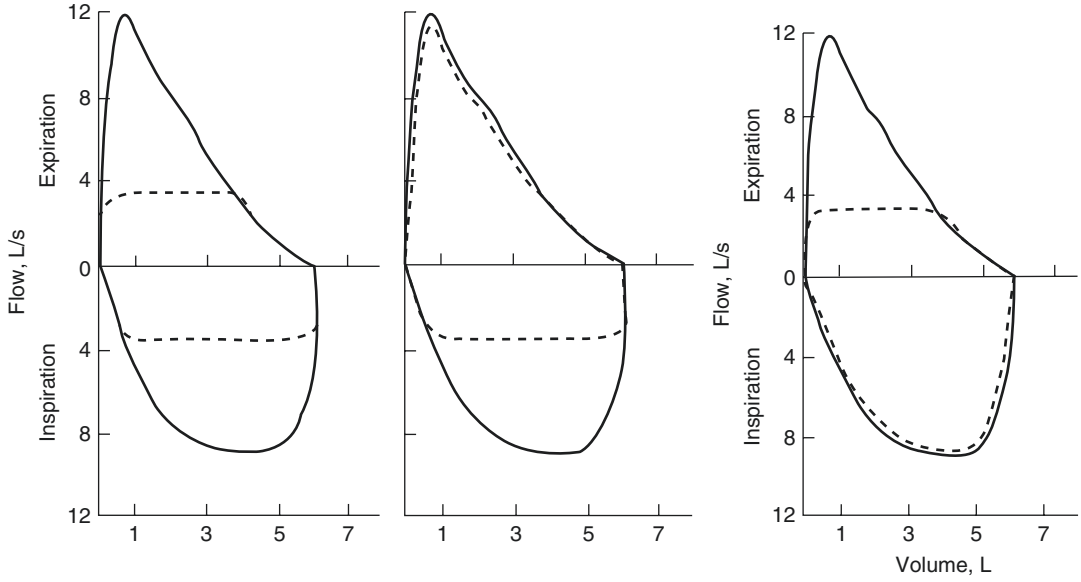

Fig. 12.8 Pulmonary function test in tracheal stenosis

Classification of Benign Tracheal Stenosis

Airway narrowing may result from intrinsic stenosis or extrinsic compression or for both. It has been classified following different parameters, in an attempt to design a useful algorithm for treatment.

Cotton et al. [56] in one of the first classifications of tracheal stenosis in 1984 used the cross-sectional area of the stenosis in a group of pediatric patients and divided this condition into four grades:

I: 50% obstruction
II: 51–70% obstruction
III: 71–99% obstruction
IV: Complete obstruction

In this classification, location and length are noted but without affecting the grading of the stenosis.

In 1992, McCaffrey [57] retrospectively reviewed the treatment of 72 cases of LTS. Although diameter and length were factors, the predominant predictor of outcome was location. Locations were confined to the glottis, subglottic area, and upper trachea.

Four stages were defined as follows:

1. Stage 1 in the subglottis or trachea, 1 cm in length
2. Stage 2 in the subglottis, .1 cm in length
3. Stage 3 in the subglottis and upper trachea
4. Stage 4 in the glottis with vocal cord fixation and paralysis

In 1999, Brichet and coworkers [8] proposed a classification based on four categories depending on bronchoscopic findings:

- Pseudoglottic stenosis: defined as typically "A"-shaped stenosis due to lateral impacted fracture of cartilages in patients with a history of tracheostomy.
- Weblike stenosis: when it involves a short segment (<1 cm).
- Membranous concentric stenosis: when there is a membrane obstructing the lumen without damage to the cartilages.
- Complex stenosis: all other stenoses, including those with an extensive scar (≥1 cm), circumferential hourglass-like contraction scarring, or malacia, were defined as such.

Moya et al. [58] reviewed 54 patients that underwent surgery for laryngotracheal stenosis and defined findings according to topographic and lesional criteria, incorporating three independent variables: stage of development (S), caliber (C), and length (L). Recently this classification has been modified. It is presented in Table 12.1.

In 2007 Freitag et al. [59] proposed a standardized scheme, presenting descriptive images and diagrams for rapid and uniform classification of central airway stenosis. In Fig. 12.9 classification was based on the type of lesion, degree, and location. They divided airway stenosis into structural and dynamic, and they included malignant causes as well.

The structural group has four major types:

- Type 1: includes exophytic intraluminal malignant or benign tumors and granulation tissue.
- Type 2: stenosis is due to extrinsic compression of all causes, including nonpulmonary tumors.
- Type 3: stenosis is due to distortion, kinking, bending, or buckling of the airway wall.
- Type 4: shrinking and scarring are the predominant features.

Stenoses were further classified in dynamic when a malacic condition that varied with the respiratory cycle was found. They included two different types:

- Type 1: triangular (tent-shaped) benign stenosis in which the cartilage is damaged.
- Type 2: it is the inward bulging of a floppy posterior membrane.

In turn, the degree of stenosis was assigned a numerical code that could be applied to any site:

- Code 0: no stenosis
- Codes 1: 25% decrease in cross-sectional area
- Code 2: 50% decrease
- Code 3: 75% decrease
- Code 4: 90% decrease

They defined five locations within the central airways:

- Location I: upper third of the trachea
- Location II: middle third of the trachea
- Location III: lower third of the trachea
- Location IV: right main bronchus
- Location V: left main bronchus

In 2008, other authors [7] classified airway stenosis into two groups, according to their morphological aspect in simple and complex, similar to the Brichet's classification. Simple stenosis included granulomas, weblike, and concentrical scarring stenosis. All these lesions were characterized by endoluminal occlusion of a short segment (<1 cm), absence of tracheomalacia, or loss of cartilaginous support (Fig. 12.10). Complex stenoses were represented by a longer lesion (greater than 1 cm) with tracheal wall involvement and subsequent scarring contraction of the latter, in some cases also associated with malacia (Fig. 12.11).

Almost all of these classifications quantify the degree of the stenosis as a percentage, which is a subjective observation during bronchoscopy. Sometimes we can have an approximation with images such as a CT scan, but this method is not exact either since measurements vary according

Table 12.1 Classification criteria for inflammatory stenosis of the trachea

Structure (S) Structure of the tracheal wall		Caliber (C) Internal diameter (at the point of smaller diameter)		Length (L) Axis of the larynx-trachea	
S1	Acute-subacute inflammation	C1	>10 mm (area > 25 μm)	L1	Stenosis ≤2 cm
S2	Organized scar fibrosis	C2	8–10 mm (area 16–25 μm)	L2	2–4 cm stenosis
S3	Malacia	C3	≤8 mm (area ≤ 6 μm)	L3	>4 cm stenosis
S4	Tracheoesophageal fistula				

Adapted from Moya et al. [58]

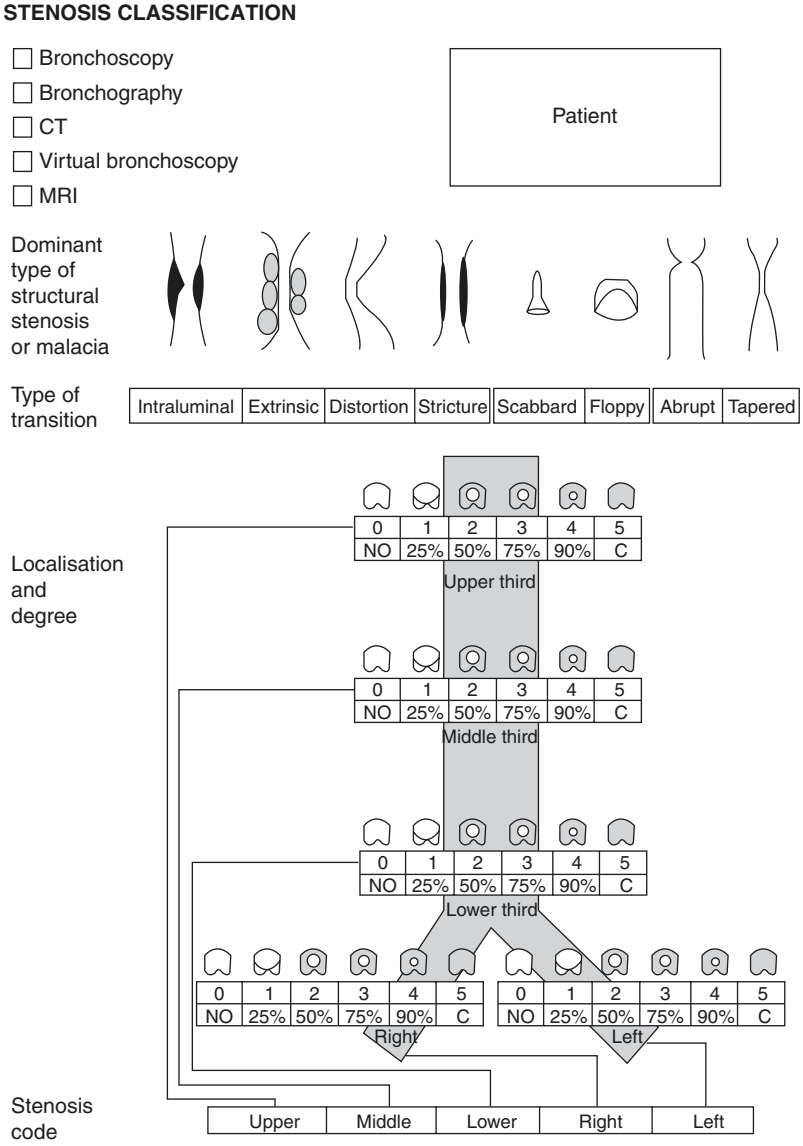

Fig. 12.9 Classification (Freitag et al. [56]). (With permission)

A worksheet marking the location, degree and type of stenosis. CT: computed tomography; MRI: magnetic resonance imaging; C: complete.

to the respiratory timing of image acquisition (inspiration, expiration).

In a recent report, Murgu and Colt published a study on subjective assessment using still bronchoscopic images of benign causes of laryngotracheal stenosis containing normal and abnormal airway cross-sectional areas that were objectively analyzed using morphometric bronchoscopy and classified as mild (<50%), moderate (50–70%), or severe (>70%). These images were then subjectively assessed by 42 experienced bronchoscopists participating in an interventional bronchoscopy course. Only 47% of strictures were correctly classified by study participants (mean 16.48 ± 2.8). Of the 1447 responses included in this analysis, 755 were incorrect: 71 (9%) were overclassifications of strictures' severity and 684 (91%) were under-classifications. There was no correlation between number of strictures correctly classified and number of

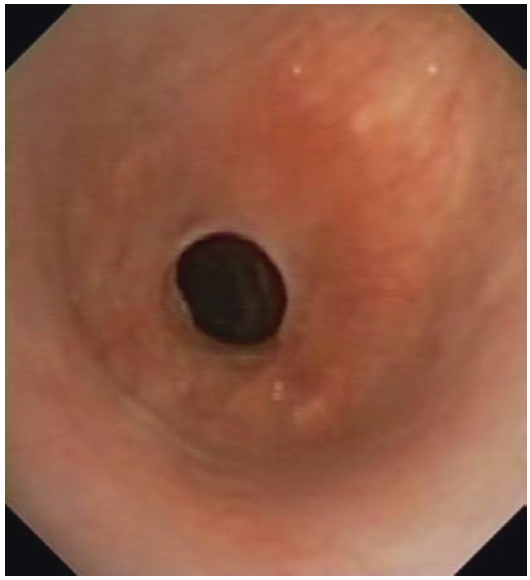

Fig. 12.10 Simple tracheal stenosis

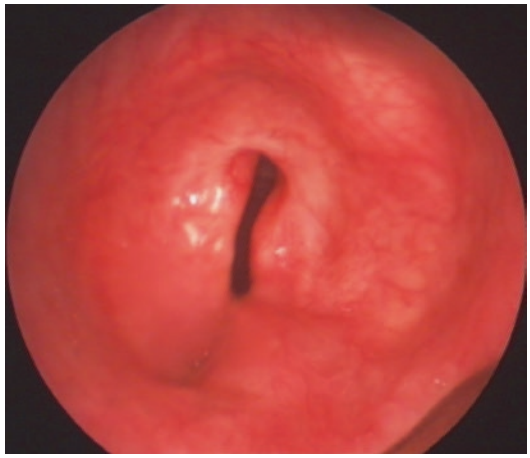

Fig. 12.11 Complex stenosis

lifetime bronchoscopies, or number of strictures seen by bronchoscopists in an average month. As a conclusion, the authors said that: "Experienced bronchoscopists often misclassify the degree of airway narrowing when using still bronchoscopic images to subjectively assess strictures of benign aetiology" [60].

In another paper a similar survey of 123 members of AAB (American Association for Bronchology) shows that the assessment in CAO central airways obstruction is currently performed in a visual manner (91% of the consulted clinicians). Eighty-six percent of the clinicians consulted agreed that there is an urgent need to avoid subjective visual evaluation and standardize calculations during in vivo explorations [61].

This demonstrates the importance of using systems that allow us to make a more objective measurement for conducting exploration.

Murgu and Colt proposed the morphometric bronchoscopy. They use an imaging system called Image J. During the bronchoscopic procedure, different captures are taken, in the center of the proximal airway, distal and directly into the lesion. Then after the procedure, with this manual method, it is possible to calculate the stenosis index (SI) [62] (Fig. 12.12).

Another method to calculate the stenosis index is the one that our group is trying to validate, working with the CVC (Computer Vision Center) of the Autonomous University of Barcelona. It is a new system that allows for real-time measurements. Recording a video during bronchoscopy procedure, this imaging system analyzes different cuts at the stenotic area level as well as at the normal tracheal level and subsequently, through a mathematical algorithm, calculates the area at the level of normal and stenotic trachea. Then it compares the caliber of stenosis with normal trachea giving us the real degree of stenosis [63] (Fig. 12.13.).

The ultimate aim of the various proposed classification is to define a treatment algorithm accepted and followed by all physicians dealing with this complex conditions. It is also very important to use the same definitions in order to carry out research projects designed to identify the best, type-specific, therapeutic option.

In 2015 the European Laryngological Society published a consensus paper proposing a five-step endoscopic airway assessment and a standardized reporting system to better differentiate fresh, incipient from mature, cicatricial LTSs, simple one-level from complex multilevel LTSs, and, finally, "healthy" from "severely morbid" patients [64].

Authors believe that, from the surgery point of view, this is an excellent article in order to choose the best treatment modality for each individual patient and assess post treatment outcomes accordingly.

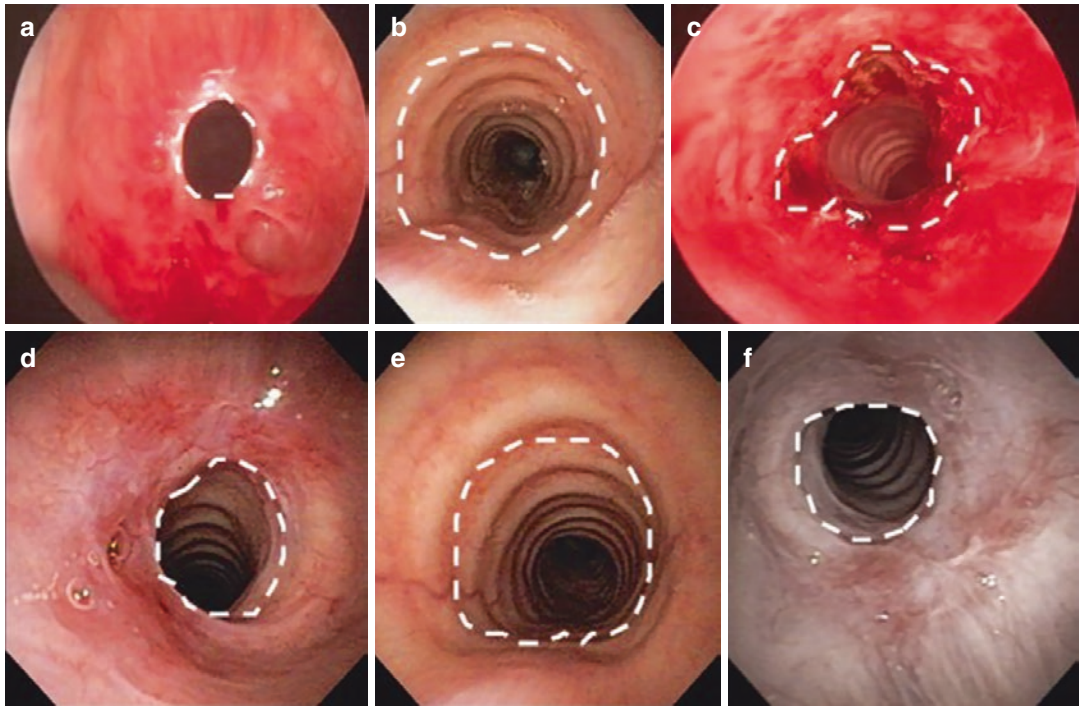

Fig. 12.12 Bronchoscopic photos of the idiopathic concentric subglottic stenosis (**a**) and the normal distal tracheal lumen (**b**). The calculated stenosis index (SI) was 80%. SI improved to 30% after laser and rigid bronchoscopic dilation (**c**). The stenosis (**d**) and the normal distal tracheal lumen (**e**) at 12 months follow-up. The calculated SI was 50%. At 18-month follow-up, the stenosis was stable with an SI of 50% (**f**). [62] (with permission)

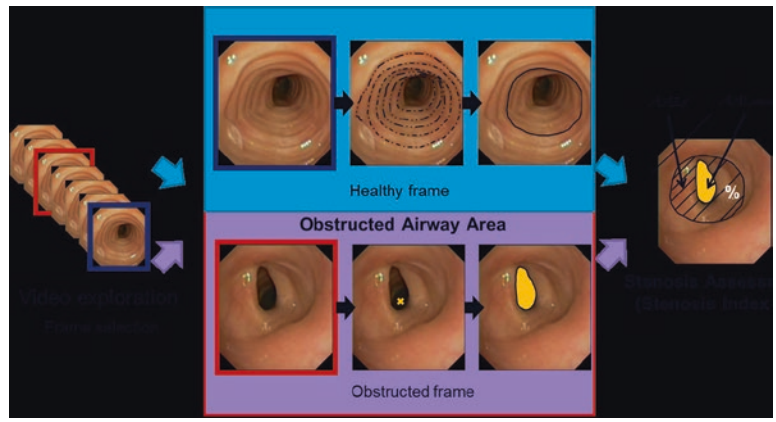

Fig. 12.13 Stenosis index using the Computer Vision Center of UAB method

Treatment

Most significant tracheal stenosis need interventional bronchoscopy or surgical resection.

Effective management of tracheal stenosis requires a multidisciplinary assessment of patient's overall clinical status and medical history in addition to etiology and morphology of the stricture. When deciding the approach, the dedicated physician has to consider whether or not the patient is a surgical candidate, determine precise intraoperative technique, the extent of the resection, and an estimation of the risk for recurrence. Other treatments to consider are repeated

dilatations or placement of an airway prosthesis. Symptoms of patients with an airway obstruction is variable and depend not only on location, severity of the stricture, and the speed of progression but also on underlying medical conditions.

We cannot overemphasize that when an obstruction of the tracheobronchial tree is suspected, a careful review of medical history, patient examination, and review of complementary methods such as pulmonary function testing and imaging studies (chest RX, CT scan) should be performed thoroughly. Virtual bronchoscopy can be used to have a preview of the airway, but it does not replace conventional flexible bronchoscopy as the most useful diagnostic tool to assess the extent of the stenosis as well as its severity and to determine its cause by direct inspection and biopsies. Patient clinical status is the main parameter in deciding next step, since it will determine how urgent the treatment is needed and which is the most appropriate instrument to perform the procedure.

Endoscopic Treatment

Rigid bronchoscopy under general anesthesia is an essential method in the treatment of severe symptomatic laryngotracheal stenosis. It allows a secure airway and the application of different interventional tools such as balloon dilatation, laser resection, electrocautery, placement of an airway stent, etc. It is an expedite procedure to reopen the airway, very safe and effective when applied by a well-trained team. The flexible bronchoscope has also an important role, complementary to the rigid bronchoscope during the first approach.

Our recommendation when treating a patient with severe central airway obstruction is to provide appropriate oxygenation and ventilation by intubating with the rigid bronchoscope. The rigid tube serves two purposes: first, it secures the airway, and second, it can be used to dilate the airway. Once successful intubation is achieved, the flexible bronchoscope can be used through the rigid scope to inspect the stenosis and the distal airway and to aspirate retained secretions.

The immediate therapeutic approach depends on the type and severity of the stenosis found. Many times rigid bronchoscopy will resolve the acute situation by dilating the stricture and will represent a bridge to definitive treatment to be performed electively.

According to endoscopic findings, several steps can be followed. For instance, simple severe stenosis (concentric membrane) can be immediately resolved with laser resection and dilatation with the rigid bronchoscope. In this particular situation, that may be the only procedure that the patient will need. A close endoscopic follow-up is indicated to detect and treat recurrences.

Complex stenoses represent a different situation. They may be addressed initially with endoscopic therapy to overcome the acute respiratory failure, but the definitive solution is always surgery providing that the patient has a good clinical status.

Patients that present with progressive symptoms can be inspected with both the rigid and the flexible bronchoscope, and a definitive procedure can be planned after discussing the case in a multidisciplinary team, once all information has been collected.

Some treatment algorithms have been recommended, to follow in benign tracheal stenosis, according to several defined criteria (Fig. 12.14 and Table 12.2).

Dilation

As we discussed above, in urgent cases the sole use of rigid bronchoscope causes dilation and enlargement of the airway, improving both extrinsic and intrinsic obstruction. Figure 12.15 shows the result of the dilation of original tracheal stenosis (a), first time treatment dilation with rigid bronchoscopy and two more dilation after 2 and 3 months (b). Bronchoscopy control: stability after 2 months (c), 10 months (d), and 22 months (e), respectively, after last dilation with rigid bronchoscopy. No more recurrencies up to the present moment.

When a rigid bronchoscope is not available, dilatation can be performed by using progressive

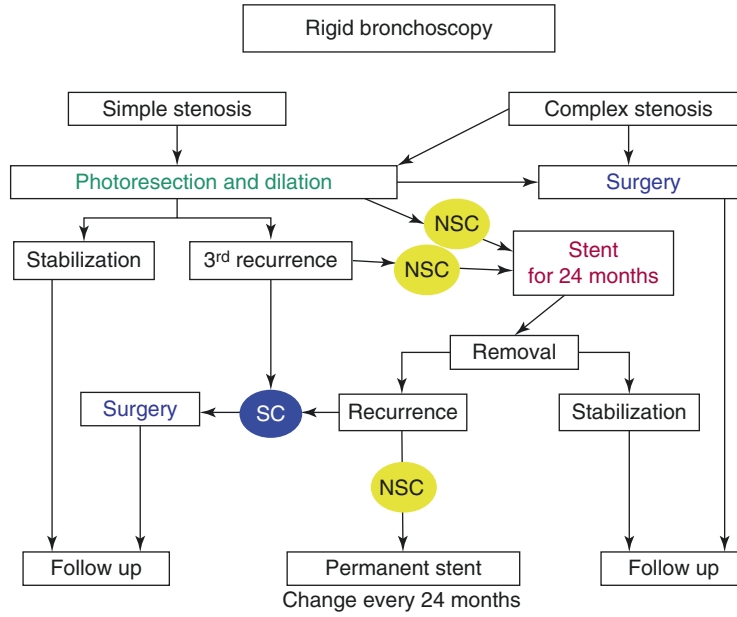

Fig. 12.14 Tracheal Stenoses Treatment Algorithm. *SC* surgical candidate, *NSC* non-surgical candidate

Table 12.2 Endoscopic treatment according to morphological criteria

Category	First option	Second option
S1/C1-2-3/ L1-2	ET +/− laser +/− prosthesis	Surgery
S1/C2-C3/L3	ET +/− laser +/− prosthesis	–
S2/C2-3/L1-2	ET +/− laser	Surgery
S2/C2-3/L3	ET +/− laser +/− prosthesis	–
S3/C2-3/L1-2	Surgery	–
S3/C1-2-3/L3	Prosthesis	–
S4/C1-2-3/ L1-2-3	Surgical correction of fistula + myoplasty	

Moya and cols
S stage, *C* caliber, *L* length

diameter balloons that are introduced sequentially, thus achieving a greater diameter of the tracheal lumen (Fig. 12.16a–c).

Balloon dilatation does not have long-lasting effects, and it is indicated to relieve the obstruction until a more definitive treatment can be offered.

Laser Therapy

Laser treatment involves application of a laser light to the lesion. The effects of laser are determined by many factors: type of laser applied, distance and surface of application, and target tissue. The most commonly used lasers in interventional pulmonology are the Nd-YAP (neodymium, yttrium, aluminum, and phosphate) and the Nd-YAG (neodymium, yttrium, aluminum, and garnet). Diode laser can be also applied to airway lesions with similar good results. Dumon published his first large series in 1982 [65]. This author presented 111 patients treated with laser to open the airway for both benign and malignant lesions, 32 of them were benign stenosis. Cavaliere et al. [66], in turn, presented their experience on 1000 patients treated with laser for benign and malignant disease, obtaining cure in 34 of the 81 cases with benign tracheal stenosis treated with laser. We also published our series including 400 cases of benign and malignant disease treated with laser [67]. Ninety-two patients were treated for benign tracheal stenosis and received 113 laser applications. Laser resection was successful in obtaining a 50% increment on the tracheal diameter in most cases.

In another publication we report our experience with laser resection followed by airway prosthesis placement in 63 patients with benign tracheal stenosis [68]. About 79% of patients obtained definitive cure.

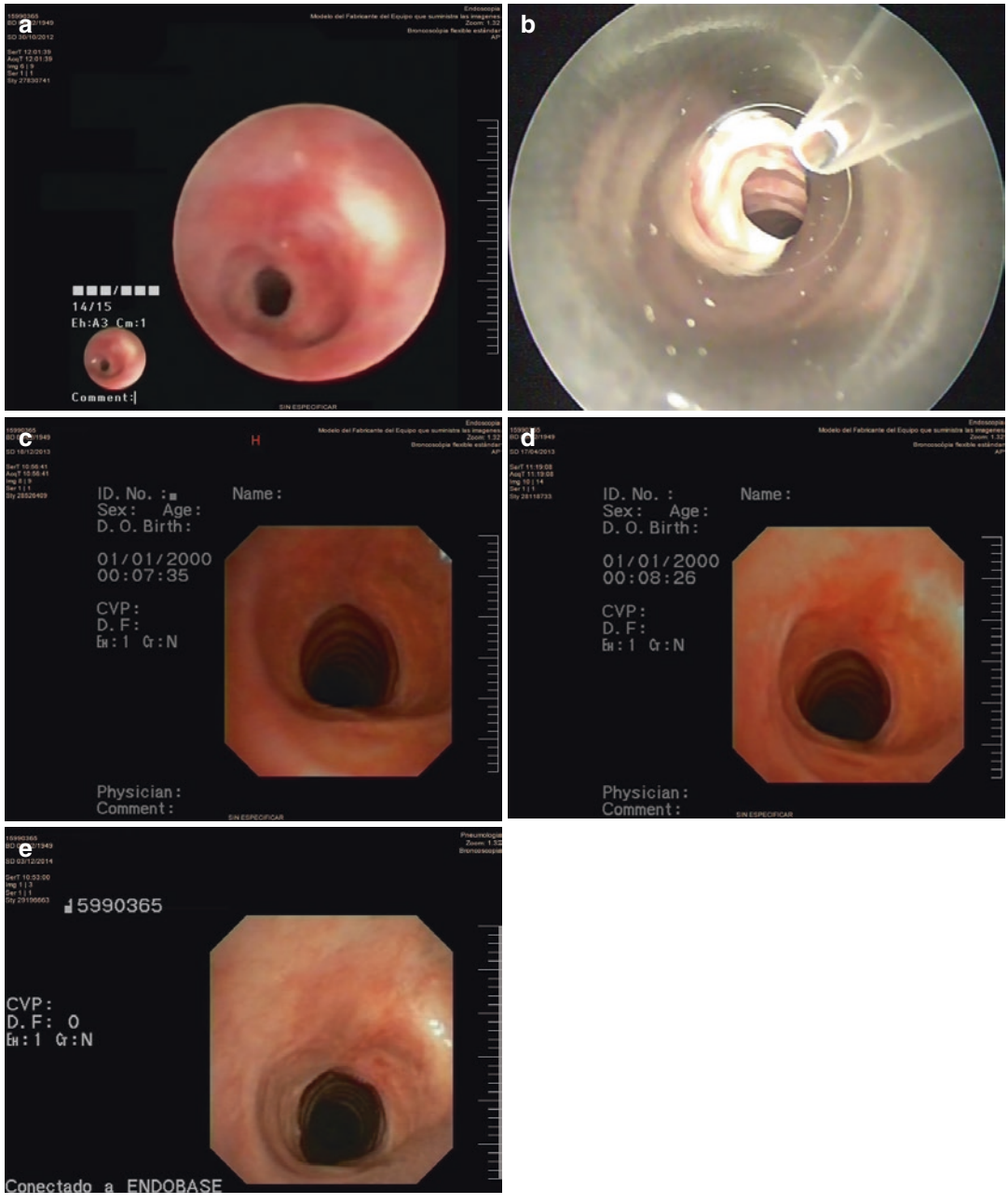

Fig. 12.15 (**a**–**e**) Dilation with rigid bronchoscope evolution of original tracheal stenosis (**a**), first time treatment dilation with rigid bronchoscopy and two more dilation after 2 and 3 months (**b**). Bronchoscopy control: stability after 2 months (**c**), 10 months (**d**), and 22 months (**e**), respectively, after last dilation with rigid bronchoscopy

In order to open the airway with laser, we recommend to apply three or four radial cuts at the cardinal points of the stenotic circumference of the trachea (Fig. 12.17a–c) and then to perform careful dilation with the rigid bronchoscope. Vaporization of cartilaginous structures is strictly contraindicated because it results in weakening of the tracheal wall and potentially induces restenosis to a more severe grade.

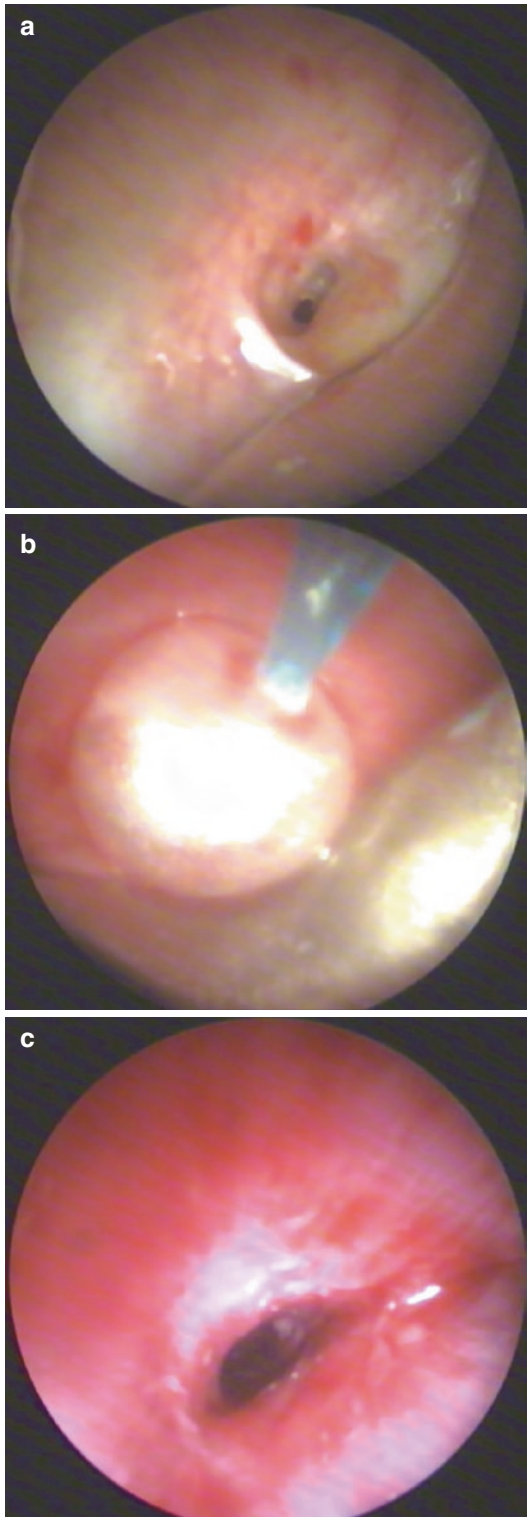

Fig. 12.16 (**a**–**c**) Balloon dilatation (before, during, and after treatment)

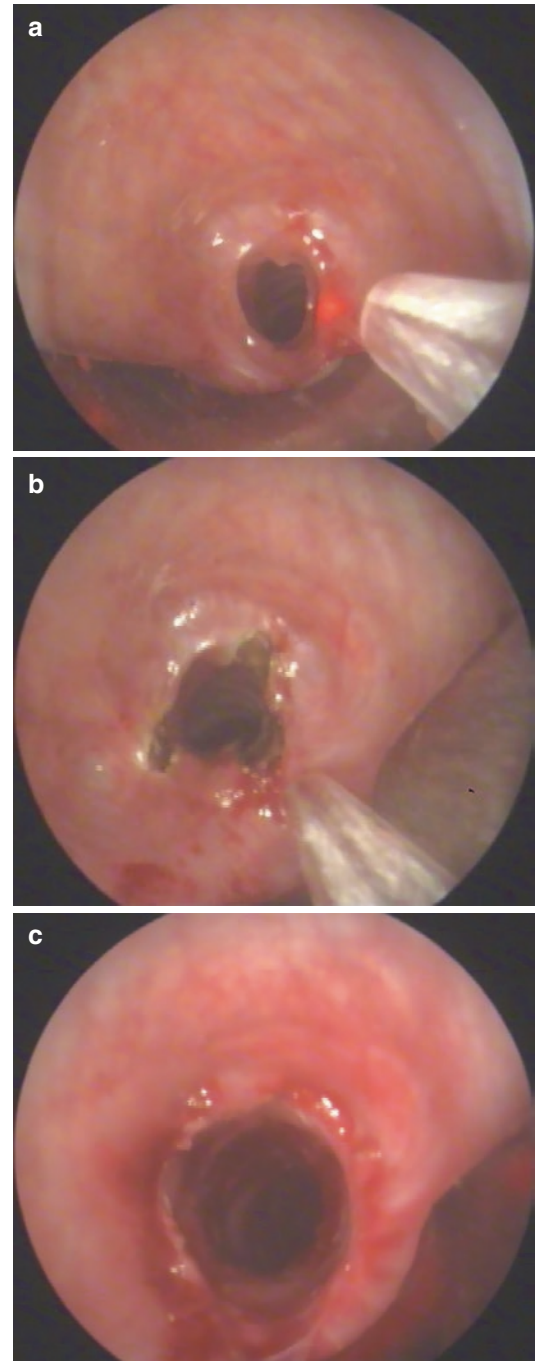

Fig. 12.17 (**a**–**c**) Laser application in tracheal stenosis. Photoresection "in cross" and dilation with rigid bronchoscope

The flexible bronchoscope can be used to apply laser as well, but we are in favor of the rigid instrument to take advantage of simultaneous dilatation.

In case of severe subglottic stenosis, we recommend the use of a CO_2 laser to take advantage of its cutting capacities avoiding inflammation, or only dilation with the rigid bronchoscopy. Instead, Nd Yag laser can increase the stenotic area due to inflammation, and put the patient at higher risk. Sometimes tracheostomy is necessary as the first procedure in those cases.

Cryotherapy, Electrocautery, and Argon Plasma Coagulation

Cryotherapy, electrocautery (EC), and argon plasma coagulation (APC) are methods that obtain variable results in tracheal stenosis treatment.

Results on the application of these techniques in tracheobronchial stenosis of varied etiology are available. Recently, Fernando HC et al. [69] treated 35 patients with a median age of 51 years with spray cryotherapy (SC). Stricture etiology included post-intubation, post tracheostomy, radiation induced, prior surgery, other causes, or unknown etiology. Seventeen patients (49%) required additional SC therapy. Only two complications occurred (3.2%) and these included pneumothorax and intraoperative tracheostomy. Twelve patients were asymptomatic, 16 improved, 4 had no improvement or were worse, and 1 patient died from an unrelated cancer.

They concluded that initial experience with SC for benign airway strictures suggested that this could be used safely and could be effective in improving symptoms and reducing the severity of airway narrowing, but almost half of the patients required re-intervention.

Some authors agree that when applied to post-intubation tracheal stenosis EC and APC can be fibrogenetic, causing more damage and scarring of the mucosa. Cryotherapy is almost ineffective given the paucity of blood vessels in the stenotic area.

These three methods, however, are very useful in granulomas, especially APC [70–72]. Laser therapy still has many advantages over all of them; since it is fast, it has high coagulation power and a minimal impact on surrounding tissues.

Prosthesis

Airway prostheses are tubes of different shapes, sizes, and materials designed to stabilize or reconstruct the lumen of the airways.

In benign tracheal stenosis, tracheal prosthesis placement may be considered in the following situations:

(a) Treatment failure after dilation of a simple stenosis
(b) First option in cases of complex stenosis as a bridge to surgical treatment
(c) As the only option in unresectable disease (length > 50% of the trachea)
(d) In inoperable patients

Metal, silicon, or other materials, endobronchial prostheses may be placed in the airways to relieve the obstruction caused by endoluminal tumors or extraluminal tumors that decrease the lumen of the airways by extrinsic compression. Likewise, benign conditions that diminish airway lumen can benefit of an airway stent as well.

Application of prosthesis is most effective when the stenosis occurs in the central airways (trachea or main bronchi). Their indication in distal bronchi stenosis is questionable.

The first airway prosthesis was developed by Montgomery and placed in 1965 [73]. The so-called Montgomery T tube has an extraluminal portion and requires tracheostomy for placement (Fig. 12.18).

In 1990, Dumon introduced a totally endoluminal silicon-made prosthesis [74] and published his first experience on treating 118 patients with airway obstructions of different etiologies.

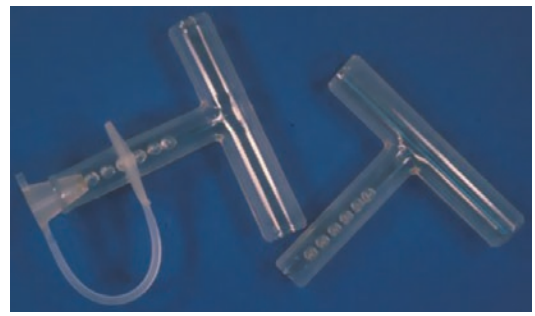

Fig. 12.18 Montgomery T tube

Since then, a large number of different airway prosthesis have been developed and are now available for medical use. However, at the moment the ideal stent has not been found yet. Many authors have listed the ideal characteristics for such a prosthesis:

- Easy to insert and remove
- Does not migrate
- Strong to support the airways
- Flexible enough to accompany the normal respiratory movements and cough and to allow adequate clearance of secretions
- Biologically inert (does not produce inflammatory response, avoiding granuloma formation)
- Available in different sizes and lengths

Published articles [68, 75, 76] reporting the application of airway stents in a variety of conditions including malignant and inoperable benign stenosis, tracheomalacia, tracheoesophageal fistula, and posttransplant stenosis showed remarkably positive results in more than 2000 patients. Stent placement was associated with significant palliative benefits, improvement of dyspnea, quality of life, and performance status. Spirometric results, when available, also demonstrated improvement after placement. Associated adverse effects and complications listed on those reports were migration, granulation tissue formation, retention of secretions, airway perforation, and fatal hemoptysis.

A combined publication from four European centers reported the 7-year experience in the application of airway prostheses. A total of 263 patients had benign conditions, and they received an average of 1.6 prosthesis per patient. Duration of stenting ranged from 14 months to 6.2 years. A follow-up demonstrated treatment success in 66% patients; 24% of them had no recurrences after one year of stent removal [77].

Both metallic and silicone stents can be used for malignant obstructions of the airway. Silicone stents are a favorite, however, since they have a low level of complications along with high efficacy and safety. They have been applied over the last 20 years with very good results.

Metallic stents have the theoretical advantage of being easy to place. In turn, they are very difficult to remove, and we discourage their generalized use based on the level of complications they produce [78].

In fact, the FDA advised against metallic stent application in benign conditions in the year 2005 [79]. In malignant diseases they are still acceptable if the expected survival period is short.

How to Proceed

Rigid bronchoscopy and laser resection have been used for more than three decades, showing excellent results on the treatment of endotracheal or endobronchial growing tissue.

Concerning treatment of benign stenosis, rigid bronchoscopy laser resection has virtually no morbidity/mortality when the technique is appropriately applied in carefully selected patients.

When implementing this treatment, we recommend to proceed as follows:

1. Careful intubation with the rigid bronchoscope, maintaining the rigid optic lens slightly behind the tip of the bronchoscope in order to have a broad view of the airway as you advance. It is important to perform a planned intubation and to take every possible precaution during the procedure, since these patients often have a history of difficult intubation and rush maneuvers can damage easily the upper airway, especially at the arytenoids and vocal cords area.
2. Once the lesion is on view, careful inspection of the area should be performed. Anatomic characteristics, extent, degree of compromise of the airway wall, and presence of inflammation should be recorded. It is important to touch the lesion with the tip of the suction catheter in order to test the nature of the stenosis, inflammation, fibrosis, cartilage affectation, etc.
3. When tracheal caliber is equal or greater than half the diameter of the rigid tube in use, the stenosis can be dilated by placing the bevel of the bronchoscope at the beginning of the stenosis and then surpassing the stricture dilating. During the maneuver, a slight rotation movement is applied to the scope as it is advanced through the stenotic area. In case of bleeding, use the bronchoscope to compress

the bleeding area for a few minutes. If the lumen diameter obtained after dilatation is not appropriate, it will be necessary to move on to a larger diameter bronchoscope.

4. When the stenosis has a caliber of less than half the diameter of the bronchoscope, laser in cutting mode can be applied, performing three or four cuts at 12, 3, 6, and 9 o'clock of the stenotic circumference. Laser should always be applied parallel to the tracheal lumen, avoiding damage to the posterior tracheal wall and the esophagus that could result in a tracheoesophageal fistula. The anterior tracheal wall can also be accidentally damaged, injuring large vessels placed beyond the wall, such as the innominate artery.

   After several cuts, the stenotic tissue tends to open or is easily removed by the rigid bronchoscope, applying again a rotation pressure and resecting the stenotic membranes. Bleeding rarely occurs or is minimal. Another option is to cut the membrane stenosing the airway with endoscopic scissors, minimizing laser application to avoid burn damage to the mucosa. After the incisions, the rigid bronchoscope is used to dilate the stenotic area.
5. Once the stricture is surpassed, the flexible bronchoscope is passed through the rigid tube, to carefully inspect the distal airways and to aspirate retained secretions or detritus.
6. Finally, the rigid bronchoscope is withdrawn above the stenotic area, to check that tracheal caliber remains appropriate. Given the case the lumen remains stenotic, one can assume that there is a complex damage to the tracheal wall such as cartilage disruption or malacia. Placement of an airway prosthesis is then the safer recommendation, since it will allow solving the situation avoiding immediate recurrence of the stenosis. Also, it will give time to collect other important information and to discuss the case in a multidisciplinary fashion in order to offer a more definitive solution.

Stent Placement

When placing an airway stent, the first consideration to evaluate is whether or not the prosthesis will really improve the clinical situation or make it worse.

Once risks and benefits have been evaluated and the assessment favored a stent placement, the dedicated physician should inspect the lesion again, noting carefully the size and length of the stenotic area and the characteristics of the surrounding healthy tissue. Two distances are particularly important: vocal cords to the beginning of the stenosis and end of stenosis to carina.

A prosthesis positioned too close to the vocal cords will bring speech problems and will be prone to granuloma formation leading to more stenosis. When the distance to the vocal cords is less than two centimeters, the best results are obtained proceeding directly to tracheostomy and placing a Montgomery T tube (Figs. 12.19 and 12.20).

In turn, when a low stent has to be placed, less than 2 cm from the carina, it is better to offer a Y prosthesis, since a tubular stent will contact and irritate carinal mucosa leading also to granuloma formation and subsequent stenosis.

The Rule of Twos for Benign Tracheal Stenosis

For a more effective and accurate tracheal prosthesis placement and in order to avoid complications in relation to the vocal cords and carina, we have designed a scheme that may obtain better results when a stent has to be placed near these areas (Fig. 12.20).

With regard to the vocal cords:

In strictures close to the vocal cords, a placement of the prosthesis can lead to the production of granuloma due to stent movement during breathing or to frequent cough. The continuous rubbing of the prosthesis with the vocal cords will generate granulomas that almost inevitably will cause new subglottic stenosis.

With regard to the carina:

The same scenario is possible when a prosthesis has to be placed close to the main carina. Due to cough or breathing movements, continuous mucosal irritation will produce granuloma formation.

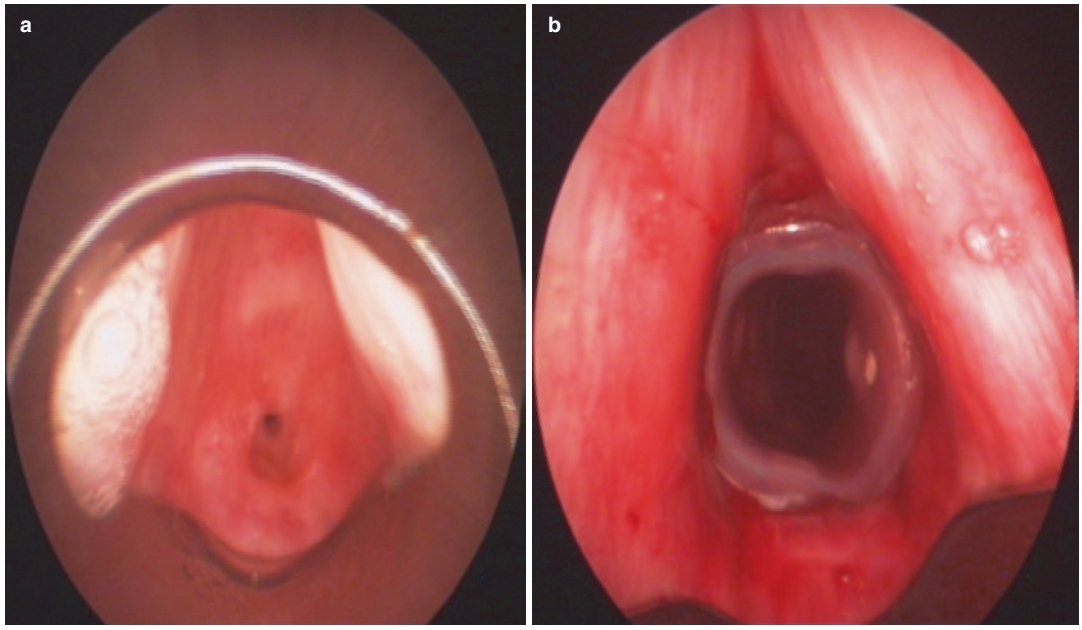

Fig. 12.19 (**a**) Tracheal stenosis less than 2 cm from the vocal cords. (**b**) After a Montgomery tube placement

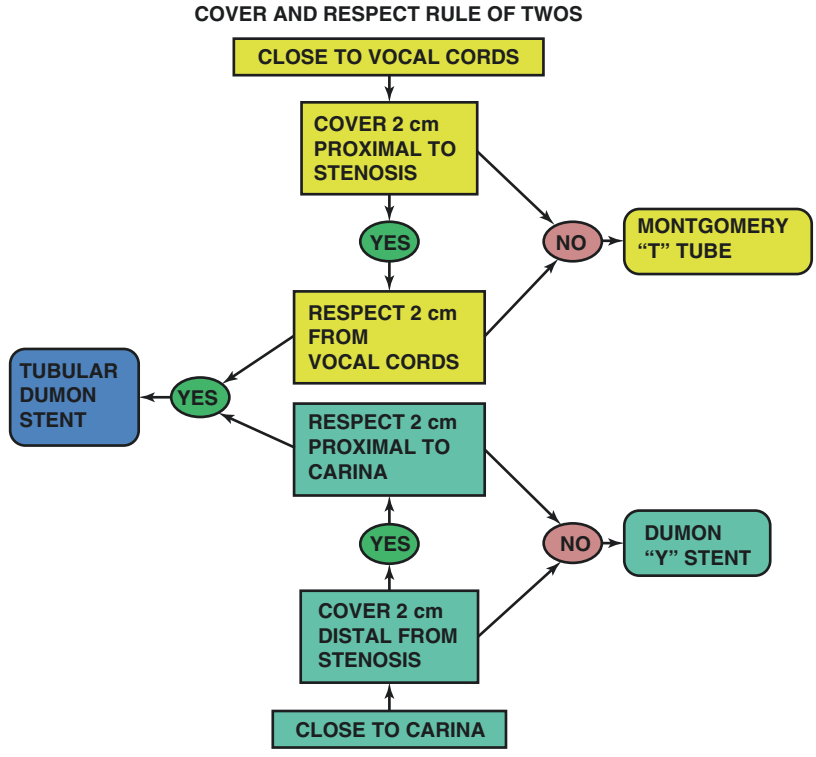

Fig. 12.20 Rule of two algorithm

After 25 years of experience in the placement of prosthesis, we advocate that a 2 cm distance between the vocal cords and the proximal edge of the prosthesis can prevent the production of granulomas on the vocal cords.

Same with the stenosis near the main carina: we advocate that a 2 cm distance between the carina and the distal end of the prosthesis will prevent the production of granulomas at this level.

So we suggest for approaching stenting:

When considering the vocal cords, stents should:

1. Cover the affected area of stenosis and two additional centimeters above and below that area.
2. Respect the 2 cm of healthy mucosa, proximal to the vocal cords.

If (1) and (2) are not possible, then a Montgomery T tube should be placed.

Related to the carina, stents should:

1. Cover the affected area of stenosis and two additional centimeters above and below that area.
2. Respect the 2 cm of healthy tissue proximal to the carina.

If (1) and (2) are not possible, then a Y stent is should be placed.

Surgery

Surgical treatment of tracheal stenosis comprises a wide range of techniques such as tracheal resection and anastomosis or tracheal reconstruction. The choice of ideal treatment should be based on the characteristics of each patient after evaluating all the advantages and disadvantages of the procedures. A tracheal stenosis that is less than 5 cm in length can be resected with end-to-end anastomosis. Longer tracheal lesions can be treated in a palliative way by placement of a stent to secure airway lumen patency.

Primary tracheal sleeve resection is considered the treatment of choice in patients who are operable. Other complex laryngotracheal techniques are necessary when the subglottis is involved.

In our opinion, surgery must be addressed when there is cartilage destruction evident on rigid bronchoscopy examination.

In case of concentric stenosis without cartilage destruction and 1 cm long, if dilation with rigid bronchoscopy with or without laser obtains a normal caliber, surgery and thoracotomy become unnecessary. In patients with more than 1 cm long stenosis and chondritis with malacia, dilation and laser are usually not enough to achieve a permanent good result, and then surgery or stenting become necessary.

Complex tracheal stenosis affecting multiple rings with involvement at various levels and a large inflammatory component is usually an indication for surgery as a first step. Inoperable patients may benefit from a permanent airway stent.

Some surgeons recommend avoiding these procedures in all patients who are potentially candidates for surgery, stating that laser treatment or stent placement can worsen the situation. However, there is no evidence to support that, In fact, most patients are inmediately relieve in their symptoms after dilatation, laser resection or stenting of the airway. Re evaluation of these patients after the acute distress is resolved will determine next step.

Cavaliere and all published the results in 73 patients: 13 (18%) weblike and 60 (82%) complex stenoses.

Most weblike stenoses were successfully treated with laser-assisted mechanical dilation (LAMD) alone; among complex stenoses, LAMD was sufficient to treat 13 patients (22%), whereas 47 patients (78%) required stent placement: 22 had their stent removed after one year and did not require any further therapy, 13 inoperable patients required permanent stent, and 12 were referred to surgery after failure of multiple endoscopic treatments. No permanent complications secondary to endoscopic treatment were observed. Forty-eight patients (66%) obtained a stable, good result with the endoscopic procedure, 13 (18%) required a permanent stent, while 12 patients (16%) were referred to surgery. Authors concluded that endoscopic treatment of post-intubation tracheal stenoses performed in an expert setting can be considered a safe first-line therapy, leaving some selected cases and the relapsing stenoses, for surgical resection [80].

In a recent excellent article by P. Delaere and D Van Raemdonk [81], the authors update recent advances in tracheal reconstructive surgery in malignant or benign pathology involving long areas of the trachea. Animal studies have shown that a prosthetic replacement of the airway wall is not possible. In large resections, a silicon prosthesis sutured to the upper and lower margings covered by skin flaps can be useful. The authors also reviewed their experience in allotransplants and highlight the importance of vascularization in allografts since to restore blood supply it is the most difficult technical inconvenience. Regarding tracheal regeneration, they state that optimism on that matter is completely unfounded.

Summary and Recommendations

Dealing with airway stenoses can be difficult. A variety of methods can be applied in order to relieve the situation. In fact, almost any technique discussed above is useful and can be applied alone or in combination with other methods. A multidisciplinary approach will always bring the best results for patients; important considerations should be thoroughly discussed with the team:

- General status of the patient and his/her wishes
- Type of injury (acute versus chronic, extrinsic or intrinsic obstruction, fixed or dynamic stenosis, benign or malignant stenosis)
- Equipment availability
- Personal experience and expertise on a given method

After that, the "best" approach for a given patient can be offered.

As we said, frequently best results are obtained with a combination of treatments, and better outcomes for the patient are achieved in multidisciplinary, referral centers that have both extensive experience and sufficient equipment to deal with these complex clinical situations. We believe that interventional pulmonologists and thoracic surgeons must discuss thoroughly the indications, contraindications, and possible complications that can arise, case by case. We favor that the interventional team should be well trained, able to apply both the rigid and flexible bronchoscope, and has to be also knowledgeable on handling airway prostheses. The ACCP guidelines to interventional procedures provide useful recommendations including training requirements and number of suggested procedures to become competent and maintain proficiency in all the procedures described in this chapter [82].

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Endobronchial Prostheses

13

Septimiu Dan Murgu and Sean Patrick Stoy

Abbreviations

6MWT	Six-minute walk test
BAO	Benign airway obstruction
BPF	Bronchopleural fistula
CAO	Central airway obstruction
CPAP	Continuous positive airway pressure
CT	Computed tomography
DATS	Dynamic A-shaped tracheal stenosis
EBUS	Endobronchial ultrasound
ECAC	Expiratory central airway collapse
EDAC	Excessive dynamic airway collapse
EPP	Equal pressure point
ERF	Esophagorespiratory fistulas
ETT	Endotracheal tube
FLS	Flow-limiting segment
HRQOL	Health-related quality of life
IOS	Impulse oscillometry
MAO	Malignant airway obstruction
MRC	Medical Research Council
P lat	Lateral airway pressure
PL	Intraluminal pressure
POTS	Postoperative tracheal stenosis
Ppl	Pleural pressure
QOL	Quality of life
R	Resistance
RP	Relapsing polychondritis
RRP	Recurrent respiratory papillomatosis
SEMS	Self-expandable metallic stents
TBM	Tracheobronchomalacia
TLC	Total lung capacity

Introduction

This chapter emphasizes on the indications, physiologic basis, and complications of airway stent insertion. Airway stents have been consistently shown to help patients suffering from benign and malignant central airway obstruction[1] and esophagorespiratory fistulas, by improving their airflow, quality of life, and potentially survival. The incidence rate of adverse events depends on patient-related factors and on specific stent-tissue interactions. Prior to inserting such a device, the bronchoscopist should determine the need and expected benefits of this procedure. A first step is to objectively classify the obstruction based on histology, mechanism of obstruction and dynamic features (Fig. 11.1). An objective assessment of the extent and severity of airway narrowing is necessary, as well as an accurate assessment of the impact of the airway narrowing on functional status (Fig. 13.1).

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[1]Central airway obstruction is defined in this chapter as any clinically significant narrowing of the airway from the subglottis to the lobar bronchi.

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Classification of Central Airway Obstruction	
Qualitative Criteria	**Qualitative Criteria**
I. Histology Benign Malignant **II. Mechanism of obstruction** Extrinsic compression Intraluminal exophytic; infiltrative; stricture Mixed **III. Dynamic features** Fixed Dynamic	**I. Severity of airway narrowing** Normal; Mild: Moderate; Severe **II. Extent of airway narrowing** Normal; Mild: Moderate; Severe **III. Functional Impairment** Normal; Mild: Moderate; Severe

Fig. 13.1 Classification of central airway obstruction based on qualitative and quantitative criteria. Dynamic features refer to the phase of respiration during which there is flow limitation. In a fixed obstruction, there is limitation to flow both during inspiration and expiration, while in dynamic obstruction, only during a respiratory phase, as is the case with tracheomalacia. The quantitative criteria could be objectively assessed. For instance, based on physiologic data, for tracheal stenosis, the severity of airway narrowing can be quantified as mild (<50% narrowing), moderate (50–70%), and severe (>70%); the extent is the vertical length of the stenosis and, based on outcomes from bronchoscopic and open surgical interventions, can be quantified as mild (<1 cm), moderate (1–4 cm), and severe (>4 cm). Functional impairment can be objectively assessed using a variety of validated tools such as MRC dyspnea scale or WHO functional class

Historical Perspective

Since the beginning of documented airway stent insertion at the end of nineteenth century, tracheobronchial prostheses have been generally made of two types of materials: metal or rubber. As the understanding of airway physiology and its interaction with the prosthetic materials has advanced, the manufacturers take into consideration the biomechanical and biocompatibility characteristics, even though this information is not always available to the practicing bronchoscopist. Clinically used airway stents are currently made of polymers, alloy metallic mesh, or a combination of the two (aka hybrid stents). In general, the pure metallic stents have been abandoned because of severe complications.

The future may see the incorporation of treatment agents such as chemotherapeutic (i.e., mitomycin C, paclitaxel), radioactive agents or bioabsorbable stents [1]. In theory, stents made of bioabsorbable polymers may be ideal, especially in pediatric population, as they can support the airway wall and dissolve after the remodeling process is completed, thus providing temporary airway stiffness, sometimes necessary in infants with tracheobronchomalacia. Such stents have the advantage of potentially avoiding the need for repeated interventions under general anesthesia for removal or revision [2–4]. Only pilot human studies of bioabsorbable stents have been published to date [5, 6]. Bioabsorbable drug-eluting stents have the potential advantage of reducing the risk of stent-related complications, but they have only been studied in animal models of benign tracheal stenosis [1]. In animal models, novel bioabsorbable stents (made of polycaprolactone) with cisplatin elution have been developed to overcome some of the problems associated with chronic indwelling stents (tumor ingrowth, fracture, migration) [7]. The mechanical strength of these stents was shown to be comparable to the strength of Ultraflex SEMS and provided a steady release of cisplatin for >4 weeks in vitro. The in vivo study showed sustained cisplatin levels in rabbit trachea for >5 weeks with a minimum drug level in blood. Histologic examination showed an intact ciliated

epithelium and marked leukocyte infiltration in the submucosa of the stented area, findings suggesting potential use in malignant CAO. In a recent human study, six biodegradable polydioxanone tracheal stents were safely implanted in four patients with benign inoperable tracheal stenosis. The authors report that all patients had "some" benefit from treatment and suggested that further research is needed to fully assess the outcomes of this therapy [8]. Whether these stents will be incorporated into clinical practice remains to be determined.

As of this writing, the originally described problems of migration, granulation, mucus plugging, infection, and even airway perforation and fatal hemoptysis are still present after stent insertion [9]. Therefore, operators have to carefully review the indications and expected results before inserting airway stents.

Indications

Airway stents are generally used for symptomatic extrinsic airway compression with or without associated airway mucosal infiltration. Stents can also be used if there is still significant (generally considered more than 50%) narrowing after the endoluminal component of a purely exophytic or mixed type of obstruction has been treated using one or more bronchoscopic techniques[2] [10]. Various stents have been used as well for sealing malignant esophagorespiratory and bronchial stump fistulas. Stents are occasionally used to improve symptoms of severe tracheobronchomalacia or excessive dynamic airway collapse, in patients who are refractory to more conservative measures (i.e., continuous positive airway pressure) and are not candidates for an open surgical procedure (i.e., tracheobronchoplasty for diffuse disease or sleeve resection for focal disease) [11, 12]. Studies performed within the last 20 years have shown that airway stents improve lung function in patients with central airway obstruction. In this section, we will describe the indications of stent insertion based on the mechanism of obstruction.

Extrinsic Compression

Extrinsic compression from benign or malignant thyroid disease, primary lung tumors (Fig. 11.2), mediastinal masses, or massive intrathoracic lymphadenopathy is the most common indication for airway stent insertion. Rarely, vascular abnormalities such as aortic aneurysm, vascular sling, and double aortic arch may cause symptomatic airway obstruction and may require stent insertion for patients who do not undergo corrective surgery.

Intraluminal Obstruction

Stent insertion may be useful in selected cases of endoluminal exophytic benign central airway obstruction (CAO); this is the case of refractory endobronchial recurrent respiratory papillomatosis (RRP) when medical and other endobronchial therapies fail to restore airway patency. Case reports show that papilloma debulking and silicone stents can offer adequate control of symptoms [13]. However, histologically benign intraluminal obstruction necessitating stent insertion is mostly caused by strictures, either idiopathic or related to other disorders. The most common cause of benign strictures is post-intubation and post-tracheostomy stenosis (Fig. 13.2), but it is important to note that a variety of other conditions associated with strictures should be ruled out before making the diagnosis of idiopathic stenosis. This is relevant as the management strategies need to be individualized. Examples include granulomatosis with polyangiitis (GPA; formerly Wegener granulomatosis), amyloidosis, sarcoidosis, ulcerative colitis, post-tuberculosis, or *Klebsiella rhinoscleromatis* infection. For example, 12–23% of patients with GPA develop tracheobronchial stenosis. A recent multicenter retrospective study of 47 patients

[2]These include rigid or flexible bronchoscopic resection, laser, electrocautery, cryotherapy, photodynamic therapy, or brachytherapy and are described in detail in other chapters in this book.

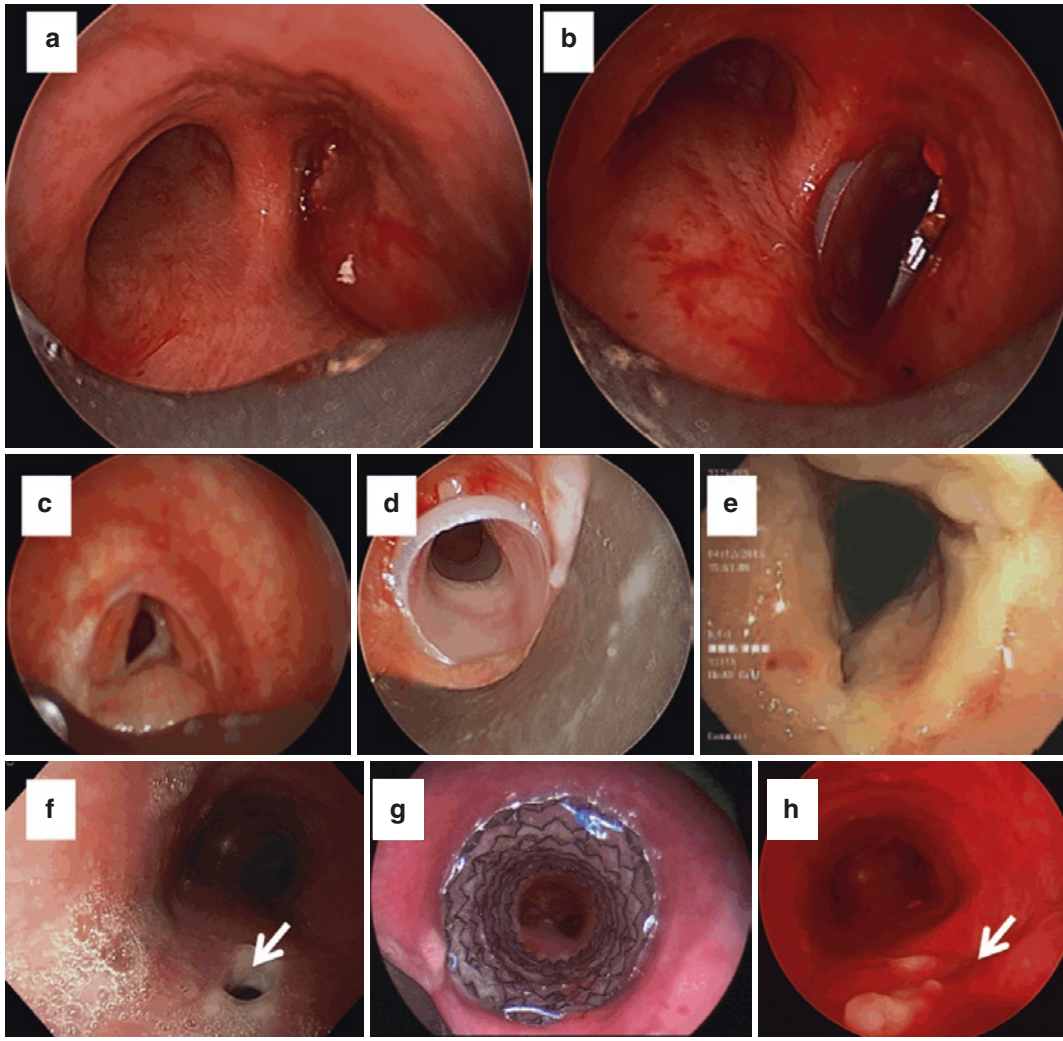

Fig. 13.2 Indications for airway stent insertion. Severe extrinsic compression of the right mainstem bronchus due to primary lung cancer, before (**a**) and after (**b**) silicone stent insertion. Severe, complex post-tracheostomy, triangular or A-shaped stenosis with malacia in a nonsurgical candidate before (**c**) and after (**d**) a 16 × 40 mm straight silicone stent was inserted. Follow-up bronchoscopy triggered by excessive coughing and inability to raise secretions demonstrated restored tracheal patency, but the stent migrated down to the main carina (**e**) and required removal. Benign gastro-tracheal fistula (**f**) after esophagectomy and gastric pull-up procedure. As repeat surgery was unsuccessful at closing the fistula, a fully covered SEMS was used (**g**). Four weeks later the stent was removed and, fortunately, the airway wall completely healed (**h**) without recurrence of the fistula during the follow-up

with GPA-associated tracheobronchial stenosis found that these patients benefit from a delay in any interventional procedures following the diagnosis, allowing for a "cooling off" period from the associated inflammation. It is also advisable to have patients on an increased dose of corticosteroids to >30 mg/day during the periprocedural period [14].

The remainder of this section will focus on the role of stent insertion for benign stenoses associated with intubation (PITS) and tracheostomy (PTTS). The incidence rate of benign tracheal stenosis following intubation has historically ranged from 0.6 to 19% and following tracheostomy from 6 to 65%. Fortuitously the advent of low-pressure cuffs has substantially decreased

these rates (by up to tenfold), yet still 1–5% of patients suffer from traumatic symptomatic PITS or PTTS, typically occurring 2–3 months following the event [15]. It remains to be determined whether the introduction of new mechanical ventilators with continuous endotracheal cuff pressure monitoring could further reduce the incidence of PITS. For post-intubation or post-tracheostomy strictures, stent placement should be considered only in inoperable patients; in addition, patients need to be symptomatic and the lumen of the airway below half of its normal after other interventional endoscopic techniques have been applied.

Benign airway obstruction can be classified in a variety of ways, and management techniques and success rates vary based on the type of stenosis. For example, a simple web-like stricture (extent less than 1 cm), which is dilated and does not recur, will not require a stent [16, 17]; a complex stricture, however, often has associated chondritis, and dilation alone (with or without laser assistance) is not usually successful, and a stent would be required to maintain airway patency [18]. Another way of classifying strictures uses the terms "structural" and "dynamic": a structural stenosis is a result of scarring and fixed constriction of the airway—this is the most common form. A dynamic stenosis is a form of focal, localized malacia with variability of obstruction dependent on the variability of transthoracic pressures during respiration. Another classification has been proposed to exist: that of a dynamic A-shaped tracheal stenosis (DATS) which is an amalgamated variation that combines both a structural stenosis from a fractured anterior cartilage ring with a dynamic stenosis from posterior malacia (Fig. 13.2). This results in a triangular "A-shaped" trachea on imaging. This is an important finding as the structural component is not the result of scaring/shrinkage of the trachea, and as such the management of DATS differs significantly from that of other structural forms of benign airway strictures. Specifically, patients with DATS do not benefit from dilation alone. At the same time, due to the dynamic component to the stenosis, patient experiences higher rates of stent migration than typical structural stenosis patients (Fig. 13.2) [15].

Silicone stent insertion performed using rigid bronchoscopy under general anesthesia is considered an acceptable alternative to surgery for inoperable patients with complex tracheal strictures. A 2016 retrospective study of 90 patients undergoing stenting for histologically benign airway obstruction showed that in patients with simple stenosis undergoing stenting, there was a 100% success rate with a single stent placed and mean stent duration of 5.6 months. On the other hand, patients with complex stenoses did not fare as well: 45% required multiple re-stenting procedures, 60% required stent repositioning, the stents remained in place for 12 months, and despite this the success rate was 70% at 1 year [17]. In an older study of 42 patients with complex stenoses, only 9 were surgical candidates, and 33 were treated with silicone stent insertion, with a success rate of 69% [19]. The success rate of bronchoscopic treatment once stents are removed (usually after at least 6 months) in cases of complex stenosis is reportedly low (17.6%) suggesting the need for long-term indwelling airway stent. A higher rate of airway stability after stent removal (46.8%, in 22 out of 47 patients) was described after stents remained in place for a longer period of time (mean of 11.6 months) [20], with almost 50% of patients (12/22) having their stents for more than 12 months. Predictors of success of bronchoscopic treatments are stenoses less than 1 cm in vertical extent and without associated malacia (i.e., chondritis). Lesion extent (i.e., height) and intubation-to-treatment latency have also been reported to independently predict the success of bronchoscopic intervention. In one study, 96% of patients with lesions <3 cm in height were successfully treated bronchoscopically, but the success rate decreased to 20% for lesions longer than 3 cm. Patients with stenosis present for more than 6 months since the original injury were also less likely to be successfully treated bronchoscopically [21], suggesting that the established fibrotic tissue counteracts the expansile force of the remaining cartilage [22]. In fact, knowing the integrity of the cartilage in post-intubation or post-tracheostomy stenoses is important in the treatment decision-making process. In complex post-intubation/tracheostomy

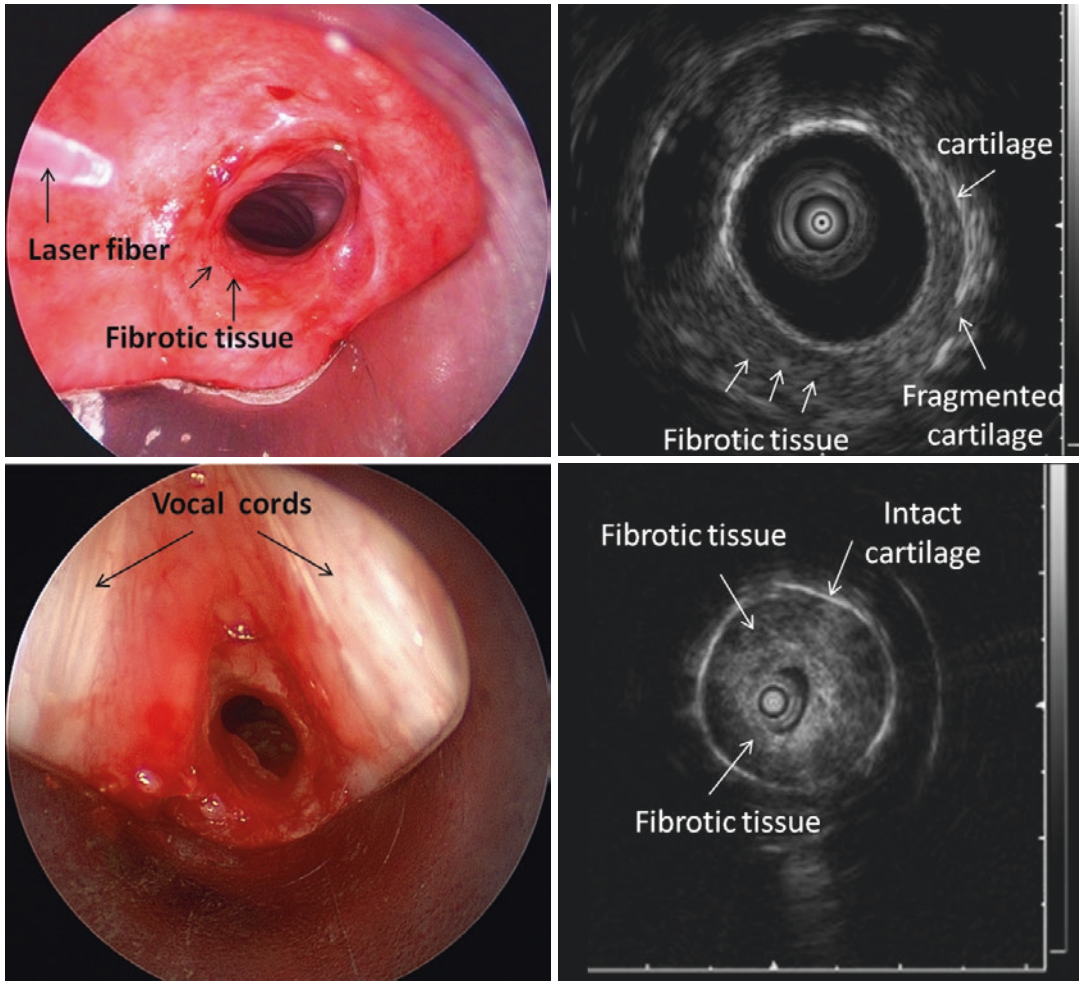

Fig. 13.3 Rigid bronchoscopic and sonographic view of laryngotracheal stenosis. In the *upper panel*, the circumferential post-intubation tracheal stenosis is noted, but on white-light imaging, the cartilage cannot be assessed. High-frequency endobronchial ultrasound (20 MHz probe) can identify the cartilage and its disruption. The knowledge that the cartilage is affected could impact management since simple laser-assisted mechanical dilation without stent insertion is unlikely to maintain airway patency in the long term. In the *lower panel*, idiopathic subglottic stenosis at the level of the cricoid is seen on white-light imaging, but the intact cricoid cartilage itself is only identified on high-frequency endobronchial ultrasound

stenosis, cartilage integrity or lack thereof is not always easily assessed on white-light bronchoscopy, mainly because of the overlying stenotic hypertrophic tissues [23] (Fig. 13.3). To assess the integrity of the cartilage, one may use high-frequency endobronchial ultrasound (20 MHz balloon-based radial probe) during the bronchoscopic intervention. The EBUS image using this system has a high resolution and allows visualization of the stenotic tissue and the cartilaginous structures and may be a surrogate of gross histology for tracheal stenosis; for instance, in idiopathic tracheal stenosis, the cartilage is known to be normal, but there is clear hypertrophy of the mucosa and submucosa as visualized by EBUS as well. On the other hand, in complex stenoses, there is partial or total destruction of cartilage histologically which can be identified by EBUS [23] (Fig. 13.3).

When used for benign stenosis, silicone stents are preferable and can be helpful for splinting post-intubation/tracheostomy stenoses and are

considered appropriate to palliate airway narrowing in nonsurgical candidates[3] [18, 24, 25]. Stent-related complications, however, are not uncommon in this disease and include migration, obstruction from secretions, infection, and significant granulation tissue formation at the proximal or distal extremities of the stent [9, 26].

Silicone T-tubes (Montgomery T-tubes) or tracheostomy tubes are sometimes used for benign tracheal strictures; they should be inserted through the area of stenosis, if possible, to conserve airway not involved by the stenosis lesion. For most patients who do not require mechanical ventilatory support, a silicone T-tube could provide symptomatic improvement [27]. These therapies are warranted in the few patients with critical stenoses who are neither candidates for surgery or indwelling airway stent insertion or who develop recurrence after such interventions [18]. T-tubes can also be used when tracheal resection and reconstruction or dilation techniques are either not available or have failed or as a solution for patients who had silicone stent placement complicated by frequent migrations [26]. In a large case series including 53 patients with complex tracheal stenoses (24 post-tracheostomy), silicone T-tube insertion was effective in 70% of patients with limited complications [28]. The sharper edge of the proximal aspect of the T-tube, in cases when it has to be cut, suboptimal tracheostomy tract (i.e., non-midline stoma), as well as its placement within 0.5 cm from the vocal cords are known risk factors for granulation tissue development[4] [28]. In addition, airway secretions may become dry and cause obstruction. Patients, families, and referring physicians probably benefit from instruction on how to care for and monitor T-tubes. Frequent bronchoscopies may be necessary to remove mucus plugs, with some investigators performing a 3–4 biweekly bronchoscopies, followed by once every 4 weeks once stent patency has been documented [28].

Self-expandable metallic stents (SEMS) have been associated with significant complications and are to be avoided, if possible, in benign disorders. Immediate symptomatic improvement is reported and expected, but the long-term complications are common and may be life threatening [29].

Self-expandable silicone stents, contrary to metal stents, have the advantage of being easily removable. They are, however, placed under rigid bronchoscopy or suspension laryngoscopy. Some of these silicone stents have been studied in benign airway obstruction including tracheal stenosis and malacia [30]. While immediate symptom palliation was established in most cases, the incidence of complications was high (75%) with stent migration occurring in 69% of cases [30, 31].

Postoperative Tracheobronchial Stenosis

A variant of histologically benign tracheal stenosis, postoperative tracheal stenosis (POTS) is a challenging problem following tracheal resection. Despite improved recognition and surgical techniques, the rate of POTS is 2–9% following tracheal resection. The majority patients with POTS are not candidates for further surgical management due to a combination high general surgical risk, poor lung function, and technical difficulties associated with previously resected tracheal segments. As such, bronchoscopic intervention is considered a therapeutic option. In a single-center retrospective review, 30 patients with POTS managed by bronchoscopic intervention were studied. Interventions included dilations (balloon or bouginage), YAG laser, and stenting (63% underwent silicone stents, no metallic stents were used). The majority (97%) achieved improvement in dyspnea within 24-h post-procedure. Stents were successfully removed in 37% of patients. Average stent duration in those amenable to removal was 7 months; 16% of those with stents removed developed tracheobronchomalacia [32].

[3] Coexistent diseases: coronary heart disease, severe cardiac or respiratory insufficiency or poor general condition.

[4] Granulation tissue formation at the proximal end of the T-tube has also been described, and it is believed that chronic airway irritation incites infection and promotes or aggravates granulation tissue formation.

Mixed Obstruction: Malignant Central Airway Obstruction

Malignant central airway obstruction (CAO) is a frequent complication of primary lung cancer and other cancers, which metastasize to the chest (especially breast, colon, melanoma, and renal cell cancers). Malignant CAO can be intrinsic (endobronchial/intraluminal), extrinsic, or a mixed obstruction, which has features of both intrinsic and extrinsic obstructive patterns. The most common form of malignant CAO is a mixed obstruction [33]. In a series of 172 patients who underwent stent insertion for malignant CAO at a tertiary cancer institution, 62.5% of the stents were placed for mixed disease, while only 16.4% and 14.8% were placed for extrinsic compression and intraluminal obstruction, respectively [9]. In general, the management principles for malignant intraluminal obstruction are the same as those for benign disease: if there is still obstruction after recanalization with various ablative techniques, if extrinsic compromise is present, or if there is a loss of airway structure (i.e., severe malacia due to cartilage invasion and destruction by tumor), a stent is placed to maintain airway patency.

Management of malignant CAO often requires a combination of multiple different management modalities. The choice of technique and method is operator dependent and is contingent not only on the etiology of the obstruction but also operator familiarity and preference. To study the impact of procedural volume and choice of technique in bronchoscopic management of malignant CAO, a large multicenter retrospective review of bronchoscopic management of patients with malignant CAO was undertaken from the American College of Chest Physicians (CHEST) Quality Improvement Registry, Evaluation, and Education (AQuIRE) registry. Overall the study found that despite significant inter-institutional differences in procedural preferences and volumes, there was no impactful difference in technical success and that one specific therapeutic modality could not be recommended over another [33].

Interventional treatment of malignant CAO is considered to be primarily palliative as once cancer progresses to the point of CAO, it is almost invariably incurable. As such endoscopic interventions focus predominantly on attempting to improve quality of remaining life. Relieving the CAO due to malignant disease has been proposed to prevent post-obstructive pneumonia, sepsis, and septic shock, allow extubation, change in level of care, permit initiation of systemic therapy, and potentially improve survival. There is evidence that bronchoscopic therapies often provide acute relief of the obstruction, improve quality of life, and serve as a therapeutic bridge until systemic treatments become effective [34–36]. Prospective studies show that bronchoscopic intervention for malignant CAO is associated with improvement in the six-minute walk test (6MWT), spirometry, and dyspnea [37]. In addition, studies show that airway stent insertion resulted in significant palliation of symptoms in patients with malignant CAO as evaluated by Medical Research Council (MRC) dyspnea scale and performance status [38].

In the AQuIRE registry mentioned above, bronchoscopic interventions were associated with a significant decrease in dyspnea (decrease in Borg score by 0.9 ± 2.2). Specifically, 48% reported clinically significant improvement in dyspnea, 43% reported no change, and 9% had worsened dyspnea. Of particular relevance, dyspnea improved proportionally to the pre-procedure severity of dyspnea: the more dyspneic prior to procedure, the more improvement in dyspnea after the intervention. Another notable finding was that those with lobar (as opposed to more central) obstruction were less likely to have much improvement in dyspnea. Bronchoscopic interventions were also associated with a significant increase in health-related quality of life (HRQOL). Overall 42% had a significant improvement of HRQOL, 33% remained unchanged, and 25% reported worsened HRQOL. Again, as with the predictors of dyspnea relief, a higher baseline Borg (i.e., worse baseline dyspnea) predicted a more pronounced improvement in HRQOL, while those with lobar obstruction were found to have less improvement in HRQOL [33]. While airway patency was improved in >90% of patients, less than half improved their HRQOL scores. These findings

suggest that we need better prediction models for who will improve dyspnea and HRQOL after such interventions. Despite the focus on palliation and improved quality of life with these procedures, a significant post-procedural survival advantage was also apparent in those without severe performance limitations prior to their procedures when compared with historical controls [38].

The presence of stridor (reflecting critical CAO) prior to intervention was found to be a poor prognostic indicator for survival in patients undergoing bronchoscopic intervention for malignant CAO: those without stridor had a 1-year and 2-year survival of 35.5% and 31%, respectively, while those with stridor had a 1-year and 2-year survival of 12.5% and 0%, respectively. Patients requiring stent placement for malignant CAO as opposed to dilation ± other non-stenting interventions had significantly lower 1- and 2-year survivals [39]. It is not clear whether lower survival rates are because of the stenting or just because patients requiring stents had more severe/extensive airway obstruction.

Subsequent chemotherapy and/or radiotherapy has been shown to increase disease-free survival during the first year after restoration of airway patency [34, 40]. A retrospective single-center study of 48 patients with malignant CAO who underwent bronchoscopic intervention reviewed the effects of chemotherapy following bronchoscopic interventions. The patients who received post-procedural palliative chemotherapy had a median survival of 6 months with a 1-year and 2-year survival of 35% and 31%, respectively. Those patients who received no post-procedural chemotherapy had a median survival of 2.5 months with a 1-year and 2-year survival of 18% on 14%, respectively [39]. In addition, it appears that airway stent insertion followed by adjuvant therapy may improve survival of treatment-naive patients with severe symptomatic airway obstruction caused by advanced lung cancer. In one study, while the performance status and dyspnea scales improved in both treatment-naive and terminal-stage lung cancer, the median survival time and 1-year survival rate after stent insertion were 1.6 months and 5.1%, respectively, in the terminal-stage group and 5.6 months and 25.0%, respectively, in the treatment-naive group [41].

Lung cancer patients who develop respiratory failure due to CAO have particularly poor prognoses: only 25% are successfully liberated from the ventilator, and 40–70% die in the hospital. In addition to the quality of life issues, ventilated patients are often not considered candidates for additional oncologic treatment. Furthermore, patients with malignant CAO are given low priority for ICU level admission in the Society of Critical Care Medicine ICU admission recommendations [42], as they are considered to have low probability of reversibility and survival. A small single-center retrospective study addressed this assumption of lack of reversibility. Twelve patients with non-small cell lung cancer with associated CAO resulting in respiratory failure requiring mechanical ventilation who were not candidates for surgical procedures were managed with bronchoscopic intervention and various combinations of mechanical debulking, laser resection, and airway stenting: 66% underwent stenting. The majority (83%) was successfully liberated from mechanical ventilation, and the post-procedural median survival was 313 days. As such bronchoscopic intervention should be considered for lung cancer patients with respiratory failure due to CAO [43].

Stump Fistulas

A less common indication for stent insertion is to cover large stump fistulas after lobectomy or more commonly, after pneumonectomy [44]. In general, management strategies for bronchopleural fistula (BPF) depend on the underlying histology (malignant versus benign), size, time to fistula formation postsurgery, and health status of the patient. Surgery is the treatment of choice of this condition, but bronchoscopic techniques have been advocated as an option when surgery is not possible or has to be postponed [45]. Surgical repair is not a good option for patients requiring mechanical ventilatory support because postoperative mechanical ventilation is associated with a high failure rate due to persistent barotrauma on

the repaired stump [45]. As a general rule, when stents are used for this indication, a large stent must be used to seal the stump fistula as tight as possible in order to prevent aspiration pneumonia and empyema and allow satisfactory single-lung ventilation when the patient requires mechanical ventilation. Stent selection would depend on the size and location of the fistula, as well as on the physical properties of the stent and the operator's ability to manage potential stent-related complications. Several case reports and case series of endobronchial stent insertion for isolated fistulas have been published [46]. The effect of case selection is difficult to assess from the limited literature on this topic.

Esophagorespiratory Fistulas

Tracheoesophageal or broncho-esophageal fistulas can be covered by airway stents. While these fistulas can be congenital, the majority are acquired either after esophagectomy, after intubation, or in the setting of malignancy. Benign esophagorespiratory fistulas (ERFs) are not expected to improve after stent insertion, and, in fact, it should only be considered as a palliative intervention if there are no operative modalities (Fig. 13.2) [47].

Malignant ERF is common in esophageal cancer, having a 5–15% occurrence, and occurs rarely in bronchogenic carcinoma (~1%). Once developed, the prognosis is poor, with a poor QOL and 3–4 month survival. Although surgical resection and reconstruction has the greatest potential benefit, it comes at a high cost of complications and prolonged hospitalized recovery. Alternatively, gastro/jejunostomy tube feeding is a strategy utilized to minimize effect of malignant ERF, but this may not be accepted by patients and has the potential to further reduce quality of remaining life [48]. Palliation for malignant ERF is usually achieved with endoscopic placement of esophageal, airway, or parallel (dual) stent insertion (in the esophagus and airway). Dual stent insertion appears to work better than a single prosthesis. Particular attention should be paid to airway compression or erosion caused by placement of esophageal stents; if there is concern for significant tracheobronchial obstruction, operators should consider placement of an airway stent prior to the esophageal one (Fig. 13.4).

The choice of tracheal stent used for ERF closure should take into consideration the size and location of the fistula. The Freitag classification system [49] was developed to systematically define the location and severity of central airway stenosis, but this system can be used to define the location of an ERF: Location I, upper third of trachea; II, middle third or trachea; III, lower third of trachea; IV, carina; V, right mainstem; VI, bronchus intermedius; VII, left mainstem; and VIII, left distal bronchus. Using this system and by defining a small fistula as one that is <1 cm in size, a single center developed an algorithm for stent choice in ERF stenting: an I-shaped stent for small fistulas in Locations I, II, and VIII; an L-shaped stent for small fistula in Locations V, VI, VII; and a Y-stent for any fistulas in Locations III or IV or large fistulas in Locations II, V, and VII. This approach resulted in complete fistula closure in 72% of patients and clinically beneficial partial closure in the remaining patients [48].

A dedicated fistula stent, the DJ cufflink-shaped prosthesis, was designed exclusively for closure of malignant ERF secondary to esophageal or lung cancer. It can be sized to the fistula diameter to occlude the abnormal communication [50, 51]. Insertion of silicone Y-stents was shown to improve symptoms, reduce infections, and improve the quality of life in patients with malignant ERF. Mean survival of these patients, however, remains dismal and is in the range of 2 months [52]. A conservative palliative approach including only symptomatic control but no palliative interventions (i.e., stent insertion) is not unreasonable especially since interventions in this frail population could be harmful. Without treatment, however, survival may be limited to only a few days [53]. On the other hand, a recent prospective study of 112 patients with malignant ERF, airway stents were inserted in 65 (58%) patients, esophageal stents in 37 (33%) patients, and both airway and esophageal stents in 10 (9%) patients. Contrary to previous data, the authors found an overall mean survival of 236.6 days

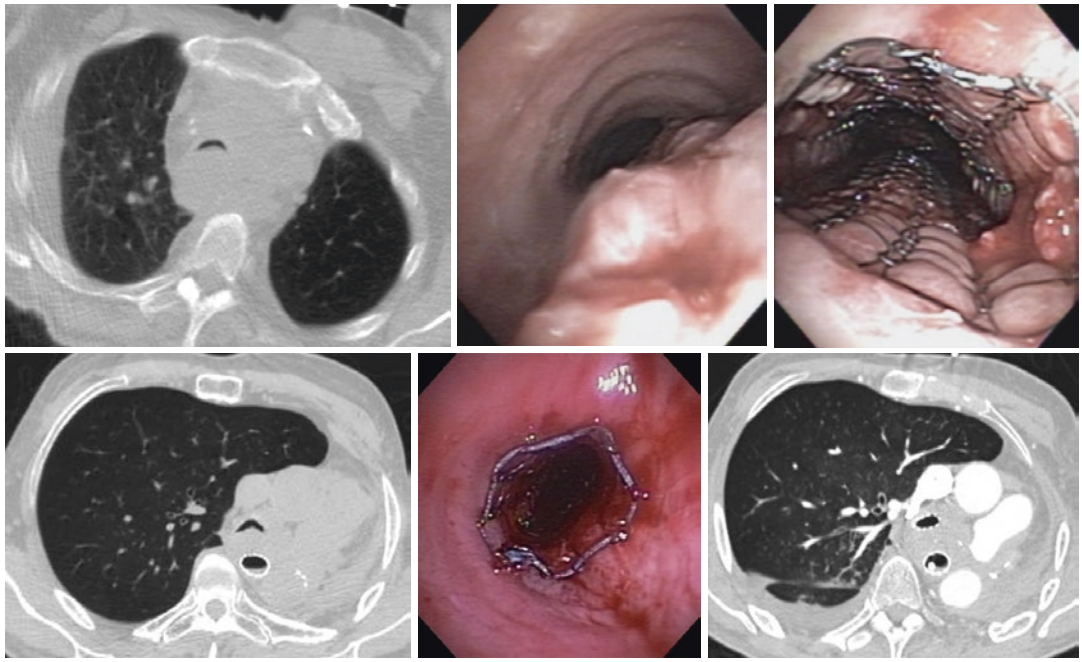

Fig. 13.4 Airway stents in obstruction caused by esophageal tumors. In the *upper panel*, chest computed tomography (CT) shows severe tracheal narrowing from a mediastinal mass, known to be esophageal carcinoma. Bronchoscopy confirmed the CT findings, and a partially covered metallic stent was placed to palliate the airway obstruction prior to esophageal stent insertion for dysphagia. In the *lower panel*, severe tracheal and right mainstem obstruction occurred after the insertion of an esophageal stent and resulted in respiratory failure in this patient with poor lung function from his previous pneumonectomy. A partially covered metallic stent was inserted from the lower trachea to the mainstem bronchus, palliating the obstruction and allowing liberation from mechanical ventilation

(airway stent 219.1 days, esophageal stent 262.8 days, and combined airway-esophageal stent 252.9 days). Since a few patients are operable, currently airway and/or esophageal stent insertion is mainly used with a palliative intent to improve the quality of life (QOL) in patients with malignant ERF [54].

Expiratory Central Airway Collapse

Airway stent insertion has been used to improve cough, secretions, and QOL in patients with expiratory central airway collapse (ECAC) [11, 12]. There are, however, different morphologic types of ECAC, for some of which stent insertion is not physiologically justifiable. Excessive dynamic airway collapse (EDAC) is due to bulging of the posterior membrane within the airway lumen during exhalation that narrows the lumen by 50% or more, and the cartilage is intact in this process. Tracheobronchomalacia (TBM), on the other hand, refers to softening of the airway cartilaginous structures [55]. The decision to insert an airway stent in these processes is complicated by at least two factors: (1) the lack of standardized definitions and cutoff values to define abnormal airway narrowing and (2) the lack of clear understanding if these entities are truly responsible for airflow limitation. In fact, the limit between normal and abnormal narrowing of the central airways has not been physiologically established, and different investigators propose different cutoff values. In addition, there is no standardized way to measure the narrowing in terms of location or respiratory maneuver (Table 13.1) [55]. To illustrate this lack of consensus, a study found that almost 80% of normal individuals met the currently accepted 50% narrowing during forced exhalation criterion [56]. In an attempt to provide a common language for these patients with ECAC, a classification system was proposed

Table 13.1 Summary of classification systems for expiratory airway collapse

First author/year	Parameters	Comments
Rayl/1965	*Extent*: proximal, mediastinal, and intrapulmonary airways	Collapse during cough on cine-bronchography
Johnson/1973	*Severity*: four degrees and focal type	TM: more than 50% collapse during coughing on fluoroscopy
Feist/1975	*Etiology*: congenital and acquired	TM: more than 50% collapse during coughing on fluoroscopy
Jokinen/1977	*Severity*: mild, moderate, severe	First classification based on bronchoscopic findings
	Extent: TM, TBM, BM	
Mair/1992	*Etiology*: congenital, extrinsic compression, acquired	Described for pediatric TBM
	Severity: mild, moderate, severe	Empirical severity score
Masaoka/1996	*Etiology* and *extent* criteria	TBM: >80% collapse during expiration
	Pediatric, adult, and secondary	
Murgu/2007	*Functional class*	Stratification criteria (Functional class, extent and severity are objectively assessed)
	Extent	Morphology includes EDAC and three forms of TBM[a]
	Morphology	Origin: idiopathic or secondary
	Origin (Etiology)	
	Severity	

TM tracheomalacia, *TBM* tracheobronchomalacia, *BM* bronchomalacia, *EDAC* excessive dynamic airway collapse
[a]There are three morphologic types of TBM: crescent type, when the anterior wall is collapsing; saber-sheath type, when the lateral walls are collapsing; and circumferential or mixed type, when the anterior and the lateral walls are collapsing, as is seen with relapsing polychondritis

based on objective quantifiable criteria, which can be applied before and after stent insertion (Table 13.1) [55].

Studies show that in the short term (up to 10–14 days), airway stabilization with silicone stents in patients with expiratory central airway collapse (malacia and EDAC) improves symptoms, quality of life, and functional status [11, 12]. QOL and functional status scores improved in 70% of patients, and dyspnea scores improved in 91% of patients after stent insertion [12]. Stent-related complications in this case series included obstruction from mucus plugging and migration, and almost 10% of patients (5/52 patients) had complications related to the bronchoscopic procedure itself. Because the dynamic features of expiratory central airway collapse continuously alter the shape of the central airways as well as the surface contact between a stent and the airway wall, stent-related complications may occur more frequently in dynamic forms of airway obstruction than in fixed benign obstruction. Although not life threatening, these stent-related adverse events required multiple repeat bronchoscopies [11]. In another series of patients with mostly TBM, adverse effects from silicone stent insertion were very common, however, with a total of 26 stent-related adverse events noted in 10 of 12 patients (83%), a median of 29 days after intervention [11]. TBM due to relapsing polychondritis (RP) is one disease for which stent insertion is often necessary due to a diffuse lack of airway cartilaginous support. Both self-expandable metallic stents and silicone stents have been used in patients with malacia from RP [57, 58]. Sometimes, more than one stent may be required if symptoms persist after stent insertion, presumably because of distally migrated choke points [58]. Because airway stents are not the best solution for this disease, a more conservative approach such as continuous positive airway pressure (CPAP) may be safer. CPAP may indeed be considered a "pneumatic stent." The excessive airway narrowing in ECAC and the resulting turbulent flow result in increased airway resistance. This requires greater trans-

pulmonary pressures to maintain expiratory airflow and will increase the work of breathing and result in dyspnea. Thus, noninvasive positive-pressure ventilation such as CPAP decreases pulmonary resistance and can be used to maintain airway patency, facilitate secretion drainage, and improve expiratory flow. Small studies showed that nasal CPAP improves spirometry values, sputum production, atelectasis, and exercise tolerance, but its long-term efficiency has not been clearly demonstrated [59]. As of this writing, however, the limited published evidence suggests that QOL and functional status are improved in patients with ECAC undergoing stent insertion, but the lung function as measured by FEV_1 has not been consistently reported to improve after stent insertion or other forms of central airway stabilization (i.e., membranous tracheoplasty) [12]. These facts raise questions about the physiologic basis for stent insertion for both fixed and dynamic forms of CAO.

Physiologic Rationale for Airway Stent Insertion

In general, for symptomatic patients with fixed tracheal obstruction, a stent is inserted to improve the lumen to less than 50% obstruction; for symptomatic patients with dynamic obstruction, stents are meant to stabilize the airway at the collapsible segment responsible for flow limitation (aka choke point).

For tracheal stenosis, symptoms depend on the amount of pressure drop along the stenosis; this depends on the degree of the obstruction but also on the flow velocity through the airway narrowing. This flow dependence of symptoms explains why different patients with similar degree of airway narrowing have different clinical presentation, depending on their level of activity. These facts highlight the need to individualize treatment based not just on degree of narrowing as assessed by radiographic or bronchoscopic imaging but also on the stenosis impact on functional status. In fact, functional status and dyspnea scales may be more relevant than static lung function measurements, which were shown to weakly correlate with the MRC dyspnea scales in laryngotracheal stenosis [60]. In addition to functional status, a classification system for tracheal stenosis should include the extent, morphology, and severity of airway narrowing, factors that impact the decision to insert an airway stent. To quantify the severity of airway narrowing, the cutoff values used in the available systems are 50% and 70% to define moderate and severe stenosis, respectively [61]. These values seem to be justified by physiologic studies in which the investigators found that the effect of the glottis narrowing was noted to be of the same order as that of the 50% stenosis; these data suggests that a 50% or less narrowing may not even be clinically detected or require treatment; however, a significant pressure drop is seen at 75, 85, and 90% stenosis, pressure drop which correlates with significant work of breathing [62]. Based on these physiologic data, therefore, one could classify stenosis as mild, when less the 50% narrowing; moderate, from 50 to 70%; and severely narrowed when more than 70% of the lumen is occluded, justifying the practice of improving the airway lumen to less than 50% narrowing, with stent insertion, if necessary.

For expiratory central airway collapse, it is still not clear what degree of airway collapse is physiologically significant; furthermore, as of this writing, there are no accepted noninvasive physiologic tests to predict response to stent insertion. However, when patients have clear inability to raise secretions and recurrent pneumonia or even respiratory failure, then a stent is inserted regardless of the cause of collapse. From flow dynamics standpoint, the clinically relevant question in this process is whether stent insertion improves the expiratory flow. Physiologists proposed a theory to explain expiratory flow limitation, theory which is useful to understand the role of stent insertion in patients with dynamic CAO such as malacia or EDAC. Physiologic studies showed that once expiratory flow becomes limited at a given lung volume, there would be a region within the intrathoracic airway where intrabronchial and extra-bronchial pressures become equal (equal pressure point, EPP) (Fig. 13.5) [63]. At a given lung volume, driving pressure upstream

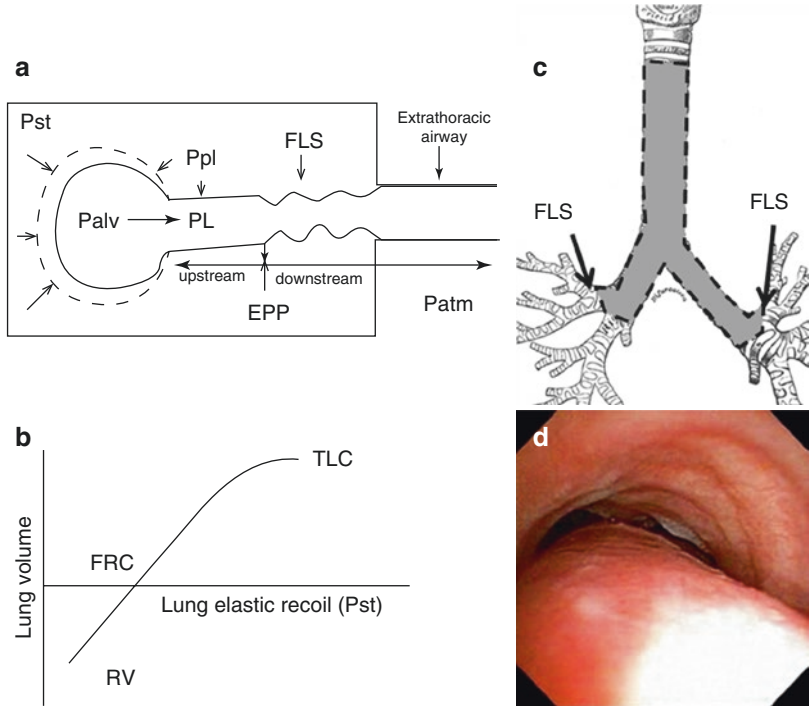

Fig. 13.5 Choke point physiology based on Starling resistor. (**a**) The alveolar pressure (Palv) is the driving pressure that causes gas to flow through airways during expiration and is approximately equal to the recoil pressure of the lungs (Pst) plus the pleural pressure (Ppl): Palv = Ppl + Pst. Normally, a pressure drop is required to accelerate a gas as it moves from an upstream (alveolarward) region of low velocity to a downstream (toward the mouth) region of high velocity. Because of this pressure drop, the intraluminal pressure (PL) eventually becomes equal to pleural pressure (Ppl). The point within the airway at which this occurs is called the equal pressure point (EPP). This equal pressure point (EPP) divides the airways into upstream segments (alveolarward from the EPP) at which transmural pressure is positive and downstream segments (mouthward from the EPP) at which the transmural pressure is positive within the extrathoracic airways and negative within the intrathoracic airways. At a given lung volume, driving pressure upstream from the EPP would be equal to lung elastic recoil, while downstream from the EPP, airways would be compressed during expiration. This region of compression of intraluminal caliber is referred to as a flow-limiting segment (FLS) or "choke point." (**b**) As lung volume decreases from TLC toward RV, the elastic recoil (Pst) decreases as well, and pleural pressure (Ppl) increases during forced expiration. (**c**) Thus, the EPP migrate upstream, resulting in a lengthening of the increasingly narrow downstream segment. This increases airway resistance and prevents further increases in expiratory airflow, causing the EPP to become fixed when airflow becomes constant. FLS has tracheal location at high lung volumes, (i.e., TLC), whereas others found FLS in lobar and segmental airways over a range in volume approximating TLC to functional residual capacity (FRC). As lung volume decreases during exhalation, the FLS move peripherally to the lobar/segmental and at most subsegmental bronchi. (**d**) Therefore, if the choke points (FLS) in humans are often located in the lobar bronchi, a mainstem bronchial or tracheal collapsibility should not result in any pressure drop between the mouth and the choke point and should not affect flow. Thus, bronchoscopic or radiologic detection of expiratory tracheal or mainstem bronchial compression (excessive dynamic airway collapse) should trigger a search for causes of airflow obstruction within the lung, not the central airways

(alveolarward) from the EPP would be equal to lung elastic recoil, because pleural pressure (Ppl) equals the intraluminal pressure (PL); downstream from the EPP (mouthward), airways would be compressed during expiration. This region of compression of intraluminal caliber is referred to as a flow-limiting segment (FLS) or "choke point." As lung volume decreases and pleural pressure (Ppl) increases during forced expiration, the EPP migrates upstream, resulting in a lengthening of the increasingly narrow downstream segment. This increases airway resistance and prevents

further increases in expiratory airflow, causing the EPP to become fixed when airflow becomes constant. EPP and therefore the FLS have tracheal location at high lung volumes (TLC), but as lung volume decreases during exhalation, the FLS moves peripherally, but they still stay in the central airways, in the lobar/segmental, the farthest in subsegmental bronchi [64]. Therefore, if the choke points in humans are often located in the lobar bronchi, a mainstem bronchial or tracheal collapsibility in the form of EDAC, often seen on CT or bronchoscopy, should not result in any pressure drop between the mouth and the choke point and should not affect flow. In fact, physiologists suggest bronchoscopic or radiologic detection of expiratory tracheal or mainstem bronchial compression (EDAC) should trigger a search for causes of airflow obstruction within the lung, not the central airways [65]. Loss of pressure in the abnormally narrowed peripheral airways in patients with asthma, COPD, or bronchiolitis will lead to decreased intraluminal pressure by the time that airflow reaches central airways, so that these airways (trachea and mainstem bronchi) will collapse at the weakest point, which is the posterior membrane. Thus, EDAC is most often a reflection of peripheral airway disease, but it can also be seen with morbid obesity due to increased pleural pressure and possible flow limitation at rest. A study of patients with obesity and COPD and normal volunteer controls found that EDAC was significantly associated with BMI (69% tracheal collapse among morbidly obese patients with BMI $\geq$ 35 compared to 57% in others, $p = 0.002$) [66]. EDAC has been documented in 22% of patients with COPD assessed by dynamic chest CT and in morbidly obese patients under general anesthesia likely due to positive pressures throughout the chest [67]. This does not mean that EDAC is responsible for flow limitation. In fact, even when defined as forced expiratory collapse of >80%, according to some reports, EDAC is not flow limiting as there is no significant correlation between end-expiratory or dynamic expiratory collapse and percent predicted FEV_1 [68].

That being said, recent epidemiologic studies show that EDAC is responsible for worse QOL in smokers [69]. A total of 8820 patients from 21 clinical centers were enrolled in the COPD gene study. On paired inspiratory-expiratory dynamic CT (measurements at aortic arch, carina, and bronchus intermedius), EDAC was found in in 443/8820 patients (5%). The primary outcome variable, quality of life (QOL) as measured by SGRQ, was worse in EDAC, which was also responsible for increased frequency and severity of exacerbations. In addition, some patients may improve their functional status after stent placement in the central airways not only for malacia but also for EDAC; one explanation is that improved central airway stability, regardless of which wall is collapsing, makes the flow less turbulent, similar to heliox, which was shown to improve exercise capacity in patients with moderate to severe COPD, even though these patients typically have choke points in the small airways (of 2 mm or less) [70]. It is possible than in the future, in addition to bronchoscopic and imaging methods, new physiologic or imaging studies may have a role in identifying the choke point physiology in CAO. For instance, using impulse oscillometry (IOS), increased resistance (i) at a low oscillation frequency (5 Hz) reflects an increase in total respiratory resistance suggestive of airway obstruction such as that found in patients with COPD, while increased R at a higher frequency (20 Hz) reflects more specifically increased central airway resistance such as that found in patients with malacia [71]. Until these methods are validated in large studies, a trial and error approach is still clinically used: temporarily place a stent and test whether the patient improves clinically; if they do, a surgeon may perform an external splinting procedure; if not, the stent is removed [72]. Another assessment method, more accurate but minimally invasive, is the intraluminal pressure monitoring using a small pressure catheter. As pointed above, dynamic airway compression causes the formation of FLS in the central airways during forced expiration. Both in animal and human studies, these FLS could be located with the use of intraluminal airway catheters by measuring lateral airway pressure (Plat) during induced flow limitation generated by either an increase in pleural pressure or a decrease in downstream pressure.

The measurements of lateral pressure in malacia before and after stent insertion show that before stenting, a large pressure difference is seen between the upper trachea and right lower bronchus and carina. After stenting, the pressure difference could vanish for both inspiration and expiration, and a regular respiratory cycle is seen [73]. By measuring lateral airway pressure on each aspect of the airway narrowing (proximal and distal) and plotting the two pressures against each other (pressure-pressure curves) during quiet breathing intraoperatively, the site of maximum obstruction and the degree of airway narrowing can be determined quantitatively [74]. Analysis of the pressure difference and the angle of pressure-pressure curve allow intraoperative estimation of the outcomes of a particular interventional bronchoscopic procedure. However, stents may improve flow but the choke points migrate distally. This process can be addressed either by additional stent insertion or by the use of noninvasive positive-pressure ventilation. Detection of choke point migration can be demonstrated bronchoscopically or by dynamic computed tomography (CT) in the form of airway wall collapse distal to the stent.

Stent Selection Criteria

Stent retrievability is an important criterion in patients with benign disease and with malignancy for which a temporary stent placement is expected. For example, for patients with malignant CAO who will undergo further systemic chemotherapy and/or radiation therapy and respond to treatment, the stent may become loose, migrate, and require removal [75]. Inserting a stent into the patient is not always the biggest challenge encountered in caring for these patients. It is advisable to select a stent that can be removed if necessary without causing further tissue damage. Another selection criterion is based on the stent's *morphology and positioning*: for instance, T-tubes require a tracheostomy, straight indwelling stents splint open the trachea and the mainstem bronchi, while bifurcated stents are placed at the main carina and sometimes at secondary carinas. One criterion to consider prior to insertion is the *stent material*. In fact, the traditional way to classify stents was based on material type: metal, polymers, and hybrid stents partially covered or fully covered.

The type of stent, however, should also be decided based on the *biomechanical characteristics* (dependent on the material but also on design and thickness) because stents differ greatly in their elasticity and resistance to angulation [76, 77]. The expansile force (strength) and ability to withhold angulation (buckling) varies among different types of stents. In this regard, the studded-silicone type stent and Polyflex stents have a high expansile force [60] and may be preferred in obstruction due to severe and extensive airway compression. However, for a distorted, curved airway, angulation properties become important because they determine whether the stent can conform to an acutely angulated airway and still remain patent, such as is often the case in patients with left main bronchial obstruction due to extrinsic compression (Fig. 13.6). In these cases, the Ultraflex stent may be a better choice than a straight silicone stent because of the Ultraflex stent's known resistance to angulation. A study evaluating the role of interventional bronchoscopy for malignant CAO showed that the most common stent used in the trachea and right mainstem bronchi (relatively straight airways) was the Dumon stent, while the most common one for the left mainstem bronchus (curved, tapered airway, often distorted in the setting of malignancy) was the Ultraflex stent, likely because of its better ability to withhold angulation[5] [78]. Therefore, stent biomechanics bench testing data such as the crush (expansile) force, infolding (angulation) properties, and fatigue life, which are for the most part considered confidential and proprietary information, may be very useful to the interventional bronchoscopist. For instance, fatigue life may become important in patients with benign etiology of CAO, especially

[5] In this study, patients with esophageal carcinoma involving the airway mostly required only stent placement without laser-assisted debulking, probably because the main problem was extrinsic compression.

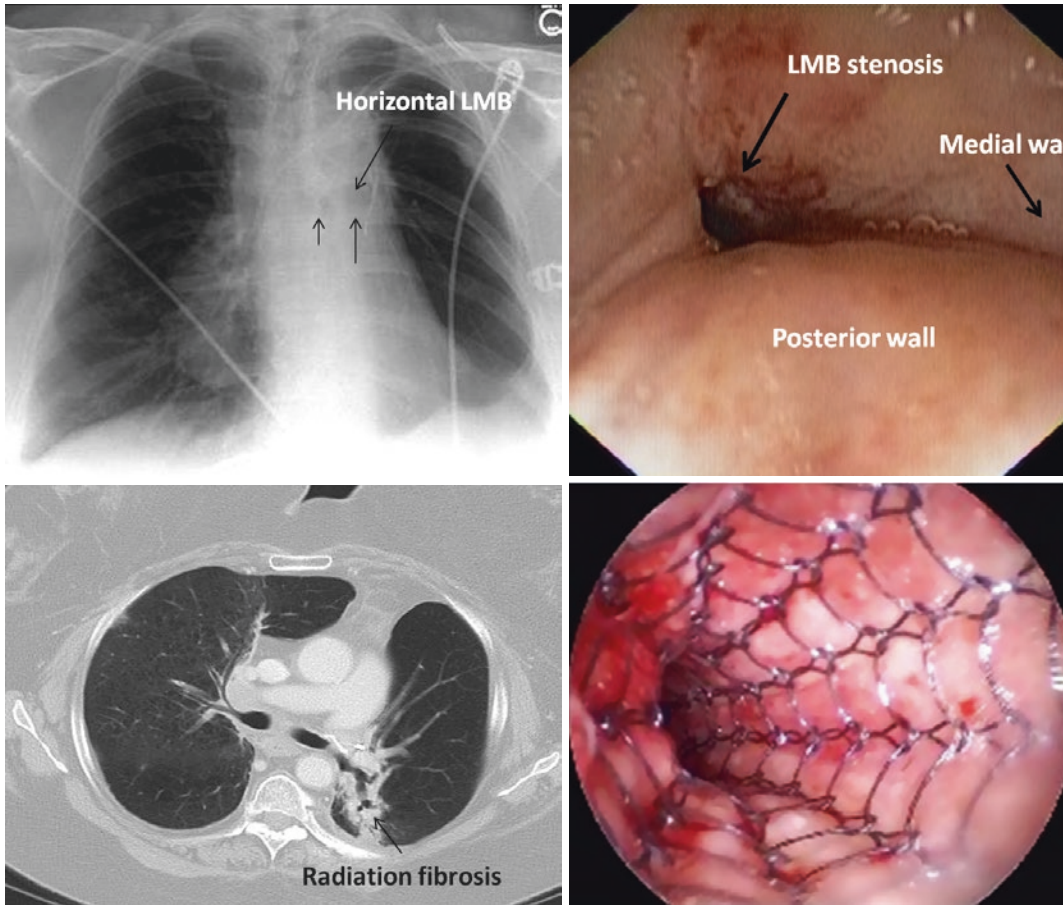

Fig. 13.6 Example of how airway anatomy impacts stent selection. Chest radiograph reveals nearly horizontal left main bronchus (*upper left*). Chest computed tomography shows that this was in part caused by volume loss from radiation fibrosis (*lower left*). Bronchoscopy revealed significant torsion of the left main bronchus and mid-distal left main bronchial stenosis (*upper right*). Due to its resistance to angulation, a partially covered self-expandable metallic stent was inserted to restore airway patency

malacia, in which cycled compression of the stent with each exhalation may lead to stent fracture and its associated complications.

In regards to *size*, following dilation, usually a stent with a diameter that is bigger than the remaining stenosis should be inserted. The actual size of the stent could be objectively determined by carefully evaluating the airway diameter using CT, measuring devices or even radial probe EBUS, or long range, anatomical optical coherence tomography. Many experienced rigid bronchoscopists, however, do not need or use these technologies and often choose the size of the stent based on the "tactile feedback" resulting from the viscoelasticity property of the airway; in general, the stent is slightly larger (1–2 mm) than the size of the dilating bronchoscope. However, if CT scanning is used to determine the stent size, one should remember that for mainstem bronchi, contrary to trachea, the diameter of the airway on the CT is different than the actual airway diameter, and corrections are necessary (Fig. 13.7) [79].

Contrary to size, the *length* of the stent does not have an important impact on flow dynamics [62]. That is simply because the resistance to flow is linearly and directly proportional to the length of stenosis and inversely proportional to the radius of the airway narrowing at

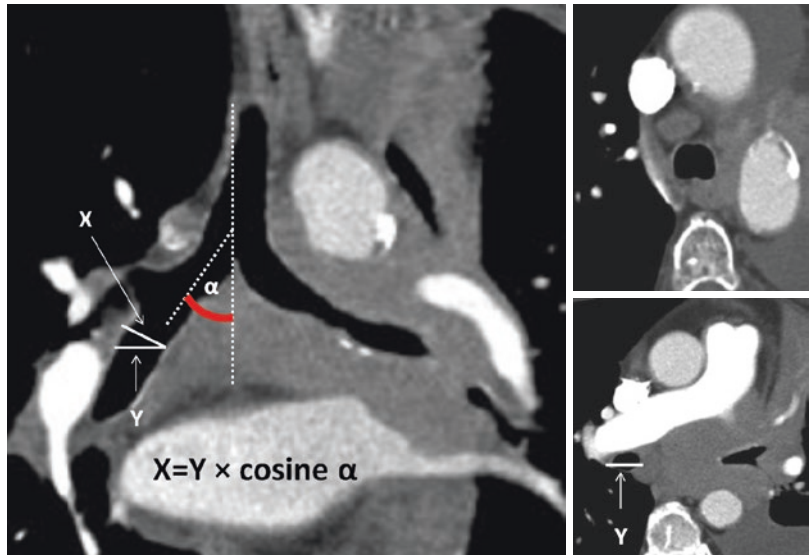

Fig. 13.7 Chest computed tomography use for stent size selection. Contrary to trachea (*upper right*), for mainstem bronchi and bronchus intermedius (*lower right*), the diameter of the airway on the CT (*Y*) is different than the actual airway diameter, and corrections are necessary (*right panel*). *Y* represents the measured transverse diameter of the bronchus on chest tomography, and *X* represents the corrected transverse bronchial diameter. *α* denotes the angle between the central axis of the trachea and bronchus, which equals the angle between *Y* and *X*

the power of 4 (for laminar flow). In simulation studies, for instance, long stenoses show a modest difference in pressure profile with a slightly bigger magnitude of total pressure drop than the web-like stenosis of comparable airway narrowing (90%) [62]. The extent of the narrowing is important, however, for surgical decisions and for stent's length selection. In general, the length of the stent should be longer than the actual stenosis, to avoid migration and obviously to properly palliate the airway narrowing. In general the stent should exceed the stenosis by 0.5–1 cm on both sides. This principle may be difficult to apply in short airway such as the right main bronchus, when the stent may need to be customized on-site in order to provide ventilation to the right upper lobe. The exact length can be measured based on previously performed chest CT scanning for a different indication. Given the risk of radiation and alternative methods, ordering a CT scan for the sole purpose to determine stent size or length may not be warranted or cost-effective. The operator can use the scope itself, the telescope or accessory instruments (available sizing devices) to measure the extent of stenosis during bronchoscopy.

All these stent factors (size, length, morphology, material, and biomechanics) become important in selecting a particular stent for a specific type of obstruction. For instance, the dynamic features of TBM can make the selection of the type and size of the stent being inserted problematic. Sometimes very large stents (20–22 mm diameter) are required for those patients with tracheobronchomegaly. In addition, the expansile force has to be high enough to prevent significant collapse during expiration. Even though they rarely migrate, we use Y-shaped stents infrequently because we try to preserve as much normal mucosa as possible and thus decrease the likelihood of stent obstruction by tenacious mucous secretions, a common complication, especially in patients with chronically inflamed airways. In addition, Y-stent insertion in a patient with complete airway collapse and inflamed and friable airway mucosa is not always straightforward and could be complicated by lack of unfolding, airway perforation and subsequent ventilation, oxygenation, and hemodynamic disturbances.

Technique and Equipment

Airway stents can be placed via flexible (for SEMS) or rigid bronchoscopy (SEMS or silicone). The principles are the same: first, the operator will dilate the lesion (extrinsic compression, stricture, or significant residual obstruction after other endobronchial therapies); second, a stent large enough is deployed inside the airway to prevent migration and properly restore airway patency.

In case of *rigid bronchoscopy*, the scope is introduced through the mouth and then between the vocal cords under direct visualization to assure a secure airway at all times. We usually choose large rigid bronchoscopes (12–13 mm diameter) to allow deployment of a large tracheal/bronchial stents and facilitate easy passage of accessory instruments (large grasping forceps or large suction tubing that may become necessary in severe airway bleeding). The beveled tip of the scope facilitates lifting of the epiglottis and atraumatic passage of the scope through the vocal cords, but also assists for dilation and removal of exophytic endoluminal lesions (i.e., rigid bronchoscopic debulking). Operators should be familiar with the length of their scope and be able to decide how much the stent introducer should be inserted inside the scope in order to avoid deployment of the stent too distally (beyond the stenosis) or too proximally (inside the rigid bronchoscope). There are two techniques of straight silicone stent insertion, as one can expulse the stent either beyond the stricture and then pull it back or to directly deploy it within the stricture itself. There are also two techniques to deploy a Y-stent, and the operator can choose the one he or she is most familiar with: the "push" technique, in which the stent is ejected from the bronchoscope above the carina and then is pushed down with an open rigid grasping forceps placed at stent bifurcation, and the "pullback" technique, in which both bronchial limbs are placed within one bronchus (usually the one involved with most disease) and then the stent is pulled back slowly until the shorter limb pops out. While this has not been studied, the "pullback" technique may be safer in patients with abnormal airway wall (friable, infiltrated mucosa, preexistent fistula) because of potential reduced risk of pushing the stent into the mediastinum. Accessory instruments such as grasping forceps may be needed post deployment to assist with stent unfolding and positioning in the desired location. If the operator works through an open system, he or she may occasionally need to use Vaseline petroleum gauze packing strip or Kerlex gauze roll to pack the nose and the mouth, respectively, in case of significant air leak and subsequent impaired ventilation and oxygenation.

Flexible bronchoscopy is used by many operators to insert SEMS. This procedure can even be performed while the patient is on the ventilator in the intensive care unit. The technique of placing these stents under fluoroscopic guidance is well described [80], but fluoroscopy in the intensive care unit is cumbersome and often unavailable. There are techniques for placing these stents without fluoroscopy, one of which will be described here. First, the bronchoscope is inserted in the mouth through a bite block alongside the endotracheal tube (ETT), after deflating the ETT cuff, and advanced into the space between the tracheal wall and the ETT. The scope is then positioned proximal to the stenosis. A guide wire is inserted through the bronchoscope and passed alongside the lesion, after which the bronchoscope is withdrawn, leaving the guide wire in place. The scope is reinserted into the ETT to confirm guide wire location. A stent delivery catheter is advanced over the guide wire, and the stent is deployed under bronchoscopic visualization. The delivery catheter and guide wire are withdrawn together, leaving the stent in position. If necessary, the stent can be repositioned by grasping its proximal loop with a flexible alligator forceps.

Stent-Related Complications

Complications following stent placement can be divided into procedure-related complication and long-term sequelae of the physical presence of an airway stent. While rarely reported, procedure-related complications can occur during stent

insertion and as a result of their deployment and include perforation of the airway wall resulting in broncho-mediastinal fistula, massive hemorrhage (from large vessel laceration) and potentially mediastinal misplacement of the stent, and hypoventilation and hypoxemic respiratory failure caused by the large stent not unfolding satisfactorily or by occlusion of the stent with mucus or blood immediately following deployment.

A study of the aforementioned AQuIRE registry found that in patients undergoing any type of bronchoscopic intervention (including stenting) for malignant CAO, the overall severe 30-day complication rate was 4%. Overall complication risk was increased by moderate sedation (as opposed to general anesthesia), urgent or emergent procedures, American Society of Anesthesiologists (ASA) score > 3, and redo therapeutic bronchoscopy. The rate of significant bleeding necessitating intervention was 0.5%. The risk for significant bleeding was increased in patients undergoing urgent and emergent procedures, APC use, redo therapeutic bronchoscopy, and patients who were never smokers. The rate of procedurally related death was 0.5%. Risk of death as a result of procedural complication was increased in urgent or emergent procedure and in never-smoking patients. In these patients with malignant CAO, the post-procedure 30-day overall mortality was 15%. Risk of death within 30 days increased with the use of stents, and Y-stents in particular had a significantly higher risk of 30-day mortality compared to straight "tube" stents: it is unclear if this is a result of the stent itself or, more likely, the increased severity and extent of disease which necessitates a stent and more-so a Y-stent. In addition, the risk of 30-day mortality was increased in patients with a Zubrod performance status score > 1, ASA score > 3 or any intrinsic or mixed obstructive disease. Overall the rate of immediate procedurally related complications is rare. Of the modifiable risk factors, the two most pertinent are utilizing general anesthesia instead of moderate sedation, a judicious decision for the use of stenting, and the type of stent employed [81].

The remainder of this section will address long-term adverse events related to the presence of indwelling airway stent. In this regard, stents are indeed foreign objects inside the airway, and adverse events are therefore expected. Several complications have been identified and reported as incidence proportion[6] [9] in case series, but only recently this issue has been systematically approached using clear definitions and statistics using incidence rate[7] rather than proportions to report these adverse events [9]. Because of different biomechanics, significant differences exist between airway stent types in terms of long-term complications related to stent infection, granulation tissue, mucus plugging, stent migration, and stent fracture which could injure the airway wall or the adjacent mediastinal vessels [82]. While perioperative complications are rare and the immediate effects of stent insertion could be gratifying, both bronchoscopists and patients should be aware that long-term complications are common and potentially life threatening [83].

Granulation Tissue

This complication may also promote the development of secondary stenoses [84]. The exact prevalence of stent obstruction by granulation tissue versus tumor overgrowth or ingrowth in patients with malignant obstruction is somewhat confounded by the fact that studies tend to report them together rather than separately but when it occurs may be clinically significant in approximately 25% of patients [85]. The estimated incidence proportion of recurrent obstruction from either granulation tissue or tumor is 9–67% in patients with metal stents and 6–15% in patients with silicone stents [86]. The likely mechanism for granulation tissue formation consists of excessive pressure on the airway wall, which may lead to ischemic necrosis due to capillary closure. From physics standpoint, if the expansion force of a stent would be distributed equally over its com-

[6] An incidence proportion is defined as the number of cases with complications divided by the number of cases overall and is an appropriate measure for analyzing immediate perioperative complications [6].

[7] It measures events per person-time at risk [6].

plete outer surface, this would result in a relatively small contact pressure on the airway wall. However, if the stent wall touches a small portion of the inner tracheal wall (as may be the case with cylindrical stents for stomal, triangular stenoses), then the local pressure at that contact zone would be much higher and would result in considerable impairment of mucosal blood flow promoting further tissue ischemia and damage. This process could be worse if a SEMS is used. Though such a stent may have the same overall expansion force as a silicone stent, it can shut down the mucosal blood flow at spots where the thin wires come in contact with the tissue (Fig. 13.8). Thus the ciliated epithelium is replaced by fibroblasts and granulation tissue. Oversizing the stent has been suspected as a risk factor especially when stents are placed in the upper trachea or subglottis. In one study, Dumon stent insertion for benign tracheobronchial stenoses showed an incidence proportion of 28% for granulation tissue after a mean period of follow-up of 303 days. The stent-to-airway diameter ratio of 90% was found to be the critical cutoff point for predicting granulation tissue formation (OR, 47.5285) [79]. The optimal ratio between the stent and the airway diameter that could reduce granulation tissue formation has yet to be determined. Friction between the sharp edges of the stent and airway mucosa and the formation of galvanic currents may cause granulation tissue formation; this is especially true if electrocautery is used, and these currents are generated[8] around the metal wires [85]. This granulation tissue ingrowth can make removal difficult and result in substantial airway wall trauma [87]. It is likely that factors such as stent kinking or fracture also contribute to granulation tissue formation. Overall, however, granulation tissue formation is not easily predictable but seems to be more common in patients with keloids and in those with chronic airway infection [88]. Management of this problem is complicated by the difficulty of removing metal stents [88, 89]. Interestingly, one study addressing malignant CAO, compared with Ultraflex stents, both silicone stents and Aero stents seem to be more likely to lead to granulation tissue formation [9]. In the multivariate model, however, only silicone stents (HR = 3.32) and lower respiratory tract infection (HR = 5.69) were associated with increased risk for granulation. It is likely that the observed differences in granulation tissue may be related to repetitive motion trauma and infection. Coated stent models such as polyurethane-coated metallic stent may reduce the histobiological reaction to foreign bodies in animal experiments (i.e., granulation tissue formation) and still maintain sufficient expansion force [90]. In vivo human studies are warranted.

[8] An electrical current in which the electron flow is in only one direction; galvanic currents cause fibroblasts proliferation resultant increase in collagen synthesis, property used for wound healing and also implicated in keloid formation.

Stent Fracture

This is a rare complication seen with metal stent insertion, but it may result in airway wall perforation and hemoptysis, potentially fatal events [9, 29, 91]. United States Food and Drug Administration warned that metallic tracheal stents in patients with benign airway disorders should be used only after thoroughly exploring all other treatment options (such as surgical procedures or placement of silicone stents) [29]. The use of these stents as a bridging therapy to surgery is also not recommended, because the removal of these stents is associated with significant complications.

Stent-Associated Lower Respiratory Infection and Mucus Obstruction

When a definition of respiratory infection is based on the presence of clinical findings (fever, increased volume and purulence of sputum, and worsening cough), with or without radiographic evidence of pneumonia but requiring the managing physician to prescribe antibiotics, the incidence proportion of lower respiratory tract infections was 36–39% in patients suffering from cancer [9]. The authors of this study found that

respiratory infections led to significant morbidity and mortality: over half the patients were hospitalized, and 23% of patients with respiratory infections died within 14 days of their infection. Respiratory infections were more frequent in patients with Aero stents compared with silicone or Ultraflex. Various degrees of obstruction by mucus are not uncommon. This tends to be more common in patients with ineffective cough and in smokers. In patients with malignant CAO, having a left-sided stent (HR = 3.07), age (HR = 0.97), having a silicone stent (HR = 2.72) versus Ultraflex stents, and having chemotherapy post-stent placement (HR = 0.32) had significant impact on time to mucus impaction. The higher risk with left-sided stents makes sense; because of the sharper angle[9] between the left main bronchus and trachea, the patient may have difficulty in raising secretions. In addition to obstructing the airway, in time this could also lead to halitosis because the stent becomes covered chronically with a biofilm (Fig. 13.8). Recent in vitro studies evaluated a new methodology to create highly hydrophobic micro-/nanostructured silver antibacterial surfaces against Gram-positive and Gram-negative bacteria, using low-pressure plasma. This micro-/nanostructured silver coating demonstrated antibacterial properties causing a reduction of Gram-positive and Gram-negative bacteria viability on airway stents [92].

Migration

While an oversized stent could cause granulation tissue formation, an undersized stent would likely migrate. In one study, stent migration was 5.26%, 6.06%, and 15.38% in patients in whom the stent-to airway diameter was between 90% and 100%, 80% and 90%, and <80%, respectively [79]. The migrated stent, in addition to not palliating the airway narrowing for which was initially placed, could result in inability to clear secretions, in continuous friction between the wall of the stent and the airway mucosa, and cause granulation as well. Ideally a stent is well compressed once is deployed, but even if it is sized appropriately and placed properly and sitting tightly at the end of the procedure, it can still migrate later because of the visco-elastic properties of the tracheal tissues (Fig. 13.8). This complication is seen more commonly in benign disease or in patients with cancer undergoing therapy, likely because patients with benign disease survive longer and because of the changes in airway viscoelastic properties (in time the airway stenosis progressively dilates). This probably explains why about 20% of patients with strictures may have their stent removed after ~18 months. For patients with ECAC, silicone stent insertion improves functional status immediately post-intervention, but is associated with a high rate of adverse effects with quite frequent stent migration. In fact, in one study of malignant CAO, among various stents (Ultraflex, Aero, and silicone), only silicone tube stents had a significant effect on migration risk with an HR of 3.52 [9]. Stent migration requires a revision procedure to maintain satisfactory airway patency and prevent further complications.

Bronchoscopy is currently the standard for the detection and treatment of stent-related complications and, in nonurgent situations, usually involves a two-step procedure. Initially, diagnostic flexible bronchoscopy is performed to detect and characterize a stent complication; if a treatable complication is detected, rigid bronchoscopy may be required for therapeutic intervention. In this regard, from regulatory perspective, the stent insertion package should probably contain information about stent's biomechanics, sterilization (although this may not affect the infection rate) [9] in addition to reporting indications, expected results, incidence rates of long-term complications, as well as potential contraindications to stent insertion.

Contraindications

There are certain circumstances when stent insertion should not be offered. For instance, in idiopathic or secondary benign subglottic stenosis

[9]Especially in patients with tumors who might have a nearly horizontal left main bronchus due to large subcarinal adenopathy.

(within 2 cm from the vocal cords), stents may extend the length of the stenotic segment [93]. This is particularly true for metallic stents. In one study, all patients with laryngotracheal stenosis who had undergone covered or uncovered metallic stent placement developed new strictures or granulation tissue that precluded definitive surgical treatment or required more extensive resections [93]. In fact, some tracheal surgeons believe that SEMS should never be used in patients who are potential candidates for resection because these are likely to cause additional airway injury

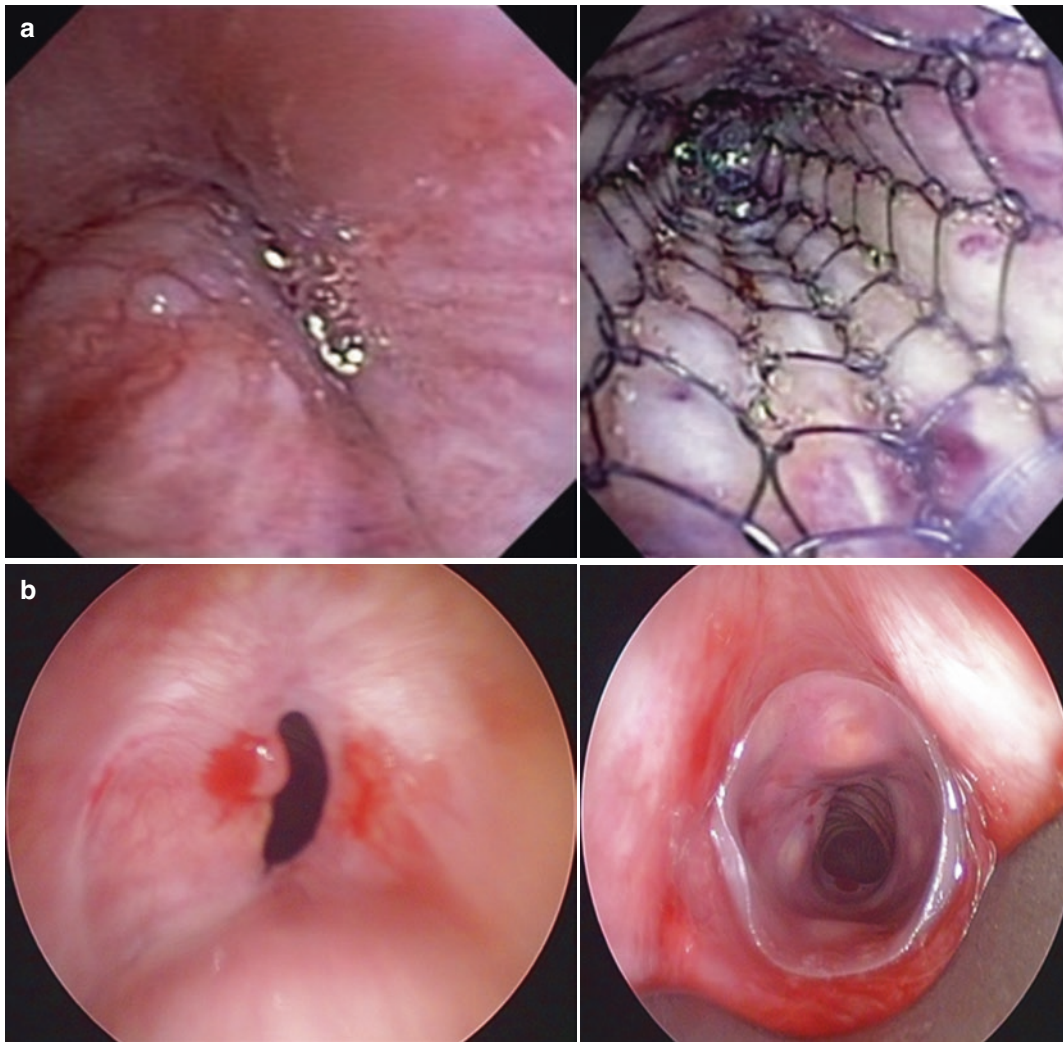

Fig. 13.8 (**a**) Severe, complete left main bronchial obstruction due to extrinsic compression and mucosal infiltration (*left panel*); a partially covered self-expandable metallic stent was inserted which caused at blanching spots where the thin wires come in contact with the tissue, suggesting mucosal ischemia from mucosal blood flow compromise (*right panel*). (**b**) Post-tracheostomy-related tracheal stenosis with chondritis and hypertrophic tissues (*left panel*). Post-dilation; a straight silicone stent was placed which was well compressed after deployment (*right panel*). (**c**) In the same patient, several months later, bronchoscopy showed that the stent migrated downward to the main carina (*left panel*); this resulted in significant obstruction of the left main bronchus and inability to clear secretions (*right panel*). (**d**) Computed tomography performed 3 months prior to bronchoscopy showed complete absence of aeration in the right lower lobe, thus precluding bronchoscopic intervention to restore airway patency (*left panel*); bronchoscopy in this case showed mucosal infiltration and friability and no evidence of airway patency distal to the obstruction (*right panel*)

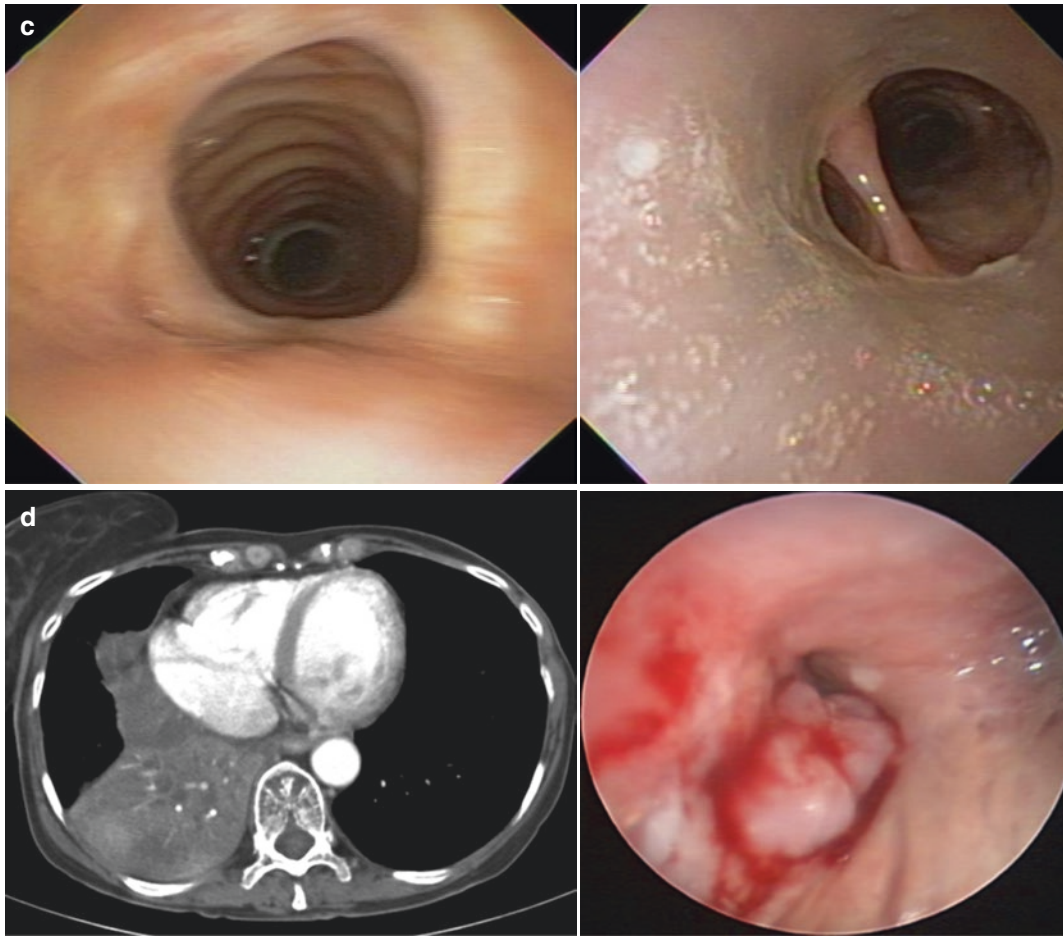

Fig. 13.8 (continued)

and possibly make a potentially resectable patient unresectable[10] [93].

The absence of a functional "distal airway" such is the case with significant and chronic (usually >1 month) distal parenchymal tumor infiltration or confirmed lack of perfusion of underlying lung are also contraindications to stent insertion and, for the same reasons, for any endoluminal therapy aimed at restoring airway patency. In patients with CAO (lobar or mainstem bronchi), assessing the functionality of the lung parenchyma distal to the obstruction is useful when considering interventions meant to establish airway patency. Functionality of the lung distal to the obstruction may not be restored in patients who have had chronic complete obstruction and lack of ventilation (Fig. 13.8). Determining whether there is functional airway and lung beyond an obstruction is essential to any successful bronchoscopic intervention,[11] in part because significant friability of bleeding from thin infiltrated bronchial mucosa, or lack of lung perfusion[12] despite restored

[10] In this regard, histologically benign CAO should be treated surgically or for nonsurgical candidates, with silicone stents whenever possible.

[11] Other conditions include experienced bronchoscopist and team, experienced anesthesiologist, control of patient's overall performance status, additional systemic or local therapy still possible, and control of comorbidities.

[12] One way to assess the perfusion status of lung parenchyma distal to an airway obstruction is to attempt bypassing the stenosis using a high-resolution EBUS radial probe.

airway patency might preclude intervention. In one study, 71% of patients who initiated radiation therapy within 2 weeks after radiological evidence of atelectasis had complete re-expansion of their lungs, compared with only 23% of those irradiated after 2 weeks [94]. Studies pertaining to successful bronchoscopic treatment and time to treatment are lacking. In addition, significant mucosal friability and bleeding of bronchial mucosa might also preclude interventions because stent insertion may result in broncho-mediastinal fistula, loss of the stent within the mediastinum, or hemorrhage (Fig. 13.8).

Follow-Up and Patient Education

Immediately after stent insertion, a chest radiograph is performed to confirm its location. Because stents are associated with significant adverse events, a stent alert card should be given to the patient upon discharge from the hospital; this provides information both for patients and for the doctors that may encounter patients with airway stents. They are informed that even though some stents (i.e., silicone) are not radiopaque, one can still identify them on the chest radiographs as straight lines. In addition, the card includes the patient's name, indication for stent insertion, type, location and size of stent inserted, contact information, and instructions for both patients and physicians in case of stent-related complications. Also, if intubation is necessary for whatever reason, bronchoscopic intubation using a cuffless # 6 ETT to avoid stent dislodgement or mucosal trauma is advisable.

Granulation tissue, secretions, migration, tumor progression, and fistula formation are usually detected during follow-up bronchoscopy or on chest CT. Studies show that the extent of air pockets around the stent on follow-up chest CT correlates with the success of stent removal, indicates regression of stenosis, and may help guide the optimal time for stent removal [95]. Stent-related complications, however, are usually detected by the onset of new respiratory symptoms and do not necessitate systematic (scheduled) routine flexible bronchoscopy. In those patients suspected of having stent-related adverse effects, however, bronchoscopy should be performed for diagnosis and potentially for therapy. While routine follow-up bronchoscopy in the lack of symptoms may not be warranted in all patients after stent insertion, given that most complications occur within 6 weeks post-stent insertion [9, 11, 12], one could choose to perform surveillance bronchoscopy in patients at high risk for complications after stent insertion. There are reports, however, suggesting that time to granulation tissue detection after SEMS insertion is longer in patients with dynamic airway obstruction than in those with structural airway obstruction (396 vs. 95 days $p = 0.02$) [84], so a need for prolonged follow-up in these patients may be warranted. Some physicians perform routine bronchoscopy every couple of months, while others only do it when patients complain of new symptoms [96]. Preventive measures for obstruction by mucus such as aerosol therapy, respiratory physiotherapy, and clinical visits are advocated. Also, while not a universal practice, saline nebulization is offered by many bronchoscopists to keep the stent humidified in order to avoid excessive mucus plugging. In fact, severely disabled patients such as those who are bedridden and with poor cough or impaired metal status are unlikely to benefit from indwelling airway stents since the risk of obstruction by mucus may outweigh the benefit gained by placing the stent and only temporarily restore airway patency.

Summary and Recommendations

Airway stents improve symptoms of selected patients with malignant and benign central airway obstruction, esophagorespiratory, and bronchial stump fistulas, but in general, their insertion should be reserved to patients for whom curative open surgical interventions are not feasible or contraindicated. Metallic stents should be avoided in benign disease unless surgery or silicone stent placement is not possible or feasible. For malignant disease, stents are placed with a palliative intent. They should therefore be placed by operators able to handle intraoperative, short-term, and long-term complications. Long-term

complications after placing such prostheses are not uncommon and can occasionally be fatal. Not all stents are equivalent in terms of biomechanics and stent-tissue interactions. Currently, this information may be considered confidential; proprietary and regulatory bodies do not mandate its reporting. However, manufacturers should probably describe some key biomechanical properties including the resistance to angulation, expansile force, and mechanical failure to help physicians predict successful airway patency restoration and immediate and long-term stent-related complications.

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Part III

Lung Cancer Diagnosis and Treatment

Early Lung Cancer: Methods for Detection

14

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Introduction and Definition of the Procedure

Lung cancer is the leading cause of cancer mortality worldwide [1]. Despite evolving knowledge of lung cancer molecular genetics and improved lung cancer detection technology, the overall lung cancer survival is still quite poor (15–18%, 5-year survival) [1]. The National Lung Cancer Screening Trial showed a dramatic, 20% relative decrease in lung cancer mortality with low-dose CT chest screening in high-risk groups [2], proving the concept that early lung cancer detection, which allows prompt surgical intervention, offers survival benefit. However, screening CT thorax detects smaller peripheral lung lesions but is insensitive for detection of microscopic tumors arising from the central airways [3]. Microscopic tumors arising in the central airways require other techniques for early detection [4].

Squamous cell carcinomas, accounting for approximately 25–30% of all lung cancers, arise in central airways. Pathobiologically, progression from normal bronchial epithelium to squamous metaplasia followed by dysplasia, carcinoma in situ (CIS), and finally invasive carcinoma has been well described [5, 6]. Studies have shown that patients with preinvasive bronchial lesions progress to develop CIS/invasive carcinoma over the median time of 24 months (range: 6–54 months) [7]. Approximately 11% of patients with moderate dysplasia and 19% to as high as 50% with severe dysplasia develop invasive carcinoma [8, 9]. The existence of COPD or heavy smoking history is at high risk of developing lung cancer [7]. Therefore, prompt detection through screening of high-risk patients (heavy smokers especially) could potentially offer early diagnosis of early preinvasive or early invasive lesions and allow for prompt therapeutic intervention and improved survival. However, conventional airway imaging modality, white light bronchoscopy (WLB) has been shown to be relatively insensitive in inspection of bronchial mucosa with only 30% sensitivity to detect early-stage carcinoma in the central airways [10].

New bronchoscopic modalities with higher spatial resolution are able to take advantage of intrinsic properties of healthy and abnormal tissues to change appearance when illuminated with different wavelengths of light and have been developed to serve the purpose of more advanced central airway imaging for the purpose of abnormal airway diagnosis [11]. Currently available in clinical practice modalities include autofluorescence bronchoscopy (AFB), narrow band imaging (NBI), and high magnification

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bronchovideoscope (HMB). More precise airway inspection can be obtained with radial probe endobronchial ultrasound (EBUS) and optical coherence tomography (OCT) [4]. Confocal laser endomicroscopy using flexible probe-based system is another useful technique, allowing in vivo microscopic assessment of the airway basement membrane and alveolar components [12]. Recently, endocytoscopy bronchoscopy system has allowed in vivo microscopic imaging of bronchial mucosa [13]. However, confocal laser endomicroscopy and endocytoscopy system are still under investigational use.

In this chapter, the advanced bronchoscopic imaging techniques of the airway including AFB, NBI, HMB, and the radial probe EBUS will be reviewed, and their roles in the early diagnosis of lung cancer will be shown.

History and Historical Perspective

Autofluorescence Bronchoscopy

AFB combined with white light observation improves sensitivity for detection of preinvasive lesions in the central airways [10]. It is a technique of advanced mucosal airway examination taking advantage of the property of the normal, pre-, and neoplastic tissues to change appearance when illuminated with different wavelengths of light depending on differential epithelial thickness, tissue blood flow, and fluorophore concentration. Preinvasive and neoplastic tissues express diminished red and subsequently green autofluorescence compared with normal tissues when illuminated with blue light (440–480 nm wavelength) [14]. Natural tissue chromophores (elastin, collagen, flavins, nicotinamide adenine dinucleotide, nicotinamide adenine dinucleotide hydrogen [NADH]) emit light when their electrons return to ground level after being excited with light of specific wavelength. The low level of tissue autofluorescence cannot be picked up with WLB given the "noise" from high-degree background reflected and backscattered light. However, AFB selectively picks up the subtle changes in natural tissue autofluoresence patterns. Tissue meta-, dysplasia, and neoplasia reduce natural concentration of airway chromophores (diminished expression of riboflavin, flavin, and NADH due to increased anaerobic metabolism and lactic acid production) [15]. Higher neoplastic tissue blood flow increases light absorption by the hemoglobin. Malignant tissue proliferation, even if only microscopic at first, results in higher degree of light scattering by tissue hyperplasia. These changes overall result in diminished tissue green autofluoroscence with the abnormal tissue assuming a red-brown color [16]. These initially subtle mucosal changes are identifiable by WBL in only less than 30% of cases, even by experienced bronchoscopists. Different AFB imaging systems have been developed all with slightly different sensitivity for detection of the mucosal abnormalities. Continuous improvement of AFB devices allows for increased specificity. In the SAFE-1000 system (Pentax, Asahi Optical, Tokyo, Japan), xenon lamp replaced used in the light-induced fluorescence endoscopy (LIFE) device laser light. AFB is highly sensitive for detection of pre- and neoplastic lesions; however, it lacks specificity for detection of preinvasive lesions. It often cannot differentiate between the areas of high blood flow and metabolism occurring in chronic inflammatory states like bronchitis. To overcome this limitation, video-autofluorescence systems such as SAFE-3000 and AFI have been developed [17] (Fig. 14.1).

Narrow Band Imaging

Narrow band imaging (NBI) is an optical image technology classified as an image enhancement endoscopy using special blue and green light wavelengths allowing for enhanced visualization of microvascular structures in the mucosal and submucosal layers [18–20]. NBI utilizes wavelengths at 415 nm (blue light) and 540 nm (green light). Narrow bandwidths reduce the mucosal light scattering and enable enhanced visualization of endobronchial microvasculature structure. The 415 nm blue light is absorbed by the superficial capillary vessels, whereas the 540 nm wavelength is absorbed by the hemoglobin in the deeper, submucosal vessels. Fine blood vessels appear brown and the deeper vessels cyan.

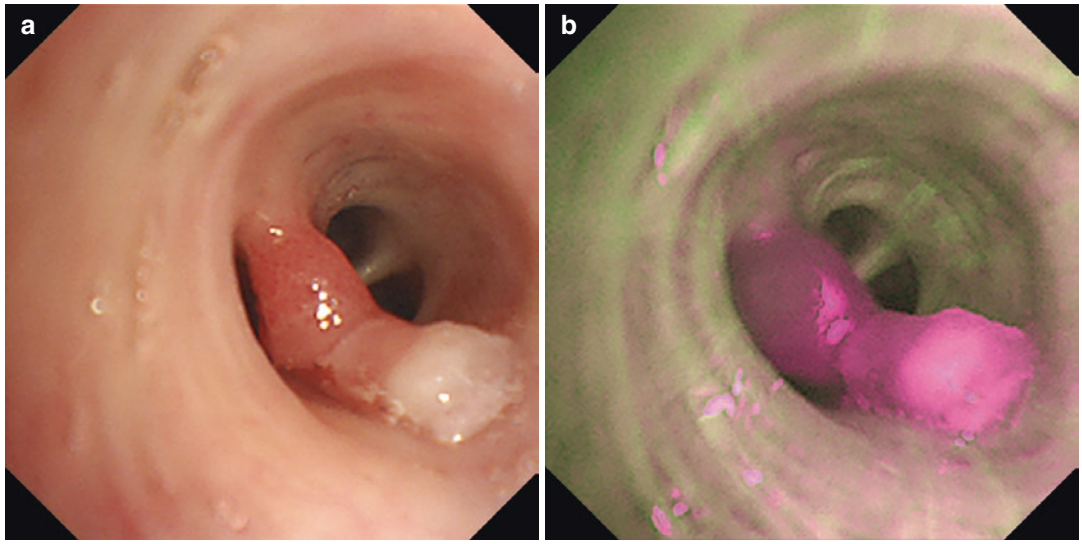

Fig. 14.1 Autofluorescence bronchoscopy (AFB) image using AFI system. Representative case of carcinoma in situ. (**a**) White light bronchoscopy showed thickening of the bifurcation and partially covered with white coat. (**b**) Corresponding AFB image using AFI system (Olympus). The cancerous area was visualized as magenta lesion with clear boarder to normal mucosa

Besides molecular changes allowing autonomous progression of cell cycle that imparts metastatic potential, cancer cells must also develop extended angiogenic capabilities allowing for rapid growth and invasion. Multistep angiogenesis process has been described in epithelial tumors [21, 22]. To fulfill high metabolic demands of rapidly dividing tumor, neoplastic cells have to develop enhanced angiogenic capabilities. Animal and human invasive neoplasia pathogenesis studies suggest that the so-called angiogenic switch is thought to occur in preinvasive lesions prior to invasive tumor formation [23, 24]. Since squamous cell cancer is thought to progress through developmental staged from squamous cell metaplasia to dysplasia and CIS, detection of each of these stages could have a significant impact on therapeutic interventions and prognosis (Fig. 14.2).

High Magnification Bronchovideoscope

High magnification bronchovideoscope (HMB) is a system that was developed to enhance detailed white light observation of bronchial dysplasia. Increased thickening of the bronchial epithelium and increased vessel growth are thought to be related to the appearance of areas of abnormal fluorescence, suggesting roles for neovascularization or increased mucosal microvascular growth in bronchial dysplasia. However, the only abnormality seen on WLB in dysplasia is swelling and redness at the bronchial bifurcations. HMB is a direct viewing WLB system that has an outer diameter of 6 mm and can easily be inserted into the tracheobronchial tree. HMB combines two systems—a video observation system for high magnification observation and a fiber observation system for orientation of the bronchoscope tip. For the video observation system, an objective optical system, in fixed focus mode rather than zoom mode, was used to give an outer diameter of about 6 mm to allow for the bronchoscope and the observation depth of 1–3 mm. Magnification is about fourfold higher than that of the regular bronchovideoscope. The bronchial mucosa is observed minutely on a 14-in. TV monitor at a high magnification of 110 times at the nearest point [25].

HMB has enabled observation of vascular networks within the bronchial mucosa in patients with respiratory disease such as asthma, chronic

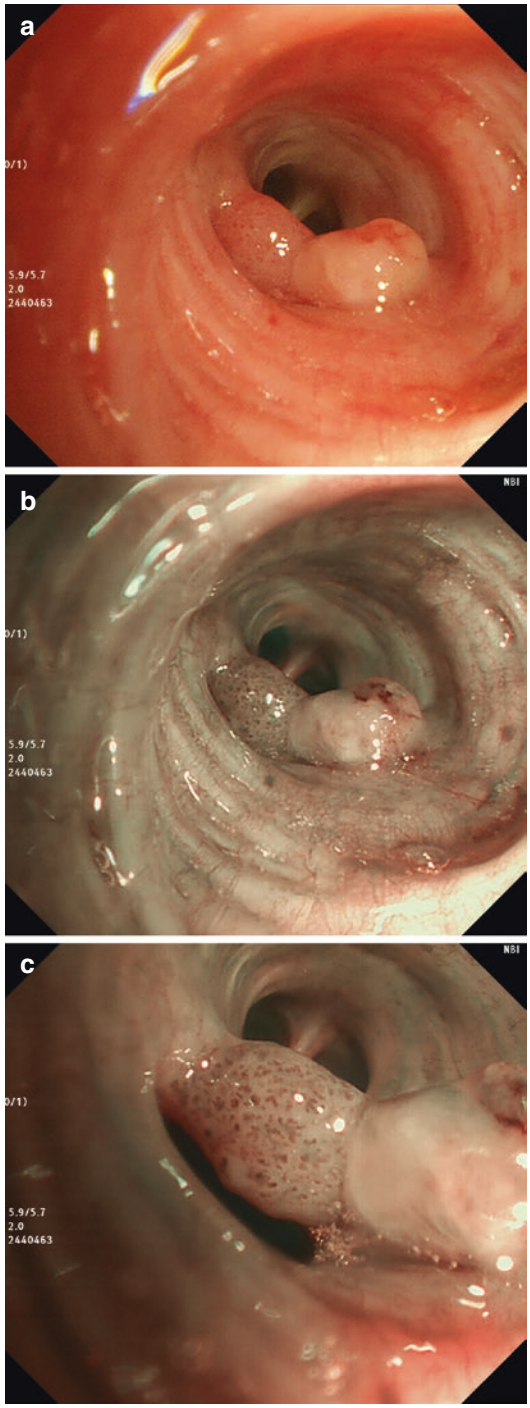

Fig. 14.2 Narrow band imaging (NBI). Representative case of carcinoma in situ (same as Fig. 14.1). (**a**) White light bronchoscopy using high-definition bronchovideoscope. (**b**) Narrow band imaging (NBI) of the same area. (**c**) Close view of NBI identified dotted vessel and spiral-/screw-type vessels which were typically observed for carcinoma in situ

bronchitis, sarcoidosis, and lung cancer. Areas of increased vessel growth and complex networks of tortuous vessels in the bronchial mucosa that are detected using HMB at sites of abnormal fluorescence may allow clinicians to differentiate between bronchitis and dysplasia. In areas of abnormal fluorescence on AFB, HMB can detect dysplasia more accurately than AFB alone with a sensitivity of 70% and specificity of 90% [25]. HMB observation in patients with asthma showed that the vessel area density and vessel length density are significantly increased compared to control subjects [26].

Endobronchial Ultrasound

Two types of endobronchial ultrasound (EBUS) are currently available for clinical use. The radial probe EBUS first described in 1992 is used for the evaluation of bronchial wall structure, visualization of detailed images of the surrounding structures for assisting TBNA as well as detection of peripheral intrapulmonary nodules [27]. On the other hand, the convex-probe EBUS first described in 2004 has a built-in ultrasound probe on a flexible bronchoscope which enables bronchoscopists to perform real-time TBNA of mediastinal and hilar lesions [28].

Premalignant lesions or small intrabronchial radiologically invisible tumors are being detected more frequently as a result of new advanced mucosal imaging technologies. The decision to use endoscopic therapeutic intervention depends on the extent of tumor within the different layers of the bronchial wall. Conventional radiological imaging alone is not capable of distinguishing the tumor extent. The radial probe EBUS is a sensitive method for detection of alterations of the multilayer structure of the bronchial wall even in small tumors [29].

Optical Coherence Tomography

OCT is an optical imaging method that uses properties of light waves instead of sound waves [30]. OCT can generate high-resolution

cross-sectional images of complex, living tissues in real time. Lam and colleagues investigated the ability of OCT to discern the pathology of lung lesions identified by AFB in a group of high-risk smokers and reported that normal or hyperplastic mucosa is characterized by one or two cell layers above a highly scattering basement membrane and upper submucosa [31]. As the epithelium changes from normal/hyperplasia to metaplasia, various grades of dysplasia, and CIS, the thickness of the epithelial layer increases. The basement membrane was still intact in CIS but became discontinuous or no longer visible with invasive cancer. Michel and colleagues examined five patients with endobronchial masses on the chest imaging with OCT [32]. OCT images showed differences between neoplasms and normal bronchial mucosa, and neoplastic lesions displayed irregular, ragged, dark lines between two light areas, which had the appearance of a fracture in the subepithelium.

Indications and Contraindications

By the use of its high sensitivity for detecting lung cancer as well as preinvasive lesions, the third ACCP guideline recommended AFB may be used as an adjunct modality when available in patients with severe dysplasia or CIS in sputum cytology who have chest imaging studies showing no localizing abnormality. In addition, patients with known severe dysplasia or CIS of central airways should be followed with WLB or AFB, when available [33]. AFB has also been shown to increase detection sensitivity of recurrent or new intraepithelial neoplasias and invasive carcinomas when added to WLB (from 25% for WLB alone to 75% when AFB is used in conjunction with WLB) in postoperative surveillance of patients who underwent curative resection for NSCLC [34]. AFB is also suggested for patients with early lung cancer who will undergo resection for delineation of tumor margins and assessment of synchronous lesions [33]. AFB combined with CT of the thorax in patients with radiographically suspicious and occult lung cancer has shown to be an effective lung cancer staging and tumor extension assessment modality with impact on therapeutic strategy choice [35, 36].

Currently the Lung SEARCH clinical trial of surveillance for the early detection of lung cancer in high-risk group is in progress [37]. The study targeted on 1568 high-risk individuals, and the patients who showed abnormal sputum receive annual CT and AFB screening to identify early lung cancer. However, before AFB and NBI can be incorporated into lung cancer screening, few issues need to be addressed. First, natural history of the squamous cell carcinoma (SCC) and bronchial dysplasia must be better characterized. SCC represents a third of all lung cancers diagnosed in the USA [1]. It is thought that pathologically, invasive cancer results from a stepwise process that begins with metaplasia, then dysplasia, followed by CIS, and finally invasive cancer. Previous studies showed development of invasive carcinoma in 40–83% of patients with severely dysplastic lesions [38, 39]. However, animal models and human studies show spontaneous regression of some of the lesions [40, 41]. Breuer et al. documented a 9–32% rate of malignant transformation for all dysplastic lesions in 52 patients followed over an 8-year period. Fifty-four percent spontaneous regression of all preinvasive lesions as well as non-stepwise transformation with development of invasive carcinoma at sites previously characterized as normal in appearance has also been described. These findings suggest that development of SCC may not always follow classic stepwise transformation pattern [41]. Also, population of patients at risk must be clearly identified and those with highest risk lesions (most likely to progress to invasive cancer) should be screened. Finally, appropriate therapeutic options and follow-up surveillance schedule must be developed based on evidence in order to decrease overall cancer mortality and recurrence [42]. Unfortunately, the recent data from the Pan-Canadian Lung Cancer Screening Study showed that the additional AFB only found one typical carcinoid tumor and one CIS lesion that were CT occult cancers. They concluded that additional AFB to LDCT in a high lung cancer risk cohort detected too few CT occult cancers (0.15%) to justify its incorporation into a lung

cancer screening program [43]. Until all these issues have been addressed, the use of AFB and NBI will be predominantly in the research setting.

Description of the Equipment Needed

Autofluorescence Bronchoscopy

Safe-3000 system (Pentax, Asahi Optical, Tokyo, Japan) incorporated single action image switching and simultaneous display. Storz D-light (Storz, Tuttlingen, Germany) and Onco-LIFE systems (Xillix Technologies, Vancouver, Canada) combine autofluorescence and reflected light, all resulting in slightly different sensitivities as compared to WLB for pre- and malignant mucosal abnormalities detection.

Autofluorescence imaging (AFI) (Olympus Medical System Corp, Tokyo, Japan) is a new AFB system. The AFI system transmitted three wavelengths: excitation blue light (395–445 nm, to induce autofluorescence), 550 nm (red reflected light), and 610 nm (blue reflected light) [44]. Improved discriminatory nature of AFI system results from its ability to integrate three signals: autofluorescence signal with reflected green and red light signals [45]. Composite image displayed depicts normal epithelium as light green, areas of abundant blood flow seen not only in malignant epithelium but also in areas of chronic benign inflammation as dark green, and magenta color for malignant tissue due to mixed red/blue reflected signals and lack of the green autofluorescence signal [46] (Fig. 14.1). AFI demonstrated improved over the LIFE AFB system specificity (83% versus 36.6%) but slightly lower sensitivity (80% versus 96.7%) in detection of pre- and malignant bronchial lesions [46].

Confocal Laser Endomicroscopy and Endocytoscopy

The confocal laser endomicroscopy system is a new in vivo microscopic imaging device allowing the endoscopist to obtain real-time in vivo optical biopsies during ongoing endoscopy. The probe-based confocal laser endomicroscopy system (Cellvizio; Mauna Kea Technologies, Paris, France), which is capable of passage through the accessory channel of a standard endoscope, is available. Thiberville and colleagues observed 27 preinvasive lesions (metaplasia and dysplasia) and 2 invasive lesions and reported some specific basement membrane alterations within preinvasive lesions [47]. Methylene blue is a potent fluorophore, and its application to the target makes it possible to reproducibly image the epithelial layer of the main bronchi as well as cellular patterns of peripheral solid lung nodules [48]. Wellikoff et al. compared the images obtained by the probe-based confocal laser endomicroscopy and histological findings of biopsied malignant specimen in the same area [49]. They found an irregular connective tissue architecture with disorganization and fragmentation as well as mottling or "black holes" that represent nests of cells interrupting the fluorescence of the underlying connective tissue was correlated with a malignant diagnosis [49]. However, whether confocal laser endomicroscopy can discriminate among diseases requires additional studies.

The endocytoscopy system (ECS; Olympus Medical System Corp) is another recently introduced, emerging endoscopic imaging technique enabling real-time in vivo diagnosis of cellular patterns at extremely high magnification [50]. The tip of the instrument contains an optical magnifying lens system and CCD. This endoscope can be inserted through the 4.2-mm biopsy channel and Olympus mother bronchoscope to become an "endocytoscope." The ECS has a 570-fold magnification and provides an observation field of 300 × 300 μm, an observation depth of 0–30 μm, and spatial resolution of 4.2 mm for bronchial imaging. Shibuya and colleagues [13] reported that ECS was useful to discriminate between normal bronchial epithelial cells, dysplastic cells, and malignant cells during ongoing bronchoscopy. Another group used ECS in four patients for the immediate in vivo diagnosis of small cell lung cancer during ongoing bronchoscopy. ECS was able to reliably identify numerous small blue cells with hyperchromatic

nuclei, which were confirmed in an in vivo diagnosis of small cell lung cancer by corresponding histopathologic diagnosis [50].

Raman Spectrophotometry

The use of Raman spectrophotometry system in addition to AFB and WLB may offer improved specificity (91%) in detection of preinvasive lesions, with only minor compromise in sensitivity (96%) as documented by a recent pilot study [52]. Laser Raman spectroscopy (LRS), currently used only in experimental setting, involves exposing the tissue to low-power laser light and collecting the scattered light for spectroscopic analyses [53]. This technology collects spectra nondestructively, and light scattered from tissues with different molecular composition can be easily differentiated. Using this technology can potentially reduce the number of false-positive biopsies for detection of preneoplastic lesions. The use of Raman spectra with AFB and WLB can offer a more objective airway mucosal assessment and detect more preneoplastic lesions. Also, Raman may be able to identify biomolecular changes in histologically preneoplastic and non-preneoplastic lesions that could be markers for development into late-stage malignancy. McGregor et al. examined 280 sites including 72 high-grade dysplasia/malignant lesions and 208 normal sites in 80 patients using real-time endoscopy Raman spectroscopy system. They could detect high-grade dysplasia/malignant lesions with a sensitivity of 90% and specificity of 65% [54]. More studies are needed to assess addition of this technology to armamentarium of tools for endobronchial neoplasia detection.

Application of the Technique

Autofluorescence Imaging and Optical Coherent Tomography

As previously described, autofluorescence imaging provides biochemical information about tissue by visualizing fluorescent tissue components such as collagen and elastin, and OCT provides high-resolution detailed information about tissue morphology. By combination of these two modalities, more precise observation of airway structure with emission of autofluorescence could be performed using ex vivo human lung [55]. This novel technology can apply for the peripheral pulmonary lesions, and the more precise observation on tumor tissue structure with vasculature information can be provided [56].

Supplemental Technology for Diagnostic Bronchoscopy

For the improvement of diagnostic rate of cytopathological material obtained by diagnostic bronchoscopy, several approaches have been attempted. By adding multitarget fluorescence in situ hybridization to conventional cytological smear, the sensitivity for detecting malignant cells was improved for bronchial brushing and washing specimens [57]. The immunohistochemistry for six protein expression including TP53, Ki67, MCM6, MCM7, KIAA1522, and KIAA0317 for bronchial brushing specimen improved the detection rate of lung cancer with sensitivity of 81.1% for non-small cell lung cancer and 83.3% for small cell lung cancer [58]. Recently a bronchial genomic classifier for the diagnostic evaluation of lung cancer has been reported [59]. In this study, epithelial cells were collected from the normal-appearing mainstem bronchus in current or former smokers undergoing bronchoscopy for suspected lung cancer. By evaluating 23 gene expressions, the diagnostic yield of bronchoscopy for the detection of lung cancer was improved with high negative predictive value of 91%. These advanced multidirectional analysis technologies will be the powerful support for detecting early lung cancer in combination with diagnostic bronchoscopy (Fig. 14.3).

Evidence-Based Review

Multiple studies demonstrated that AFB improves detection of preinvasive central airway lesions and when combined with WLB also of squamous dysplasia, CIS, and early lung

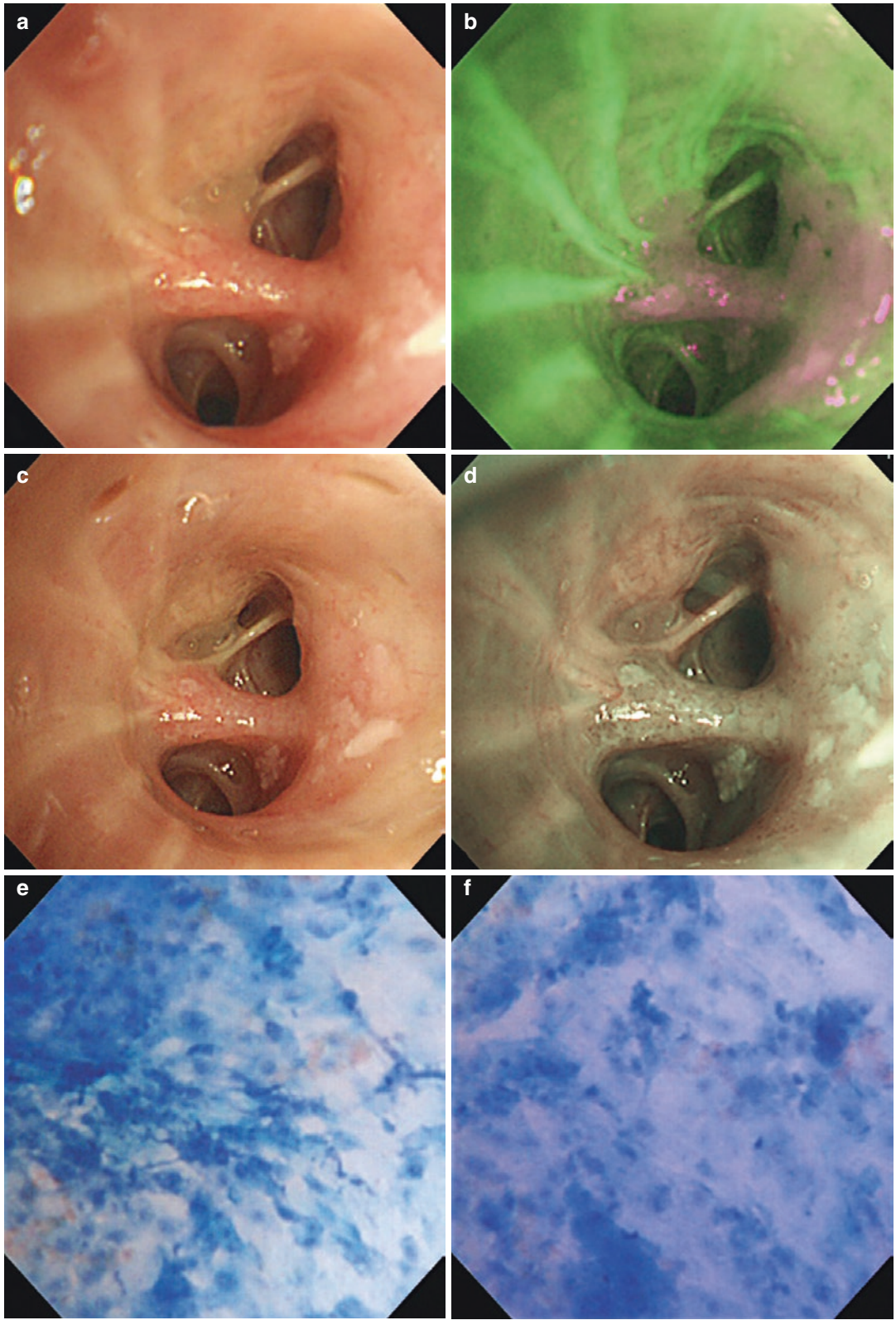

Fig. 14.3 Several bronchoscopic imaging techniques of the airway. Representative case of microinvasive squamous cell carcinoma. (**a**) White light bronchoscopy, (**b**) AFB using AFI system, (**c**) white light bronchoscopy using high-definition bronchovideoscope, (**d**) narrow band imaging, and (**e**, **f**) endocytoscopy images using methylene blue staining of the mucosa

carcinoma. The meta-analysis of 21 studies comparing WLB used with AFB versus WLB alone in diagnosis of intraepithelial neoplasia and invasive lung cancer, involving 3266 patients, reported a pooled relative sensitivity of 2.04 (95% CI 1.72–2.42) on a per-lesion basis in favor of combined AFB and WLB approach [45]. Another meta-analysis showed that the pooled sensitivity of AFI and WLB was 0.89 (95% confidence interval [CI] 0.81–0.94) and 0.67 (95% CI 0.46–0.83), and the pooled specificity of AFI and WLB was 0.64 (95% CI 0.37–0.84) and 0.84 (95% CI 0.74–0.91), respectively [60]. However, the superiority of AFI in comparison with WLB is still controversial; as documented in previous individual studies, the sensitivity for detection of CIS and early invasive carcinomas was not superior to WLB alone (the RR of 1.15 at 95% CI 1.05–1.26) [45]. This suggests that while screening for invasive cancer WLB may be sufficient and more cost effective.

AFB can become a useful tool in endobronchial pre- and malignant lesion detection screening, especially in high-risk groups (patients with head and neck cancers, chronic obstructive pulmonary disease [COPD], and smokers) knowing that the incidence of synchronous lesions ranges from 0.7 to 15% and metachronous lesions might occur in as many as 5% high-risk patients annually [61, 62]. However, more studies are needed to determine how the AFB can best be incorporated into clinical practice in an economically efficient way and with reasonable reduction in lung cancer mortality.

NBI shows higher sensitivity compared to AFB in detection of metaplastic and moderately dysplastic bronchial mucosal squamous lesions. It has equivalent sensitivity as AFB in detection of early preinvasive malignant lesions (CIS) and invasive cancer (ranging between 90 and 100% for NBI and 83 and 89.2% for AFB). However, NBI has a higher than AFB specificity for detection of early lung cancer [63]. The recently published meta-analysis data from eight studies on NBI showed a pooled sensitivity of 0.80 [95% confidence interval (CI), 0.77–0.83] and a pooled specificity of 0.84 (95% CI, 0.81–0.86) [64].

Combining AFB and NBI increases both the sensitivity (93.7%) and specificity (86.9%) of early lung cancer detection. But the improvement is small as compared to each technique alone. Therefore, combining the two technologies in cancerous and precancerous lesion detection does not have significant impact on diagnostic accuracy and may result in unnecessary cost without significant clinical benefit. Judging by the results of the studies, NBI can be used alternatively to AFB in cancerous and precancerous lesion screening of the endobronchial epithelium without compromising sensitivity and with significantly improvement in specificity [65].

Using NBI and HMB, previous studies have shown angiogenesis and microvascular structure alteration of bronchial dysplastic lesions at sites detected as abnormal autofluorescence [66]. Using NBI combined with high magnification bronchovideoscopy, Shibuya et al. showed statistically significant increase in capillary blood vessel diameter occurring as tissue progresses from angiogenic squamous dysplasia (ASD) to CIS, microinvasive cancer, and invasive squamous cell carcinoma [22]. Architectural organization of the vessels also differed between the premalignant and malignant lesions. Classification system was proposed based on vascular appearance of endobronchial lesions of varying invasiveness. It showed high correlation with lesions' histopathologic features [22, 67]. However, more studies using the classification are needed to further validate it.

A comparison between the ultrasound and the histologic findings in 24 lung cancer cases revealed that the depth diagnosis was the same in 23 lesions (95.8%) [29]. In another study in a series of 15 patients, EBUS showed a high diagnostic yield of 93% for predicting tumor invasion into the tracheobronchial wall [68]. EBUS also improves the specificity (from 50 to 90 percent) for predicting malignancy in small AFB-positive lesions that were negative on white light bronchoscopy [69].

Photodynamic therapy (PDT) is an alternative treatment for selected patients with central-type early-stage lung cancer. EBUS was performed to evaluate tumor extent in 18 biopsy-proven early-stage squamous cell carcinomas (including three CIS) [70]. Nine lesions were diagnosed as intracartilaginous by EBUS, and PDT was subsequently performed. The other nine patients had

extracartilaginous tumors unsuspected by computed tomographic scanning and were considered candidates for other therapies such as surgical resection, chemotherapy, and radiotherapy. Using EBUS, 100% complete remission rate was achieved in the endoluminal-treated group.

Summary and Recommendations, Highlight of the Developments During the Last 3 Years (2013 on)

Recent advances in the field of bronchology have allowed bronchoscopists to evaluate the airway with advanced high-resolution imaging modalities discussed in this chapter. Centrally arising squamous cell carcinoma of the airway, especially in heavy smokers, is thought to develop through multiple stages from squamous metaplasia to dysplasia, followed by carcinoma in situ, progressing to invasive cancer. Early detection is key for improved survival. It would be ideal if we can detect and treat preinvasive bronchial lesions defined as dysplasia and carcinoma in situ before progressing to invasive cancer. Bronchoscopic imaging techniques capable of detecting preinvasive lesions currently available in clinical practice including AFB, NBI, HMB, and EBUS were discussed in this chapter.

AFB increases the diagnostic accuracy for squamous dysplasia, carcinoma in situ, and early lung carcinoma when used simultaneously with conventional white light bronchoscopy. However, the specificity of AFB for detecting preinvasive lesions is moderate. AFB displays areas of epithelial thickness and hypervascularity as abnormal fluorescence which suggests a role for neovascularization or increased mucosal microvascular growth in bronchial dysplasia. HMB enables visualization of these vascular networks. HMB can detect increased vessel growth and complex networks of tortuous vessels of various sizes in the bronchial mucosa. To further evaluate the vascular network in the bronchial mucosa, a new imaging technology NBI was developed and is now commercially available.

AFB and NBI are complimentary for the evaluation of preinvasive bronchial lesions. The strength of AFB is its high sensitivity acting as a monitor to pick up potentially neoplastic lesions. However, the potential limitation is its moderate specificity. NBI on the other hand enhances the mucosal and vascular patterns which is best suited for detailed inspection of the mucosa. A combination of autofluorescence and NBI into a single bronchovideoscope system would decrease the time for the procedure as well as unnecessary biopsies. For a bronchoscopist, AFB, NBI, and HMB are just the same as performing a routine WLB without any complicated procedures necessary. Interpretation of the results seems to be fairly straight forward. The radial probe EBUS is an excellent tool for the evaluation of the airway structure which is useful for the determination of the depth of tumor invasion. Minimally invasive treatment may be suitable for selected patients with central-type early-stage lung cancer.

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Diagnostic of Lung Cancer: Confocal Bronchoscopy

15

Luc Thiberville and Mathieu Salaun

Introduction

The principle of confocal microscopy, first described in 1957, relies on both the use of a narrow point illumination light source, which focuses on a single spot in the sample, and of a small aperture or pinhole on the detection path, which focuses the light emitted back by the sample onto the detector. This results in the rejection of out-of-focus information from the material above and below a very thin plane of focus. The illumination and detection systems being conjugated on the same focal plane are termed "confocal." As only one point in the sample is illuminated at a time, confocal microscopes make use of systems that scan the sample in both lateral dimensions to produce a two-dimensional image—or "slice"—of a few microns depth, parallel to the sample surface. This principle allows confocal microscopes to provide "optical" sectioning of cells and tissue with micrometric lateral and axial resolutions, without tissue destruction. Confocal microscopes have recently been so successfully miniaturized [1, 2], which they can be integrated into endoscopic systems and used for both animal [3–5] and human in vivo explorations [6–8]. This is achieved by using a small optical device held in direct contact with the area to be imaged. Such systems have recently been applied to the in vivo microscopic imaging of both the proximal [7] and distal respiratory systems [8]. With these recent developments, fiber-optic endoscopy of the respiratory tract has now entered the era of in vivo microscopic imaging.

In general, the aim of confocal endomicroscopes is to produce "optical biopsies," i.e., in vivo microscopic imaging, of a living tissue during endoscopy [9, 10]. Ideally, this direct microscopic imaging could replace tissue sampling or at least allow a very precise targeting of the biopsy area. However, because of optical limitations due to refraction indexes and specular reflexion of the light at the surface of the tissue, *reflectance* (or "white light") confocal endomicroscopes are not currently available. Instead, manufacturers have designed fluorescence confocal devices, where the excitation light can easily be filtered out before the light reaches the detector, to only image the fluorescence emitted from the tissue. Obviously, the main limitations of these systems come from the fact that they exclusively record the signal coming from fluorescent structures in response to appropriate excitation wavelengths. Therefore,

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besides the unusual "en face view," recorded images may appear for the clinical quite different from its classical histopathology counterparts or require specific cellular fluorophores. On the other hand, in future applications, fluorescence confocal systems may take advantage of molecular-targeted imaging using smart fluorescent probes.

Confocal Endomicroscopes for Human Exploration

The first confocal endomicroscopic systems for human exploration were available in 2005. Two systems have been commercialized, which can be distinguished by the technical approach used to conduct the light to the tissue.

The distal scanning principle is used in the Optisan®/Pentax endomicroscopic system. This system is also called a confocal laser endomicroscope—CLE. In distal scanning, the light is conducted by a single fiber back and forth from the distal tip of the system, and the scanning function is accomplished by a very small scanhead (4.5 cm long × 3.5 mm diameter) which is included in the distal end of the endoscope. Tissue fluorescence is induced by a 488 nm laser wavelength. The sensitivity of the system needs the use of IV fluorescein as an external fluorophore. The system has an impressive lateral resolution below 1 μm and produces optical slices of 7 μm for a field of view of 475 × 475 μm. The system offers the possibility to adjust the *Z*-depth range from 0 to 250 μm below the contact surface, so that three-dimensional structures in the specimen and successive layers of the mucosae can be imaged. However, because of the added sizes of the distal scanhead, working channel, conventional light guide, and CCD camera, the diameter of the distal tip of the endoscope is larger than 12 mm, a size barely compatible with the exploration of the human trachea and large main bronchi, which explains why only a confocal GI endoscope had been launched over the past years. Another limitation is due to the miniaturization of the distal scanhead, which results in scanning rates of one frame/s, which needs a very efficient stabilization system of the distal tip of the endoscope onto the mucosae, in order to produce crisp microscopic images of the epithelium. In spite of these limitations, Optiscan® endomicroscopic images from the gastrointestinal tract appear very close to conventional histology.

This prototype system is able to provide "en face" imaging of the bronchial epithelium with a lateral resolution of less than one micrometer.

Recently endomicroscopic images of the proximal bronchial tree of both normal and tumoral epithelium have been obtained by Musani et al. from five patients, using a miniaturized prototype of the Optiscan system [11]. The confocal device was composed of a 6.2 mm flexible bronchoscope, devoid of working channel and distal optics, in which the distal end has been replaced by a 4.4 cm scanning device. This prototype was introduced within a 12.5 mm rigid bronchoscope in parallel to the rigid optics. IV fluorescein infusion was administered before the procedure. Because of the rigidity of the prototype distal tip, the confocal exploration was limited to the primary and secondary carina of the main bronchus and to an endobronchial mass in one patient. En face images of the respiratory produced by the system were impressive, with a lateral resolution of less than 1 μm, which allowed clear imaging of the intercellular margins between the normal epithelial cells, as well as imaging of the basement membrane/subepithelial areas due to folds of the epithelium (Fig. 15.1). Motion artifacts are observed in 60% of the frames, which allowed interpretation of the images in all patients.

The second commercially available confocal endomicroscopy system (Cellvizio®, Mauna Kea Technologies, Paris, France) uses the principle of *proximal scanning* in which the illumination light scans the proximal part of a coherent fiber bundle or miniprobe. This bundle conducts the light back and forth from the imaged area at the tip of the miniprobe [4]. The light delivery, scanning, spectral filtering, and imaging systems are located at the proximal part of the device, the distal part being a separate miniprobe, including both the fiber bundle and its connector to the laser scanning unit (Fig. 15.2).

This fiber bundle-based system, also described as "fibered confocal fluorescent microscopy

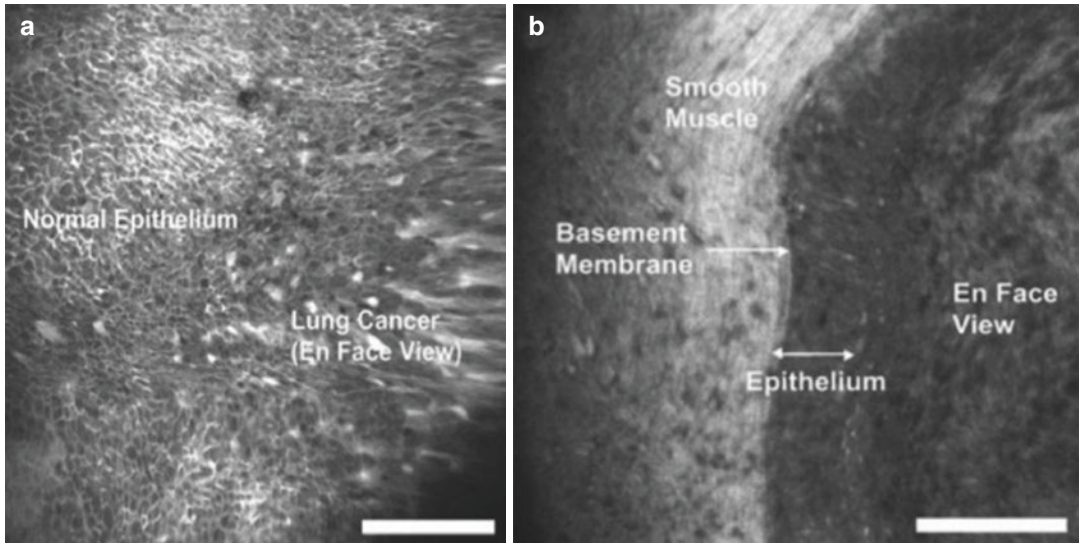

Fig. 15.1 Fluorescein/488 nm in vivo CLE imaging of the proximal bronchus, Pentax prototype. Modified from Musani et al. *J Bronchol Intervent Pulmonol*, 2010

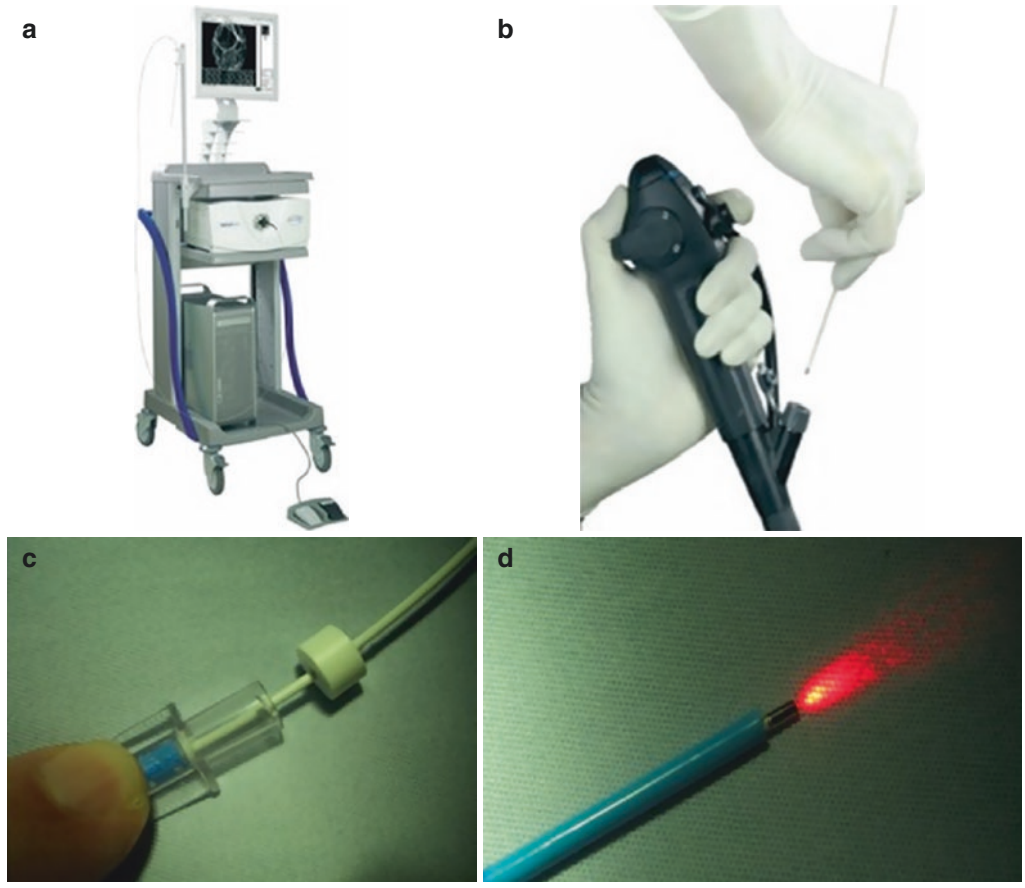

Fig. 15.2 pCLE/Cellvizio system and AlveoFlex® miniprobe. (**a**) Cellvizio® and laser scanning unit. (**b**) AlveoFlex® entering the bronchoscope working channel. (**c**) AlveoFlex® inside the EBUS extended working channel. (**d**) AlveoFlex® inside the superDimension extended working channel

(FCFM)" or more recently "probe-based confocal laser endomicroscopy" or "pCLE," uses very thin and flexible miniprobes (300 μm to 2 mm in diameter) that can contain up to 30,000 compacted microfibers. Similar to bench confocal microscopes, pCLE uses two rapidly moving mirrors to scan the microfibers across the coherent fiber bundle in a raster fashion. Each microfiber, which is scanned one at a time by the laser light, acts as a light delivery and collection system and is, in essence, its own pinhole. The main advantages of this design are the very small size and the flexibility of the probe that can reach the more distal part of the lungs [8], as well as the fast image collection speed that helps to avoid artifacts due to tissue movement. The system produces endomicroscopic imaging in real time at 9–12 frames/s.

Specific miniprobes for bronchial and alveolar imaging (AlveoFlex®) have a diameter of 1 mm or less that can enter the working channel of any adult bronchoscope. These probes are designed for only twenty uses, at an approximate cost of 5000 Euros/miniprobe. AlveoFlex® miniprobes are devoid of distal optics and have a depth of focus of 0–50 μm, a lateral resolution of 3 μm for a field of view of 600 × 600 μm. Thinner and more flexible probes are available for other applications as for the bile duct exploration (CholangioFlex®) or even probes that can fit into a 19-gauge needle (AQ-Flex®) for endoscopic ultrasound (EUS) lymph node/cyst explorations. Those probes may prove useful in the future for specific intrathoracic applications.

Two pCLE devices using different excitation wavelengths are currently available. The Cellvizio 488 nm is used for autofluorescence imaging of the respiratory tract as well as for fluorescein-induced imaging of the GI tract [7, 8, 12]. Another device at 660 nm excitation can be used for epithelial cell imaging after topical application of exogenous fluorophores such as methylene blue [13–15]. Whereas these two systems are currently sold as separate devices, a dual-band system is currently available for small animal imaging, which avoids to disconnect the miniprobe from the LSU in case a dual imaging (488 nm/660 nm with methylene blue) would be indicated.

pCLE Imaging of the Proximal Bronchi

pCLE can easily be performed during a fiber-optic bronchoscopy under local anesthesia [7, 8]. The technique of in vivo bronchial pCLE imaging is simple: the miniprobe is introduced into the 2 mm working channel of the bronchoscope and the probe tip applied onto the bronchial mucosae under sight control. The depth of focus being 50 μm below the contact surface, the system can image the first layers of the bronchial subepithelial connective tissue, presumably the lamina densa and the lamina reticularis [7].

At 488 nm excitation, pCLE produces very precise microscopic fluorescent images of the bronchial basement membrane zone (Fig. 15.3). pCLE bronchial microimaging reveals a mat of large fibers mainly oriented along the longitudinal axis of the airways with cross-linked smaller fibers, as well as larger openings—100 to 200 μm—corresponding to the bronchial glands origins. In vivo, the technique also makes it possible to record high-resolution images of small airways such as terminal bronchioles, which are recognizable by the presence of the helicoidal imprint of the smooth muscle on the inner part of the bronchiole. [7]

Fluorescence properties of the bronchial mucosae at 488 nm excitation are determined by the concentration of various cellular and extracellular fluorophores, including the intracellular flavins, which could originate from the epithelial cells, and specific cross-links of collagens and elastin present in the subepithelial areas [2, 16, 17]. Microspectrometer experiments coupled with pCLE imaging have clearly demonstrated that the main fluorescence signal emitted after 488 nm excitation from both bronchial and alveolar human system originates from the elastin component of the tissue [7, 8, 18]. Indeed, flavin cellular autofluorescence appears too weak to allow imaging of the epithelial layer using 488 nm pCLE without exogenous fluorophore [19]. Similarly, the collagen fluorescence does not significantly affect the pCLE image produced at 488 nm, the fluorescence yield of collagen at

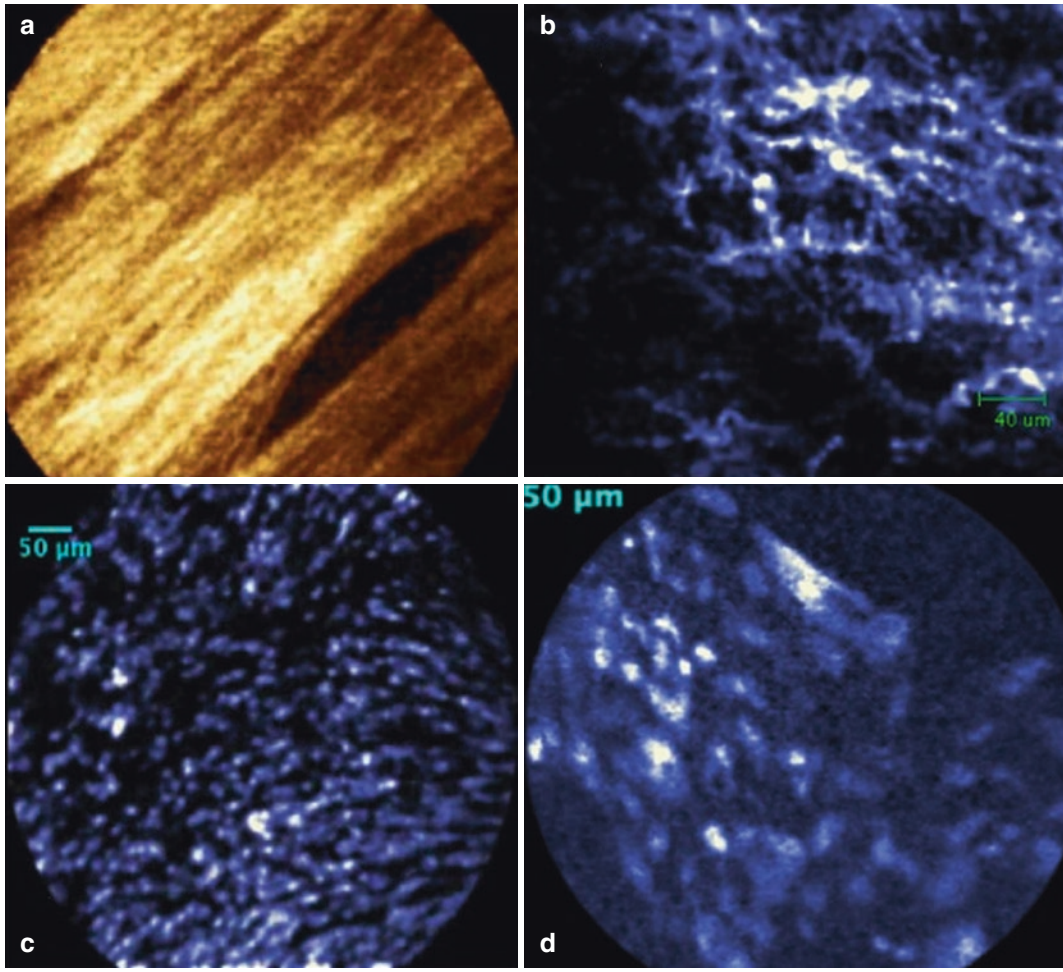

Fig. 15.3 Bronchial confocal microendoscopy imaging. (**a**) Normal elastic fibered network of the basement membrane zone. (**b**) Disorganized basement membrane zone elastic network at the vicinity of a bronchial CIS. (**c**) Regular normal bronchial epithelium 660 nm excitation FCFM after topical application of methylene blue (0.1%). (**d**) CIS imaging, FCFM at 660 nm, and topical methylene blue. Modified from Musani et al. *J Bronchol Intervent Pulmonol,* 2010 [11], with permission of the author

this wavelength being at least one order of magnitude smaller than that of elastin.

As a result, 488 nm excitation pCLE specifically images the elastin respiratory network that is contained in the basement membrane of the proximal airways and participates to the axial backbone of the peripheral interstitial respiratory system. In the future, it is possible that a modified pCLE device using several wavelengths [20] or devices based on a multiphoton approach [21–23] may enable imaging of collagen, elastin, and flavins simultaneously.

Distal Lung pCLE Imaging In Vivo: From the Distal Bronchioles Down to the Lung Acini

In the acinus, elastin is present in the axial backbone of the alveolar ducts and alveolar entrances, as well as in the external sheath of the extra-alveolar microvessels [24, 25]. pCLE acinar imaging is easily obtained by pushing forward the probe a few centimeters after the endoscope is distally blocked into a subsegmental bronchi. When progressing toward the more distal parts of

the lungs, the entry into the alveolar space is obtained by penetration through the bronchiolar wall. Alveolar fluorescence imaging in active smokers dramatically differs from imaging in nonsmokers. The alveolar areas of smokers are usually filled with highly fluorescent cells corresponding to alveolar fluorescent macrophages, the presence of which appears very specific of active smoking [8]. In situ alveolar microspectrometric measurements have been performed in active smokers, which evidenced that the main fluorophore contributing to the pCLE alveolar signal corresponds to the tobacco tar by itself, explaining this difference [8, 18].

Potential Clinical Applications for Lung Cancer Detection in the Proximal Tree Using pCLE

Preliminary studies have shown that per endoscopic pCLE could be used to study specific basement membrane remodeling alterations in benign or malignant/premalignant bronchial alterations [7, 26]. In the first human study using pCLE in the respiratory tract in vivo, the structure of the bronchial wall was analyzed in twenty-nine patients at high risk for lung cancer that also underwent an autofluorescence bronchoscopy [7]. In this study, the fibered network of the basement membrane zone underlying premalignant epithelia was found significantly altered. This was observed in one invasive cancer, three CIS, two mild and one moderate dysplastic, and three metaplastic lesions. In these precancerous conditions, the elastic fibered pattern of the lamina reticularis was found absent or disorganized (Fig. 15.4). This supported the hypothesis of an early degradation of the basement membrane components in preinvasive bronchial lesions. However, while this observation shed some light on the origin of the autofluorescence defect in precancerous bronchial lesions, the absence of epithelial cell visualization did not allow the technique to differentiate between the different grades of progression of the precancerous bronchial lesions such as metaplasia/dysplasia/carcinoma in situ.

In order to be successfully applied to the exploration of precancerous/cancerous bronchial epithelial layer, the pCLE technique would need to be coupled with the use of an exogenous nontoxic fluorophore. Ex vivo studies have shown that the resolution of the system is not a limitation for nuclear or cellular imaging [7, 8].

A few exogenous fluorophores could be activated at 488 nm.

Acriflavine hydrochloride is an acridine-derived dye containing both proflavine and euflavine, which binds to DNA by intercalating between base pairs. Acriflavine produces a strong nuclear fluorescence with 488 nm pCLE when topically applied on the top of the bronchial epithelium ex vivo [7]. Acriflavine has been used in a couple of in vivo studies using CLE in the GI tract [27], without demonstrated side effect. However, comet assay of cells exposed in vitro to acriflavine solution shows significant DNA damage after 2 nm illumination with 488 nm Cellvizio (personal data). This observation needs further studies before acriflavine use for bronchial explorations, especially in patients at risk for cancer. Acriflavine is not currently approved for bronchial use.

Fluorescein has been used in Musani study with some success [11]. However, fluorescein, which does not enter the cells and therefore does not stain the nuclei [28], does not provide cellular imaging using pCLE. This is probably linked to the lower lateral resolution of pCLE compared to CLE and the impossibility to distinguish intercellular space with pCLE. Recently, Lane et al. have used a confocal microendoscope prototype at 488 nm excitation and topical physiological pH cresyl violet to provide cellular contrast in the bronchial epithelium both in vitro and in vivo [29].

Methylene blue is a nontoxic agent which is commonly used during bronchoscopy for the diagnostic of bronchopleural fistulae. MB is also used in gastroenterology for chromoendoscopic detection of precancerous lesions [30–32], as well as for in vivo microscopic examination of the GI tract and bronchus using a novel endocytoscopic system [33, 34]. MB is a potent fluorophore which enters the nuclei and reversibly

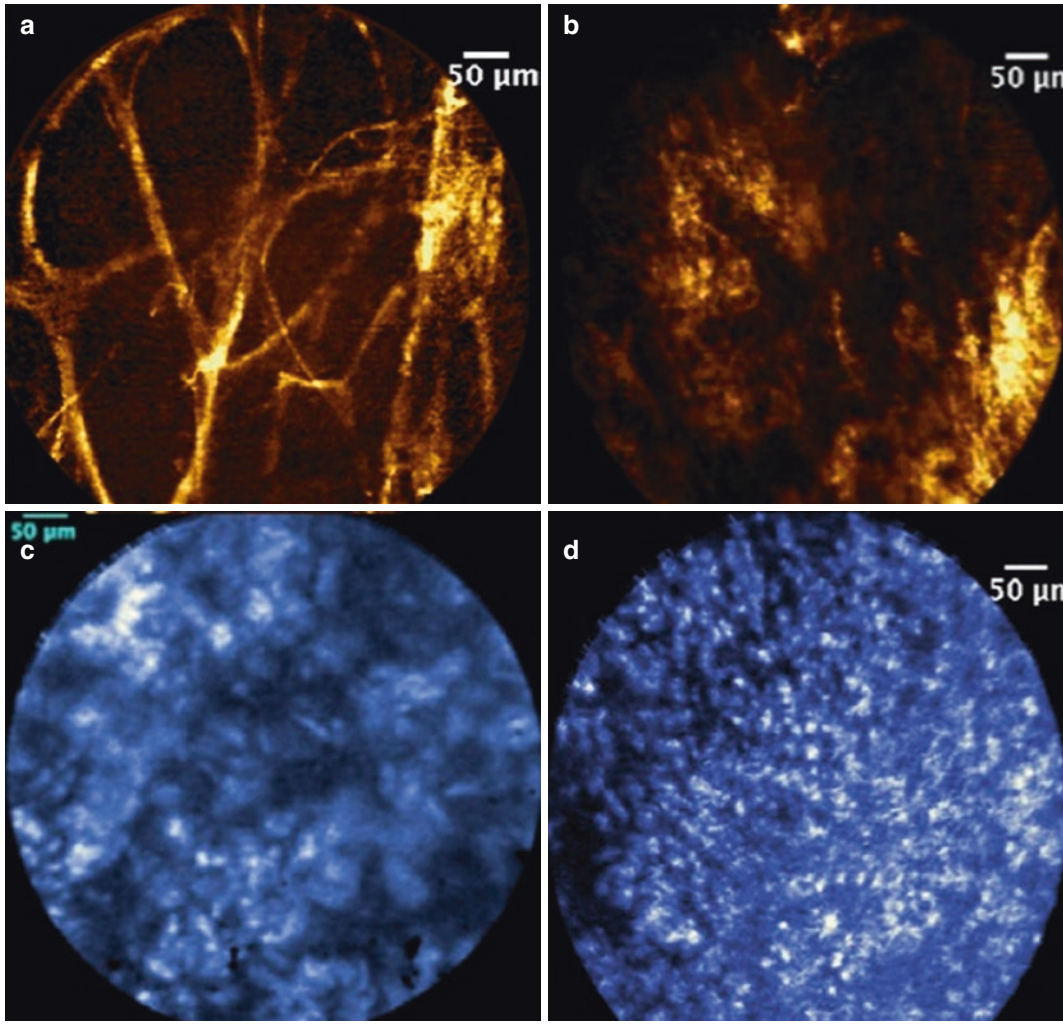

Fig. 15.4 pCLE imaging of normal distal lung and peripheral lung nodule. (**a**) pCLE imaging of normal distal lung. (**b**) Interstitial fiber network disorganization in a peripheral lung adenocarcinoma (488 nm excitation wavelength). (**c**) pCLE cellular imaging of a peripheral lung adenocarcinoma (660 nm excitation and topical methylene blue). (**d**) pCLE cellular imaging of a peripheral small cell lung cancer (660 nm excitation and topical methylene blue)

binds to the DNA, before being reabsorbed by the lymphatics. In order to give a fluorescent signal, MB needs to be excited around 660 nm and is therefore accessible to FCFM intravital imaging using this excitation wavelength. In our hands, no DNA damage could be observed using comet assay from lymphocytes exposed to methylene blue in vitro and 660 nm Cellvizio for 2 min.

Human preliminary study has demonstrated that Cellvizio 660/topical methylene blue makes it possible to reproducibly image the normal and tumoral epithelial layer of the main bronchi [15, 35]. Unpublished data from our center also show that the technique easily differentiates small cell lung cancer from non-small cell lung cancer in vivo and normal epithelium from CIS (Fig. 15.3). Future studies using this technique have to show whether the technique allows to differentiate normal, premalignant, and malignant alterations at the microscopic level. If this strategy is successful, FCFM may become a very powerful technique for in vivo diagnostic of early malignant

and premalignant conditions of the bronchial tree, allowing the analysis of both the epithelial and subepithelial layers during the same procedure.

pCLE for the Exploration of Peripheral Lung Nodules

Potential applications for in vivo distal lung imaging using pCLE appear wide. Some limitations of the technique could be predicted from its basic principles, such as artifacts linked to fragile parenchymal lung structures compression, as well as difficulties of interpretation of an imaging technique mainly based on elastin network assessment. However, preliminary results are encouraging in specific diffuse or focal lung diseases, such as in pulmonary alveolar proteinosis [36], diffuse emphysema [37], or peripheral lung nodules.

Coupled to electromagnetic navigation or radial EBUS, pCLE has the potential to image microstructural and cellular patterns of peripheral solid lung nodules in vivo at both 448 and 660 nm [14, 15] (Fig. 15.4). After navigation of bronchoscopy to the peripheral nodule has been achieved and the peripheral nodule located, the AlveoFlex® miniprobe can enter the extended working channel of both radial EBUS and superDimension system, except for the posterior and apical segments of the upper lobe due to the relative rigidity of the miniprobe. In such case, a smaller probe such as the CholangioFlex® should be used.

Confocal imaging of the peripheral nodule can be performed at either 488 nm (autofluorescence) or 660 nm after distal deposition of a few microliter of methylene blue for cellular imaging.

Recently, Arenberg et al. made use of pCLE at 488 nm to explore peripheral lung nodule in 39 patients from two centers [38]. Three investigators with different pCLE experiences met to develop descriptive criteria through a consensus review of five teaching and five training cases. Twenty-nine randomized pCLE sequences of lung nodules were secondly blindly reviewed and scored. The more reliable criteria for lung cancer diagnostic were the "solid" or "compact" pattern (Fig. 15.4). Interobserver agreement for this item was moderate (0.54). Using this single item, the sensitivities of detection of cancer are 70%, 70%, and 80% for the three observers, with specificities of 58%, 58%, and 74%, respectively. Future studies will assess the technique as an aid to localize the peripheral nodule and to differentiate benign from cancerous lesion.

Besides autofluorescence solid pattern at 488 nm, we have shown that topical methylene blue/660 nm pCLE makes it possible to image the cellular organization of peripheral lung nodules [14] and to differentiate small cell lung cancers from the other histological type (Fig. 15.4). Again, more studies are needed to determine if the technique has a place in the clinical assessment of peripheral nodules.

Conclusion

Confocal fluorescence endomicroscopy is an emerging fascinating technique that allows optical microimaging of both the proximal and distal bronchial tree. Potential applications for lung cancer diagnosis include the exploration of both basement membrane alteration and epithelial layer of the proximal airways, as well as peripheral nodule assessment. Until now, pCLE only used endogenous autofluorescence or simple fluorescent contrast agents. In the future, the use of fluorescent molecular compounds will make it possible to extend applications of the technique. Pilot studies exploring this strategy have recently been published, which provided specific confocal imaging of molecular probes in precancerous conditions of the oral cavity ex vivo [39] and of colonic dysplasia in vivo [40] and even invasive fungal diseases [41]. Coupled to FCFM, molecular imaging may help in the future to enable early diagnosis, rapid typing of molecular markers, and assessment of therapeutic outcome in many lung diseases.

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Optical Coherence Tomography: A Review

16

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Introduction

Globally, lung cancer is the most common cause of cancer deaths with over 1.6 million deaths per year [1]. Adenocarcinoma is the predominant cell type among women. In men, aside from a few European countries, such as France, Spain, and the Netherlands, adenocarcinoma has surpassed squamous cell carcinoma as the predominant cell type [2]. The shift in lung cancer cell types from the more centrally located squamous cell and small cell carcinomas to the more peripherally located adenocarcinomas, as well as smaller lesions detected by thoracic CT, necessitates a change in the approach to bronchoscopic diagnosis of peripheral lung lesions that are generally beyond the range of a standard flexible bronchoscope ≥3 cm in outer diameter. Radial probe endobronchial ultrasound with or without an electromagnetic navigation or virtual bronchoscopy navigation system improves the diagnostic yield from an average of 34% to 69% [3–7]. This is lower than CT-guided transthoracic lung biopsy with a diagnostic yield ≥80% even for lesions ≤2 cm [8, 9]. In the context of a CT lung cancer screening program, only 20–34% of the screening CT-detected lung cancers are diagnosed by bronchoscopy (Table 16.1) [10, 11] and unpublished data). Although endoscopic biopsy has a lower complication rate in pneumothorax and bleeding than CT-guided transthoracic lung biopsy [8, 9, 12, 13], improvement in the accuracy of endoscopic biopsy for small peripheral lung lesions is needed if bronchoscopy is going to play a major role in lung cancer diagnosis. For centrally located bronchial cancers that are not visible by CT, it is often difficult to differentiate between in situ carcinoma and invasive carcinoma. The ability to diagnose the depth of tumor invasion can guide therapy. In this chapter, the role of optical coherence tomography (OCT), Doppler OCT, polarization-sensitive OCT (PS-OCT), and autofluorescence OCT in the diagnosis of lung cancer and the potential application in nonmalignant lung diseases are discussed.

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History and Historical Perspective

Optical coherence tomography (OCT) was originally developed for noninvasive cross-sectional imaging of biological systems [14, 15]. This optical imaging method offers near histologic resolution for visualizing cellular and extracellular structures at and below the tissue surface up to

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Table 16.1 Mode of diagnosis and accuracy for screening CT-detected lung cancers

Modality	NLST		PanCan	
	Diagnostic method (%)	Positive rate (%)	Diagnostic method (%)	Positive rate (%)
Bronchoscopy	34	55.5	20	55.6
CT-FNA/core	19	66.5	38	81.1
Surgery	47	73.9	42	77.6

CT computed tomography, *FNA* fine needle transthoracic lung biopsy, *NLST* National Lung Screening Trial, *PanCan* Pan-Canadian Early Detection of Lung Cancer Study

2–3 mm. The utility of this imaging modality was first demonstrated in ophthalmology and cardiology [16, 17]. It was later developed as an optical imaging and biopsy tool in other organs such as the esophagus and lung [18–21].

OCT is similar to B-mode ultrasound. Instead of sound waves, light waves are used for imaging. Optical interferometry is used to detect the light that is scattered or reflected by the tissue to generate a one-dimensional tissue profile along the light direction. By scanning the light beam over the tissue, two-dimensional images or three-dimensional volumetric images can be recorded. For bronchoscopic application, the imaging procedure is performed using fiber-optic probes that can be miniaturized to enable imaging of airways down to the terminal bronchiole. These probes can be inserted down the instrument channel during standard bronchoscopic examination under conscious sedation. The axial and lateral resolutions of OCT range from approximately 5 to 30 μm, and the imaging depth is 2–3 mm depending on the imaging conditions. This combination of resolution and imaging depth is ideal for examining changes originating in epithelial tissues such as airways. Unlike ultrasound, light does not require a liquid coupling medium and thus is more compatible with airway imaging. There are no associated risks from the weak near-infrared light sources that are used for OCT.

In time domain OCT, a depth-resolved line profile of tissue is obtained by measuring the autocorrelation function [14, 22] using a low-coherence time light source and an interferometer comprised of a variable-length reflective reference arm and a sample arm where the tissue is illuminated. A signal is generated when the path length of light scattered from a particular tissue depth matches that from the reference arm. In frequency domain OCT, the spectral density function is measured to obtain a depth-resolved optical scattering of the tissue through Fourier transformation. The spectral density function can be measured with interferometers using either a broadband light source and a spectrometer or a wavelength-swept light source and a square-law detector. This approach was shown to provide orders of magnitude enhancement in detection sensitivity compared to time domain OCT [23–27].

In Doppler OCT, the energy of photons from a moving system is transformed according to the four-vector momentum and the Lorentz transformation. According to the special theory of relativity, the energy of photons emitted from an object moving relative to an observer is transformed the same way leading to different energies compared to those seen by an observer that is stationary relative to the photon source. These different energies that correlate with different frequencies are called Doppler effect that can be used to detect moving sources by measuring a change in the frequency of the optical field emitted from the source. The OCT signal contains the information about the phase of the optical field scattered from a tissue sample. Therefore, moving objects can be detected by evaluating frequency shifts in their OCT signals [28, 29]. This technique can be used to visualize pulmonary vasculature in vivo during endoscopic imaging [30]. Doppler signals are created by analyzing the OCT data stream using the Kasai velocity estimator to evaluate the Doppler phase shift between A-scans in each frame. Endoscopic Doppler OCT can be difficult due to the motion artifacts such as from cardiac pulsations and

breathing movement. Bulk tissue motion correction algorithms are used to reduce artifacts.

Polarization-sensitive OCT (PS-OCT) is another extension to OCT to improve detailed tissue differentiation. By analyzing the polarization state of backscattered light, PS-OCT can provide information about tissue birefringence, diattenuation, optical axis orientation, and depolarization. Using PS-OCT, highly organized, anisotropic tissue layers such as muscles, bones, and blood vessel walls can be identified by their innate birefringence. Clinical applications of PS-OCT have been demonstrated in the determination of burn depth in vivo [31], the measurement of collagen and smooth muscle cell content in atherosclerotic plaques [32], the differentiation of benign lesions from malignant lesions in the larynx [33], and the detection of nerve fiber bundle loss in glaucoma [34, 35]. Obtaining polarization-dependent optical properties of tissue with PS-OCT entails two essential requirements. Firstly, the incident light on the tissue needs to have known polarization states (commonly circular polarization) [36, 37] or multiple sequential polarization states (not necessarily known) with defined polarization relation between them [38, 39]. Secondly, the polarization state of light scattered from tissue needs to be detected using a polarization diversity detection scheme. Polarization-sensitive detection can also be used to reduce the effects of polarization in structural OCT imaging that uses rotary probes. As the spinning fiber-optic probe is continuously flexing and in motion, the polarization state of the light exiting the tip of the probe is constantly varying, creating artificial intensity variations during OCT imaging. These variations can be significantly reduced using polarization diversity detection [40].

A recent advance in OCT imaging is co-registered autofluorescence OCT (AF-OCT) [41]. Autofluorescence imaging makes use of fluorescence and absorption properties to provide information about the biochemical composition and metabolic state of endogenous fluorophores in tissues [42, 43]. Most endogenous fluorophores are associated with the tissue matrix or are involved in cellular metabolism. The most important fluorophores are structural proteins such as collagen and elastin and those involved in cellular metabolism such as nicotinamide adenine dinucleotide (NADH) and flavins [43]. Upon illumination by violet or blue light (380–460 nm), normal tissues fluoresce strongly in the green (480–520 nm). Malignant tissues have a markedly reduced and redshifted autofluorescence signal due to the breakdown of extracellular matrix components as well as increased absorption by blood. These differences have been exploited to detect preinvasive and invasive bronchial cancers in central airways [44]. AF-OCT overcomes the limitation of autofluorescence bronchoscopy because the OCT imaging probes are much smaller than flexible video bronchoscopes allowing access to small peripheral airways beyond bronchoscopic view. AF-OCT allows rapid scanning of airway vasculature less prone to motion artifacts compared to Doppler OCT [45].

Endoscopic AF-OCT System

Figure 16.1 illustrates the components of an AF-OCT prototype system is shown in Fig. 1, and an AF-OCT prototype is shown in Fig. 16.1. A Mach-Zehnder interferometer driven by a wavelength-swept source comprises the OCT subsystem (Fig. 16.2a). The AF subsystem uses a 445 nm excitation laser and a photomultiplier tube for the detection of autofluorescence emission. Endoscopic imaging of airways is implemented using fiber-optic catheters that scan in a rotational manner using proximal motors. A large-scale motor actuates the rotor of a fiber-optic rotary joint (FORJ) that is connected to an imaging catheter, enabling proximally driven rotational scans of the catheter's fiber assembly. The imaging catheter consists of a double-clad fiber (DCF) catheter. This fiber assembly is fixed inside a torque cable that transfers rotational and pullback motions from the proximal end to the distal end (Fig. 16.2b). The rotating assembly is placed inside a close-ended 900 μm diameter stationary plastic tube if the catheter is going to be reused.

In one configuration (Fig. 16.2b), the AF excitation light is coupled to the DCF inner

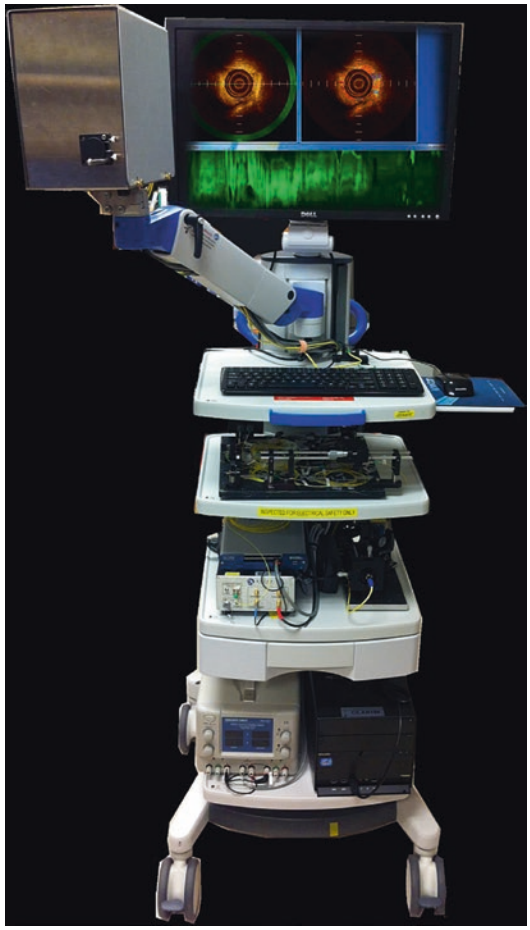

Fig. 16.1 Illustrates the components of an AF-OCT prototype system

cladding [41], and in another system configuration (Fig. 16.2c), the AF excitation light is coupled to the DCF core using fused fiber components [46–48] and a custom-designed FORJ [49]. The latter allows a tightly focused AF excitation light that exits the catheter, enabling higher-resolution AF imaging.

Preclinical Studies

Ex vivo studies have shown that OCT can visualize structural features in airways, adjacent alveoli, and pulmonary nodules that correspond closely to the histopathology (Fig. 16.3) [20, 50–54]. The basement membrane can be clearly seen between the epithelial and submucosal layer. Cartilage usually appears as darker signal-poor regions due to its low scattering properties. OCT measurements of mean luminal diameter, inner luminal area, airway wall area, and percent airway wall thickness prior to surgical resection were found to correlate significantly with the histology down to the ninth-generation bronchi in the resected specimens [55].

Clinical Studies

Endoscopic OCT imaging is performed during flexible bronchoscopy under local anesthesia applied to the upper airways and conscious sedation [21, 56]. The OCT probe can be inserted inside a guide sheath similar to radial endobronchial ultrasound through the working channel of the bronchoscope into the targeted airways. When clinically indicated, following removal of the catheter, histological and/or cytological samples are collected. OCT imaging adds about 5–10 min to the standard procedure time. It is usually well tolerated by patients. Repeat OCT measurements of airways were found to be reproducible and hence can be used for longitudinal assessment of changes in airway morphology [57].

Lung Cancer

The ability of OCT to discern invasive cancer versus CIS or dysplasia was investigated [21]. Normal or hyperplasia is characterized by one or two cell layers above a highly scattering basement membrane and upper submucosa. As the epithelium changes from normal/hyperplasia to metaplasia, various grades of dysplasia, and CIS, the thickness of the epithelial layer increases; quantitative measurement of the epithelial thickness showed that invasive carcinoma is significantly thicker than carcinoma in situ ($p = 0.004$) and dysplasia is significantly thicker than metaplasia or hyperplasia ($p = 0.002$). The nuclei become more readily visible in high-grade dysplasia or CIS. The basement membrane is still intact in CIS but became discontinuous or

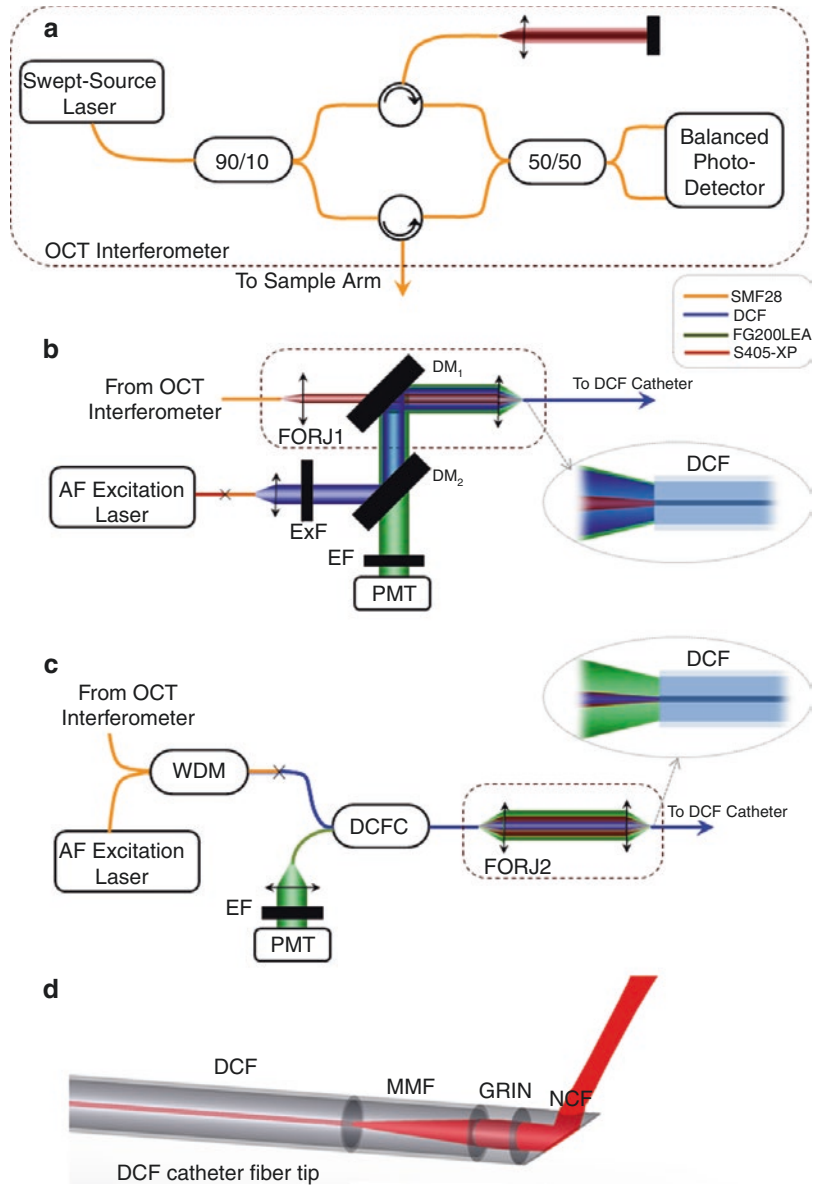

Fig. 16.2 Schematic diagram of OCT and AF-OCT. (**a**) OCT, (**b**) inner cladding AFI excitation, (**c**) core AFI excitation subsystems, and (**d**) optical elements at the tip of the DCF catheter. *DM* dichroic mirror, *ExF* excitation filter, *EF* emission filter, *PMT* photomultiplier, *WDM* wavelength division multiplexer, *DCFC* double-clad fiber coupler, *FORJ* fiber-optic rotary joint, *DCF* double-clad fiber, *MMF* (step-index) multimode fiber, *GRIN* graded index fiber, *NCF* no-core fiber

no longer visible with invasive cancer [21]. Squamous cell carcinoma has different OCT features than adenocarcinoma [52, 53] (Fig. 16.4).

The morphology of the peripheral lung nodules has been characterized. Lung parenchyma can be identified by the presence of signal-void alveolar spaces that appear as a honeycomb-like structure. Pulmonary nodule is identified by replacement of alveoli with solid tissue [45, 58, 59]. Adenocarcinomas with lepidic growth pattern are recognized by their thickened alveolar walls [45] (Fig. 16.4). After OCT interpretation training sessions, clinicians can diagnose common primary lung cancers (adenocarcinoma, squamous cell carcinoma, and poorly differentiated carcinoma) with an average accuracy of 82.6% (range 73.7–94.7%) [60]. Although OCT cannot replace histology in the diagnosis of lung carcinoma, it has the potential to aid in diagnosing lung carcinomas as a complement to tissue biopsy, particularly when insufficient tissue is available for pathology assessment. OCT may be

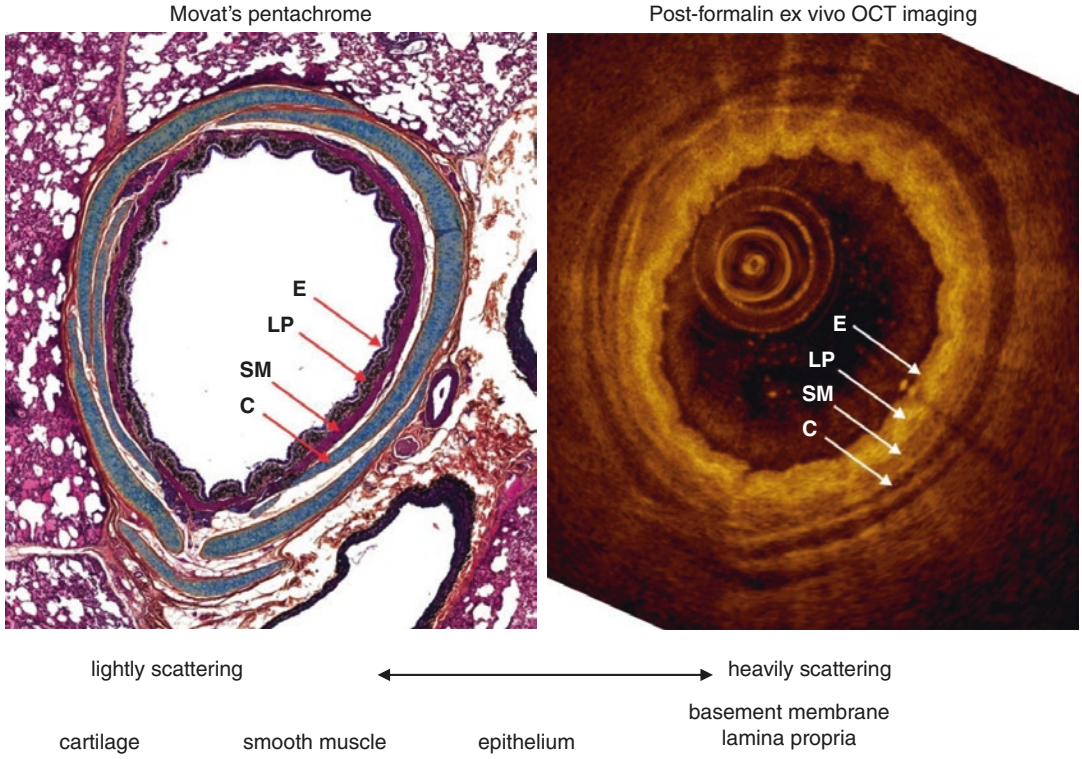

Fig. 16.3 Correlation of OCT image with histopathology in porcine airway. *Black* = nuclei, elastic fibers; *yellow* = collagen, reticular fibers; *blue* = ground substance, mucin; *bright red* = fibrin; *red* = muscle

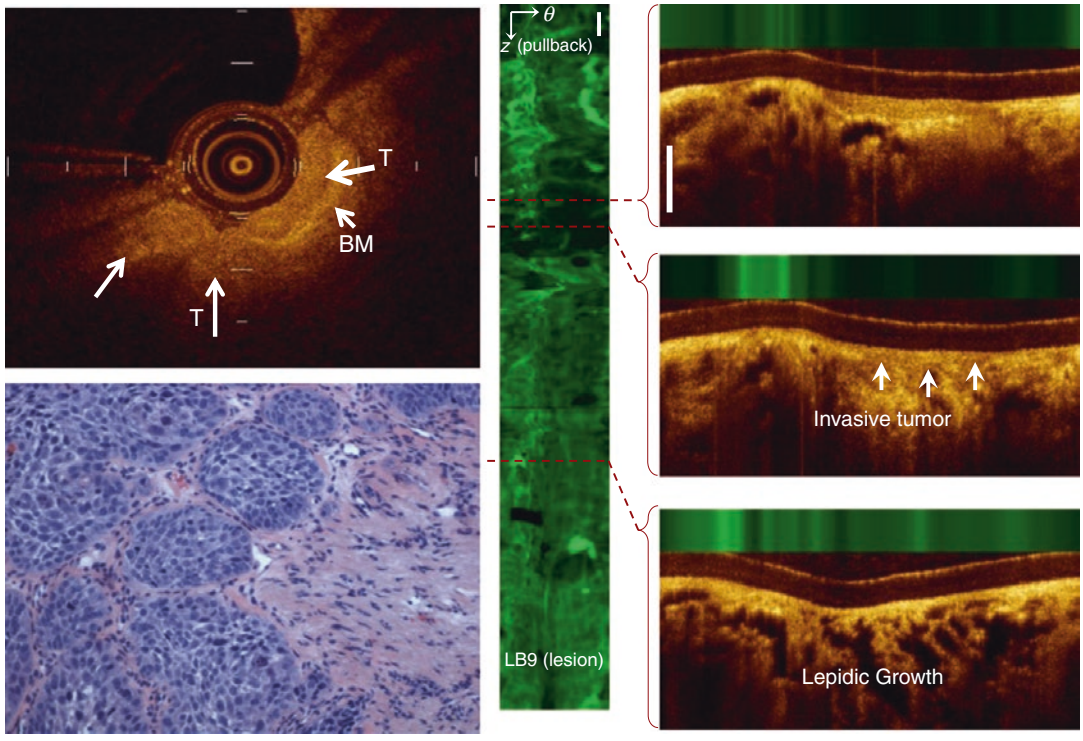

Fig. 16.4 (**a**) OCT and histological image of a squamous cell carcinoma showing the in situ component and invasion through the basement membrane (*arrows*). (**b**) AF-OCT of an adenocarcinoma with lepidic growth. In the AF image, there is a loss of green autofluorescence

useful for confirming the nature of the lesion before taking a biopsy. Since OCT probes can be miniaturized, they can be inserted inside biopsy needles/catheters to guide biopsy under real time without removing the imaging probe from a guide sheath and reinserting the biopsy forceps or needle with the possibility of displacement or migration to a different airway [56].

Asthma

It is known that asthma phenotypes are heterogeneous and influence the response to treatment. Bronchial thermoplasty (BT) is a non-pharmacologic method to treat patients with chronic persistent asthma [61]. Currently, there is no method to select patients who will benefit from BT. OCT imaging was performed in two patients with chronic persistent steroid-dependent asthma prior to and immediately after bronchial thermoplasty as well as at 3 weeks, 6 weeks, 6 months, and 2 years after bronchial thermoplasty. Prior to BT, distinct asthma phenotypes were observed between the patient (patient A) who had sustained benefit from BT for over 2 years and the one who did not (patient B) (Fig. 16.5) [62]. PS-OCT [36, 63, 64] that can define highly organized tissue layers such as smooth muscle and collagen may be a useful non-biopsy tool to study the effect of pharmacologic and non-pharmacologic therapies.

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease characterized by both small airway and parenchymal abnormalities. There is increasing evidence to suggest that these two morphologic phenotypes, although related, may have different clinical presentations, prognosis, and therapeutic responses to medications. A recent ex vivo study using micro-CT showed that narrowing and disappearance of small conducting airways occur prior to the onset of emphysematous destruction and that these changes can explain the increased peripheral airways resistance reported in COPD [65]. Clinical CT using an acceptable dose of radiation provides airway images up to the fifth generation. Unfortunately, the resolution of CT is not adequate to image critical events that begin at the seventh branching generation nor can it measure morphological changes in different layers of the airway wall. OCT can overcome this limitation with small optical probes that can image airways

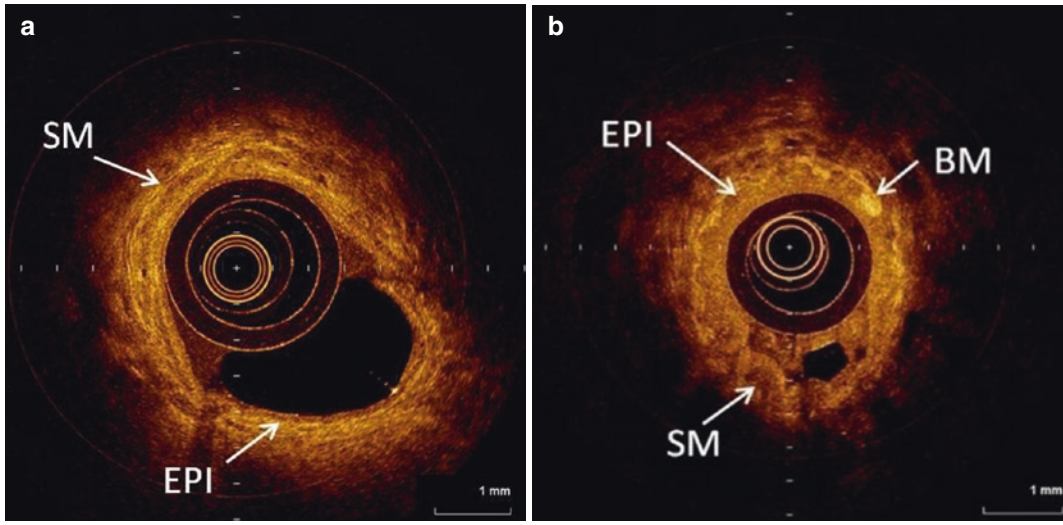

Fig. 16.5 OCT images of two patients before bronchial thermoplasty (BT) illustrating different phenotypic features. (**a**) Long-term responder following BT; (**b**) nonresponder with BT. *EPI* epithelium, *BM* basement membrane, *SM* smooth muscle

as small as terminal bronchioles with high resolution [55, 65, 66]. Coxson et al. compared OCT measurements with CT scans and lung function in COPD patients [67]. In 44 current and former smokers, OCT imaging was used to measure the airway dimensions in specific bronchial segments. These data were compared with CT measurements of the exact same airway using a three-dimensional reconstruction of the airway tree (Pulmonary Workstation 2.0; VIDA Diagnostics, Inc., Iowa City, IA). A strong correlation between CT and OCT measurements of lumen and wall area was observed. The correlation between FEV_1%-predicted and CT- and OCT-measured wall area (as percentage of the total area) of fifth-generation airways was good for both imaging modalities, but the slope of the relationship was much steeper using OCT than using CT, indicating greater sensitivity of OCT in detecting changes in wall measurements that relate to FEV_1. They concluded that OCT is more sensitive for discriminating the changes in the more distal airways of subjects with a range of expiratory airflow obstruction compared with CT. In addition to airway wall remodeling, alveolar wall destruction in COPD can also be clearly visualized using OCT with the emphysematous alveoli appearing as large voids compared with the small alveoli seen in those with normal lung function [53] (Fig. 16.6).

Sex differences in airway remodeling in COPD have also been investigated using OCT to help understand why women have a 50% increased risk of COPD compared with men after adjustment for the amount of smoking. Female human smokers have significantly thicker airway walls compared to male human smokers similar to the changes in a mouse model of COPD [68].

Airway and Lumen Calibration

Airway diameter measurement via bronchoscopy is not reliable due to optical distortion of the bronchoscope lens that varies among bronchoscopes and limited ability to gauge depth. Respiratory motions interfere with airway measurement. Airway measurement can be performed using CT scans. However, real-time examination is not always available, and radiation exposure is a concern. Using phantoms, excised pig airways, and in vivo human airways during bronchoscopy, Williamson et al. demonstrated that airway measurements using anatomic OCT are accurate and reliable and compare favorably with CT imaging [69]. OCT was used to measure airway diameter in patients with subglottic tracheal stenosis, main bronchial stenosis, and tracheomalacia. The real-time OCT information was found to be helpful for determining the length of the stenosis, extent of tumor involvement beyond the bronchoscopic view, and severity of the tracheomalacia or guide the choice of airway stent. The investigators conclude anatomic OCT with conventional bronchoscopy

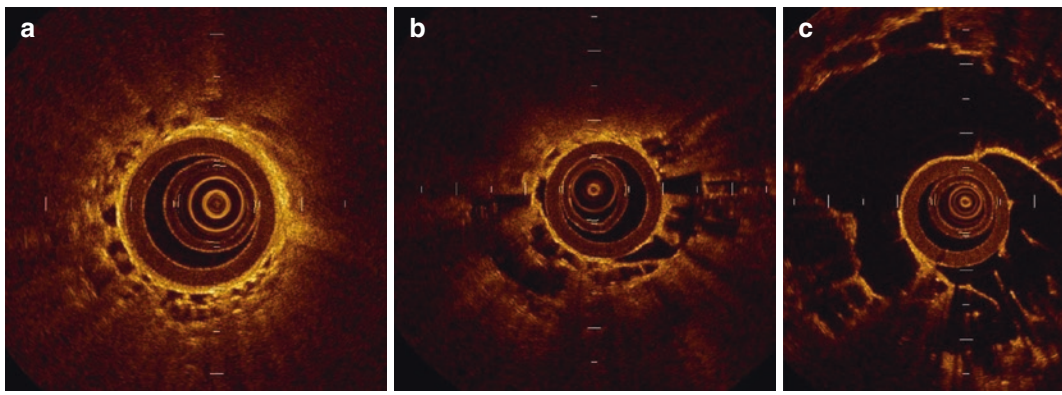

Fig. 16.6 OCT image of terminal bronchiole and adjacent alveoli. (**a**) Normal bronchiole; (**b**) patient with moderate emphysema; (**c**) patient with severe dysplasia showing progressive destruction of alveolar walls

allows accurate real-time airway measurements and may assist bronchoscopic assessment [70].

Obstructive Sleep Apnea

Changing of the upper airway sizes during sleep is the key pathophysiologic change in patient with obstructive sleep apnea (OSA). Reduction in pharyngeal size correlates with increased sleep disorder breathing and degree of nocturnal desaturation [71]. CT scan has been used to measure the upper airway size. However, measuring upper airway dimension during sleep and awake with CT is not practical plus concern with radiation exposure. Anatomic OCT offers a real-time quantitative measurement of the upper airway shape and size during sleep or awake comparable to CT scan [72]. Individuals with OSA were found to have a smaller velopharyngeal cross-sectional area than BMI-, gender-, and age-matched control volunteers, but comparable shape suggesting it is an abnormality in size rather than shape that is the more important anatomical predictor of OSA [73].

Future Applications

The ability to image the bronchial vasculature down to 12 μm diameter in 5–7 cm airway segments during bronchoscopy along with structural information using AF-OCT (Fig. 16.7) enables comparison of vasculature in normal and abnormal airways. The ability to visualize detailed vascular networks could provide opportunities to study angiogenesis to differentiate benign from malignant lung nodules, characterize biological

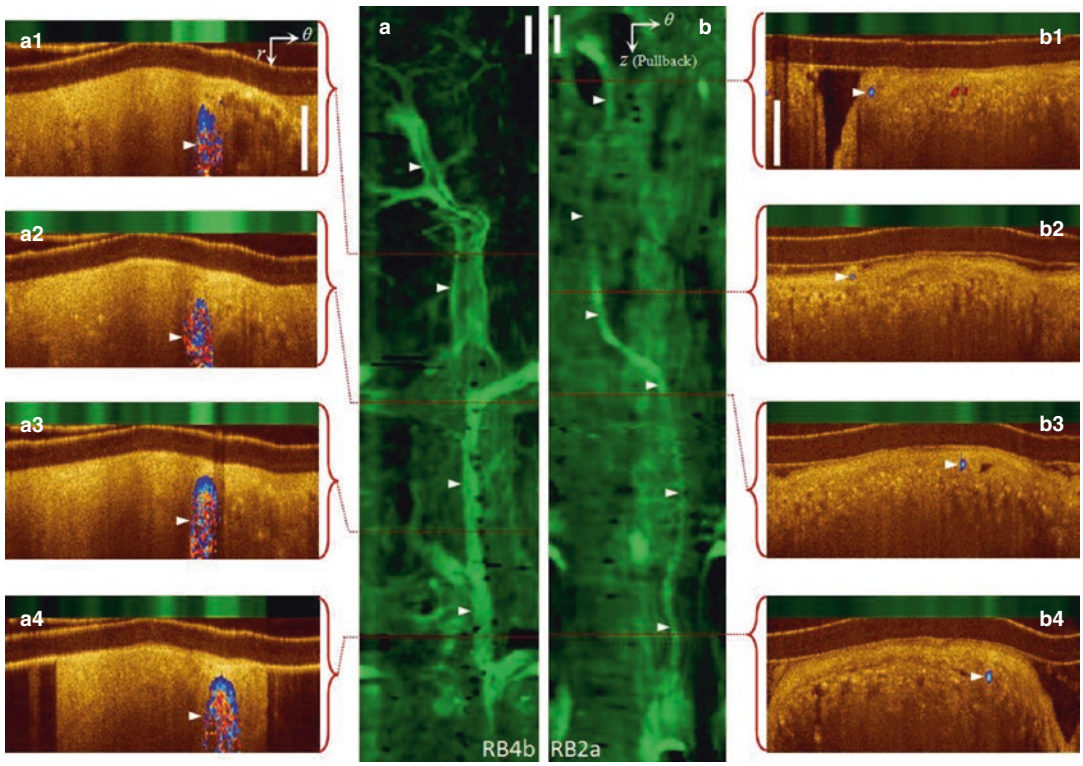

Fig. 16.7 Bronchial vasculature detection by AF-OCT with validation by Doppler OCT. (**a**) A large blood vessel running parallel to the airway (RB4b) with several smaller branching vessels is clearly visualized in the AF image. Doppler OCT (a_1–a_4) confirms these structures as blood vessels. (**b**) Another example of smaller airway blood vessels identified by AF-OCT confirmed by Doppler-OCT. (b_1–b_4) Small vessels down to 12 μm in diameter are visualized by dark lumen in the magnified image. White scale bars are 1 mm

aggressiveness of lung cancer, study vascular remodeling in different lung diseases such as COPD and asthma [74–76], and improve safety of cryobiopsy by avoiding biopsy of larger blood vessels. AF-OCT may provide the means to monitor rejection following lung transplantation. The effect of therapy in patients with pulmonary fibrosis can be studied by PS-OCT that can characterize collagen and elastin [59].

Summary

OCT, PS-OCT, Doppler OCT, and AF-OCT provide unprecedented opportunity to provide high-resolution structural and functional information on airway and lung tissue that cannot be otherwise obtained by other imaging modalities such as CT or MRI. In the central airways, it can differentiate in situ from invasive squamous cell carcinoma to guide therapy. In the peripheral lung, it has the potential to diagnose peripheral lung nodules, to guide biopsy in real time with improved accuracy and safety, as well as to study the effect of pharmacologic and non-pharmacologic therapies. It is a minimally invasive procedure that can be performed in conjunction with standard flexible bronchoscopy under conscious sedation. It has tremendous potential to be integrated into pulmonary medicine as a standard diagnostic procedure.

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Electromagnetic Navigation: A Review

17

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Introduction

Conventional transbronchial biopsy (TBBx) is frequently used to determine the etiology of peripheral pulmonary nodule (PPN). However, when it comes to the nodules located in the peripheral one-third of the lung and less than 2 cm in diameter, the procedure is of limited value, and establishing the diagnosis remains challenging [1]. Percutaneous needle aspiration of such lesions is frequently complicated by pneumothorax requiring chest tube placement and hospitalization in half of the subjects [2, 3]. In addition, TBBx via flexible bronchoscopy (FB) has reached its plateau in terms of its diagnostic yield for the PPN. In most instances the diagnostic yield is limited by our inability to steer endobronchial accessories directly to the lesion.

The sensitivity of bronchoscopy for diagnosing etiology of a PPN depends on several factors including (1) the size of the nodule, (2) the proximity of the nodule to central airway, and (3) the prevalence of cancer in the study population. The reported overall sensitivity ranges between 20 and 84% [4–10].

For PPN less than 20 mm in diameter, the yield is 14% for those located in the outer third of the lung, and it goes up to 31% for the lesions located in the central two-thirds [11]. If the CT reveals a positive "bronchus sign," the yield of FB increases up to 90%, unfortunately, not a common occurrence for smaller lesions [12].

Although the addition of radial probe endobronchial ultrasound (rEBUS) to the traditional bronchoscopy has improved the diagnostic yield, its usefulness is technically limited as the ultrasound probes cannot be easily steered beyond the visible portions of the airways. The next step in guiding the endobronchial accessories through the lung periphery has been the electromagnetic navigation (EMN). Real-time guidance and the ability to steer biopsy instruments to the peripheral lesion are critical for a successful FB procedure. EMN is a novel technology that facilitates approaching peripheral lung lesions which are difficult to sample with conventional TBBx. The following is a concise review on the present-day experience with EMN.

To date, there are two major platforms for EMN which are available in the US: (1) iLogic® (Covidien Corporation, Dublin, Ireland) and (2) SPiNView® (Veran Medical Technologies, Inc., St Louis, MO, USA).

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What Is Electromagnetic Navigation?

The navigation system involves creating an electromagnetic (EM) field around the patient's chest and then directing endoscopic accessories using a microsensor placed upon previously acquired CT images. In other words, EMN is an image-guided localization device which assists in placing endobronchial biopsy tools in the target areas of the lung. The principles and the components of the EMN are provided below [13–17]:

Electromagnetism

EMN operates on the principles of electromagnetism. Electromagnetic location board (EMLB) produces low-frequency EM waves. The size and the placement of the board vary according to the system used. The patient's torso is placed within the electromagnetic field created by the board (Fig. 17.1).

A retractable microsensor probe is mounted on the tip of a flexible cable locatable guide (LG) (Fig. 17.2). This microsensor is the cardinal feature of the system. Once placed within the EM field, its position in *x*, *y*, and *z* axes as well as in motion (rotate, forward, and backward) is captured by the EMN system and displayed on the monitor in real time. These images are superimposed upon previously acquired CT images (Fig. 17.3).

The Edge™ Catheter: Extended Working Channel (EWC)

Since the adult-size flexible bronchoscope cannot be advanced beyond the fourth- or fifth-generation bronchus, the iLogic® system provides extended working channel with the distal end angulated at different degrees to facilitate approaching the PPL (Edge™). The Edge™ catheter is a 130-cm-long,

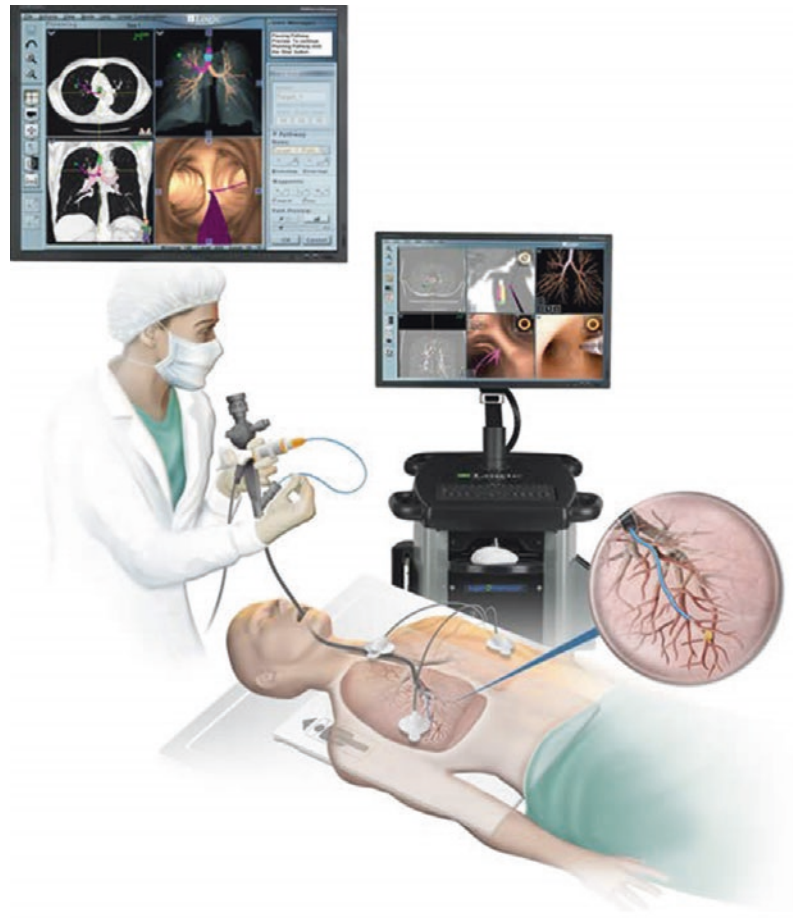

Fig. 17.1
Electromagnetic location board placed at the cephalic end of the bronchoscopy table

1.9-mm-diameter flexible catheter, serving as a EWC for the FB. It is available with its distal end curved at 45°, 90°, or 180° angles. The distal tip of this catheter could be soft or hard and based on the bronchoscopist's preference. These options are to facilitate navigation between the PPN and the adjacent bronchus, as judged by the bronchoscopist. The Edge navigation catheter can be steered to the PPN in 360° fashion. The proximal white steering knob has a socket for connecting a wire, which relays the information from the sensor to the main computer (Figs. 17.4 and 17.5).

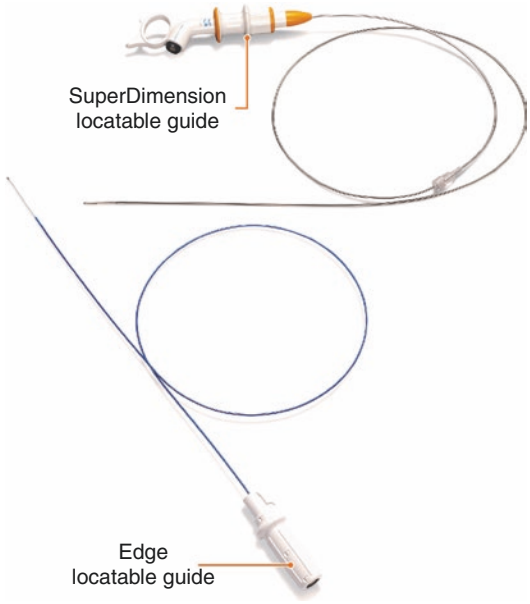

Fig. 17.2 Edge locatable guide

Once the tip of the bronchoscope is wedged into the segmental bronchus of interest, the LG is advanced along with the EWC under the guidance provided by the navigation system. Upon reaching the desired target, the LG is withdrawn leaving the EWC in place. Endobronchial accessories (needle, brush, forceps) then are inserted through the EWC to sample the target. The GenCut biopsy device is the most recent biopsy tool in endobronchial lung navigation system. It is activated with aspiration to create shearing force and collect multiple tissue samples with a single pass. There was a single study in porcine lung model which reported the performance and safety of this catheter. The future study is required to establish the utility of this catheter in humans [18].

Computerized Tomography

To overlay the patient's radiographic information on the patient's anatomy in the electromagnetic field, a high-resolution spiral CT scan of the chest is performed (with or without the contrast) and reconstructed with a protocol specific to the scanner manufacturer. The recommended reconstruction protocols optimize CT images suitable for planning and navigation (Tables 17.1 and 17.2).

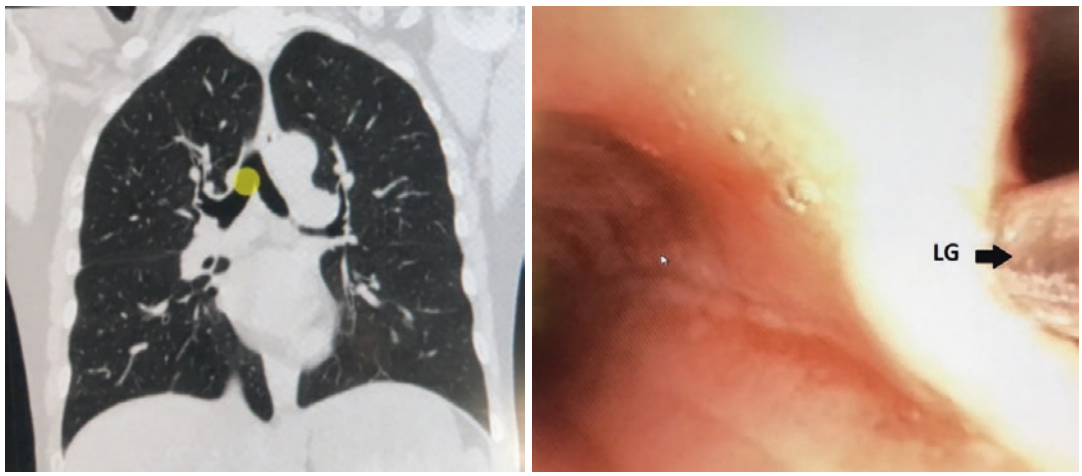

Fig. 17.3 (*Left*) The position of locatable guide (LG) at the main carina in coronal view CT scan and (*right*) real-time superimposed bronchoscopic image of LG at the main carina

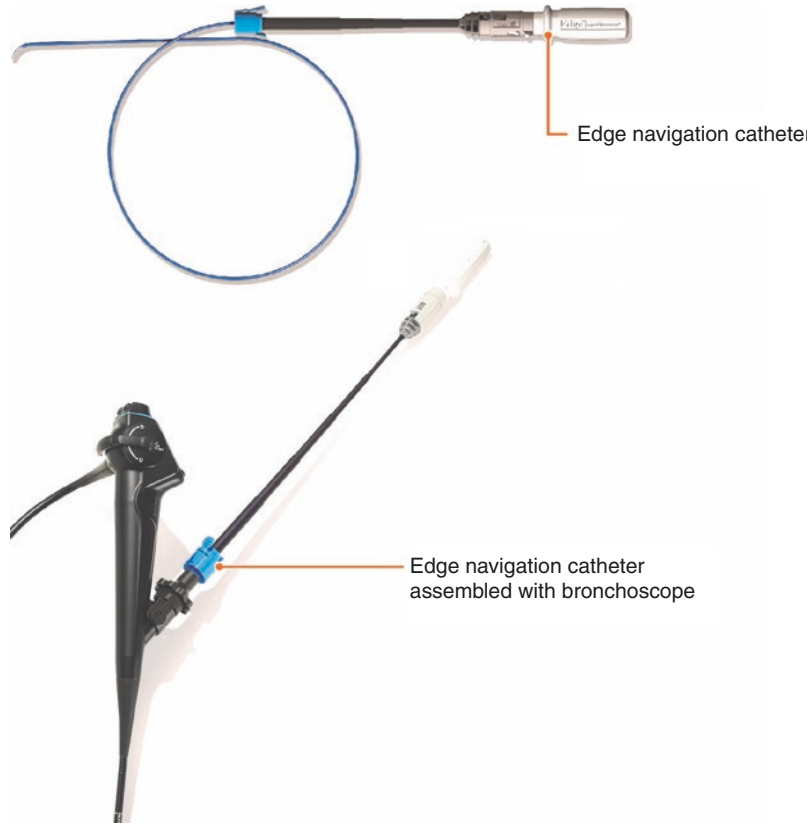

Fig. 17.4 (*Top*) The Edge navigation catheter with sensor at the distal tip. (*Bottom*) Edge navigation catheter assembled with working channel of bronchoscope

DICOM (Digital Imaging and Communications in Medicine) images from a low-dose CT scan can be accepted and viewed in the planning module; however, the detail and quality of the images produced may not be suitable to enable the advanced features of the ENB system. The information is gathered in the DICOM format and placed either on a compact disk or directly downloaded on the system's laptop from the picture archiving and communication system (PACS).

Computer Interphase

The EMN system provides dedicated software for "planning" and "navigation procedure." The CT chest images can be transferred from PACS into DICOM CD. The DICOM CD can be uploaded directly into the planning software. The planning software program provides images of the chest in coronal, sagittal, and axial fashion as well as a virtual bronchoscopic image and a three-dimensional representation of the patient's tracheobronchial tree and pleura. These images are used to plan all aspects of the procedure. The main computer software and the monitor allow the bronchoscopist to view the reconstructed images of the patient's anatomy together with superimposed graphic information depicting the position of the LG as well as position of the target lesion.

The virtual 3D bronchial tree made possible with the technology extends deep into the lung parenchyma and enables several automated features such as automatic registration, automated pathway planning, and airway sync. Further, the customized high-definition views offer the bronchoscopist multiple navigation perspectives to improve detection and diagnosis. A high-definition wide screen allows six viewports to be displayed simultaneously, including one video input, enabling the physician to evaluate positional data and optimize central and peripheral guidance within the lung (Fig. 17.6).

Procedure

The procedure of EMN is performed in the following steps:

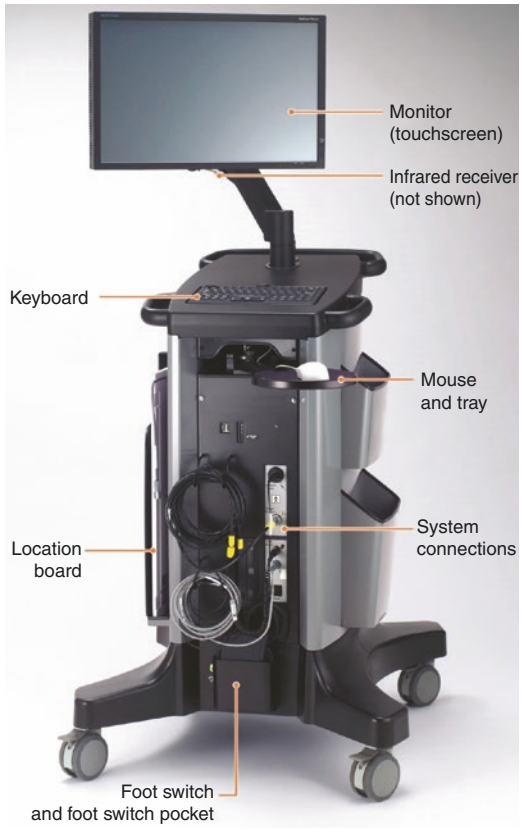

Fig. 17.5 The main processor of the iLogic navigation system

Table 17.1 Recommended CT scan and reconstruction parameters

Image resolution	512 × 512
Overlap	20–50%
Field of view	At least 1 cm of trachea and entire lung volume
Maximum images	690

Planning

Planning involves identifying the target, selecting anatomical landmarks, and identifying a virtual approach to the target using digital software provided by the system.

(a) Identification of the target:
Target(s) are identified by scrolling through the CT cross sections in axial, coronal, and sagittal axes. Once identified, the location of the target(s) is marked using a curser and highlighted. The dimensions of the target are also measured.

Table 17.2 The lists of the slide thickness and slice interval for a 50% and 20% overlap

Slice thickness (mm)	Minimum slice interval (mm) (at 50% overlap)	Maximum slice interval (mm) (at 20% overlap)
1.0	0.5	0.8
1.25	0.625	1.0
1.5	0.75	1.2
2.0	1.00	1.6
2.5	1.25	2.0
3.0	1.50	2.4
4.0	2.00	3.2
5.0	2.50	4.0

(b) Detecting anatomical landmarks:
A virtual bronchoscopy image extending to the fourth generation of tracheobronchial tree is required to enable automatic superimposition of the CT images on the patient's body. If a 3D map is not available, anatomical landmarks (primary and secondary carinas) can be identified using the CT cross sections. Five or more easily recognizable endobronchial locations (landmarks) are selected for the purpose: more specifically main carina as well as two points in each lung, one in the upper lobe and one in its middle or lower lobe. These radiographic landmarks are matched with the actual anatomic landmarks of the patient during the bronchoscopic procedure either automatically or manually.

(c) Pathway planning:
If a 3D map is available, one or more automatic pathways to each target can be constructed to assist in navigation. The automatic pathway is constructed using the 3D map as a reference (Fig. 17.7). A review of the automatic pathway should be completed utilizing the CT cross sections and the 3D map. Additionally, a virtual navigation of the pathway can be performed using the pathway preview feature. The suggested pathway can be modified, can be extended with waypoints, or can be accepted for guidance as it is.

Fig. 17.6 Computer interphase: dedicated program on the laptop provides coronal, axial, and sagittal views of the chest along with virtual bronchoscopy

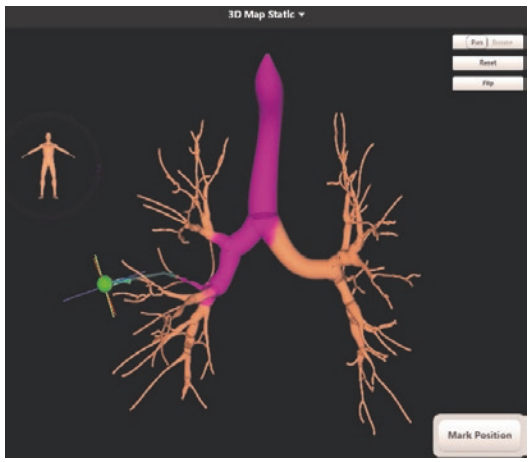

Fig. 17.7 Automatic pathway. Planning involves selecting the target (*green*) and the anatomical landmarks (*purple*)

(d) Saving the plan and exiting:
When the procedure plan is complete, it is exported to a CD, to a removable disk (USB), or to a network storage location for transfer to the procedure system.

Registration

The information gathered during the planning stage is uploaded into the system's main computer using the external memory device. The electromagnetic censors are placed on the patient's chest wall to accommodate for respiratory motion, coughing, and nominal patient movements. FB is performed in a usual fashion. The Edge catheter is inserted via the working channel of the scope.

During the automatic registration process (Fig. 17.8), the system records the location of the LG, while the bronchoscopist performs a bronchoscopic airway examination, creating a virtual cloud of navigation points that approximates the tracheobronchial tree. The system completes the registration process by matching the navigation cloud to the 3D map. The virtual bronchoscopy (VB) will appear during the bronchoscopic survey when the system has collected the minimal amount of data needed to match to the 3D tree. After completing the balanced survey, visual verification and image rotation for the registration is

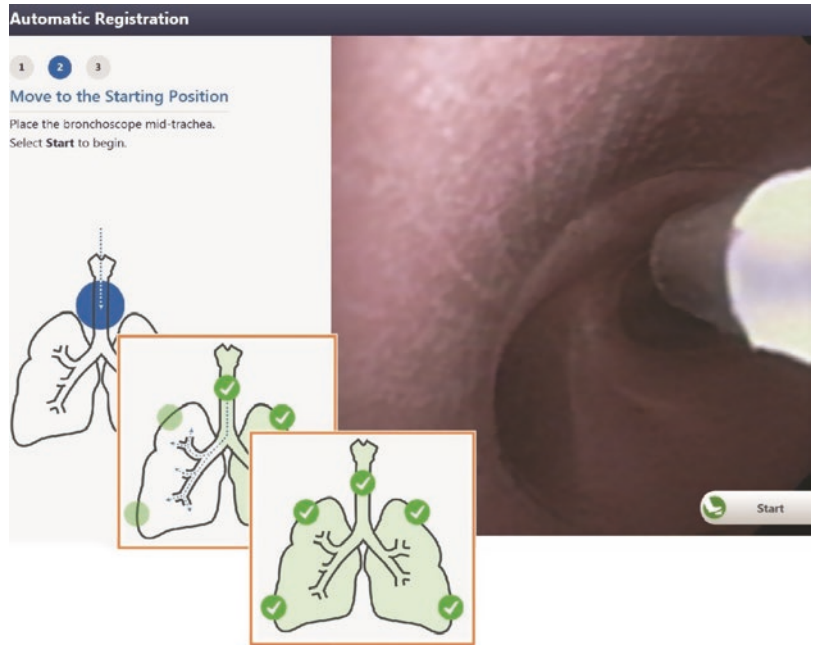

Fig. 17.8 Automatic registration

accepted, and the navigation phase of the procedure begins.

In a small percentage of procedures, the CT images will not support generation of a 3D tree. In this case, manual registration will be required. The radiological landmarks (registration points) selected on the virtual bronchoscopy images in planning are identified in vivo and touched with the tip of the LG to register their location in the system's main computer to establish radiographic-anatomic alignment. Registration of all the above information into the computer software automatically synthesized a navigation scheme to approach the lesion with precision. Accuracy of the navigation depends upon this radiographic-anatomic alignment also referred as "average fiducial target registration error" (AFTRE), which defines registration quality. The AFTRE can be improved or corrected by repositioning the misplaced landmarks or by eliminating that with a greatest deviation. The registration error of 5 mm or less can be considered acceptable.

Real-Time Navigation

Following a successful registration, the scope with the LG in place is advanced toward the segmental bronchus of interest. The navigation screen consists of six different viewports. The configuration of viewports is customizable with 11 different viewports available. Each viewport provides information that is meaningful at different points in the navigation procedure. The targets and pathways defined during planning will be available for selection during navigation. Once a target and pathway have been selected, the available views are used to guide the LG to the target.

The following are the viewports available to aid navigation (Figs. 17.9 and 17.10):

- Planar CT axial, coronal, and sagittal image (three views). The views show the selected target and, optionally, the selected pathway and waypoints.
- Static 3D map. A view of the 3D map showing the selected target, pathway, waypoints, and real-time location of the LG tip.
- Dynamic 3D map. A view of the 3D map showing the selected target, pathway, waypoints, and real-time location of the LG tip. The 3D map is automatically rotated, panned, and zoomed during navigation.

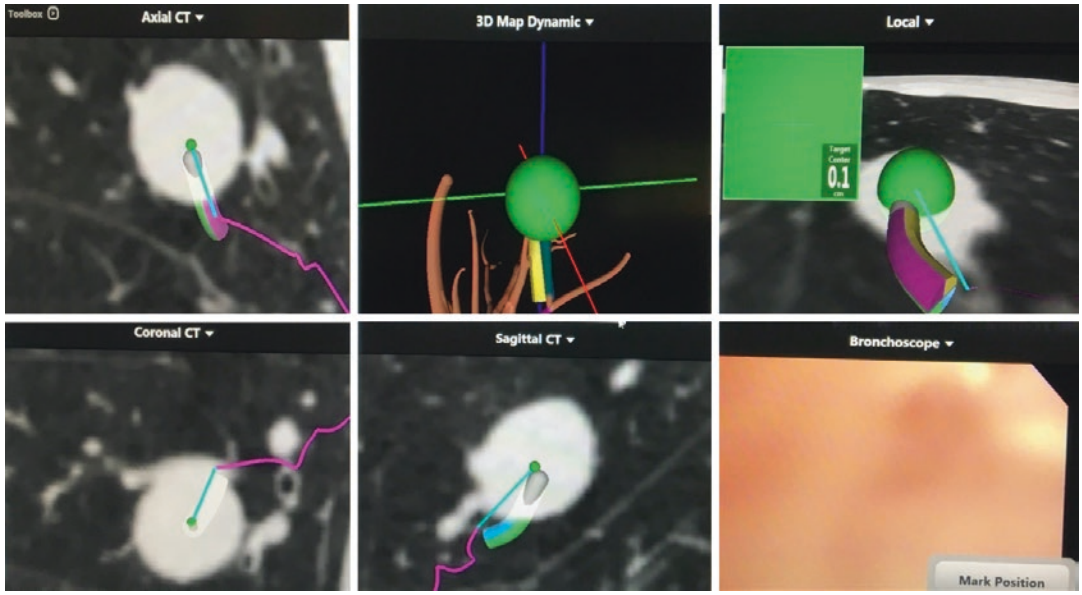

Fig. 17.9 Peripheral navigation view

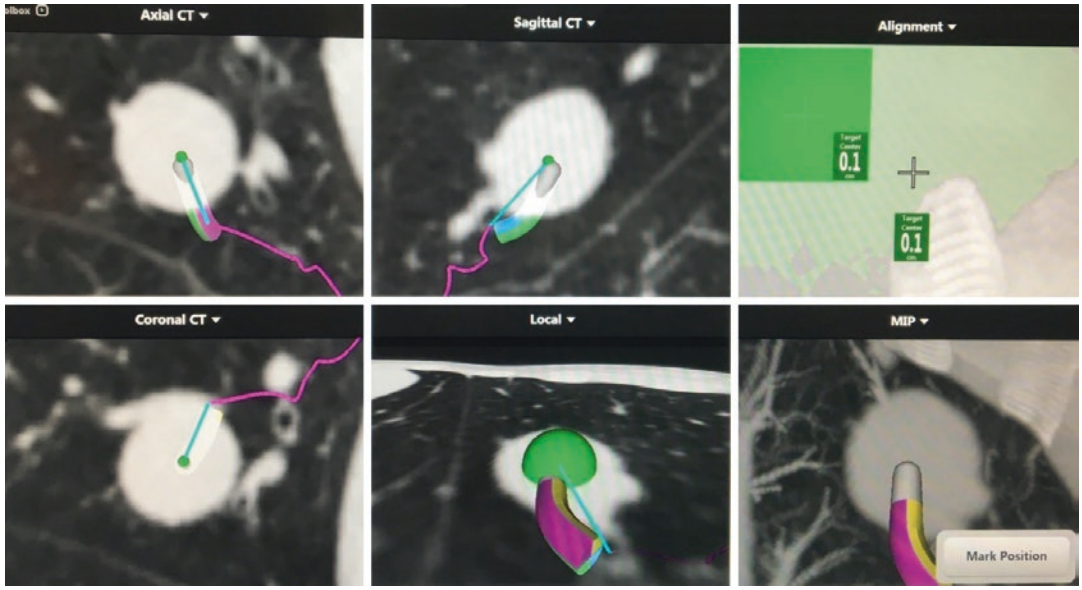

Fig. 17.10 Target alignment view

- Tip view. A graphical representation of the steering wheel on the LG handle. This view shows the direction to rotate the steering wheel to turn the LG toward the selected navigation object (target, pathway, or waypoint).
- 3D CT. A planar projection of the CT volume located directly in front of the LG tip.
- Video bronchoscope. Live display of the video input feed, typically used to show the bronchoscope video.
- Virtual bronchoscopy. A live display of the virtual bronchoscopy showing the real-time location of the LG tip. The selected pathway, waypoints, and 3D map centerlines can be overlaid on the view.

- Local view. A planar CT image located at and aligned with the LG tip. The view shows the selected target, pathway, waypoints, and 3D map branches.
- Alignment view. A view of target alignment with the LG tip.
- MIP (maximum intensity projection). A pseudo-three-dimensional projection of the CT volume below the LG tip. MIP shows high-intensity structures, such as blood vessels and lesions.

Navigation guidance to the target is primarily given through the selected pathway. The pathway is displayed in the 3D map, local view, virtual bronchoscopy, and CT cross sections. The objective during navigation is to steer and advance the LG along the pathway.

In addition to pathway guidance, steering directions are provided to specific navigation objects using the tip view. Navigation objects include targets, the automatic pathway, and waypoints and are represented by spheres in all views.

The lesion is represented as a green sphere on all of the system viewports. As the LG gets closer to the lesion, the green dot continues to get larger in a relative fashion. The screen also shows the distance between the LG and the targeted lesion in millimeters (mm). Once the LG reaches the desired target location, the EWC is fixed at the proximal end of the biopsy channel of the bronchoscope by a special locking mechanism and the LG is withdrawn. Fluoroscopy can be performed to view the LG in the desired location before its removal. A rEBUS probe can also be inserted for additional location confirmation. Bronchoscopic accessories such as biopsy forceps, transbronchial aspiration needle, and endobronchial brush can be inserted via the EWC to obtain a tissue specimen.

SPiNView®

The SPiNView system uses an Always-On Tip Tracked technology. The sensor tracking is built into the biopsy instruments allowing for real-time navigation of the biopsy tools.

There are two additional features of the SPiNView system: (1) it incorporates a transthoracic needle system to biopsy lesions similar to CT-guided transthoracic needle aspiration (TTNA), and (2) the SPiNView offers the 4D respiration technology that monitors patient respiration during the procedure. Respiratory motion can be a problem during TBBx because an average motion of pulmonary lesions has shown to be approximately 17.6 mm. With this much respiratory motion, it may affect the diagnostic yield of EMN-guided TBBX or any other lung biopsy procedures [19].

Procedure

The procedure of SPiNView is performed in the following steps.

Planning

This phase is similar to iLogic system. The system uses inspiratory CT images of the patients' airways to plan the route to the lesion. The target PPN is marked and the software then creates a 3D road map of targeted lesion. The SPiNView software uses an expiration CT scan to match patient's respiration state. Then, the pathway is transferred and is uploaded for the navigation phase.

Navigation

vPads patient tracker is placed on the patient chest. It contains electromagnetic sensors which enable automatic registration and respiratory motion tracking. A SPiNView bronchoscopy catheter is available with steerability. The SPiNView system can automatically perform registration without bronchoscopist's effort. During this phase, the electromagnetic generator tracks the Always-On Tip Tracked® instrument as it advances toward the lesion in the lung. The View Peripheral Catheter provides digital laser optics which has built-in electromagnetic sensors. It provides guidance throughout the procedure.

Biopsy

The targeted lesion is reached by a phantom catheter. The bronchoscopist performs biopsies of the lesion while the instrument is left in place.

The tip tracked steerable working channels, tip tracked aspiration needles, and navigation guide wires enable ultrathin bronchoscopes to be navigated to the peripheral regions of the lung all with clear virtual visualization. The SPin FleX needle is made with nitinol, making it possible to turn 180° and get to difficult lesions in the lungs. The bronchoscopist always knows where the sensor is within the body while sampling. The confirmation by fluoroscopic image is optional.

Results of EMN-Guided TBBx

A number of studies have been published establishing effectiveness of the EMN in the diagnosis of peripheral lung lesions (Table 17.3).

In 2003, Schwarz et al. [13] performed the first animal trial to determine the practicality, accuracy, and safety of the real-time EMN in locating peripheral lung lesions in a swine model. The study proved that EMN was accurate when added to the standard bronchoscopy to assist in reaching peripheral lung lesions. Artificially created lung lesions were sampled without difficulty or complications, using conventional accessories.

Becker et al. [14] published results of a pilot study in humans. They obtained biopsies of the peripheral lesions under the guidance of EMN in 30 adults. Evaluation was possible in 29 patients; definitive diagnosis was established in 20 patients (69%). EMN added a mean of 7.3 min of time to the bronchoscopy procedure. There was one pneumothorax requiring chest tube insertion. They concluded that EMN is feasible and safe as an aid to obtaining biopsies of peripheral lung lesions.

Hautmann et al. [15] performed a prospective evaluation of an EMN system for the diagnosis of peripheral infiltrates or solitary lesions. In all of the pulmonary infiltrates and solitary lesions, the navigation system was able to guide the sensor tip to the center of the lesion, despite some being undetectable by fluoroscopy. All the lesions were reached by EMN, and tissue was sampled successfully for the histological examination. The biopsy results in three of the five solitary lesions were positive for carcinoma, whereas normal lung tissue was obtained in the two remaining cases. All "masses" were positive for carcinomas. Biopsy results for infiltrates were diagnostic in five cases. In the remaining three, histological findings were nonspecific. There were no complications. Overall, EMN was well tolerated and proved to be safe and useful in localizing small and fluoroscopically invisible lung lesions with an acceptable level of accuracy.

Then Schwarz et al. [16] also performed a human study following their animal trial on unreachable peripheral lung lesions (15–50 mm in size) under EMN guidance. The diagnostic sensitivity of the procedure was reported as 69%. This success rate was felt to be due to the road map created by the navigation system which reduced trial and error attempts during the use of endobronchial accessories. No complications were reported.

A prospective, single-center, pilot study was conducted by Gildea et al. [17] to determine the ability of EMN to sample peripheral lung lesions and mediastinal lymph nodes. Sixty subjects were enrolled and the diagnostic yield was 74% for the peripheral lesions and 100% for mediastinal lymph nodes. A diagnosis was obtained in 80.3% of bronchoscopic procedures with EMN. The lesions were accessed in all subjects. Two patients developed pneumothorax. There was no significant relationship between diagnosis and size or the location of the peripheral lesions or lymph nodes.

Prospective studies were undertaken by Makris et al. [20] and Eberhardt et al. [21] to determine the yield of EMN without using fluoroscopy in the diagnosis of peripheral lung lesions. The diagnostic yield was found to be 67% and 62.5%, respectively, and was independent of lesion size. The EMN yield was found to be 77.2% if AFTRE was less than 4 mm [23]. Diagnostic yield was lower for the upper lobe lesions probably due to the acute angle of the corresponding bronchus as well as for the lower lobes, probably related to the diaphragmatic movement [24]. Both studies concluded that EMN can be used as a stand-alone procedure (without fluoroscopy) without compromising diagnostic yield or increasing the risk of pneumothorax.

Table 17.3 Diagnostic yield of EMN-aided FB

Reference	Technique	*N*	Size (mm) Range or mean	Diagnostic yield (%)	Prevalence of lung cancer	AFTRE (mm) (mean ± SD) or range	Procedure duration (min) (mean ± SD) or range	Fluoro	PNX % (*n*)
Becker, 2005 [14]	EMN+fluoro	29	12–106	69	83%	RE: 6.1 ± 1.7	NT: 7.3 RT: 2	+	3.3 (1)
Hautmann, 2005 [15]	EMN+fluoro	16	22 ± 6	Not given	No data	4.2	NT: +3.9 min	+	0
Schwarz, 2006 [16]	EMN+fluoro	13	15–50	69	92%	NE: 5.7	TPT: 46 min	+	0
Gildea, 2006 [17]	EMN+fluoro	58	PL: 22.8 LN: 28.1	PL: 74% LN: 100%	74%	RE: 6.6 ± 2.1 NE: 9 ± 5	RT: 3 ± 2 NT: 7 ± 6 TPT: 51 ± 6	+	3.4 (2)
Makris, 2007 [20]	EMN	40	23.5	62.5	85%	RE: 4 ± 0.15 NE: 8.7 ± 0.8	Not studied	–	7.5 (3)
Eberhardt, 2007 [21]	EMN	89	24	67	76%	RE: 4.6 ± 1.8 NE: 9 ± 6	RT: 3.2 ± 2.3 NT: 4.5 ± 3.4 TPT: 29.9 ± 6.5	–	2.2 (2)
Wilson, 2007 [22]	EMN+fluoro+ROSE	248	PL: 2.1 LN: 1.8	70–86%	57%	RE: 0.5 ± 0.02	Not studied	+	1.2 (3)
Eberhardt, 2007 [24]	EMN+EBUS	40	26	88	78%	Not studied	Not studied	–	6[a] (3)
McLemore, 2007 [25]	EMN+EBUS	48	23 (6–60)	90	No data	Not studied	Not studied	–	2.1 (1)
Lamprecht, 2009 [26]	EMN+PET-CT+ROSE	13	30	76.9	69%	Not studied	TPT: 60	–	0
Seijo, 2010 [27]	EMN+ROSE	51	25 (15–35)	67	72%	RE: 4	Not studied	–	0
Eberhardt, 2010 [28]	EMN+EBUS	53	23.3 (11–29)	75.5	ND	3.6 (1.8–5.7)	RT: 2.9 (1–9) NT: 3.5 (0.3–14) TPT: 25.7 (16–45)	–	1.9 (1)
Mahajan, 2011 [29]	EMN+fluoro	48	20 ± 13	77	57%	Not studied	Not studied	+	11 (4)
Pearlstein, 2012 [30]	EMN+ROSE	101	32	85	81%	4	Not studied	–	5.8 (6)
Lamprecht, 2012 [31]	EMN+ROSE	112	27 (6–46)	75.6–89.6	85%	Not studied	TPT: 45 ± 2 (>20 mm)	–	1.8 (2)

EMN electromagnetic navigation, *ROSE* rapid on-site evaluation, *EBUS* endobronchial ultrasound, *PL* peripheral lesions, *LN* lymph nodes, *RE* registration error, *NE* navigation error, *NT* navigation time, *RT* registration time, *TPT* total procedure time

[a]When only EMN was done

It has also been established by a prospective, randomized trial that combination of EBUS (endobronchial ultrasound) and EMN improves the diagnostic yield of FB in peripheral lung lesions without compromising safety [24]. In this particular study, 72% of all 118 patients recruited had a positive diagnostic yield via FB. Combined EBUS and EMN had a significantly higher diagnostic yield of 88% compared to that of EBUS (69%) and EMN (59%) alone. The diagnostic yield from the lower lobes was significantly lower, consistent with the previous study by Eberhardt [24]. The improved yield of the joint procedure ascribed to combining the ability of EBUS to directly visualize the peripheral lung lesions with the precise navigation capabilities of EMN. The overall pneumothorax rate was 6% (seven patients) and 6.3% (five patients) when EMN was used. Four of the seven patients required a chest tube placement. Although this combination provides a higher diagnostic yield compared to either one of them alone, the issues of cost and training need to be addressed.

In another report using the combined EBUS and EMN approach, 48 patients with peripheral lung lesions were studied [25]. Successful navigation was possible in 42 patients. The diagnostic rate was 90% with 45% true positive and 45% true negative rate. Five out of the six failed procedures were because of mechanical limitations of the EMN (lesions in the upper lobes). The authors calculated that with the concomitant use of EMB and EBUS, 32 thoracotomies were averted at the expense of only one pneumothorax.

A retrospective, single-center study was carried out to evaluate the diagnostic yield of bronchoscopy, guided by EMN plus the rapid on-site evaluation (ROSE) of the cytology specimens [22]. Of 248 subjects, 65% received a definitive malignant or nonmalignant diagnosis on the day of the procedure. During the follow-up 12 patients (5%) were confirmed to be free of malignancy, and 8 patients (3%) were confirmed as having malignant disease. Sixty-seven patients (27%) were lost for follow-up (inconclusive). Thus, on the day of the procedure in 173/248 (70%) of all patients, correct information was gathered. If all inconclusive cases are treated as nondiagnostic (worst-case scenario), the yield was 70%, but if all inconclusive cases were treated as diagnostic (best-case scenario), the estimate was 97%. The diagnostic yield probably ranged between 70 and 97% based upon the assumptions made regarding the outcome of the cases that had an inconclusive diagnosis on the day of the procedure. In this particular study, pneumothorax was encountered in three patients and a few other minor complications, yet none of the latter were related to the use of EMN. It was concluded that combination of EMN and ROSE can provide a better diagnostic yield in patients with a peripheral lung lesion.

The combination of EMN, PET-CT, and ROSE was further studied for the routine diagnostic work-up of peripheral lung lesions [26]. EMN was performed in 13 subjects, where the PET-CT scans were part of the diagnostic work-up. In 76.9% of the patients, EMN resulted with a definitive diagnosis. No pneumothorax or any other complications related to the procedure were encountered. In patients with peripheral lung lesions, EMN in combination with ROSE and prior PET-CT was shown to be safe and highly effective.

The influence of having CT bronchus sign on the yield of EMN was evaluated in a study of 51 patients with pulmonary nodules [27]. The overall diagnostic yield of EMN was 67% (34/51). EMN was diagnostic in 79% (30/38) patients with a bronchus sign on chest CT but only in 4/13 (31%) with no discernible bronchus sign. Both univariate and multivariate analysis identified bronchus sign as statistically significant variable. No procedure-related complications were observed.

Catheter aspiration was compared to the traditional forceps biopsy technique of small pulmonary nodules suspicious for malignancy using EMN [28]. Both tools were used to sample suspicious malignant lesions in 53 patients. EBUS was used to verify the accuracy of target lesions as well. Diagnosis was obtained in 75.5%. Sampling by catheter aspiration was associated with a higher diagnostic yield than sampling by forceps biopsy alone ($p = 0.035$). When EBUS verified the lesion location after navigation, the diagnostic yield was

93% compared to only 48% when lesion location was not confirmed [28]. There was one pneumothorax, treated conservatively.

In large meta-analysis, including 11 ENB studies, the weight diagnostic yield of ENB was at 67% [32]. Nine of these studies utilized ENB alone without other diagnostic modalities such as radial probe EBUS. Another meta-analysis and systematic review of ENB included 1033 lung nodules which showed the overall definite diagnostic yield of 64.9%. Several variables including the size of the nodule, location in lower lobe, bronchus sign, average fiducial target registration error (AFTRE), visualization of nodule with radial probe EBUS, and catheter suction technique were reported to be significant predictors in univariate analysis. However, only bronchus sign was reported to be a significant predicting factor in multivariate analysis [33]. Meanwhile, the use of general anesthesia and rapid on-site evaluation was associated with better diagnostic yield. However, there were only four trials using these techniques, precluding final conclusions. The large AQuIRE registry which included 581 patients showed diagnostic yield of 38.5% with the use of EMN as single modality and 57% with rEBUS alone. The combination of EMN and rEBUS provides a diagnostic yield of 47.1% [34].

Electromagnetic Guidance Transthoracic Needle Aspiration (ETTNA)

There is only one report related to the experience of using SPiNView system for electromagnetic guidance transthoracic needle aspiration [35]. The pilot study in 24 patients underwent both EMN-guided TBBx and ETTNA. The diagnostic yield for ETTNA alone was 83% and increased to 87% when ETTNA was combined with navigational bronchoscopy. With the combination of EBUS for complete staging, ETTNA and NB had diagnostic yield of 92%. There was no major bleeding. However, there was 21% risk of pneumothorax of which only two (from five) patients required drainage.

Therapeutic Interventions

EMN is a promising technology not only in diagnosing the peripheral lung lesions and mediastinal lymph nodes but also may provide a means for treating patients with possible lung cancer.

Localizing non-visible and non-palpable peripheral lung nodules during thoracoscopic resection can be challenging. A variety of techniques have been described to mark the pleural surface in the vicinity of these nodules to guide the surgeon. The use of EMN-guided pleural tattoo injection with methylene blue or indigo carmine to assist video-assisted thoracoscopic surgical (VATS) wedge resection of pulmonary nodules has been reported in six patients [36].

The use of EMN has been reported in two cases where subpleural fiducial markers were placed under EMN guidance [37]. This was followed by successful VATS wedge resection during the same procedure. Fiducial placement of an average of three markers led to an adequate retention rate to allow for successful treatment of lung cancer in patient undergoing stereotactic radiation. There are several brands of fiducial marker available in the market which have different retention rates. The VortX coil fiducial had a retention rate of 96.7% [38, 39].

In external beam radiation of lung cancer, the metallic fiducials are usually implanted transcutaneously under CT or fluoroscopic guidance. Kupelian et al. compared this method to transbronchial placement of metallic fiducials using EMN [40]. Eight of the 15 patients who had the implantation transcutaneously developed pneumothorax, and six of them required a chest tube. No pneumothorax was observed in the eight patients who underwent the placement using EMN bronchoscopy. The implanted markers were stable within the tumors throughout the treatment duration regardless of implantation method.

Recent advances in minimally invasive thoracic surgery have renewed an interest in the role of interstitial brachytherapy for lung cancer [41–44]. One of the studies has described the principles of navigated brachytherapy for treatment of a medically inoperable peripheral non-small cell

lung cancer [44]. A right upper lobe lesion was treated with external beam radiotherapy and navigated endoluminal brachytherapy (Iridium-192). After successful localization of the lesion, rEBUS was performed, and a brachytherapy catheter was placed within the tumor. After the application of high-dose-rate brachytherapy, rEBUS and CT demonstrated a partial, while histology showed a complete remission of the tumor. This finding advocates that navigated brachytherapy for peripheral pulmonary tumors not responsive to conventional treatment is achievable [44]. In another report, the ENB-guided brachytherapy showed a complete remission in 50% of the patients (9 of 18). Only one small pneumothorax was observed after the procedure [45].

Studies have demonstrated that a minimally invasive robot-assisted (MIRA) lung brachytherapy system produced results that are equal to or better than those obtained with VATS and comparable to results with open surgery for peripheral, malignant lung lesions [43]. Following this finding an integrated system involving modified EMN, EBUS, and MIRA is being evaluated for brachytherapy for the peripheral lesions. It appears that EMN with an improved robotic controller may help to perform minimally invasive robot-assisted lung brachytherapy which may have better outcome than standard VATS [42].

Stereotactic radiosurgery (CyberKnife) is a treatment option for patients who are medically unfit to undergo lung tumor resection [46]. This technology has been complimented by more targeted chemotherapeutic regimens, novel methods of administering more accurate and more concentrated doses of radiation therapy, and innovative local excisional methods. For an exact tumor ablation, CyberKnife requires fiducial marker placement in or near the tumor. In the past it was being carried out via transthoracic route under CT guidance with an obviously high risk of pneumothorax. When the fiducials are placed via standard bronchoscopy, they have a tendency to dislodge [47]. In a single study, a total of 39 fiducial markers were successfully deployed in eight of nine patients using EMN guidance without any complication [48]. This finding supports the notion that EMN can be used to deploy fiducial markers for CyberKnife radiosurgery, safely and accurately.

A recent study described the use of coil-spring fiducial markers in inoperable patients with isolated lung tumors planned for CyberKnife treatment [49]. A total of 52 consecutive patients underwent fiducial marker placement using EMN bronchoscopy. Of these, 4 patients received 17 linear fiducial markers, and 49 patients with 56 tumors received 217 coil-spring fiducial markers. A total of 234 fiducial markers were successfully deployed in 52 patients with 60 tumors. At CyberKnife planning, 8 (47%) of 17 linear fiducial markers and 215 (99%) of 217 coil-spring fiducial markers were still in place ($P = 0.0001$). Of the four patients with linear fiducial markers, two required additional fiducial placements, while none of the patients with coil fiducial markers required additional procedures. Three pneumothoraces (5.8%) were encountered (two of them needed a chest tube). The bronchoscopy procedures were performed under moderate sedation in an outpatient bronchoscopy suite.

A novel EMN system that provides tracking for percutaneous procedures has been introduced to aid radiologists in their different pulmonary interventions [50, 51]. The tracking is performed percutaneously without using bronchoscopy. This system did not show any benefit in terms of reducing CT fluoroscopy time or radiation dose when compared to the traditional percutaneous CT fluoroscopy-guided biopsy of small lung lesions [50]. This EMN system was also evaluated to determine its potential to reduce the number of skin punctures and instrument adjustments during CT-guided percutaneous ablation and biopsy of lung nodules [51]. This early experience suggested a low number of skin puncture and instrument adjustments when using the system.

In terms of radiofrequency-induced tissue ablation (RFA), this approach offers a minimally invasive modality [52]. A small prospective trial for RFA demonstrated the early histopathological changes following RFA in a surgical setting. There was near-complete ablation (>90%) in 9 of 18 patients. ENB-guided RFA was considered as an alternative method for local tumor control in

inoperable candidates with PPL [53]. However, several complications could be encountered in 16–35% of patients (pain, hemothorax, pneumothorax, and pleural effusion) [54–56]. In addition, one limitation of endoscopic RFA is that coagulated necrotic tissue can be formed around the tip. It can lead to inadequate tissue ablation. ENB-guided RFA seems to be a good alternative for treatment of lung cancer in inoperable candidates. However, further trials are necessary to determine the efficiency and safety of this therapeutic modality compared with current standard of care such as surgery resection or stereotactic body radiation therapy (SBRT). The EMN bronchoscopy can also be used to draw a path to locate a distally located foreign body. Such an approach can preclude the need for lobectomy [57].

Complications

Pneumothorax is the most common complication encountered with the use of EMN and occurs in the range of 0–7.5% [14–17, 21, 22]. In the published studies related to EMN effectiveness in the diagnosis of peripheral lung lesions, 18 patients have developed pneumothorax (Table 16.1). Four of these patients needed chest tube drainage, while in the remaining 14, it resolved spontaneously**.** Theoretically, the rate of pneumothorax could be affected by AFTRE, as an error of even a few millimeters could be crucial in these small peripheral lesions, especially if the fluoroscopic guidance is not utilized.

Self-limiting bleeding may be encountered in some cases [14, 22]. It is believed that the EWC also facilitates to tamponade the bleeding by allowing the scope to remain wedged at the subsegmental bronchus throughout the procedure [17, 21].

There is also a possibility of EWC being dislodged from its primary site during sampling of the tissue requiring repeat navigational stage of the procedure [31]. The use of fluoroscopy during the sampling of the tissue can help identify the problem. In a single case, repeated insertion and removal of biopsy forceps perforated the EWC [21].

Limitations

We believe that the major obstacles to the widespread use of the EMN are its cost and the need for expensive disposable LG and EWC. Medical economics can certainly limit its use in developing and third world countries. In addition, there was a concern of using magnetic field, and EMN has been considered relatively contraindicated in patients with pacemakers and implantable cardioverter-defibrillators (ICDs). Khan et al. have shown that the magnetic field in EMN-guided biopsy is less than 0.001 T and the procedure is safe to perform in patients with pacemakers and ICDs [58].

Summary

Electromagnetic navigation is a novel tool which aids diagnostic yield of flexible bronchoscopy for the peripheral lung lesions and mediastinal lymph nodes. The procedure is safe, effective, and easy and can be performed with or without the use of fluoroscopy. It plays a complementary role with endobronchial ultrasound. It has a potential to be a helpful tool in improving outcomes from thoracoscopic resections, external beam radiotherapy, interstitial brachytherapy, CyberKnife treatment, and radiofrequency-induced tissue ablation as well as in the removal of the distally located foreign bodies. Its up-front cost and its association with the disposable LG could hinder its popularity.

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18 Tissue Acquisition in Patients with Suspected Lung Cancer: Techniques Available to the Pulmonologist

Jason A. Akulian and M. Patricia Rivera

Introduction

In the process of evaluating a patient suspected of having lung cancer, the clinician must consider the type of lung cancer, small cell lung cancer SCLC or non-small cell lung cancer (NSCLC), the size and location of the primary lesion, the presence of intrathoracic lymph nodes, extrathoracic metastasis, and the overall clinical status of the patient [1]. While the accuracy of differentiating between SCLC and NSCLC in specimens generated by various diagnostic techniques is excellent [1], the treatment of NSCLC now relies on accurate histopathologic diagnosis and molecular characterization of the tumor. In the last decade, we have witnessed a revolution in our understanding of the molecular genotype of lung cancer, and certain molecular determinants not only guide treatment decision-making but also have a prognostic and predictive function.

NSCLCs are heterogeneous tumors recognized as a collection of distinct molecularly and immunologically driven cancers. This distinction is critical and has resulted in the overhaul of standard therapies targeted at broad histologic subtypes that then changed the treatment landscape toward a more personalized approach. We first learned that NSCLCs respond to different therapeutic agents based on histologic phenotypes and that histology was a potential predictive factor in advanced NSCLC treated with chemotherapy [2]. In a study by Scagliotti et al., a significant interaction was reported between treatment by histology and response/survival in non-squamous NSCLC treated with pemetrexed and cisplatin compared to squamous cell cancer (SCC) [3]. In a study by Ciuleanu and colleagues, maintenance pemetrexed plus best supportive care was well tolerated and offered improved progression-free and overall survival compared with placebo in patients with advanced non-squamous cell NSCLC [4]. More than a decade ago, we learned that a subset of patients with NSCLC whose tumors harbor activating epidermal growth factor receptor (EGFR) mutations respond with acceptable toxicity when treated with EGFR tyrosine kinase inhibitors (TKIs), compared with standard chemotherapy [5–8]. On the basis of the results of six phase III trials confirming the benefit of EGFR TKI therapy in patients with NSCLC and EGFR mutations, the American Society of Clinical Oncology (ASCO) provisional clinical opinion on EGFR mutation testing states that "patients with advanced NSCLC who are being considered for first-line therapy with an EGFR TKI should have their tumor tested for EGFR mutations to determine whether an EGFR TKI or chemotherapy is the appropriate first-line

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J.P. Díaz-Jimenez, A.N. Rodriguez (eds.), *Interventions in Pulmonary Medicine*,
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therapy" [9]. We subsequently learned of additional actionable mutations including oncogenic fusion genes consisting of EML4 and anaplastic lymphoma kinase (ALK) inhibition, reported to be present in 3–7% of adenocarcinomas of the lung [10], and ROS-1 gene rearrangement, described in 1.7% of NSCLCs [11]. The inhibition of ALK or ROS-1 rearrangements with the orally available small-molecule inhibitor crizotinib resulted in dramatic response rates and stable disease in most patients [10, 11], expanding further the armamentarium of personalized therapy in NSCLC. In the last 5 years, comprehensive genotyping of NSCLCs has identified an oncogenic driver mutation in 62% of adenocarcinomas, a number expected to increase, and is now also being performed in squamous cell and small cell cancers of the lung [12]. A more recent breakthrough in lung cancer therapy involves immunotherapy agents including checkpoint inhibitors such as programmed cell death-1 (PD-1) and cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitors. The PD-1 inhibitor pembrolizumab has been approved for use in patients with lung cancer whose tumors express programmed death-ligand 1 (PD-L1) based on immunohistochemical (IHC) analysis [13].

Because the detection of driver mutations in selected patients with NSCLC has shifted the paradigm of treatment to personalized therapy which in turn has resulted in improved outcomes, the clinician evaluating the patient with suspected lung cancer must understand the critical role she or he plays in obtaining adequate amounts of tissue at the time of diagnostic procedures so that accurate histologic differentiation (squamous cell vs. adenocarcinoma) can be achieved and, when applicable, the tissue can be evaluated for driver mutations (*KRAS*, EGFR, EML-4 ALK, and ROS1 translocations among others) and analyzed for PD-L1.

Ideally, one would like to obtain core or surgical biopsies in patients with lung cancer in order to accurately define histology and obtain molecular analysis. However, the majority of patients with NSCLC present with unresectable advanced disease which means that small biopsies or fine-needle aspirations for cytologic specimens are usually the primary means of diagnosis and staging. Obtaining adequate amounts of tissue can be challenging especially in current clinical practice when minimally invasive procedures such as endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) are more commonly utilized, but the clinician must remember that limited tissue acquisition and failure to judiciously handle the specimens contribute to the difficulty of accurate molecular and histologic subtyping. For this reason, multidisciplinary thoracic oncology teams, which include pulmonologists, thoracic surgeons, chest radiologists, medical and radiation oncologists, and pathologists, must collectively decide how best to obtain tissue and then optimally utilize the available tissue by performing the minimal immunohistochemical stains needed to diagnose the likely NSCLC subtype (squamous cell vs. adenocarcinoma) so that more tissue is available for molecular diagnosis [14].

Diagnostic Bronchoscopic Procedures for Tissue Acquisition

There are several procedures available to the pulmonologist to obtain tissue for diagnostic and biomarker analyses in patients suspected of having lung cancer (Table 18.1). The sampling technique should be chosen on the basis of the primary tumor location (central vs. peripheral), presence and location of lymph nodes, extrathoracic lesions, local expertise, safety, availability, diagnostic accuracy, and patient preference [1]. Once tissue is obtained, multiple tests must be

Table 18.1 Bronchoscopic procedures available for tissue diagnosis of lung cancer

1. Conventional flexible bronchoscopy with forceps biopsy, bronchial brushing, washing
2. Conventional transbronchial fine-needle aspiration (TBNA)
3. Endobronchial ultrasound (EBUS)-guided TBNA
4. Endoscopic ultrasound (EUS)-guided TBNA
5. Electromagnetic navigation bronchoscopy (ENB)-guided forceps biopsy
6. Radial-probe endobronchial ultrasound

performed in order for the pathologist to accurately provide histology, immunohistochemical profile, and molecular characterization of the tumor.

Flexible Bronchoscopy

Traditionally, the diagnosis of lung cancer has been made with flexible bronchoscopy (FB) and its attendant procedures: bronchial washings, endobronchial or transbronchial brushes, bronchoalveolar lavage (BAL), transbronchial biopsies, and conventional transbronchial fine-needle aspiration (TBNA) of mediastinal lymph nodes.

The sensitivity of bronchoscopic biopsy for central, endobronchial lesions has been reported to be very high; however, the yield for peripheral lesions is not so promising. In a review of 30 studies that reported diagnostic yield [15], the diagnosis of central, endobronchial tumors by bronchoscopy showed the highest sensitivity for endobronchial biopsies (74%) followed by bronchial brushing (59%) and washing (48%). The sensitivity for central tumors for all modalities combined was 88%. For peripheral lesions, cytobrushing demonstrated the highest sensitivity (52%), followed by transbronchial biopsy (TBB) (46%), and BAL/washing (43%). The overall sensitivity for all modalities for peripheral lesions was 69% [15]. The diagnostic yield of bronchoscopic sampling procedures is very much dependent on tumor visibility during bronchoscopy, the location of the bronchoscopically visible tumors, and, in the case of peripheral lesions, the size of the lesion (diagnostic yield higher for lesions greater than 3 cm in size) [1]. Other critical factors in the diagnostic yield of bronchoscopic biopsies are the forceps size and the number of biopsies obtained [16]. Forceps of 2 mm open diameter are felt to be the most useful in order to decrease artifacts that can impede the correct diagnosis. The more biopsies obtained, the better; however, increasing the number of biopsies taken results in increased risk of bleeding [16]. It is reported that between one third and one half of the bronchial biopsies taken from visible endobronchial tumors contain no viable tumor [17]. Cryobiopsies may be a more effective way to obtain larger biopsies, but the technique is not yet widely used in clinical practice [16].

Transbronchial Needle Aspiration

Conventional TBNA (without endobronchial ultrasound) can be performed during flexible or rigid bronchoscopy in order to sample endoscopically visible bronchial abnormalities especially when there is evidence of extrinsic compression, submucosal infiltration, or an exophytic mass [18] as well as sampling hilar and mediastinal lymph nodes for staging of NSCLC [19]. It is particularly well suited for sampling paratracheal (stations 4R, 4L), subcarinal (station 7), and hilar (stations 10R, 10L) lymph nodes. Conventional TBNA is however a procedure that is performed without direct visualization of the lymph node being aspirated, and because of this limitation, the reported yield for TBNA for hilar and mediastinal lymph nodes varies widely (from 14% to 1%) [20]. In a meta-analysis of 12 studies in 910 patients, the sensitivity rate of TBNA was 76%, while the specificity rate was 96% [20]. In an updated systematic review performed by Silvestri and colleagues for the American College of Chest Physicians (ACCP) lung cancer guidelines update that included 2408 patients, the overall median sensitivity of TBNA was 78% (ranged from 14% to 100%), and the median negative predictive value (NPV) excluding studies with a prevalence of >80% was 77% [21]. The high false-negative rate of conventional TBNA makes it a less attractive modality for staging of the mediastinum. Therefore, TBNA would probably be the preferred minimally invasive method for patients with radiographic evidence of enlarged mediastinal lymph nodes adjacent to the airways, as bronchoscopy is usually performed in lung cancer patients and assessment for endobronchial lesions can be performed during the same procedure [22]. The optimal diameter of the needle is between 19G and 22G although the 19G needle is preferred as more clumps of tumor cells are sampled with the larger needle [16]. Rapid on-site evaluation (ROSE) of the aspirates by a

cytopathologist/technologist improves the yield, is cost-effective, and eliminates unnecessary passes during the procedure [23].

Endobronchial Ultrasound (EBUS)-Guided Transbronchial Needle Aspiration (TBNA)

EBUS-TBNA has revolutionized the approach to the diagnosis and staging of NSCLC. The technique is minimally invasive; provides access to nearly all lymph node stations (upper and lower paratracheal, subcarinal, hilar, and interlobar); has the ability to combine diagnosis and staging in a single procedure; has resulted in higher diagnostic yields than typically associated with conventional TBNA that are equivalent to, if not better than, diagnostic yield when compared with mediastinoscopy; and has the ability of providing adequate tissue for molecular analysis [24–30]. In a prospective cohort study of 108 patients, real-time EBUS-guided TBNA detected malignant lymph node involvement with a sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of 95, 100, 100, 90, and 96%, respectively [29]. In a meta-analysis, EBUS-TBNA was reported to have a high pooled sensitivity of 93% and specificity of 100% for the confirmation of malignancy [31]. Even in patients with lymph nodes under 1 cm (cN0 by CT criteria), with the use of EBUS-TBNA, a significant percentage could still be shown to have pN2/pN3 disease (some despite also being negative on CT and PET-CT) [32, 33]. A randomized study evaluated a staging strategy combining endosonography and surgical staging compared with surgical staging alone [34]. Two hundred forty-one patients with potentially resectable NSCLC were randomized to surgical staging alone and to endosonography (EBUS and EUS) followed by surgical staging if negative. Nodal metastases were found in 41 patients (35%) by surgical staging vs. 56 patients (46%) by endosonography ($P = 0.11$) and in 62 patients (50%) by endosonography followed by surgical staging ($P = 0.02$). This corresponded to sensitivities of 79% vs. 85% ($P = 0.47$) and 94%, respectively ($P = 0.02$). Thoracotomy was unnecessary in 21 patients (18%) in the mediastinoscopy group vs. 9 patients (7%) in the endosonography group ($P = 0.02$). The complication rate was similar in both groups [34]. A systematic review performed for the ACCP lung cancer guidelines update of 2756 patients who met inclusion criteria for mediastinal staging with EBUS-TBNA revealed an overall sensitivity rate of 89% with a range from 46% to 97% and a median NPV of 91% [21].

In addition to its role in the diagnosis and staging of lung cancer, EBUS-TBNA has been shown to be a useful diagnostic modality in patients suspected of having lymphoma, metastatic disease to the mediastinal nodes from an extrathoracic cancer, and benign diseases such as sarcoid. Steinfort [35] et al. evaluated 98 patients who underwent EBUS-TBNA for evaluation of isolated mediastinal lymph nodes. Clinicoradiologic features suggested sarcoidosis as the likely diagnosis in 43 patients. In the remaining 55 patients, EBUS-TBNA achieved definitive diagnosis in 42 patients (76%; 95% confidence interval [CI] 55–90). Lymphoma was ultimately diagnosed in 21 of 55 patients (38%). EBUS-TBNA demonstrated lymphoma in 16 (76%) patients; however, in four patients, surgical biopsy was required to completely characterize lymphoma subtypes that were not readily amenable to diagnosis with low-volume specimens. Sensitivity and specificity for definitive diagnosis of lymphoma were 57% (95% CI 37–76) and 100% (95% CI 91–100), respectively [35]. Kennedy [36] et al. demonstrated EBUS-TBNA sensitivity of 90.9%, specificity of 100%, PPV of 100%, and NPV of 92.9% for the diagnosis of lymphoma. In a study by Tournoy et al., 92 patients with extrathoracic malignancies with suspicion of mediastinal or hilar metastases were evaluated with EBUS-TBNA. Mediastinal and hilar metastatic spreads were detected in 52 patients (57%) with a sensitivity and negative predictive value of 85% and 76%, respectively [37]. Garwood et al. [38] demonstrated noncaseating granulomas on EBUS-TBNA in 41 of 48 patients (85%) suspected of having pulmonary sarcoid. Factors affecting the diagnostic yield of

EBUS-TBNA include decreased lymph node size (<5 mm), paratracheal location, airway distortion, and nodal calcification [38].

Endoscopic Ultrasound (EUS)-Guided Needle Aspiration (NA)

The mediastinal lymph nodes that are accessible through EUS include the aortopulmonary (station 5), subcarinal (station 7), paraesophageal (station 8), and inferior pulmonary ligament (station 9) [22, 39]. In a prospective cohort study of 104 patients, EUS-NA detected malignant lymph node involvement with a sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 92, 100, 100, 94, and 97%, respectively [40]. In addition to the mediastinal nodal stations, EUS-NA is particularly well suited to NA of the left adrenal gland and has been shown to frequently alter the staging and management of patients with NSCLC [41]. A major drawback of EUS-NA is the high false-negative rate; therefore, EUS-NA should be performed primarily on patients with radiological evidence of mediastinal lymphadenopathy [22]. Two studies report the combined use of EBUS and EUS to evaluate the mediastinum [42, 43]. For mediastinal staging, EUS provided additional information to EBUS-TBNA in 20 lung cancer patients with enlarged mediastinal lymph nodes or mediastinal lesions [42]. In a larger study of 33 patients for the staging of lung cancer, a total of 119 lesions were sampled by EUS-NA (n = 50) and EBUS-TBNA (n = 60) [43]. When EBUS-TBNA samples were compared with EUS-NA samples, 11 additional cancer diagnoses and three samples with suspicious cells were obtained by EBUS-TBNA that had not been obtained by EUS-NA. Conversely, EUS-NA diagnosed 12 additional cancer diagnoses, one suspicious and one specific benign diagnosis in addition to EBUS-TBNA. With a combined EBUS-EUS approach using a single bronchoscope, the sensitivity for cancer detection can be as high as 96% (EUS 89%, EBUS 91%), specificity 100%, and the negative predictive value 96% (EUS 82%, EBUS 92%) [44]. In an analysis of seven studies with 811 patients, the pooled sensitivity and specificity for combined EBUS-TBNA and EUS-NA were 91% and 100%, respectively, with a median NPV of 96% [21].

Ultrasound-guided needle techniques are minimally invasive and safe techniques with excellent performance characteristics (sensitivity rates of 89%, 89%, and 91% for EBUS-TBNA, EUS-NA, and combined EBUS-TBNA and EUS-NA, respectively) and are currently recommended as the best first diagnostic tools to obtaining tissue in the work-up of lung cancer [21].

Electromagnetic Navigation Bronchoscopy (ENB)

Electromagnetic navigation bronchoscopy (ENB) is a localization device that guides endoscopic tools (forceps, brush, and needle) to preselected locations within the periphery of the bronchial tree, allowing the clinician to biopsy lesions with increased accuracy in areas that are traditionally either inaccessible or associated with low diagnostic yields when compared with traditional unguided or fluoroscopically guided bronchoscopy [15]. ENB has also been used to guide TBNA of peribronchial lymph nodes and placement of fiducial markers for stereotactic radiosurgery. Three companies currently make ENB systems, superDimension (Minneapolis, MN, USA), Veran Medical Technologies (St. Louis, MO, USA), and Broncus (Mountain View, CA, USA). The superDimension system utilizes a locatable guide inserted through a working channel catheter. Once navigation to the lesion(s) in question has been achieved, the locatable guide is removed, and instruments are deployed down the catheter for biopsy or fiducial placement. In a study by Gildea et al. [45], 54 patients with peripheral lesions underwent ENB. The mean lesion size was 23 mm (range, 8–78 mm), and 57% were less than 2 cm in diameter. A definitive diagnosis was made in 40/54 (74%) peripheral lesions and in 31/31 (100%) of the lymph nodes sampled. For all malignant lesions (total 43), 32 (74.4%) were successfully diagnosed by ENB. Pneumothorax occurred in two patients

(3.5%). Eberhardt et al. [46], reported their experience performing ENB biopsy of 92 peripheral lesions in 89 subjects. No fluoroscopy was used. The mean lesion size was 24 mm (range, 10–58 mm). The overall diagnostic yield was 67% and appeared to be independent of size. The sensitivity for malignant disease was only 60%, and the NPV for malignant disease was 44%. The incidence of pneumothorax was 2.3%. Lamprecht [47] et al. studied ENB sampling using rapid on-site evaluation during the procedure, which showed a sensitivity and specificity of 84.6% and 100%, respectively. In a randomized trial using ENB, radial-probe EBUS, and EBUS combined with ENB [48], the authors hypothesized that the use of electromagnetic navigation along with radial-probe EBUS visualization of the peripheral lesion would increase the diagnostic yield. One hundred eighteen patients with peripheral nodules were randomized to EBUS, ENB, or EBUS combined with ENB. The diagnostic yield of 88% obtained by combined ENB and EBUS was superior to the diagnostic yield of either technique alone, 59% and 69%, respectively. More importantly, the NPV for malignant lesions increased from 44% to 75% with the combined use of ENB and a radial-probe EBUS [48]. The Veran system uses tip-tracked instruments via an ultrathin bronchoscope or scope catheter to navigate to peripheral lung lesions for biopsy. In addition, the system allows for electromagnetic navigation-guided transthoracic needle biopsy (EMTTNA) of anterior and lateral peripheral lung lesions. Yarmus et al. recently reported their experience with the system in which they sequentially enrolled 24 patients with peripheral lung nodules without radiographic evidence of lymphadenopathy (N0) for biopsy [49]. All patients underwent EBUS for lung cancer staging followed by ENB and EMTTNA; ROSE was not utilized during the procedures. The combined diagnostic yield of EMTTNA was 83% alone and 87% when ENB was combined with EMTTNA. The addition of EBUS to complete the staging paradigm further increased the diagnostic yield to 92%. Pneumothorax occurred in five patients (21%), of which only two (8%) required chest tube placement [49].

The success of peripheral lung biopsies has long been determined largely by lesion size and location. Lesions typically need to be greater or equal to 8 mm in size. Above this size, the diagnostic yield has depended most upon accessibility from the bronchial tree. Lesions in direct line with a bronchus that is visible on CT are more likely to be successfully biopsied. Lesions in the apical segments of the upper lobe and the superior segments of the lower lobes tend to be more challenging [45–48].

It must be emphasized that the false-negative rate of ENB (closely related to the NPV) is significant. The false-negative rate of transthoracic needle aspiration is in the range of 20–30% [1], and it is probable that this is a similar finding with ENB done without radial EBUS [50]. Thus, in a patient with a suspicious nodule, a negative or nondiagnostic biopsy result on ENB cannot be used to rule out malignancy. While the studies by Eberhardt and Yarmus et al. [48, 49] are encouraging, they have yet to be confirmed by other institutions or in large prospective multicenter trials.

ENB has also been used to place fiducial markers for stereotactic radiosurgery. Anantham et al. [51] placed 39 fiducials via navigation bronchoscopy into nine patients. A 10% migration rate after placement was reported, one patient suffered a chronic obstructive pulmonary disease exacerbation, and there were no instances of pneumothorax. In another study, a combination of ENB and radial EBUS was used to place fiducials in 43 patients. Although 13 of the patients suffered displacement of fiducials (30%), all were able to undergo stereotactic radiosurgery. Only one pneumothorax was seen [52].

Radial-Probe Endobronchial Ultrasound (R-EBUS)

Radial-probe EBUS (R-EBUS) consists of a flexible wire attached to a miniature ultrasound probe containing a rotating crystal tip that provides a 360° image of the surrounding structure. The ultrasound probe can be passed down the working channel of the bronchoscope and deployed

into the lung parenchyma either alone or housed within a guide sheath catheter. In a recent meta-analysis [53] evaluating R-EBUS, the sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio were reported to be 73%, 100%, 27%, and 28% for the diagnosis of lung cancer, respectively. Significant interstudy variation was noted with the EBUS method used. In addition, significant interstudy heterogeneity for sensitivity of malignancy was noted, with prevalence of malignancy, lesion size, and reference standard reported as possible explanations. The rate of pneumothorax was only 1%. The authors concluded that R-EBUS is a safe and relatively accurate tool in the investigation of peripheral pulmonary nodules [53]. Recently, Chen et al. reported their 5-year experience utilizing R-EBUS in 467 cases. Nodules for biopsy were categorized by 1 cm size increments. R-EBUS views were classified as concentric or eccentric depending on lesion location in relation to the tip of the ultrasound probe. Successful identification of the lung nodules occurred in 96% of cases with an overall diagnostic yield of 69%. Diagnostic yield when comparing concentric vs. eccentric views was 84% vs. 48% ($p < 0.0001$) and 72% vs. 70% ($p > 0.05$) when comparing the use of a guide sheath to an ultrathin bronchoscope. The pneumothorax rate was 2.8% with a chest tube required in 1.5% [54].

Memoli et al. conducted a meta-analysis [55] to determine the overall diagnostic yield of several guided bronchoscopic techniques (electromagnetic navigation bronchoscopy (ENB), virtual bronchoscopy (VB), radial-probe endobronchial ultrasound (R-EBUS), ultrathin bronchoscope, and guide sheath) developed to improve the yield of transbronchial biopsy (TBBx) for diagnosing pulmonary nodules (PN). A total of 3052 lesions from 39 studies were included. The pooled diagnostic yield of guided bronchoscopic techniques was 70%, higher than the yield for traditional TBBx. The yield increased as the lesion size increased. The pneumothorax rate was only 1.6%, which is significantly smaller than the 15% reported for TTNA. The meta-analysis showed that the diagnostic yield of guided bronchoscopic techniques is better than traditional TBBx, and although the yield remains lower than TTNA (reported diagnostic yield of TTNA is 90%), the procedural risk is lower. Guided bronchoscopy may be an alternative or be complementary to TTNA for tissue sampling of PN [55].

Pathologic Evaluation of Bronchoscopy Specimens

Adequacy of Samples Obtained During Bronchoscopic Procedures

After ultrasound scanning of the mediastinum and hilum is performed to identify accessible lymph nodes/lesions, the needle aspiration of the lymph node(s) is performed under real-time ultrasound visualization. The stylet found within the needle bore is left in place during puncture of the airway wall and then agitated in an up-and-down motion to remove debris and minimize bronchial wall contamination of the TBNA sample. Suction can then be applied while the needle samples the target lesion. While the use of suction is reported to improve cellularity of the specimen, it is also associated with potential blood contamination of the specimen and has not been shown to increase the diagnostic yield [56]. After being deployed, the needle is passed to and fro within the target lesion/lymph node between 10 and 20 times. The needle is then retracted, and the specimen can be given to a cytopathologist/technologist for ROSE or prepared by the bronchoscopy team for subsequent analysis.

The number of needle passes required for optimal diagnostic yield when employing conventional TBNA and EBUS-TBNA has previously been reported as three to five passes per lymph node station, respectively [57, 58]. While we know that in order to perform additional molecular analysis a sufficient number and concentration of tumor cells are needed, the number of needle passes needed by EBUS-TBNA to provide adequate tissue for molecular analysis remains unknown. Indirectly answering the question of how many needle passes are required to obtain the tissue needed is that EBUS-TBNA

with three passes has been shown to provide adequate samples for the molecular analysis of adenocarcinoma and NSCLC-NOS tumor markers in over 95% of patients [59–62]. The optimal utilization of cytologic fine-needle aspirates in order to render the subtype of lung cancer and to perform molecular analysis is critical and may also depend on collaboration between the cytopathologist/technologist and the bronchoscopist.

The question of needle size and diagnostic yield has also been evaluated with a recent large multicentered retrospective study finding no significant difference in diagnostic yield between the 21 and 22 gauge needles for EBUS [63]. While the current literature does not provide evidence of a difference in diagnostic yield between available EBUS-TBNA needle sizes, a retrospective study did note superior cellular quality of specimens harvested using the 21 gauge needle [64]. Because the volume of tumor cells in needle aspirates may be small resulting in insufficient material for molecular analysis, it is recommended that material obtained from needle aspirates should be preserved as cell blocks, so that tumor is archived for immunohistochemical and molecular studies [65].

Mutation and Fusion Gene Analysis and PD-L1 Expression Status

It is currently recommended that all adenocarcinomas be tested for KRAS and EGFR mutations, regardless of age, gender, or ethnicity. Extended panels of gene mutations can be performed to include such potential targets as BRAF, HER2, MET, and MEK1. A current testing algorithm uses the mutual exclusivity of KRAS with the other common mutations. As the presence of a KRAS mutation is the most common and effectively rules out ALK and EGFR mutations, KRAS has been recommended to be the first-line test in a molecular analysis of NSCLC. If negative, subsequent testing of EGFR and ALK is recommended [66]. It should be noted, however, that the recent International Association for the Study of Lung Cancer (IASLC) guidelines recommend testing both EGFR and EML4-ALK simultaneously and that testing occurs at the time of the initial diagnostic procedure. Furthermore, it is recommended that the turnaround time from sampling to results be 5–10 working days and, perhaps most importantly, that the pulmonologist work with their oncology and pathology colleagues to define a multidisciplinary plan that can be implemented at their institution for which patients get which test [66].

Despite studies showing EBUS-TBNA equivalence and even potential superiority to more invasive surgical techniques, a common misconception is that specimens obtained during EBUS-TBNA are generally not sufficient to perform molecular analyses because of inadequate cellularity. It is reported, however, that cellularity in the order of 100–500 cells is sufficient for DNA sequencing assays and 100 tumor cell nuclei are sufficient for fluorescent in situ hybridization (FISH) technique [5, 6, 65]. With the recent advances in molecular profiling of lung cancer and the expansion of targetable mutations, novel diagnostic tests and subsequent therapies have emerged that require additional tissue for sample analysis [67]. Multiple publications have since shown EBUS-TBNA to be more than adequate in the acquisition of tissue for molecular analysis. Mohamed et al. [68] investigated the feasibility of EBUS-TBNA for obtaining tissue samples from mediastinal lymph nodes for immunohistochemical (IHC) analysis and noted that immunostaining was feasible in all studied specimens. In a study by Nakajima et al. [69], histologic cores of lymph node samples obtained from 30 patients with lymph node metastases diagnosed by EBUS underwent DNA extraction, bisulfate modification, and methylation status of a panel of six genes using methylation-specific polymerase chain reaction (PCR). Methylation status could be assessed in all of the samples obtained [69]. Schuurbiers [70] et al. concluded that molecular testing of EGFR and KRAS on cytologic material obtained by EBUS-TBNA is feasible and could be performed on 77% of their specimens. Another study by Smouse [71] et al. showed that 67% of cytology specimens were adequate for molecular testing with some of the samples having as little as 25% tumor cellularity. Arcila et al. [72] noted

that 79% of cytology specimens and 89% of small biopsy specimens submitted for molecular testing were sufficiently cellular. The rate of EGFR and KRAS mutations detected in cytologic specimens in the study was comparable to the rate detected in surgical specimens [72].

In a study of 46 patients with metastatic NSCLC to mediastinal lymph nodes, samples obtained via EBUS-TBNA were analyzed for EGFR mutations using a loop-hybrid mobility shift assay, PCR, and direct sequencing [73]. EGFR mutations were found and confirmed in 25.6% of 43 cases eligible for analysis. In a recent published trial, EGFR gene analysis of EBUS-TBNA samples was technically feasible in 26 out of the 36 (72.2%) patients with lymph node metastasis [74]. In a study of DNA sequencing for EGFR and KRAS mutations performed on 209 cytologic specimens (99 EBUS, 67 TTNA, 27 body fluid, and 10 image-guided FNA), from patients with lung cancer [60], the overall specimen insufficiency was quite low at 6.2%. For EBUS specimens, the insufficiency rate was 4% and 3.7% for body fluid cases. EGFR mutations were detected in 34 of 175 specimens (19.4%) of NSCLC with a significantly higher frequency in adenocarcinoma (29%). KRAS mutations were detected in 23.6% of NSCLCs with no statistical differences between adenocarcinoma and non-adenocarcinoma. The results support clinical utilization of routinely prepared cytology specimens [60]. A recent prospective analysis in the United Kingdom of 410 consecutive patients referred for EBUS-TBNA analyzed the diagnostic yield of TBNA samples collected with 21 or 22 gauge needles and prepared as histopathologic samples. Ninety-one samples were confirmed to be lung adenocarcinoma, and 80 of these were sent for EGFR mutation testing. EGFR mutation testing was possible in 79/80 cases (98.7%). ALK gene analysis was successfully performed in 21/21 samples (100%). The combined genotyping success rate was 100/101 (99%). The needle gauge did not affect the genotyping efficacy, and ROSE was not utilized [75]. To determine the feasibility of detecting ALK fusion genes in samples obtained by EBUS-TBNA, 109 cases with hilar/mediastinal lymph node metastases detected by EBUS-TBNA were analyzed through IHC, fluorescence in situ hybridization (FISH), and PCR [76]. IHC revealed ALK positivity in seven cases (6.4%), all of which showed the fusion gene by FISH and PCR. Multigene mutation analysis can be performed in EBUS-TBNA samples of metastatic lymph nodes from NSCLC patients, and in a recent study, genetic alterations (EGFR, KRAS, p53) were analyzed in metastatic hilar or mediastinal lymph nodes sampled by EBUS-TBNA in 156 patients [62]. All samples could be evaluated for EGFR mutations, with 42 mutations found. Of the remaining samples, 4/113 and 47/113 had KRAS and p53 mutations, respectively.

Immunotherapy for the treatment of advanced lung cancer is rapidly evolving. In 2015, the Food and Drug Administration (FDA) approved the PD-1/PD-L1 inhibitor pembrolizumab to treat patients with advanced NSCLC whose tumors express the PD-L1 protein based on IHC analysis [13]. PD-L1 expression status was evaluated by IHC staining of an anti-PD-L1 antibody in 100 specimens collected by EBUS-TBNA. Among 100 samples, 14 contained 100–999 cells, 61 contained 1000–9999 cells, and 23 specimens contained more than 10,000 cells. Ninety-six of the 100 samples were suitable for PD-L1 expression testing [77].

Rapid On-Site Evaluation of TBNA Samples

Despite its apparent utility, the use of ROSE with TBNA remains controversial. Two prospective randomized trials failed to show a diagnostic benefit with the use of ROSE during conventional TBNA but did show a decrease in procedure-related complications due to a decreased need to sample the parenchymal lung lesion [78, 79]. In a study of 827 needle aspirates, Papanicolaou-based rapid stain prepared by a technician and read by a cytopathologist was compared to the Wright-Giemsa rapid stain prepared and read by a cytopathologist [57]. False-negative aspirates were more frequent in the Wright-Giemsa stain compared to the Papanicolaou stain (14.2% vs.

7.3%, respectively, $p = 0.008$). Studies have shown that ROSE increases the diagnostic yield of non-bronchoscopic and extrathoracic FNA [80, 81] and its utility in increasing the diagnostic yield by 25–46% of TBNA for peripheral lung lesions has similarly been documented in non-randomized controlled trials [23, 82]. In evaluating EBUS-TBNA, ROSE has been shown to help provide accurate and sensitive methodologies for the diagnosis and staging of lung cancer [83]. Recently, Trisolini et al. published data supporting the use of ROSE during EBUS-TBNA to optimize tissue collection for cancer genotyping. They reported that ROSE prevented the need for repeat sampling for additional tissue collection solely for molecular profiling in at least 1 out of 10 patients with advanced non-squamous cell lung cancer [78].

Specimen Preparation

Material obtained by EBUS-TBNA can be prepared using air-dried and wet-fixed methods. TBNA material is extruded through the needle, and a small amount of material is placed on a glass slide. This is followed by either repeatedly flushing the needle into saline or an alcohol-based preservative for later centrifugation and/or creation of a cell block using the tissue coagulum clot cell block (TCC-CB) method [84, 85]. It is important to note that if lymphoma is suspected, the material should not be placed in alcohol, as flow cytometry will not be able to be performed. The air-dried slides are stained using the Diff-Quik method, while wet-fixed slides are immersed in 95% alcohol and stained by Papanicolaou method in a cytology laboratory. When ROSE is employed, an immediate assessment is given to the bronchoscopist after each needle puncture into the lymph node. If rapid on-site evaluation reveals diagnostic material, the remaining material from additional aspirations is processed for cell block [84]. Once diagnostic material is seen, additional passes are performed, processed, and reviewed until the cytotechnologist reports that the material present in the coagulum contains an estimated tumor burden of over 25% [86, 87]. If the evaluation does not reveal tumor, a minimum of three needle passes into the lymph node at each station is recommended [58].

Preparation of the tissue coagulum clot cell block is performed by gently extruding the material within the cytology needle using the wire stylet onto a precut filter paper with the needle tip directed in a tight circular motion to build up a coagulum of tissue and blood mixture [84]. The tissue coagulum is then fixed in formalin and processed in a histology laboratory to prepare the cell block. Paraffin sections of tumors in 4–5 μm sections are then mounted on glass slides and reviewed by a pathologist to confirm a diagnosis of NSCLC; once confirmed, the specimens can be sent for molecular testing.

Treece et al. [88] have recently reported a third method of acquiring tissue for molecular analysis. Recognizing that insufficient or poor quality cell block material leads to an inability to perform molecular analysis, they analyzed FNA smears and touch preparations for EGFR and KRAS using next-generation sequencing of primary and metastatic lung adenocarcinoma. They reported that FNA smears were able to be sequenced in all cases and were concordant with previous clinical testing of the samples.

Conclusion

Traditionally, lung cancer had been classified as SCLC or NSCLC, and treatment decisions were based on this differentiation. We now appreciate that NSCLCs are heterogeneous tumors that respond to different therapeutic agents based on histologic phenotypes and molecular characteristics. Advancement in the understanding of the molecular heterogeneity of this disease resulted in the development of new therapeutic regimens and paradigm shifts in the treatment of advanced NSCLC. We are now in the era of personalized therapy, one that has yielded improved response rates and survival in selected patients. Our job as clinicians trained to perform diagnostic procedures is to recognize the importance of accurate tissue acquisition so that distinct histologic diagnosis and molecular characterization are performed on every patient with lung cancer.

We have at our disposal an array of diagnostic tools, and we must make every effort to ensure that the right test and the right studies on the tissue obtained are performed in each of our patients. Our task is often difficult as we have newer, less invasive procedure such as EBUS-TBNA, which means that fine-needle aspirations for cytologic specimens are usually the primary means of diagnosis. There is ample evidence however that even with needle aspirates of lung lesions or lymph nodes, accurate molecular and histologic subtyping can be achieved. As we move forward with research and expand our knowledge of lung cancer, multidisciplinary thoracic oncology teams will play an even more important role to ensure state of the art care of all lung cancer patients.

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Lung Cancer Screening

19

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Introduction

Lung cancer remains the most common cause of cancer-related deaths in the USA and worldwide. An estimated 220,000 new cases are diagnosed, while nearly 160,000 patients die from lung cancer each year in the USA alone, accounting for more cancer-related deaths than the next three most common cancers combined: colon, breast, and prostate [1, 2]. In spite of the major advances achieved in lung cancer diagnosis, medical and surgical treatment, and palliative care, the overall 5-year survival for lung cancer has not noticeably changed over the past 20 years and is estimated around 16% [3]. These dismal statistics compare poorly with those of other common cancers such as colon, breast, and prostate cancers characterized by 5-year survival rates of 65%, 88%, and 99%, respectively. Among the many potential explanations advanced to explain such differences, the lack of effective screening for lung cancer is often contrasted to what are generally assumed and accepted screening strategies for those other malignancies. Lung cancer is in the majority of cases diagnosed at advanced stages, as symptoms prompt patients to seek medical attention, when curative therapeutic options are at best limited.

The high case fatality rate of lung cancer, its relatively high prevalence, a tendency to primarily affect easily identifiable "at-risk" individuals, and a prolonged preclinical phase are characteristics that should theoretically position lung cancer as an ideal candidate for some type of screening [4]. Indeed, the published results of a large randomized controlled trial, the National Lung Screening Trial (NLST), suggest that in a closely defined high-risk population, annual screening with low-dose high-resolution chest computed tomography (LDCT) results in a 20% relative reduction in lung cancer mortality [5]. Based on these results, the US Preventive Services Task Force (USPSTF), American Thoracic Society (ATS), and American College of Chest Physicians all recommend annual lung cancer screening for carefully selected patients [6, 7]. This shift to actively screen for early-stage lung cancer undeniably represents the most significant advance in lung cancer research achieved over the past 20 years and should inform future recommendations for lung cancer screening. However, many unanswered questions need to be addressed as this screening strategy is implemented across the community. A consistent finding in all studies on LDCT as a screening tool for lung cancer is the excessive number of "false-positive" studies. Additionally two smaller major

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LDCT screening studies failed to demonstrate a mortality benefit in the intervention group [8, 9]. This highlights the need for further research aimed at defining appropriate management strategies for screen-detected lung nodules, a substantial proportion of which will likely require the diagnostic tools available to most interventional pulmonologists. While many of these questions will most certainly be addressed by further analysis of the NLST data and screening registries in the years to come, important insight can be gained from considering previous studies on lung cancer screening that paved the way to the NLST and from understanding the biases inherent in screening that are systematically introduced and affect the significance of their results.

Early Attempts at Screening: Chest Radiography and Sputum Cytology

Chest radiography is an appealing option for lung cancer: it is simple, inexpensive, available to most medical providers, and only exposes patients to a small amount of radiation (0.1 mSv, the equivalent of 10 days of background radiation). While some would argue that the effectiveness of chest X-rays (CXR) for lung cancer screening remains to be clarified, most experts agree that the available evidence argues against it. In the early 1970s, the National Cancer Institute (NCI) sponsored three large randomized controlled trials designed to address the value of frequent sputum cytology screening (every 4 months for 6 years) in addition to the historically "accepted" screening strategy consisting of an annual CXR [10–12]. Both the Johns Hopkins Lung Project and the Memorial Sloan Kettering Lung Project enrolled approximately 10,000 subjects each and showed no difference in lung cancer mortality between experimental and control arms.

The third study, the Mayo Lung Project (MLP), was slightly different in that patients were randomized after an initial round of screening by CXR in an attempt to exclude prevalent cancers. Furthermore, the value of intense CXR screening in addition to sputum cytology (every 4 months for 6 years) was compared "routine care" which at the time consisted of a rather loose recommendation for annual CXR for at-risk patients [10]. A total of 9211 subjects were randomized, with 206 patients diagnosed with lung cancer in the experimental arm vs. 160 in the control arm. The 5-year survival rate clearly favored more intense screening, estimated at 35% vs. 15% for the control arm, consistent with historical estimates for lung cancer. However, lung cancer-specific mortality was not significantly different between the experimental and control arms, estimated at 3.2/1000 person-years and 3.0/1000 person-years, respectively.

Furthermore, long-term data of the MLP with a median follow-up of 20.5 years confirmed the absence of lung cancer mortality benefit [13]. While substantial limitations of the MLP have been described in detail, this study was arguably the most influential in informing healthcare policies and in providing evidence against CXR for lung cancer screening.

Among the reported limitations of the study are the poor compliance in the experimental arm (approximately 75%) and a relatively frequent CXR screening in the control arm, the exclusion of lung cancer patients after the initial screening round (so that all patients underwent by design some screening), and the fact that intense screening with CXR was addressed rather than annual CXR screening. Nonetheless, CXR screening was largely abandoned based on these data. It is important to realize that several case-control studies have conversely added support for CXR screening [14–18] and that the equipoise provided the rationale for yet another NCI-funded study exploring the role of CXR in lung cancer screening among other screening interventions, the prostate, lung, colorectal, and ovarian cancer trial (PLCO), the results of which were recently published and support abandoning CXR for the purpose of lung cancer screening [19].

Survival Is a Tricky Endpoint in Screening Studies

The apparent contradiction between survival and mortality observed in the abovementioned studies deserves further comments. Screening

systematically introduces a number of biases that need to be considered as one tried to make sense of the available data. The heated debate that has surrounded lung cancer screening and provided the scientific rationale for the NLST, which will likely remain one of the largest and most expensive screening studies ever performed (53,454 subjects and more than 200 million US dollars), has largely revolved around the concepts of lead time and length time biases and, possibly, overdiagnosis [20]. While the former (lead time and length time biases) are universally accepted as potential confounders in lung cancer screening, the concept of overdiagnosis in lung cancer remains a source of intense controversy.

While a comprehensive review of this topic is clearly beyond the scope of this chapter, a brief description is helpful in order to understand some of the questions raised by the NLST. The self-evident purpose of screening is to detect cancer before it becomes apparent. The interval of time between a screening diagnosis and a clinical diagnosis (when symptoms prompt clinical investigations) is called lead time. The inclusion of lead time will therefore prolong survival from the time of diagnosis in the absence of any therapeutic interventions, which could be misinterpreted as benefit of screening, i.e., lead time bias (see Fig. 19.1). The concept of length time bias relies on the premise that not all lung cancers are "created equal." Some lung cancers are biologically more aggressive than others, as clearly shown for lung cancer by varying volume-doubling times on imaging studies. Hence, a screening strategy consisting of regular screens at regular intervals of time is more likely to intercept more indolent cancers than the most aggressive ones that may elude screening (i.e., interval cancers; see Fig. 19.2). Hence, if survival associated with screening is based on a population of cancers in which indolent tumors are overrepresented, it will also appear falsely prolonged, the so-called length time bias. An extreme form of length time bias is overdiagnosis, which simply represents the bias introduced when screening identifies cancers that would never have become clinically apparent, a concept that has been well described in other cancers such as prostate or thyroid cancers but remains highly controversial in lung cancer. What is less controversial is the observation that subjects at risk for lung cancer are also at risk for a host of

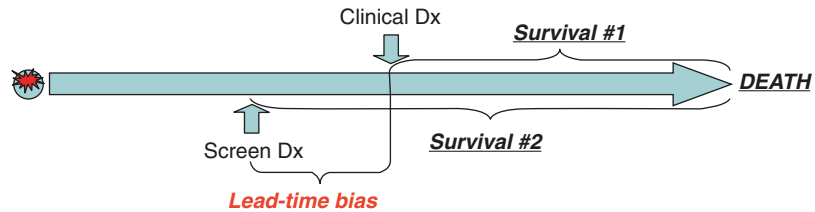

Fig. 19.1 Lead time represents the interval of time between screen detection and symptom-driven detection of cancer

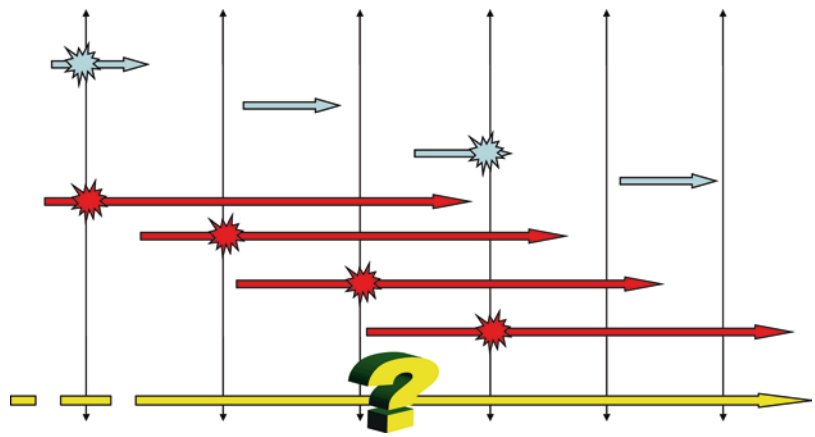

Fig. 19.2 Length time bias is introduced by the propensity of screening to identify cancers (*red*) more indolent than their clinically detected counterparts (*blue*). Overdiagnosis (*yellow*) is an extreme form of length time bias and is due to cancers detected by screening that never would have become apparent otherwise

other potentially life-threatening conditions (such as cardiovascular diseases or emphysema) and that indolent lung cancers may in some cases be of little clinical significance for patients more likely to die from these other conditions (see Fig. 19.2). For obvious reasons, length time bias and overdiagnosis are more likely present when considering the first round of screening, as a significant proportion of these indolent cancers should be intercepted and excluded from further rounds of screening.

These concepts emphasize the importance of considering mortality as an endpoint rather than survival in lung cancer screening; this will be discussed further in a following chapter (limitations of LDCT screening for lung cancer; see below).

Low-Dose Computed Tomography: The Way of the Future?

Conventional chest radiographs have a poor sensitivity for lung cancer when compared to high-resolution computed tomography (HRCT), particularly with early lung cancers. The probability of identifying stage I lung cancer with CXR has been estimated around 16%. The use of HRCT for the screening of lung cancer has long been hampered by the excessively stringent technical requirements of HRCT (acquisition times of several minutes with multiple breath holds using single-row detector machines) and the amount of cumulative radiation exposing patients to possible long-term risks of secondary malignancy (7 mSv, the equivalent of 2 years of background radiation). Low-dose computed tomography, however, has a sensitivity for lung nodules similar to that of conventional HRCT, but with a fraction of the radiation (1.5 mSv, equivalent to 6 months of background radiation). In addition, multi-row detector CT scans now allow full chest scans in less than 15 s with a single breath hold.

Numerous single-arm noncontrolled observational prospective studies using LDCT for lung cancer screening have been performed to date and have been reviewed elsewhere [21]. These studies have consistently reported a high detection rate of lung cancer at early stages, with excellent curability and survival rates. One of the most influential studies in that regard combined the results of the Early Lung Cancer Action Project (ELCAP) initiated in 1993 with those of the International Early Lung Cancer Action Project (I-ELCAP), an ongoing multicenter collaborative effort distributed across North America, Europe, Israel, and East Asia [22]. A total of 31,567 asymptomatic subjects at risk for lung cancer (including a minority of non-smokers at risk from occupational exposure or secondhand smoke) were screened from 1993 to 2005. A clearly defined protocol was made available to participating centers to guide the management of screen-detected lung abnormalities. A total of 484 subjects were diagnosed with lung cancer based on positive screening LDCT. The vast majority of these subjects (412 subjects, 85%) had clinical stage I lung cancer (77% were pathologic stage I), and the estimated 10-year survival for these patients was 88% and 92% for those undergoing surgical treatment within 1 month of diagnosis. The actual median follow-up was 40 months. It is noteworthy that 84% of these 412 subjects had lung cancer diagnosed on the first screening round (i.e., prevalent cancer) and that the vast majority of these cancers belonged to the adenocarcinoma spectrum of the disease (71%), a subset of lung cancer known to include more indolent tumors than in other cell types. Nonetheless, these encouraging results were in line with previously reported similar, though smaller in size, observational noncontrolled studies and supported the notion that LDCT may indeed represent an attractive strategy for lung cancer screening.

Another influential report published shortly after the I-ELCAP study reached apparently opposite conclusions. Using two validated lung cancer prediction models, Bach and colleagues collated the results of three other single-arm observational prospective studies on LDCT screening for lung cancer and compared overall lung cancer diagnoses, lung cancer surgical resections, advanced lung cancer diagnoses, and lung cancer deaths observed in these studies to what could have been expected in the same

population in the absence of screening [23]. Similar to what had previously been described in the CXR studies, more lung cancers were identified (three times more) leading to ten times more surgical resections, but the numbers of advanced lung cancers and lung cancer deaths were not significantly different. Limitations of this study included a relatively short follow-up (median 3.9 years), a relatively wide 95% confidence interval (allowing for up to a 30% relative reduction in lung cancer mortality), and the reliance of prediction models rather than true control groups. This study suggested that overdiagnosis may indeed be a potential limitation of LDCT screening and that at least some of the screen-detected lung cancers could be fundamentally different than their clinically detected counterparts. If anything, these results reemphasized the importance of waiting for the long-anticipated NLST results before considering profound changes in recommendation for lung cancer screening.

Interestingly, another prediction model-based study using the Mayo LDCT screening trial data based on a different prediction model, the Lung Cancer Policy Model, reached conclusions very similar to those observed in the NLST [24]. This model differed from those used in the previous study in that it simulated survival based on individual disease characteristics, explicitly modeled benign disease, and, perhaps more importantly, incorporated competing causes of death, an important consideration as described above. Using the screening regimen used in the Mayo LDCT screening trial (five annual LDCT), the predicted relative reduction in lung cancer mortality was 28% at 6 years (number needed to screen to save one patient from lung cancer, or NNS = 205), while the relative reduction in overall mortality, including lung cancer mortality, was 3.6% at 6 years (NNS = 262). The discrepancy between lung cancer and overall mortality was attributed to the frequent coexistence of severe comorbidities, potentially lessening the impact of lung cancer screening in a population at risk not only for lung cancer but also for a host of other life-threatening conditions.

Two contemporary studies to the NLST—the Detection and Screening of Early Lung Cancer by Novel Imaging Technology (DANTE) and the Danish Lung Cancer Screening Trial (DLCST)—did not show a mortality benefit to lung cancer screening. The DANTE trial included subjects aged 60–74 years old with a 20 pack-year smoking history or more with 10 years or less since smoking cessation. The DLCST had the same tobacco exposure with age limited to 50–70 years old—with subjects having less tobacco exposure than those enrolled in the NLST. Still, significantly more stage I lung cancers were detected in the screening arm of the DANTE trial with 47 versus 16 cancers over the 5-year period. Similarly, significantly more early-stage lung cancers (stage Ia–IIb) were detected in the screening arm of the DLCST, 48 versus 21 over their 8-year follow-up period, raising the concern of lead time bias. Each trial has substantially less power to detect a mortality benefit with a cumulative of 6554 subjects between the two trials compared with the 53,454 subjects in the NLST. There is hope to pool multiple smaller European trials to better understand the benefits of LDCT screening for high-risk patients [8, 9].

The National Lung Screening Trial

The NLST was a large randomized controlled trial that enrolled 53,454 subjects at high risk for lung cancer at 33 US medical centers [5]. At-risk subjects were defined as being between 55 and 74 years of age with a significant smoking history (30 pack-years, having quit less than 15 years prior to enrollment for former smokers). Subjects were randomized to an experimental arm consisting of three annual screening LDCT or a control arm, consisting of three annual screening CXR, with a median follow-up of 6.5 years. The rationale for using CXR in the control group rather than the "standard of care" (i.e., no screening) was that the yet-to-be-released results of the PLCO could potentially show some benefit of CXR screening, in which case a study comparing LDCT to no screening would have been of lesser value.

A positive LDCT scan consisted of lung nodules of 4 mm or more (adenopathy or pleural

effusion could also be considered a positive result), while any visible nodule or mass on CXR was considered positive. Overall, LDCT yielded positive results in 24.2% of cases, while CXR was considered suspicious for lung cancer in 6.9% of cases. A total of 1060 lung cancers were diagnosed in the LDCT group, 649 of which were diagnosed after a positive screening. In the CXR group, 941 cancers were diagnosed, 279 of which were identified after a positive CXR screen. Early-stage lung cancers were more frequent after a positive screening test, in both the LDCT and CXR groups. Stages I and II represented 70% of LDCT-detected lung cancers. Perhaps more importantly, stage IV lung cancers were less frequent in the LDCT than in the CXR group, supporting real stage shift, a sine qua non attribute of effective screening.

A total of 356 lung cancer-related deaths were observed in the LDCT group vs. 443 in the CXR group, representing a 20% relative reduction in lung cancer-specific mortality (NNS = 1/320). A statistically significant relative reduction in overall mortality of 6.7% (including lung cancer mortality) was also observed. Contrary to the explanation advanced in the Lung Cancer Policy Model study described above, the calculated NNS for overall mortality is only 220. While the significance of this observation deserves further study, one possible explanation is that LDCT may have additional health benefits that remain to be characterized.

While no clear guidelines for management of suspicious lesions detected on LDCT or CXR were provided to participating centers, the frequency of invasive investigations was low, most of the follow-up consisting of further imaging studies, and the complications from invasive investigations or surgery were rare (1.4% with at least one complication in the LDCT group and 1.6% in the CXR group). A total of 16 patients died within 60 days of an invasive procedure, six of whom did not have evidence of lung cancer. Bronchoscopy was performed in 76 of the 649 lung cancers identified by LDCT, resulting in four deaths, and 227 of the 17,053 subjects without lung cancer but abnormal LDCT, also resulting in four deaths.

This arguably represents the most significant advance in lung cancer management achieved over the past 20 years, and LDCT screening is being implemented in clinical practice based on these results with slight modifications from both the USPSTF and Medicare in terms of screening window and reimbursement [6, 7]. Clearly, LDCT screening allows for at least some clinically relevant lung cancers to be identified and treated earlier, resulting in significant improvement in mortality. However, a number of problems and unanswered questions will need to be addressed before the full benefits of LDCT screening may be appreciated.

Implementation of Lung Cancer Screening

For the reasons outlined above, the USPSTF formally recommended lung cancer screening in high-risk individuals in the late 2013. Based on modeling, they expanded the age criteria from that studied in the NLST to reach from ages 55 to 80 years old. The ATS/ACCP guidelines adhere strictly to the NLST criteria. The USPSTF recommends annual LDCT screening based on the NLST inclusion criteria: current or former smokers within 15 years of cessation aged 55–80 years old with a minimum of 30 pack-year tobacco exposure. Recommendations to cease screening include 15 years or more of tobacco abstinence for ages greater than 80 years old or inability to benefit from definitive therapy for lung cancer. The USPSTF expanded the upper limit of age eligibility based on modeling data, and Medicare has settled in between, reimbursing lung cancer screening for appropriately selected patients aged 55–77 years old [7].

The NLST depicts the theoretical “best-case” scenario of lung cancer screening, conducted mostly at major academic centers with multidisciplinary approaches to lung cancer and expertise in both thoracic radiology and oncology. Given that the preferred definitive management is thoracic surgery, access to this specialty will be essential to ensure the mortality benefit seen in the NLST [25]. There is concern that widespread

implementation of LDCT screening across the community may not realize the same mortality benefit seen in the NLST. For these reasons, the ATS and ACCP released a joint statement outlining guidelines for implementation of a "quality" lung cancer screening program, many of which may become needed metrics for reimbursement: specifically a need for structured radiology reporting, a registry of screened patients, counseling regarding smoking cessation, and practitioners' ability to adequately discuss the risks and benefits of lung cancer screening.

Practical concerns exist regarding cost-effectiveness and the ability to best target the patient population. The NLST included a higher proportion of former smokers with higher education status than seen in the general population of current smokers in the USA [26]. Current US smokers are more likely to be less educated, report poorer health status, and not have access to regular medical care. Additionally, current smokers tended to adopt a more fatalistic attitude toward lung cancer screening [27]. This raises logistic challenges regarding how to best reach and counsel the high-risk group in which screening is being implemented.

The psychological effects of lung cancer screening are unknown including the impact on mental health of incidental findings as well as the impact on tobacco use; however, the data available suggest that without clear communication between ordering providers and patients, there is the real possibility for psychological distress on behalf of the patient [28]. With 39.1% of patients in the NLST experiencing at least one positive screen, the psychological burden of screening will need attention [5].

Limitations of Screening with Low-Dose Computed Tomography and Clinical Implications

The relative reduction in lung cancer-specific mortality of 20% reported in the NLST is a compelling argument for integrating LDCT in a screening program for lung cancer, particularly when contrasted with existing mass screening programs such as mammogram for breast cancer, associated with conservative estimates for number needed to screen 1/2500 (vs. 1/320 in the NLST) [29]. A number of important questions not directly answered by the NLST will however need to be addressed as LDCT screening is adopted on a larger scale. These include the questions of cost-effectiveness, the high frequency of false-positive studies, the persistent question of overdiagnosis, and the long-term risk of exposure to ionizing radiations. The question of false-positive management and overdiagnosis will be discussed here.

The frequency of false-positive studies observed in the NLST was high in both LDCT and CXR (control) groups, respectively, 96.4% and 94.5%. This was an expected finding as this high frequency of abnormal LDCT scans in high-risk individuals has been a consistent finding in the majority of previous LDCT studies. Prior observational single-arm noncontrolled studies on LDCT have reported screen-detected lung nodules in 5–51% of the cases [30]. Randomized controlled trials, including the NLST, have yielded similar results. The rate of false-positive studies appears to be a direct correlation of LDCT slice thickness (collimation), with more nodules detected with thinner slices. In addition, one needs to consider that some investigators (including the NLST investigators) have decided to call nodules <4 or 5 mm negative studies in order to limit false-positives but thereby also increasing the number of false-negatives [5, 22].

The vast majority of these nodules eventually prove benign (96.4% in the NLST). This raises understandable concern for the applicability of this strategy at a population level in the absence of validated and standardized management strategy aimed at keeping unneeded invasive interventions to a minimum. As previously noted, unnecessary invasive interventions were rare in the NLST, as appropriate imaging follow-up was recommended for the majority of screen-detected lung nodules. Indeed, only 671 bronchoscopies were performed after positive LDCT screening result in the three screening rounds, as well as only 322 percutaneous

examinations/biopsies and 713 surgical procedures (mediastinoscopy, thoracoscopy, or thoracotomy). Mortality within 60 days of an invasive procedure was very low in patients without confirmed lung cancer, with only six deaths. The NLST data on nodule size is unavailable, but considering prior studies, these observations can easily be understood. In the Mayo LDCT screening trial, 3356 nodules were identified over a 5-year period in 1520 participants with only 68 cancers eventually confirmed, representing 98% false-positive studies. Only 284 (8%) of these nodules were >8 mm in size and therefore realistically amenable to some type of invasive diagnostic procedure, the vast majority only requiring additional follow-up [31, 32].

Approximately eight million Americans fit the strict NLST inclusion criteria, more into the USPSTF criteria. This would translate into approximately 200,000 bronchoscopies if we assume that similar management strategies would be applied, more if screening was extended to other populations at risk for lung cancer. However, participants in the NLST were enrolled in large academic tertiary centers with significant expertise in the management of lung nodules, and it is possible that less-experienced providers would recommend more aggressive approaches, resulting in significantly more invasive procedures and consequently more complications. Interventional pulmonologists are likely to become actively involved in the management of screen-detected pulmonary nodules. An understanding of the limitations of LDCT screening will be crucial to extend our role beyond that of proceduralists to inform and discuss appropriate management strategies with referring providers and carefully select appropriate candidates for more invasive procedures.

This issue is further complicated by the concept that LDCT-screen-detected lung cancers are likely to include a subset of tumors more indolent than their clinically detected counterparts. Studies analyzing volume-doubling times (VDT) of screen-detected lung cancers show a wider distribution of VDT than either clinically identified or CXR-screen-detected lung cancer, with an average doubling time exceeding 400 days, a usual threshold beyond which lung cancers are assumed to be of limited clinical relevance [33]. The Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON) trial is an ongoing large trial of LDCT screening in Europe that may help address this concern. Their group is using VDT categories to determine their nodule follow-up [34].

Currently, there is an estimated 18.5% rate of overdiagnosis in the screening arm of the NLST. This translates into 1.4 cases of indolent lung cancer per death prevented [35]. Clinically relevant lung cancers are, however, detected by LDCT screening, as confirmed by the positive results of the NLST, arguing against a strictly bipartite model of the natural history of lung cancer previously described. A bipartite model of lung cancer suggests that all or most screen-detected lung cancers are biologically different than clinically detected ones and likely overdiagnosed [36, 37]. This contrasts sharply with the other extreme position that all histologically proven lung cancers are likely to become clinically relevant and should be aggressively managed. The truth likely lies somewhere in the middle, but if not all LDCT-screen-detected lung cancers need surgical resection, evidence-based strategies aimed at stratifying screen-detected lung cancers in order to recommend optimal management will need to be developed and validated. Computer-aided detection systems show promise to reduce false-positive rates; however, there is insufficient evidence at this point to recommend any one system, and further research is needed in this field to determine how this technology can aid in selecting which patients are most likely to benefit from further invasive testing [38]. This latter point would be of even more significance if lung cancer screening is offered by providers less experienced than those involved in the NLST.

These more indolent tumors typically belong to the adenocarcinoma spectrum of disease. The classification of lung adenocarcinoma is based on the concept that specific histologic criteria

appear to be accurate predictors of biological behavior [39]. Higher percentage of lepidic growth (neoplastic growth that respects the underlying lung architecture) and limited invasion (≤5 mm in greatest dimension) correlates well with indolent behavior. By definition, this assessment implies resection of the tumor and cannot be made on limited biopsies obtained either bronchoscopically or via percutaneous cytology sampling or biopsy. The corollary to this observation is that noninvasive methods of assessment of underlying histology and future behavior are needed and currently lacking and that the role of interventional pulmonologists is in that regard limited by the size of biopsies achievable by bronchoscopic techniques.

Conclusion

Interventional pulmonologists are likely to become significantly more involved with the management of lung nodules now that LDCT screening is endorsed by major professional societies and recommended for subjects at risk for lung cancer. In order to move the field beyond that of a strictly proceduralist service, the limitations and questions raised by the recently published NLST results need to be understood and studied further. Interventional pulmonologists have to seize the opportunity to contribute scientifically to the development of optimal strategies for the diagnostic management of screen-detected lung nodules and continue to be actively communicating with referring physicians in order to provide guidance on the possibilities and limitations of available diagnostic tools. Major advances in bronchoscopic techniques have been achieved over the past decade which has led to an ever-increasing diagnostic yield, but the landscape of lung cancer is also rapidly evolving, and interventional pulmonologists should strive to remain at the forefront of the ongoing debate surrounding lung cancer screening. Only then may we be regarded not only as skilled proceduralists but also as valuable partners in the necessary multidisciplinary approach to lung cancer screening.

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Lung Cancer Epidemiologic Changes: Implications in Diagnosis and Therapy

20

Philip Ong and David Ost

Introduction

Despite significant progress in diagnosis and treatment, lung cancer remains a disease with significant economic and health burdens. Globally, the latest data from the WHO World Cancer Report indicate that there were an estimated 1.8 million lung cancer deaths (20% of total cancer deaths) in 2012, making it the leading cause of cancer death in men in 87 countries and women in 26 countries [1].

In the United States, lung cancer represents 13% of all new cancer cases, second only to prostate cancer in men and breast cancer in women (Fig. 20.1). It is the number one cause of cancer death in the country and accounts for 27% of all cancer deaths in males and 26% in females [2].

Thus, lung cancer is an entity that represents a formidable challenge. To understand the development of this epidemic, this chapter will review the evolution of the epidemiology of lung cancer in the context of the history of the tobacco epidemic. In relation to this, a review of the temporal changes in the geographic distribution and histologic changes will be made as well. Lastly, a brief overview of lung cancer in never-smokers and an overview of the clinically relevant mutations will be provided.

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History

A description of the current epidemiology of lung cancer would not be complete without a discussion of the complicated relationship between the history of tobacco smoking and the epidemiology of the disease. Today, the causative relationship between tobacco smoking and lung cancer is universally accepted. However, a review of history reveals that the relationship between the smoking and lung cancer was not easily established.

Given the magnitude of the health problem that is lung cancer today, it may be surprising to note that as recent as 100 years ago, lung cancer was considered an extremely rare disease that warranted reporting. In the mid-1850s, medical texts [3] considered the lungs "less prone than most other organs to cancerous disease." A review done at the Institute of Pathology of the University of Dresden in Germany in 1878 [4] showed that cancers of the lung represented only 1% of all cancers seen at autopsy. In 1912, Adler [5] published a book entitled *Primary Malignant Growths of the Lungs and Bronchi* where he reviewed the reports of major hospitals in the United States and Western Europe and verified only 374 cases of lung cancer, constituting less than 0.5% of autopsied cancer cases.

Cigarette smoking, on the other hand, only became popular at the turn of the twentieth century. At that time, cigarettes were hand rolled and

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Estimated New Cases

Males				Females		
Prostate	180,890	21%		Breast	246,660	29%
Lung & bronchus	117,920	14%		Lung & bronchus	106,470	13%
Colon & rectum	70,820	8%		Colon & rectum	63,670	8%
Urinary bladder	58,950	7%		Uterine corpus	60,050	7%
Melanoma of the skin	46,870	6%		Thyroid	49,350	6%
Non-Hodgkin lymphoma	40,170	5%		Non-Hodgkin lymphoma	32,410	4%
Kidney & renal pelvis	39,650	5%		Melanoma of the skin	29,510	3%
Oral cavity & pharynx	34,780	4%		Leukemia	26,050	3%
Leukemia	34,090	4%		Pancreas	25,400	3%
Liver & intrahepatic bile duct	28,410	3%		Kidney & renal pelvis	23,050	3%
All Sites	**841,390**	**100%**		**All Sites**	**843,820**	**100%**

Estimated Deaths

Males				Females		
Lung & bronchus	85,920	27%		Lung & bronchus	72,160	26%
Prostate	26,120	8%		Breast	40,450	14%
Colon & rectum	26,020	8%		Colon & rectum	23,170	8%
Pancreas	21,450	7%		Pancreas	20,330	7%
Liver & intrahepatic bile duct	18,280	6%		Ovary	14,240	5%
Leukemia	14,130	4%		Uterine corpus	10,470	4%
Esophagus	12,720	4%		Leukemia	10,270	4%
Urinary bladder	11,820	4%		Liver & intrahepatic bile duct	8,890	3%
Non-Hodgkin lymphoma	11,520	4%		Non-Hodgkin lymphoma	8,630	3%
Brain & other nervous system	9,440	3%		Brain & other nervous system	6,610	2%
All Sites	**314,290**	**100%**		**All Sites**	**281,400**	**100%**

Fig. 20.1 Ten leading cancer types for the estimated new cancer cases and deaths by sex, United States, 2016. Estimates are rounded to the nearest 10 and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. From: Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66(1):7–30

expensive, which limited their popularity. This changed significantly with the introduction of machines to mass produce cigarettes in 1876 [4]. Cigarettes were routinely distributed to soldiers in World War I and were considered part of their essential provisions during the wartime period [6].

The ensuing decades were marked by rapidly increasing incidence rates in lung cancer in men and later women. The increasing incidence of lung malignancies was of concern in the 1930s; however, its connection to cigarette smoking took time to establish. Early studies in 1923 [7] and 1929 [8] had posited the connection between lung cancer and cigarette smoking but failed to garner interest. The 1930 edition of the influential *Springer Handbook of Special Pathology* noted that lung malignancies had begun to increase in incidence at the turn of the century and accelerated after World War I and were still on the rise. Although a multitude of other putative etiologies were mentioned (air pollution, automobile traffic, the 1918 influenza epidemic, and even exposure to gas in World War I), smoking was only briefly mentioned as a "possibility." It was pointed out that there were as many investigations that failed to show an association between smoking and lung cancer as there were positive studies [4].

In 1950, landmark studies were published by Wynder and Graham [9] in the *Journal of the American Medical Association* and by Doll and

Hill [10] in the *British Medical Journal*. Both were case control studies involving more than 600 patients each, revealing that smokers comprised 98.7 and 99.7% of those who developed cancer in their reports, respectively.

Despite this, smoking continued to be popular well into the 1950s and was considered fashionable at that time. In movies of the era, it was common to note that actors smoked and, at medical meetings, most doctors were smoking [5]. Physicians could be seen advocating smoking in tobacco advertisements, and the claims by the tobacco industry went unchallenged [6]. The incidence of tobacco use reached its peak at this time despite the mounting evidence of harm.

It was not until 1964 that a landmark publication by the US Surgeon General categorically stated that smoking was harmful. The public was then encouraged to not take up the habit or to quit [11]. This resulted in a decline in the rate of smoking, with a decrease in lung cancer rates 20 years later [6]. The annual US per capita cigarette consumption among adults 18 years of age or older rose from almost 0 in the early 1900s to more than 4000 in the 1960s, before declining to 1700 in 2006, a level not seen since 1935 [12].

Lung cancer incidence trends follow that of tobacco, except that there is a roughly 20-year lag, so that changes in tobacco use result in changes in lung cancer incidence approximately 20 years later. However, while tobacco use is declining in the developed world, tobacco use is increasing in developing countries.

Trends in Lung Cancer Incidence and Survival

Because of the high case fatality rate of lung cancer, incidence and mortality rates are nearly equivalent [13]. Due to advocacy for tobacco cessation that started since the US Surgeon General's report in 1964 [11], the incidence of lung cancer in most countries in the developed world has started to decline in the past decade.

In the United States, lung cancer incidence can be readily obtained from the National Program of Cancer Registries (NPCR) of the US Centers for Disease Control (CDC) and the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program [14]. Data from SEER 9 (1975–2013) show that the age-adjusted incidence rate of lung cancer increased from 52.2/100,000 in 1975 to a peak of 69.8/100,000 in 1991. The latest rate is now 53.2/100,000 in 2013 (Fig. 20.2). After a general trend of increasing 2.5% per year from 1975 to 1991, incidence rates are now decreasing at a rate of 2.4% per year since 2007 (Fig. 20.3). Age-adjusted lung cancer incidence rates in males peaked and started to decline consistently since 1984, but in females, the peak occurred later, plateauing in 1992–2009, and only started to decline at a slower rate starting in 2010 (Fig. 20.4). Tobacco use rates in women peaked at a later time than in men, which is thought to account for the difference in the trends in lung cancer incidence [15].

In Europe, lung cancer incidence rates were estimated using available national rates for 2012 [16]. Available data suggest that the highest rates were seen in Hungary and lowest in Cyprus. In men, the incidence was highest in Central and Eastern European countries (Serbia, Hungary, Macedonia, and Poland) and lowest in Northern European countries (Finland and Sweden). The reverse was seen in women, with higher rates in Northern Europe and lower rates in Eastern Europe. Lung cancer, however, is still the leading cause of cancer death in Europe in 2012 [16]. Incidence and mortality rates in men are decreasing particularly in Northern and Western European countries, while rates in Central and Eastern Europe remain high and are showing signs of stabilization or decline [17]. Rates in women are still largely increasing in Europe [17], but there are signs that this may be stabilizing.

At the start of the lung cancer epidemic, the highest incidence rates were found in Europe and the United States, with the lowest rates found primarily in South America and Asia [6]. However, the epidemic in the developing world is just unfolding, and the geographic pattern is rapidly changing. The figures in developing countries are thought to be underestimated as many go undiagnosed or unreported in areas

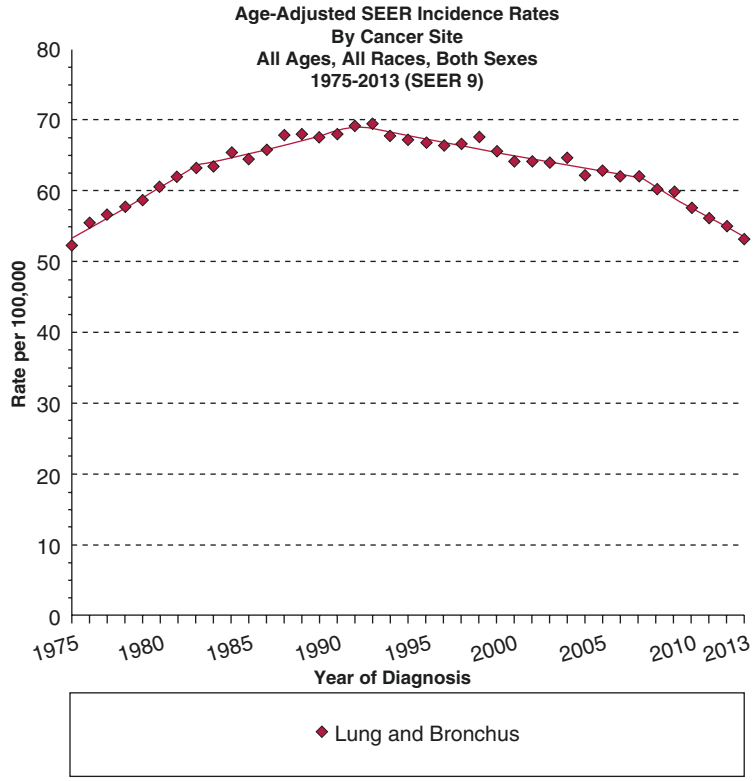

Fig. 20.2 Cancer sites include invasive cases only unless otherwise noted. Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups—Census P25–1130). Regression lines are calculated using the Joinpoint Regression Program Version 4.2.0, April 2015, National Cancer Institute. Incidence source: SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta). *Source:* NCI-SEER 9. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) Research Data (1973–2013), National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2016, based on the November 2015 submission

where healthcare is not available [18, 19]. The International Agency for Research on Cancer (IARC) reports that as of 2012, the estimated age-standardized incidence rate is now high in both Central and Eastern Europe (53.5/100,000) and East Asia (50.4/100,000) [20]. Notably lower incidence rates are seen in Africa (Fig. 20.5).

An important case study of the current epidemiologic trends in lung cancer in the developing world is China. It is estimated that 67% of the male population is smoking in China, which is equivalent to the highest rate ever seen in the United States [19, 21]. It is estimated that one third of the world's smokers reside in China [21]. In 2000, the age-standardized incidence rate in China was 35.2/100,000. That rate increased to 46/100,000 by 2010 [22]. China contains 19% of the world population, with 36% of all newly diagnosed lung cancer cases and 38% of lung cancer deaths worldwide [20]. There is data to suggest that high lung cancer mortality rates among Chinese women may not be associated with the high prevalence of cigarette smoking. Exposure to other risk factors such as indoor air pollution from cooking fumes is theorized to be a significant contributor [23]. The burden of the tobacco epidemic in China exemplifies the shift in the global burden of lung cancer from high-income Western countries to low- and middle-income countries, particularly in Asia [13]. In 2008, newly diagnosed lung cancers in developing countries (884,5000) exceeded the number in developed countries (724,300) by 22% [23].

The survival rate for lung cancer has improved in the past few decades, albeit slowly. The 5-year survival rate for lung cancer in the United States was 12.3% in 1978 to 1977, which has increased to 17.7% in 2006–2012 [24]. However, this varies widely depending on the stage of diagnosis, from 55.2%, to 28%, to 4.3% for localized, regional, and distant disease, respectively [24]. Based on the SEER 18 data (2006–2012) [24], 57% of patients present with

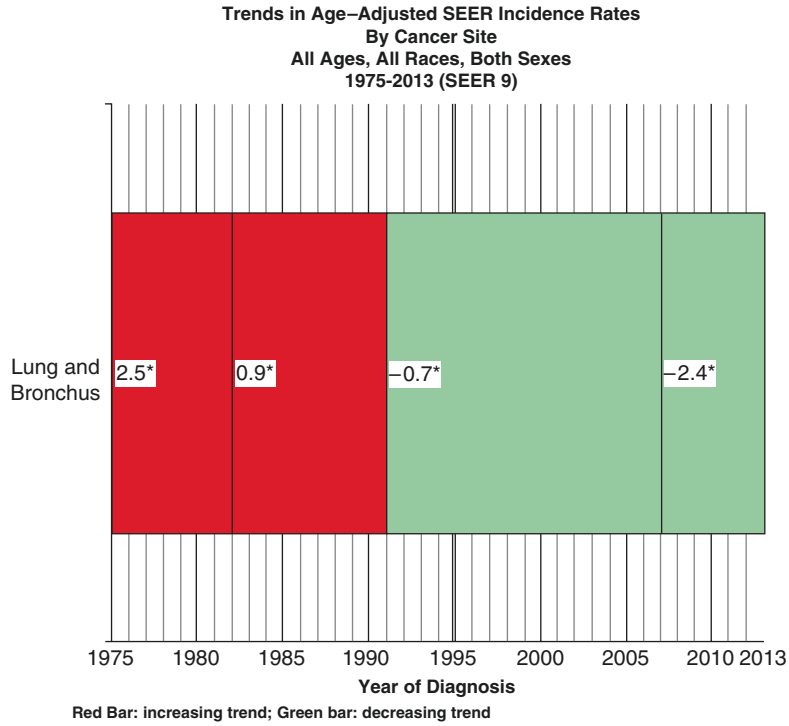

Fig. 20.3 Cancer sites include invasive cases only unless otherwise noted. The APC is the Annual Percent Change based on rates age-adjusted to the 2000 US Std Population (19 age groups—Census P25–1130). The APCs were calculated using the Joinpoint Regression Program Version 4.2.0, April 2015, National Cancer Institute (http://surveillance.cancer.gov/joinpoint/). *The APC is statistically significant from zero ($p < .05$). Incidence source: SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta). *Source:* NCI Seer 9. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) Research Data (1973–2013), National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2016, based on the November 2015 submission

distant/metastatic disease, 22% with regional disease, and 16% with localized disease. Undoubtedly, stage at presentation influences overall mortality significantly. It is uncertain at this time whether the advent of low-dose computed tomographic screening will change these rates [25].

Based on the above data, it is clear that the epidemiologic trends in lung cancer incidence are intimately related to tobacco use rates. Histologic patterns have also changed dramatically during this time as smoking patterns and cigarettes have changed. The next section explores this further.

Histopathologic Trends and Their Implications

Four types of lung cancer account for more than 90% of lung cancer cases in the United States: [26] adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and small cell carcinoma. These are traditionally identified by histologic appearance. However, there has been a concerted effort in the scientific community to revise the classification system using molecular markers that may convey clinically meaningful and prognostic information [27, 28]. At this time, however, epidemiologic studies still use histologic classification.

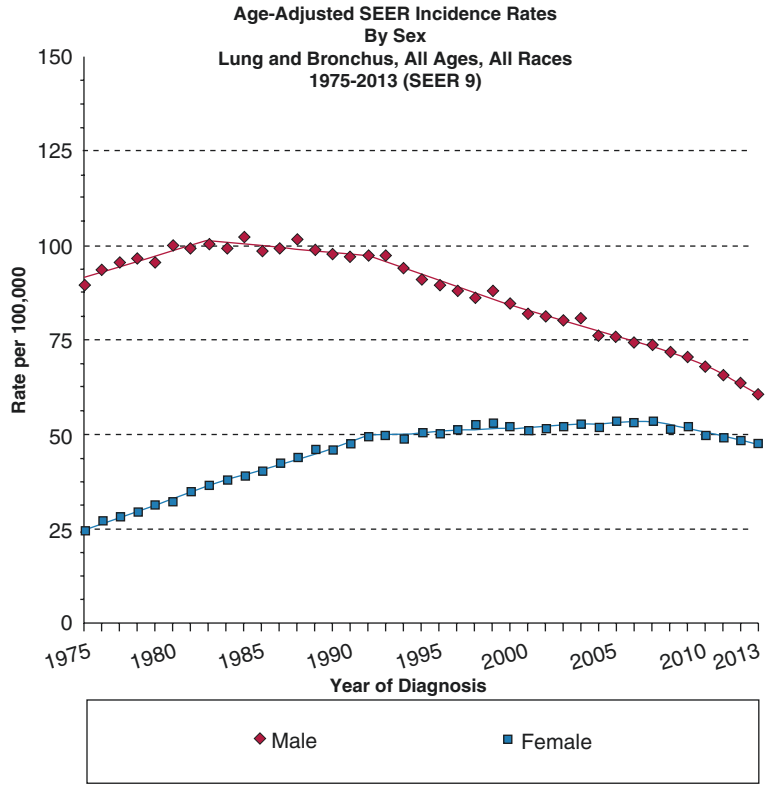

Fig. 20.4 Cancer sites include invasive cases only unless otherwise noted. Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups—Census P25–1130). Regression lines are calculated using the Joinpoint Regression Program Version 4.2.0, April 2015, National Cancer Institute. Incidence source: SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta). *Source:* NCI Seer 9. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) Research Data (1973–2013), National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2016, based on the November 2015 submission

All four histologic subtypes mentioned above are associated with tobacco exposure. However, the relative risk (RR) associated with tobacco exposure may vary significantly depending on the subtype. The relative risk of smoking has been noted to be higher for squamous cell carcinoma (RR 10–50) than for adenocarcinoma (RR 2–15) [29–31]. The decline in risk after smoking cessation has been less consistent for adenocarcinoma [32] than for squamous cell, small cell, or large cell carcinoma, which may have implications for future histologic trends of lung cancer.

In the United States, squamous cell carcinoma was historically the most common type of lung carcinoma in the United States until the 1970s. Since the 1970s, adenocarcinoma has become more common [33]. Adenocarcinomas are now the most common histologic type of lung cancer in both men and women [34]. Age-specific histologic rates by year of birth show strong birth cohort effects. Rates for squamous cell carcinoma were higher among cohorts born earlier (e.g., 1930s), while rates for adenocarcinoma are higher among those born more recently [35].

The changes in histologic trends have been theorized to be largely due to the composition and usage pattern of tobacco products. When cigarettes were first introduced, they were largely unfiltered. The smoke composition discouraged deep inhalation, thereby exposing the trachea and the proximal bronchi to a greater degree, producing more squamous cell carcinomas [12]. Filters were later introduced, enabling smaller particles to be inhaled deeper into the respiratory tract, which may predispose to adenocarcinomas [12]. Changes in the formulation of cigarettes have also resulted in lower amounts of tar being released but a higher concentration of nitrosamines. These compounds have been found to induce lung adenocarcinomas in an animal model [36, 37]. Such changes in the design and formulation of cigarettes over time may in part explain some of the observed variability in histology and location of tumors observed over time in the population.

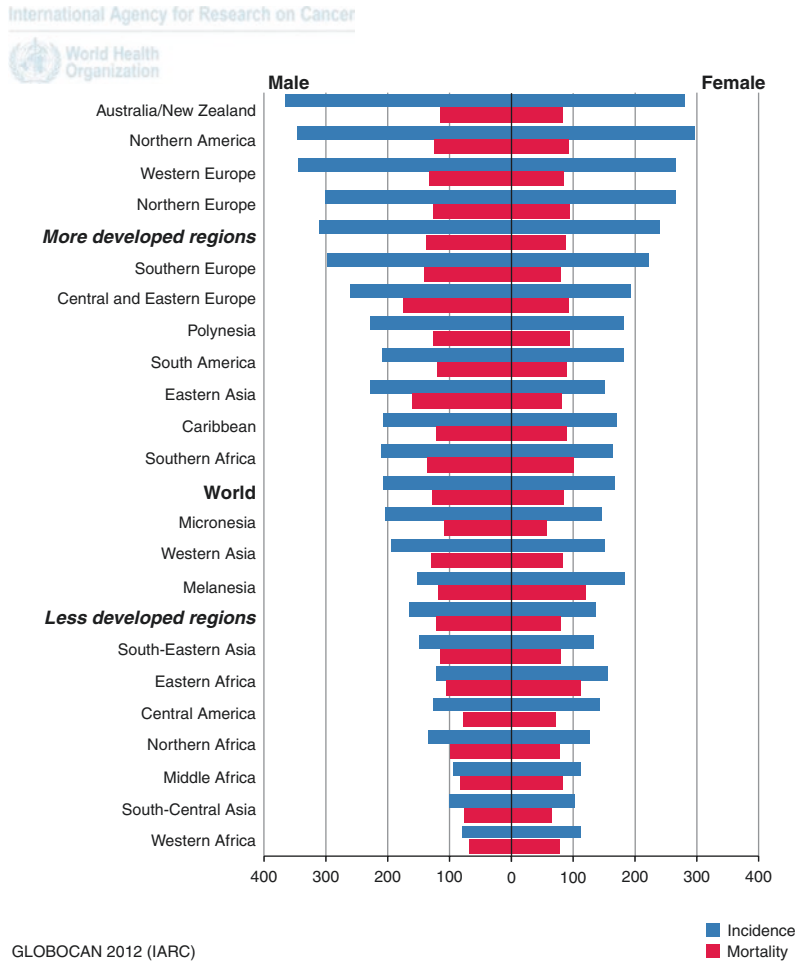

Fig. 20.5 Estimated age-standardized rates (World) per 100,000. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on 5/11/2016

Lung Cancer in Nonsmokers

As tobacco use in the developed world declines, it is also important to consider factors associated with lung cancer in never-smokers. While the majority (80–90%) of all lung cancer deaths in the United States are caused by cigarette smoking [13], the remaining 10–15% represent between 17,000 and 26,000 deaths per year [38]. This number would rank among the seven to nine most common fatal cancers in the United States if these deaths were considered a separate category. This is comparable to the number of deaths due to myeloma in men and cervical cancer in women [13]. Thus, the number of lung cancer deaths in never-smokers is not insignificant.

Data regarding the incidence of lung cancer in never-smokers is difficult to obtain, but has been reviewed [39]. In a review of lung cancer incidence and death rates from 13 large cohort studies representing over 630,000 subjects, the age-standardized incidence rates of lung cancer among never-smokers varied widely by more than 30-fold between countries. Low incidence rates were seen among women in Africa (Algeria and Mali) and India. Incidence rates were also low in the Basque region of Spain (<9 cases/100,000). High incidence rates were seen in the Philippines (30.9/100,000) and Thailand (87.8/100,000) [39]. Among never-smokers, lung cancer incidence rates were higher and more variable among women in East Asia. Exposure to indoor air pollution such as coal smoke [40], volatile oils from cooking at high temperatures

[41], and exposure to secondhand smoke [42] have been theorized to be contributing factors.

Since the early 1990s, the question of whether women are more susceptible to develop lung cancer than men has been debated [38]. Early case control studies found higher odds ratios in women than in men with putatively comparable levels of smoking [43, 44]. However, these reports were not replicated by large prospective trials that measured lung cancer mortality rates [45, 46].

More recently identification of somatic mutations in the epidermal growth factor receptor (EGFR) in NSCLC has facilitated target therapy for these tumors. What is notable is that these tumors have been found to be more common in specific populations in nonsmokers, women, and Asians. So the biology of tumors, as reflected by their mutation status, may be different in nonsmokers than in smokers.

Epidemiology of Clinically Relevant Mutations in NSCLC

Genetic mutations that are key components of oncogenesis have been identified in small subsets of non-small cell lung cancers (NSCLC). Two have been validated as reliable targets for selective pathway-directed systemic therapy [47]. These genetic mutations have epidemiologic and histologic patterns which will be the focus of this section. The impact of mutational profiling on personalized medicine will be discussed in the next chapter.

The presence of activating epidermal growth factor receptor (EGFR) mutations is predictive for the response to the EGFR tyrosine kinase inhibitors (TKIs), such as gefitinib, erlotinib, and afatinib [48]. In a review of over 2000 NSCLC cases [49, 50], EGFR mutations were found to be more common in those with adenocarcinoma histology (30% vs. 2%, $p < 0.001$), never-smokers (45% vs. 7%, $p < 0.001$), east Asians (33% vs. 6%, $p < 0.001$), and females (38% vs. 10% $p < 0.001$) [49] (Fig. 20.6a, b).

The presence of anaplastic lymphoma kinase (ALK) fusion oncogenes is predictive of the response to the inhibitor of the ALK tyrosine kinase, crizotinib [51]. ALK gene rearrangements are present in 4% of patients with adenocarcinomas [52] and are mutually exclusive with mutation in EGFR or KRAS [53]. Kwak et al. [51] screened samples from approximately 1500 patients with NSCLC for the presence of ALK rearrangements and identified 82 patients. In their cohort, patients with the ALK rearrangement had a mean age of 51 years, with the majority of them being never smokers (76%). ALK-positive tumors overwhelmingly tended to be adenocarcinomas (96%). In a separate review [54] of 141 NSCLC tumor specimens screened for mutations, patients with ALK-mutant NSCLC were significantly

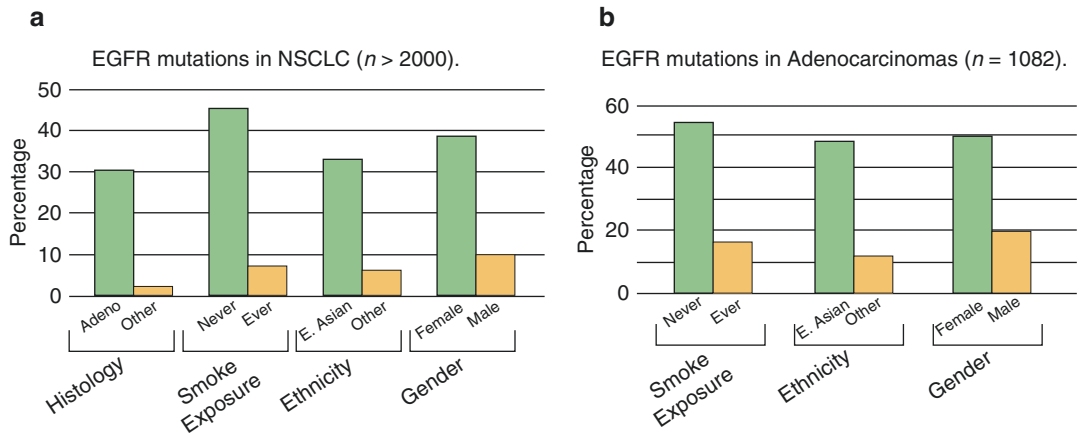

Fig. 20.6 (**a**, **b**) Proportion of EGFR mutations in different demographic groups. Shigematsu H, Gazdar AF. Somatic mutations of epidermal growth factor receptor signaling pathway in lung cancers. Int J Cancer 2006;118(2):257–62

younger (52 years vs. 66 years, $p < 0.001$) and more likely to be men (58% vs. 26%, $p = 0.036$) than those with EGFR mutations.

Other targets for applying systemic molecular-based approaches (such as BRAF, ROS1, HER2, and RET) are currently under evaluation [48, 55].

Given the globally increasing proportion of adenocarcinoma, the targeting of these mutations as part of the therapy of patients with lung cancer will be important. The American College of Pathologists, the International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology published recommendations regarding molecular testing of patients with NSCLC [56]. Although specific demographic and clinical characteristics have been found to be associated with the presence of EGFR or ALK mutations, they have been deemed insufficiently specific to be used to select individual patients for treatment with a targeted inhibitor. EGFR and ALK testing is now recommended for all adenocarcinomas and mixed lung cancers with an adenocarcinoma component regardless of histologic grade. Further discussion regarding personalized treatment of lung cancer will be discussed in the next chapter.

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Personalized Lung Cancer Treatment: A Teamwork

21

Silvia Quadrelli and Marco Solís

Introduction

Lung cancer accounts for 20% of all cancer deaths. Its global incidence is estimated in 1.83 million cases [1].

Most of these cases will be non-small cell lung cancer (NSCLC). Seventy-five percent of them will be unresectable at diagnosis, due to locally advanced or metastatic disease [2].

Even when the 5-year survival rate is still poor (around 15%), the recent identification of targetable oncogenic drivers and the development of oral targeted therapies have dramatically changed the understanding and management of NSCLC.

A few decades ago, no effective treatment was available for most patients with advanced disease. Only during the 1970s, the relevance of identifying non-small cell lung cancer versus small cell lung cancer (SCLC) was established. In the late 1980s, cisplatin, combined with a second drug, showed to improve survival, and this scheme became the first-line treatment in advanced NSCLC. Research in the following years demonstrated modest but significant improvements in survival of advanced NSCLC patients [3].

In the last decade, the development of molecular classification of lung cancer (particularly adenocarcinoma) and the consequent treatment of lung cancer with the use of targeted agents improved survival significantly. Currently, at least seven tyrosine kinase inhibitors (TKIs) are used as therapy for the treatment of advanced lung adenocarcinomas with specific genomic alterations in the epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and ROS proto-oncogene 1 (ROS1). Consequently, current standards of care for the treatment of NSCLC recommend therapy based on histological and epidermal EGFR and ALK status. These treatments in selected patients have shown significant benefits in quality of life (QoL) and clinical evolution [4].

The goal in patients with advanced disease is to obtain all the necessary information for correct classification and treatment selection and, at the same time, minimize the use of invasive techniques. As a result of this new scenario, small biopsy specimens are becoming key diagnostic tools. The availability of more precise staging techniques has meant a significant decrease in the number of futile thoracotomies. It means that a small biopsy and/or cytology sample will be enough for diagnosis for almost 80% of the

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patients who need treatment for advanced diagnosis [5].

These developments (and the refinement of techniques such as immunohistochemistry or fluorescent in situ hybridization) require (1) proper diagnostic specimens for the selection of treatment and (2) a multidisciplinary team including a pathologist and a radiologist.

In the current era of personalized treatment, only teamwork can optimize the yield of pulmonary diagnostic procedures. We will describe the markers of current diagnostic and therapeutic relevance, the justification for the acquisition of specific histologic and molecular data, and the basis of an institutional multidisciplinary team who can guarantee optimal cytological and histologic samples for appropriate molecular diagnosis.

Tumor Histology as a Biomarker in NSCLC

A few years ago, all NSCLC patients were treated without considering histologic subtype. Squamous cell carcinoma and adenocarcinoma are the major histologic subtypes of NSCLC with an increased prevalence of the latter in the past decades. Routine use of immunohistochemistry (IHC) is standard of care for samples (20–30%) that cannot be morphologically characterized [6]. IHC may be performed in any small sample (bronchoscopy or even transthoracic aspiration) from which formalin-fixed, paraffin-embedded tissue slides can be obtained.

The poor prognostic factor of squamous histology has been described in several retrospective and prospective studies [7]. More recent research has shown that drugs such as bevacizumab and pemetrexed have different safety and activity profile in patients with squamous cell versus nonsquamous cell carcinoma. Bevacizumab [8] has proved to be effective but shows higher levels of toxicity (hemorrhage) in patients with squamous histology, and consequently, current Food and Drug Administration (FDA) approval is restricted to the treatment of patients with nonsquamous histology. On the other hand, Scagliotti and colleagues [9] have demonstrated the efficacy of pemetrexed in nonsquamous NSCLC patients. Squamous histology has thus become a useful biomarker to exclude patients from unsuitable therapies. Thus, the acquisition of adequate samples for the histologic subtyping of NSCLC has become a mandatory component of lung cancer management [8].

The Rationale of Molecular Testing of NSCLC: Genetic Markers of Current Clinical Relevance

The major advance in the treatment of NSCLC at the beginning of the twenty-first century was the discovery that specific genetic alterations define subsets of NSCLC [10]. Research showed that Asian nonsmoking females with adenocarcinoma responded better to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), such as erlotinib or gefitinib, than non-Asian male smokers [11]. The sequencing of tumor samples from responding patients in clinical trials of TKIs led to the finding that the presence of EGFR mutations was responsible for the higher benefit associated with EGFR-TKI therapy. Several clinical trials demonstrated that patients with EGFR mutations had improved progression-free survival (PFS) and overall survival (OS) when treated with TKIs compared with standard of care chemotherapy [12]. The convergence of those clinical trials and the development of genetic sequencing have permitted the evolution of therapies specifically targeted to certain biomarkers, allowing for the selection of patients who will receive a higher clinical benefit (Fig. 21.1).

Epidermal Growth Factor Receptor (EGFR) Gene Mutations as a Biomarker

The EGFR is a 170-kDa plasma membrane glycoprotein composed by an extracellular region, a single transmembrane domain, and an intracellular

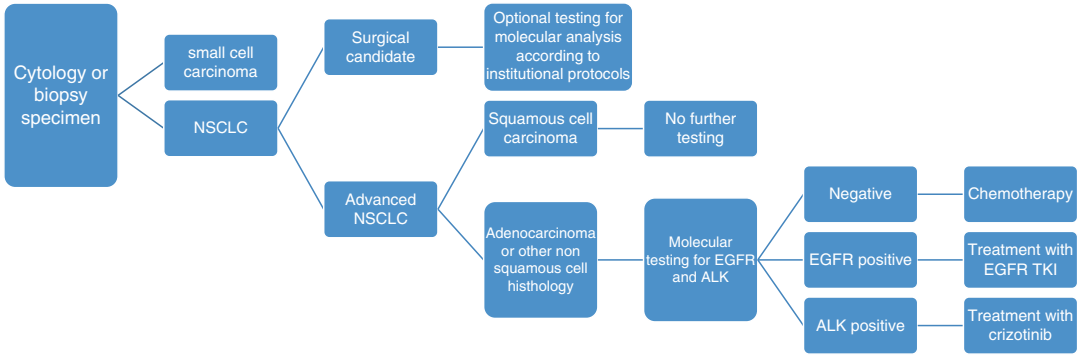

Fig. 21.1 Decision making algorithm for small samples

domain with tyrosine kinase activity and a C-terminal tail. Activation of the EGFR receptor via phosphorylation produces downstream signals to the phosphatidylinositol 3-kinase (PI3K)/AKT and RAS/RAF/mitogen-activated protein kinase (MAPK) pathways, which are responsible for the normal regulation of cellular proliferation and apoptosis. These intracellular signaling pathways are modified by neoplastic cells with EGFR mutations [13].

The Asia-Pacific patients with NSCLC adenocarcinoma (ADC) subgroup had the highest EGFR mutation frequency at 47%. EGFR-mutated lung cancers represent around 15–20% of all lung ADCs diagnosed in the United States [14], 6–41% in Europe (mean 15%) [15], and 36% (range 14–51%) [16] in Latin America, where there is important heterogeneity.

In the Caucasian population, a mutation of the EGFR gene is more frequent in patients with adenocarcinoma NSCLC with an acinar or papillary pattern (found in 27% of patients); the mucinous adenocarcinoma is usually negative.

Beyond the unequivocal influence of Asian ethnicity, prevalence of EGFR in different ethnic groups is unclear. Some studies have shown no significant difference in EGFR mutation rates between African-American (19%) and white patients (13%), while others suggest a lower frequency of EGFR in African-Americans [17]. Worldwide literature shows that EGFR mutation frequency in lung adenocarcinoma is higher in women than men and in never-smokers versus smokers (66% vs. 22%) [18].

However, the substantial lack of data from several geographic regions of the world (mainly Africa, Middle East, Central Asia, and Central America) and ethnic subgroups limits interpretation.

EGFR 6 (also known as HER-1 or Erb1) belongs to the ErbB receptor tyrosine kinase (RTK) family. This group also includes HER-2/neu (ErbB2), HER-3 (ErbB3), and HER-4 (ErbB4). These transmembrane receptor tyrosine kinases involved in signal transduction pathways regulate proliferation and apoptosis. Known EGFR mutations have been detected in the tyrosine kinase domain of the EGFR gene, which spans exons 18–24. Most mutations are deletions of exon 19 that affect a three-amino acid (LRE) sequence or a point mutation L858R on exon 21 [19]. On the other hand, mutations affecting exon 20, mainly small insertions in T790M (that explain 3–5% of all EGFR mutations), are related with primary resistance to EGFR TKIs. In contrast to the reported higher response rates, better quality of life (QoL), and longer PFS in the whole group of EGFR-mutated ADC compared to wild-type subgroup, a retrospective study in Korean patients with exon 20 insertion reported objective response in only 25% of patients treated with gefitinib [20]. Patients with exon 19 deletion-type EGFR mutation have also shown more significant benefit than patients with L858R mutation. Increased OS (38 months vs. 17 months) has been reported in patients with EGFR exon 19 deletion, compared with patients with L858R mutation [21]. The low frequency of the

less common types of EGFR mutations involving exon 18 or 20 has not allowed the definition of the prognostic impact of these genetic alterations.

Based on the available clinical trial data, current guidelines indicate testing all patients with metastatic NSCLC adenocarcinoma for the presence of activating EGFR mutations and recommend first-line EGFR-TKI treatment for patients with adenocarcinoma and a known EGFR mutation [14]. Gefitinib (since 2009 in Europe/Asia and 2015 in the United States), erlotinib (since 2011 in the United States), and afatinib (since 2013 in the United States) have been approved with the condition that, in first-line setting, their use should be restricted to the treatment of lung ADCs with sensitizing EGFR mutations as exon 19 deletions or L858R mutations.

Secondary mutations in EGFR may appear in patients that develop resistance to EGFR TKIs. The most common resistance mutation is the T790M activating point mutation in exon 20 thus interfering with binding of reversible TKIs. Almost 50% of tumors from patients who develop acquired TKI resistance show a T790M, but they may also be found in patients who have never received TKI treatment.

KRAS Mutations

KRAS is a commonly detected mutation in NSCLC, harbored by approximately 20–25% of lung adenocarcinomas in the United States [22] and 14% in France [23]. Most frequently, these mutations involve codon 12 or 13 and, rarely, codon 6 [24].

KRAS mutations are more common in tumors with adenocarcinoma histology than in squamous type NSCLC. KRAS mutations are less common among patients of Asian ethnicity and more common in smokers (43% vs. 0%) [25]. That strong link between cigarette smoking and KRAS mutations in adenocarcinoma of the lung supports some pathogenic role of this mutation in the carcinogenetic properties of tobacco in NSCLA. In small studies, the occurrence of KRAS and EGFR mutations seems to be mutually exclusive [26].

Meta-analyses have shown that patients with KRAS mutations have a poorer response to EGFR-TKIs [27]. Most of the trials were small and this presumed negative association has not been indicated by larger studies [28]. On the other hand, some studies have shown that KRAS mutations have little impact on PFS in contradiction with the presumed nonresponse of KRAS-mutated patients to TKI therapy [29]. According to Cadranel et al., EGFR and KRAS status independently impacts outcomes in advanced NSCLC patients under EGFR-TKI therapy, but EGFR status impacts both PFS and OS while KRAS only impacts OS [23].

An association between KRAS mutational status and benefit of anti-EGFR monoclonal antibodies has not been demonstrated in NSCLC, and no trials can demonstrate the potential value of testing for KRAS mutations and according tailored therapy [30]. As a consequence, the role of KRAS mutations remains unclear. The results of ongoing clinical trials in KRAS-mutant NSCLC will establish if KRAS mutational status should or should not be included in the selection of treatment for NSCLC.

Anaplastic Lymphoma Kinase (ALK)

The oncogenic activity of ALK in anaplastic large cell lymphoma was reported in the 1990s [31]. ALK is a receptor tyrosine kinase normally expressed in several tissues like the small intestine, testes, and the nervous system. In 2007, a translocation in the gene encoding the receptor tyrosine kinase anaplastic lymphoma kinase (ALK), leading to the expression of ALK fusion proteins, was identified as an oncogenic driver in a subset of patients with NSCLC [32]. The genes encoding echinoderm microtubule-associated protein-like 4 (EML4) and ALK are both located on the short arm of chromosome 2 (2p21 and 2p23) [32]. The ALK gene rearrangement consists of a small inversion in the short arm of chromosome 2 between exon 20 of the ALK gene and different exons of the echinoderm microtubule-associated protein-like 4 (EML4) gene, resulting in the abnormal expression and

activation of this tyrosine kinase in the cytoplasm of cancer cells. This translocation leads to a chimeric protein with constitutive activation of ALK that presents oncogenic activity demonstrated both in vitro and in vivo. This rearrangement occurs in 2–5% of NSCLC, predominantly in young (50 years or younger), never or light smokers with adenocarcinoma [33] without other genetic disorders, such as mutations of the epidermal growth factor receptor gene [34]. However, clinical characteristics are not as precise as predictive biomarkers to select patients for ALK-targeted therapies. Since the discovery of the ALK-EML4 fusion protein, at least 11 different ALK fusion variants have been identified [35]. Thus, the current guidelines of the International Association for the Study of Lung Cancer (IASLC) and the European Society for Medical Oncology (ESMO) recommend that all patients with advanced-stage lung adenocarcinoma or tumors with an adenocarcinoma component should be tested for ALK, regardless of clinical characteristics.

The presence of alterations in the ALK gene carries a poorer prognosis. It has been reported that patients with ALK translocation have an increased risk of brain and liver metastases (40% vs. 21%) and a greater number of metastatic sites [36] as well as a higher risk of disease progression in comparison with ALK negative patients [37].

Most importantly, ALK gene translocation has been shown to be a predictive biomarker of the efficacy of different agents targeting the ALK kinase activity like crizotinib, ceritinib, and alectinib. Preclinical and single-arm phase I studies have demonstrated that patients with ALK-rearranged NSCLC can be successfully treated with crizotinib. The first published human study of ALK inhibition used the dual ALK/c-MET inhibitor, crizotinib, in patients with ALK-translocated, advanced lung carcinoma [38]. The results of the PROFILE 1007 phase III trial confirmed significantly higher response rates (65 vs. 20%) and longer progression-free survival (7.7 months vs. 3.0 months) compared with chemotherapy as second-line treatment for ALK+ NSCLC [4] and proved better results than standard first-line platinum/pemetrexed chemotherapy in untreated advanced ALK+ NSCLC. Despite the efficacy of crizotinib therapy in patients with ALK-positive lung cancer, most patients develop resistance to crizotinib within the first 12 months [39]. Second-generation ALK inhibitors as ceritinib, alectinib, and brigatinib (AP26113) were developed to overcome crizotinib-resistant mutations. Ceritinib is 5–20 times more potent than crizotinib and has achieved a response rate of 58% and a median PFS of 7 months when tested in ALK-positive patients with a very acceptable profile of adverse effects [40]. These and other research results led to the accelerated approval of ceritinib by the FDA in April 2014 for the treatment of patients with ALK+ metastatic NSCLC with disease progression or who present intolerance to crizotinib. In February 2015, the EMA Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, authorizing conditional marketing for ceritinib for patients with advanced ALK+ NSCLC previously treated with crizotinib [41]. Other new-generation ALK kinase inhibitors such as alectinib with potent in vitro activity are showing promising clinical efficacy at extracranial and intracranial sites in ALK-positive NSCLC.

C-Ros Oncogene 1

The c-ros oncogene 1 (ROS1) is a member of the insulin receptor family controlling cell cycling and proliferation. It has been identified as a driver mutation of lung cancer cells and primary tumor tissue and has recently been found rearranged in 2% of patients with NSCLC [42]. Multiple ROS1 fusion proteins have been described. ROS1 rearrangements are rarely accompanied by other mutations such as EGFR, ALK, or KRAS. Patients with ROS1 rearrangement have a very similar profile to those with ALK rearrangement, including a good response to crizotinib. Resistance to crizotinib has already been observed in patients with ROS1(+) NSCLC, and newer agents such as foretinib (GSK1363089) are being studied with initial promising results [43].

Other Molecular Markers

New molecular targets are being described. In October 2015, pembrolizumab was approved for the treatment of PD-L1-positive NSCLC, and the relevance of BRAF mutations in NSCLC by applying BRAF-targeted treatment is being studied. HER-2, human epithelial receptor 2 (HER-2/ErbB2), is a member of the HER group which is activated by homo- or heterodimerization with ErbB1–4 leading to the activation of the PI3K/AKT/mammalian target of rapamycin (mTOR) pathway. There are several ongoing clinical trials exploring newer-generation kinase inhibitors such as dacomitinib, afatinib, and neratinib for HER-2(+) lung cancer.

BRAF mutation—BRAF is a downstream signaling mediator of KRAS which activates the MAP kinase pathway. Small studies have shown that BRAF inhibition with selected TKIs (vemurafenib and dabrafenib) may be effective.

MET abnormalities are a tyrosine kinase receptor for hepatocyte growth factor (HGF). Increased MET expression may predict response to MET-targeted drugs and also appears to be associated with a worse prognosis. Initial studies show that a potential response to crizotinib and capmatinib (an investigational MET inhibitor) may be effective in patients with NSCLC and MET mutations.

Due to the widespread use of next-generation sequencing (NGS), additional numerous potential targets will be developed in the next years, but only clinical trials will show which will be appropriate for clinical application.

Optimizing Tissue Sampling for Histologic and Molecular Analysis of Lung Cancer

Most lung cancer patients are diagnosed after examination of a small biopsy (transbronchial or endobronchial) or cytology (fine-needle aspiration or body fluid) specimen. Specimens are processed for diagnosis, staging, and molecular marker analysis. As personalized treatment is now the standard of care for advanced lung cancer, current guidelines recommend that rapid EGFR and ALK mutation testing be performed at diagnosis in all patients with advanced adenocarcinoma regardless of gender, race, smoking history, or other risk factors. Testing is not recommended for tumors without an adenocarcinoma component. However, it should also be considered in large cell carcinoma or poorly differentiated carcinoma because limited sampling does not effectively exclude an adenocarcinomatous component [44].

Molecular testing is essential for patients with unresectable advanced lung cancer who will be offered targeted therapies. Patients with a potential surgical cure may never need antineoplastic drugs. The initial surgical specimen at resection is a high-quality tissue sample and may avoid new biopsies in case of relapse. However, the cost-benefit ratio of potential unnecessary testing must be considered.

If molecular testing of lung cancer is easily available and adequately reimbursed, shortening the waiting time for treatment selection seems reasonable. The sequential performance of molecular testing may be justified in the case of financial constraints that exist in molecular testing. In those cases, starting with KRAS in Caucasian and EGFR in Asian patients may be reasonable. Alternatively, IHS screening for ALK- or ROS1-negative lung cancer may be performed to detect cases that require FISH testing for ALK or ROS1 translocations. Sequential molecular testing of lung cancer can reduce the volume and cost of analysis by roughly 30%; however, this must be offset with the delay in obtaining the necessary information for the right treatment choices.

Early studies [45] have shown discordance in the results of mutational analysis between primary tumor and metastatic disease. However, the current consensus is that discordance in the rates of mutation detection between primary or metastatic tumors is infrequent and consequently the primary or metastatic site can be tested [46].

On the other hand, there is no evidence of intratumoral heterogeneity of mutations in NSCLC, and current data suggest that it is not necessary to test multiple areas of the same tumor.

Synchronous primary tumors should be tested independently as different tumors. Molecular analysis of synchronous lesions may contribute to define if lesions are likely to be clonally related.

Despite the multiple biomarkers mentioned above, tissue should be prioritized for EGFR and ALK testing. The cautious use of material should be taken into consideration to avoid new invasive diagnostic procedures.

Different Assay Technologies for Histologic and Molecular Diagnosis

The current classification of lung adenocarcinoma calls for more frequent use of IHC. At least 20–30% of tumor samples cannot provide an accurate diagnosis using routine histology or cytology and require the additional use of IHC [47]. Consequently, most guidelines recommend privileging biopsies over cytology since the former can provide more appropriate material for morphological and molecular diagnosis [48]. The use of FFPE tissue slides obtained from small biopsies (as those obtained by bronchoscopy) is usually sufficient for IHC. The cell block technique requires more cells than simple smears but offers better quality for diagnosis.

For molecular analysis, a variety of diagnostic assays can be used to identify abnormalities.

IHC shows poor or no correlation with EGFR mutations; therefore, it is not considered an acceptable test for EGFR TKI treatment selection. IHC is being explored in regard to overexpression of ALK. Though IHC was not initially considered reliable for ALK rearrangement screening, the development of new monoclonal antibodies has increased its potential [49]. The sensitivity of these new methods (if properly validated) is considered high enough, and the current recommendation is that tumors that fail to demonstrate ALK immunoreactivity with the new IHC methods need not be tested by FISH. However, tumors that test positive for ALK IHC should still be referred to FISH since there is no evidence yet for the use of ALK IHC as a sole determinant for ALK TKI therapy.

FISH is a widely used technology for the detection of gene fusions in lung cancer. It may be performed on tissue, cytology cell block, or smears. It detects genomic and chromosomal changes through hybridizing labeled DNA probes to a sample. Those fluorescently labeled DNA probes bind to specific parts of the chromosomes and thus may be visualized by fluorescence microscopy [50]. FISH is not a validated methodology for assessing patients for EGFR mutational status. Guidelines do not recommend EGFR copy number analysis (i.e., FISH or chromogenic in situ hybridization) for selection of EGFR TKI therapy because EGFR copy number testing (by FISH or chromogenic in situ hybridization) is less predictive than mutation testing [51]. On the other hand, published evidence indicates that FISH assay is acceptable for treatment selection with an ALK TKI. The assay is considered positive for ALK rearrangement if more than 15% of tumor cells have split green and red signals.

There are several extraction methods of DNA, and there is no consensus on which is the best. There are also several methods to detect EGFR mutations including direct sequencing, the amplification refractory mutation system (ARMS), length analysis, and denaturing high-performance liquid chromatography. Direct DNA sequencing is performed by different commercially available mutation-specific kits. Direct sequencing of PCR-amplified regions is a very common method for identifying EGFR and KRAS mutations [52].

The 2013 guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology does not recommend any particular method but emphasizes the need that laboratories validate their methods for acceptable quality [51]. EGFR test methods should detect mutations in specimens with at least 50% cancer cell content. If a laboratory cannot perform these more sensitive tests, it should share that limitation with the lung cancer team so that clinicians know clearly on what grounds they are making their decisions.

The serial mutational tests are time-consuming, and multiplex testing is being explored in the last years. The cost of multiplexing

is higher than conventional serial mutation testing. New platforms such as Sequenom or SNaPshot allow for detection of multiple genomic abnormalities with sequencing, and some of them (like Foundation One) also incorporate detection of gene rearrangements as EML4-ALK and changes in gene copy number. Currently, high costs and amounts of tissue required are limiting factors, but the constant developments in these technologies may make them more easily available and affordable in the next future.

In some countries, there are accreditation protocols to certify laboratories with appropriate quality control standards. Even in the absence of official accreditation bodies, only laboratories that are able to comply with standards should carry out this type of molecular testing. It is recommended that different laboratories share protocols and exchange positive and negative control samples to improve their performance by an external quality control. The availability of such laboratories is limited, which complicates the coordination among teams and the integration of all available data. The workup proposed by the IASLC-European Thoracic Oncology Platform multidisciplinary workshop suggests that the final results (including the molecular testing) should be available in 1 week. In the daily life scenario, that may be possible only for a few selected big academic centers but is not for smaller community hospitals or facilities that refer the molecular testing outside the original institution. In any case, the process should not take longer than 2 weeks. The achievement of this goal usually requires a huge effort for smaller institutions which must organize multiple teams from pathologists, oncologists, pulmonologists, and thoracic surgeons in addition to reference laboratories.

Minimal Requirements for Specimens Used for Molecular Analysis

Since the different techniques [immunohistochemistry, molecular diagnostics, fluorescent in situ hybridization (FISH)] require a predetermined minimal cell number and a tumor-cell-to-normal cell ratio of the sample [53], the main initial goal is to obtain a high-quality, high-volume tumor specimen, which would largely depends on the biopsy technique but also on the optimization of the available tissue by a correct processing technique.

Handling of tumor specimens has to be standardized in each institution through fluent communication between clinicians and pathologists. In general, required specimens are formalin-fixed, paraffin-embedded (FFPE) samples or fresh, frozen, or alcohol-fixed ones for polymerase chain reaction (PCR)-based EGFR mutation tests. Other tissue treatments such as acidic or heavy metal fixatives or decalcifying solutions should not be used in specimens that will be sent for EGFR testing. The most widely used fixative is 10% neutral-buffered formalin. The fixation time should be as short as possible yet sufficient to permit diagnosis. Best results have been rendered with 6–12 h fixation time for small biopsy samples and 8–18 h for larger surgical specimens. For other techniques, such as DNA extraction and polymerase chain reaction (PCR), the optimal fixation times have yet to be established [54].

Cytology specimens such as malignant pleural effusions may be useful. Cell blocks are strongly recommended over smear preparations because they correlate with malignant cell content. Recent research has shown that cytology smears can be effectively used to detect ALK gene rearrangements using FISH [55]. However, tissue biopsy samples are preferred because there is not enough evidence to accept the clinical reliability of mutational data obtained from cytology.

The minimum number of tumor cells required for adequate mutation testing is not fully determined. Although an ideal sample should contain at least 200–400 tumor cells, it is not easy to obtain this type of specimen in routine clinical practice. The performance of DNA sequencing requires at least 50% of tumor cells. As mentioned above, more sensitive techniques allow reliable results with as little as 10–20% of tumor cells. More sophisticated next-generation sequencing technologies are being developed, and probably, in the near future, 5% of tumor cells will be sufficient for reliable results.

Recommendations for Handling the Diagnostic Material for Histologic Examination and Molecular Analysis

The different diagnostic tools available for the study of lung cancer (transthoracic needle aspiration, bronchoscopy, etc.) will mainly provide two different kinds of specimens: cytology and biopsies. Each requires careful processing considerations in order to preserve the obtained material and optimize its diagnostic value.

Cytology Specimens

The presence of a pathologist at the moment of retrieval of the specimen is essential to qualify its appropriateness. The material should be examined in situ to assess the presence of blood, necrotic areas, and small tissue fragments and granular material suitable for ulterior examination. In the presence of carcinomatous tissue, the granular material is often grossly visible. The rapid on-site evaluation or ROSE has shown to increase the diagnostic yield [56]. If the cytopathologist notifies that there is not sufficient or adequate material under microscopic examination, additional passes should be performed to obtain additional samples. A meta-analysis demonstrated that ROSE has a sensitivity of 80–88% in EBUS-TBNA without increasing procedure length [57]. Although some data are encouraging about the ability of ROSE to optimize cell aspiration procedure and ensure that sufficient material is collected for cytologic diagnosis and for cell block preparation, the effect of ROSE itself has not been adequately studied, and evidence has been considered insufficient to recommend its use in every procedure by the WABIP evidence-based guideline [58].

Slides are usually prepared by the cytopathologists, but the operator performing the procedure (surgeon or pulmonologist) may be in charge of that step according to the organization of each working team. The slides are prepared generally with Diff-Quik (DQ)-stained air-dried smears, H&E/Pap-stained alcohol-fixed smears, or Pap-stained ThinPrep monolayer slides with cells transferred in suspension. If possible, H&E-stained cell blocks (paraffin-embedded cell pellets prepared using centrifugation of CytoLyt fluid after the addition of HistoGel) are prepared. All those procedures must be standardized according to the routine of each anatomic pathology laboratory.

Special care is required for the samples obtained by EBUS. The bronchoscopist has the greatest responsibility in that scenario, as he is the one coordinating a more complex team of different parties.

Technical aspects of sample retrieval are important. The diagnostic yield of conventional TBNA appears to be better when 19-gauge needles are used, instead of 22-gauge needles. Concerning EBUS, retrospective studies have failed to find a difference in the overall diagnostic yield between 22- and 21-gauge needles. On the other hand, the number of aspirates per lymph affects the diagnostic yield, quantity, and quality of the obtained specimen (Fig. 21.2). There is enough evidence that three aspirations with EBUS-TBNA and three to four aspirations with conventional TBNA provide near the maximum yield, higher than 90% [58]. There is no evidence that the type of needle, use of miniforceps, suctioning and type of sedation, time spent inside the node, and a number of revolutions inside the node have any influence on the ulterior molecular test.

Once obtained, the aspirates are placed onto a glass slide. Such procedure may be performed by blowing air with a syringe through the needle or replacing the stylet. Saline is then poured with a syringe through the EBUS needle into CytoLyt solution to obtain any remaining cells. Some of the resulting material will be whitish tissue particles that should be separated from the blood/mucus and smeared on at least two different slides. The remaining material on the original slide is used to prepare a clot. One of the two slides should be prepared with the white material, and the other is air-dried for ROSE (usually stained with DQ stain or Giemsa) and placed in 95% ethanol for Pap staining which will enhance nuclear cytological detail [59]. The collection of

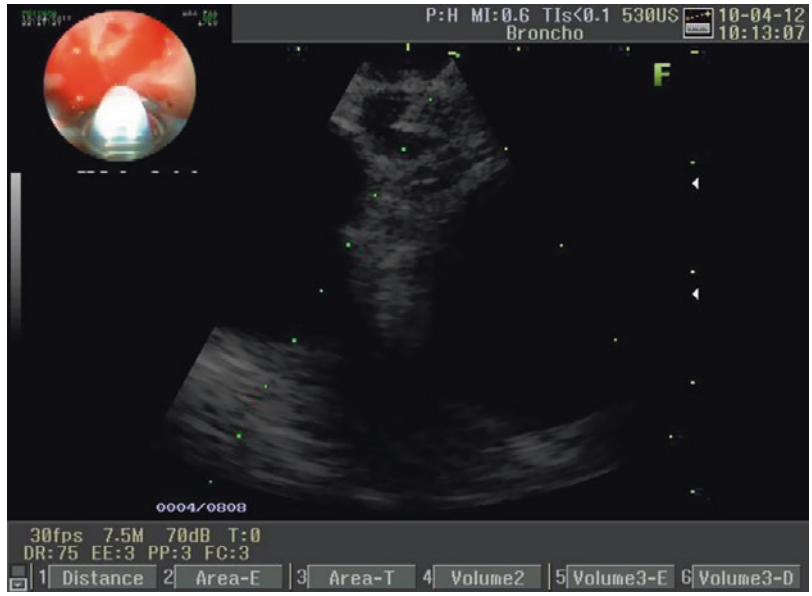

Fig. 21.2 EBUS-TBNA and cTBNA have a similar yield for specimen adequacy of driver mutations

fresh material and the clot should be encouraged. The main advantage of direct smears over cell block for molecular analysis is the possibility of immediate analysis to assess specimen adequacy and amount at the time of retrieval. When collection of tissue core is possible, it should be placed on filter paper to eliminate the excess of blood and fixed with 10% neutral buffered formalin. The FFPE sample is later stained with H&E for histologic diagnosis and IHC.

Cell block slides may permit the identification of adenocarcinoma architectural patterns and allow the subsequent use of IHC to achieve accurate histologic subtyping of NSCLC, especially for poorly differentiated carcinomas. An advantage of cell blocks is that FFPE tissue prepared from cell blocks allows a longer term sample preservation that may help as a source of DNA for future examination. In 87% of the cases in which EBUS allowed a diagnosis of malignancy, the cell block specimen was adequate for IHC, and in 85% of them, histologic subtyping was possible. Cell blocks provide paraffin-embedded tissue for DNA mutation and FISH testing [60]. However, cell blocks are not always sufficient for molecular testing.

There is no trial comparing cell block or tissue core techniques in terms of effectiveness for diagnosis of lung cancer, although several studies confirm the ability to prepare a cell block for morphologic and (IHC) analysis. There is no evidence recommending any method for specimen preparation, which may be defined according to the expertise and preferences of the pathologists who are going to work on the sample. Most of the reported methods appear to achieve similarly acceptable diagnostic performance [58]. Molecular analysis can be routinely performed on the majority of cytological samples obtained by EBUS-guided and conventional TBNA. The critical factor is the absolute number of vital tumor cells, the percentage of tumor cells present in the material, and the sensitivity of the molecular test utilized. The WABIP evidence-based guideline defines that smear and cell block preparations or core tissue can be utilized for molecular testing. Cell blocks and core tissue are indispensable to assess ALK translocation, but cytological slides can be successfully used to determine the status of EGFR and KRAS even if cell blocks or core tissue are not available (Fig. 21.3).

Biopsy Specimens

A biopsy in a visible endobronchial tumor during flexible videobronchoscopy has an average diagnostic yield of at least 85%. Diagnostic yields as high as 70% have been reported with the

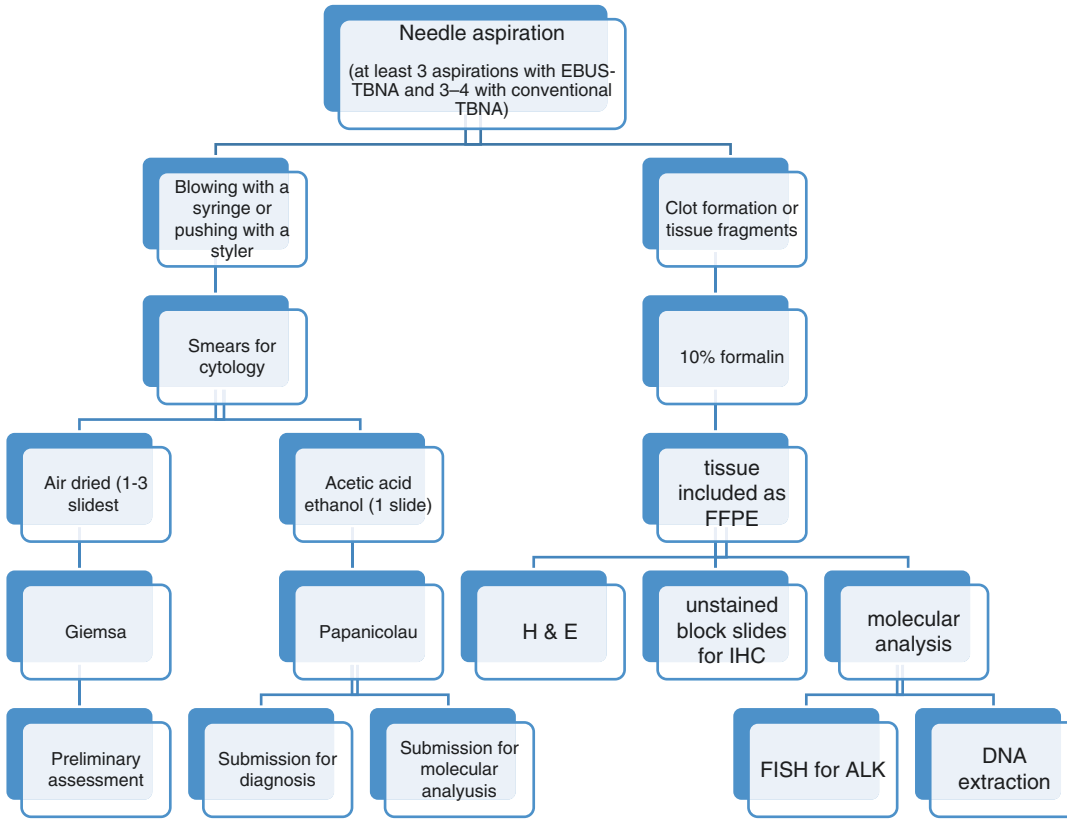

Fig. 21.3 Handling of cytology samples

use of modern guidance techniques in peripheral tumors >20 mm in size, farther from the direct bronchoscopy vision but in proximity to a patent bronchus. However, those techniques are not available in most small centers, and diagnostic rates under 30% are more realistic for peripheral tumors. In order to obtain optimal samples for histopathological subtyping and genotyping, at least three forceps biopsy samples should be obtained (if possible five) with at least a 2-mm open diameter. At least five additional bronchial forceps biopsies should be performed in order to obtain enough volume of tissue for NSCLC phenotyping and genotyping. The limiting factor for reaching the desired number of biopsies is usually a mild (10%) or severe, life-threatening (<0.02%) bleeding. Maximal efforts must be made to obtain optimal material knowing that, in patients with proven malignancies, between one-third and one-half of biopsy fragments contain no tumor and that a suboptimal volume of tissue will mean a repeat flexible bronchoscopy with new endobronchial forceps biopsy. The diagnostic yield is significantly higher for the cryobiopsy technique than the endobronchial forceps biopsy (95% vs. 85%). The diameter of a sample taken by cryoprobe technique is twice the size/diameter of forceps biopsies, and it usually provides sufficient and free-artifact tissue for DNA genotyping. Thus, if available, the acquisition of two cryobiopsy samples might complement routine clinical practice when the purpose includes the molecular analysis of lung cancer [61]. Biopsies may also be obtained by CT-guided coaxial core biopsy. That method is preferred to the conventional aspiration cytology when possible, because it allows larger samples. A diagnostic yield around 90% has been reported when the target lesion to biopsy is near the chest wall and >15 mm in size. Two core needle

biopsies should be performed using an 18–20 G needle, but if histologic subtyping and genotyping are required, at least three to six core needle biopsies are recommended. Complications (pneumothorax or bleeding) are the potential limiting factors.

In order to preserve the quality of the biopsy sample, it is important to perform minimally invasive sectioning for an initial look and a preliminary diagnosis on the initial slides. Multiple cutting (approximately 20) of unstained sections is recommended until a preliminary diagnosis. The pathologist should mark the most suitable tumor area on the slide to extract optimal tumor content from the paraffin-embedded material and achieve best molecular test results [62]. Although technical aspects of the processing of the biopsy specimen fall within the domain of pathologists, continuous feedback about processing methods is essential to assure the best technical choices.

There is growing information about technical handling the diagnostic materials. Updated statements about the pre-analytical requirements of tissue sampling for molecular diagnosis will soon be developed. The creation of quality control programs and accreditation bodies is necessary in order to assure the highest diagnostic yields and minimize time and cost. Local adaptations of programs and accreditation norms will be necessary as resources, network possibilities, and logistic organization may be different in each country. Also the continuous development of new technologies may rapidly modify (and eventually simplify) the requirements of samples retrieval and handling.

The Organization of a Working Team

Lung cancer treatment is increasingly personalized. The technologic progress in cancer genomic research during the last decade has accelerated discoveries and clinical applications. The increasing need for tumor genotyping, based on these newly established relationships between the type of targetable gene mutation and response to targeted agents, means a challenge for certification bodies, institutional teams, medical association, and daily life practitioners. Medical associations need to establish standards and provide recommendations even in the context of the literature limitations.

Medical institution needs to bring together all medical, logistic, and cost-effectiveness factors and optimize their effectiveness. Multidisciplinary panels made up of personnel experienced in different areas of cancer care are essential to define the best working protocols that assure further benefits.

Lung cancer management committees must be organized to facilitate fluent and effective communication among the different involved parties (pulmonologists, surgeons, pathologists, interventional radiologists, oncologists). All those involved in material acquisition and processing should define the working flow, methodologies, and logistics of the process. Experience in different institutions with different levels of complexity has shown that the main limitations to provide a complete, accurate, and timely diagnosis (including the genotyping) come from the logistic organization and not from the scarceness of human or material resources.

International guidelines and standardized recommendations are essential, but the local implementation of those recommendations is a daily life challenge that requires the active participation of different levels of any hospital facility. The competing demands of every single participant of the team (with different timetables, different locations and routines inside the institution, and even different working philosophies) make the constitution of multidisciplinary teams a difficult challenge, mostly in institutions with huge workloads and limited resources. However, the effort is worthwhile. Committees based on interdisciplinary cooperation and patient-centered decision-making should be responsible for optimizing collection, handling, processing, and reporting of the needed materials for optimal management of lung cancer samples. Beyond any external quality control, the periodic feedback of the whole management team should be the best alert about

the rate of success of the process in place. Collaboration and communication between pulmonologists, surgeons, oncologists, and pathologists are the key elements to address any potentially needed change in the implemented policy about collection and management of samples.

A multidisciplinary approach requires initial meetings with all the parties involved to define the feasibility of the ideal protocols and how to fit them (and the individual request of any member of the team) into the resources and working routines of the other parties. But it is also necessary that cancer board meetings involve the whole team, in order to keep everyone informed about the results of the technical and logistic decisions initially made by the working team.

The new management of NSCLC gives a pivotal role to committees who must build a bridge of communication between the clinical and molecular laboratory team. That collaborative group will become increasingly important in the era of personalized medicine, and making it really workable and active is the major current challenge for all parties involved in the management of lung cancer.

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Part IV

Lung Cancer Staging

The Newly Proposed Lung Cancer TNM Classification: Review and Clinical Implications

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Roberto F. Casal and Rodolfo F. Morice

Lung cancer remains the number one cause of cancer-related mortality in the Western world, with more than 1,000,000 deaths each year [1]. Staging is vital in the approach to lung cancer since it offers both prognostic information and a guide for treatment decisions. A unified and universally accepted staging system is also essential to standardize nomenclature for international comparisons of clinical trials. The TNM system provides a detailed description of cancers based on the extent of the anatomic involvement, by defining the primary tumor (T), the regional lymph node involvement (N), and the presence of distant metastases (M) [2]. In this chapter we will review the proposed changes for the eighth edition of the International Association for the Study of Lung Cancer (IASLC) TNM staging system, and we will discuss its clinical implications, strengths, and limitations.

History

The tumor-node-metastases (TNM) staging system currently applied to almost all solid malignancies was coined by Dr. Pierre Denoix in the 1940s [3]. As chair of the Union Internationale Contre le Cancer (UICC) staging committee, he coordinated the standardization of TNM staging for 23 solid organ cancers [4]. The first proposal for lung cancer TNM staging was developed by Dr. Clifton Mountain and adopted by the American Joint Committee on Cancer (AJCC) and the UICC in 1973 and 1974, respectively [5]. This original system was based on outcome data from a single institution (MD Anderson Cancer Center, Houston, TX, USA) and a limited number of patients (2155, 1712 with non-small cell lung cancer (NSCLC)). Three subsequent revisions occurred in the following 25 years, all based on Dr. Mountain's database which continued to grow up to 5319 cases by the time of the last revision in 1997 [6]. Some of the limitations of this system such as the small number of patients—particularly for subgroup analysis—the single institution origin, and the lack of external validation prompted the IASLC to create the IASLC staging committee. This group composed of international members of all disciplines involved in lung cancer was set to develop and analyze a more powerful, current, and universal database of patients with lung cancer in order to review its staging. An unrestricted grant from Eli Lilly helped establish the database (the company had no role in data collection or analysis), which was created in collaboration with the CRAB (Cancer Research and Biostatistics Office, Seattle, Washington). Subcommittees were formed to retrieve and analyze data on T, N, and M descriptors,

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prognostic factors, nodal mapping, bronchopulmonary carcinoid tumor, and small-cell lung cancer (SCLC) [7]. The IASLC recommendations for the seventh TNM staging system were published in a series of articles in the *Journal of Thoracic Oncology* in 2007–2009 [8–18]. While the sixth edition of the AJCC and UICC lung cancer TNM staging system published in 2002 was mainly a review of Dr. Mountain's work, the seventh edition, adopted in January 2010, was based on a truly international database of patients treated by all modalities, with rigorous analysis and validation [13]. Despite the vastness of this database, not all T, N, and M descriptors could be thoroughly analyzed, and this prompted the IASLC Staging and Prognostic Factors Committee to launch a second phase of its Lung Cancer Staging Project with the objective to overcome the limitations of the initial project [19].

Data Source and Methodology

A new database was utilized to inform the eighth edition of the TNM classification of lung cancer [19]. This new database consists of 94,708 patients diagnosed from 1999 to 2010. Their data originated from established databases (90,041 patients) or were submitted via the electronic data capture (EDC) system set by Cancer Research and Biostatistics (4667 patients). The inclusion criteria were new lung cancer diagnosis (not recurrent cancer), adequate follow-up for survival analysis, histological subtyping, and complete clinical (c) TNM and/or pathological (p) TNM staging. Europe contributed 46,560 patients; Asia, 41,705; North America, 4660; Australia, 1593; and South America, 190. These new data came from 35 sources in 16 countries. After excluding 17,552 patients, mainly because of unknown or different histology and incomplete stage information, 77,156 patients (70,967 with NSCLC and 6189 with SCLC) remained for analyses. The majority of these patients (99%) had been collected by consortia or registries, with no patients coming from clinical trials. Nearly 85% of the patients underwent surgical treatment either alone or in combination with chemotherapy or radiotherapy.

In this new database, the TNM descriptors were collected according to the seventh edition. In addition, a total of 23 non-anatomical elements was collected to aid with prognostic calculations. These included, among others, patient-related elements (i.e., demographics, lung function tests, performance status, smoking history), tumor related (i.e., T and N SUV max, histology and degree of differentiation, vascular invasion), and environment related (i.e., method of detection, treatment, geographic of origin). This was done with the idea of combining anatomical and non-anatomical elements for a more accurate prognosis. Although this database includes a smaller number of patients, it is richer than the prior one in details allowing for refinement in the analysis of the different descriptors.

Proposal for the Revision of T Descriptors

In the NSCLC group, 33,115 patients met the T descriptors subcommittee's initial analytic requirements of M0 NSCLC, a complete set of either clinical (c) TNM or pathological (p) TNM, known tumor size, and sufficiently detailed T descriptors to support the assigned T category [20]. Survival was measured from the date of diagnosis for clinically staged patients to the date of surgery for pathologically staged patients, and overall survival was assessed with Kaplan-Meier method. Log-rank statistics were derived from hypothetical size cut points, and the highest log-rank statistic was used to select the optimum cut point.

Tumor Size

The size cut point of 3 cm was confirmed and retained to differentiate T1 from T2 tumors, and it continues to be the best cut point for all sizes over all T categories. Five-year survival was analyzed at 1-cm increment in tumor size: ≤1 cm (92%), >1–2 cm (83%), >2–3 cm (76%), >3–4 cm (67%), >4–5 cm (60%), >5–6 cm (56%), >6–7 cm (46%), and >7 cm (38%). This analysis showing a progressive decrease in survival for each 1-cm

cut point led to a new proposal for the T status according to tumor size (see summary of proposed changes in Table 22.1).

Involvement of the Main Bronchus

Involvement of the main bronchus less than 2 cm from the main carina, without invasion of the carina (currently a T3 descriptor), was found to have better prognosis than other T3 descriptors. The distance from the carina (up to 2 cm or >2 cm) does not seem to increase risk of death after adjusting for tumor size. Hence, it was proposed to group all tumors invading the main bronchi regardless of the distance to the carina—as long as the carina is not invaded—as T2.

Involvement of the Diaphragm

Involvement of the diaphragm, a current T3 descriptor, was found to confer a worse prognosis than other T3 descriptors both in clinical and pathological settings. Hence, it is proposed to reclassify involvement of the diaphragm as T4.

Table 22.1 Proposed descriptors for the eighth TNM classification of lung cancer

Descriptor	Subgroup	Definition
T (tumor)		
T0		No evidence of primary tumor
T1		Tumor ≤3 cm, surrounded by the lung or visceral pleura, not more central than the lobar bronchus
	T1a (mi)	**Minimally invasive adenocarcinoma** (solitary adenocarcinoma <3 cm, with predominant lepidic pattern and <5 mm invasion)
	T1a	≤1 cm
	T1b	>1 cm and ≤2 cm
	T1c	>2 cm and ≤3 cm
T2		Tumors >3 cm and ≤5 cm or with any of the following features: – **Involves main bronchus without invading main carina, regardless distance to main carina** – Involves visceral pleura – **Associated atelectasis or pneumonitis of part or all the lung**
	T2a	>3 cm and ≤4 cm
	T2b	>4 cm and ≤5 cm
T3		**Tumors >5 cm and ≤7 cm** (prior T2b) or with separate nodule(s) in same lobe, invading chest wall, phrenic nerve, or parietal pericardium
T4		**Tumors >7 cm** (prior T3) or with separate nodule(s) in a different ipsilateral lobe, **invading diaphragm** (prior T3), mediastinum, heart, great vessels, trachea, carina, recurrent laryngeal nerve, esophagus, or vertebral body
N (regional LN)		
N0		No regional metastases
N1		Metastases to ipsilateral peribronchial, perihilar, or intrapulmonary LN
N2		Metastases to subcarinal or ipsilateral mediastinal LN
N3		Metastases to contralateral hilar or mediastinal LN or involvement of any scalene or supraclavicular LN
M (metastasis)		
M0		No metastasis
M1		Metastasis present
	M1a	Separate nodule(s) in contralateral lung, malignant pleural/pericardial effusion, or pleural/pericardial nodule
	M1b	**Single extrathoracic metastasis**
	M1c	**Multiple extrathoracic metastases in one or more organs**

Note: Changes to the seventh edition of TNM are in bold. *LN* lymph node. Adapted from Goldstraw et al. [25]

Atelectasis/Pneumonitis

This new analysis showed that complete atelectasis/pneumonitis may have a better prognosis than other T3 descriptors, and besides the small number of patients with this characteristics, it is proposed to reclassify these patients from T3 to T2. The new proposal is to include in T2 category patients with any degree of atelectasis or pneumonitis.

Ground Glass/Lepidic Features and Pneumonic-Type Tumors

Tumors presenting with ground glass/lepidic pattern (GG/L) and "pneumonic" type infiltrates are typically multifocal and have different biologic behavior, and they are difficult to classify with our current TNM. A subcommittee of the IASLC was created to provide a consistent nomenclature for these particular presentations of lung cancer [21]. Since the IASLC database did not capture information on GG/L and pneumonic-type tumors, an evidence-based approach was taken, systematically reviewing the literature from 1995 to 2015. Multifocal GG/L lung adenocarcinoma should be classified by the T category of the lesion with the highest T, with the number (#) of lesions or simply (m) for multiple indicated in parentheses. The size is determined by the largest diameter of the solid component (by CT) or the invasive component under the microscope. The designation of T should be used for adenocarcinomas in situ (AIS) and T1a (mi) for minimally invasive adenocarcinomas (MIA) (e.g., T1a (mi) (m) N0 M0). The (#) or (m) is applied regardless of location (e.g., same lobe, different lobe of the lung). The T component should include all tumors whether resected or not that are thought to be malignant (either suspected or proved), as well as to those that are only discovered on pathological examination [20]. A single N and M category is applied to all GG/L tumors. Pneumonic-type lung cancer has a worse prognosis than GG/L type, yet nodal or extrathoracic metastases are rare. In cases of pneumonic-type cancers with a single area of tumor, the current TNM is easily applied. Unlike with GG/L tumors, in cases of multiple areas of involvement, the T or M category will be applied: T3 within same lobe, T4 within different lobe of same lung, and M1a in contralateral lung. This classification applies to both grossly and microscopically found tumors. If a tumor crosses a boundary between two lobes, a T4 classification should be applied. If a tumor is confined to one lobe but hard to measure, a T3 classification is given.

Summary of "Proposed" T Changes for the Eighth Edition of the TNM Classification of Lung Cancer

- The subclassification of T1 into:
  T1a: tumor 1 cm or less in greatest dimension
  T1b: tumor more than 1 cm but not more than 2 cm in greatest dimension
  T1c: tumor more than 2 cm but not more than 3 cm in greatest dimension
- The subclassification of T2 into:
  T2a: tumor more than 3 cm but not more than 4 cm in greatest dimension
  T2b: tumor more than 4 cm but not more than 5 cm in greatest dimension
- The reclassification of tumors more than 5 cm but not more than 7 cm in greatest dimension as T3.
- The reclassification of tumors more than 7 cm in greatest dimension as T4.
- The grouping of the involvement of the main bronchus as a T2 descriptor, regardless of distance from the carina, but without invasion of the carina.
- The grouping of partial and total atelectasis or pneumonitis as a T2 descriptor.
- The reclassification of diaphragm invasion as T4.
- Multiple GG/L tumors should be given the T category of the largest lesion with the number of lesions between parenthesis or simply (m) next to the T category, with bilateral lesions not considered as M1a.

- Both clinical and pathological information (when available) should be applied to GG/L tumors when describing the TNM.
- Pneumonic-type tumors are classified according to the size of the involved area, and they follow the standard definitions of T3, T4, and M1a for lesions in different lobes.

Proposal for the Revision of N Descriptors

Nodal status continues to be one of the most reliable indicators of prognosis in lung cancer, and it is a major determinant of the optimal therapeutic option. The seventh edition of the TNM staging categorized the N status based on the location of the involved lymph nodes (LN) as N0 (no LN involved), N1 (ipsilateral hilar LN involvement), N2 (ipsilateral mediastinal LN involvement), and N3 (contralateral hilar or mediastinal or ipsilateral/contralateral supraclavicular LN involvement), regardless the number of LN involved. This seventh edition of the TNM also accepted the IASLC nodal map as the standard of care to describe LN involvement in lung cancer [11, 13]. The new database was analyzed to corroborate the prognostic ability of the current N categorization and to explore if there is a more sophisticated method for describing LN involvement [22]. Among 70,976 patients with NSCLC, data on the "N component" were available in 38,910 (54.8%) patients for "clinical" nodal (cN) status and in 31,426 (44.3%) patients for pathological nodal (pN) status. Of note, Japan submitted the most data, which consisted of 23,012 (59.1%) patients for cN status and 23,463 (74.7%) patients for pN status, in which the "Naruke-Japanese map" was exclusively used to designate the location of metastatic lymph nodes and to determine the nodal status [23]. Despite the fact that in 2009 the new international lymph node map (IASLC map) was promulgated by the IASLC and recommended by the seventh edition of the TNM, this map was rarely utilized. With the collected data, it was not possible to reconcile the discrepancies between the two maps.

Nodal Staging

Clear differences in overall survival were evidenced again in the new database for both clinically and pathologically staged cases, supporting the traditional classification of N0, N1, N2, and N3, without changes from the seventh TNM (new 5-year survival rates were 60%/75% for cN0/pN0, 37%/49% for cN1/pN1, 23%/36% for cN2/pN2, and 9%/20% for cN3/pN3). For T1 and T2 tumors, cN status continued to show a difference in prognosis for each category. For T3 and T4 tumors, there was no statistically significant difference between cN0 and cN1, but there was a difference between cN1 and cN2 and cN2 and cN3. Further analyses were performed to explore the prognostic impact of combining the number of involved LN stations with the current nodal categories in T—any M0 patients. Unfortunately this specific data on the number of involved stations was only available on pathological data and not clinical. Pathological N categories were further subdivided: pN1 was divided into pN1 single (pN1a) and pN1 multiple (pN1b), and pN2 was divided into pN2 single (pN2a) and pN2 multiple (pN2b). The survival curves for pN1b and pN2a overlapped, with 5-year survival rates of 50% and 49% for R0 resections, respectively (Fig. 22.1). The presence of skip metastasis was further taken into consideration: pN2a was divided into pN2 single with skip (no pN1 involvement, pN2a1), pN2 single without skip (pN1 involvement as well, pN2a2), and pN2b. There was a statistically significant difference in 5-year survival between pN2a1 (skip) and pN2a2 (no skip) (54% vs. 43%, respectively). However, there was no significant difference in prognosis between pN1b and pN2a1 (50% vs. 52%, respectively). These results indicated that the prognosis of pN2a1 (skip metastasis) was close to that of pN1b (multiple N1 stations). Since these interesting findings derived from pathological data and could not be corroborated in clinical staging, they could not be utilized to propose modifications in the N descriptors. Moreover, the analysis on the N descriptor was thought to be partly hampered by differences between the Naruke and the MD-ATS nodal maps.

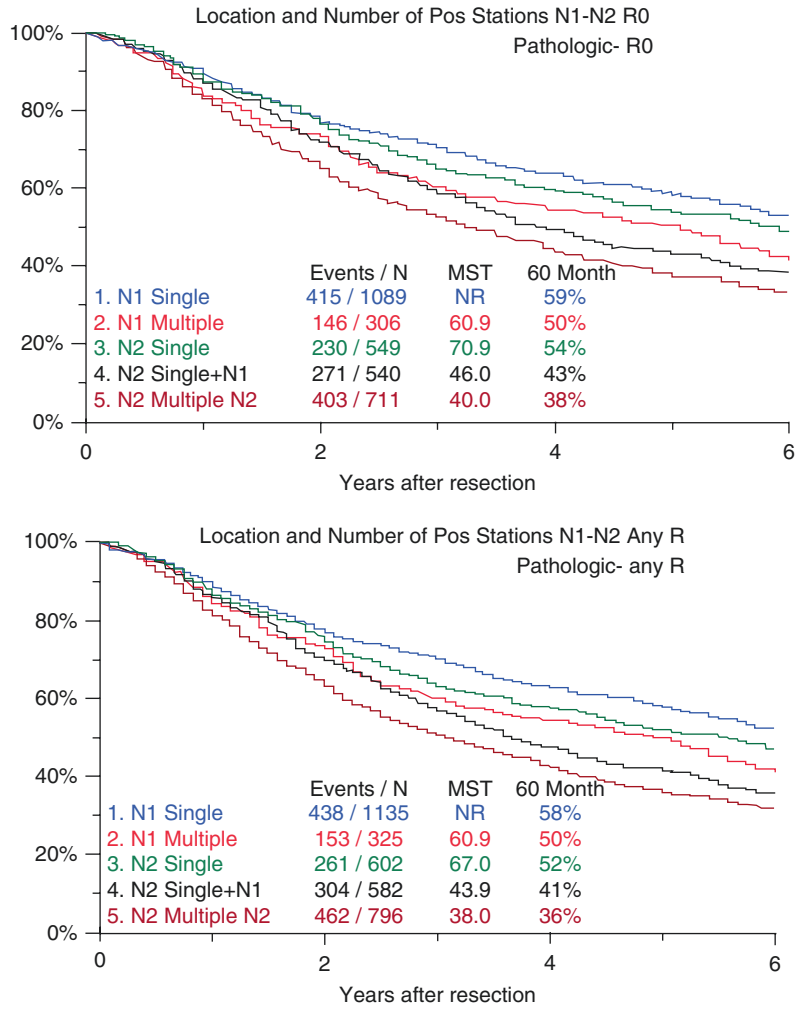

Fig. 22.1 Analysis of survival in patients with pN1 and pN2 disease with single and multiple station involvement, both for R0 and any R resections. R0 = complete resection. Any R = complete and incomplete resections. Copyright IASCL 2015

Summary of "Proposed" N Changes for the Eighth Edition of the TNM Classification of Lung Cancer

- No changes were made in N descriptors, retaining the traditional N0, N1, N2, and N3.
- Further N category classification based on single versus multiple involved stations and presence or absence of skip metastases needs further prospective evaluation before it can be applied to our TNM system.
- The IASLC nodal map recommended by the seventh edition of TNM continues to be recommended to provide precise anatomic definitions for all LN stations.

Proposal for the Revision of M Descriptors

Since the database generated for the seventh edition of the TNM, there have been multiple advances in diagnosis, staging, and management of lung cancer. The widespread use of PET-CT and MRI, the more precise local radiation therapies, the advent of minimally invasive surgery, and the individualized molecular-targeted oncologic treatments have

changed our approach to patients with advanced disease. With the new and prospectively collected database being much richer than the prior one, the IASLC Staging and Prognostic Factors Committee has revised the M descriptors focusing on the burden of metastatic disease [24]. While data from 2411 non-resected M1 patients was available for analysis, only 1059 patients submitted through EDC had the specific data required to assess the objectives set out by IASLC, and the analysis was restricted to this group of patients. Median follow-up for M1a and M1b cases in the EDC was 29.3 months. Overall survival was measured since the day of diagnosis for clinically staged patients, and survival was estimated with Kaplan-Meier method. The analysis corroborated the difference in prognosis between the seventh edition TNM M1a (pleural/pericardial effusions, contralateral/bilateral tumor nodules, pleural/pericardial nodules) and M1b patients (extrathoracic metastases). The former category is showing a median survival of 11.5 months and the latter 7.5 months. In addition, the new database showed that patients with a single extrathoracic metastatic site had a similar survival to patients with M1a disease (median survival of 11.4 months) and much better survival than those patients with multiple extrathoracic metastases (median of 6.3 months). This prompted the reclassification of extrathoracic disease into M1b (single metastasis) and M1c (multiple metastatic disease in one organ or metastasis in multiple organs).

Summary of "Proposed" M Changes for the Eighth Edition of the TNM Classification of Lung Cancer

- Maintain M1a category (pleural/pericardial effusions, contralateral/bilateral tumor nodules, pleural/pericardial nodules).
- Reclassify current M1b category for patients with a single extrathoracic metastatic lesion.
- Introduce the new category M1c for patients with extrathoracic metastatic disease characterized by either multiple lesions in a single organ or lesions in multiple organs.

Proposal for the Revision of Stage Groupings

Based on the previously described proposed changes to T and M descriptors (Table 22.1), new subsets of group stages were also developed [25]. Proposed TNM stage groupings were evaluated for survival based on clinical, pathologic, and best stage. Survival was calculated with Kaplan-Meier method, and it was measured from the date of diagnosis for clinically staged tumors to the date of surgery for pathologically staged tumors. The newly proposed stage groupings are summarized in Table 22.2. The proposed changes in T or M categories are translated into multiple migrations between stage groups. These migrations are highlighted with up or down arrows in Table 22.2. The overall survival for clinical and pathologically stage in the proposed stage grouping of the eighth edition of TNM is summarized in Table 22.3.

Small Cell Lung Cancer (SCLC)

SCLC represents approximately 15% of all lung cancers. Since SCLC is rarely amenable for surgery, the use of TNM staging for SCLC is seldom utilized, and for simplicity, disease is either referred to as "limited" (LD) or "extensive" (ED). The former corresponds to disease confined to one hemithorax with or without ipsilateral LN or pleural effusion, and the latter to all other cases. This broad classification can potentially hide patients who would benefit from more aggressive therapies [7, 10]. The results of the analyses performed by this IASLC subcommittee confirmed that TNM staging closely correlates with survival of SCLC by stage, identifies patients with different prognosis, and can be applied to surgically managed patients [7, 10]. Hence, the seventh edition of TNM recommended applying the TNM criteria, particularly to early SCLC. The proposed revision for the eighth edition of TNM classification discussed above was applied to SCLC [26]. A total of 5002 patients, of which 4848 were clinically staged, 582 pathologically staged, and 428 both clinically and pathologically

Table 22.2 Proposed stage groupings for the eighth TNM classification of lung cancer

Seventh TNM descriptor	Proposed eighth TNM descriptor	N0	N1	N2	N3
T1 ≤1 cm	T1a	**IA1** (IA)	**IIB** (IIA) ▲	IIIA	IIIB
T1 >1–2 cm	T1b	**IA2** (IA)	**IIB** (IIA) ▲	IIIA	IIIB
T1 >2–3 cm	T1c	**IA3** (IA)	**IIB** (IIA) ▲	IIIA	IIIB
T2 >3–4 cm	T2a	IB	**IIB** (IIA) ▲	IIIA	IIIB
T2 >4–5 cm	T2b	**IIA** (IB) ▲	**IIB** (IIA) ▲	IIIA	IIIB
T2 >5–7 cm	T3	**IIB** (IIA) ▲	**IIIA** (IIB) ▲	**IIIB** (IIIA) ▲	**IIIC** (IIIB) ▲
T3 >7 cm	T4	**IIIA** (IIB) ▲	IIIA	**IIIB** (IIIA) ▲	**IIIC** (IIIB) ▲
T3 endobronchial 3–4 cm (location/atelectasis)	T2a	**IB** (IIB) ▼	**IIB** (IIIA) ▼	IIIA	IIIB
T3 endobronchial 4–5 cm (location/atelectasis)	T2b	**IIA** (IIB) ▼	**IIB** (IIIA) ▼	IIIA	IIIB
T3 invasion	T3	IIB	IIIA	**IIIB** (IIIA) ▲	**IIIC** (IIIB) ▲
T3 diaphragm invasion	T4	**IIIA** (IIB) ▲	IIIA	**IIIB** (IIIA) ▲	**IIIC** (IIIB) ▲
T4	T4	IIIA	IIIA	IIIB	**IIIC** (IIIB) ▲
M1a	M1a	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)
M1b single metastasis	M1b	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)
M1b multiple metastases	M1c	**IVB** (IV) ▲	**IVB** (IV) ▲	**IVB** (IV) ▲	**IVB** (IV) ▲

Note: Stage migrations are bolded, prior stage is within parenthesis, and arrows indicate up- or downstaging. Adapted from Goldstraw et al. [25]

Table 22.3 Overall survival by clinical and pathological stage according to the proposed eighth TNM stage groupings

Proposed stage	MST (months) (clinical/pathological)	Twenty-four-month survival rate (%) (clinical/pathological)	Sixty-month survival rate (%) (clinical/pathological)
IA1	NA/NA	97/97	92/90
IA2	NA/NA	94/94	83/85
IA3	NA/NA	90/92	77/80
IB	NA/NA	87/89	68/73
IIA	NA/NA	79/82	60/65
IIB	66/NA	72/76	53/56
IIIA	29.3/41.9	55/65	36/41
IIIB	19/22	44/47	26/24
IIIC	12.6/11	24/30	13/12
IVA	11.5/NA	23/NA	10/NA
IVB	6/NA	10/NA	0/NA

MST median survival time, *NA* not available

staged, were included. The proposed changes to T and M descriptors were able to discriminate as well as the prior ones (seventh edition). The revision of the TNM stages was also evaluated in this new database; however, some stage categories were underrepresented. Statistically significant differences in prognosis were only seen between stages IIB and IIIA and between stages IIIC and IV. The IASLC committee continues to recommend the use of TNM classification for patients with SCLC who have limited disease.

Discussion

The seventh TNM staging system represented a major step forward in lung cancer care with a clear progression from previous versions of the staging

system. Despite its large size, the database utilized for this seventh edition of TNM was purely retrospective and not all descriptors could be validated. This prompted the creation of a new database that gathered both prospective and retrospective data and that were utilized to inform the eighth revision of the TNM. Multiple changes in T descriptors, M descriptors, and group stages are being proposed for the eighth edition, and, of course, with these changes the new TNM system has inevitably gained higher complexity. We will briefly discuss some limitations and clinical implications of the methodology and different descriptors.

Methodology

Though the IASLC Staging and Prognostic Factors Committee is devoted to prospectively collect data that is specifically designed to revise the TNM, the added complexity of such data has led to the continuous utilization of retrospective sources of data that was collected for other purposes. Of note, although the new database continues to be international in nature, it has a higher proportion of patients from Asia (mostly from Japan, contributing to 41%), which has increased the proportion of patients receiving surgery as part of their treatment from 53 to 85%. In addition, there was an increase in the number of cases coming from registries and a lack of cases from clinical trials. These variations resulted in an increased stage-for-stage survival in all stages and a decrease in survival for advanced stages. The migration of descriptors and stages has sacrificed the backwards compatibility with previous TNM staging. This backward incompatibility makes it difficult to extrapolate established treatment algorithms to the new stage groupings. However, it is important to remember that stage alone does not dictate treatment. Changes to treatment algorithms based on new stages should be assessed in clinical trials [13]. Although many people might expect a staging system to be able to allocate patients to different treatment strategies, this would only be an oversimplification of lung cancer management. The TNM staging system has a limited capacity to define prognosis with a particular treatment, and it was not intended to do so. Optimal treatment can only be defined with clinical trials. Suitability for a particular therapy is based on the interaction of different factors: patient related (i.e., performance status), tumor related, and therapy related.

T Descriptors

The proposal for the eighth TNM has clearly reinforced the crucial impact that tumor size has on prognosis, with well-defined and validated new cut points. The survival analyses according to 1-cm cut points showed that from 1 to 5 cm, every cm counts, and the larger the tumor, the worse the prognosis. In lung cancer screening programs, where 60–70% of lung cancers are detected in stage I, recognizing the difference in prognosis of these smaller tumors is highly relevant [27]. While data regarding the involvement of the main bronchus that informed the seventh edition of TNM was not reliable, a distinction was made based on the distance to the carina (T3 if <2 cm, T2 if 2 cm or more). The new database has proven that the prognosis is the same, regardless the distance from the carina (as long as the carina is not involved), hence simplifying this descriptor to a single T2. Though invasion of the diaphragm has been grouped in T3 invasion by the seventh TNM, it has been shown to confer worse prognosis, and it has been upstaged to T4 in the proposed revision. Complete atelectasis was now showed to have a similar prognosis as partial atelectasis, and they were grouped together as T2. It is important to notice that there is a paucity of patients in this new database that underwent chemotherapy or radiation therapy as the sole treatment modality. Since the prognostic implications of these different T descriptors may differ when different therapies are applied, the generalizability of the new database findings is reduced.

N Descriptors

No major changes resulted from the analyses of the N descriptors, and it was proposed that the current

N0, N1, N2, and N3 definitions were carried to the eighth edition of TNM without modifications [22]. While the number of involved LN (tumor burden) is relevant in the nodal categorization of most tumors, for lung cancer the N category is solely based on the location of the involved LN. Unfortunately this new database did not have information regarding the exact number of LN involved. However, data on the number of LN "stations" was available from a few institutions, and further analysis was performed, evaluating the prognosis of single versus multiple LN stations at N1 and N2 levels and the prognosis of skip metastasis (N2 without N1). Patients with multiple N1 stations were found to have a similar prognosis as those with a single N2 stations, and patients with skip N2 metastases were found to have a better prognosis than those without skip metastases (who had N1 in addition to N2 disease). A major limitation of the new database with regard to the N descriptors is that roughly two thirds of the cases originated in Japan, where, despite the recommendations of the seventh TNM of adopting the IASLC lymph node map, the Naruke map was utilized [23]. One of the major discrepancies between the Naruke map and the IASLC map is that the Naruke map considers LN in the subcarinal space along the inferior border of the main stem bronchus to be station 10 (hence, N1), whereas these are considered as station 7 (and, therefore, N2) in the well-established IASLC nodal map. Thus, the above findings based on single versus multiple stations or skip metastases were not proposed as changes for the eighth edition TNM. The IASLC staging manual requires that three mediastinal and three N1 lymph nodes or stations be sampled. What remains unclear is whether they refer to the number of individual nodes or stations, which can create a significant difference in staging. Unfortunately, to date, there is no validated data to support a specific number of LN or stations to be sampled, and systematic intraoperative node assessment is recommended by clinical guidelines [11, 13].

M Descriptors

The new database was able to specifically analyze the prognostic impact of the burden of metastatic disease [24]. Single metastatic disease (M1b) was found to have a prognosis similar to that of M1a (pleural/pericardial effusion or nodules or contralateral lung nodule). Though metastatic disease to the adrenals seemed to confer a worse prognosis (in comparison to other organs), this could not be confirmed in all patient groups. Multiple metastases in one or multiple organs (M1c) were found to confer a worse survival in comparison to single metastatic disease. While retrospective data had already suggested this difference in prognosis between single and multiple metastases in lung cancer, this is the first time the concept is validated prospectively [28–30]. Future collection of the exact number of metastatic sites, size of metastatic lesions, pathological confirmation of lesions, and number of involved organs may help us discriminate subsets of patients with more favorable prognosis that may benefit from potentially curative therapies within clinical trials [24].

Summary

The UICC seventh edition of the TNM classification system was undoubtedly a major improvement in our scientific basis for the staging of lung cancer, supported by a large international database, and subjected to thorough internal and external validation process. The much richer and prospectively collected database that supports the recommendations for the eighth edition TNM has allowed the IASLC committees to propose multiple key modifications to the T and M descriptors as well as to the stage groupings. As these proposals are accepted and placed in practice, more ambiguities will come up to light, and it is paramount to gather, scrutinize, and share this data to better comprehend the limitations of this TNM system and to rise above them.

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Lung Cancer Staging Methods: A Practical Approach

23

Gerard Silvestri and Emerald Bañas

Abbreviations

CT	Computed tomography
EBUS-FNA	Endobronchial ultrasound fine needle aspiration
ECM	Extended cervical mediastinoscopy
EUS-FNA	Endoscopic ultrasound fine needle aspiration
FN	False negative
MRI	Magnetic resonance imaging
NPV	Negative predictive value
NSCLC	Non-small cell lung cancer
PET-CT	Positron emission tomography-computed tomography
RCT	Randomized controlled trials
SCM	Standard cervical mediastinoscopy
TBNA	Transbronchial needle aspiration
TNM	Tumor node metastasis
TTNA	Transthoracic needle aspiration
VATS	Video-assisted thoracoscopic surgery

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Introduction

The goal in evaluating patients presenting with symptoms concerning for lung cancer or with an incidental finding on chest imaging is the accurate determination of the extent of the disease and to group patients with similar prognosis together. Accurate staging of lung cancer is crucial for determining whether therapy should be initiated with curative intent or palliation for more advanced disease. The tumor node metastasis (TNM) staging for non-small cell lung cancer provides a reliable description of the degree of anatomical involvement by defining the different characteristics of the primary tumor (T), the presence or absence of regional lymph node involvement (N), and the presence or absence of metastases (M) [1]. If disease is localized within the thorax, the status of the mediastinal lymph nodes becomes critical for determining the best curative treatment approach. Staging with regard to a patient's potential for surgical resection however is most applicable to non-small cell lung cancer (NSCLC). Accurate staging also provides a common language for communication among healthcare providers and provides an avenue for appropriate enrollment in clinical trials.

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Initial Evaluation

The initial evaluation of a patient suspected of having lung cancer should begin with a thorough history and physical examination. Symptoms may arise from local effects of the tumor, from regional or distant extension, or from paraneoplastic phenomena. There is a wide range of symptoms due to intrathoracic effects of the tumor with cough, dyspnea, pain, and weight loss being the most common [2]. The most frequent sites of extrathoracic metastasis are the brain, bone, liver, and adrenal glands, in decreasing order [3]. Special emphasis should be given to organ-specific and non-organ-specific clues to potential metastatic disease so that the appropriate diagnostic tests can be utilized. For example, new onset severe headaches should alert the clinician to the possibility of brain metastases and be followed by ordering a brain magnetic resonance imaging (MRI). Paraneoplastic manifestations are remote effects not due to direct mass effect or metastasis. The two most common are humoral hypercalcemia of malignancy in squamous cell carcinoma and the syndrome of inappropriate antidiuretic hormone secretion in small cell lung cancer [4].

Asymptomatic patients may present with an incidental radiographic finding or as a result of screening. In such cases, every attempt should be made to review prior imaging studies to characterize the age and growth pattern of said abnormalities. Solid lesions stable in size for at least 2 years and ground glass non-solid nodules stable in size for at least 3 years have a low probability of being malignant [5].

Noninvasive Approach to Staging the Mediastinum

Radiographic Staging

The staging of patients with lung cancer begins with radiographic imaging, either with conventional imaging with chest computed tomography (chest CT) or further whole-body positron emission tomography (PET) or integrated PET-CT imaging even if the clinical evaluation is negative due to a high incidence of unsuspected metastatic disease [6]. An important initial first step is a chest CT scan, preferably with intravenous contrast, to differentiate mediastinal invasion of the primary tumor and mediastinal lymph nodes from vascular structure. This can be extended to include the upper abdominal region to assess the liver and adrenal glands for metastatic disease. The ultimate goal is to determine the highest radiographic stage prior to tissue diagnosis so as to appropriately guide which tissue sampling modality will provide the most advanced stage with the least possible risk. For example, a patient presenting with a 3 cm lung mass with mediastinal lymphadenopathy and a 2 cm liver lesion should undergo a liver biopsy as this would establish a diagnosis and provide a stage (stage IV) simultaneously.

Patients with lung cancer can generally be separated into four categories according to radiographic characteristics (Table 23.1, Fig. 23.1). Group A refers to patients with bulky disease invading the mediastinal structures so that discrete lymph nodes cannot be distinguished from the primary tumor. Stage here is able to be made based on radiographic features. The tumor that invades the mediastinum is designated T4,

Table 23.1 Definition of intrathoracic radiographic categories of lung cancer

Group	Description	Definition (by chest CT scan)
A	Mediastinal infiltration	Tumor mass within the mediastinum such that discrete lymph nodes cannot be distinguished or measured
B	Enlarged discrete mediastinal nodes	Discrete mediastinal nodes ≥1 cm in short-axis diameter on a transverse CT image
C	Clinical stage II or central stage I tumor	Normal mediastinal nodes (<1 cm) but enlarged N1 nodes (>1 cm) or a central tumor (within proximal one-third of the hemithorax)
D	Peripheral clinical stage I tumor	Normal mediastinal and N1 nodes (<1 cm) and a peripheral tumor (within outer two-thirds of hemithorax)

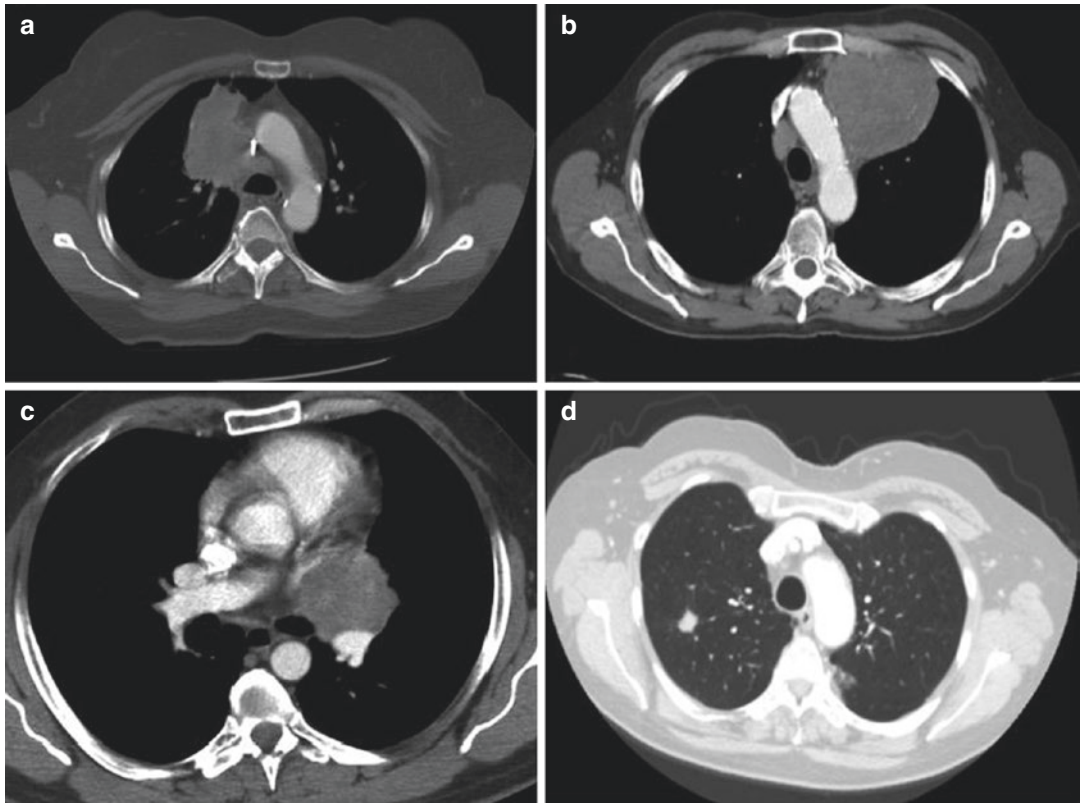

Fig. 23.1 The American College of Chest Physicians intrathoracic radiographic (CT scan) categories for lung cancer. (**a**) Mediastinal infiltration by tumor. (**b**) Enlarged discrete N2/N3 nodes. (**c**) A central tumor or a tumor with enlarged N1 nodes but a normal mediastinum. (**d**) A peripheral small tumor with normal-sized lymph nodes

effectively stage IIIB. Group B involves patients with mediastinal lymphadenopathy in whom an isolated lymph node can be distinguished from the primary tumor [6]. The last two groups have normal-sized mediastinal lymph nodes. Group C refers to patients with a centrally located primary tumor or suspected N1 disease, increasing the risk for N2/N3 nodal involvement. Group D refers to patients with peripheral clinical stage I tumor where the chance of distant metastases or mediastinal involvement is low [7–9].

Role of Positron Emission Tomography (PET) Imaging

Whole-body PET imaging in preoperative staging of lung cancer has been shown to increase identification of patients with mediastinal and extrathoracic disease compared to conventional staging [10]. In addition, PET improves discrimination between N0/N1 and N2/N3 diseases [11]. However, one of the downsides to increasing sensitivity in detecting occult metastases is incorrectly upstaging the disease in more patients, potentially withholding possible curative management. In five randomized controlled trials (RCTs) involving PET scans, this would have occurred in 5–42%; however, in these studies, the requirement of confirmation of these abnormal findings prevented this [6].

There have been several small randomized controlled trials with conflicting results. Two RCTs utilizing PET scanning to accurately stage lung cancer found a significant reduction, from approximately 40 to 20%, in the number of futile thoracotomies performed (defined as thoracotomy with the finding of a benign

lesion, pathologically confirmed lymph node involvement, unresectable disease, discovering metastatic disease, or recurrence or death from any cause within 1 year) but did not affect overall mortality [12, 13]. However, this was not replicated in an RCT evaluating patients with stage I–II NSCLC [14].

PET scanning is not a conclusive test, and suspicious lesions do not obviate the need for histologic evaluation of the mediastinal lymph nodes for accurate staging. In an analysis of a previously reported trial, PET-CT had a 70% sensitivity and 94% specificity; however, of the 22 patients with PET-positive mediastinal nodes, 8 did not have tumor. The positive predictive value and negative predictive value are 64% and 95%, respectively, corroborating the need for pathologic confirmation with a positive PET-CT [15]. The frequency of false-negative mediastinum on PET-CT has been reported to range between about 15 and 28% [11, 16]. Furthermore, the PET imaging results should be interpreted in relation to lymph node size. The negative predictive value in normal-sized lymph nodes (<10 mm) is significantly higher (96% vs. 70%), and the positive predictive value is lower (43% vs. 71%). Thus, in patients without mediastinal lymphadenopathy, a negative PET-CT is highly valid and patients may proceed to surgery unless they have a central tumor. However, the false-negative rate is considerable in enlarged lymph nodes without FDG uptake (30%) [11]. In such cases, needle techniques to assess the mediastinum (EUS-FNA, EBUS) would be the most rational next step.

Invasive Approach to Staging the Mediastinum

The initial radiographic staging helps the clinician categorize the patient into one of the four radiographic groups previously discussed (Table 23.1). This classification helps guide the selection of invasive test and defines the performance characteristics of these tests. The former relies on anatomic factors (i.e., location, accessibility, and size of the nodes), while the latter is dependent on the local availability and operator experience.

Transthoracic Needle Aspiration

Leyden performed the first transthoracic needle aspiration (TTNA) to confirm a pulmonary infection in 1883 [17]. Since then, TTNA has become an efficacious procedure with no significant morbidity mainly due to two major factors, advances in imaging technology and improvements in histopathology [18].

It involves passing a needle percutaneously under image guidance to either aspirate or biopsy (TTNB) tissue. The transition from fluoroscopy to computed tomography led to improved visualization of even smaller lesions that can be approached with a greater margin of safety and accuracy.

The sensitivity of TTNA for staging the mediastinum has been reported to be high at 91% in a meta-analysis of five studies involving 215 patients [19]. These studies may be inherently biased because the study patients enrolled had bulky mediastinal disease and extrapolation of these results to patients with lesser amounts of mediastinal spread for staging purposes may be inappropriate. In addition, due to the proximity of the major thoracic vessels and the heart to the mediastinal lymph nodes, TTNA is mostly limited to the superior mediastinal lymph nodes. Iatrogenic pneumothorax is the most common complication, averaging 10% when using a "protective technique" but may go up to 60% if the lung parenchyma is traversed [20]. These factors limit the use of TTNA in staging the mediastinum especially in COPD patients with severe emphysema.

Transbronchial Needle Aspiration

Transbronchial needle aspiration (TBNA) was first reported by Dr. Schieppati in 1949 although it was in 1978 when Wang and colleagues described the diagnosis of a paratracheal mass by TBNA through a rigid bronchoscope [21].

TBNA for mediastinal staging is performed through the bronchoscope. It involves passing the needle catheter, which comes in different sizes, through the working channel of the bronchoscope

and then directed to the target lesion. The needle is then passed through the bronchial wall, and material is aspirated for tissue sampling. It can be performed as an unguided procedure during bronchoscopy or under image guidance using a bronchoscope with endobronchial ultrasound or electromagnetic navigational capability. It is used most commonly to assess subcarinal lymph nodes and less frequently with paratracheal lymph nodes due to difficulty in adequately directing the bronchoscope and needle. Rapid on-site cytological evaluation of the tissue obtained is a cost-effective method to improve the yield, eliminating unnecessary passes during a procedure [22].

The overall median sensitivity was moderate at 78% (range 14–100%), and the negative predictive value was 77% in systematic review evaluating 2408 patients. The reported specificity and false-positive rates were 100% and 0%, respectively [6]. The patients included in the studies mainly had N2/N3. As such, these results can be reliably applied to patients with bulky mediastinal disease; however, the high false-negative rate makes TBNA less useful for staging the mediastinum in patients with normal-sized lymph nodes. A negative TBNA therefore cannot effectively rule out mediastinal nodal involvement, and additional staging procedures should be performed. In a comparative study directly evaluating the accuracy of TBNA against endobronchial ultrasound fine needle aspiration (EBUS-FNA) and endoscopic ultrasound fine needle aspiration (EUS-FNA), TBNA was less sensitive when individually compared to EBUS-FNA and EUS-FNA in identifying mediastinal involvement (36% vs. 69%). This effect was seen across different subgroups including individuals with stations favorable to TBNA, such as a PET-positive subcarinal node or enlarged subcarinal node [23].

Endoscopic Ultrasound with Needle Aspiration

Endoscopic ultrasound with fine needle aspiration (EUS-FNA) for cytologic diagnosis was initially used in pancreatic diseases but was first described for mediastinal node aspiration in 1993 [24]. It is generally safe and well tolerated under local anesthesia and conscious sedation.

EUS is performed using an endoscope with an ultrasound transducer at the tip, also known as an echoendoscope. There are two types of echoendoscopes, radial and curvilinear; the former provides a 360° view, while the latter is used for aspiration and provides a 180° view of the structures adjacent to the gastrointestinal tract. The inferior and posterior mediastinum is localized through the esophageal wall providing direct visualization of stations 4L, 5, 7, 8, and 9. However, EUS cannot evaluate the anterior mediastinum and right paratracheal lymph node stations due to air interference from the trachea; thus, complete visualization of the mediastinum cannot be achieved with EUS alone. The left adrenal gland can also be sampled when it is enlarged and PET avid, potentially offering diagnosis and complete staging with a reported sensitivity and NPV of 86% and 70%, respectively [25]. On the other hand, the diagnostic yield of EUS-FNA for detecting malignant disease in liver lesions is significantly lower at 58% [26].

In a meta-analysis looking at 18 eligible studies, the utility of EUS-FNA for staging mediastinal lymph nodes (N2/N3) was evaluated [27]. The pooled sensitivity was 83%, and the pooled specificity was 97%. The sensitivity and specificity were slightly higher at 90% and 97%, respectively, among patients with mediastinal lymphadenopathy on imaging. Comparatively, among patients enrolled without enlarged lymph nodes, the pooled sensitivity was significantly lower at 58% [27]. Furthermore, in a systematic analysis of 2433 patients, the median sensitivity and specificity were comparable at 89 and 100%; however, most of these patients were generally selected because they had nodal disease amenable to EUS-FNA (6). Due to its modest negative predictive value at 78%, a nondiagnostic result will need to be further evaluated [27].

In a small RCT evaluating the value of EUS-FNA in mediastinal staging, EUS-FNA together with rapid on-site evaluation by a cytopathologist was found to reduce the need for surgical staging by 68% and was found to have a higher but not

statistically significant sensitivity (93% vs. 73%) in detecting malignant disease. The complication rate was less in the EUS group at 0% vs. 5%, although this was not statistically significant [28].

Endobronchial Ultrasound with Needle Aspiration

Endobronchial ultrasound (EBUS) is performed during bronchoscopy that uses ultrasound to visualize surrounding structures within the airway wall and mediastinum. There are two types of EBUS, the radial probe EBUS (RP-EBUS) and the convex probe (CP-EBUS). Briefly, RP-EBUS has a higher resolution such that airway structure and parenchymal lesions are visualized in better detail for subsequent TBNA; however, it cannot be used to biopsy targets in real time. The capacity to allow for real-time ultrasound-guided TBNA was first reported in 2004, with the incorporation of a convex ultrasound probe [29].

The RP-EBUS is performed by placing a conventional bronchoscope in the area of interest and by inserting a radial ultrasound probe through the working channel followed by inflating the probe balloon with water and subsequent TBNA. The same technique is used for CP-EBUS, providing a view that is 35° forward oblique. Color flow and Doppler features allow identification of vascular and cystic structures.

EBUS can access a wide range of mediastinal and hilar lymph nodes including 2R, 2L, 3P, 4R, 4L, 7, 10R, 10L, 11R, and 11L (Fig. 23.2).

The overall median sensitivity of EBUS-NA in mediastinal staging is reported to be at 89% in a systematic review of 2756 patients, with values ranging from 46 to 97%. The median NPV was 91% [6]. Most of the studies in this review included patients with bulky lymphadenopathy, mostly radiographic group B and some A and C. However, two studies evaluated the performance of EBUS-FNA in patients with normal mediastinum by CT scan and PET-CT, respectively. The prevalence of mediastinal disease was lower in the negative PET-CT group, likely due to the higher sensitivity of PET-CT to detect disease. Despite this, the negative predictive value was comparable in both groups at around 96% [30, 31].

Combined EUS-FNA and EBUS-FNA

EUS-FNA and EBUS-FNA have a complimentary diagnostic yield and can potentially allow complete access to all nodal stations with EUS providing access to posterior and inferior mediastinum as well as the evaluation of the left adrenal gland in selected cases and EBUS providing access to the anterior and superior mediastinal lymph nodes. In a systematic review of seven studies including 811 patients, the pooled median sensitivity and specificity were 91% and 100%, respectively [6]. Although the concept of performing both procedures in one setting is ideal, it is often difficult to achieve due to the uncoordinated use of EUS and EBUS in most centers.

Surgical Staging

The most common surgical modalities used for mediastinal staging of non-small cell lung cancer include standard cervical mediastinoscopy, video-assisted thoracoscopic surgery (VATS), and anterior mediastinotomy (Chamberlain procedure). Technique selection usually relies on clinical judgment, knowledge of diagnostic accuracy, operator proficiency, and local expertise.

Standard Cervical Mediastinoscopy (SCM)

Standard cervical mediastinoscopy is an invasive modality that is used to evaluate the superior and middle mediastinum for lung cancer staging. It was first described by Harken in 1954 when they inserted a laryngoscope into the mediastinum through a supraclavicular incision, and lymph node biopsies were taken [32]. Carlens from Sweden developed the pretracheal, suprasternal approach, as it is practiced today [33].

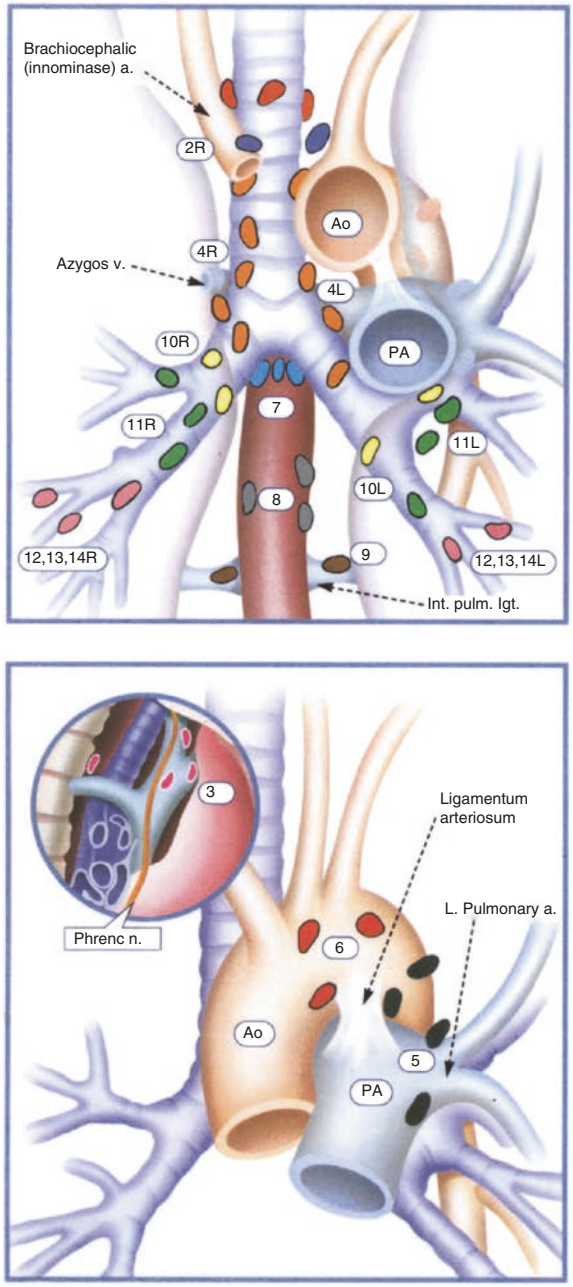

Fig. 23.2 Regional lymph node stations for lung cancer staging. Printed with permission from Naruke et al. and the ATS/North American LCSG

Its major advantage over minimally invasive techniques is direct visualization of nodes for sampling and dissection, thereby allowing relatively large biopsies to be obtained, yielding more than adequate samples for culture, immunohistochemical, and molecular analysis.

Mediastinoscopy is usually an outpatient procedure performed in the operating room under general anesthesia requiring around 1–2 days for

recovery. A single institutional review of 2145 patients undergoing mediastinoscopy over 9 years showed an overall reported morbidity and mortality of 1.07 and 0.05%. The most frequent reported complications included recurrent laryngeal nerve injury, hemorrhage, tracheal injury, and pneumothorax [34].

A midline transverse incision is made immediately above the sternal notch providing access to pretracheal (1, 3), paratracheal (2R, 2L, 4R, 4L), anterior subcarinal (7), and occasional hilar (10R, 10L) stations (Fig. 23.2). Nodal stations that cannot undergo sampling using this technique include the posterior subcarinal (7), the inferior mediastinal (8, 9), the aortopulmonary window (5), the anterior mediastinal, and the lobar/interlobar (11–14) stations. The advent of video mediastinoscopy has permitted the concurrent use of multiple surgical instruments via the mediastinoscope which allows better visualization, more extensive sampling (including posterior station 7), and true mediastinal lymphadenectomy.

In a review of 9257 pooled patients, the overall median sensitivity of standard cervical mediastinoscopy compared to videomediastinoscopy and mediastinal lymphadenectomy was reported to be 78%, 89%, and 94%, respectively. The median NPV was 91%. The FN cases were predominantly nodal stations that were not accessible by the traditional mediastinoscopy and most likely affected operator diligence in node dissection and sampling. Ideally, the paratracheal and anterior subcarinal lymph nodes should be dissected routinely with at least one node sampled from each station especially in patients without clinical suspicion of node involvement [6].

Anterior Mediastinoscopy

Due to lymphatic drainage patterns, malignancies involving the left upper lobe have increased tendencies to involve nodes in the aortopulmonary window (station 5) and prevascular (station 6) stations (Fig. 23.2). Traditionally, these lymph nodes are classified as N2 nodes and are difficult to gain access to and cannot be reached by minimally invasive techniques or by standard cervical mediastinoscopy. In 1966, McNeill and Chamberlain described a technique of left anterior mediastinotomy via an incision in the second or third intercostal space just to the left of the sternum in order to gain access to these stations [35]. It has the advantage of providing access to left upper lobe tumors for simultaneous resection in the instance that there is no evidence of nodal involvement or distant metastasis.

In a systematic review, the reported median sensitivity of the Chamberlain procedure in the detection of metastatic nodal disease was approximately 71% among a pool of 238 patients while the median NPV was 91% [6]. There is a paucity of data comparing the efficacy of the Chamberlain procedure with VATS and other minimally invasive techniques, but in a small study of 112 patients, VATS was able to correctly identify malignancy in 100% patients compared to 83% patients that underwent Chamberlain procedure [36].

Extended Cervical Mediastinoscopy

Extended cervical mediastinoscopy (ECM) offers increased access to the sampling region usually offered by standard cervical mediastinoscopy whereby the subaortic and para-aortic lymph nodes can be reached in addition to nodal stations 1, 2, 3, 4, 7, and 10 (Fig. 23.2). The main advantage of ECM is its ability to provide additional access to the APW when staging tumors of the left upper lobe without the surgical risk associated with a Chamberlain procedure. However, ECM is not widely used and is only limited to a few centers that are specialized to this staging technique.

Video-Assisted Thoracic Surgery

The practical use of thoracoscopy was first reported by Dr. Jacobaeus in 1910 when he utilized a cystoscope for a thoracoscopic diagnosis of tubercular intrathoracic adhesions [37]. The traditional thoracoscope had several limitations including a limited view of the field that is also mostly restricted to the operator [38].

With the introduction of video-assisted imaging, the functional capacity of thoracoscopy has been significantly amplified. It magnifies the image with the aid of better instruments as well as shares the images with other clinicians performing the procedure.

It is a major surgical procedure that requires general anesthesia and hospital stay, incurring higher costs for training and equipment. It is typically utilized when other alternative modalities cannot access the tumor or are nondiagnostic. The major advantage of VATS is direct visualization of the lung and mediastinal structure including almost all nodal stations. It can potentially evaluate the extent of involvement by the primary tumor (T), mediastinal lymph node involvement (N), and pleural involvement (M1a) possibly offering intraoperative diagnosis, staging, and therapy. The major disadvantage of the latter is the increased morbidity and mortality associated with surgery.

The staging accuracy of VATS is widely varied. In a 2013 meta-analysis of four studies, the reported median sensitivity was 99% (range 58–100%) and the NPV was 96% (range 88–100%) [6]. The study with the lowest reported sensitivity was a prospective, multicenter study, which is probably more applicable to most institutions compared to highly specialized centers with a more focused interest [39].

VATS has also been shown to provide additional information in the evaluation of T4 lesions. T4 lesions usually represent inoperable stage III disease. Staging by VATS may downstage the disease and potentially offer surgery as part of management. In a prospective, observational study, patients with suspected IIIB NSCLC underwent thoracoscopy. Among 30 patients with T4 disease, 9 were downstaged to IIIA making them potentially operable and 2 to stage II, which is operable. This study also reported the ability of VATS to upstage the disease to stage IV by identification of pleural studding in unsuspected cases [40].

Comparison of Surgical Staging and Minimally Invasive Techniques

Accurate staging is a major driver of appropriate lung cancer management and relies heavily on invasive biopsy, which can be approached through surgical and minimally invasive techniques. In a randomized controlled trial of 241 patients, mediastinal nodal metastasis by surgical staging was significantly less sensitive than endosonography (EUS-FNA and EBUS-FNA) followed by surgical staging in case no nodal involvement was found at endosonography (79% vs. 94%), with NPV at 86% and 93%, respectively [41]. As such, in the most recent iteration of the American College of Chest Physicians (ACCP) Lung Cancer Guidelines, minimally invasive needle techniques are the first tests of choice to confirm mediastinal involvement in accessible lymph node stations and to be followed by surgical biopsy if these are negative. Table 23.2 compares the sensitivities and specificities between surgical and minimally invasive techniques in a meta-analysis [6].

Imaging to Evaluate for Metastatic Disease

The initial evaluation and routine imaging typically alerts the clinician for possible metastatic disease. The importance of a thorough history and physical exam cannot be emphasized enough.

Table 23.2 Accuracy of staging tests in lung cancer patients: meta-analysis ACCP guidelines

Procedure	Number of studies	*N*	Sensitivity	Specificity
Mediastinoscopy	33	9267	78	100
EUS	26	2443	88	100
EBUS	31	2756	89	100
EBUS/EUS	7	811	91	100

Brain

In a review of 18 studies evaluating the utility of CT scanning in detecting metastasis, 9 studies included patients with a negative clinical evaluation, and the median predictive value of a negative clinical evaluation was 97% (79–100%) [42]. In a screen-detected population, among patients with clinical stage IA, one in eight underwent brain imaging, but none had intracranial metastasis [43], suggesting that this is not a cost-effective approach to detecting metastatic disease. However, routine limited brain MRI was found to increase detection of brain metastasis to 20.8% (38/183 patients) compared to symptom-directed imaging 4.6% (6/131 patients) [44], suggesting a role of brain MRI in symptomatic patients.

The utility of PET scanning in detecting brain metastases is poor due to the background brain FDG uptake, small size of most brain metastases, and the variable biologic features of brain metastases, which can either be hypermetabolic or hypometabolic.

Bone

PET scanning appears to be superior to radionuclide bone scintigraphy for detection of bone metastases in two direct comparative studies with sensitivities of 93–100% compared to 82.8–92.5% [45, 46]. Bone scintigraphy can be used if PET scan is not available; however, there is a high false-positive rate due to the high prevalence of degenerative and traumatic disease in the general population, particularly those who are in the age range to be diagnosed with lung cancer.

Abdomen

The sensitivity of a negative clinical evaluation for abdominal metastasis was shown to be 97% (82–100%) [42]. However, it is common to encounter adrenal and liver lesions with routine CT scanning. The dilemma lies on what diagnostic modality to utilize afterward to distinguish benign from malignant disease.

In a case series of 94 patients with 113 adrenal masses, the sensitivity, specificity, and accuracy of PET for detection of metastatic disease was 93%, 90%, and 92%, respectively [47]; however, small lesions less than 1.5 cm may be missed.

Over the past decade, whole-body PET scanning has become increasingly utilized to aid in the detection of metastatic disease in distant sites. This concept is highlighted by several studies focusing on possible metastases to the adrenal glands [48, 49] and liver [50] where PET has outperformed other modalities in accurately differentiating cancer from benign disease.

In a study evaluating 122 adrenal masses, CT scans with specific adrenal imaging protocols was reported to have a sensitivity of 100% and specificity of 95%, which is significantly improved from conventional CT [51]. Percutaneous biopsy and rarely adrenalectomy are considered for isolated adrenal lesions; however, biopsy would not be needed in the setting of widespread metastatic disease.

Triphasic CT (non-contrast CT, nonarterial, and portal venous phases) can usually differentiate benign hepatic lesions such as hemangioma, focal nodular hyperplasia, and hepatic adenoma from malignant lesions [6]. Data suggests that PET scanning can increase detections of malignancy compared to CT. In a case series with 64 patients with malignancy and possible liver involvement, PET demonstrated a sensitivity of 97% and specificity of 88% compared to 93% and 75%, respectively, for CT [52].

Approach to the Patient

A practical approach to the patient with suspected lung cancer dictates a timely diagnosis and exact staging so that appropriate treatment can be administered. This should be tailored according to the patient's values and preferences, clinical presentation, and local technical expertise with imaging providing a road map and invasive biopsy serving as an instrument for histologic diagnosis and staging.

The ACCP recommends an initial thorough clinical evaluation to accurately define the tumor

stage. In patients eligible for treatment, a CT scan of the chest with contrast is the imaging of choice followed by additional extrathoracic imaging in the presence of an abnormal clinical evaluation. PET imaging is recommended to evaluate for metastases except for the brain, where MRI is a more appropriate diagnostic exam. If there is suggestion of metastasis by imaging, further evaluation of the abnormality with tissue sampling should be done to confirm the stage before treatment is initiated. Patients with discrete mediastinal lymph node enlargement (with or without PET activity) or normal mediastinum but with PET activity require invasive staging over staging by imaging alone. If there is intermediate to high suspicion of N2/N3 involvement, a needle technique over surgical staging is recommended as the best first test. In patients with a peripheral clinical stage IA tumor, invasive preoperative evaluation of the mediastinal nodes is not required. And finally for patients with left upper lobe cancer, it is suggested that invasive assessment of the aortopulmonary window nodes be performed if other mediastinal node stations are found to be uninvolved [6].

Case-Based Approach

Case 1

A 67-year-old man who is a former smoker with a 45-pack-year smoking history presented with unintentional 20 pound weight loss, productive cough, hemoptysis, and jaundice over 2 months. Initial CT scan of the chest showed a right upper lobe paramediastinal mass which extends into the mediastinum 3.7 × 4.5 cm with mediastinal lymphadenopathy (Fig. 23.3). Subsequent PET-CT showed increased metabolic activity in the right upper lobe and mediastinum with multiple focal areas of increased uptake in the liver (Fig. 23.4). A percutaneous liver biopsy was performed and pathology revealed squamous cell carcinoma with a lung primary. Thus, this patient was staged as 4B. He did not want palliative chemotherapy and instead opted for comfort care.

Case 2

A 58-year-old Caucasian woman who is a current smoker with a 32-pack-year smoking history presented to an urgent care facility with right-sided pleuritic back pain radiating to the front associated with anorexia and a 7 lb weight loss. A CT chest was done which showed a 4.9 × 5.2 × 6.3 pleural-based mass in the posterior periphery of the right upper lobe with central cavitation. A PET-CT was done which showed hypermetabolic activity in the right lower lobe and right hilar lymph node (Fig. 23.5). Endobronchial ultrasound with needle aspiration was performed to stage the mediastinum, which showed N2 disease. She was diagnosed with stage IIIA adenocarcinoma of the lung and underwent chemoradiotherapy.

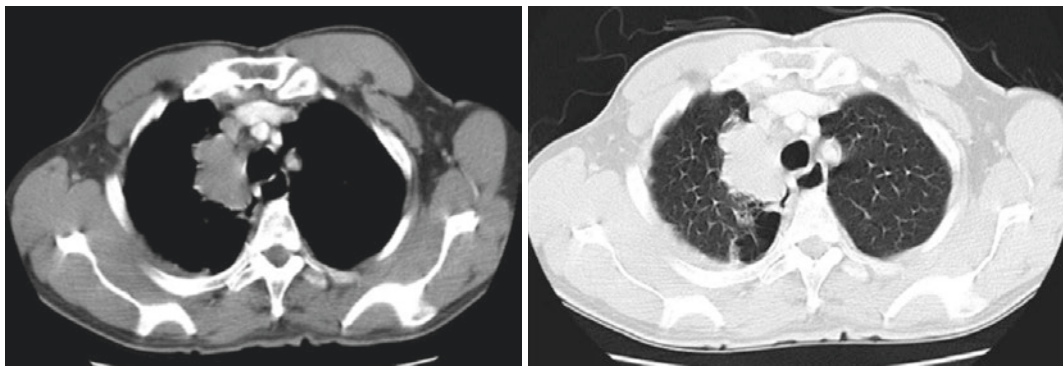

Fig. 23.3 Right upper lobe paramediastinal mass which extends into the mediastinum with mediastinal lymphadenopathy

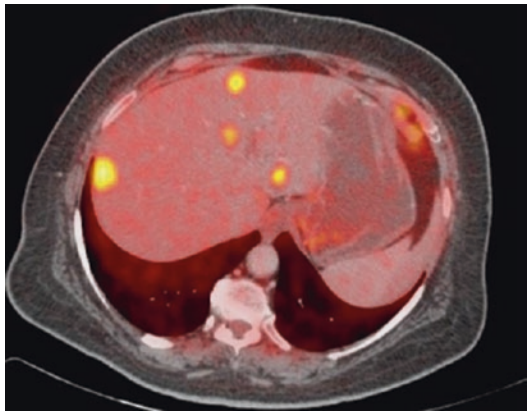

Fig. 23.4 PET-CT showing multiple focal areas of increased metabolic activity in the liver

Case 3

A 64-year-old man, previous smoker with a 15-pack-year smoking history, presented with an abnormal PET-CT scan. He initially presented to the emergency department with a productive cough, dyspnea, and tachycardia. A CT chest with contrast was done to rule out pulmonary embolism (PE). He did not have a PE but was found to have a 1.1 × 1.9 cm right upper lobe nodule with a 1.0 cm 4R lymph node. PET-CT was then ordered by his primary care provider, which showed mildly increased activity in the right paratracheal lymph node with an SUV of 2.6 (Fig. 23.6). Thus, the clinical stage was IIA. An EBUS with needle aspiration of a 4R lymph node was performed which showed

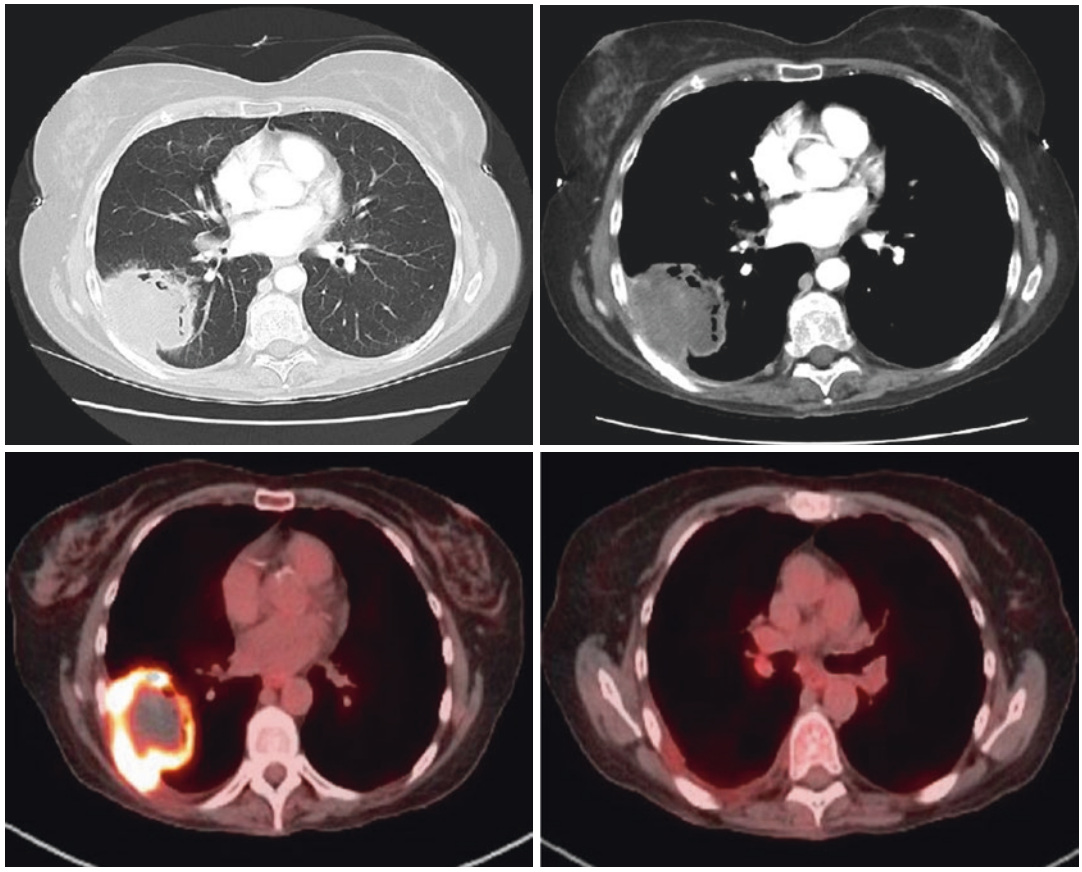

Fig. 23.5 Pleural-based mass in the posterior periphery of the right upper lobe with central cavitation with subsequent PET-CT showing hypermetabolic activity in the right lower lobe and right hilar lymph node

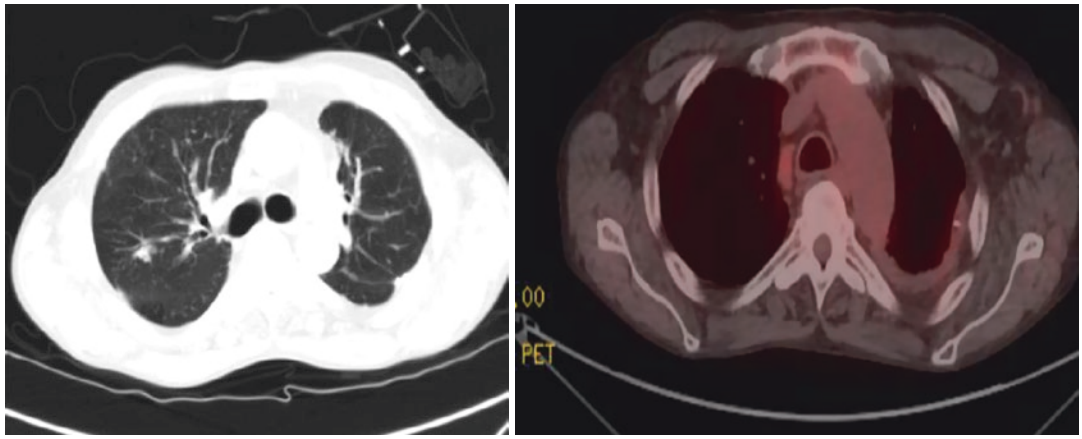

Fig. 23.6 Right upper lobe nodule measuring 1.1 × 1.9 cm with a hypermetabolic 1.0 cm 4R lymph node with an SUV of 2.6

reactive lymphocytes and no evidence of malignancy. The pathologic stage at the time of surgery was T1AN0M0.

Summary

The initial approach to patients suspected of having lung cancer is to acquire sufficient clinical and radiologic information to guide further imaging, which then serves as a road map to tissue sampling, histologic diagnosis, and accurate staging, at the same time taking into consideration the patients' values and preferences. CT scan of the chest is the first imaging of choice with further extrathoracic imaging dictated by the clinical evaluation. The role of PET-CT in the lung cancer staging has proven to be invaluable because it can provide important information about the tumor, mediastinum, and distant metastases with the exception of the brain. However, not all abnormalities detected by these imaging studies are always malignant and thus require tissue confirmation of malignancy so that patients are not denied the chance for potential curative treatment.

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Mediastinoscopy, Its Variants and Transcervical Mediastinal Lymphadenectomy

24

Ramón Rami-Porta and Sergi Call

Introduction and Definition of the Procedure

Mediastinoscopy is a surgical procedure that allows the inspection and the palpation of the upper mediastinum as well as the taking of biopsies of lymph nodes, tumours or any other tissue within the range of the exploration. For lung cancer staging, the range of exploration includes the cervical lymph nodes of the sternal notch; the lymph nodes along the trachea and both main bronchi, that is, the superior and inferior, left and right, paratracheal lymph nodes; the subcarinal nodes; and the right and left hilar lymph nodes, according to the International Association for the Study of Lung Cancer (IASLC) lymph node map [1]. Inspection and palpation of the upper mediastinum are essential to identify the lymph nodes, see their aspect and feel their consistency and degree of attachment to mediastinal structures, as well as differentiate between mere contact and tumour invasion of the mediastinum. The removal or the taking of biopsies of lymph nodes is performed under direct vision, and these specimens allow the pathologist to examine the status of the nodal capsule and the involvement of the extranodal tissues that are criteria of incomplete resection [2].

History and Historical Perspective

When Eric Carlens described the technical details of mediastinoscopy and reported six exemplary cases in 1959, he had already performed more than 100 procedures without complications [3]. Mediastinoscopy was the culmination of a series of procedures developed to diagnose intrathoracic diseases without relying on thoracotomy. As early as 1942, Albanese, from Buenos Aires, Argentina, described an incision over the sternocleidomastoid muscle to explore and biopsy the paratracheal and the para-oesophageal lymph nodes [4]. Seven years later, in 1949, Daniels described the biopsy of the scalene fat pad through a small supraclavicular incision. This biopsy allowed the diagnosis and staging of lung, digestive and gynaecological cancers and the diagnosis of intrathoracic inflammations and infections, such as sarcoidosis and tuberculosis, respectively [5]. A step forward was the insertion of a laryngoscope through the cervical incision performed to reach the scalene fad pad. This exploration was a limited unilateral

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mediastinoscopy and was published in 1954 by Harken et al. [6]. One year later, Radner used an incision over the cervical midline to explore the paratracheal lymph nodes [7].

Mediastinoscopy was quickly spread in Europe as the books by Otto Jepsen [8] and by Tauno Palva [9] show. The main advantage of mediastinoscopy was that it allowed the diagnosis of intrathoracic diseases with no need to open the chest cavity. For lung cancer, diagnosis and staging were simultaneous in many cases. Tuberculosis, sarcoidosis, silicosis, vascular anomalies, mediastinal tumours and inflammation could also be diagnosed via this transcervical approach. Its systematic indication in the clinical staging before lung resection showed that those lung cancers with involved mediastinal lymph nodes identified at mediastinoscopy had worse prognosis than those with nodal disease identified at thoracotomy [10]. This gave a prognostic perspective to the procedure in addition to diagnosis and staging. With the introduction of computed tomography (CT) in clinical practice, the most common trend was to indicate mediastinoscopy when there were abnormal lymph nodes [11]. However, its systematic use, regardless of the size of the lymph nodes on CT scan, was favoured by some authors even for early stages [12].

The design of the video-mediastinoscope by Lerut in 1989 and of the two-bladed video-mediastinoscope by Linder and Dahan in 1992 increased the possibilities of the exploration for staging and therapeutic indications, leading to mediastinal lymphadenectomy and complex therapeutic procedures, such as closure of bronchopleural fistula and lobectomy through the transcervical approach [13–17].

Indications and Contraindications

For lung cancer staging, the guidelines of the American College of Chest Physicians (ACCP) revised in 2013 recommend invasive nodal staging in the following situations: (a) discrete mediastinal lymph node enlargement with or without PET uptake in mediastinal lymph nodes, (b) PET activity in mediastinal lymph nodes and abnormal lymph nodes on CT, (c) high suspicion of N2 or N3 disease either by lymph node enlargement on CT or PET uptake and (d) intermediate suspicion of N2 or N3 disease by CT and PET and a central tumour or N1 disease. According to these guidelines, invasive mediastinal staging would not be indicated in patients with massive mediastinal infiltration or in those with stage IA tumours without any mediastinal nodal abnormality on CT and PET [18].

In a similar way, the recommendations for invasive mediastinal staging of the revised European Society of Thoracic Surgeons (ESTS) guidelines are (a) positive mediastinal nodes on CT, PET or PET-CT and (b) when there is no evidence of N2-N3, but there is suspicion of N1 disease, in central tumours larger than 3 cm and in adenocarcinomas with high PET uptake. Invasive staging could be spared in patients with no enlarged lymph nodes on CT or abnormal uptake on PET and tumours less than 3 cm in greatest dimension located peripherally in the outer one-third of the lung [19].

The ACCP and the ESTS favour the use of endoscopic procedures for initial invasive staging, such as transbronchial needle aspiration (TBNA), endobronchial ultrasound-guided fine needle aspiration (EBUS-FNA) or oesophageal ultrasound-guided FNA (EUS-FNA). If these explorations are positive for cancer, the information may be adequate to start a multidisciplinary treatment protocol. However, if they are unavailable or are negative, a surgical technique is recommended to confirm their negative results, because their negative predictive value is too low to make further therapeutic decisions [18, 19]. The most common surgical technique is mediastinoscopy, but for staging purposes, mediastinotomy or thoracoscopy could be performed if the target lesion is within the range of these explorations.

The ESTS guidelines also recommend to pathologically confirm tumour response after induction therapy. As at initial staging, this can be done by endoscopic techniques, but if their results are negative, then a surgical procedure is recommended. Over the years, remediastinoscopy has proved to be a safe and reliable restaging

method [20–22]. It is important to confirm or rule out persistent nodal disease and tumour progression after induction therapy. Persistent nodal involvement and progressive disease are unfavourable prognostic factors, and lung resection should be avoided because it does not add any survival benefit [20, 23, 24].

There are very few contraindications. Severe neck rigidity and large goitres are anatomic abnormalities that can prevent the correct insertion of the mediastinoscope, but they are extremely rare in lung cancer patients. Aortic aneurism is a contraindication, because the aortic arch is compressed by the mediastinoscope when it is inserted in front of the trachea and may be injured. Abnormal coagulation tests are a relative contraindication. As in any other intervention, they should be corrected before the operation and the operation rescheduled when they are normalized. In the past, superior vena cava obstruction, a previous mediastinoscopy or a previous mediastinal operation by median sternotomy, tracheostomy and total laryngectomy were considered contraindications, but experience has proved that mediastinoscopy can be performed safely when other less invasive procedures have not established a diagnosis [25, 26].

Description of the Equipment Needed

General

For the incision and initial dissection, the following instruments are needed: standard surgical knife, dissection forceps, Mayo and Metzenbaum scissors and a right angle dissector. Silk 2-0 sutures may be necessary to ligate small veins. Absorbable 2-0 and 3-0 sutures are used to close the incision in two layers.

Specific

There are two types of scopes: the conventional ones and the video-mediastinoscopes that, since the late 1980s, are progressively replacing the former. Mediastinoscopes are in the right angle shape, with the vertical arm as handle and the horizontal arm, in the shape of a truncated cone, as the scope proper. The conventional mediastinoscopes are in a single piece, and the video-mediastinoscopes are made either in a single piece or in two spreadable blades to widen the operative field. Video-mediastinoscopes are connected to a camera, and the exploration is seen on a television monitor. The equipment is completed with a light source and a recorder to register the operations.

The dissection-suction-coagulation device is fundamental to dissect and identify the lymph nodes from the peritracheal fatty tissue. Suction keeps the operative field clean at all times, and coagulation controls bleeding from small veins, lymph nodes or fatty tissue.

A glass tube connected to a needle on one side and to suction on the other is used for puncture test when the nature of the structure to be biopsied is not clear. This is more useful when the conventional mediastinoscope is used. Mediastinal structures are much better seen with the video-mediastinoscope, and this makes the puncture test rarely necessary.

There are several types of biopsy forceps. Some are spherical and others oval, and they come in different sizes.

There also are several types of graspers and ring forceps that allow the surgeon to hold the tissue with one hand and dissect with the other, while the assistant holds the mediastinoscope in place.

Endoscopic clips should be available in case clipping of the bronchial arteries is necessary. Although not strictly necessary, the new energy devices for haemostasis and cutting may reduce the risk of bleeding and are easy to use especially with the two-bladed video-mediastinoscope that allows a larger operative field for the insertion of these devices. They are especially valuable at the beginning of the learning curve to reduce the risk of bleeding and of injury of the left recurrent laryngeal nerve.

Figure 24.1 shows the basic instruments for mediastinoscopy and Fig. 24.2 the endoscopy tower and the general view of the operative field.

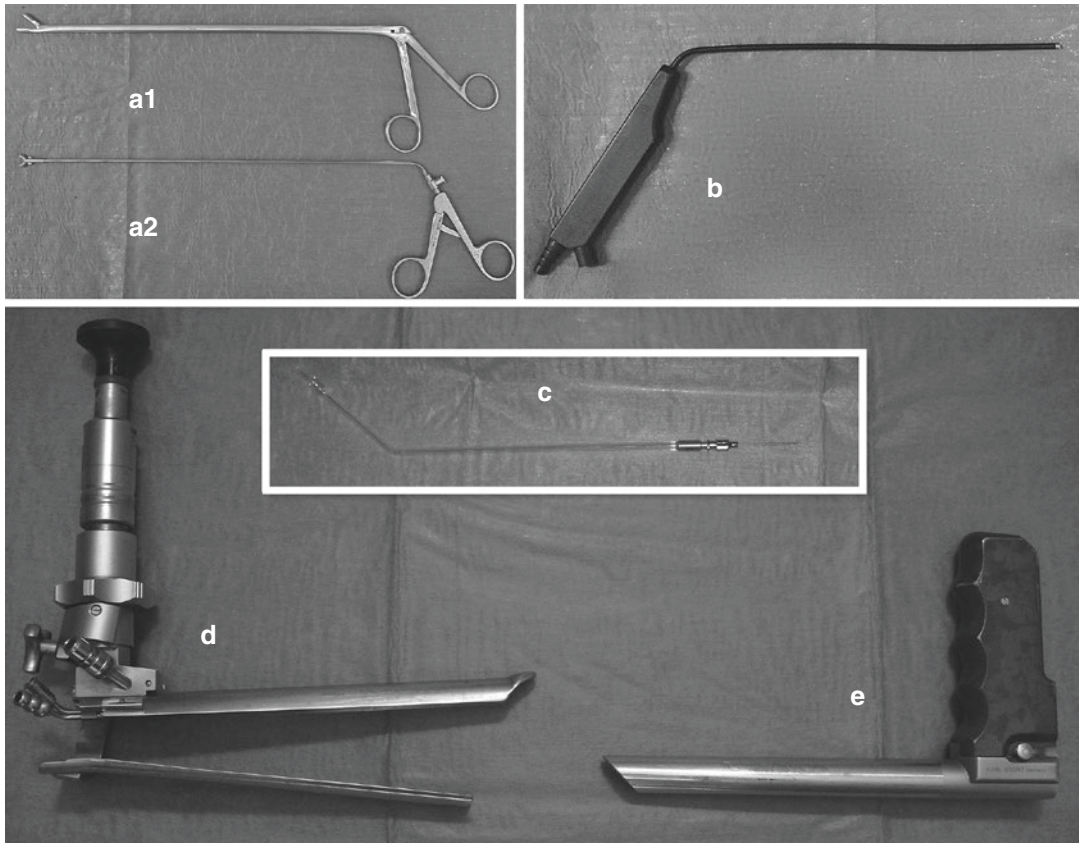

Fig. 24.1 Basic instruments set: (**a1**) biopsy forceps with oval jaws, size 8 mm × 16 mm. (**a2**) Biopsy forceps with spherical jaws, size 5 mm. (**b**) Dissection-suction-coagulation cannula. (**c**) Glass tube connected to a needle for puncture test. (**d**) Linder-Dahan two-bladed spreadable video-mediastinoscope. (**e**) Lerut video-mediastinoscope

Application of the Technique

The surgical technique is essentially the same with what Carlens described in 1959, [3] but several variants have been developed to widen the range of the exploration and to increase its sensitivity.

Preoperative Care

Patients planning to undergo mediastinoscopy should have a complete history and physical examination. It is important to know if the patient had previous interventions in the neck and in the mediastinum, i.e. cervicotomy for goitre or neck tumours and tracheostomy, laryngectomy or median sternotomy for mediastinal or heart diseases. These rarely contraindicate mediastinoscopy, but the surgeon should be aware of them. Neck flexibility should be checked, too, because it is important to properly insert the mediastinoscope. Complete blood count and biochemistry, as well as coagulation tests, should be available before the operation. For those patients with high or moderate risk for thromboembolism (patients with a mechanical heart valve, atrial fibrillation or venous thrombosis), bridging anticoagulation is recommended with therapeutic doses of subcutaneous low-molecular-weight heparin 5 days before the operation. Regarding the perioperative antiplatelet therapy, it is recommended to stop aspirin and clopidogrel 5–7 days prior to surgery

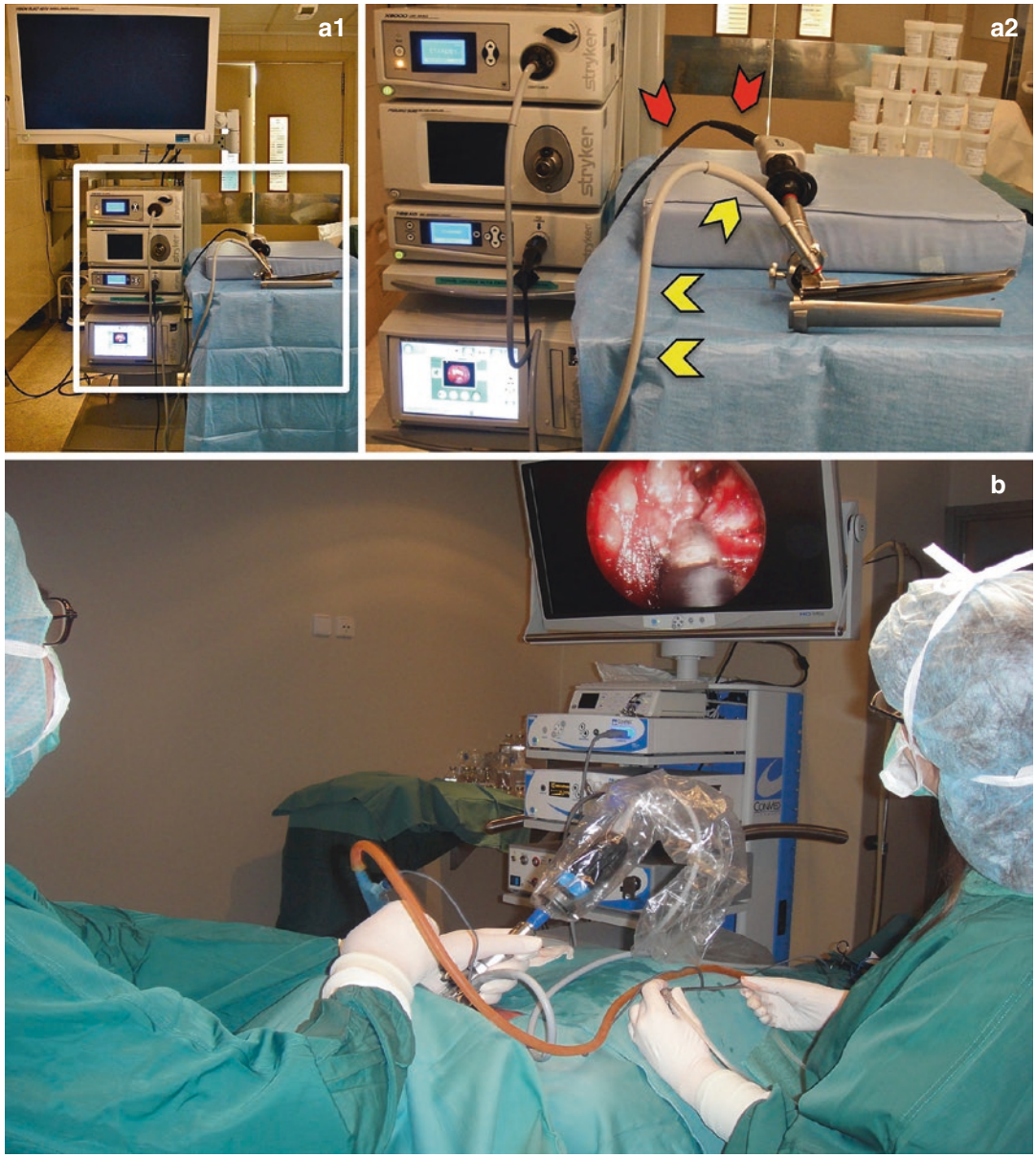

Fig. 24.2 Endoscopy tower: (**a1**) Components of the video-mediastinoscopy tower: monitor, image processor system, light source and recording device. The main components of the video image detection (*white box*) are expanded in (**a2**): video-endoscope cable (*red arrows*) is connected to the image processor device. Fibre-optic cable (*yellow arrows*) is connected to the light source. (**b**) Operating room view. The monitor is located in front of the surgeon at the patient's feet and on the left. The surgeon sits comfortably on a chair at the patient's head

and restart within 24 h after surgery, except for doses of 100 mg of aspirin that do not need to be stopped [27].

Chest x-rays, CT of the chest and PET scans are necessary to identify the target areas in the mediastinum and should be available at the time of the operation. Although mediastinoscopy should be as complete as possible in all cases, if the surgeon knows the location of the abnormal lymph nodes or the site where the tumour contacts

the mediastinum, these areas are not likely to be missed. The patient should be seen by an anaesthesiologist to assess the risk associated with general anaesthesia and should be informed of the most frequent complications (left recurrent laryngeal nerve palsy, pneumothorax) and of the rare but potentially fatal ones (bleeding, tracheobronchial and oesophageal perforation), as well as of the potential need for blood transfusion. The patient is required to sign an informed consent form.

Patient's Position and Operative Field

Under general anaesthesia and oro-tracheal intubation, the patient is positioned in the supine decubitus. A double-lumen oro-tracheobronchial tube may be necessary if additional procedures are planned. For standard intercostal thoracoscopy or for mediastino-thoracoscopy, for which opening of the mediastinal pleura to reach the pleural space is required during mediastinoscopy, selective single-lung ventilation is needed to inspect the pleural space properly. The patient's shoulders are raised with a long sand cushion. This allows some hyperextension of the neck and exposure of a long segment of the intrathoracic trachea, especially in young patients. The patient's head is allowed to rest on a circular rubber pillow to prevent displacement during the operation. In addition to the EKG leads and the blood pressure cuff, a pulse metre is fixed in one right-hand finger to control the occlusion of the innominate artery that may occur during mediastinoscopy, when excessive pressure is exercised on the artery with the mediastinoscope against the anterior chest wall. Pressure is easily relieved by repositioning the mediastinoscope (Fig. 24.3).

An operative field is prepared and draped from the mandible, cranially, to the xiphoid, caudally, and from nipple to nipple, laterally. An extra drape is positioned caudal to the sternal notch to cover the sternum. In case median sternotomy is needed during mediastinoscopy, this drape can be quickly removed.

The surgeon either stands or sits at the head of the patient, depending on the moment of the operation. The assistant and the scrub nurse stand on the right. The television monitor, if the procedure is performed with a video-mediastinoscope, is positioned at the patient's feet, slightly on the left.

Incision and Initial Dissection

A 5-cm collar incision is performed as close to the sternal notch as possible. After incising the skin, subcutaneous tissue and platysma, the avascular midline is incised, and the paratracheal muscles are dissected and separated laterally. Although this is a low-neck incision, sometimes the thyroid gland can be found covering the trachea. By blunt dissection and finger retraction, the thyroid gland can be pulled cranially to allow the insertion of the mediastinoscope. The pretracheal fascia is intimately attached to the trachea. It is hold with dissection forceps and incised with scissors. The fascia is further separated from the trachea by finger dissection: the index finger is inserted into the fascial opening, and the finger is carried caudally tearing most of the length of the pretracheal fascia.

Palpation

Contrary to other endoscopies performed in virtual cavities, i.e. the pleural cavity (pleuroscopy), the peritoneum (laparoscopy) or a joint (arthroscopy), there is no mediastinal space as such. A space must be created in the upper mediastinum by finger dissection. In addition to creating an adequate mediastinal space, palpation allows the surgeon to feel the size, consistency and degree of attachment of mediastinal lymph nodes, mediastinal tumours or bronchogenic carcinomas with direct mediastinal contact or invasion.

Palpation must be systematic, and the anatomical landmarks must be recognized. In the typical case, after inserting the distal phalange of the index finger, the pulsation of the innominate

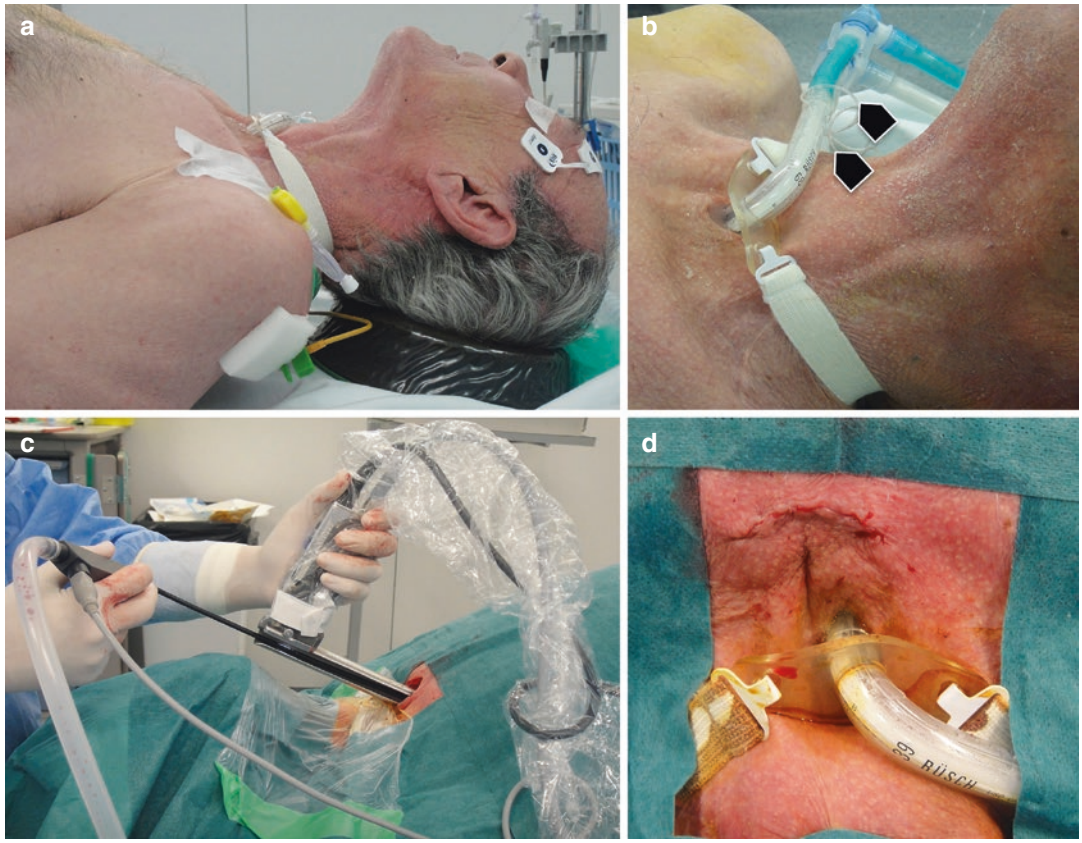

Fig. 24.3 Patient with tracheostomy, a classic contraindication of mediastinoscopy. The patient had a centrally located tumour, and mediastinoscopy was indicated to rule out mediastinal nodal disease. (**a**) Position of the patient for video-mediastinoscopy. The neck is hyperextended, and the head rests on a circular pillow. (**b**) A double-lumen oro-tracheobronchial tube (*black arrows*) is inserted because a pleural inspection was planned. (**c**) Insertion of the video-mediastinoscope. (**d**) View of the wound after closing the incision with absorbable intradermal suture

artery can be felt. In young patients, when the neck is hyperextended, the innominate artery may become cervical and may be seen after completing the cervical incision. In older patients, the innominate artery may be located more caudally, if the neck cannot be hyperextended, or more cranially if the aortic arch is elongated. In all these circumstances, care must be taken not to injury it in these initial manoeuvres. Following the course of the innominate artery on the left, the aortic arch can be felt. Then, the finger is passed more distally behind the aortic arch. By palpation, the tracheal cartilages can be felt. Close to the carina, they are disrupted, as the trachea separates into the two main bronchi.

Insertion of the Mediastinoscope and Mediastinal Inspection

After creating a peritracheal space by finger palpation, the mediastinoscope is inserted into the upper mediastinum. At this point, the exploration is performed more comfortably if the surgeon sits on a chair. The height of the operating table and of the chair has to be regulated to relieve tension at the surgeon's shoulders and elbows.

From top to bottom, the pulsation of the innominate artery is seen first. The pulsation of the ascending aorta is seen on the left. More caudally, at the level of the right tracheobronchial angle, the azygos vein can be identified. The

fatty tissue of the right paratracheal space has to be dissected to find the azygos vein. This landmark is important because, according to the new regional lymph node map, nodes caudal to the inferior rim of the azygos vein are coded as right hilar nodes, or 10R, although they are anatomically located in the mediastinum [1]. If the dissection is carried out more distally on the right, the whole length of the right main bronchus can be seen and, in some patients, even the origin of the right upper lobe bronchus. Over the right main bronchus, the right pulmonary artery is found, usually the distal end of the exploration on the right. Over the subcarinal space, the prolongation of the pretracheal fascia has to be torn to reach the subcarinal nodes. The right pulmonary artery crosses in front of them, and the oesophagus is behind. Care must be taken not to injure these structures. If the integrity of the oesophagus is questionable, a naso-oesophageal tube can be inserted and air injected into it. With the subcarinal space flooded with saline, an air leak will be evident if there is an oesophageal perforation. In more than 3000 mediastinoscopies, we have inserted a naso-oesophageal tube once, only, to rule out oesophageal perforation. On the left, it is important not to injure the recurrent laryngeal nerve that runs along the left paratracheal margin. The left tracheobronchial angle can be identified and, distal to it, the left pulmonary artery, marking the end of the exploration on the left. Nodes caudal to its upper rim are now coded as left hilar nodes, or 10L [1].

Biopsy

Lymph node biopsies for lung cancer staging must be systematically taken to obtain the maximal benefit from the exploration. Ideally, the taking of biopsies should start on the contralateral side to the tumour to rule out N3 disease. Macroscopically abnormal nodes should be sent for frozen section examination, and if nodal involvement is identified, mediastinoscopy may be terminated unless the patient is in a protocol that requires more information on the extent of nodal disease. Then, the subcarinal and the ipsilateral paratracheal nodes are biopsied. If the nodes are not removed entirely, the initial biopsies of each lymph node are ideal to examine the involvement of the nodal capsule and the extranodal tumour invasion. Each complete node or all the biopsies from one node are kept in a different container and properly labelled according to the present nodal nomenclature [1]. This makes the counting of the removed and involved nodes much easier and reliable. Whenever possible, it is better to remove the entire nodes to avoid missing micrometastases and increase the sensitivity of the exploration. Mediastinal lymph nodes are embedded in the peritracheal fatty tissue. Exploration of this fatty tissue with the dissection-suction-coagulation device allows the surgeon to identify them and free them from their surrounding. Sometimes, fragments of lymph nodes or whole small lymph nodes are suctioned during dissection. In this case, it is recommendable to filter the contents of the suction container to retrieve the suctioned lymph nodes or their fragments for pathological examination.

Mediastinoscopy allows the surgeon to reach the cervical nodes at the sternal notch, the superior and inferior paratracheal nodes on both sides, the subcarinal nodes and the right and left hilar nodes. However, the superior paratracheal nodes are hidden by the mediastinoscope when it is inserted and are not easy to identify. They are better explored and biopsied in the open fashion at the time of cervicotomy. The European Society of Thoracic Surgeons (ESTS) guidelines require biopsies from, at least, one right and one left inferior paratracheal nodes and one subcarinal node for an acceptable mediastinoscopy in clinical practice. In addition, the superior paratracheal and hilar stations should be explored, if there is imaging suspicion of nodal involvement. For cancers of the left lung, exploration of the subaortic and para-aortic nodes is also required, either by left parasternal mediastinotomy, extended cervical mediastinoscopy or left thoracoscopy [19] (Fig. 24.4).

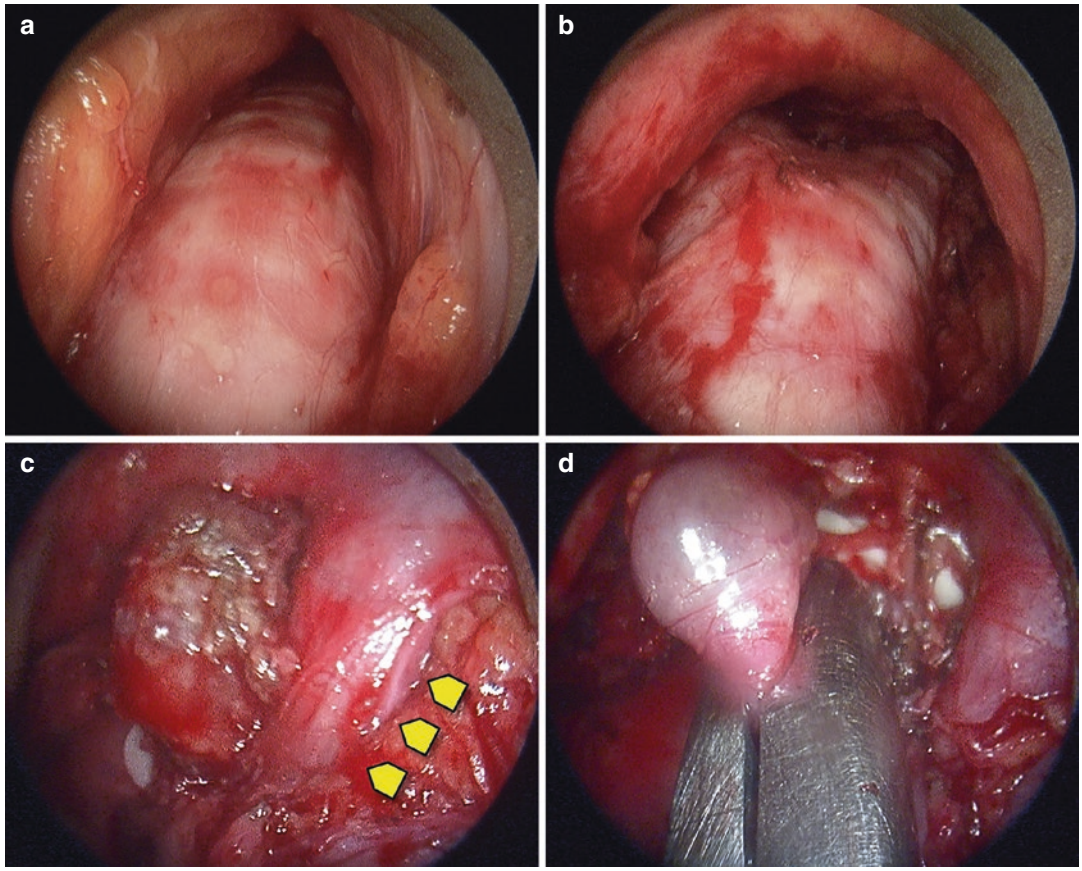

Fig. 24.4 Endoscopic images of video-mediastinoscopy. (**a**) Proximal trachea. (**b**) Distal trachea and right and left main bronchi. (**c**) Right hilar lymph node. This lymph node is located caudal to the inferior rim of the azygos vein (*yellow arrows*). (**d**) Hilar lymph node biopsy

Control of Haemostasis and Closure

The use of the dissection-suction-coagulation cannula minimizes bleeding during dissection of peritracheal tissue. Mediastinal lymph nodes usually are dark blue or black because of their anthracotic content. The azygos vein or a partially visualized superior vena cava may resemble lymph nodes. In case of doubt, especially if the standard mediastinoscope is used, a puncture test should be performed. If blood is seen along the glass suction tube, the needle should be removed and the bleeding site gently pressed with gauze for haemostasis. During this manoeuvre, care must be taken not to puncture through the trachea, because perforation of the endotracheal cuff is possible and already has been described [28]. All biopsy sites should be checked before closure. Coagulation of biopsied lymph nodes or peritracheal fatty tissue is enough to control bleeding. Control of bleeding from the bronchial arteries in the subcarinal space, especially those running in front of the left main bronchus, should be tried first with gauze packing and coagulation. If bleeding persists, clipping of the bronchial artery may be necessary. The gauze used for packing must be removed through the mediastinoscope to minimize tumour seeding in the cervical incision. Tumour cell dissemination during mediastinoscopy is possible. Cytological analyses of mediastinal lavage fluid have shown that tumour cells can be identified before and after taking biopsies, although long follow-up periods are needed to understand their

prognostic value [29]. Major bleeding is an uncommon complication that may occur in 0.4% of procedures and may come from the azygos vein, the pulmonary arteries, the innominate artery—the most common sites of serious bleeding—the superior vena cava and the aorta. Packing and median sternotomy or thoracotomy, depending on the location of bleeding, is the usual procedure of haemorrhage control [30]. The glass cannula for puncture test may be connected to a syringe to puncture and aspirate lymph nodes. This is especially useful when the nodes are fixed to vessels. In this case, pulling or taking biopsies from the nodes may injure the attached vessel. The aspirate is then sent for cytological examination.

The paratracheal muscles are not sutured to the midline. This facilitates remediastinoscopy, if it is needed. The incision is closed in two layers: platysma and subcutaneous tissue together with 2-0 continuous absorbable suture and skin with 3-0 absorbable intradermal suture. Drainage is not necessary. The wound is dressed with gauze that can be removed in 24 h.

Postoperative Care

The patient is awakened and extubated in the operating room and sent to recovery room till the patient is fully conscious and the vital constants are normal and stable. Then the patient is transferred to the normal ward or to the outpatient surgery room. Oral intake is started 6 h after the operation. The patient can be discharged on the same day, if an outpatient surgery programme is active in the hospital, or the next day. The admission rate after outpatient mediastinoscopy for all indications ranges from 1 to 4%, and the main reasons are supraventricular arrhythmias, pneumothorax, bleeding from bronchial artery or late end of the operation [31]. Postoperative chest x-rays are not necessary unless something unusual has occurred during (opening of the mediastinal pleura or bleeding) or after surgery (fever, dyspnoea or chest pain).

Complications

Intraoperative complications are infrequent, ranging from 0.6 to 3.7% [32, 33]. The occlusion of the innominate artery and bleeding from the most common sites have been described above. Other complications are wound infection, pneumothorax, mediastinitis, left recurrent laryngeal nerve palsy, oesophageal perforation, bronchial injury, chylomediastinum, haemothorax and incisional metastasis [34–39]. Mortality is below 0.5% [4, 40, 41].

Technical Variants

Technical variants of mediastinoscopy have been devised over the years to reach mediastinal locations beyond the reach of the standard exploration and to expand the possibilities of this transcervical approach.

Extended Cervical Mediastinoscopy

Subaortic and para-aortic nodal stations cannot be reached with mediastinoscopy. Left parasternal mediastinotomy, performed over the second or third intercostal space, facilitates the exploration of this area but requires an additional incision and very often the removal of a costal cartilage [42, 43]. In 1987, Ginsberg et al. [44] reported their experience in extended cervical mediastinoscopy as a staging procedure for cancers of the left upper lobe, using the approach first described by Specht in 1965 [45]. To stage cancers of the left lung, after mediastinoscopy has been completed and from the same cervical incision, a passage is created by finger dissection over the aortic arch, between the innominate artery and the left carotid artery, either in front or behind the left innominate vein. Once the fascia between these two vessels is torn with the finger, the finger can be advanced easily over the aortic arch. Then, the mediastinoscope is inserted, and the lymph nodes in the subaortic station can be explored and biopsied. By moving the mediastinoscope medially, the para-aortic nodes also can be explored, although differentiating

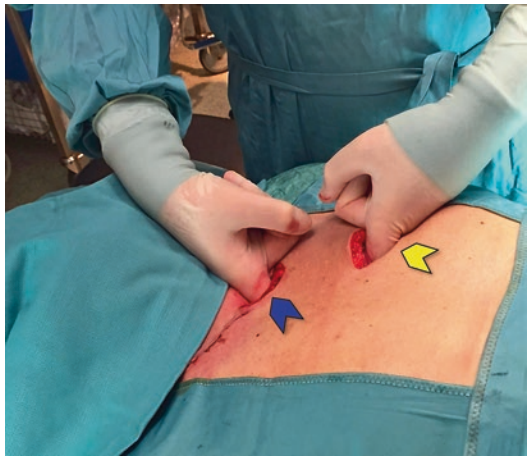

Fig. 24.5 Bimanual palpation from the collar incision of mediastinoscopy (*blue arrow*) and the left parasternal mediastinotomy (*yellow arrow*)

between subaortic and para-aortic nodes is not easy because mobilization of the mediastinoscope is limited by the bony structures of the chest wall. Extended cervical mediastinoscopy does not allow the surgeon to palpate the subaortic space well. If palpation is needed to differentiate between mere contact and tumour invasion in this area, then parasternal mediastinotomy is a much better approach. The parasternal incision allows the surgeon to inspect the subaortic space directly, but the mediastinoscope can also be used to facilitate the exploration. Additionally, a small rib spreader can be inserted to widen the operative field. Bimanual palpation from the collar incision and from the parasternal incision is useful to explore the integrity of the aortic arch (Fig. 24.5). Access to the pericardium, pleural space and lung is also possible from this incision. Right parasternal mediastinotomy is useful to assess the superior vena cava, the azygos vein, the right pulmonary artery, the right superior pulmonary vein and the right anterior mediastinal nodes [46].

Mediastinoscopic Biopsy of Scalene Lymph Nodes

From the cervical incision of mediastinoscopy, the mediastinoscope can be passed under the insertions of the sternocleidomastoid muscle on one or both sides of the neck to reach the scalene lymph nodes. There is one publication on this technique, only, but the reported results are clinically relevant: 15% of patients with N2 disease and 63% of those with mediastinal N3 diagnosed at mediastinoscopy had subclinical N3 disease in the scalene lymph nodes [47]. These results have to be taken into account when selecting patients for clinical trials on N2 disease.

Inferior Mediastinoscopy

The mediastinoscope is inserted into the anteroinferior mediastinum from a subxiphoid approach. Although this is rarely needed, inferior mediastinoscopy is useful to explore mediastinal lesions beyond the reach of mediastinoscopy [48, 49]. By opening the pericardium and inserting the mediastinoscope into the pericardial space, a subxiphoid pericardioscopy can be easily performed [50].

Mediastino-thoracoscopy

From the superior mediastinum, at the time of mediastinoscopy, the mediastinal pleura can be opened and the pleural space explored. On the right side, this can be performed either between the trachea and the superior vena cava or between the superior vena cava and the anterior chest wall. On the left, the supra-aortic approach is the most direct one, as used for extended cervical mediastinoscopy. Single-lung ventilation facilitates the exploration of the pleural space in patients with pleural effusion, lung nodules, parietal pleura nodules and diaphragmatic and pericardial lesions. If the target lesions cannot be reached with the mediastinoscope, a thoracoscope can be passed through it; by doing so, even the diaphragm can be reached. Pleurodesis also can be performed through this approach [51, 52]. The two-bladed video-mediastinoscopes also allow the insertion of endoscopic staplers to perform wedge resections of the lung in case of lung cancer and additional peripheral lung nodules [53] (Fig. 24.6).

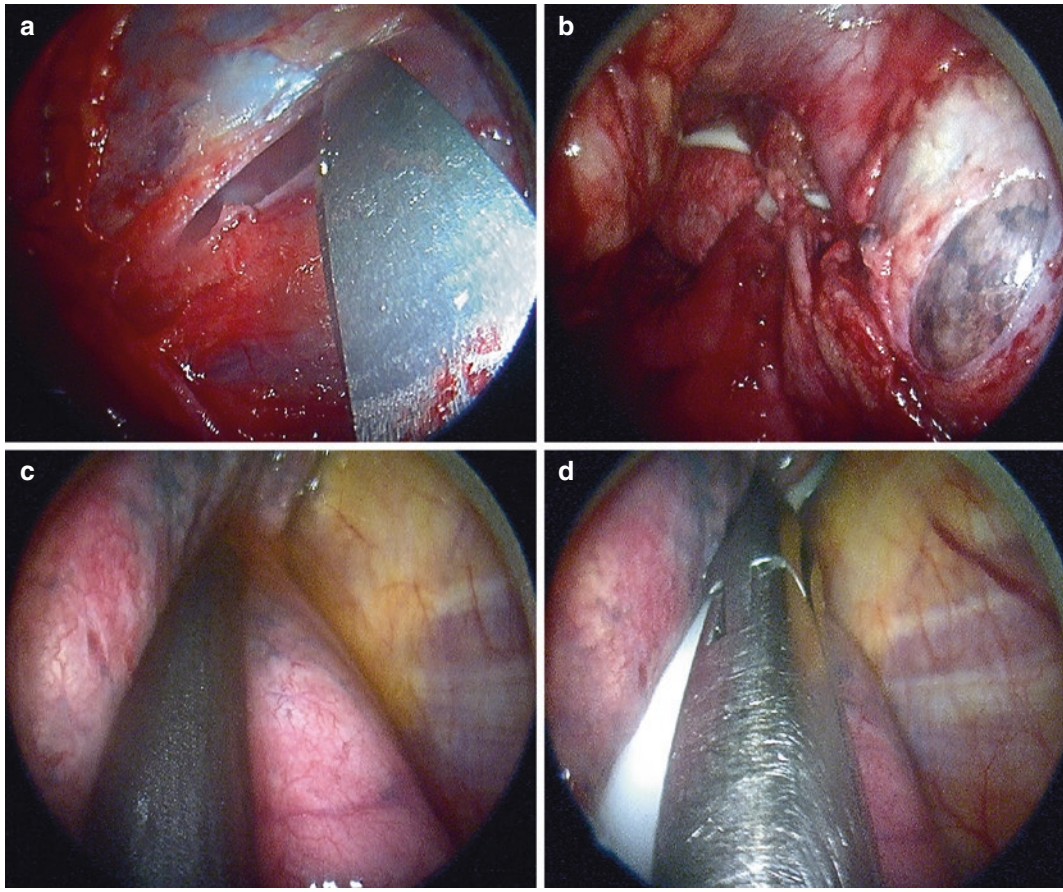

Fig. 24.6 Mediastino-thoracoscopy. (**a**) The mediastinal pleura is opened by endoscopic scissors. (**b**) View of the right lung through the incision of the mediastinal pleura. (**c**) Exploration of the pleural space with single-lung ventilation. Pleural effusion of clear fluid is identified, and it is suctioned by suction cannula. (**d**) Small-bore chest tube is inserted by endoscopic forceps

Transcervical Mediastinal Lymphadenectomy

Video-Assisted Mediastinoscopic Lymphadenectomy

Video-assisted mediastinoscopic lymphadenectomy (VAMLA) is a very thorough mediastinoscopy with the objective to remove the upper mediastinal lymph nodes. It is performed with the two-bladed video-mediastinoscope through the standard collar incision for mediastinoscopy. A holder can be used to fix the video-mediastinoscope so that the surgeon can work with two hands, holding the specimen with a forceps with one hand and the dissector with the other. The subcarinal and the right inferior paratracheal lymph nodes are removed en bloc with the mediastinal fatty tissue. Those located in the left inferior paratracheal station are removed one by one not to injure the left recurrent laryngeal nerve [10, 11]. VAMLA can be combined with video-thoracoscopy to improve the radicality of lymphadenectomy [54] (Fig. 24.7).

Adhesion to the standardized technique and anatomic limits is important in VAMLA to avoid complications. The subcarinal space is explored first. The fatty tissue containing nodes is dissected off the margins of the main bronchi and the carinal angle. Once this is done, the bloc is grasped with forceps on one side, and its dissection is continued towards the other using the dissection-suction-coagulation cannula or endo-

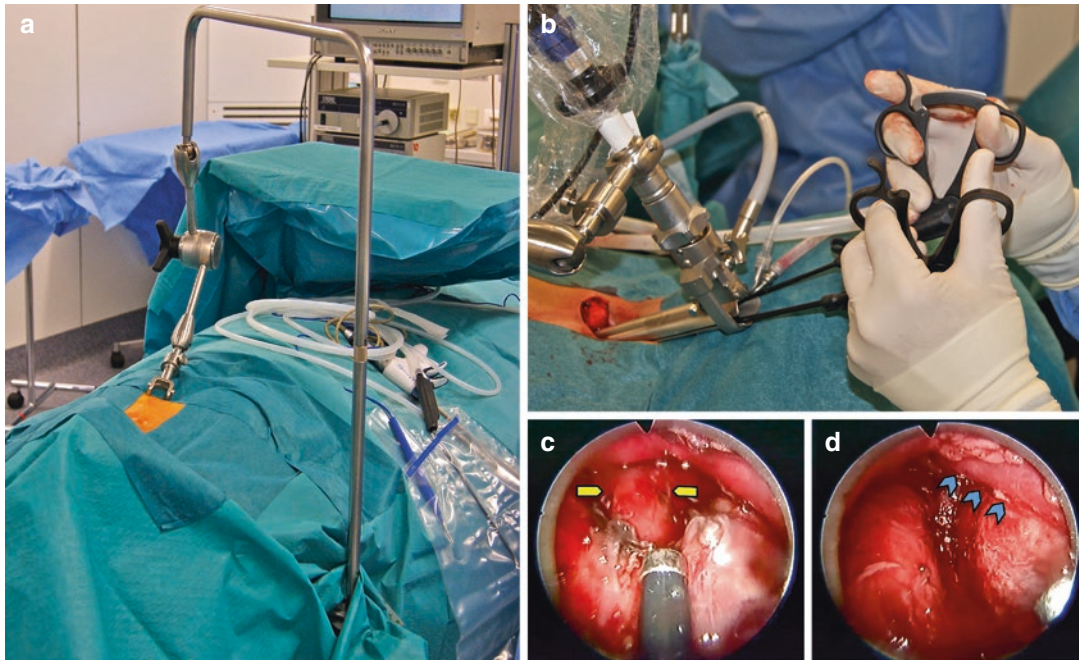

Fig. 24.7 Video-assisted mediastinoscopic lymphadenectomy (VAMLA). (**a**, **b**) The surgeon can work with two hands because the video-mediastinoscope is fixed by an articulated holder. (**c**) View of the subcarinal space after removing all subcarinal lymph nodes. The tip of the dissection-suction-coagulation device is located at the carina, between the two main bronchi. *Yellow arrows* show the oesophagus completely dissected. (**d**) View of the right mediastinal pleura after removing right inferior paratracheal lymph nodes en bloc with the mediastinal fatty tissue. *Blue arrows* show the superior vena cava

scopic scissors. The bloc has to be freed from the adhesions that keep it attached to both main bronchi, laterally, to the pulmonary arteries, anteriorly, and to the oesophagus, posteriorly. During this manoeuvre, clipping of the bronchial artery that usually runs anterior to the left main bronchus may be necessary, if coagulation is not enough to control bleeding around this bloc of fatty tissue and lymph nodes. Once the bloc is removed, the oesophagus protrudes anteriorly. A wet gauze is left in the subcarinal space for haemostasis, while the procedure is continued in other nodal stations.

On the right paratracheal nodal station, dissection is started from the inferior margin of the innominate artery. The bloc of fatty tissue and lymph nodes is detached from the mediastinal pleura and the superior vena cava and moved medially and caudally towards the azygos vein. This manoeuvre can be facilitated by finger dissection or by inserting a gauze and pushing it caudally. Finally, the bloc is detached from the ascending aorta with coagulation or scissors. It is important to remove the nodes that are located anterior to the trachea between the ascending aorta and the superior vena cava. They can pass unnoticed, hidden by the mediastinoscope. On this side, the procedure can be completed with the exploration of the right hilar nodes, that is, those caudal to the inferior margin of the azygos vein around the right main bronchus.

On the left paratracheal nodal station, it is important to identify the left recurrent laryngeal nerve to prevent its injury. Once this is done, the left inferior paratracheal lymph nodes are either biopsied or removed one by one (not en bloc as in the subcarinal and right inferior paratracheal nodal stations). Coagulation should be restricted to the minimum necessary; a warm wet gauze is usually enough to control bleeding from the nodes or the fatty tissue. As on the right side, the procedure can be completed with the exploration

of the left hilar nodes, those caudal to the upper rim of the left pulmonary artery.

Once the dissection is finished, the gauzes are removed, and a final inspection is performed to check for bleeding. Drainage is not needed, and the incision is closed as for mediastinoscopy.

Transcervical Extended Mediastinal Lymphadenectomy

In comparison with VAMLA, transcervical extended mediastinal lymphadenectomy (TEMLA) is a more extensive procedure. The objective of TEMLA is to remove all the mediastinal nodes from the cervical station to the para-oesophageal station. A cervical incision slightly longer than that for mediastinoscopy is performed, and the sternum is elevated with a hook fixed to a metal frame mounted on the operating table. The procedure is almost exclusively performed in an open fashion, but a two-bladed mediastinoscope is used to dissect the subcarinal and the para-oesophageal lymph nodes, and a videothoracoscope is inserted to have a better vision at the time of dissection of the subaortic space [12].

Evidence-Based Review

Conventional Mediastinoscopy Versus Video-Mediastinoscopy

There are evident advantages of video-mediastinoscopy over conventional mediastinoscopy. The view of the operative field is much larger and can be seen simultaneously by all personnel in the operating theatre. The whole procedure or parts of it can be recorded for future use in clinical sessions, medical meetings and educational materials. However, because there are no prospective randomized trials comparing both procedures, there is no clear evidence indicating that video-mediastinoscopy is safer or more effective than conventional mediastinoscopy. Video-mediastinoscopy seems to be a more thorough exploration, because of an increased number of biopsied lymph nodes and explored lymph node stations compared with conventional mediastinoscopy, as well as a better tool for training [55].

Staging Values of the Different Techniques

A review of 26 reports published between 1983 and 2011, including a total of 9267 patients who had undergone conventional mediastinoscopy, showed a median sensitivity of 0.78 and a median negative predictive value of 0.91. An additional series of 995 patients, who had undergone video-assisted mediastinoscopy and were reported in seven papers published from 2003 to 2011, showed a median sensitivity of 0.89 and a median negative predictive value of 0.92. By convention, specificity and positive predictive value of mediastinoscopy is 1, although positive results are not confirmed by other tests [18].

The combined analyses of 456 patients who underwent extended cervical mediastinoscopy reported in five articles published between 1987 and 2012 reveal a median sensitivity of 0.71 and a median negative predictive value of 0.91 [18].

The initial reports from the two groups who developed VAMLA in 2002 and 2003, describing their results with 40 and 25 patients, respectively, showed sensitivities, negative predictive values and diagnostic accuracies of 1 [10, 11]. An updated publication from one of the groups, with 144 patients, reported a sensitivity of 0.88 and a negative predictive value of 0.98 [56]. The largest series published to date, with 160 procedures for lung cancer staging, reported the following staging values: sensitivity 0.96, negative predictive value 0.99 and diagnostic accuracy 0.99 [57].

Sensitivity and negative predictive value of TEMLA are high: 0.9 and 0.95, respectively, in the first report including 83 patients, [12], and 0.94 and 0.97, respectively, in an updated reports with 256 patients [58]. In addition, TEMLA has proved to be highly reliable as a restaging method in those patients with lung cancer initially staged by endoscopic techniques and fine needle aspiration. In these cases, sensitivity, negative predictive value and accuracy were 0.95, 0.97 and 0.98, respectively [59].

Summary and Recommendations

Mediastinoscopy explores the upper mediastinum and is useful in the assessment of nodal disease and direct tumour invasion. To expand the range of the exploration, procedures such as parasternal mediastinotomy, extended cervical mediastinoscopy, mediastino-thoracoscopy, and inferior mediastinoscopy have been devised during the past decades. VAMLA and TEMLA have the objective to perform a mediastinal lymphadenectomy as thorough as that performed by thoracotomy. They are indicated when the mediastinum is normal on CT and PET scans and their sensitivity and negative predictive values are higher than those for mediastinoscopy. Therefore, they should be incorporated in future staging algorithms. At the present time, the ESTS guidelines are valuable; have been prospectively validated, with sensitivity and negative predictive values of 0.84 and 0.94, respectively [60]; and, therefore, should be applied in the management of patients with lung cancer.

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Endobronchial Ultrasound: The Basics of Ultrasound

25

Felix J.F. Herth

Medical ultrasound imaging consists of using high-pitched sound bouncing off tissues to generate images of internal body structures. The ultrasound waves are created from mechanical or electronical oscillations of crystals in a so-called transducer, which are excited by electrical pulses (piezoelectric effect).

The ultrasound waves are sent from the transducer into the depth of the body, running through different tissues and layers. Once reflected by the tissue, they return to the transducer as reflected waves or echoes. If the difference in density is increased, the proportion of reflected sound is increased and the proportion of transmitted sound is proportionately decreased. The returned echoes are converted back into electrical impulses by the transducer crystals (Fig. 25.1). The ultrasound processor forms an ultrasound image shown on a screen.

A reflection of the beam is called an echo and the production and detection of echoes form the basis of ultrasound. A reflection occurs at the boundary between two materials provided that a certain property of the materials is different. This property is known as the acoustic impedance and is the product of the density and propagation speed. If two materials have the same acoustic impedance, their boundary will not produce an echo. If the difference in acoustic impedance is small, a weak echo will be produced, and most of the ultrasound will carry on through the second medium. If the difference in acoustic impedance is large, a strong echo will be produced. If the difference in acoustic impedance is very large, all the ultrasound will be totally reflected. Typically in soft tissues, the amplitude of an echo produced at a boundary is only a small percentage of the incident amplitudes, whereas areas containing bone or air can produce such large echoes that not enough ultrasound remains to image beyond the tissue interface [1].

The direction from where the sound returns tells it in which direction the structure is. The time taken for the sound waves to reach the structure and return back to the transducer tells how far away a structure is. The longer the sound waves take to return, the further away the structure is. If the difference in tissue density is very different, then sound is completely reflected, resulting in total acoustic shadowing like bones (Fig. 25.2), calculi and air (lung).

Homogenous fluids like urine, simple cysts, ascites, and pleural effusion are seen as echo-free structures due to the missing difference of the density within the tissue or between tissues (Fig. 25.3).

The wavelength is the distance traveled by sound in one cycle or the distance between two

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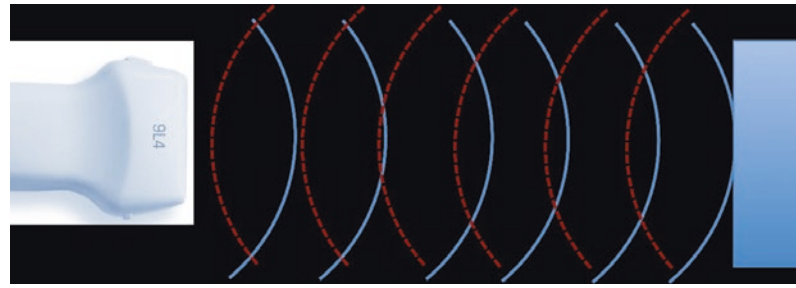

Fig. 25.1 Submitted (*solid lines*) and reflected (*dashed lines*) waves

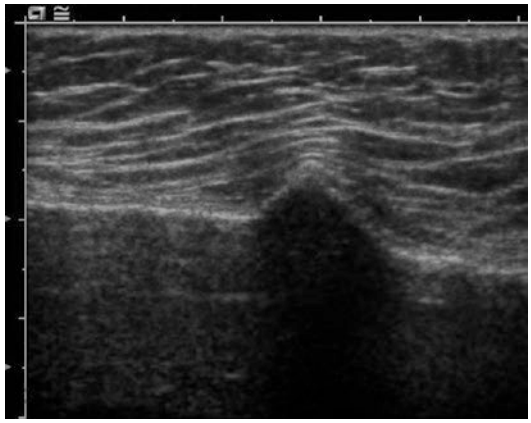

Fig. 25.2 Acoustic shadowing behind the ribs

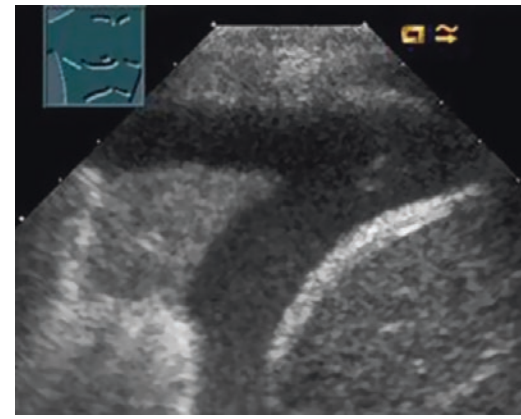

Fig. 25.3 Pleural effusion

identical points in the wave cycle, i.e., the distance from a point of peak compression to the next point of peak compression. It is inversely proportional to the frequency. Wavelength is one of the main factors affecting axial resolution of an ultrasound image. The smaller the wavelength (and therefore the higher the frequency), the higher the resolution, but the lesser the penetration. Therefore, higher-frequency probes (5–10 MHz) provide better resolution but can be applied only for superficial structures and in children. Lower frequency probes (2–5 MHz) provide better penetration albeit lower resolution and can be used to image deeper structures.

For more than 50 years, many kinds of transducers have evolved for medical ultrasound imaging. Transducers operate at different center frequencies, have different physical dimensions, footprints, and shapes, and provide different image formats. Systematic selection criteria that allow matching of transducers to specific clinical needs are available. The criteria include access to and coverage of the region of interest, maximum scan depth and image extent, and coverage of essential diagnostic modes required to optimize a patient's diagnosis. For completeness, single-element transducers, primarily used in intraluminal or catheter applications, are also included in the considerations. In the field of endobronchial ultrasound, two different techniques are used. Depending on the indication, the examiner needs information from an area close to the transducer (nearfield) or whats to see a larger image [2, 3].

Frequency refers to the number of cycles of compressions and rarefactions in a sound wave per second, with one cycle per second being hertz. Medical ultrasound frequencies range from 2 to approximately 20 MHz, depending on the indications and the situations. The depth of penetration is related to the frequency of the ultrasound wave. Higher frequencies have a shorter depth of penetration. Lower frequencies have a longer depth of penetration. On the other hand, probes with a high frequency are not able to provide information for distant areas. Therefore EBUS-TBNA scopes

normally use frequencies around 7.5–12.5 MHz to provide information up to 5–6 cm away from the airways. The radial ultrasound, used to analyze the internal structure of the bronchial wall and solid lesions, uses 20 MHz (Figs. 25.4 and 25.5) [4].

Mechanical EBUS (Mini-probes)

The radial EBUS procedure is performed by inserting a miniature ultrasound probe (radial EBUS probe) through the working channel of a flexible bronchoscope or catheter (guide sheath). Real-time imaging of the surrounding tissue enables the clinician to determine the lesion's exact location and size. The probes move forward into the peripheral lung until a circular contact of the probe with the airways is available. Radial EBUS provides a 360° image of the airway wall and surrounding structures external to the airway. The unique mechanical scanning technique produces a real-time ultrasound image enabling direct visualization of the exact position of the lesion for sampling (Fig. 25.5).

For application inside the central airways, we therefore developed flexible catheters for the probes with a balloon at the tip that allows circular contact for the ultrasound, providing a complete 360° image of the parabronchial and paratracheal structures. As the balloon is providing enhancement of the ultrasound, penetration of the waves produced by 20 MHz probes is increased (Fig. 25.6a, b) [5].

As the balloon is providing enhancement of the ultrasound, penetration of the waves produced by 20 MHz probes is increased. The probes are on the market since 1999 and are compatible with channel diameters of 2.0, 2.6, and 2.8 mm; radial EBUS probes can be inserted directly through the bronchoscope or used with the Olympus Guide Sheath Kit for a cost-effective solution that can aid in accessing and sampling peripheral pulmonary lesions.

EBUS-TBNA

The most used EBUS application is special bronchoscope with an integrated curvilinear electronic transducer at the tip. The high-resolution, real-time ultrasound imaging enables direct visualization of the needle as it penetrates the lymph node. This facilitates correct capsule-to-capsule technique, which helps to optimize sample collection. So a real-time needle puncture under endoscopic

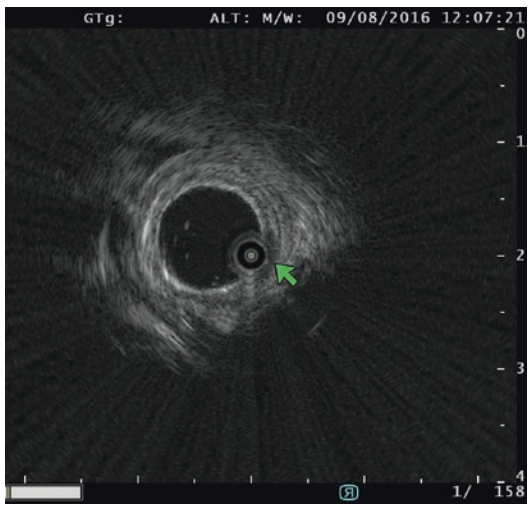

Fig. 25.4 Analysis of the bronchial wall with the radial EBUS probe (nearfield). EBUS probe is marked by the *arrow*

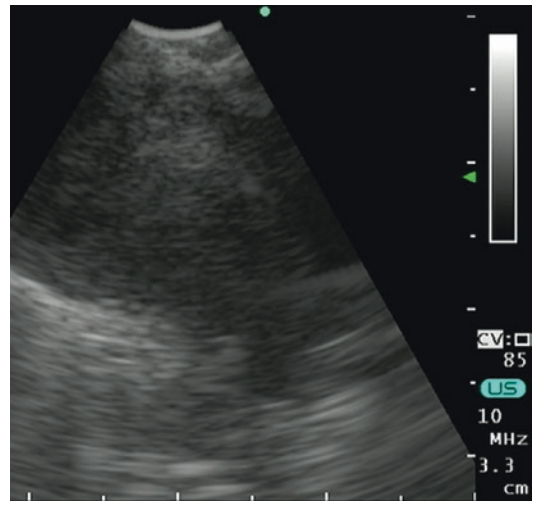

Fig. 25.5 Ultrasound image of the EBUS-TBNA scope. Even the scope has full contact to the bronchial wall. The structures of the wall are not visible (Farfield). A lymph node is visible

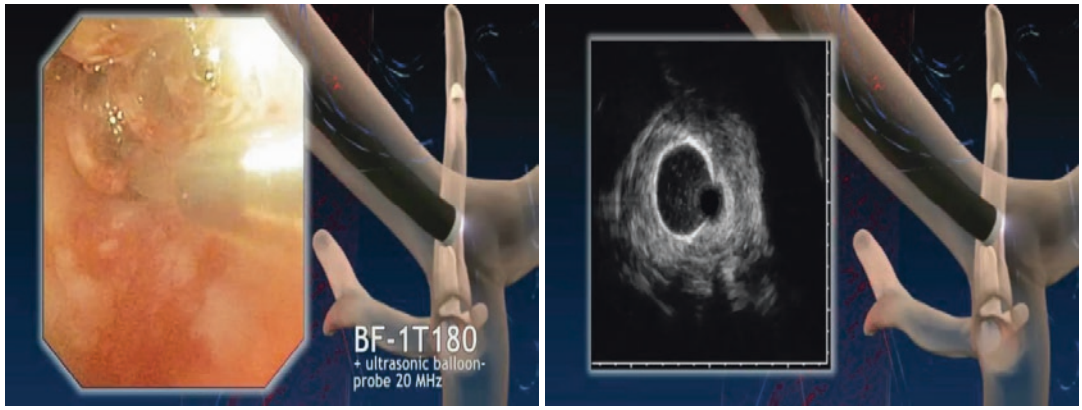

Fig. 25.6 (**a**) Image of the probe within the filled balloon. (**b**) Corresponding ultrasound image shows a complete destruction of the wall due to tumor invasion

control is possible. The outer diameter of the insertion tube is 5.8. The angulations range of the distal end of the endoscope is 160° upward and 90° downward. The instrument has a small curved linear array electronic transducer, length 10 mm, located at the distal end of the endoscope in front of a 30° oblique forward viewing fiber-optic lens (angle of view 80°). The ultrasonic frequency is 7.5 up to 12.5 MHz with a penetration depth of 5 cm. The scanning direction is parallel to the longitudinal axis of the endoscope with a scanning angle of 50° which enables full ultrasonic monitoring of a needle when inserted via the biopsy channel during scanning [6].

The ultrasonic bronchoscope is introduced via an endotracheal tube under visual control or under local anesthesia to the area of interest. EBUS-TBNA is performed by direct transducer contact with the wall of the trachea or bronchus. When a lesion is outlined, a TBNA needle is introduced via the biopsy channel of the endoscope. Under real-time ultrasonic guidance, the needle will be placed in the lesion and suction will be applied.

Due to the electronically scanning mode, also Doppler examinations are possible with the EBUS-TBNA scopes.

The Doppler effect is the change in frequency of a wave for an observer moving relative to its source. The transmitted ultrasound wave has a specific frequency. The wave that returns to the probe also has a frequency. When the wave is bounced back from a stationary object such as a bone, both the transmitted and the returned waves have the same frequency. If an object is moving, the time of the frequency of the returned wave will not be the same as the frequency of the transmitted wave. The wave that bounces off an object moving toward the probe will have a higher frequency than the frequency of the wave transmitted from the probe. This is because the moving object "squashes" the waves as it moves toward the probe. This is an example of the Doppler effect. When a wave is sent to an object that is moving toward the transmitting probe, the Doppler effect makes the frequency of the returning wave to be higher than the frequency of the wave sent out. The faster the object moves toward the transmitting probe, the higher will be the difference [7].

So the Doppler effect causes the frequency of waves reflected from a moving object to be different from the frequency of the wave sent out of the probe. If the object is moving toward the probe, the reflected frequency is increased. If the object is moving away, the reflected frequency is decreased. Ultrasound machines tell us Doppler effect information using color. It uses different colors to show the direct and speed of flow. This helps you to identify vessels.

During the EBUS-TBNA procedure the Power Doppler examination is used before the biopsy in order to avoid unintended puncture of vessels between the wall of the bronchi and the lesion.

Summary

In conclusion with regard to the technique, the clinical application, and its diagnostic results, endobronchial ultrasound is in the center of a routine procedure. In different studies the indication for endobronchial ultrasound is established as compared to conventional radiological methods and other diagnostic procedures.

Radial EBUS proved to be useful in high-resolution imaging of the multilayer structures of the bronchial wall and the adjacent mediastinal structures and especially in solitary pulmonary nodules. In many instances it was superior for staging of lung cancer and other pathologies.

Mediastinal lymph nodes could be easily localized by the EBUS-TBNA scopes, and those scopes are nowadays the gold standard to access the mediastinum.

At the end, for both techniques the basics of ultrasound should be known to optimize the results.

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Endobronchial Ultrasound: Clinical Applications

26

Lakshmi Mudambi, Donald Ray Lazarus, and George A. Eapen

Introduction

Ultrasound is an imaging modality that utilizes the mechanical properties of high-frequency sound waves when passing through tissues of different densities to produce images of the interrogated tissue. Ultrasound has long been used to image thoracic structures, and the use of an ultrasound endoscope allowing visualization of structures surrounding the esophagus was first described in 1980 [1]. In the early 1990s, endobronchial ultrasound (EBUS) was introduced, dramatically changing the practice of bronchoscopy [2, 3]. Before the advent of EBUS, the bronchoscopist's view was limited to those structures visualized within the airways or with fluoroscopy. The bronchoscopist can now visualize the structures surrounding the airway wall using EBUS. This chapter will review the clinical applications of EBUS. A more detailed discussion of the technical aspects of EBUS will be undertaken elsewhere in this text.

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Basic Equipment and Technique

There are two distinct forms of EBUS, a radial probe (RP-EBUS) or a convex probe (CP-EBUS), that are typically utilized in different clinical scenarios [4]. The radial probe offers a 360° view of the airway wall as well as the structures surrounding it [2]. When using a RP-EBUS, the flexible bronchoscope is advanced to the area of interest, and the ultrasound probe is introduced into the airway through the working channel of the bronchoscope [5]. RP-EBUS,) using the standard 20 MHz probe, allows a depth of penetration of up to 5 cm with a resolution of less than 1 mm [2].If the intended use is for the evaluation of the airway wall, the tip of the ultrasound probe can be encased in a balloon sheath to facilitate acoustic coupling [5]. Once the probe is in the area of interest, the balloon sheath is inflated with water, optimizing contact with the airway wall [6]. For the evaluation of peripheral lesions, the balloon sheath is not typically required.

In contrast, the , convex probe EBUS consists of a specialized bronchoscope which has an integrated 7.5 MHz curvilinear ultrasound transducer at its tip. The optical view is forward oblique at an angle range of 10°–30°. The ultrasound angle of view is between 70° and 90° with respect to the longitudinal axis of the bronchoscope. While the lower-frequency transducer used in the CP-EBUS does not provide an image resolution as good as RP-EBUS, it does offer greater depth

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of penetration. The integrated design of the, CP-EBUS bronchoscope permits real-time transbronchial needle aspiration to be performed under ultrasound guidance through the standard working channel [7]. Echogenic needles of various calibers are available to obtain the samples [6]. Miniature forceps are also available that allow tissue biopsies to be taken under real-time ultrasound guidance using the CP-EBUS bronchoscope [8].

Clinical Applications of Radial Probe EBUS

Although the clinical applications of radial probe and convex probe EBUS overlap somewhat, they are largely complementary. The indications for RP-EBUS are summarized in Table 26.1.

RP-EBUS for the Evaluation of Endobronchial Lesions

Lung cancers are often detected late when treatment outcomes are poor. Detection of lung cancer while the disease is still preinvasive or minimally invasive may allow more effective treatment. Patients who are at high risk for lung cancer may also have early central lung cancers: radiographically occult central lesions that can be detected at an early stage by bronchoscopy or sputum cytology. Standard white-light bronchoscopy, autofluorescence imaging, and the RP-EBUS can be used to diagnose these lesions. The addition of autofluorescence imaging to standard white-light bronchoscopy improves the sensitivity for detecting such lesions, but its low specificity means that it is often unable to distinguish early neoplastic lesions from inflammation, scarring, or other non-neoplastic localized changes [9, 10]. This can lead to unnecessary biopsies with increased cost and risk to the patient [10]. Autofluorescence bronchoscopy also cannot accurately determine the depth of invasion of early endobronchial lesions which is a major determinant of the most appropriate and effective type of therapy [9]. The application of RP-EBUS to such lesions allows the bronchoscopist to clearly distinguish the five normal layers of the bronchial wall of the trachea and cartilaginous bronchi, making it an ideal tool for evaluating such endobronchial lesions [5, 11] (Fig. 26.1).

Herth et al. prospectively evaluated patients undergoing autofluorescence bronchoscopy at two institutions. Those patients with nonspecific changes ($n = 32$) or findings suspicious for malignant changes ($n = 42$) on autofluorescence imaging were also evaluated with RP-EBUS. The RP-EBUS was then used to categorize these patients into those with benign ultrasound features (having a preserved layered bronchial wall structure) or malignant ultrasound features (having thickened wall, destroyed layer structure, or peribronchial infiltration). Then endobronchial biopsies were obtained and the histology was correlated with the findings by RP-EBUS. RP-EBUS was more accurate than autofluorescence in both benign (92% vs. 55%) and malignant lesions (97% vs. 69%). This suggests that RP-EBUS significantly improves the diagnostic specificity of

Table 26.1 Indications for radial probe EBUS

Diagnostic evaluation of endobronchial lesions
Guiding therapy of endobronchial lesions or lesions adjacent to the bronchi
Diagnostic evaluation of pulmonary parenchymal nodules
Staging of non-small cell lung cancer
Diagnosis of mediastinal lesions
Guiding placement of fiducial markers

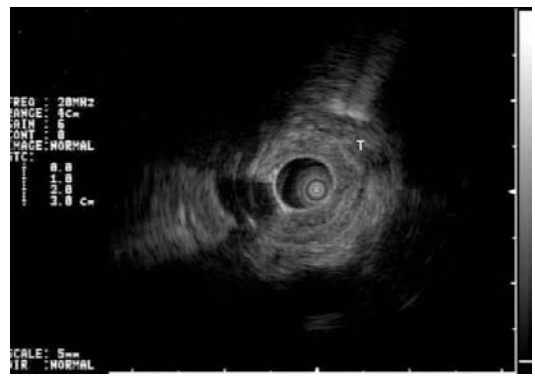

Fig. 26.1 Left main stem tumor with cartilage disruption

autofluorescence bronchoscopy for such central early lung cancers and may be useful in conjunction with autofluorescence bronchoscopy when available [10].

Several studies have shown RP-EBUS to be useful in assessing the depth of invasion of endobronchial tumors, which can be an important factor in determining therapy for such lesions. Using 24 lung lobes resected for known lung cancer, Kurimoto and colleagues compared RP-EBUS determination of depth of tumor invasion with histologic findings and found a 95.8% correlation between their conclusions [5]. Other authors have also reported similar close correlation between in vivo RP-EBUS findings and subsequent histologic examination of surgically resected specimens [12]. Miyazu et al. have also demonstrated the utility of RP-EBUS in helping clinicians choose the most appropriate therapy for central early lung cancers. Their group first evaluated six patients with central early lung cancer detected by autofluorescence bronchoscopy using RP-EBUS and used the information provided about depth of invasion to determine the suitability of each patient for photodynamic therapy (PDT). The two patients who had no cartilaginous involvement were deemed candidates for PDT and were treated with that modality with good outcome [13]. In another study, their group used RP-EBUS to evaluate 12 patients with 18 biopsy-proven central squamous cell carcinomas who were thought to be good candidates for PDT based on standard bronchoscopy and high-resolution CT scan. Nine of 18 lesions assessed by RP-EBUS were found to be intracartilaginous and therefore candidates for PDT. All nine underwent PDT and had sustained complete remission at 32 months. The other nine lesions were determined to be extracartilaginous by RP-EBUS. Of these six were resected, and histology confirmed the RP-EBUS estimate of the depth of invasion in all six cases. RP-EBUS successfully identified the nine lesions not amenable to PDT so they could receive more appropriate treatment [14].

Herth et al. prospectively assessed the utility of RP-EBUS in therapeutic bronchoscopy. They evaluated 1174 patients who underwent therapeutic bronchoscopy and RP-EBUS over a 3-year period. It was used in conjunction with tumor debridement (mechanical, laser, APC), in airway stent placement, with endobronchial brachytherapy, in endobronchial foreign body removal, and in endobronchial abscess drainage. The authors reported that RP-EBUS changed the therapy or guided the intervention in 43% of the cases in which it was used. Reported examples included longer stent length for undetected peribronchial tumor spread, aiding decisions about when to stop ablative treatments due to proximity to vital structures, and changes to staging in brachytherapy [15].

RP-EBUS for the Diagnostic Evaluation of Peripheral Pulmonary Lesions

Radial probe EBUS can be a useful tool in the diagnostic evaluation of peripheral pulmonary lesions. RP-EBUS provides information about the ultrasound characteristics of these lesions, assists with location verification, and has been used in combination with other guided-bronchoscopy modalities to improve diagnostic yield.

Ultrasound characteristics of the peripheral pulmonary lesions visualized with RP-EBUS may provide helpful information in addition to clinical and radiographic features commonly used to determine the probability that a nodule is malignant [4]. Kurimoto et al. analyzed 124 patients with peripheral pulmonary lesions who had both a confirmed histologic diagnosis and a preoperative RP-EBUS to attempt to identify ultrasound characteristics that could predict tumor type. They identified three major patterns. Type I lesions demonstrated a homogeneous pattern and were mostly benign (92%). Type II lesions (hyperechoic dots and linear arcs) and type III lesions (heterogeneous pattern) were mostly malignant: 98 of 99 lesions [16]. Chao's group subsequently attempted to develop a simpler predictive model. Peripheral lung lesions of an initial group of 20 patients with known histologic diagnosis were used to identify four ultrasound image patterns: a continuous hyperechoic

margin, homogeneous or heterogeneous internal echoes, hyperechoic dots in the lesion, and concentric circles along the echo probe. They then enrolled 131 additional patients to assess these patterns prospectively. Five were excluded because the investigators could not agree on the pattern. Of the remaining 126 patients, 93 had a definitive diagnosis and were included in their analysis. After multivariate analysis, only one of the characteristics—the presence of concentric circles—retained a statistically significant predictor of the nature of the lesion. Eighteen of 19 lesions with concentric circles were benign [17]. Kuo et al. assessed 224 patients with peripheral lung lesions who underwent RP-EBUS and were eventually given a definitive diagnosis. RP-EBUS images were reviewed, and three ultrasound characteristics were selected for analysis: continuous or noncontinuous margin between the lesions and the adjacent lung, presence or absence of an air bronchogram within the lesion, and homogenous or heterogeneous echogenicity of the lesion. The presence of a continuous lung margin, absence of a discrete air bronchogram within the lesion, and a heterogeneous echogenicity of the lesion were all found to be predictors of malignancy. A lesion with none of the three features had a negative predictive value of 93.7% for malignancy, and a lesion with two of the three features had a positive predictive value for malignancy of 89.2% [18].

By employing its unique property of location verification, RP-EBUS is frequently used to confirm the lesion sampling site for the diagnosis of peripheral pulmonary lesions. In the past, minimally invasive options for the diagnosis of these lesions included percutaneous needle biopsy or conventional bronchoscopy with or without fluoroscopy. A recent meta-analysis of CT-guided percutaneous core needle biopsy and fine needle aspiration reported pooled sensitivities of 95% and 90%, respectively [19]. However, the superior sensitivity of percutaneous biopsy is not without complications. Pneumothoraces after percutaneous biopsy of peripheral pulmonary lesions are reported between 15–43% and 4–18%

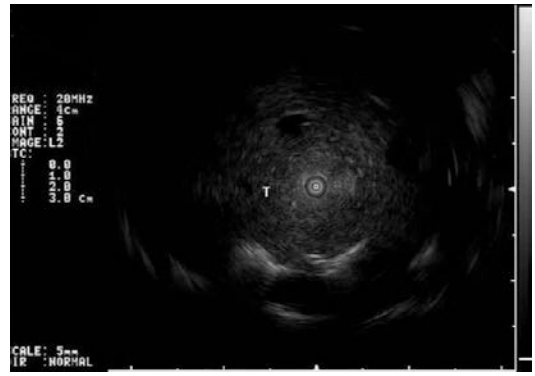

Fig. 26.2 Radial probe image of right upper lobe lung cancer

which require chest tube drainage [20]. That risk is increased for those patients whose nodules are further from the pleura, who have emphysema, and who have smaller nodules. Diagnostic accuracy also decreases with greater distance from the pleura and is less reliable for diagnosing nonmalignant lesions than malignant ones. With respect to conventional bronchoscopy, a systematic review reported that the pooled sensitivity for central pulmonary lesions and peripheral pulmonary lesions beyond the level of the segmental bronchi was 88% and 78%, respectively, and depended largely on the size of the lesion (pooled sensitivity of 63% for peripheral lesions >2 cm and 34% for lesions ≤2 cm) [21]. When compared to image-guided percutaneous needle aspiration, RP-EBUS is less sensitive but has a much lower complication rate (Fig. 26.2).

In 2002, Herth et al. evaluated 50 consecutive patients with peripheral pulmonary lesions in a crossover study. The patients were randomized to either receive TBLB with RP-EBUS followed by TBLB with fluoroscopy or vice versa. For the RP-EBUS biopsies, the EBUS probe was placed into the bronchi suspected to be the location of the lesion until it was seen with ultrasound. The probe was then removed and the forceps placed into the same bronchus and biopsies taken. The fluoroscopic biopsies were taken in the usual fashion. No significant differences in diagnostic yield were seen between the two methods.

Diagnostic accuracy using RP-EBUS TBLB was around 80% [22]. In a randomized controlled trial of 221 patients, Paone and colleagues were able to show improved sensitivity (79% vs. 55%) and diagnostic accuracy (85% vs. 69%) with TBLB using RP-EBUS vs. TBLB without RP-EBUS [23]. Soon thereafter, a guide sheath was introduced to improve the yield of RP-EBUS-guided TBLB for peripheral lung lesions. This technique involves advancing the radial probe through a guide sheath to the lesion and then withdrawing the probe once it has been localized while leaving the guide sheath in place. The biopsy tools are then advanced through the guide sheath to the lesion [24, 25]. In some reports using RP-EBUS with guide sheath to sample peripheral pulmonary nodules has demonstrated impressive diagnostic yield, with Kurimoto and colleagues achieving a yield of 76% in lesions 10 mm or less in size [25]. Many factors have been seen to increase the yield when using RP-EBUS for peripheral pulmonary lesions in different studies. These include lesions >2 cm in size, lesions closer to the hilum, visualization on fluoroscopy, malignant disease (as compared to benign), having the probe within the lesion rather than adjacent to it, and taking at least five biopsy specimens [25–30]. Another factor that may improve yield when diagnosing peripheral pulmonary lesions is the use of transbronchial needle aspiration (TBNA) for parenchymal lesions. Traditionally TBNA has been employed to sample mediastinal and hilar lymph nodes rather than peripheral pulmonary nodules. However, Chao et al. examined this in a randomized trial of 182 patients. They used RP-EBUS without guide sheath or fluoroscopy to locate peripheral lung lesions. The patients were randomized to sampling with conventional techniques (including TBLB and bronchial washings) or conventional techniques with the addition of TBNA. The addition of TBNA to conventional techniques increased the overall diagnostic yield from 60 to 78%. TBLB and bronchial wash demonstrated lower yield when the EBUS probe was located adjacent to the lesion rather than within it, but TBNA did not suffer a decrease in diagnostic yield [31]. Despite its ability to improve the diagnostic yield of bronchoscopy for peripheral lung lesions, TBNA remains underutilized [32]. Unfortunately, only two factors, the lesion seen concentrically around the probe and lesions >2 cm in size, have been consistently seen to improve diagnostic yield with RP-EBUS. This fact emphasizes the clinical variability in the studies reporting these results. Overall, the use of RP-EBUS has been shown to improve the performance characteristics over that of conventional bronchoscopy alone. Two recent meta-analyses report the pooled sensitivity of RP-EBUS to be more than 70% but acknowledge significant heterogeneity between studies [33, 34].

Synergistic combinations of different bronchoscopic modalities with varying properties of maneuverability (e.g., thin and ultrathin bronchoscopy), navigation (e.g., virtual bronchoscopy and electromagnetic navigation), and location verification (e.g., RP-EBUS) may improve diagnostic yield for peripheral pulmonary nodules. Asahina and colleagues combined virtual bronchoscopy with RP-EBUS and guide sheath in 29 patients with small peripheral pulmonary lesions. Their sensitivity was 92% for lesions between 20 and 30 mm in size, but only 44% for those less than 20 mm in size [35]. Combining a technique that improves maneuverability and navigation (such as electromagnetic navigational bronchoscopy) with one that confirms the location (such as RP-EBUS) is another appealing option [36]. Eberhardt et al. conducted a prospective randomized trial to precisely this approach. They randomized 120 patients (118 of which had a definitive diagnosis in their final analysis) to electromagnetic navigational bronchoscopy (ENB), EBUS, or a combination of both techniques. Diagnostic yield was higher with combined EBUS/ENB (88%) than with EBUS or ENB alone (69% and 59%, respectively) [37]. Ishida's group showed similar results in a trial of 199 patients with small peripheral lung lesions who were randomized to EBUS with virtual bronchoscopic navigation or bronchoscopy with RP-EBUS but no virtual bronchoscopic navigation. They reported a diagnostic

yield of 80% in the combined modality group against 67% in the group with EBUS alone [38]. The evidence suggests that using RP-EBUS in conjunction with other modalities—such as a guide sheath, peripheral TBNA, and navigational bronchoscopy—may significantly improve diagnostic yield for small peripheral lung lesions.

Other Clinical Applications of RP-EBUS

Other clinical applications of RP-EBUS in both malignant and benign disease have been reported. Although CP-EBUS has supplanted RP-EBUS in systematic mediastinal staging for non-small cell lung cancer (NSCLC), RP-EBUS, due to its property to visualize airway wall infiltration, is still used to accurately assess the distance of the endobronchial tumor from the carina, which is an important element of cancer staging [4]. RP-EBUS can also be used to differentiate external compression of a bronchus by tumor from direct tumor invasion of the airway wall which affects the stage of cancer. Herth et al. examined this prospectively in 105 patients who presented with central airway lesions. CT scan was first performed, followed by bronchoscopy with EBUS. The 105 patients who were analyzed went on to surgical procedures for treatment or staging which also involved sampling the airway so histologic confirmation of the bronchoscopic findings was available. EBUS was far superior to CT scan in predicting tumor invasion of the airway wall, with sensitivity, specificity, and diagnostic accuracy of 89%, 100%, and 94% for EBUS compared with 75%, 28%, and 51% for CT scan [39]. RP-EBUS, with and without navigational bronchoscopy as an adjunct, has also been used to aid in placing fiducial markers in order to guide stereotactic radiosurgery for lung tumors [40].

Applications of RP-EBUS in benign diseases such as lung transplantation and asthma have also been reported, although their general use has not yet been widely adopted. In one study of ten patients who underwent lung transplantation, RP-EBUS was used to measure the thickness of the layers of the autologous and allogenic parts of the central bronchi. In patients with evidence of acute graft rejection on transbronchial biopsies, the relative area of the second submucosal layer of the autologous airways was smaller than in those without graft rejection. Additionally, the relative area of the second layer of the autologous airways was thicker in those patients with evidence of infection on bronchoalveolar lavage [41]. Asthma is a disease process characterized by airway wall remodeling, and measurements of the total bronchial wall thickness by RP-EBUS have been shown to be comparable to that made by high-resolution computerized tomography scans [42]. In the same study including 35 asthmatics and 23 controls, the thickness of the first two layers of the bronchial wall measured with RP-EBUS was significantly larger in asthmatics and negatively correlated with forced expiratory volume in 1 s [42].

Clinical Applications of Convex Probe EBUS

In the past, conventional TBNA was one of the minimally invasive options to obtain a tissue diagnosis of intrathoracic lymphadenopathy, but it had a variable diagnostic yield. In one study comparing conventional TBNA with RP-EBUS-guided TBNA, the diagnostic yield for lymphadenopathy in sites other than the subcarinal area was seen to be higher with RP-EBUS (84% for RP-EBUS vs. 58% for conventional TBNA) [43]. The disadvantage of RP-EBUS guidance for TBNA of mediastinal lymph nodes is the inability to perform the needle aspiration under direct, real-time guidance which led to the development of the specialized bronchoscope with an integrated convex probe and working channel for needle aspiration [7].

The indications for CP-EBUS are summarized in Table 26.2.

Table 26.2 Indications for convex probe EBUS

Staging of non-small cell lung cancer
Diagnosis of mediastinal lesions
Guiding transbronchial biopsy/aspiration of central pulmonary parenchymal nodules
Guiding placement of fiducial markers

CP-EBUS for Nonmalignant Mediastinal or Hilar Adenopathy

Mediastinal abnormalities, especially lymphadenopathy, are common incidental imaging findings. Although malignant causes remain high in the differential, there are a variety of benign diseases that can cause intrathoracic lymphadenopathy.

For pulmonary sarcoidosis, the evidence suggests that there is an improvement in the diagnostic yield of conventional bronchoscopy (transbronchial lung biopsy and endobronchial mucosal biopsy) with the addition of CP-EBUS-TBNA. There are several studies evaluating the role of CP-EBUS-TBNA in populations with high pretest probability for sarcoidosis. In a prospective, randomized controlled trial comparing conventional TBNA with a 19-gauge needle and EBUS-TBNA with a 22-gauge needle in 50 patients with hilar and/or mediastinal lymphadenopathy and a clinical suspicion for sarcoidosis, Tremblay et al. demonstrated that the diagnostic yield of EBUS-TBNA for sarcoidosis was significantly better at 83% compared with 54% with conventional TBNA [44]. Another large, prospective, randomized, multicenter trial compared the diagnostic yield of transbronchial lung biopsy (TBLB) and endobronchial mucosal biopsy (EBB) with endosonographic fine needle aspiration of intrathoracic lymph nodes (esophageal or CP-EBUS) for detecting noncaseating granulomas in patients with clinical and radiographic suspicion of stage I or II sarcoidosis [45]. The diagnostic yield by endosonographic biopsy was significantly better than that of bronchoscopy with TBLB and EBB (74% vs. 48%, respectively). A systematic review and meta-analysis of the efficacy of EBUS-TBNA for the diagnosis of sarcoidosis included 553 patients with the disease from 15 studies and reported that the diagnostic yield ranged from 54 to 93% with the pooled diagnostic yield of 79% [46]. Given these findings, EBUS-TBNA is recommended in the evaluation of suspected sarcoidosis with mediastinal or hilar lymphadenopathy [47].

Intrathoracic lymphadenopathy may occur as a result of bacterial, mycobacterial, and fungal infections. EBUS-TBNA has been used to diagnose these infectious diseases presenting with mediastinal masses or lymphadenopathies [48–50]. A recent study evaluated the role of EBUS-TBNA in the diagnosis of tuberculosis in an endemic population. It included 102 patients and 216 lymph nodes were sampled. The diagnostic yield for tuberculosis (defined as positive for acid-fast bacilli by staining, positive for Gene-Xpert MTB-RIF test, or positive for necrotizing granulomas with supportive clinical investigations) was 84.8% [51].

Published case reports have also shown EBUS-TBNA to be useful in the evaluation and treatment of bronchogenic cysts located in the mediastinum. While most bronchogenic cysts can be diagnosed by CT imaging alone, some with more mucoid contents mimic the attenuation of soft tissue on CT. In these cases EBUS-TBNA can be used to make the diagnosis, and needle aspiration with or without antibiotics have been used to treat patients with bronchogenic cysts who were not willing to undergo surgery [52, 53]. EBUS-TBNA has also been used to sample thyroid nodules in patients with small-cell lung cancer and intrathoracic goiters and parathyroid adenomas as well [54, 55] (Figs. 26.3 and 26.4).

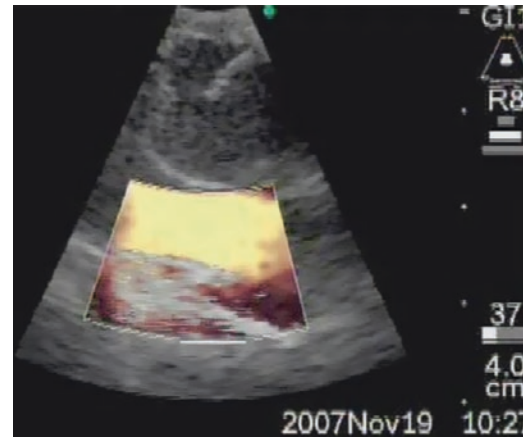

Fig. 26.3 EBUS-TBNA station 4R

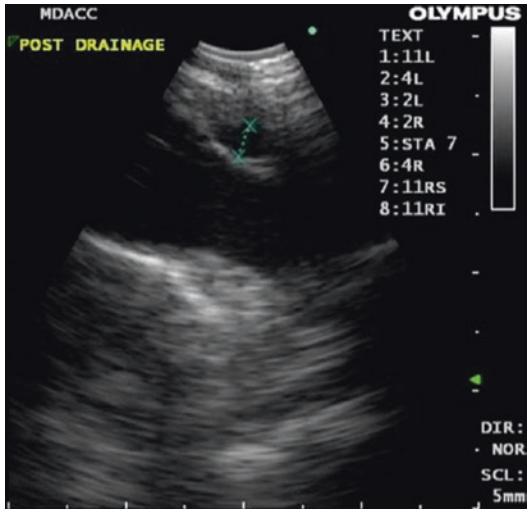

Fig. 26.4 Ultrasound image of right hilar cyst at station 11Rs before and after drainage. Of note, the right pulmonary artery, which was compressed behind the cyst, is widely patent after drainage

CP-EBUS for Malignant Mediastinal or Hilar Lymphadenopathy

Applications of CP-EBUS in malignant disease extend to diagnosis and staging of lung cancer, malignant diseases of structures within the mediastinum such as lymphomas and thymomas, and metastatic disease to the mediastinum [56–60]. The role of CP-EBUS in the diagnosis and staging of lung cancer will be reviewed in detail later in this chapter.

Lymphomas have been reported to present with intrathoracic lymphadenopathy in up to 75% of patients with Hodgkin's lymphoma [61]. The diagnosis and subtyping of lymphoma are made by evaluation of the cytomorphologic, immunophenotypic, genetic, and molecular features of the tumor. In the past, reports of discordance between cytologic and histologic samples in lymphoma raised the concern that fine needle aspiration of intrathoracic lymphadenopathy could not accurately provide a diagnosis in suspected lymphoma leading to more invasive procedures such as mediastinoscopy, thoracoscopy, and thoracotomy to obtain histological samples [48]. However, these invasive procedures are not without risks. Since the development of CP-EBUS, several retrospective studies have evaluated the value of EBUS-TBNA to diagnose and subtype lymphoma. There is significant variability in these studies as demonstrated by the wide range in the sensitivities reported (from 38 to 90.9%) [48, 62–65], likely related to local cytopathology expertise.

In 2008, Kennedy et al. first assessed the diagnostic yield of EBUS-TBNA in 25 patients with mediastinal lymphadenopathy and a suspicion for lymphoma using the 22-gauge needle with on-site cytology. They attained adequate lymph node sampling in 24/25 patients, and EBUS-TBNA samples identified lymphoma in 10 patients and benign disease in 14 patients. One patient had a false-negative result from EBUS-TBNA. In their cohort, EBUS-TBNA had a sensitivity of 91%, a specificity of 100%, and a negative predictive value of 93% for the diagnosis (but not subtyping) of lymphoma [65].

Steinfort et al. retrospectively reviewed a prospectively collected database to assess the utility of EBUS-TBNA in diagnosing lymphoma. They evaluated patients referred for assessment of isolated hilar or mediastinal lymphadenopathy while excluding those with clinical and radiologic features strongly suggestive of sarcoidosis. Fifty-five patients were included. When EBUS-TBNA was not diagnostic, the patients underwent subsequent surgical biopsy or at least 6 months of clinical and radiographic surveillance. Lymphoma was found in 21/55 patients (38%), and EBUS-TBNA was diagnostic in 16 of these for a diagnostic sensitivity for lymphoma of 76%. Of the 16 patients with lymphoma diagnosed by EBUS, 4 needed additional surgical procedures to guide management. If the four patients who needed additional diagnostic procedures are considered to have had inadequate diagnostic tissue, a more accurate sensitivity for the definitive diagnosis of lymphoma may actually be 57% [48]. Finally, a retrospective study published in 2015 evaluated the value of the EBUS-TBNA to exclude lymphoma as a diagnosis based upon the results of

EBUS-TBNA [63]. In this study, 181 patients with clinical symptoms of lymphoma or a history of lymphoma with intrathoracic adenopathy who underwent EBUS-TBNA to obtain tissue were included. 41.5% of the patients had lymphoma. The sensitivity of EBUS-TBNA to diagnose and subtype lymphoma, de novo lymphoma, relapsed lymphoma, and Hodgkin's lymphoma was 77, 67, 81, and 57%. They also found that the likelihood ratio for a patient to have lymphoma when the cytology results from the EBUS-TBNA showed granulomatous inflammation was 0.00 (95% CI, 0.00–0.276) and adequate/inadequate lymphocytes was 0.31 (95% CI, 0.181–0.545) providing significant clinical information depending upon the pretest probability of the disease. At this time, the available literature supports the use of EBUS-TBNA as an initial, minimally invasive diagnostic test which may be able to prevent other invasive diagnostic procedures for some patients [47].

CP-EBUS for the Staging of Non-small Cell Lung Cancer

EBUS, particularly CP-EBUS, has found its most widespread use in the lymph node staging of non-small cell lung cancer. There has been great interest in this application of EBUS because the nodal stage has great impact on whether or not a patient will benefit from surgery. Imaging modalities have been unsatisfactory for determining nodal stage. Pooled analysis of CT scan and positron emission scanning (PET) for the noninvasive staging of the mediastinal and hilar lymph nodes yields a sensitivity for CT of only 55% and for PET of only 77% [66]. Many patients with NSCLC therefore require invasive staging of the mediastinal lymph nodes. The most recent edition of the American College of Chest Physicians' evidence-based clinical practice guideline on the staging of non-small cell lung cancer recommends invasive staging of the mediastinal lymph nodes in the absence of known distant metastasis when there is discrete enlargement of mediastinal or hilar lymph nodes, when there is a central tumor, when there is a peripheral tumor ≥3 cm in size, and when mediastinal lymph nodes demonstrate increased uptake on PET scan [66] (Table 26.3, Fig. 26.5).

EBUS-TBNA is one of the most common methods used to accomplish invasive mediastinal staging of NSCLC. The ability of CP-EBUS to guide real-time TBNA of mediastinal lymph nodes has led to its largely replacing RP-EBUS for this purpose. The use of CP-EBUS for staging the mediastinal lymph nodes of patients with NSCLC was first described by Yasufuku et al. in 2005. They performed TBNA with CP-EBUS on 163 lymph nodes of 105 patients who had confirmed or suspected non-small cell lung cancer with mediastinal lymph nodes that were suspicious for metastasis in N2 or N3 position. EBUS-TBNA yielded results positive for cancer in 64 patients. Of the remaining 44, 7 were followed clinically for 12 months with a benign course. The other 37 patients with negative EBUS-TBNA underwent thoracotomy, with 33/37 having no evidence of N2/N3 lymph node metastasis. This yielded a diagnostic accuracy of 96%, a sensitivity of 94.6%, and a negative predictive value of 89%. Specificity and positive predictive value were 100% [67]. Since then many other studies of EBUS-TBNA in staging of NSCLC have been published, often comparing this technique to other staging techniques.

Yasufuku et al. prospectively compared the performance of EBUS-TBNA for mediastinal staging to that of CT and PET scanning in 102 patients with proven or suspected lung cancer who were thought to be candidates for surgical resection. All patients received CT with contrast and full-body PET prior to undergoing EBUS-TBNA prior to surgery. Patients with proven or suspected lung cancer who were staged I, II, or IIIA with only a single positive N2 lymph node by EBUS-TBNA were considered operable and underwent resection with thoracic lymphadenectomy and comparison to staging by imaging and EBUS. Those patients who were not deemed operable had their staging results compared to

Table 26.3 Definitions for descriptors of the seventh edition TNM classification for lung cancer

	Subgroup	Definition
T (tumor)		
T0		No primary tumor
T1		Tumor ≤3 cm, surrounded by the lung or visceral pleura, but more central than the lobar bronchus
	T1a[a]	≤2 cm
	T1b[a]	>2 cm and ≤3 cm
T2		>3 cm and ≤7 cm, or with any of the following: visceral pleura invasion, involvement of main bronchi but ≥2 cm distal to main carina, atelectasis/obstructive pneumonitis not involving the entire lung
	T2a[a]	>3 cm and ≤5 cm
	T2b[a]	>5 cm and ≤7 cm
T3		
	$T3_{>7}$[a]	>7 cm
	$T3_{Inv}$	Tumor directly invading the chest wall, diaphragm, phrenic nerve, mediastinal pleura, or parietal pericardium
	$T3_{Centr}$	Tumor in the main bronchus <2 cm from the main carina or complete lung atelectasis/obstructive pneumonitis
	$T3_{Satell}$[a]	Separate tumor nodule/s in the same lobe as primary tumor
T4		
	$T4_{Inv}$	Tumor of any size with invasion of the heart, great vessels, trachea, carina, esophagus, vertebral body, or recurrent laryngeal nerve
	$T4_{Ipsi\ Nod}$[a]	Separate tumor nodule/s in different lobe, ipsilateral to primary tumor
N (regional LN)		
N0		No regional metastases
N1		Metastases to ipsilateral peribronchial, perihilar, or intrapulmonary LN
N2		Metastases to subcarinal or ipsilateral mediastinal LN
N3		Metastases to contralateral hilar or mediastinal LN or involvement of any scalene or supraclavicular LN
M (metastases)		
M0		No distant metastases
M1		
	$M1a_{Contr\ Nod}$[a]	Separate tumor nodule/s in contralateral lung
	$M1a_{Pl\ Dissem}$[a]	Malignant pleural or pericardial effusion
	M1b[a]	Distant metastases
Special situations		
TX, NX		T or N status cannot be assessed
T_{is}		In situ tumor
$T1_{ss}$		Superficial spreading tumor of any size, confined to the wall of the trachea or main bronchi

[a]New subgroups added in the seventh TNM
LN lymph node, *Inv* invasion, *Centr* central, *Satell* satellite, *Ipsi Nod* ipsilateral nodule/s, *Contr Nod* contralateral nodule/s, *Pl Dissem* pleural dissemination

the clinical course of their disease. EBUS correctly staged 24 of 26 patients who were ultimately proven to have mediastinal lymph node metastasis. Comparison of the three modalities showed that EBUS-TBNA had a sensitivity of 92%, specificity of 100%, negative predictive value of 97%, and overall diagnostic accuracy of 98%. This was superior to both CT (sensitivity

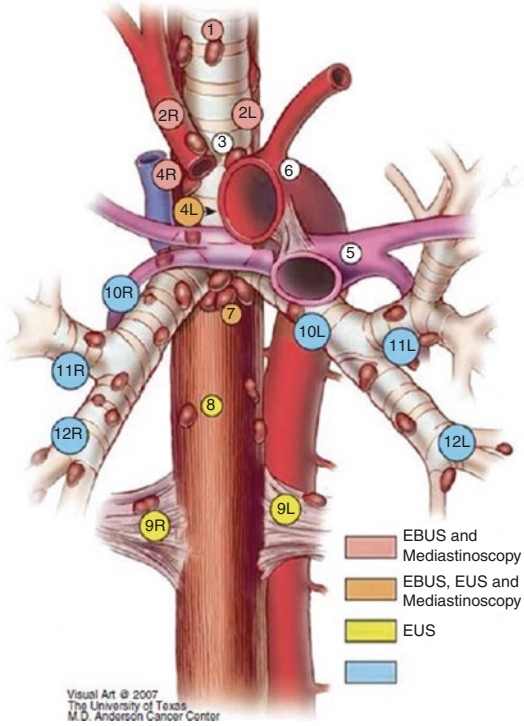

Fig. 26.5 Nodal stations

77%, specificity 55%, NPV 88%, diagnostic accuracy 61%) and PET (sensitivity 80%, specificity 70%, NPV 92%, diagnostic accuracy 73%) [68]. Herth et al. subsequently prospectively evaluated 100 patients with suspected NSCLC who had CT scans without evidence of enlarged mediastinal lymph nodes and PET scans which were negative for significant mediastinal uptake. After the imaging tests were completed, all patients underwent bronchoscopy with EBUS evaluation of the mediastinal and hilar lymph nodes. All nodes greater than 5 mm in short-axis diameter were sampled, and all patients had at least one node of that size. All 100 patients subsequently underwent either thoracotomy or mediastinoscopy, and the results of surgical pathology were used as the standard of reference. Eight patients with CT and PET scans negative for mediastinal involvement had EBUS-TBNA positive for lung cancer. Only one patient with negative EBUS-TBNA had additional lymph node metastasis (N1) detected at the time of surgery. In this group of patients, EBUS-TBNA had a sensitivity of 89%, specificity of 100%, and negative predictive value of 99% for detecting mediastinal lymph node metastasis missed by CT and PET [69]. EBUS-TBNA was also compared to integrated PET/CT by Hwangbo et al. They enrolled 129 patients with histologically confirmed or suspected operable NSCLC. All patients underwent integrated PET/CT prior to bronchoscopy. They then underwent bronchoscopy with EBUS-TBNA of all identified target lymph node stations without on-site cytopathological support. Ultimately 117 patients were evaluated after excluding those with alternative diagnoses, with unexpected pleural metastases at the time of surgery, and who refused recommended surgery. Twenty-seven patients had mediastinal lymph nodes positive for malignancy with EBUS-TBNA. Of the 90 patients without malignancy on EBUS-TBNA, only 3 patients had malignancy found in mediastinal or hilar nodes at the time of surgery. EBUS-TBNA had sensitivity of 90%, specificity of 100%, negative predictive value of 97%, and diagnostic accuracy of 97% as compared to sensitivity of 70%, specificity of 60%, negative predictive value of 85%, and diagnostic accuracy of 62% for PET/CT. All the differences were significant except for sensitivity, which was nearly significant [70].

Mediastinoscopy has traditionally been considered the gold standard for invasive staging of the mediastinal lymph nodes in lung cancer with reported sensitivity ranging from 40 to 92%. Despite its long-standing status as the gold standard, mediastinoscopy is limited to accessing the paratracheal and subcarinal nodal stations, without the ability to sample the hilar nodes. Ernst et al. enrolled 66 patients who had lesions suspicious for NSCLC, who were surgical candidates otherwise, and whose enlarged mediastinal lymph nodes (if present) were confined to paratracheal and subcarinal lymph node stations in a prospective crossover study. All patients underwent mediastinoscopy with EBUS-TBNA incorporated into the preoperative bronchoscopy of each patient—all performed within a week of the mediastinoscopy. Patients with negative mediastinal evaluation and those with limited IIIA disease (single positive N2 lymph node) were

offered surgical resection. A definitive diagnosis was established by either mediastinal procedure in 49/66 patients (74%), and 61 patients went on to have surgery. In the per-patient analysis, EBUS-TBNA and mediastinoscopy did not differ in diagnostic yield (89% vs. 79%; $p = 0.1$). In the per-lymph node analysis, EBUS-TBNA had a higher diagnostic yield than mediastinoscopy (91% vs. 78%; $p = 0.007$) with the entire difference coming from better yield for EBUS for the subcarinal lymph node station [71]. Annema et al. randomized 241 patients with potentially resectable NSCLC to compare surgical mediastinal staging (mediastinoscopy with left parasternal mediastinotomy if needed) with endosonographic staging (consisting of endoscopic ultrasound-FNA and EBUS-TBNA). All patients who underwent endosonographic staging also underwent surgical staging afterward if no nodal metastases were found by endosonography. Endosonography plus surgical staging showed greater sensitivity than surgical staging alone (94% vs. 79%; $p = 0.02$). There was not a significant difference in negative predictive value between the groups. One secondary outcome was also significantly less in the endosonography group: 7% underwent unnecessary thoracotomies vs. 18% in the surgical staging group [72]. Yasufuku et al. analyzed 153 patients with NSCLC who required mediastinoscopy as part of the staging evaluation of their cancer. All patients who were analyzed underwent EBUS-TBNA followed immediately by standard cervical mediastinoscopy. The surgeons were blinded to the cytopathology results, and each patient served as his or her own control. The patients who had no evidence of N2/N3 disease on EBUS-TBNA and mediastinoscopy then underwent pulmonary resection with systematic lymph node resection, enabling correlation of the results with prior EBUS-TBNA and mediastinoscopy results. EBUS-TBNA and mediastinoscopy were comparably accurate, with respective sensitivity, negative predictive value, and diagnostic accuracy of 81% vs. 79%, 91% vs. 90%, and 93% vs. 93%. Both tests had a specificity of 100%. There were fewer complications with EBUS-TBNA than with mediastinoscopy. These results suggest that EBUS-TBNA is equivalent to mediastinoscopy for staging of NSCLC, even without the addition of EUS-FNA as was done in the trial by Annema [73].

Endoscopic ultrasound (EUS) with FNA, generally performed by gastroenterologists, preceded the development of EBUS by several years. EUS-FNA has also been used to diagnose mediastinal lesions and assist in the mediastinal staging of lung cancer. EUS alone has somewhat limited application for sampling mediastinal lymph nodes because it is unable to sample those nodal stations anterior to or to the right of the trachea and also unable to sample hilar lymph nodes. EBUS, on the other hand, is able to reach those nodal stations anterior to the trachea as well as the hilar nodes. Its anatomic limitations for nodal staging are primarily in reaching the lymph nodes of the aortopulmonary window, the lower esophageal nodes, and the nodes of the inferior pulmonary ligament [67]. The two techniques are complementary in their reach and at least theoretically should be able to reach all the mediastinal lymph node stations except for the aortopulmonary window and perhaps the upper retrotracheal stations. Several groups have assessed their collaborative use in staging the mediastinum of patients with NSCLC. Small preliminary studies of a combined EBUS-TBNA/EUS-FNA approach using separate bronchoscopes and endoscopes appeared promising, and these have led to subsequent larger studies evaluating such a combined approach [74, 75]. Herth et al. assessed 150 consecutive patients with non-small cell lung cancer and no evidence of extrathoracic metastases. The investigators included 139 patients who were confirmed to have NSCLC in their analysis. The same operator performed both EBUS and EUS for each procedure using a single CP-EBUS bronchoscope. Endoscopic mediastinal diagnosis was confirmed with thoracotomy, thoracoscopy, or 6–12 months of clinical follow-up. The prevalence of mediastinal lymph node metastasis was 52% (71/139 patients). EBUS-TBNA detected the malignant nodes in 65/71 patients (91%), and EUS-FNA detected the malignant nodes in 63/71 patients (89%). The combined technique found the malignant lymph

nodes in 68/71 patients (96%). The negative predictive value of the combined approach was 96% and was superior to that of either EBUS-TBNA (92%) or EUS-FNA (82%) alone [76]. Hwangbo et al. also assessed EBUS-TBNA and EUS-FNA using a single EBUS bronchoscope for each procedure. They enrolled 150 patients with confirmed or suspected NSCLC who required mediastinal staging. All underwent EBUS with 299 mediastinal lymph node stations sampled. EUS was performed in 149 patients, with FNA of 64 mediastinal nodal stations obtained in 53 patients. Mediastinal lymph node metastasis was found by EBUS in 38 patients and by EUS in an additional 3 patients. Of the remaining 109 patients, 102 were evaluated—7 were excluded because they either did not have surgery, did not have lymph node dissection performed, or were given an alternative diagnosis precluding surgery. Of the 102 patients with negative mediastinal lymph nodes by EBUS + EUS who underwent surgery with lymph node dissection, only 4 had mediastinal lymph node metastases. The combined approach did not differ significantly from EBUS-TBNA alone in terms of sensitivity, specificity, negative predictive value, and diagnostic accuracy. The combined approach did show a significantly higher proportion of accessible mediastinal lymph node stations when compared to EBUS-TBNA alone (85% vs. 79%; $p = 0.015$) [77]. Although combined EBUS and EUS staging of the mediastinum by a single operator using an EBUS bronchoscope holds great promise, limitations of operator training, credentialing, and possibly equipment may restrict its generalizability.

Restaging mediastinal lymph nodes after induction chemotherapy for stage IIIA-N2 NSCLC is another potential application of EBUS-TBNA. Ongoing studies are assessing the role of surgery for these patients after potential downstaging with neoadjuvant chemotherapy, but the optimal method for restaging the mediastinum has yet to be determined. Imaging techniques, including CT and PET, are insufficiently sensitive or specific to restage the mediastinum. Mediastinoscopy has been used for this purpose, but is significantly more technically difficult in this setting due to fibrosis induced by both the initial procedure and the subsequent chemotherapy. This has resulted in decreased yield and increased complications for mediastinoscopy for restaging. Herth et al. assessed EBUS-TBNA for restaging of the mediastinum in such patients after induction chemotherapy. The investigators enrolled 124 patients with stage IIIA-N2 NSCLC who had undergone neoadjuvant chemotherapy and then shown either a response to therapy or stable disease on follow-up CT. All patients then underwent EBUS-TBNA with a plan to proceed to surgical resection and lymph node dissection regardless of the results of EBUS-TBNA. Residual N2 disease was confirmed in lymph node aspirates of 89 patients (72%), with 35 patients (28%) without any evidence of residual disease by EBUS-TBNA. Thoracotomy confirmed persistent N2 disease in all 89 of the patients who had positive lymph node aspirates. Additionally, 28/35 patients (80%) of the patients without evidence of persistent N2 malignancy on EBUS-TBNA had malignant cells present on thoracotomy. EBUS-TBNA demonstrated a sensitivity for residual mediastinal N2 disease after neoadjuvant chemotherapy of 76%, with a specificity of 100%, a negative predictive value of 20%, and an overall diagnostic accuracy of 77%. Of the 28 false-negative N2 lymph nodes, 91% had been correctly identified by EBUS, and the failure to diagnose persistent malignancy was due to sampling error. This may be in part due to changes produced in the lymph nodes by the neoadjuvant therapy. When the results of this study are considered, the real utility of EBUS-TBNA in restaging NSCLC after neoadjuvant therapy may simply be as a way to identify patients with persistent disease who may therefore not need to proceed to surgery. Those with negative results on EBUS would still require surgical restaging to reach an acceptable negative predictive value [78].

Two groups have also evaluated the ability of ultrasonographic features of mediastinal or hilar lymph nodes to predict nodal metastasis when staging the mediastinum using CP-EBUS. Fujiwara et al. performed a retrospective analysis of 1061 lymph nodes from 461 patients who underwent EBUS-TBNA for staging of NSCLC at a single center. Images of all the nodes that were sampled

using CP-EBUS during the period of the study were evaluated in JPEG and digital video formats by three reviewers who were blinded to the results of the TBNA. The ultrasonographic appearance of the nodes was classified using six characteristics, and these characteristics were compared to the final pathologic diagnosis for each lymph node. Four of these nodal features were found to be independently predictive of lymph node metastasis: round shape, distinct margin, heterogeneous echogenicity, and presence of coagulation necrosis sign (a hypoechoic area within the node that has no blood flow). The presence of any of the four features increased the risk of metastasis to the node. The absence of all four features had a negative predictive value of 96% for malignancy within the node [79]. Wang-Memoli et al. prospectively evaluated 227 lymph nodes in 100 patients who had suspected or confirmed NSCLC, who had PET scan performed prior to the procedure, and who were referred for EBUS-TBNA to a single center. EBUS was performed and lymph node characteristics were recorded prior to TBNA. The ultrasound characteristics that were recorded and assessed were size, shape, echogenicity, border definition, and number of lymph nodes at each lymph node station. They found that the only ultrasonographic characteristics that increased the probability of malignancy in their cohort were size greater than 10 mm and round or oval shape. Interestingly, despite the increased probability of malignancy in lymph nodes larger than 10 mm, 10% of sampled lymph nodes less than 10 mm in size were confirmed to have malignant metastases. This suggests that while certain ultrasonographic characteristics may be correlated with an increased probability of lymph node metastases, their negative predictive value is not good enough to allow biopsy to be deferred because the characteristics in question are absent [80].

Summary

Since its advent, endobronchial ultrasound has proven to be one of the most versatile and powerful diagnostic tools available to the bronchoscopist. Its most widespread uses have been found in the staging of non-small cell lung cancer, diagnosis of diseases of the mediastinum, evaluation of the airway wall, and sampling peripheral pulmonary parenchymal lesions. Other applications continue to be investigated, and EBUS continues to be among the most valuable techniques available to the interventional bronchoscopist.

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TBNA in the Endobronchial Ultrasound Era

27

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Introduction

The last decades have witnessed a huge revolution of interventional pulmonology's role in diagnostic work-up and management of thoracic diseases. The advent of transbronchial aspiration techniques represents one of the most important advances in this context, as it has extended pulmonologists' perspective beyond the airways, leading to obtain both diagnosis and staging of cancers during the same procedure, avoiding additional or more invasive interventions [1].

Conventional transbronchial needle aspiration (c-TBNA) came first into light in 1949 [2], but the first prototype needle for flexible bronchoscope was designed by Ko-Pen Wang in the early 1980s [3]. Since then, several studies, worldwide, have confirmed the valuable cost-effectiveness and safety profile of TBNA in different clinical scenarios. This procedure, indeed, is currently included in the diagnostic work-up of central and peripheral lesions as well as of hilar/mediastinal lymphadenopathies and masses [4].

More recently, advances in technology have led to development of imaging-assisted TBNA by using reflecting sound waves, named as endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) [5]. Echoendoscope offers the operator a real-time visualization of lesions and surrounding structures, enabling to direct the tip of the needle to the target area. Although a superiority of the imaging-guided over the conventional procedure could be reasonable supposed by indirect comparisons of pooled estimates from literature [6, 7], the lack of evidence-based data from randomized studies does not yet allow to definitely assess the best diagnostic strategy in different clinical settings. To date, indeed, only two randomized investigations, limited on sarcoidosis patients, have been actually performed [8, 9]. Moreover, in daily practice, because of the higher costs, timing and specific skills related to more advanced technology, TBNA is still the only available diagnostic tool in several institutions.

The main purpose of the present chapter is to review the current evidence on diagnostic role of

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c-TBNA for hilar/mediastinal as well as for peripheral lesions, nowadays, in the context of "endobronchial ultrasound era".

Hilar/Mediastinal Lesions

The role of c-TBNA for the diagnosis and staging of hilar/mediastinal lesions is well established. It is a safe, low-cost, minimally invasive sampling technique that allows to both diagnose and stage mediastinal diseases while avoiding additional procedures and unnecessary surgical approaches. Some authors referred to this technique as "blind TBNA", as it is not possible to directly visualize the target, but we consider more suitable to use the term "conventional" or "standard", since a deep evaluation of computed tomography (CT) scans and a thorough knowledge of intraluminal landmarks and mediastinal anatomy actually allow an indirect, but accurate, localization of the lesions. In order to guide operators to the correct puncture site, in 1994, Wang et al. proposed a map of 11 lymph node stations accessible from the airways, describing well-defined endobronchial landmarks that correlate with specific CT features [10]. The first step towards performing c-TBNA is, indeed, to properly choose the exact puncture site after a careful CT scans evaluation, in order to assess the location of mediastinal lesions and its relationship with trachea or bronchi.

The subsequent steps deal with the technique in itself and can be summarized as follows: (a) insert the needle into the working channel of the bronchoscope while keeping the instrument as straight as possible and after having verified that the tip of the needle is completely retracted into the sheath in order to avoid any damage to the instrument; (b) extract the tip of the needle from the sheath only when the tip of the catheter is visible outside the bronchoscope (Fig. 27.1a); (c) keep only the needle and the distal metal hub of the catheter outside the bronchoscope, in order to facilitate the movement of the instrument inside the airways (Fig. 27.1b); (d) anchor the tip of the needle in the intercartilaginous space corresponding to the puncture site and bend the bronchoscope in the same direction where the needle should penetrate (Fig. 27.1c); and (e) insert the needle as perpendicularly as possible through the tracheobronchial wall (Figs. 27.1d and 27.2). Three main techniques have been described to insert the needle. The first one, named "jabbing method", consists in applying a firm and quick jab to the catheter while the scope remains fixed. The second technique is called "pushing" or "piggyback" method, according to which the operator fixes the catheter to the scope at the insertion port of the working channel with his/her little finger or with the other hand (Fig. 27.3). The bronchoscope and the needle are, then, pushed forward together by the operator himself/herself using the other hand or by an assistant. The last method is the "hub against wall" technique, according to which the needle is initially kept in, the catheter hub is pushed against the wall, and the needle, then, is brought out and penetrates into the target [11]. No evidence-based data on a direct comparison between these methods are available, but, overall, the piggyback technique is considered the preferred option by the experts, as it allows a better perpendicular penetration of the needle [11]. To our experience, the "hub against wall" technique may be useful in case of c-TBNA at smaller airways level, as it could be difficult in this context to bend the scope with the needle outside the sheath.

Once the needle has been properly inserted, a suction is applied through the syringe attached to the proximal end of the needle, and the catheter should be quickly moved up and down for no longer than 10 s overall, in order to avoid coagulation of blood. Another crucial step is represented by a proper handling of the material obtained, blown by an air-filled syringe onto a slide. It is, then, smeared using another slide and immediately fixed in alcohol 95%. If tissue cores are present on the slide, these should be gently removed with a small forceps and put in formalin. If histological needle are employed, the material can be directly put into a formalin test tube. Different types of needle are, indeed, available on the market, with sizes ranging from 19 to 22 gauge (G). 21-G and 22-G needles are intended for cytological evaluation, while the 19-G allows to provide tissue core

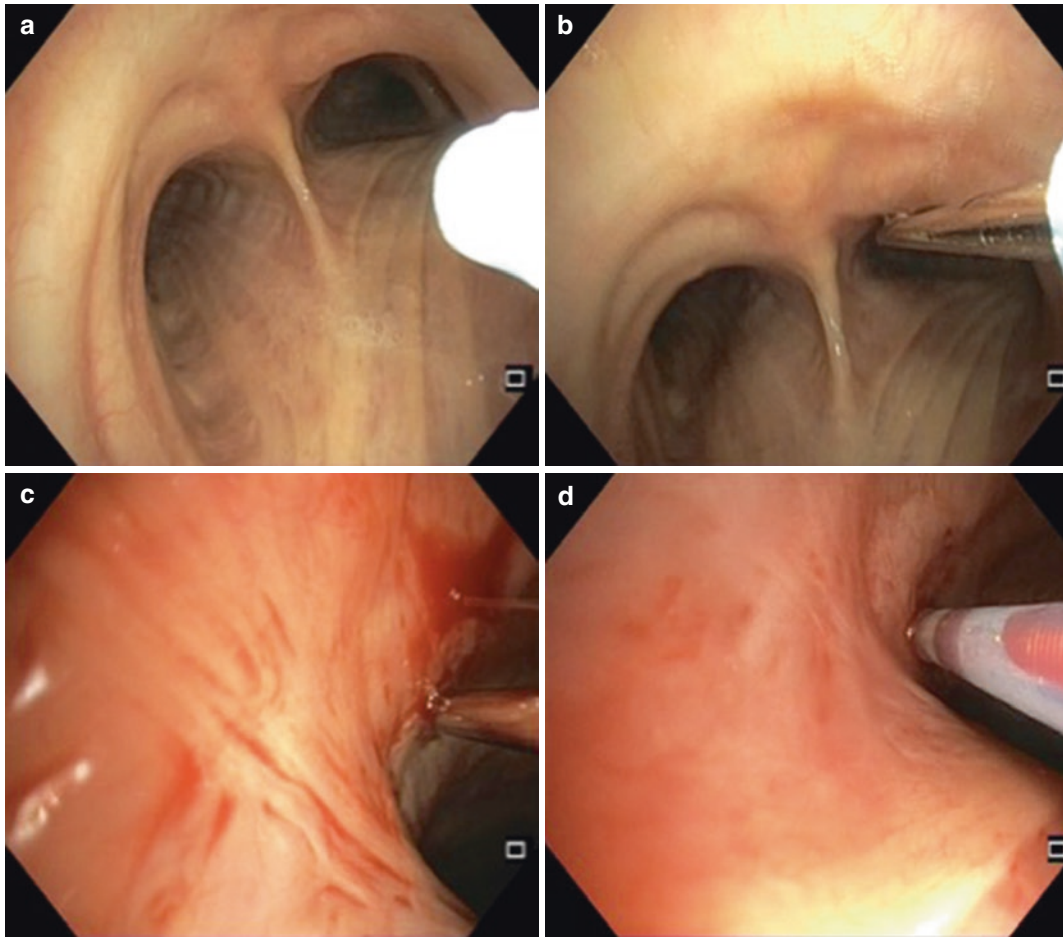

Fig. 27.1 The steps of TBNA technique. (**a**) The catheter is inserted in the working channel of the bronchoscope with the tip of the needle retracted into the sheath, and the scope is keeping straight; (**b**) the tip of the needle is extracted from the sheath, and only the needle is kept outside the scope; (**c**) the tip of the needle is anchored in the intercartilaginous space, and the tip of the scope is bended in the same direction where the needle should penetrate (subcarinal lymph node in the figure); (**d**) the needle is inserted as perpendicularly as possible through the bronchial wall

for histological assessment [4]. There is not yet a definite consensus on the number of specimens needed to optimize the diagnostic yield of TBNA, although it is reasonable to propose a minimum of three needle passes or two "adequate" samples [1]. In this context, the rapid on-site evaluation (ROSE) of cytologic smears has been suggested to play an important role, as it allows to assess the adequacy of specimens obtained, providing relevant information to the operator, who can modify the technique or the target site in case of inconclusive results [12]. Furthermore, the operator can determine whether additional material needs to be collected to further characterize the lesions in ancillary studies, as, in the era of targeting lung cancer therapy, a sample should be considered as diagnostic only if it provides an amount of cells suitable for both immunocytochemical and molecular studies [13].

The whole procedure is performed under local anaesthesia with conscious sedation in the endoscopy suite. Overall, c-TBNA is a safe procedure with no additional risks to a standard bronchoscopy, as complications rarely occur and include pneumothorax, haemomediastinum and major bleeding [14].

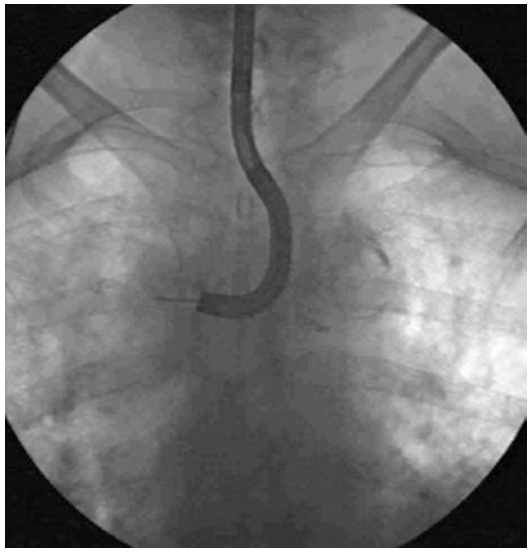

Fig. 27.2 Fluoroscopic view of a right paratracheal lymph node TBNA. Note that the needle is penetrated perpendicularly to the tracheal wall

Against a very high specificity (96–100%), the sensitivity of TBNA varies greatly in the published literature. To date, two meta-analyses of data on c-TBNA accuracy for lung cancer staging have been performed: one reported an average pooled sensitivity of 76%, ranging from 14% to 100% [15], while the other, restricted to studies including patients with non-small lung cancer (NSCLC), provided two separate estimates according to low or high prevalence of mediastinal disease, 39% and 78%, respectively [16]. The range of c-TBNA sensitivity was even larger in the diagnostic work-up of suspected sarcoidosis (6–90%), with a pooled value of 62%, as reported in a meta-analysis conducted by Agarwal et al. [17].

Besides the underlying clinical setting, the reasons for variability in TBNA accuracy appear to be related to baseline clinical characteristics, as well as to procedural aspects, evaluated as potential predictors of a successful aspirate in

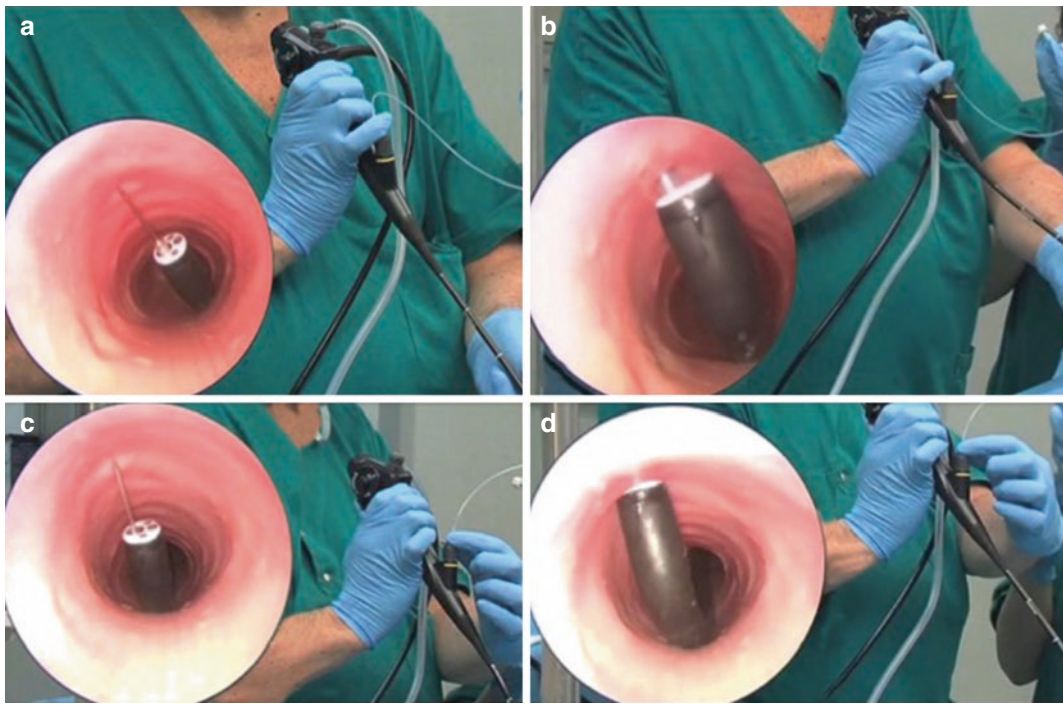

Fig. 27.3 "Pushing" or "piggyback" technique. The needle and the scope are fixed and pushed forward together. The needle may be fixed to the scope by the little finger of the bronchoscopist (**a**), and the bronchoscope is pushed by the operator using the other hand (**b**), or, alternatively, the needle is fixed with the other hand of the operator (**c**); in this case the scope is pushed forward by the assistant (**d**)

several investigations, reporting, however, conflicting results. In order to provide an extensive description and synthesis of available evidence in this context, we performed a systematic review of literature, and 53 studies, involving more than 8000 patients and evaluating 23 potential predictive factors, were identified [1]. Major predictors of c-TBNA yield for the diagnosis of mediastinal lymphadenopathies/masses included an increasing lymph node size, the presence of abnormal endoscopic findings, underlying malignant conditions, station 4R and 7 as site of samples and the use of histological needle by an "experienced" bronchoscopist, although the type and duration of educational interventions evaluated varied widely among studies. In the subgroup of patients with suspected/known lung cancer, other predictors were selected features of primary tumour, as the presence of SCLC subtype rather than NSCLC, most likely due to higher biological aggressiveness and lower adhesion of small cells, and right-side location [1].

Factors possibly influencing the c-TBNA results in patients with suspected sarcoidosis have been investigated in few small studies, and, of these, only one has evaluated this issue as the primary outcome, providing statistical analyses. In this study, sampling more than one lymph node station was the only variable significantly associated with the likelihood of a positive aspirate. This finding was indirectly confirmed by Tremblay and colleagues, who performed a randomized trial to primarily compare the yield of EBUS-TBNA versus c-TBNA in suspected sarcoidosis patients and suggested that the superiority of EBUS-TBNA could have been related to the greater average number of lymph node stations sampled. Moreover, about 50% of the study population also underwent transbronchial lung biopsy (TBLB) and endobronchial biopsy (EBB), and, interestingly, the cumulative yield of all bronchoscopic samples was 81% in c-TBNA compared with 92% in EBUS-TBNA arm, which was not statistically different [9].

A further randomized investigation comparing c-TBNA and EBUS-TBNA in sarcoidosis, but including also other techniques, has been recently conducted in a larger study population. Overall, EBUS-TBNA demonstrated the highest diagnostic yield if compared with conventional bronchoscopic procedures like c-TBNA or EBB, but not with TBLB, which has been shown to significantly enhance the accuracy of the imaging-guided technique. In fact, when EBB and TBLB were combined with either EBUS-TBNA or c-TBNA, the achieved diagnostic yield was similar, underlying their essential role in the diagnostic work-up of sarcoidosis [8].

In summary, c-TBNA is a useful and safe diagnostic technique, although its sensitivity may be influenced by selected clinical and procedural factors. C-TBNA could be excellent, if performed by an experienced bronchoscopist with histology needle providing both cytological and histological specimens, in patients with enlarged lymphadenopathies in paratracheal or subcarinal regions, endoscopic findings and clinical suspect of lung cancer, as well as moderate, if none of these conditions occur.

Although EBUS-TBNA has been suggested to improve the diagnostic yield of conventional TBNA for the diagnosis of hilar/mediastinal lesions [6, 7], no evidence-based data on a direct comparison between these two procedures are yet available, and in real-world daily practice, the higher costs and specific skills related to ultrasound technology prevent its routine use in several institutions worldwide. Moreover, c-TBNA and EBUS-TBNA should not be necessarily intended as competitive, as, in selected scenarios, they can be considered as subsequent steps in a staged strategy with c-TBNA as initial test, followed by EBUS-TBNA, in case of inconclusive results at ROSE evaluation, during the same bronchoscopy session.

Peripheral Lesions

Mini-invasive approaches for the diagnosis of peripheral pulmonary lesions (PPL) include imaging-guided transthoracic as well as bronchoscopic techniques, with different sampling instruments (forceps biopsy, flexible needles, brushing) that can be inserted through the working channel of the flexible bronchoscope and pushed into the

peripheral airways to obtain tissue from lesions located outside of the visible range of the scope. The use of a guidance system is required, and the most diffuse tool in this context is fluoroscopy, even if innovative technologies, such as ultrasound mini-probe and electromagnetic navigation, have been recently introduced [18, 19]. The only prospective randomized trial comparing CT fluoroscopy versus standard fluoroscopy for the diagnosis of peripheral lung lesions and mediastinal lymph nodes failed to show any significant difference between the guidance systems in terms of accuracy [20]. A rotating C-arm or a biplane fluoroscope allows the assessment of sampling instruments location both in the anteroposterior and lateral view. Technically, after a careful evaluation of CT scans, the tip of the bronchoscope should be, first, wedged into the segmental bronchus supposed to be more closely related to the lesion. The sheath should be, then, inserted through the working channel of the scope, and a fluoroscopic control at this point is highly recommended in order to direct the sampling instrument towards the target by bending or rotating the tip of the scope and to find the most appropriate way to achieve the lesion. In this context, the sheath is expected to be as flexible as possible in order to reach the most angulated bronchi but also to remain straight after the insertion, without bending, and, to our opinion, the needles with a metallic sheath are the preferred option.

About the safety profile, major adverse events, including pneumothorax and bleeding, occur in less than 5% of cases [21] (Fig. 27.4a, b).

The third edition of the American College of Chest Physicians (ACCP) evidence-based clinical practice guidelines reported a transbronchial approach sensitivity for PPN/M ranging from 5 to 76%, mostly derived from retrospective studies [22]. In a previous experience of our group, assessing the role of an integrated diagnostic algorithm including the transbronchial as well as the percutaneous approach in more than 1000 patients with PPLs, the sensitivity of TBNA was 69.3% [23]. More recently, other studies have confirmed such results, with a ROC curve analysis showing that TBNA was the single bronchoscopic procedure with the best performance

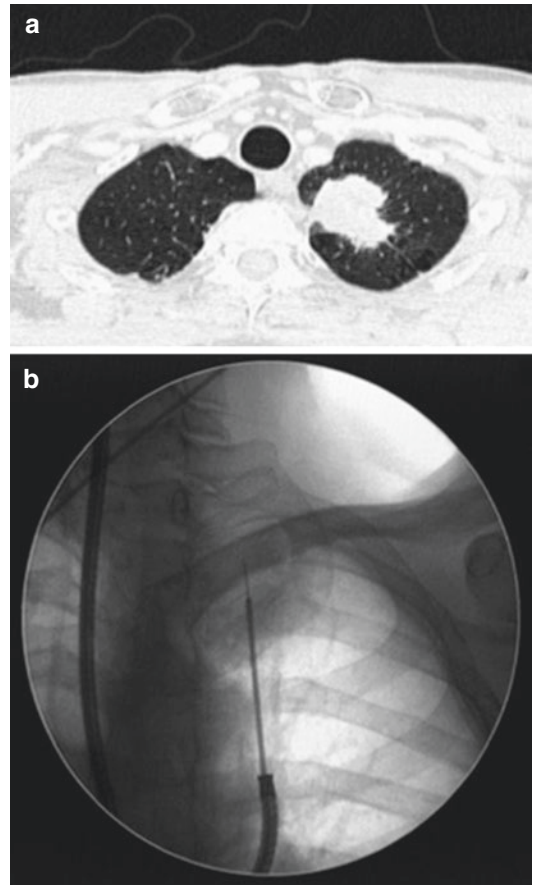

Fig. 27.4 TBNA of a peripheral lesion located in the left upper lobe. (**a**) CT scan showing a spiculated nodule in the apical segment of the left upper lobe; (**b**) fluoroscopic view of the needle into the lesion

characteristics, if compared to transbronchial lung biopsy and bronchial brushing [24]. This might be due to the ability of the needle to penetrate the lesion, even if it does not infiltrate the bronchial wall.

Due to the great heterogeneity in terms of sensitivity from published data, we have recently performed a systematic review of the available studies evaluating fluoroscopy-guided c-TBNA for the diagnosis of PPL to provide a pooled estimate of yield and to identify the predictors of a positive aspirate according to different clinical conditions [25].

The pooled c-TBNA yield, from 18 studies, involving 1687 patients, was 0.53 (95% confidence interval, CI, 0.44–0.61). Major predictors

of a higher sensitivity included the presence of CT bronchus sign, the malignant nature of the abnormalities, the diameter of the lesions >3 cm and ROSE employment. Data on comparison between TBNA and TBB, resulting only from studies in which both procedures were performed in the same patients, showed a significant superiority of TBNA, respectively 0.60 (95% CI, 0.49, 0.71) and 0.45 (95% CI 0.37, 0.54) [25].

Another diagnostic option for PPL is represented by the transthoracic needle aspiration (TTNA), also named percutaneous needle aspiration (PCNA), performed under biplane fluoroscopy or, more frequently, under CT-guidance. Overall, the sensitivity of PCNA is higher than that of c-TBNA, ranging from 70 to 97% in the published literature [22]. However, concerns have risen about its complication rates, as pneumothorax occurs in 10–50% requiring tube placement in less than 10% of cases. Other adverse events include haemoptysis (up to 5–10% of cases), but usually mild and self-limiting, air embolism (<1%), haemothorax, empyema, tumour diffusion along the needle tract and haemopericardium.

In conclusion, over the last decade, the increasing diffusion of innovative and more powerful imaging-guided techniques, such as endobronchial ultrasound (EBUS) and electromagnetic navigation, has further broadened the bronchoscopist's horizons in the management of peripheral pulmonary nodules. However, in most of institutions worldwide, due to the lack of resources and specific skills, the routinely diagnostic approach to PPL is represented by bronchoscopic approach with fluoroscopic guidance and PCNA. In this context, it is reasonable to propose a sequential diagnostic algorithm, according to which c-TBNA should be performed as first option, due to the acceptable sensitivity and the safer profile, especially in the presence of predictors of positive aspirates. Moreover, it offers the advantages to provide, during a single examination, a pathological diagnosis of nodules and information on mediastinal staging and airways involvement and to identify potential synchronous lesions.

As the success of a diagnostic test results from a proper balance between accuracy, complications and costs, c-TBNA should still play a central role in the diagnostic work-up of thoracic diseases, and an adequate training for specialists is highly recommended.

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Part V

Pleural Conditions

Pleural Anatomy: a Pathological and Surgical Perspective

28

Juan Antonio Moya Amorós and Anna Ureña Lluveras

Pleural Embryology

The pleural membranes are originated from the embryonic coelomic cavity lining, from which vital organs such as the heart, intestines, and lungs also develop. Coelomic cavity is divided into peritoneal and pleural cavity, which in turn is divided into two by the pericardium. Later, the lungs develop through primary buds that grow from a central mesenchymal mass, and as they grow laterally, they invaginate into each pleural space, thus taking the pleural lining. The pleura covers the entire chest cavity (parietal pleura) and the lungs (visceral pleura).

Histologically, the pleura is composed by five layers:

- A single layer of mesothelial cells
- A thin submesothelial connective tissue
- A thin elastic superficial layer
- A layer of loose connective tissue
- A deep fibroelastic layer

The surface of mesothelial cells contains microvilli. These microvilli are believed to function in liquid absorption, but recently it has been shown that they contain glycoproteins to lubricate the sliding of the two pleural layers.

Pleural Layers

Parietal Pleura

The parietal pleura is lining the pleural cavity internally, and it can be divided into three parts: costal, diaphragmatic, and mediastinal:

1. *Costal pleura*: It lines the inner part of the chest wall, extending over the ribs and intercostal muscles, cartilage, and a small portion of the sternum. Its upper limit is the first rib, and the lower limit is formed by the diaphragmatic fingerings; backwards, it reaches the side of the vertebral bodies and anteriorly the anterior pleural sinus (Fig. 28.1a).
2. *Diaphragmatic pleura*: It is tied closely to the corresponding hemidiaphragm. It has a firm connection to the phrenic center level (preventing its cleavage) and a looser union at the muscular portion of the diaphragm (Fig. 28.1b).
3. *Mediastinal pleura*: It extends over all mediastinal organs, between the costovertebral canal in the back and the sternum anteriorly, interrupted by the pulmonary hilum. The pulmonary hilum divides the mediastinal pleura into three parts: anterior mediastinal pleura, superior mediastinal

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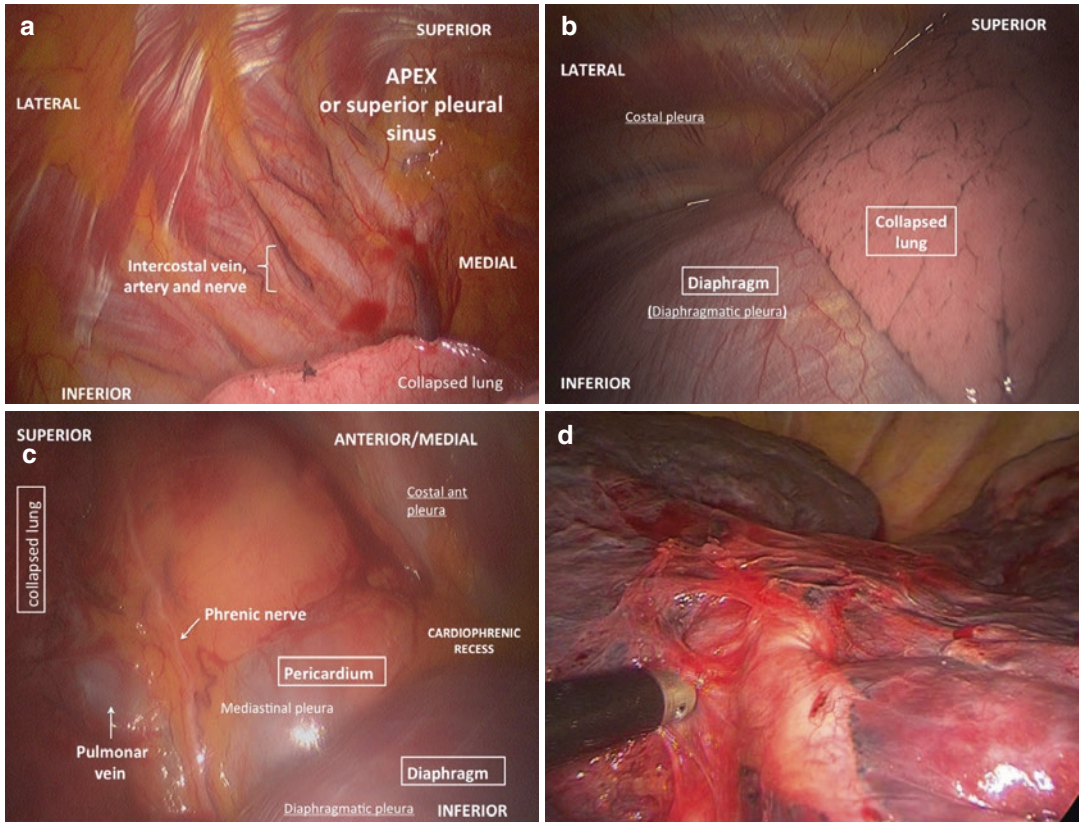

Fig. 28.1 Pleural endoscopic images. *INF* inferior, *4R* right paratracheal lymph node region according to Naruke's classification, *SVC* superior vena cava, *LUL* left upper lobe, *LLL* left lower lobe. (**a**) Endoscopic image of the costal pleura. (**b**) Endoscopic image of the diaphragmatic pleura. (**c**) Endoscopic image of the mediastinal pleura. (**d**) Endoscopic image of the visceral pleura (left lung)

pleura, and posterior mediastinal pleura. In the right hemithorax, it produces the interazygos-esophageal recess and in the left hemithorax, the interaortic-esophageal recess (Fig. 28.1c) [1, 2].

Visceral Pleura

The visceral pleura is intimately attached to the outer surface of the lung (Fig. 28.1d). There is no cleavage plane, so that it cannot be dissected without injuring the lungs. It covers all lung surface, penetrating and producing the lung fissures; however, on the internal lung surface (lung hilum), it reflects to continue with the mediastinal parietal pleura. Here, there is a small lung surface without pleural lining, and the pleural reflection extends down to the diaphragm, and it is called the triangular or inferior pulmonary ligament.

The hilar region is shaped as a long inverted teardrop, with a rounded superior end covering the lung pedicle and a triangular space whose base is superior that elongates downwards, and it is called triangular ligament as discussed above. This ligament helps fixing the lung not only to the mediastinum but also to the diaphragm, where it ends. Between the two pleural reflection sheets that form the triangular ligament, nodal station 9 is found (Naruke's classification).

Pleural Recesses

The pleural space is a virtual space delimited between the parietal and the visceral pleura. This space has important anatomical accidents, and the most important of them are called sinuses or pleural recesses, which are the following:

1. *Pleural apex or superior pleural sinuses*: they are cervical since they are situated above the clavicle, at the base of the neck. At the apex, the costal and mediastinal pleura join forming the upper cone (Fig. 28.2a). On the outer side, the three suspensor ligaments of Sebileau insert:
   - Transverse-pleural ligament: it goes from C7 transverse apophysis to the pleural apex and issues an expansion to the first rib. If it contains muscle fibers, it is called scalenus minimus muscle.
   - Costo-pleural ligament: it runs from the first rib neck to the pleural apex.
   - Vertebro-pleural ligament: it runs from C7 vertebral body to the pleural apex.
2. *Anterior costophrenic recesses or cardiophrenic*: at a retrosternal level, they form an acute angle. They represent the point where the parietal costal, diaphragmatic, and mediastinal pleura intersect. In the left side the costophrenic recess is displaced by the heart 2.5–4 cm from the vertical line (Fig. 28.2b).
3. *Posterior costophrenic recesses*: they are located posteriorly, at the level of the intersection of the diaphragmatic parietal, costal, and mediastinal pleura on the vertebral body. Those recesses represent the most dependent points in the pleural cavity.
4. *Costodiaphragmatic or costo-lateral recesses*: they are the greatest of all pleural recesses and the first ones that come to mind when speaking of pleural recesses. They are formed by the reflection of the costo-parietal pleura with the diaphragmatic pleura. They extend from the seventh costal cartilage anteriorly to the neck of the twelfth rib posteriorly, running on the costal diaphragmatic insertions, surpassing them behind the arcuate ligament. They may exceed the lower edge of the twelfth rib (Fig. 28.2c).

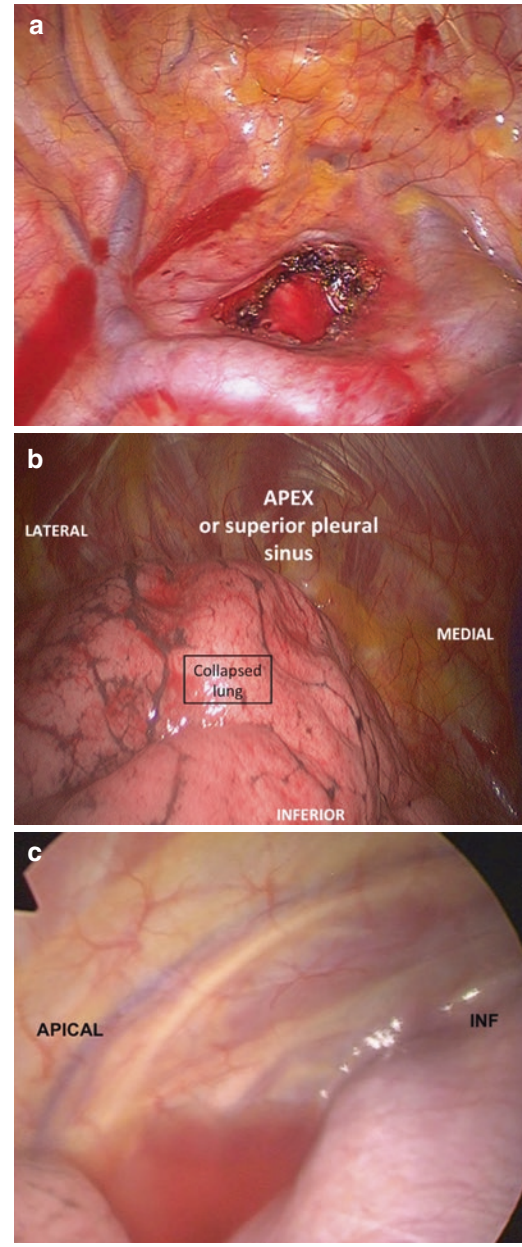

Fig. 28.2 Pleural endoscopic images. *INF* inferior, *4R* right paratracheal lymph node region according to Naruke's classification, *SVC* superior vena cava, *LUL* left upper lobe, *LLL* left lower lobe. (**a**) Apical pleural recess. Endoscopic view. (**b**) Anterior costo-mediastinic or cardiophrenic recess. Endoscopic view. (**c**) Posterior costodiaphragmatic or costophrenic recess. Endoscopic view

Fissures

They are recesses of the visceral pleura. If they are complete, they can cross the entire lung from front to back. They divide each lung into different lobes, three lobes in the case of the right lung and two lobes in the left lung. Supernumerary fissures may exist and also fissure defects (Fig. 28.3).

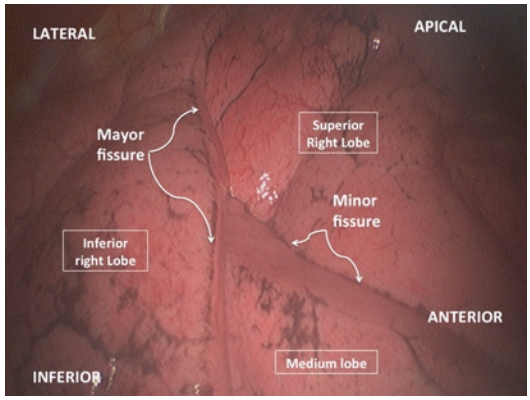

Fig. 28.3 Pulmonary fissures. Endoscopic image of a collapsed right lung. Both pulmonary fissures, separating the three lobes of the lung, can be seen

1. *Major fissure/oblique*: it originates from the fourth thoracic vertebra and ends up in the fifth intercostal space. In the right lung, it starts at the level of the fourth rib in the spinal portion of the costal side of the lung. It then descends obliquely downward and forward to reach the diaphragmatic surface. It crosses this side from lateral to medial, reaches the mediastinal perihilar side, and reflects up and backwards to get to the front and bottom of the hilum.

   In the posterosuperior portion, it separates the upper lobe from the lower lobe. In the infero-anterior portion, it separates the lower lobe from the middle lobe.

   In the left lung, there is only a major fissure, and it has a slightly different path as it descends in a helical manner from the top, anteriorly and downwards.
2. *Minor fissure/horizontal*: it ascends slightly from the level of the fourth intercostal space upward to the third. It is directed forward and medially, reaching the anterior edge of the lung through the mediastinal perihilar side and reaches the hilum. The minor fissure separates the lung into two lobes: middle lobe and upper lobe. In an anterior view, the lower lobe, which is posterobasal, cannot be observed.
3. *Accessory fissures*:
   – Superior accessory fissure or azygos fissure: caused by the azygos vein arch, which in its embryonic movement cuts the mesenchyme of the upper lobe. It separates the upper lobe into two parts, a medial or Wrisberg azygos lobe and a lateral or upper lobe (proper upper lobe).
   – Inferior accessory fissure: located in the lower lobe separating the lobar segment 6. When it is present, the portion of the lung related to this segment is called Fowler lobule.

Blood Supply and Venous Drainage

The parietal pleura receives its blood supply from systemic capillaries: small branches of the intercostal arteries supply the costal pleura, while the mediastinal pleura is mainly irrigated by pericardium-phrenic arteries. The diaphragmatic pleura is supplied by the superior phrenic arteries [3].

The blood supply of the visceral pleura comes from the systemic circulation through the bronchial arteries.

Venous drainage of the parietal pleura goes to the intercostal veins (systemic veins), while the visceral pleura drains into the pulmonary veins.

Lymphatic Drainage

The parietal pleura lymphatics drain pleural fluid and harmful particles that reach the pleura. The lymphatic system starts with small nests that communicate with lymphatic foci draining through lymphatic vessels to the lymph nodes that run along the internal thoracic artery and internal intercostal nodes (along the ribs heads). Pleural lymphatics can eliminate 20 times the fluid generated under normal conditions (up to 0.2 mL per kg per hour approximately).

The visceral pleura drains through two systems:

(a) A superficial system that floats on the surface of the lung reaching the hilum
(b) A deep system that penetrates into the lung parenchyma to reach the hilar lymph nodes

Pleural Innervation

Sensory nerve endings are present in the costal and diaphragmatic parietal pleura. The intercostal nerves innervate the costal pleura and the peripheral portion of the diaphragmatic pleura. When any of these areas is stimulated, pain is referred to the adjacent chest wall.

By contrast, the central part of the diaphragmatic pleura is innervated by the phrenic nerve, and the stimulation of this part of the pleura causes referred pain at the ipsilateral shoulder.

The visceral pleura does not contain pain fibers.

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Medical Thoracoscopy

29

Francisco Rodriguez-Panadero

Introduction and Historical Perspective

In the second half of the nineteenth century, a thoracoscope was defined in some French dictionaries as an "Instrument for observing changes of the respiratory tract and of the lungs." Today thoracoscopy is defined as "a procedure involving internal examination, biopsy, and/or resection of disease or masses within the pleural cavity and thoracic cavity." In two excellent historic reviews by Moisiuc and Colt [1] and by Marchetti et al. [2], there was agreement in that the first reported thoracoscopy was performed in Dublin in 1865 by the Irish urologist Francis Richard Cruise, who designed a binocular cystoscope [3]. That first procedure was reported in 1866 by Dr. Samuel Gordon at the end of a case presentation of an 11-year-old girl with empyema [4]. However, Cruise himself never published anything on the thoracoscopy exploration that he had performed, and there is no further reference to that procedure until Jacobaeus, who still deserves the honor to be considered as the father of thoracoscopy, because he used thoracoscopy both as a diagnostic and a therapeutic tool. He also overcame the problems involved with incomplete lung collapse by inducing pneumothorax through cutting adhesions with a galvanocautery (the *Jacobaeus operation*) [5] and then allowing for collapse of cavitary tuberculous lesions. After the 1950s, due to the success of medical treatment for tuberculosis, the "Jacobaeus operation" was gradually abandoned, and use of thoracoscopy subsequently declined.

Thoracoscopy began to recover in the 1970s, in particular in Continental Europe where some pulmonologists became reference persons for this technique: Boutin in France, Brandt and Loddenkemper in Germany, Sattler in Austria, Swieringa in the Netherlands, Viskum in Denmark, and Cantó in Spain, among others.

The term "medical thoracoscopy" was proposed by Professor Boutin and adopted by others to distinguish "video-assisted thoracoscopic surgery" (VATS) from the old conventional thoracoscopy technique that had been introduced by Jacobaeus in 1910 [6]. Medical thoracoscopy can be performed by pulmonologists in the endoscopy suite under local anesthesia and intravenous conscious sedation/analgesia in most of the cases, while VATS requires general anesthesia and double-lumen tracheal intubation and is performed by thoracic surgeons in the operating room [7]. Medical thoracoscopy is mostly used for diagnostic purposes (especially in pleural

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effusions) and for talc pleurodesis ("poudrage") to prevent recurrence of persistent pleural effusions or pneumothorax.

Equipment for Medical Thoracoscopy

Jacobaeus demonstrated that pleuroscopy could be performed simply with an optical instrument (cystoscope) inserted into the pleural cavity through a trocar. With the technical improvements achieved in the instruments and video cameras for endoscopy, the quality of the vision has been greatly enhanced, and the safety of the procedure increased. In order to keep both up to the highest standards, there are a few recommendations to follow:

- *Thoracoscope.* There are both rigid and semi-rigid (*flexi-rigid*) instruments available for thoracoscopy, and each type has some advantages over the others. The rigid thoracoscope provides excellent vision, allows for big biopsy samples using a single-port entry (in most of the versions available), facilitates the orientation inside the pleural cavity, and also is of great help when biopsies have to be taken from hard lesions (or located over the ribs) or when immediate local compression over bleeding biopsied zones is necessary. On the other hand, the *flexi-rigid* thoracoscope is more familial to pulmonologists due to similarities with flexible bronchoscopes used in everyday practice [8]; in addition, it can be autoclaved, allows for lateral vision very easily (we would need a telescope with oblique view for that purpose when using the rigid ones), gets access to difficult areas in the pleural cavity, or even permits retro-visualization of the point of entry [9]. A meta-analysis of 744 patients with undiagnosed exudative pleural effusions who underwent flexi-rigid pleuroscopy had a 91% sensitivity and 100% specificity for pleural malignancy [10]. The flexi-rigid instrument is more expensive and fragile than the rigid thoracoscope, its working channel is smaller, and biopsies are consequently smaller too. However, the size and quality of pleural biopsy samples can be greatly improved by using a flexible cryoprobe with flexi-rigid pleuroscopy, which is especially important when mesothelioma is suspected [11].
- *Trocar.* Obviously, a large trocar would permit insertion of a large telescope too, thus enhancing the quality of the exploration, but—especially when working in local anesthesia—we need a compromise between the size of the instruments and the width of the intercostal spaces. I performed most of my thoracoscopic procedures with a 10 mm thoracoscope in local anesthesia (mepivacaine), plus intravenous analgesia (dolantine) in the past, but I currently recommend a 7 mm—or even 5 mm—thoracoscope as the best choice for medical thoracoscopy, especially if the thoracoscope is provided with a working channel allowing biopsies through a single-port entry (see Fig. 29.1). The *shape of the trocar tip* is important, and the conical one is clearly preferred to the others, in order to prevent damaging the intercostal vessels or nerves during insertion into the pleural cavity [12].
- The *light and video source* for the thoracoscope has to be of good quality, and the last-generation lamps are recommended. Make sure that the connecting cables between the source and the thoracoscope are safely attached.
- *Other aspects regarding the equipment*. A good *suction system* is mandatory in every endoscopy procedure, and thoracoscopy is no exception, in order to remove all the pleural fluid before exploring completely the pleural cavity and taking biopsies, or when bleeding occurs. *Continuous monitorization of the patient* (including oxygen saturation, electrocardiogram, and noninvasive blood pressure recording) should be prepared in advance. Percutaneous CO_2 continuous monitorization is also recommended in order to prevent severe hypoventilation [13]. The drain and water-seal system should also be prepared prior to the thoracoscopy procedure, in order to act quickly should a complication occur and

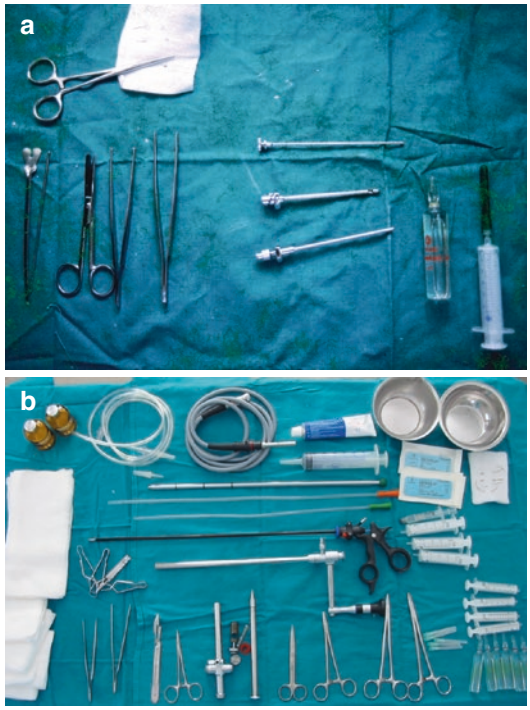

Fig. 29.1 (**a**) Equipment for pleural biopsy with Abrams needle. (**b**) Equipment needed for medical thoracoscopy and talc poudrage (plus video and light source)

immediate lung reexpansion is needed. The physician performing thoracoscopy has to be well trained in management of pleural drainage during the recovery period also, including lung reexpansion.

One or Two Ports of Entry for Medical Thoracoscopy?

Though it is clear that several entries are needed for VATS, I much prefer using one single entry for diagnosis and treatment of pleural effusions (talc poudrage) and have needed two ports in very few occasions. They have to be created when the thoracoscope has no working channel available, when electrocautery has to be used, whenever a hardly accessible area of the pleural cavity needs to be explored, and when very small telescopes are used (for pediatric patients or other selected cases). The second point of entry is usually located one intercostal space superior or inferior to the main entry and close to it, in order to manipulate the instruments easily under visual control. Mini-thoracoscopy was developed a few years ago as an alternative for diagnostic thoracoscopy under local anesthesia. Tassi and Marchetti used a 3 mm thoracoscope for diagnostic thoracoscopy under local anesthesia [14], and the diagnostic yield was 93% in their study.

Technique for Thoracoscopy

Preparation of the Patient

Although medical thoracoscopy is safe and relatively simple when the performing physicians are well trained and familial with the *endoscopic anatomy* of the thorax (which is not always the same than conventional anatomy, due to the point of view and the limited field of vision, as compared with open thoracotomy or autopsy), a few rules have to be followed carefully:

(a) *Explanation of the technique to the patient*. This is especially important when the procedure is going to be done in local anesthesia plus conscious sedation, because he or she will be more confident during the exploration when knowing the details of the procedure in advance. Written informed consent is mandatory, as with any interventional procedure.
(b) *Evaluation of the patient's performance status*. We have to be especially careful with patients who are in very poor clinical condition, hypoproteinemic, or with diffuse neoplastic infiltration of the chest wall. Patients with a Karnofsky index <50 should be excluded, especially when thoracoscopic talc poudrage is planned. Also, patients with uncontrollable cough should be deferred for medical thoracoscopy, because the exploration will likely be very difficult and with more complications (subcutaneous emphysema!).
(c) *Studies to be done prior to thoracoscopy*. A posteroanterior and lateral *chest X-ray film* is mandatory, in order to evaluate the most convenient port of entry, to exclude presence of *contralateral pulmonary lesions* (which

could lead to acute respiratory insufficiency at the time of inducing pneumothorax during thoracoscopy), and to evaluate the size and shape of the pleural effusion to be explored. A *contrast CT scan* is highly recommended in the evaluation of every pleural effusion of unclear origin, although a significant proportion of patients being investigated for malignant disease will have malignancy despite a negative CT report [15]. *Ultrasound examination* prior to thoracoscopy can be very useful to assess the characteristics and volume of the pleural effusion and to choose the best point of entry [16, 17]. Ultrasound is mandatory when malignancy is suspected and thoracoscopy has to be performed in the absence of pleural effusion [18], which can particularly happen in mesothelioma patients. *Electrocardiogram*, *coagulation tests*, *and blood gas analysis* are also necessary.

Premedication for Thoracoscopy

Preoperative preparation may involve chest physiotherapy, bronchodilators, antibiotics, and corticosteroids to optimize pulmonary function in patients with obstructive lung disease. With the exception of neutropenic patients, routine prophylactic antibiotics are not necessary.

Injection of 0.4–0.8 mg atropine (intramuscular or subcutaneous) prior to the procedure is recommended, in order to prevent vasovagal reactions. Sedation during the procedure can be performed using incremental dosages of a narcotic (morphine, pethidine, or fentanyl) and a benzodiazepine (midazolam). Agents to antagonize both morphine and benzodiazepines should be available. Intravenous titrated midazolam can be very useful, and titrated propofol has also been proposed, but propofol should be managed with special care in medical thoracoscopy [19], and a recent study reported up to 64% hypotension episodes with propofol [20]. When comparing propofol vs. midazolam, another study found 27% vs. 4% episodes of hypoxemia and 84% hypotension vs. 40%, respectively, and those authors stated that propofol should not be the first choice for medical thoracoscopy [21]. Instead, we used titrated intravenous pethidine—keeping the patient awake—in more than 500 procedures involving thoracoscopic talc poudrage, without major complications (Table 29.3).

In order to prevent pulmonary embolism, especially in patients with malignant pleural effusions who are submitted to talc pleurodesis, we advise giving prophylactic during all the hospital stay.

Endoscopy Room

Whenever available, a well-equipped operating room is excellent for every invasive procedure, including thoracoscopy, but this is not the case in most of the centers, where operating rooms are very busy with other major procedures or operations. Instead, medical thoracoscopy can be performed safely in the respiratory endoscopy suite, provided that a sterile setting can be prepared, the electrical installation and patient monitorization is adequate, and the mandatory resuscitation equipment is available.

Thoracoscopy Procedure

Patients should have an intravenous cannula. Basic monitoring includes ECG and pulse oximetry. Supplementary oxygen should be provided to the patient to maintain oxygen saturation above 90%.

The patient is positioned in lateral decubitus position, with healthy lung in the dependent side. Keep the ipsilateral arm to the exploration above the head to widen the intercostal spaces and then make introduction of the trocar easier. The optimal point of entry depends upon the disease to be investigated: thus, a higher entry is preferred for pneumothorax, in order to explore more easily the upper part of the pleural cavity, where most of the bullae are located; on the other hand, the midaxillary line of the fifth or sixth intercostal spaces is the best option to explore patients with pleural effusions. A few technical details are important, as follows:

- *Local anesthesia* has to be applied generously and carefully around the chosen point of entry. A common mistake with beginners is the application of large amounts of anesthetics in the subcutaneous tissue, while the deep tissue and intercostal muscles are often neglected. The lack of deep local anesthesia would provoke acute pain when the trocar compresses the intercostal nerves during the thoracoscopic exploration.
- We prefer applying the *sutures for the drain* in advance at the beginning of the exploration (just before inserting the trocar) in order to get everything prepared should an emergency insertion of a chest tube is needed for rapid lung reexpansion.
- *The trocar* should always be inserted perpendicularly to the chest wall with a rotating motion. It is safer to locate the tip over the inferior rib in the chosen port of entry, in order to prevent damage to the intercostal vessels and nerves. Introduction of the trocar can be difficult in presence of pleural adhesions, and it should be performed slowly and carefully. Again, previous ultrasound examination is strongly recommended. The inner part of the trocar must be withdrawn when a reduction of resistance is felt after passage of the parietal pleura.
- Once the trocar has been inserted into the pleura, suction should be gently applied and all the fluid removed to have an optimal vision of the pleural cavity. Keeping the catheter in continuous motion helps preventing cough, which could be provoked by the attachment of the catheter to the visceral pleura and the underlying lung during suction maneuvers. While fluid is removed, air is entering passively into the pleural cavity to keep the lung collapsed and then prevent high pleural negative pressures.
- If there are adhesions, the thinner ones can be severed with the biopsy forceps or cautery, but this maneuver has to be performed very carefully and by experienced thoracoscopists to prevent bleeding.
- For the complete exploration of the pleural cavity, a slow circular motion of the thoracoscope is advisable, taking into account that—in order to identify organs inside—the diaphragm shows respiratory movements, the lung has a transmitted pulsating motion, and the costal pleura appears to be still. Biopsies should be preferably taken from lesions located at the inferior and posterior zone of the parietal pleura, and preferably *over (and not between)* the ribs, whenever possible (see Fig. 29.2).

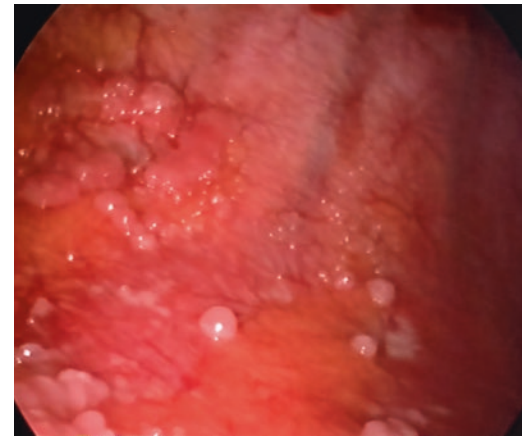

Fig. 29.2 Scattered nodules in the parietal pleura from metastatic breast carcinoma. In order to prevent complications, biopsies should preferably be taken *over the ribs*, and *not between them*, where intercostal vessels can be seen

A *chest drain* should be inserted in every case just at the end of the procedure and then connected to a water-seal system; gentle step-by-step suction is applied afterward and the drain kept in place until a complete reexpansion of the lung has been achieved. This is especially important when talc poudrage for pleurodesis has been performed. In this case, the drain stay should not be less than 2 days, in order to achieve a tight symphysis between the visceral and parietal pleura. When pleurodesis is not performed and the lung is easily reexpandable, *outpatient thoracoscopy* is feasible and safe [22]. However, the patient should not be discarded from hospital too early after lung reexpansion, because pulmonary edema can occur within 2–3 h after lung reexpansion in some cases, even with no pleurodesis performed [23].

Indications for Medical Thoracoscopy

Thoracoscopy can be performed for diagnostic and therapeutic purposes as well. Investigating a pleural effusion of unknown origin is the most frequent indication for diagnostic thoracoscopy, but it can also be useful in spontaneous pneumothorax. On the other hand, pleurodesis (mostly chemical) to prevent recurrence of pleural effusion or pneumothorax is the main indication for therapeutic thoracoscopy.

Medical Thoracoscopy in Pleural Effusions

Diagnostic thoracoscopy aims to obtain a specific diagnosis in pleural effusions of unknown origin. Most of the current guidelines recommend the addition of a biopsy procedure when a first cytology is negative [24, 25], and percutaneous needle pleural biopsy is frequently advised in those cases [26]. The average yield of cytology in malignant pleural effusions is around 60%, and it varies with the type of tumors (see Table 29.1). In our experience, mesotheliomas and lymphomas are the most problematic in yielding positive results by cytology, while thoracoscopy is very good in those cases. Pleural fluid acid-fast stain or culture positivity for *M. tuberculosis* is very low in tuberculous pleural effusions, and closed needle biopsy has been widely used to confirm diagnosis. All available biopsy needles provide a better yield in pleural tuberculosis than in malignancy, and this is due to the different degrees of diffuse involvement of the parietal pleura in those conditions [27]. Closed pleural biopsy with ultrasound guidance has still a role in countries with high prevalence of tuberculosis [28, 29], although there is evidence that medical thoracoscopy has a greater yield than blind pleural biopsy in those cases [30]. If needle biopsy does not provide diagnosis, thoracoscopy is the best option [31].

In a prospective study including 150 patients with pleural effusion of unknown origin, Boutin and coworkers obtained a positive yield of Abrams needle in 36% of the cases, whereas thoracoscopy achieved the diagnosis in up to 87% [32]. In another prospective study, Loddenkemper et al. obtained similar results comparing simultaneous Tru-Cut needle biopsy and thoracoscopy [33].

Table 29.1 Yield of simultaneous cytology and thoracoscopic biopsy in our series of 556 consecutive malignant pleural effusions (Adapted from Rodriguez-Panadero [50])

Origin of tumor	Biopsy+ (%)	Cytology+ (%)	B−/C− (%)
Total (556)	95	60	4
Lung (135)	91	57	9
Breast (101)	98	78	–
Mesothelioma (81)	94	41	6
Ovary (27)	100	83	
Lymphoma (51)	86	18	14
Colon (18)	92	62	–
Kidney (24)	100	54	–
Others (56)	100	67	–
Unknown origin (63)	95	71	5

With advances of image techniques, CT-guided needle biopsy could replace blind needle biopsy in more than two thirds of the cases [34]. CT-guided pleural biopsy is especially recommended in cases with marked pleural thickening or lesions that are clearly visible on CT scans, while direct thoracoscopy is preferred for patients showing only pleural effusion of unexplained origin. In cases where only scarce or hardly accessible pleural lesions are present or when large specimens are needed for histological diagnosis (like in mesothelioma or non-Hodgkin lymphoma), blind needle biopsy is unlikely to yield satisfactory results, and thoracoscopy is the preferred choice [35] (see Figs. 29.3, 29.4, and 29.5).

Both closed pleural biopsy and thoracoscopy can have complications, and both require adequate training, and—while medical thoracoscopy is growing in many countries—needle biopsy appears to be declining [36, 37]. In a randomized controlled study, Haridas et al. compared closed pleural biopsy using Abrams needle versus medical thoracoscopy and found that medical thoracoscopy had a diagnostic yield of 86.2% with complication rate of 10.3%, compared to 62.1% yield and 17.2% complications in closed pleural biopsy [38]. Moreover, Boutin et al. reported in the largest series published on Abrams needle pleural biopsy (1000 cases) a 3.1% incidence of pneumothorax and 1.3% hemorrhages [39], which is a higher rate of complications than the

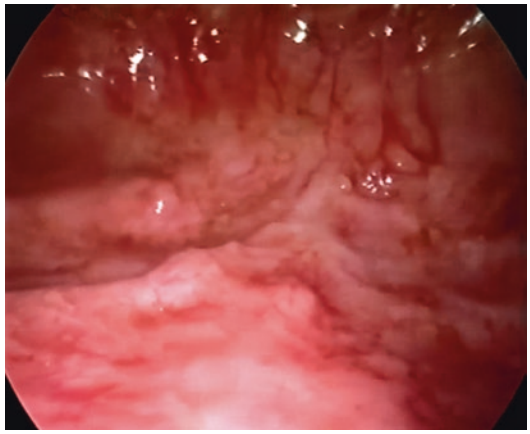

Fig. 29.3 Diffuse malignant mesothelioma in the parietal pleura. Although closed needle biopsy could yield some results in this case, large specimens (more easily obtained with thoracoscopy) are required to establish the tumor type

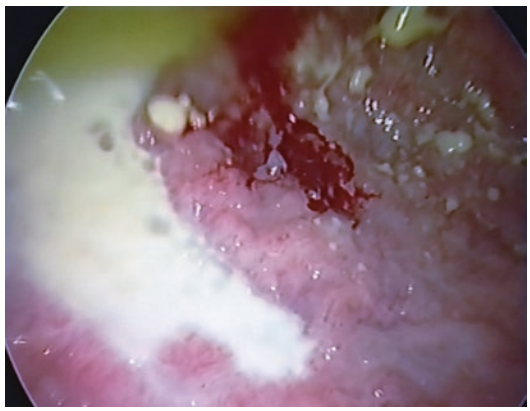

Fig. 29.4 Diffuse malignant mesothelioma coexisting with pleural plaques in one patient with history of asbestos exposure. Several biopsies have been taken with no significant bleeding (*top of the figure*)

ones we observed in our thoracoscopy series (see Table 29.3).

Pleural needle biopsy can be performed in an outpatient basis [41], whereas thoracoscopy is more complex and often requires hospitalization, especially when talc pleurodesis is performed. *Outpatient diagnostic thoracoscopy* can also be performed in well-experienced centers without major complications if the lung can be easily reexpanded after completing the exploration. When indicated, a tunneled indwelling pleural catheter (TIPC) can be left in place [42], especially if a lung entrapment makes it unexpandable. Although rapid

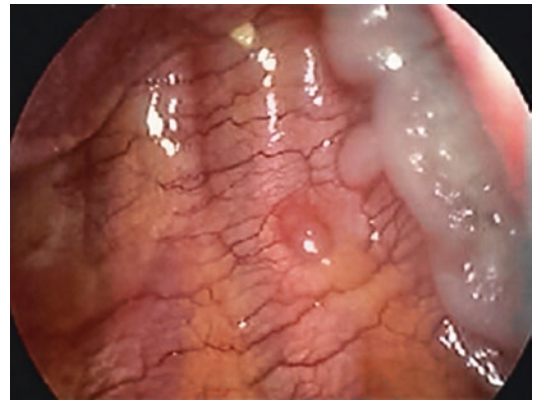

Fig. 29.5 Localized pleural involvement by non-Hodgkin lymphoma in the lower part of the parietal pleura (close to the diaphragm, seen on the right). A previous blind needle biopsy was nondiagnostic

outpatient talc pleurodesis with TIPC placement has been advocated in some cases [43], there are good reasons to be cautious with this, because chemical pleurodesis induces a marked local (and also systemic) transient inflammation [44, 45], which might cause acute respiratory problems a few hours/days after intrapleural application.

Medical Thoracoscopy in Lung Cancer with Ipsilateral Pleural Effusion

The finding of a pleural effusion coexisting with lung cancer is usually associated with a poor prognosis. In one series including 971 consecutive patients with lung cancer, Martin Diaz and coworkers found pleural effusion in 188 cases (19%), but it was visible on chest X-ray films only in 72 of them (38%, 7% of the total series). The remaining 116 effusions were detected on CT or ultrasound examination or were found only at thoracotomy. Although cytology was positive in only 40% of the effusions that were visible on chest radiographs, pleural metastases were actually found in up to 75% of those cases [46]. We therefore recommend performing exploratory thoracoscopy prior to resection in patients with lung cancer coexisting with ipsilateral pleural effusion, in order to detect unsuspected pleural metastases [47].

If the mediastinum is midline or shows an ipsilateral shift, obstruction of the mainstem bronchus should be suspected, and bronchoscopy

performed prior to thoracoscopy, in order to debulk the tumoral obstruction and then assess the lung expandability.

When the effusion is found at thoracotomy only, one could think about the possibility of a *paramalignant* pleural effusion (associated to obstructive pneumonitis, atelectasis, or lymphatic blockade), and resection of the tumor has to be considered. However, the prognosis is poorer in those patients than in those without pleural effusion [48]. The finding of a positive cytology in pleural lavage performed at thoracotomy has been associated with a worse prognosis in cases submitted to resection [49, 50].

Conventional thoracoscopy is not always conclusive in establishing presence/absence of pleural involvement in malignancy, and the usual reported diagnostic yield is about 95% [51, 52]. Autofluorescence thoracoscopy can enhance visualization of malignant lesions in the pleura, either using blue light source [53] or narrow-band imaging [54]. Fluorescence diagnosis (FD) with 5-aminolaevulinic acid (5-ALA) or other agents has been used with diagnostic purposes for various malignancies and improves visualization of additional lesions or even micrometastases [55], which may be relevant in evaluation of patients with lung cancer who are candidates for resection [56, 57]. Fluorescein-enhanced autofluorescence thoracoscopy (FEAT) can also be very useful in this respect, using inhaled fluorescein (with a short half-life in plasma, about 1.7 min after i.v. injection) [58].

Medical Thoracoscopy in Pneumothorax

There is no consensus about treatment of spontaneous pneumothorax, especially on the first event. However, there is general agreement in that some treatment is mandatory when pneumothorax recurs. Treatment options include pleurodesis, pleurectomy associated with bullectomy by thoracotomy or VATS, or talc poudrage by medical thoracoscopy. Many therapeutic approaches combine talc or surgical pleurodesis with bullectomy or bleb resection or coagulation. If bullectomy or pleural abrasion is planned, VATS would be preferred over medical thoracoscopy. Jannsen et al. showed no significant differences in video-thoracoscopic appearance between first and recurrent pneumothorax and concluded that the presence of bullous lesions did not predict recurrence [59], which would favor a simpler approach. However, another study from Tschopp and coworkers found that presence of bullae >2 cm in diameter had a greater risk for recurrence and need of thoracotomy [60]. *Fluorescence thoracoscopy* can be of great help to identify lesions responsible for air leak in spontaneous pneumothorax [61]. A multicenter prospective study demonstrated that simple thoracoscopic talc poudrage under local anesthesia is a safe, low-morbidity, cost-effective treatment for patients with primary spontaneous pneumothorax requiring chest tube drainage. A 5.1% recurrence rate was observed in patients submitted to thoracoscopic talc poudrage in this study, as compared with 34% recurrences in patients with tube drainage only. Efficient control of pain by opioids is always necessary [62].

Advanced Indications in Medical Thoracoscopy

Management of pleural effusions and pneumothorax is the most common indication for medical thoracoscopy. However, and depending upon the medical facilities and the availability of a thoracic surgery service, there are other situations that can be managed by pulmonologists using medical thoracoscopy [63]:

- *Thoracoscopy in empyema*. The management of complicated parapneumonic pleural effusions requires a careful clinical control and early intervention whenever loculations are seen in ultrasound examination. Early instillation of fibrinolytics with ultrasound guidance can be very helpful in managing complicated effusions, but thoracoscopy can be indicated in some cases, especially if performed early after failure of chest tube drainage [64, 65]. In more complex cases, VATS would be the preferred choice; in particular, the presence of separate loculations not in apparent communication with each other often leads to a surgical approach [66].
- *Lung biopsy by thoracoscopy*. Forceps lung biopsy—with or without electrocautery—has been performed for many years by pulmonologists using medical thoracoscopy,

and I did it in more than 50 patients with pleural effusion of unknown origin who had relevant findings on the visceral pleura and underlying lung parenchyma at thoracoscopic examination. However, a VATS procedure with endoscopic stapling—that can obtain large specimens, more suitable for extended pathological examination—is clearly recommended for management of diffuse lung diseases.

- *Other thoracoscopic procedures*, such as sympathectomy for control of severe hyperhidrosis, can be easily performed by well-trained thoracoscopists. Again, VATS would be the preferred technique in order to completely collapse the ipsilateral lung during the procedure, thus providing a better access to the paravertebral sympathetic nervous structures.

Contraindications for Medical Thoracoscopy

Most complications can be avoided by proper selection of patients for thoracoscopy. Patients with *severe COPD and respiratory insufficiency*, with hypoxemia (PO_2 <50 mm hg) and hypercapnia, will not tolerate induction of a pneumothorax without further deterioration of the gas exchange and are therefore no suitable candidates for medical thoracoscopy. Likewise, when there is a *contralateral lung or pleural involvement*, medical thoracoscopy is not advisable, and VATS would be recommended. Any patient with a history of *cardiovascular disease*—especially those with unstable angina or recent history of myocardial infarct—should be carefully evaluated before undertaking thoracoscopy. Morbid obesity is a relative contraindication for medical thoracoscopy, and special care should be taken with these patients because of the risk of hypoventilation. *Cough*, *fever*, *and infection* are relative contraindications for thoracoscopy, and treatment should be considered before a procedure is scheduled. Coagulation defects should also be corrected before thoracoscopy.

Thoracoscopy will not be feasible in case of *complete symphysis of the visceral and parietal pleura*. In case of localized pleural adhesions seen on ultrasound examination, an alternative point of entry might be chosen. In some select cases, it might be possible to create a pleural space by extended thoracoscopy using digital dissection on the chest wall and then introduce the thoracoscope to take biopsies from suspicious lesions [67]. However, this technique should be performed only by experienced thoracoscopists because of the risk of damaging intercostal vessels or nerves. Medical thoracoscopy is not safe in *advanced pulmonary fibrosis*: after induction of pneumothorax, a severe acute hypoxemia might occur, and reexpansion of the lung can be difficult due to the loss in lung elasticity. Pulmonary biopsy in case of honeycombing lung may result in prolonged air leakage and impaired reexpansion of the lung. Also, biopsy should be avoided in *hydatid cyst disease*, *arteriovenous malformations*, *and other highly vascularized lesions* (see Fig. 29.6a, b).

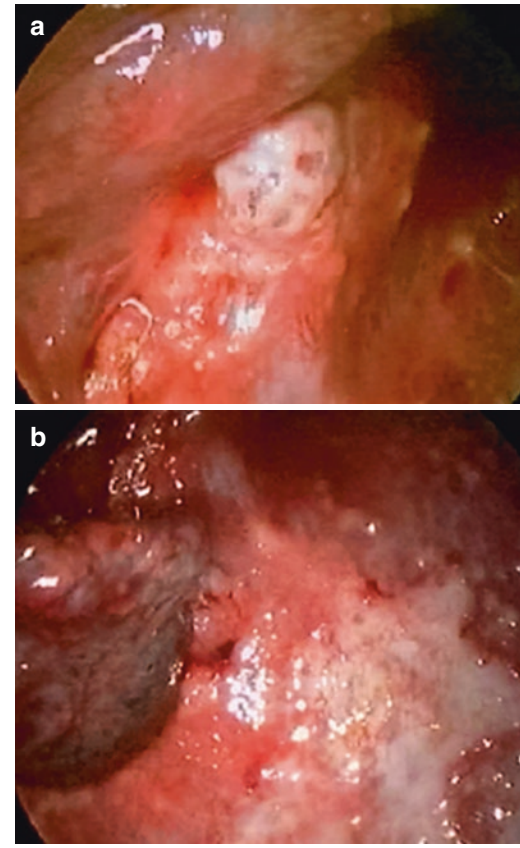

Fig. 29.6 (**a**) Tumor nodules over the aortic arch, where biopsy would be extremely risky. (**b**) Instead, diagnostic biopsies (metastatic lung cancer) were obtained from the parietal pleura, close to the aorta

Complications of Thoracoscopy

When performed by well-trained personnel, thoracoscopy is a safe procedure. Unless heavy sedation is applied, O_2 desaturation during thoracoscopy with local anesthesia is unusual, and—in our experience—thoracoscopy is especially well tolerated when large pleural effusions are removed just after insertion of the trocar into the pleural cavity, thus improving the respiratory function. Very few deaths associated to thoracoscopy itself have been reported in the literature (see Tables 29.2 and 29.3), but we have to be aware that fatal complications can occur. When talc poudrage is added to the procedure, the rate of complications is expected to rise, especially in patients with poor general condition prior to thoracoscopy.

In order to understand better how to manage complications, it is convenient to separate them in several categories.

Table 29.2 Complications of thoracoscopy reported in the literature

Viskum and Enk (Poumon-Coeur 1981;37:25–28): revision of 2298 reported procedures in 15 (general) series
– Subcutaneous emphysema, 1.3%
– Empyema, 2%
– (Significant) bleeding, 2.3%
– Air embolism, 0.2%
– Death due to the technique, 0.09%
Viallat et al. (Chest 1996;110:1387–93): (360 patients submitted to *talc poudrage*)
– Subcutaneous emphysema, 0.6%
– Empyema, 2.5%
Ribas et al. (Chest 2001;119:801–806): 614 pts. with *talc poudrage*
– Empyema, 2.7%
– Reexpansion pulmonary edema, 2.2%
– Respiratory failure, 1.3%
– Air leak, 0.5%
– Postoperative bleeding, 0.4%

Table 29.3 Complications of thoracoscopy in patients submitted to thoracoscopic talc poudrage in our personal series

Complications of thoracoscopic talc poudrage in MPE	Patients ($N = 512$)
Transient dyspnea after talc	50 (9.8%)
Acute pain after talc	44 (8.6%)
Prolonged air leak	46 (9%)
Subcutaneous emphysema	25 (4.9%)
Neoplastic invasion of the thoracoscopy tract	14 (2.7%)
Pulmonary embolism	12 (2.3%)
Skin infection (at the port of entry)	15 (2.9%)
Empyema	12 (2.3%)
Bleeding (requiring blood transfusion)	2 (0.4%)
Acute respiratory distress	1 (0.2%)

Complications Associated to the Thoracoscopy Procedure Itself

- *Laceration of the lung during insertion of the trocar*. Some authors advise to create a pneumothorax a few hours or even the day before thoracoscopy. This technique may reduce blood flow in the periphery of the lung and also may prevent damaging the lung during introduction of thoracoscopy instruments. However, direct introduction of a blunt trocar into the thoracic wall, without prior induction of pneumothorax, is in our experience safe and effective if there is enough free pleural fluid. Ultrasound examination is also very helpful to identify loculations in the pleural cavity and to locate the best entry for thoracoscopy.
- *Bleeding*. Patients with pancytopenia or coagulation disorders can be at risk, and no invasive procedure should be done when platelets are below 60,000/mm^3. To take a safe biopsy in patients using anticoagulant medication, INR should be <2.0. The use of aspirin may prolong bleeding time but is not an absolute contraindication for biopsies, while clopidogrel or other antiplatelet agents might be more problematic and should be discontinued at least 5 days before thoracoscopy. In order to prevent taking biopsies inadvertently from vascular structures, a perfect knowledge of the anatomy is mandatory. Biopsies from internal parts of the fissures of the lung should be avoided because large vessels are close to the surface on those zones (Fig. 29.7), and special

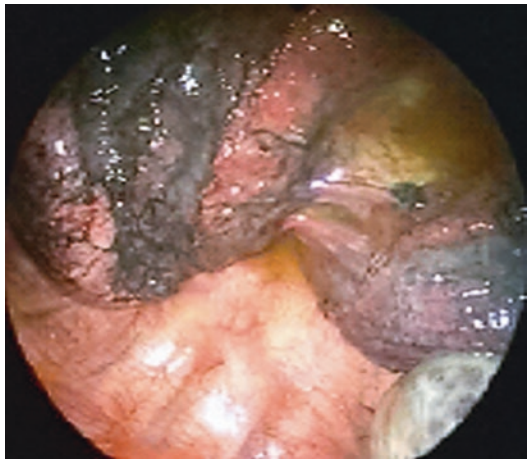

Fig. 29.7 Lung fissure in a patient showing black spot on the lung surface (pneumoconiosis). Biopsies should be avoided in this area because of the risk of damaging vessels inside. This patient had a cystic lesion (shown in part on the right of the figure) that should also be avoided for biopsy. Angiofibroma was diagnosed at thoracotomy

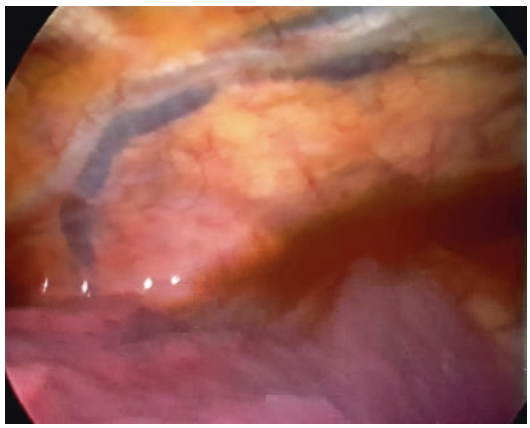

Fig. 29.8 Internal mammary vessels. They can easily be identified on the anterior part of the parietal pleura (close to the mediastinum), but could eventually be covered by tumor or fibrin, and never should be sampled

care is also necessary when sampling areas close to the internal mammary artery or vein (anterior mediastinal pleura). Although they can be identified easily by expert thoracoscopists (see Fig. 29.8), those vessels might sometimes be covered by tumor lesions or fibrin and then be inadvertently sampled, with fatal consequences if emergency surgery is not immediately available.

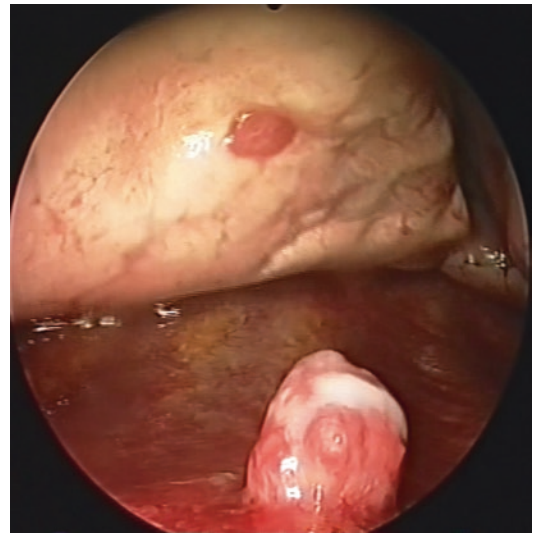

Fig. 29.9 Tumoral mass in the parietal pleura in a patient with metastatic renal carcinoma. A "kissing lesion" is seen opposite in the visceral pleura (top of the figure). Metastatic tumors from renal origin can have an increased intrinsic fibrinolysis and then bleed copiously when sampled by the thoracoscopy forceps, which occurred in this case. Immediate lung reexpansion and intrapleural injection of tranexamic acid (*see text*) helped to control this complication

- In case of excessive bleeding after biopsy (Fig. 29.9), we would recommend applying local compression with the (rigid) forceps over the sampled area, together with external compression over the same point. Local application of *tranexamic acid* (antifibrinolytic agent) can—according to our experience—help in stopping the hemorrhage, both in thoracoscopy and bronchoscopy [68]. Anyway, application of electrocautery is highly recommended. If bleeding is copious, the following steps should be followed:
  - Insert a large-bore tube and reexpand the lung as soon as possible, in order to tamponade the bleeding (assuming that it comes from the parietal pleura). *At the same time*, contact surgical backup immediately.
  - Once the lung is getting reexpanded, inject at least 1 g tranexamic acid intrapleurally (diluted in 30 mL saline), to control increased local fibrinolysis, which is

common with most of metastatic tumors, especially those from renal origin.
  - ICU support—including blood transfusion—is necessary in those cases, regardless the need for emergency surgical intervention.
- *Infection*. Although routine prophylactic antibiotics are not necessary, they should be used in neutropenic patients. Deep antiseptic cleaning of the chest wall is mandatory, and very strict care of the drain and the chest wound is also essential. The likelihood of infectious complications is higher in neutropenic patients and in those with prolonged chest drains, and we therefore never leave the drain for more than 5 days after thoracoscopy, even in cases with talc poudrage performed.
- *Neoplastic invasion of the thoracoscopy tract*. It is frequently seen in mesothelioma but can be observed in long-surviving patients with pleural metastatic carcinoma also. To prevent invasion by mesothelioma, application of local radiation therapy over the scar 10–14 days after thoracoscopy has been recommended (7 grays/day for 3 days) [69], although there is no general agreement on this.

Complications Associated to Lung Reexpansion

A chest drain should be inserted in every case just at the end of the procedure and then connected to a water-seal system; gentle step-by-step suction is applied afterward and the drain kept in place until complete reexpansion of the lung has been achieved.

- *Pulmonary reexpansion edema* can occur if suction is too strong, especially in patients with a trapped lung. In order to prevent it, careful and graded suction should be applied, especially when a pleurodesis procedure has been performed: we usually leave the drain connected to water seal without suction for at least 3 h following the pleurodesis procedure and then apply increasing suction gradually. Pulmonary edema can occur when expanding the lung in pneumothorax and malignant effusions, even without application of any sclerosant [23]. The mechanism for this complication is not fully understood; however, a too rapid reexpansion, especially if the lung was collapsed for several weeks, may play an important role. Other mechanisms invoked are excess negative pleural pressure, hypoxic damage to the chronic atelectatic lung, increased alveolar capillary permeability, and reperfusion injury [70]. It appears that a high production of IL-8 and other pro-inflammatory cytokines has some role in the development of this complication [71]. Although the edema usually appears on the ipsilateral hemithorax, it can happen on the contralateral side with fatal consequences [72, 73].
- *Prolonged air leak*. According to our experience, it can happen most frequently in neoplastic patients who have undergone prior chemotherapy. In those cases, necrotic tumor nodules can be seen on the surface of the lung, and some of them could eventually get broken during lung reexpansion. If this occurs, suction must be stopped immediately, and the drain left only in water seal (without suction) until the air leaking stops.
- *Subcutaneous emphysema* is frequently associated to prolonged air leak and would require specific surgical measures in some cases, especially if there is any compromise to the upper airways. It can also be observed in patients who have persistent cough during thoracoscopy exploration. If this occurs, the trocar should be left open, so that development of high intrathoracic pressures be prevented. Manual compression over the area surrounding the port of entry and the trocar may prevent the subcutaneous spreading of air (that is expelled around the trocar by coughing, especially if the trocar's valve is closed).

Complications Associated to Pleurodesis

Thoracoscopy is associated with a transient impairment in lung function, which is more pronounced when pleurodesis is performed [74]. With the exception of some complications related to the technique itself that could be prevented

with good training and the support of ultrasound examination, the most relevant are systemic complications associated to intrapleural instillation of the sclerosant:

- *Acute respiratory distress or pneumonitis*. This has been described in some cases of talc pleurodesis [75], but the pathophysiologic mechanism responsible for this severe complication is still unclear. There is a concern about systemic inflammation that appears to be common with almost all agents instilled into the pleural space [76] and also with talc containing small particles (<10 mm in diameter) [77, 78]. Acute respiratory complications arise more frequently in patients with poor clinical condition prior to the pleurodesis procedure, and careful evaluation of the performance status of those patients is therefore highly recommended.
- *Possible activation of systemic coagulation after pleurodesis*. There is evidence that thoracoscopy—like many other interventional procedures—can provoke some systemic inflammation, but it is clear that talc pleurodesis induces a stronger reaction in many cases. According to some studies from our group, an activation of the systemic coagulation might be observed after talc poudrage [79], and this side effect can be partially controlled with prophylactic heparin.
- The complication rates in our thoracoscopy series—including talc poudrage—are reported on Table 29.3.

In conclusion, medical thoracoscopy can be performed by well-trained pulmonologists in the endoscopy suite using local anesthesia with proper general analgesia and mild sedation, both for diagnostic and therapeutic (pleurodesis) purposes, with no major complications. According to Professor Boutin, complications can best be prevented by observing the following rules [80]:

1. Postpone thoracoscopy for several days if the patient is coughing.
2. Measure blood gases, and monitor cardiac signs by simultaneous ECG.
3. Oxygenate the patient during thoracoscopy.
4. Avoid taking biopsy samples from the internal parts of the fissures or from the mediastinum.
5. Coagulate and ensure hemostasis if hemorrhage exceeds 20 mL.
6. Insert a chest tube (at least until the lung expands) to prevent subcutaneous emphysema.
7. Start physiotherapy on the day of thoracoscopy to exercise the diaphragm and avoid accumulation of secretions and obstruction.
8. To prevent invasion in cases of mesothelioma, administer radiation therapy of 7 grays/day for 3 days to the scar area on postoperative day 10.

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30 Overview of the Spectrum of Chest Tubes with Focus on the Tunneled Pleural Catheter: Disease-Specific Selection

Mohammed Alnijoumi, Ghazwan Acash, and Carla Lamb

Introduction and Definition of Chest Tube Placement

Chest tube placement has been a long-standing therapeutic intervention in the setting of pneumothorax, empyema, and hemothorax. Competency in placement is required by surgeons, intensivists, pulmonologists, emergency room physicians, and radiologists.

There is a core set of medical knowledge and procedural technique that must be understood by the physician placing a chest tube. Over the past decade, there is an ongoing evolution of tube sizes available along with variation in technique that allow for improved patient comfort while providing optimal management of the pleural disease warranting chest tube placement. This chapter will review the approach to the patient with specific pleural diseases requiring chest tube placement. The indications, contraindications, spectrum of tubes available, basic technique, and management will be discussed with a focus on the indwelling pleural catheter. Review of the existing literature regarding optimal chest tube size for disease-specific pleural diseases and regarding the static analog and digital pleural drainage units will be included. An update on training tools for the procedure will be reviewed. An update on digital chest tube monitoring systems will also be discussed.

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History

Malignant pleural effusion (MPE) is a significant cause of morbidity in patients with advanced cancer and usually signifies a poor prognosis. The median survival following diagnosis ranges from 3 to 12 months dependent on the originating tumor type of underlying malignancy. The Karnofsky score has also been found to be a predictor for survival in the setting of malignant pleural effusion.

Lung cancer is the most common cause of MPE in men, while in women breast cancer is the leading cause of MPE. Other malignancies such as ovarian, gastric, and mesothelioma can also cause MPE to a lesser extent. Options in the management of MPE include chest tube insertion with subsequent injection of sclerosing agent such as talc or doxycycline, TPC with or without chemical pleurodesis, medical thoracoscopy with talc poudrage with or without TPC, surgical thoracoscopy with chemical pleurodesis, or mechanical pleural abrasion. Patient selection for management of symptomatic malignant pleural effusion should include several factors such as the relief of shortness of breath with the initial thoracentesis, patient preference, performance

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status, life expectancy, comorbidities, as well as availability of procedural expertise. It is critical to plan a definitive procedure after the initial thoracentesis, and pleural diagnosis is made to minimize symptoms from the outset.

Indications and Contraindications

The primary indications for chest tube placement include pneumothorax, pleural effusion specifically malignant pleural effusion, empyema, and hemothorax.

Early intervention is the key to management of the symptomatic patient with any of these pleural diseases. Contraindications include the uncorrected coagulopathy, an uncooperative patient, absence of informed consent, and lack of proper procedural training.

Patient preparation and technique will be reviewed followed by disease-specific tube selection.

Contraindications for Indwelling Tunneled Pleural Catheter

The patient who does not experience any significant relief of dyspnea after initial thoracentesis will not benefit from the placement of TPC. Infection should be ruled out before placing TPC as an infected pleural space is a contraindication to TPC placement. The site of insertion should be intact and no evidence of broken skin or cellulitis. Uncorrected coagulopathy is a contraindication to TPC placement, and checking of CBC, PT, and PTT is required before proceeding. Evidence of multiple loculations within the pleural space would also be a contraindication to TPC. If the patient does not have an adequate support system to maintain proper care and sterile drainage of the TPC, it would not be recommended.

Complications: (Table 30.1)

Complications and Troubleshooting Chest Tubes

While the complication rate is 1–2%, it is important to recognize the potential complications that may occur with chest tube placement, maintenance, and removal (Table 30.1). Managing the chest tube after placement is equally important.

Table 30.1 Complications of chest tubes insertion

Complication	No.	%
Unsuccessful insertion	10	4
Symptomatic loculation	21	8.4
Asymptomatic loculation	10	4
Empyema	8	3.2
PTX, SQ Air/BPF	6	2.4
Cellulitis	4	1.6
Recurred fluid	4	1.6
Dislodged	3	1.2
Bleeding	2	0.8
Tumor seeding	1	0.4
Pain requiring removal	1	0.4
Extrapleural catheter	1	0.4

PTX pneumothorax, *BPF* bronchopleural fistula

Once the chest tube has been placed, there are a number of daily assessments that must be performed. Patient symptoms, pain management, respiratory variation, degree and duration of air leak, amount of drainage output per 24 h, character of output, chest tube entry site, radiographic imaging, and timing of tube removal are indicators as to whether the chest tube is optimally managed. While there may be controversy in the literature regarding some of these factors, we will review practical clinical pearls regarding these aspects. If there is a persistent air leak, assess all of the chest tube connections by removing the dressing to assure that the chest tube has not migrated out resulting in air entering into the pleural space from one of the open side ports. Proceed from the chest wall along all of the tubing to assure that all of the connections are sealed. If you do not identify a leak in the system, consider replacing the pleural drain tubing as small punctures in the tubing are difficult to isolate. If there is still an ongoing air leak, then there is most likely a bronchopleural fistula. If there is no respiratory variation with deep inspiration or cough, this could suggest that the chest tube may be occluded with fibrin or clot. Manual milking of the chest tube and adjacent tubing can remedy this; however, saline or fibrinolytics may be required. The chest tube or connector tubing could be kinked

due to patient positioning but can be easily identified and corrected at the bedside. This can be recognized when drainage output markedly decreases, or there is evidence of reaccumulation of a pneumothorax. Lastly, it could signify that the lung has now fully expanded and is now occluding the chest tube. Criteria for determining the timing of chest tube removal vary in the literature. For pneumothorax, it is the resolution of a visible air leak in the drainage system and radiographic resolution. Generally, once this is established the chest tube is placed to water seal for 12–24 h, and if there is no recurrence, then the tube can be clamped for several hours and then removed.

Most would maintain a functioning chest tube while a patient is receiving positive pressure with mechanical ventilation when used to treat a pneumothorax; however, similar steps for standard removal as previously described may be considered as well. When treating empyema, the chest tubes are maintained until there is no spontaneous output, clinical status has improved, and chest imaging confirms resolution of the fluid collection. In the setting of malignant pleural effusion and pleurodesis, the chest tube may be removed with drainage output of <150 mL in a 24-h period without consequence.

Review of Technique

Pre-procedure preparation of the patient is fundamental. After consent has been obtained, platelet count, PT, INR, and PTT should be assessed. Current medications should be checked, specifically screening for antiplatelet agents or other anticoagulants. Discontinuation of the medication and reversal of the effect of these agents whenever possible is required. The patient should be placed in the supine position or decubitus position dependent on the chest tube site location with elevation of the head of bed approximately 30 °. For example, with a pneumothorax the second intercostal space along the midclavicular line is recommended. In the setting of pleural effusion, placing the patient with the noninvolved side down in the decubitus position placing the chest tube in the fourth or fifth intercostal space in the midaxillary line is recommended. Locating the xiphoid process and drawing a mental line at that level to the midaxillary line is a practical way to find this location. Physical exam, chest imaging review, and thoracic ultrasound are utilized to confirm the location for chest tube entry followed by marking the site. Universal protocol is exercised with final verbal confirmation of the correct anatomic side by the medical team. Intravenous analgesia and/or anxiolytics are recommended prior to chest wall preparation to alleviate patient symptoms in addition to topical anesthetic with 1% lidocaine. The site is then cleaned with chlorhexidine followed by placement of a sterile drape. Topical 1% lidocaine (not exceeding 5–7 mg/kg) is generously introduced subcutaneously, intercostally, and along the periosteum. Often pleural fluid or air (in the setting of pneumothorax) will be identified during this process, confirming entry into the pleural space. There are two basic techniques for chest tube placement defined as operative or the wire-guided modified Seldinger technique. The trocar method will not be discussed as it is not recommended. The operative technique requires a 1–2 cm intercostal incision parallel to the rib just above the rib that is the desired point of entry.

Using a sterile clamp applying steady controlled pressure over the rib, a tactile "pleural pop" will be felt. Once the pleural space has been entered, the clamp is spread apart to dilate an entry tract. The operative method allows for placement of a gloved sterile finger into this entry to perform a 360 ° finger sweep to remove any fibrous adhesions and to manually confirm that the lung is not against the chest wall.

The wire-guided modified Seldinger technique is less tactile; however, it is equally effective in placing a chest tube. The manufactured kits include the addition of a guidewire with one to three sequential dilators to gently dissect the intercostal muscles creating the entry tract for the chest tube and introducer. The available chest tube sizes range from 8 to 36 Fr using the Seldinger technique (Figs. 30.1, 30.2, and 30.3).

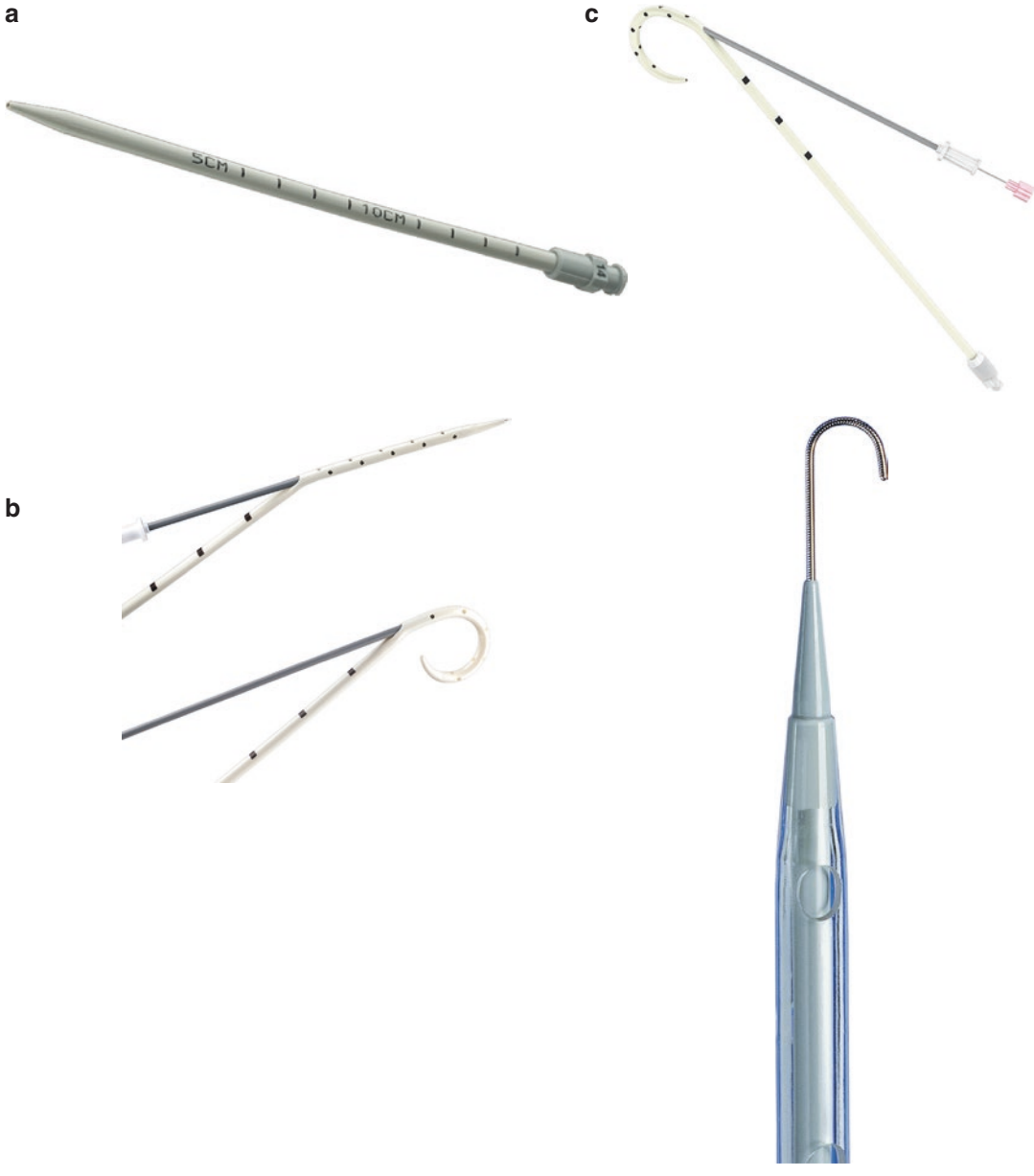

Fig. 30.1 (**a**) Thal-Quick introducer needle. (**b**, **c**) Wayne trocar

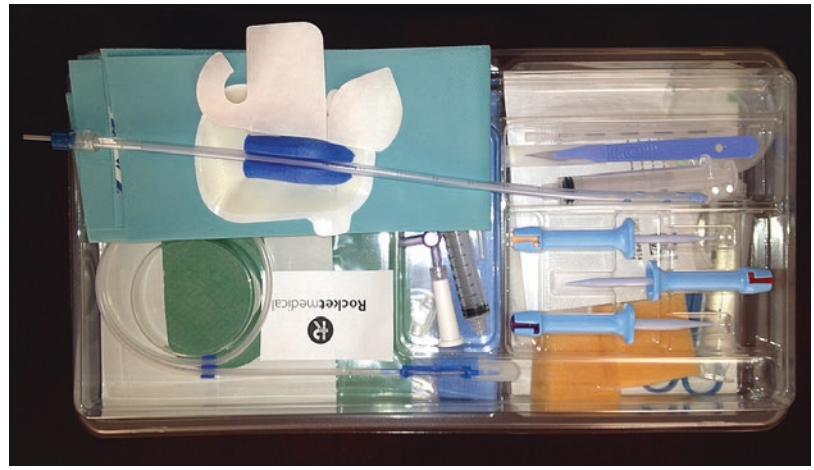

Fig. 30.2 Insertion kit: trocar and catheters

Fig. 30.3 Thal-Quick chest tube

Description of Technique (Figs. 30.4, 30.5, 30.6, 30.7, 30.8, 30.9, and 30.10)

After informed consent is obtained from the patient, the patient is placed in a supine or decubitus position with the affected side slightly elevated. Thoracic ultrasound is employed in all cases to verify the point of entry and to ensure there is a safe pocket of fluid for TPC insertion. The correct site is marked as "yes" in the visible field of the operator, and a time-out is called where patient name, medical record number, and date of birth are verified. The skin is then prepped with chlorhexidine and covered with a large sterile drape. The patient is connected to a telemetry monitor and continuous pulse oximetry monitoring as well as placement of a peripheral IV in the event of any need for medication administration. The skin is anesthetized with 1% lidocaine at both the insertion site and the planned tunneling site. The pleural fluid pocket is accessed with the needle using Seldinger technique, and the guide wire is inserted through the needle and directed into the largest fluid collection seen on the ultrasound examination. A small incision (0.5 cm) is made at the guidewire entry to facilitate the insertion of the dilating trocar. A small incision (1 cm) is made at the skin level a few centimeters anterior to the insertion site with the catheter tunneled subcutaneously until the polyester cuff is buried 0.5 cm underneath the skin and catheter exits

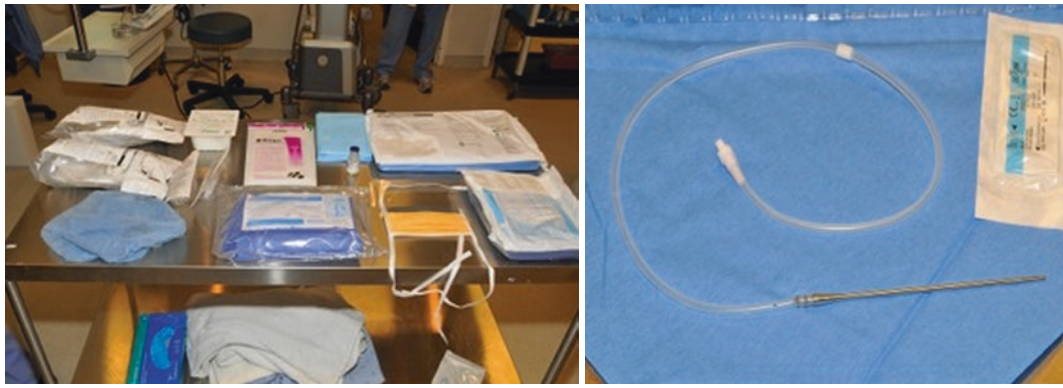

Fig. 30.4 Pleural catheter and equipment needed

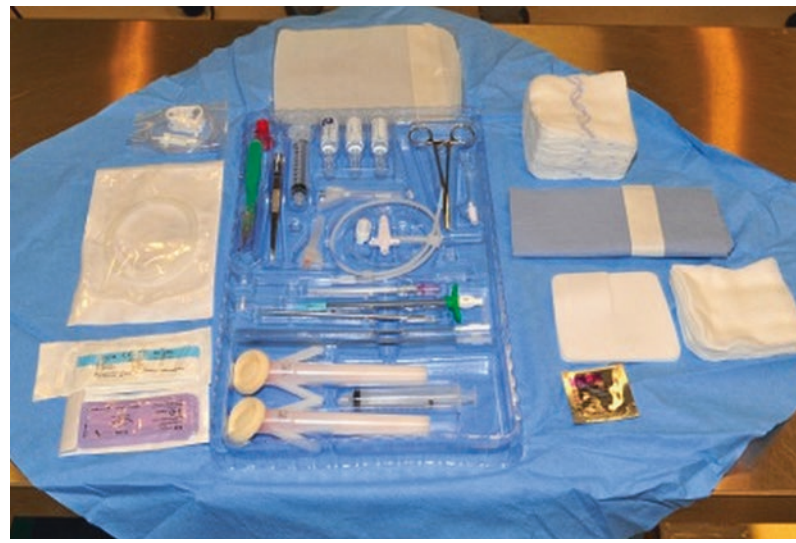

Fig. 30.5 Pleural catheter kit

from the guidewire insertion site. Gentle dilatation with the sequential dilators is performed over the guidewire with eventual insertion of the trocar and removal of the guidewire. The catheter is then fed through the breakaway trocar which is peeled until the catheter is fully inserted into the pleural space. The catheter is then secured with sutures and drained to ensure proper function and provide the patient with immediate relief of dyspnea. A follow-up CXR is ordered to confirm proper placement. The patient is scheduled for follow-up visit in 7–10 days for suture removal and to review the drainage data.

Fig. 30.6 Preparing the patient for TPC insertion and accessing the pleural space

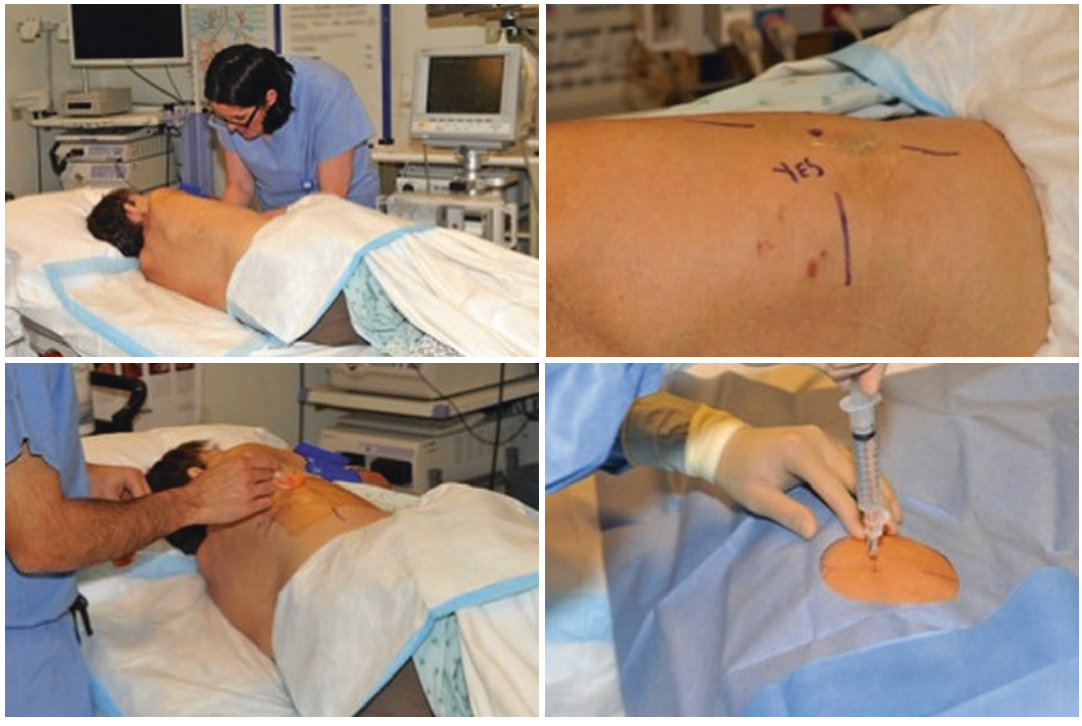

Fig. 30.7 Patient positioning and local anesthesia

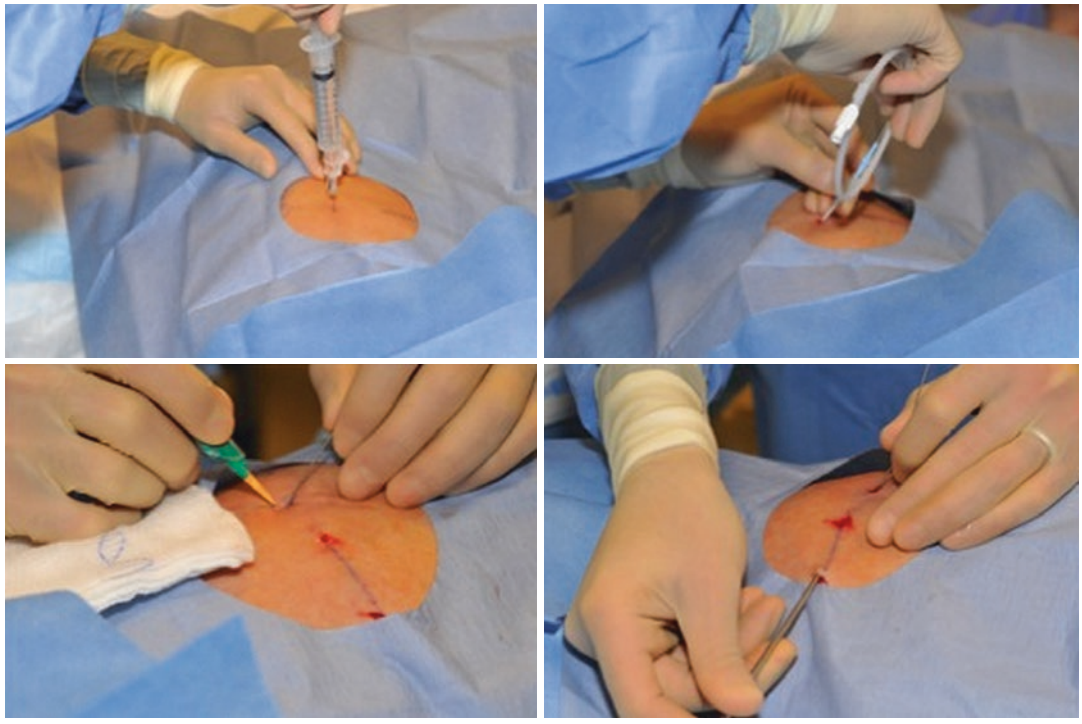

Fig. 30.8 Guidewire insertion, followed by pleural catheter tunneling

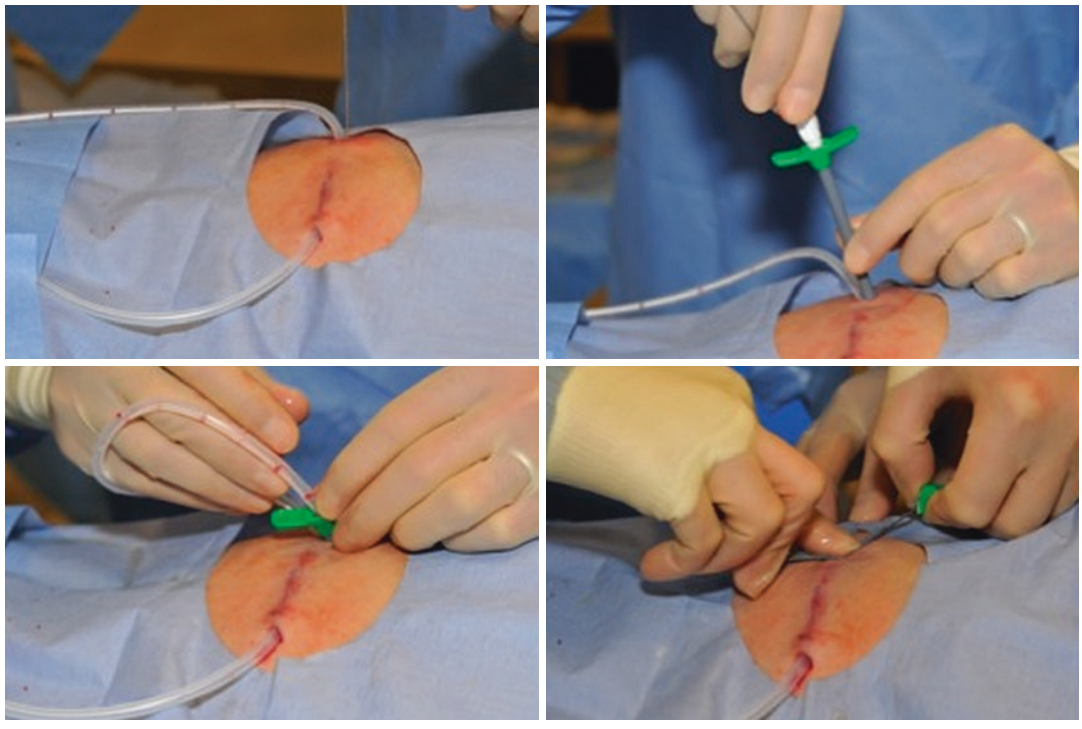

Fig. 30.9 Trocar insertion followed by feeding the catheter into trocar and finally peeling off the trocar

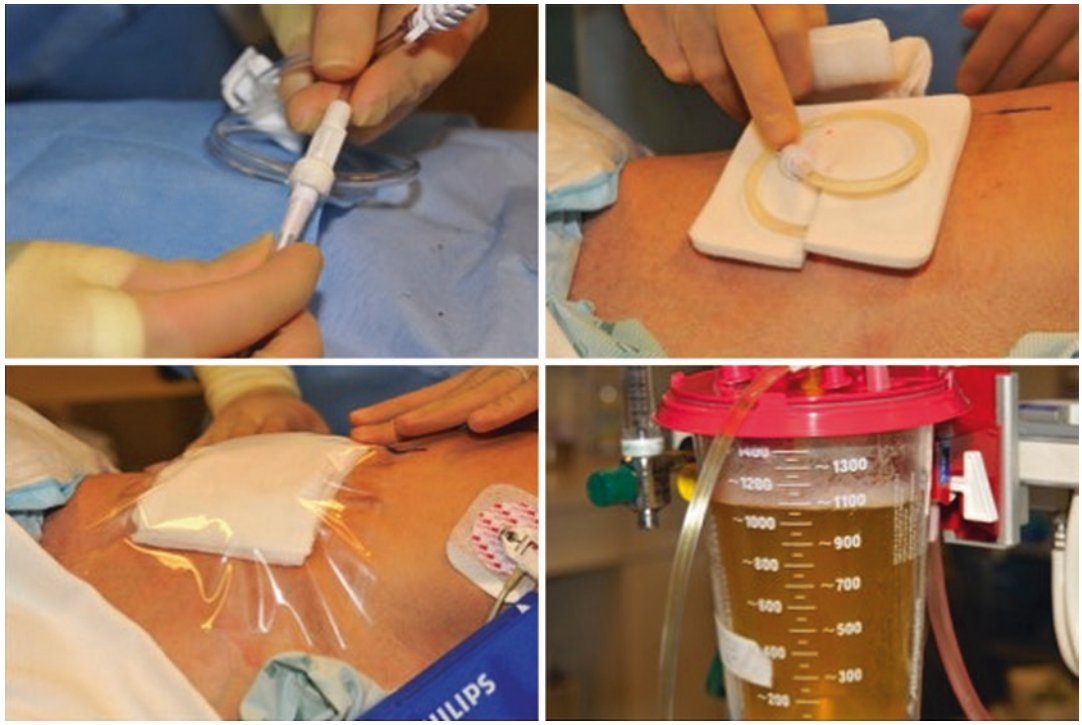

Fig. 30.10 Draining the fluid and placing the final dressing

Application by Disease Process

Pneumothorax

Chest tube placement in this setting will be directed anteriorly and apically in the supine patient. The anterior second intercostal space along the midclavicular line is the standard location. The exception to this would be in the setting of the iatrogenic pneumothorax from cardiac pacemaker or defibrillator placement. In order to avoid the risk of possible subcutaneous chest wall infection in a newly placed device, it is recommended to place the chest tube along the fourth or fifth intercostal space in the midaxillary line. If the patient is noted to have a loculated pneumothorax with varying pleural adhesions, then CT guidance for chest tube placement would be advised. With the availability of smaller-bore chest tubes and literature supporting that these are as effective and better tolerated by the patient, the larger-bore tubes have been replaced by the smaller-bore tubes ranging from 8 to 14 Fr. At the time of chest tube placement, manual aspiration of the pneumothorax with a luer lock syringe until resistance is met can result in a quicker resolution of the pneumothorax.

Empyema

When a diagnosis of pneumonia is made and a pleural effusion is identified, a thoracentesis should be performed immediately with complete evacuation and analysis of the pleural fluid. This may prevent the need for further intervention. However, if the fluid reaccumulates and the patient does not demonstrate clinical improvement with antibiotics or the initial pleural fluid analysis diagnosis an empyema, then a chest tube should be placed. There is evidence that small-bore chest tubes defined as <14 Fr are as effective as the traditional larger-bore chest tubes for evacuating pleural space infections.

The smaller tubes are better tolerated by the patients. The British Thoracic Society guidelines also suggest that to prevent premature clogging of the smaller-bore tubes, routine saline flushes 30–50 mL every 6–8 h is effective. We recommend the use of the 14 Fr catheter due to its resilience and lower incidence of fibrin clogging as compared to the smaller-bore tubes. Fibrinolytics can be utilized such at tissue plasminogen activator (TPA) (2–50 mg) instilled at varying intervals to further maintain an existing chest tube. If the patient has clear evidence of multiple loculations from the outset, then image-guided placement of more than one chest tube may be required, and thoracic surgical consult would also be recommended in the event that surgical decortication is required.

Hemothorax

This is most often associated with thoracic trauma or iatrogenic thoracic complications. It is recommended to utilize a 28–32 Fr chest tube due to the viscosity of the hemothorax, and there is a higher risk for occlusion with a smaller tube. It is critical in this scenario to be able to have a patent tube in order to accurately assess the rate of output as this would determine the need for surgical intervention.

Malignant Pleural Effusion

Malignant pleural effusion is common in lung cancer, breast cancer, and lymphoma. This impacts patient's quality of life. After the initial pleural diagnosis is made, a definitive management plan to prevent recurrence should follow. This will be fully discussed later with the indwelling pleural catheter. TPC is typically done in a patient with MPE who has poor performance status indicated by Karnofsky score less than 60% (Table 30.2). Patients with known MPE and a good performance status may elect for TPC rather than medical thoracoscopy and pleurodesis to further minimize hospitalization.

Indwelling Tunneled Pleural Catheter (TPC)

An indwelling tunneled pleural catheter (TPC) is a device involving a minimally invasive procedure typically performed to alleviate dyspnea

Table 30.2 Karnofsky score

Able to carry on normal activity and to work; no special care needed	100	Normal, no complaints, no evidence of disease
	90	Able to carry on normal activity, minor signs or symptoms of disease
	80	Normal activity with effort, some signs or symptoms of disease
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed	70	Cares for self, unable to carry on normal activity or to do active work
	60	Requires occasional assistance but is able to care for most of his personal needs
	50	Requires considerable assistance and frequent medical care
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly	40	Disabled, requires special care and assistance
	30	Severely disabled, hospital admission is indicated although death not imminent
	20	Very sick, hospital admission necessary, active supportive treatment necessary
	10	Moribund, fatal processes progressing rapidly
	0	Deceased

resulting from recurrent malignant pleural effusion (MPE) with or without a partially trapped lung. There is also a role in the recurrent benign pleural effusion that is refractory to medical management as in the case of congestive heart failure or end-stage liver disease. It may also be used in conjunction with medical thoracoscopy in a rapid pleurodesis model (Fig. 30.10). Generally speaking, the procedure is performed in the outpatient setting and requires drainage by a visiting home nurse, a trained family member, or the patient after appropriate education.

The Denver Pleurx catheter is a 66 cm long, 15.5 F, silicone rubber catheter with fenestrations along the distal 24 cm. A valve at the proximal end of the catheter is a one-way valve and can be accessed only by using the special drainage line provided in the kit. There is a polyester cuff which serves to prevent infection and anchors the catheter in place just beneath the skin (Fig. 30.4).

Pleurodesis

Patients with MPE have fluid accumulating in the pleural space and compressing the lung resulting in significant dyspnea and poor quality of life. Pleurodesis is the treatment used to drain that fluid and prevent it from reaccumulation. In many instances pleurodesis involves injecting a sclerosing agent into the pleural space to induce inflammation and fibrosis to obliterate the pleural space.

Spontaneous pleurodesis with TPC alone can occur in 50–58% of cases in a mean of 39 days. Sclerosing agents can be injected into TPC by overcoming the one-way valve and inserting a three-way stopcock at the end of the drainage line. Doxycycline or talc is used to achieve pleurodesis. No significant differences in side effects or safety profile were found between these sclerosing agents, although some studies reported concerns regarding the possibility of ARDS when using smaller particles of talc.

Chest tubes are another option to achieve pleurodesis in MPE. Small-bore chest tubes (10–14 F) inserted with ultrasound guidance proved to be as effective as large-bore chest tubes in the management of MPE. Two studies using those tubes reported pleurodesis success rate between 72 and 94%. A variety of small-bore chest tubes are available, and the sclerosing agent can be instilled through the three-way stopcock at the end of chest tube. The British Thoracic Society recommended starting pleurodesis once effusion drainage is achieved and lung expansion has been confirmed radiologically. Disadvantages of chest tube insertion include prolonged hospital stay, limited mobility, and increased chest wall pain as compared to the outpatient TPC.

Evidence-Based Review of Indications

1. Malignant pleural effusion
   In the largest series published for TPC, Tremblay et al. reported placing 250 TPC for MPE in 223 patients during a 3-year period. Complete symptom control was achieved in 38.8% procedures, partial symptom control in 50%, and failure to control symptoms in 3.6%, failure to insert the catheter in 4%, and 3.6% without assessment of symptoms at the follow-up visit. Spontaneous pleurodesis occurred in 43% of cases, and the catheter stayed in place for a median duration of 56 days. No further ipsilateral pleural procedure was required in 90% of cases. The complication rate was low.

   When compared to chest tube insertion and chemical pleurodesis, TPC was found to achieve equivalent relief of dyspnea and safety with the advantage of a significant decrease in the need for a hospital stay and hospital expenses. TPC can be used in conjunction with other procedures such as medical thoracoscopy. In a study involving 30 patients with MPE who underwent medical thoracoscopy and talc poudrage pleurodesis, the insertion of TPC significantly reduced median duration of hospitalization and the duration of TPC use

compared with historical controls of either procedure alone.

2. Partial trapped lung
   Patients with partial trapped lung typically have a dense peel of tissue encasing the visceral pleura preventing the lung from fully reexpanding following thoracentesis. Accordingly, pleurodesis is frequently unsuccessful as pleural apposition is difficult to achieve. These patients are frequently symptomatic because of lung atelectasis secondary to pleural effusion as well as dysfunction of the affected diaphragm. After fluid removal, dyspnea in these patients improves because of partial lung expansion and relief of the ipsilateral diaphragm.

   The use of TPC in patients with MPE and trapped lung was reported in a series of 11 patients with lung cancer, lymphoma, and mesothelioma. All patients reported symptomatic relief, and the catheter remained in place till death in ten patients. Complications included cellulitis at insertion site and catheter infection.
3. Chylothorax
   Chylothorax is defined as a pleural effusion with triglyceride level > 110 mg/dL. It usually develops as a result of direct invasion of the thoracic duct by a tumor or as a result of obliteration of the lymphatics following radiation therapy. Of the malignant etiologies, lymphoma is the most common, although any metastatic cancer from any organ to the thorax can cause it. Other causes of chylothorax can be divided into traumatic, nontraumatic, and idiopathic.

   Recurrent chylothorax is debilitating, and the management can be challenging despite treatment of the underlying condition. Options include recurrent thoracentesis, dietary management to reduce long-chain triglycerides, somatostatin analog such as octreotide, thoracoscopy with chemical sclerosis, and insertion of a TPC.

   In a case control study, Jimenez et al. reviewed the charts of 19 patients with confirmed chylothorax. Ten patients underwent TPC placement, and nine patients had other palliative interventions including repeated thoracentesis, thoracoscopic talc pleurodesis, and pleuroperitoneal shunt placement. Patients with TPC were drained according to a specific protocol, and there was no baseline significant difference between the two groups regarding age, functional status, weight, albumin level, or absolute lymphocytes count.

   TPC group had a statistically significant lower risk of requiring a second pleural intervention after the index procedure during the following 500 days compared to the other pleural interventions. There was a decrease in albumin following TPC insertion which was not worse than that observed in the other group and recovered to baseline after TPC removal. No statistically significant difference was noted in successful pleurodesis rate or symptom control between the two groups, and the author concluded that TPC may be considered as first-line palliative management for patients with symptomatic recurrent chylothorax poorly responsive to treatment of underlying malignancy.
4. Benign recurrent pleural effusion
   TPC is also an option for the patient with refractory pleural effusion in the setting of congestive heart failure that persists despite maximal medical therapy. In the setting of hepatohydrothorax and advanced liver disease, TPC placement can serve as a temporary bridge to transjugular intrahepatic shunt (TIPS) or as a palliative therapeutic measure in the patient who is not a candidate of liver transplant. This is especially beneficial in this patient population due to ongoing coagulopathy and rapid rate of pleural effusion recurrence by reducing frequent thoracentesis and hospital visits to manage a very debilitating component of disease.

Chest Tube Insertion Competency and Training

Chest tube insertion is an invasive procedure with a low complication rate. Training is imperative to ensure patient safety as well as reduce

procedure-related complications, regardless of the type of chest tube being used (large bore vs. small bore). The British Thoracic Society (BTS) 2010 Pleural Disease Guidelines [20] states: "All doctors expected to be able to insert a chest drain should be trained using a combination of didactic lecture, simulated practice, and supervised practice until considered competent." There are no further directions on the specifics of accomplishing such competency. On the other hand, the American College of Chest Physicians (ACCP) states: "Trainees should perform at least 10 procedures in a supervised setting to establish basic competency. To maintain competency, dedicated operators should perform at least five procedures per year." It is felt that numbers alone are not the sole indicator of how competent a trainee is, as medical education has been shifting toward competency-based instruction and education.

TUBE-iCOMPT™ is an assessment tool that was developed and validated to assess physician competency at chest tube insertion in both mannequins and live patients. TUBE-iCOMPT™ tool consists of five assessment domains: (1) pre-procedure checks; (2) patient positioning and local anesthetics; (3) blunt dissection skills; (4) Seldinger skills; and (5) suturing, drain connection, and dressing. At validation, the tool was able to stratify the 29 participants based on experience with a non-overlapping 95% confidence interval. Those groups were novice with no prior experience, intermediate (attendance at chest tube insertion workshop but no insertion in live patients), and experts (more than 30 chest tube insertions in live patients). The groups remained distinct when chest tube insertion in live patients was assessed. The TUBE-iCOMPT tool showed great reproducibility of test-retest scores and inter-tester scores. The authors concluded that TUBE-iCOMPT is a useful contribution to the instruments and tool available to assess the procedural skills of pulmonologists and should be incorporated into chest tube insertion training programs. Nonetheless, the score required to indicate a particular level of competence wasn't answered nor the number of procedures needed to achieve such competence.

A 40-point, 20 item assessment tool, named a Tool for Assessing Chest Tube Insertion Competency, or TACTIC™, was developed and validated in pediatric emergency physicians and fellows performing chest tube insertion. The TACTIC™ tool included assessment of four phases of chest tube insertion: (1) preparation, (2) insertion of the chest tube, (3) securing the chest tube, and (4) confirmation of placement. In this single-center study, the TACTIC was scored at baseline and after receiving targeted training using web-based training and hands-on insertion and practice on a rib model. A total of 22 procedures were performed by two groups of pediatric emergency medicine participants (attending physicians and fellows). The TACTIC scores improved significantly between pre-course and post-course scores. The improvement was significant in the fellows group, but it showed a trend toward improvement in the attending physicians group. One could postulate that a combination of didactic and simulation training would improve competency in trainers.

We recommend a combination of didactic (lectures, videos, web-based training, etc.) and simulation-based training either low- or high-fidelity for novices at the beginning of their specialty training. Continued assessment for competency during training is crucial. Graduated responsibility in participation in the procedure throughout training by observing, assisting, and then supervised-performing of chest tube insertion ensures gaining the confidence, experience, competency, and the number needed to perform such invasive procedure independently and efficiently at the time of graduation.

Pleural Drainage Systems

Since the pleural space pressure is negative, the pleural drainage systems must prevent air entry while draining fluid, pus, blood, or air. There are two primary drainage systems.

The Heimlich one-way valve consists of a flutter valve that is effective for the treatment of pneumothorax. This valve closes when the pressure inside the tubing is less than atmospheric

pressure (during patient inspiration) to prevent entrainment of unwanted air into the pleural space. It opens when the pressure inside the tubing is above atmospheric pressure (during patient exhalation).

The three-bottle system is made up of (1) a water pressure chamber that determines the cmH2O of suction applied relative to the amount of water placed into this chamber, (2) air leak chamber that identifies the presence of air and respiratory variation, and (3) drainage chamber to allow for volume assessment of fluid output.

Recently, digital pleural drainage units have combined the above setup of a pleural drainage unit with the advantage of digital recording and saving of pleural fluid, airflow, and pleural pressure variations. Digital pleural drainage units have recently been incorporated to assist with monitoring of flow and drainage that would help with timing of chest tube removal. Commercially available digital pleural drainage units are Thopaz™ (Medela, Switzerland) and Atmos™ (Atmosmed, Allentown, PA, USA).

AIRFIX™ was the first digital chest tube airflowmetry used to quantify postoperative air leak. AIRFIX™ measurement device is based upon a "mass airflow sensor" with a specially designed software package and an embedded data acquisition system. The device was used in 204 patients after lung surgery, connected in line with chest tube. The definitive amount of leakage was displayed and recorded as milliliter leakage per breath (mL/b) and milliliter leakage per minute (mL/min). To validate the system, the leakage was compared with the simultaneous intraoperative spirometry and leak measurement. Almost identical values were observed. A total of 7269 measurements were performed (~ 35.76 measurement/patient). In that study, 26 out of 174 patients with no visible air leak on days 2–5 postoperatively had measureable air leak digitally into the seventh postoperative day. In 31 patients, air leak was digitally measureable beyond the seventh postoperative day. The researchers were able to quantify air leak with different breathing maneuvers (tidal breathing, deep breathing, and coughing) and with different levels of applied suction (−12 cmH2O, −20 cmH2O, and Heimlich valve). They concluded that the device could be introduced in algorithms for evaluation and treatment of air leaks.

DigiVent™ chest drainage system was the first, commercially available, drainage system. Dernevik et al. published their experience with the system in postoperative patients. The evaluation process involved three steps: (1) clinical use in five patients, (2) management and acceptance in 15 patients, and (3) reliability and routine use in 50 patients. Dernevik et al. noted the positives of the system to include the ability to quantify air leak, precise measurements of applied negative pressure, and measurement of respiratory variation or "swings." By the end of their study, they replaced their conventional pleural drainage units with the DigiVent™. Small studies comparing digital systems to analog systems showed reduced time to chest tube withdrawal using digital systems suggesting reduced hospital stay. The Thopaz™ digital system was found to be user-friendly and helped survey respondents in making objective and scientific decisions. In a pilot study digital pleural units (Thopaz)™ in 13 medical patients with pneumothorax, the researchers concluded that using digital devices in pneumothorax may be a tool in decision making.

In a recent single-center, randomized, controlled, open-label trial comparing digital versus analog pleural drainage units with and without air leak after lung resection, there was no difference between the median duration of chest tube drainage and the median length of hospital stay regardless of presence or absence of air leak. Similar results were observed in the air leak group. Nevertheless, the clamping trials in the digital group were significantly less in the presence or absence of air leak. The researchers concluded that digital devices didn't impact the duration of chest tube drainage, and hospital stay was not statistically significant even after stratifying by postoperative air leak status.

In conclusion, digital pleural drainage systems have the potential to reduce the duration of postoperative air leak as well as benefit patients with primary or secondary spontaneous pneumothorax. Digital units have the advantage of digital monitoring and displaying airflow per minute

and improve the interobserver reliability in assessing and quantifying the presence of air leak. Further larger studies are needed to evaluate the utility of digital units.

Summary

Over the past several years, it has been established that small-bore chest tubes have become the mainstay for management for the spectrum of diseases to include pneumothorax, parapneumonic effusions, and empyema. The use of the indwelling tunneled pleural catheter continues to demonstrate a significant impact in the quality of life in management of the recurrent symptomatic malignant pleural effusion as well as the extended use in benign recurrent symptomatic pleural effusion as well. Ongoing progress with establishing validated tools to standardize training and competency in procedural training specifically for chest tube placement is proving to be promising. Digital drainage systems may provide improved accuracy in assessing air leaks and assisting with management decisions for this patient population.

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Part VI

Interventional Bronchoscopy in Asthma and Emphysema

Endoscopic Methods for Lung Volume Reduction

31

Luis M. Seijo Maceiras

Introduction and Definition of the Procedure

Pulmonary emphysema is a chronic, debilitating, often fatal disease, characterized by progressive destruction of the lung parenchyma, hyperinflation, reduced lung elasticity, and impaired gas exchange. Patients with severe emphysema complain of progressive dyspnea as the hyperinflated lung becomes entrapped in a rigid chest wall. Medical treatment of emphysema offers limited symptomatic relief but has failed thus far to improve survival. Lung volume reduction surgery, a therapeutic option in advanced emphysema, while successful in a selected group of patients, is associated with considerable morbidity and mortality [1]. The landmark National Emphysema Treatment Trial (NETT) found a striking improvement in survival in patients undergoing surgery with upper lobe predominant emphysema and poor exercise tolerance [1]. Despite such promising findings, the NETT may be credited with a widespread reluctance to refer patients for the procedure because of the reported 5% mortality, which was alarmingly high in some high-risk patients [2]. Furthermore, 50% of the patients in the surgical arm suffered from prolonged hospitalizations, air leaks, and/or infection. Consequently, only 538 procedures were reported in the USA in an 8.5 year time period between 2003 and 2011 [3].

Pulmonologists have been searching for a minimally invasive alternative to lung volume reduction surgery for years. The promise of a technique or device capable of reproducing the benefits of the surgical procedure without incurring the side effects, mortality, and morbidity of surgical lung volume reduction is appealing for obvious reasons. Not surprisingly, interest in endoscopic lung volume reduction (ELVR) peaked after the NETT findings were made public. In general, ELVR can be defined as a minimally invasive bronchoscopic procedure devoted to the reduction of total or regional lung volumes in patients with severe emphysema and profound dyspnea [4]. Some procedures rely on device insertion, including endobronchial valves, coils, and bypass stents, while others instill bioactive substances such as a polymer or water vapor with identical therapeutic intentions. The methods are diverse but are usually applied using the flexible bronchoscope under deep sedation or general anesthesia. Most procedures last less than 1 h and may target one or both lungs. Patients may undergo pulmonary rehabilitation prior to treatment and must be on standard medical therapy for COPD, including bronchodilators and occasionally low-dose steroids. In general, patients

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with frequent exacerbations are excluded as they may be at greater risk for complications following device implantation.

Historical Perspective

Pioneers of ELVR focused on obtaining improvements in lung function and seeking measurable lung volume reduction, essentially attempting to reproduce surgical results [5]. However, the paradigm has shifted back and forth as failure to obtain significant lung volume reduction despite improvements in quality of life made many investigators weary of attempting to match surgical outcomes. Also, while ELVR was initially reserved for ideal surgical candidates with upper lobe predominant emphysema, subsequent studies have included patients with homogeneous emphysema as well as patients with heterogeneous emphysema not necessarily upper lobe predominant.

The role of computed tomography (CT) has also widened. It was originally limited to patient selection but has become a useful tool for follow-up since it can quantify regional lung volume changes in the absence of overall lung volume reduction. Collateral ventilation, a major limitation of many ELVR approaches, has also been studied with CT [6]. A recent multicenter European study demonstrated that fissure analysis by CT correlates well with endoscopic collateral ventilation measurements [7]. If fissure integrity on CT analysis is >95%, collateral ventilation can be considered negligible [8]. Such analysis may improve patient selection for a given procedure since valve treatment success is highly dependent on the absence of collateral ventilation, while other methods of ELVR are not.

Indications and Contraindications

Endoscopic lung volume reduction is indicated for a highly selected group of patients with advanced emphysema. Originally, ELVR was reserved for patients with upper lobe predominant disease (Fig. 31.1). However, indications for ELVR have widened to include a more diverse population of patients suffering from emphysema in response to the recent proliferation in techniques and devices. New approaches have led to broader indications, including patients with homogeneous emphysema, alpha-1 antitrypsin deficiency, or lower lobe predominant disease.

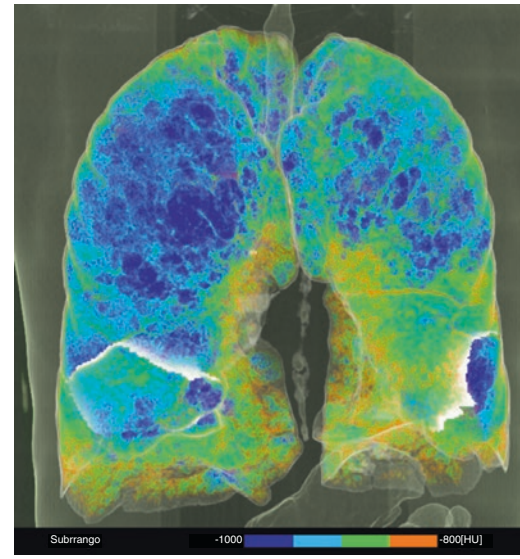

Fig. 31.1 CT reconstruction of a patient with upper lobe predominant emphysema (Diseased lung is represented in *blue*). This patient with an FEV1 of 0.73 L (24% of predicted) was a candidate for endoscopic lung volume reduction, but a hereditary cardiomyopathy, frequent exacerbations, and pulmonary hypertension were considered contraindications to the procedure

In general, candidates for ELVR must suffer from severe emphysema and moderate to severe dyspnea despite optimal medical therapy. Patients with alpha-1 antitrypsin deficiency have been excluded from clinical trials, although as with other indications, ongoing trials are investigating the role of ELVR for those patients, including the use of coils and valves (NCT02273349 and NCT01357460), and at least one small series showed significant benefit from ELVR in that setting [9]. Ideal candidates for ELVR must be ambulatory and capable of walking at least 100 m with or without supplemental oxygen during a 6 min walk test. They must

abstain from smoking and demonstrate severe obstruction on spirometry as well as air trapping and hyperinflation on plethysmography. ELVR should probably not be attempted in patients with residual volumes <175% of predicted. Patients with extremely low diffusing capacities, as well as those with severe gas exchange abnormalities, especially hypercapnic patients, are not considered good candidates for ELVR. Giant bullous or reactive airways disease, severe pulmonary hypertension, frequent exacerbations, or major medical comorbidities are also considered important contraindications. Patients with coexisting bronchiectasis, especially those colonized by *P. aeruginosa*, should not be treated, while patients with FEV1s less than 20–25% of the age-adjusted predicted value are generally not treated. Also, elderly patients have generally been excluded from clinical trials, so outcomes of ELVR in patients older than 75 are uncertain. Most procedures are performed under general anesthesia or deep sedation, so patients unable to tolerate either cannot be treated. One should keep in mind that each device or technique designed to achieve ELVR is unique, so indications, patient selection, and/or treatment strategy (i.e., unilateral vs. bilateral treatment) may vary.

Description of the Equipment Needed

ELVR can be performed in a variety of hospital settings. Many procedures are performed in the bronchoscopy suite and do not require special equipment beyond that which can generally be found in a well-stocked unit. A diagnostic or therapeutic flexible bronchoscope may be used, depending on the method chosen. Devices tend to require the larger 2.8 mm channel of the therapeutic bronchoscope. Vapor-induced ELVR requires special equipment unique to this procedure.

In general, deployment of most devices, including valves, is straightforward for an experienced bronchoscopist and requires little additional training (Fig. 31.2). That notwithstanding, valve removal can be quite challenging if not impossible in some cases. Coil therapy is best performed under fluoroscopic guidance, a technique familiar to many bronchoscopists who perform transbronchial biopsies or stent implantation. Some bronchoscopists use the Chartis™ system in order to assess fissure integrity and collateral ventilation, but others rely on CT scan data. Finally, some bronchoscopists prefer to treat

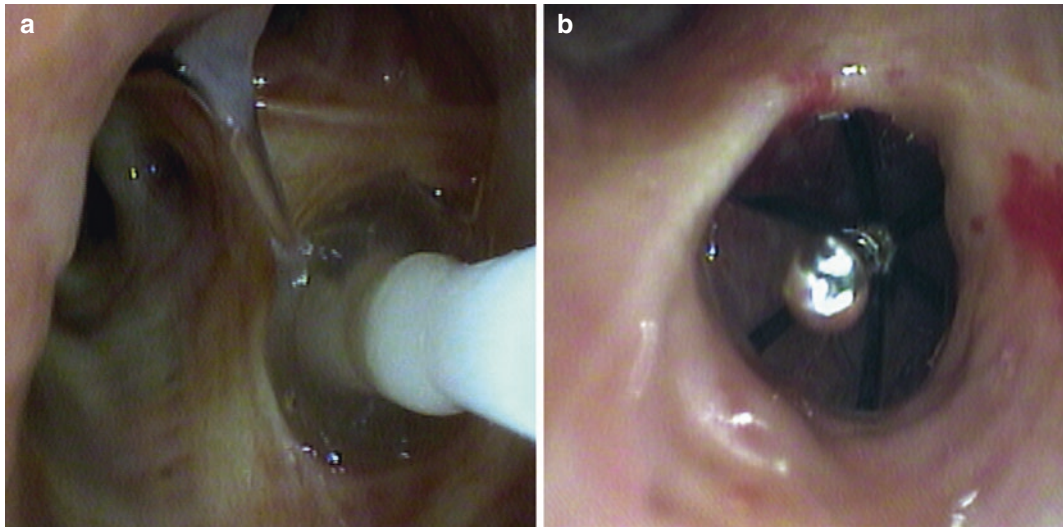

Fig. 31.2 Balloon calibration (**a**) and placement (**b**) of an IBV device in a patient with severe upper lobe predominant emphysema

patients under general anesthesia using the rigid bronchoscope or an endotracheal tube. Anesthesia support is mandatory in such cases, while others prefer conscious sedation which may be administered by the endoscopic team.

Evidence-Based Review

Endobronchial Valves

Endobronchial valves were among the first devices to be developed for ELVR. They have been widely studied, and results from well-designed randomized trials are available and continue to enrich our understanding of how ELVR might benefit selected patients with severe emphysema. The landmark VENT, a multicenter randomized controlled trial, demonstrated that endobronchial valves can achieve modest statistically significant improvements in a variety of endpoints, including lung function, exercise capacity, and quality of life [10]. The study was completed in 2007 and enrolled 321 patients. It compared the safety and efficacy of endobronchial valve therapy employing a unilateral lobar approach in patients with heterogeneous emphysema with optimal medical care. Despite achieving statistical significance, the results were considered by many, including the FDA, underwhelming [11]. Improvements in FEV1 (60 mL), the 6 min walk distance (19 m), and reductions in the SGRQ scores with treatment (3.4 points) have been considered by some clinically insignificant. Careful scrutiny of VENT results, however, left much room for optimism. Improvements in the BODE index, more common among valve treated patients, are provocative since this index correlates well with prognosis in COPD [12]. In addition, patients with complete fissures who achieved a greater than 50% reduction in lobar volume demonstrated clinically relevant improvements in FEV1 (23%) which may have survival implications as demonstrated in a subsequent report from a group of investigators using the same valves as the VENT [13]. These authors found a survival benefit in a small cohort of patients among those who achieved atelectasis at the expense of more pneumothoraces, suggesting that ELVR may match surgical results in some patients with heterogeneous emphysema. A recently published study by Davey et al. confirmed the hypothesis that patients with intact interlobar fissures benefit from ELVR using endobronchial valves [14]. In that randomized, sham-bronchoscopy controlled trial, unilateral lobar occlusion with endobronchial valves placed in patients with heterogeneous emphysema and intact interlobar fissures as measured by CT was associated with significant improvements in lung function and quality of life. Results of the STELVIO randomized trial which assessed collateral ventilation using the Chartis™ system provided further evidence supporting this strategy [15]. In that study, patients treated with endobronchial valves showed a statistically significant benefit from valve treatment with improvements in FEV1, FVC, and 6MWT distance that were clinically relevant. The overall responder rate was 75% when the interlobar fissure was largely intact precluding significant collateral ventilation.

In its ruling denying approval for the Zephyr device (Fig. 31.3) employed in the VENT (a self-expanding nitinol stent with a silicon one-way duckbill valve), the FDA expressed concern regarding the complications of ELVR, including a major increase in the number of hospitalizations for COPD exacerbations in the treatment arm (17 vs. 1) and other complications such as hemoptysis [11]. Fear of the risks undermined the modest benefits of the trial. As a result, more research was requested. Such research is ongoing, including trials investigating patient selection and collateral ventilation, ELVR with valves in patients with less severe obstruction, and treatment of patients with homogeneous emphysema. Furthermore, two studies including long-term follow-up of patients treated with endobronchial valves have shown a significant survival benefit in ELVR responders [13, 16]. An ongoing German multicenter study (NCT01580215) is evaluating long-term follow-up with survival of 5 years posttreatment as a key outcome.

Results from a randomized sham-bronchoscopy controlled trial using the Spiration IBV system (an umbrella-shaped, self-expanding

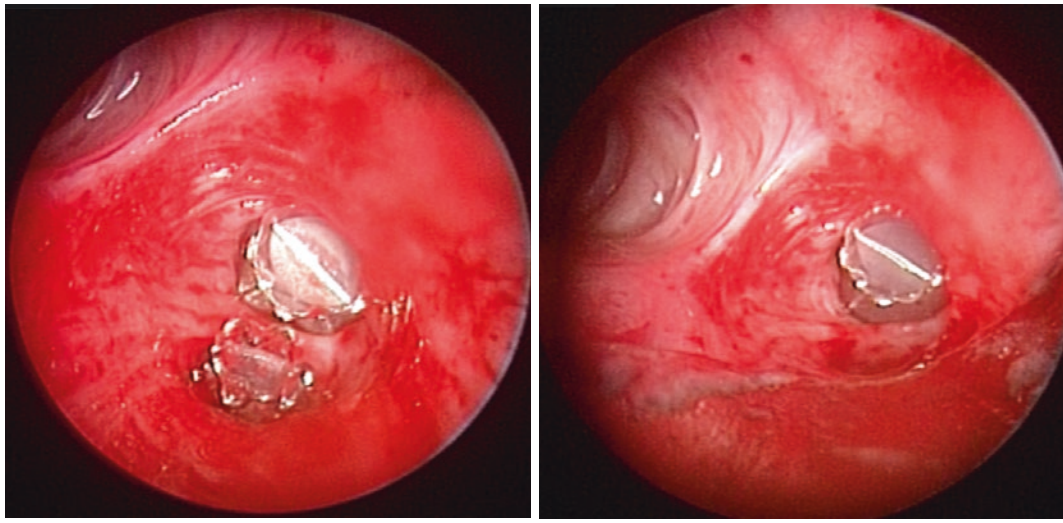

Fig. 31.3 Duck-billed shaped endobronchial valves (Zephyr). Courtesy Dr. Dutau

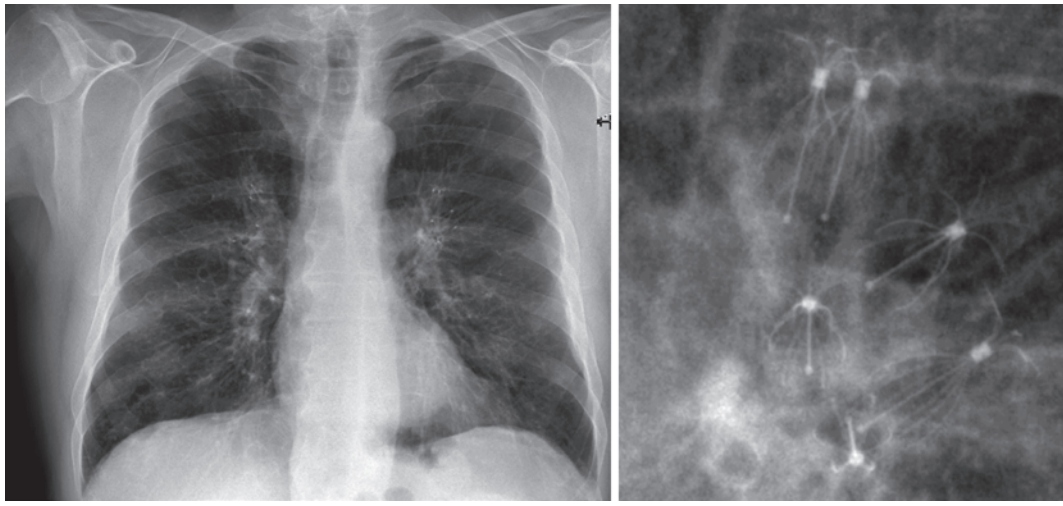

Fig. 31.4 Chest radiograph of a patient with upper lobe predominant severe emphysema treated with ten endobronchial valves (IBV). The characteristic umbrella-shaped valves can be seen in both upper lobes. Lobar occlusion was avoided in this patient

device) were reported some years ago (Fig. 31.4). This smaller trial kept patients blinded for 3 months [17]. The treatment strategy differed significantly from the VENT, since it focused on a bilateral approach purposefully avoiding lobar occlusion by sparing a segmental or subsegmental bronchus in the right upper lobe as well as the lingula on the left side. The trial failed to achieve clinically relevant improvements in hard outcomes such as FEV1, gas exchange, or exercise capacity but demonstrated statistically significant improvements in a combined endpoint including quality of life and regional lung volume changes as measured by CT. At the conclusion of the Spiration trial, 31% of the treated patients demonstrated an improvement of 8 points in the SGRQ score and a significant regional lung volume reduction in the treated upper lobes. The

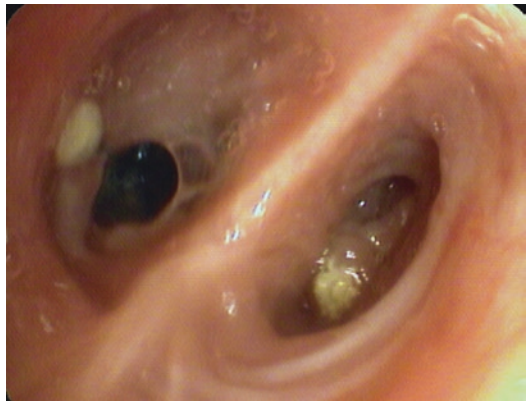

Fig. 31.5 Endobronchial valves (IBV) in the right upper lobe 3 years after deployment

companion and larger US trial using the IBV system but prolonging blinded follow-up to 6 months was also underwhelming [18]. In that trial, only 6 out of 121 patients in the treatment arm were considered responders. Although lobar volume changes were significantly better in the treated arm vs. control (−224 mL vs. −17 mL), there were no significant differences in quality of life as measured by the St. George's Respiratory Questionnaire. As expected, serious adverse events were more common in the treatment group (14.1%) compared with the control group (3.7%), although most were neither procedure nor device related (Fig. 31.5). The disappointing results of the bilateral approach avoiding lobar collapse coupled with demonstrable improvements by responders with intact fissures treated with the lobar occlusion method have rendered the strategy used in the Spiration trials obsolete. Interestingly, a pilot trial seeking lobar occlusion found significant improvements in lung function and more impressive reductions in SGRQ scores in patients who achieved atelectasis with the IBV system [19]. The risks associated with this complication motivated the subsequent change in treatment strategy. However, it is clear from the available evidence that while avoiding atelectasis improves safety, it does so at the expense of efficacy. The ongoing EMPROVE study (NCT01812447) will explore the efficacy of the IBV system using the unilateral complete occlusion approach.

Perhaps the most striking finding of the Spiration trials was the impressive magnitude of the placebo effect. Many patients undergoing sham bronchoscopy reported significant benefits in quality of life. Such findings match results from a bronchial thermoplasty trial employing sham bronchoscopy [20]. Clearly, the placebo effect has a significant impact in device-related interventions and should be taken into account in trials using soft endpoints such as quality of life as the primary outcome.

Airway Bypass Tracts

While most ELVR techniques are designed to promote lung volume reduction by limiting flow to the most affected lung parenchyma, Broncus (Mountain View, CA) developed a technique which reduces air trapping by promoting nonanatomic collateral flow. This method of ELVR is known as the Exhale™ emphysema treatment system shunned atelectasis, currently an essential goal of valve treatment, striving instead to create airway fenestrations in order to facilitate exhalation of trapped air. A Doppler system was used in order to avoid damaging major vessels and select the appropriate site for stent deployment using a needle. This approach reduced end-expiratory volume without altering lung recoil and could be tested in patients with both homogeneous and heterogeneous emphysema.

Preliminary evidence treating explanted lungs was quite encouraging. Improvements in FEV1 following deployment of multiple stents in one small study of 12 explanted lungs were dramatic [21]. Outcomes in vivo however were frustrating, mostly as a consequence of stent occlusion by granulation tissue. Drug eluting stents have been created to avoid this complication and seem to work in animal studies, prolonging patency [22]. An open-label study of the drug-eluting stents showed that the Exhale™ system can reduce hyperinflation for a limited time in a selected group of patients with severe emphysema [23]. Unfortunately, while results at 1 month were impressive including improvements in FEV1, quality of life, and total lung capacity in more

than 30 treated patients, results at 6 months were less encouraging. Post-procedure complications including COPD exacerbations were relatively frequent, and one patient died as a consequence of massive hemoptysis induced by stent implantation.

The Exhale™ system was used in a multicenter randomized, sham-bronchoscopy controlled trial known as EASE (Exhale Airway Stents for Emphysema) [24]. Three hundred and fifteen patients with severe hyperinflation defined as a ratio of residual volume to total lung capacity of ≥0.65 from 38 centers worldwide were enrolled. Patients were followed for 12 months. Treated patients did not achieve the co-primary endpoints of a 12% improvement in FVC and one-point improvement in the mMRC dyspnea score when compared to controls, though the latter did show a statistically significant improvement. Only 30 out of 208 treated patients met the co-primary endpoint, although a considerable mean reduction in residual volume averaging 0.5 L was achieved in 40% of the treated patients. This finding predicted clinical success. The 6-month composite primary safety endpoint combining five severe adverse events was 14.4% for the treatment arm which compared favorably with 11.2% for the control group and was judged non-inferior. This ELVR technique is currently not available in the USA or Europe [25].

Biologic/Polymer Lung Volume Reduction

Biologic lung volume reduction, unlike its predecessors, was not device based. This method of ELVR, developed by Aeris Therapeutics (Woburn, MA), sought to achieve its goals employing tissue engineering principles [26]. Remodeling of damaged lung parenchyma by the next-generation polymer-based treatment created progressive atelectasis in treated subsegments of the upper lobes, thus promoting true lung volume reduction (Figs. 31.6 and 31.7). The ability of the polymer to spread through the airway limited the impact of collateral ventilation, a major concern with

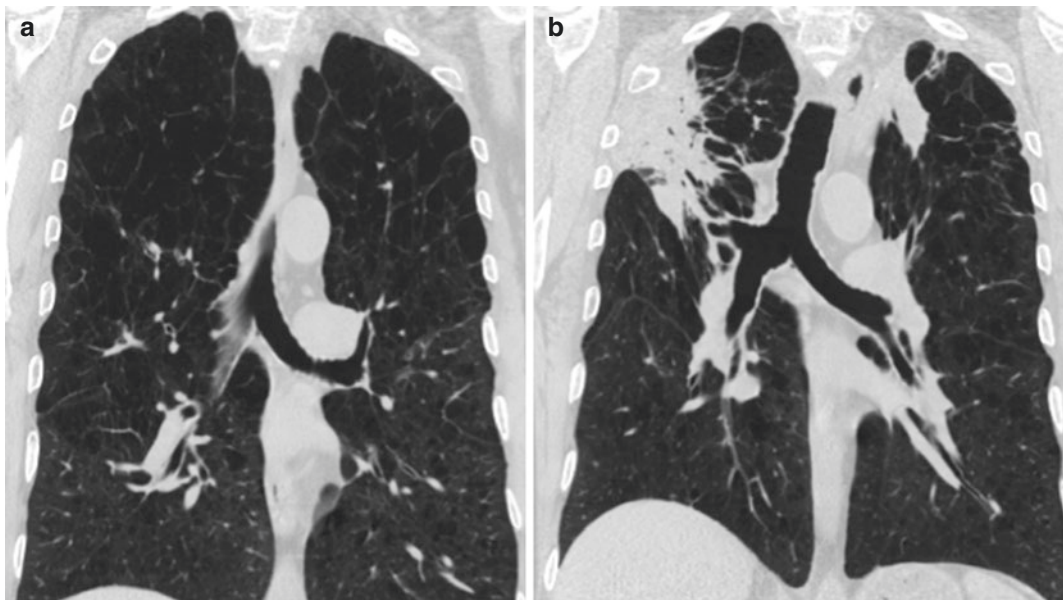

Fig. 31.6 Before (**a**) and after (**b**) coronal CT images of a patient with heterogenous upper lobe predominant emphysema treated with AeriSeal. The patient's FEV1 improved by 69%, his SGRQ score diminished by 8.3 units, and the RV/TLC ratio dropped by 9% (courtesy of Dr. Ingenito)

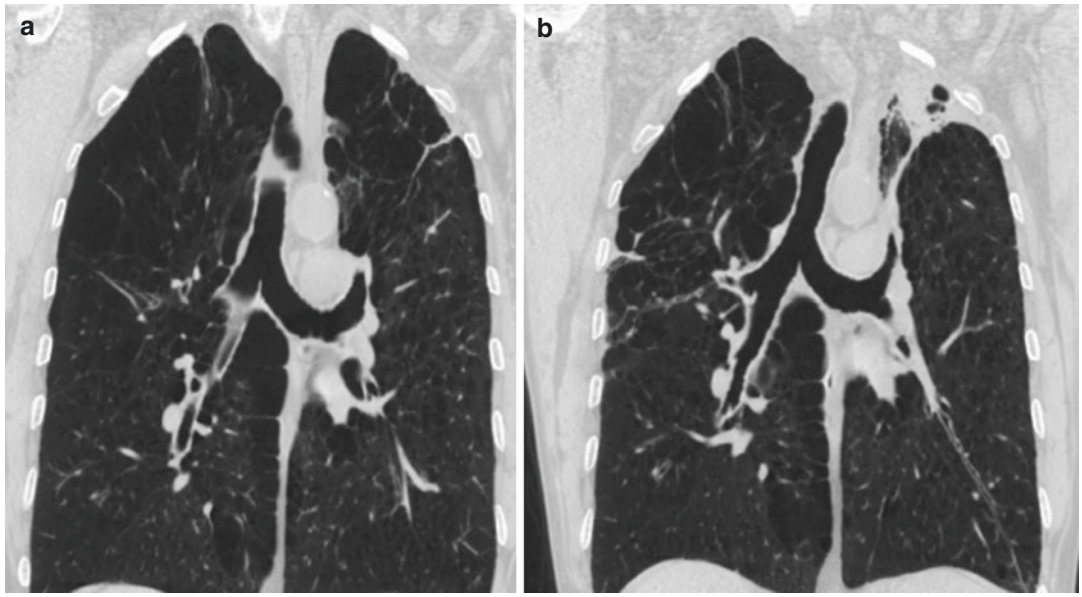

Fig. 31.7 Before (**a**) and after (**b**) coronal CT images of a patient with homogenous emphysema treated with AeriSeal. The patient's FEV1 improved by 29%, his SGRQ score diminished by 8.5 units, and the RV/TLC ratio dropped by 8% (courtesy of Dr. Ingenito)

endobronchial valves. Treatment was found to be irreversible and frequently associated with considerable, though relatively brief, inflammation which mandated prophylactic treatment with steroids and antibiotics, akin to a COPD exacerbation in most treated patients. A preliminary small open-label phase I trial showed the treatment to be safe and moderately effective in a small group of patients [27]. Results from a phase 2 clinical trial enrolling 50 patients were subsequently reported [28]. High-dose therapy was effective in that trial and yielded sustained benefits, but COPD exacerbations were frequent, occurring in 28% of treated patients. A subsequent trial enrolling patients with homogeneous emphysema also showed benefit with high-dose treatment and had a similar safety profile [29]. Evidence from three separate clinical trials demonstrated the benefit of polymer treatment independent of fissure integrity, rendering it a promising option for ELVR in patients with significant collateral ventilation [30]. A prospective multicenter randomized trial of polymer-induced lung volume reduction known as the ASPIRE trial (NCT01449292) was initiated but terminated prematurely for lack of funding. Ninety-five patients had been randomized prior to study termination. FEV1, dyspnea scores, and quality of life showed improvements at 3 months following treatment. The benefit was sustained at 6 months, but unfortunately 44% of treated patients required hospitalization, and two deaths were reported ($p = 0.01$) [31]. The premature termination of the study was a blow to the technique, but following the acquisition of Aeris Therapeutics by Pulmonx, AeriSeal® received CE mark approval at the end of 2015 and is currently pending re-introduction in 2016 (Fig. 31.8).

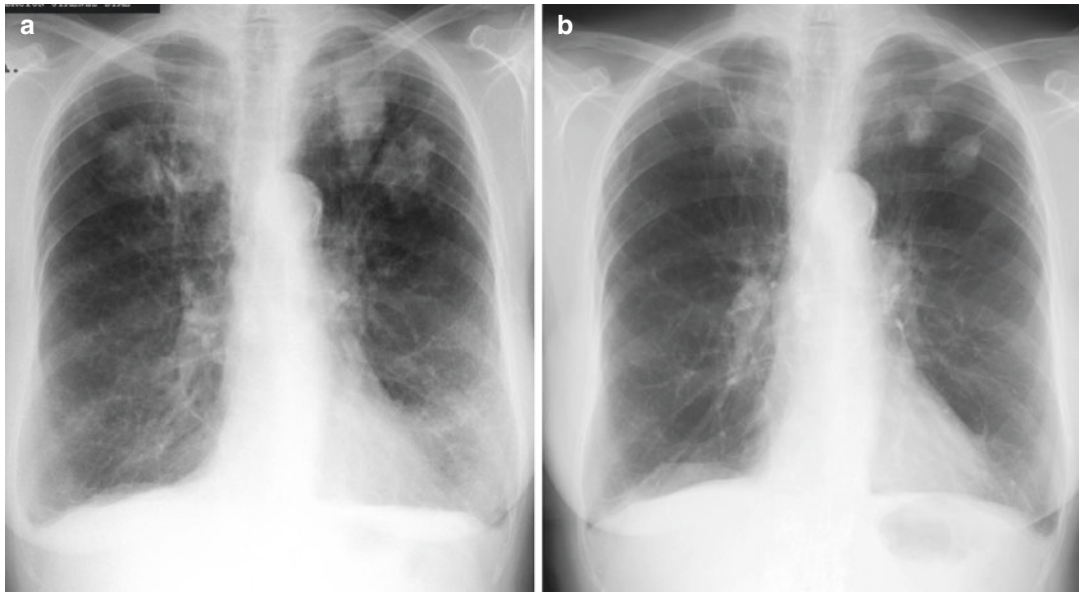

Fig. 31.8 Chest X-rays of a patient with upper lobe predominant emphysema and collateral ventilation treated with AeriSeal, immediately following ELVR (**a**) and after 3 years of follow-up (**b**). Radiographic changes persist and evolve overt time complicating radiographic surveillance

Coils

Nitinol self-actuating reduction coils (PneumRx Inc.; Mountain View, CA) have been developed as an alternative method of ELVR. Nitinol's shape memory is ideally suited for this application since it facilitates deployment of the coils using a small caliber catheter (Fig. 31.9). Once deployed, the coils recover their preformed shape retracting the surrounding lung tissue, and therefore reducing lung volumes. Initial reports demonstrated the feasibility and relative safety of the procedure [32, 33]. The RESET trial, a randomized controlled trial enrolling 47 patients, reported coil-related statistically significant improvements in quality of life [34]. A subsequent multicenter trial enrolling 60 patients confirmed sustained benefit at 1 year following ELVR with coils [35]. The treatment strategy was bilateral in most patients deploying a median of 10 coils per treated lobe. Serious adverse events were common, however, occurring in 18 patients (30%) including COPD exacerbations, pneumonia, pneumothorax, and hemoptysis (Fig. 31.10). Clinically relevant improvements in SGRQ scores (−11.1 ± 13.3 points) and 6 min walk tests (+51.4 ± 76 m) were observed at 12 months. Lung function improvement was not as impressive with FEV1 improving marginally at 1 year (+0.11 ± 0.30 L) despite an impressive reduction in residual volumes (−0.71 ± 0.81 L).

Evidence from two randomized controlled trials is now available. The REVOLENS trial reported a 36% responder rate for patients treated with coils based on changes in 6 min walk distance as compared to an 18% responder rate in the usual care group ($P = 0.03$) [36]. However, no difference in FEV1 was found comparing both groups and only a slight difference in quality of life, which accounted for a disappointing

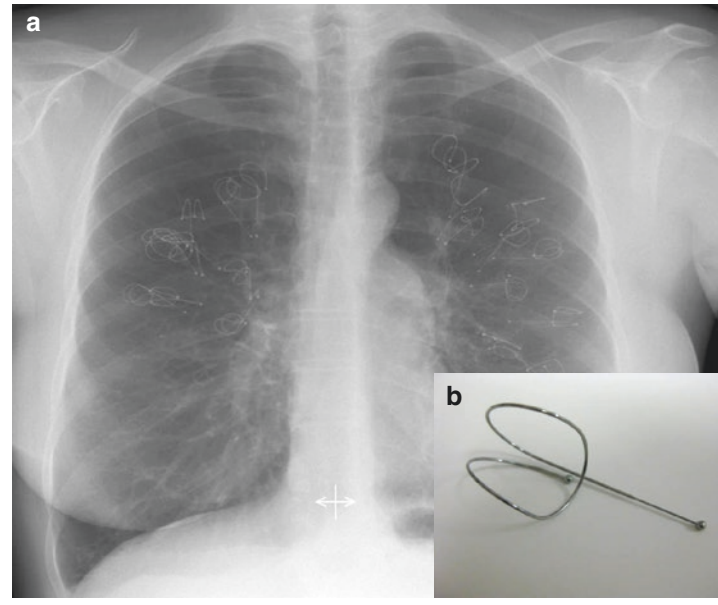

Fig. 31.9 Chest radiograph of a patient treated with the pneumRx coils (**a**). The coil in more detail (**b**)

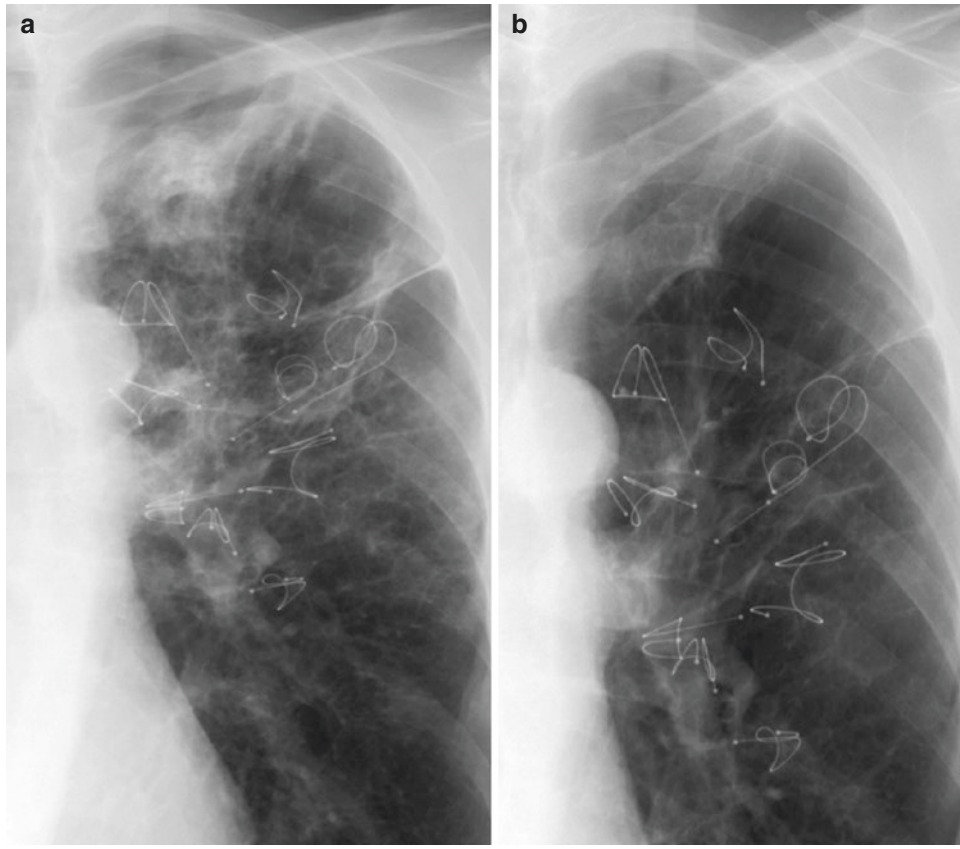

Fig. 31.10 Chest radiographs of a patient treated with coils. Symptomatic pneumonia developed in the treated right upper lobe (**a**). The infection subsided after appropriate antibiotic treatment (**b**)

cost-effectiveness assessment of $782,598 per additional quality-adjusted life-year. Results of the larger RENEW (NCT01608490) trial were recently reported [37]. The RENEW trial enrolled 315 patients. Those treated with coils showed a statistically significant though clinically underwhelming improvement of 10 m in the 6 min walk test (6MWT) at 12 months when compared to a control group. Clinically meaningful improvements in SGRQ scores and lung function were reported. The authors concluded that the use of endobronchial coils compared with usual care achieved only a modest improvement in median exercise tolerance of uncertain clinical significance, with a higher likelihood of major complications.

Other Methods of ELVR

Bronchoscopic thermal vapor ablation (Update Medical Inc.; Seattle, WA) has been studied as yet another method of ELVR. Conceptually akin to the polymer treatment, thermal ablation seeks to create inflammation and subsequent atelectasis of a treated diseased lobe thereby promoting lung volume reduction. A small multicenter trial enrolling 44 patients with upper lobe predominant emphysema reported sustained benefits in quality of life, lung function, and exercise tolerance at 1 year [38]. However, serious adverse events occurred in 53% of patients, chief among them COPD exacerbations. Results from the STEP-UP trial (NCT01719263) enrolling 70 patients were recently published [39]. The mean relative improvement in FEV1 favoring the treatment group was +14.7%. Mean SGRQ scores were also improved in the treatment arm by 9.7 points. COPD exacerbations were once again common in the treatment arm occurring in 24% as compared with 4% of the control group, accounting for one death possibly related to treatment. The study investigators claimed that targeted thermal vapor ablation offers clinically meaningful and statistically significant improvements in lung function and quality of life at 6 months, with an acceptable safety profile.

Summary and Recommendations

A growing body of evidence suggests that ELVR is reasonably safe and can offer modest regional or total lung volume reduction and significant improvements in quality of life in carefully selected patients with severe emphysema. However, lung volume reduction surgery outcomes cannot be expected with established approaches to ELVR. ELVR should not be considered an alternative to LVRS. Unfortunately, clinically relevant efficacy is lacking or underwhelming for most procedures, and as a general rule, randomized trial data show marginal benefit in key outcomes while highlighting the risks associated with some methods of ELVR as evidenced by serious adverse events in the treatment arm of several randomized trials. Patient selection must be optimized, treatment strategies refined, and safety on a broader scale confirmed before ELVR can be considered standard of care for selected patients with severe emphysema. The placebo effect, a powerful confounder in studies focusing exclusively on soft outcomes such as quality of life, must be accounted for. Although modest gains in such endpoints may be considered a relative success of ELVR therapies since they often exceed those achieved with bronchodilators, I believe we should continue to strive for improvements in lung function and survival [40, 41]. Only then will device-related complications or significant increases in morbidity become acceptable in this patient population.

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32 Bronchoscopic Lung Volume Reduction with Endobronchial Valves

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Abbreviations

6MWD	Six-minute walk distance
AATD	Alpha-1 antitrypsin deficiency
BLVR	Bronchoscopic lung volume reduction
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
CV	Collateral ventilation
D_LCO	Diffusing capacity of the lung for carbon monoxide
EBV	Endobronchial valve
ELVR	Endoscopic lung volume reduction
FEV_1	Forced expiratory volume during the first second
FVC	Forced vital capacity
GOLD	Global initiative on lung disease
HI	Heterogeneity index
HRCT	High-resolution computed tomography
HS	Heterogeneity score
HU	Hounsfield unit

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IC	Inspiratory capacity
IP	Inspiratory pressure
LAA -856_E	Percentage of low attenuation areas ≤856 HU in the lung on expiratory CT
LAA -950_I	Percentage of low attenuation areas ≤950 HU in the lung on inspiratory CT
LAA	Low attenuation area
LVR	Lung volume reduction
LVRS	Lung volume reduction surgery
MDCT	Multidetector computed tomography
MMP	Matrix metalloproteinase
MRI	Magnetic resonance imaging
NETT	National Emphysema Treatment Trial
QCT	Quantitative computed tomography
RCT	Randomized controlled trial
RUL	Right upper lobe
RV	Residual volume
SGRQ	Saint George's Respiratory Questionnaire
SPECT	Single photon emission computed tomography
TLC	Total lung capacity
TLVR	Total lung volume reduction
VATS	Video-assisted thoracic surgery
WHO	World Health Organization

Introduction

In the past 12 years, advancements in the treatment of lung emphysema have been intrinsically linked to interventional bronchoscopy. The expression "bronchoscopic lung volume reduction," or BLVR, has become an umbrella term that encompasses several techniques, including valves, stents, thermal ablation, coils, and fibrin sealants.

The present chapter will be dedicated to the most studied BLVR technique, the endobronchial valve (EBV), covering relevant aspects for effective treatment, historical aspects, state of the art of EBV therapy, and challenges for EBV therapy. Finally, the authors' 14 years of experience with EBVs will be discussed with an emphasis on the lessons learned during this period.

Contextualizing Chronic Obstructive Pulmonary Disease and Emphysema

Data from the World Health Organization (WHO) show that chronic obstructive pulmonary disease (COPD) was the fourth among the ten leading causes of death (by percentage) in the world in 2012 [1]. By 2020, COPD is expected to have climbed to the third position in this tragic ranking, as a result especially of the increase in the number of smokers in developing countries and of the world population aging. COPD is also the only chronic disease with increasing mortality. Among different types of COPD, lung emphysema accounts for 1.5–2% of deaths/year worldwide (45,000 cases in year 2000) [2].

COPD is mainly caused by cigarette smoking, but not all smokers develop COPD. This suggests possible genetic differences in susceptibility to adverse events [3]. These differences, as well as particular aspects of specific COPD phenotypes, have not been taken into account for drug development, and thus the existing drug therapies for COPD are still insufficient to improve the quality of life of affected individuals. In turn, surgical treatments (lung volume reduction surgery or lung transplant) have their own limitations and are not capable of meeting the growing demand of emphysema patients [4]. The development of BLVR techniques has served to propel the knowledge regarding complex pathophysiological aspects that still challenge the success of emphysema treatments.

Pathophysiology of Emphysema

The loss of elastic recoil associated with destruction of the lung parenchyma distally to terminal bronchioles, without evident fibrosis, is the most widely accepted definition of emphysema. In smokers, emphysema results from an imbalance between proteases released by neutrophils and liver antiproteases. The number of macrophages is increased in the region of terminal bronchioles, the area originat-

ing the centrilobular emphysema that is typical in smokers. It is likely that alveolar macrophages play a pathologic role, expressing potent elastolytic enzymes, cathepsins, and matrix metalloproteinases (MMPs), which are induced by smoking. The comparison of bronchoalveolar lavage from patients with and without COPD clearly shows the increased expression of proteases in alveolar macrophages of emphysema patients [5].

A specific cause of emphysema is severe alpha-1 antitrypsin deficiency (AATD), which predisposes to early development of air trapping particularly in smokers. This inherited autosomal condition involves a mutation in the SERPINA1 gene. The prevalence of severe AATD ranges from approximately 1/2000 to 1/5000 based on population screenings [6]. Emphysema is often heterogeneous and typically affects the lower lobes first. In AAT-deficient patients, fissures are generally much better preserved than in "ordinary" emphysema patients.

There seem to be no reasons to exclude AATD from BLVR [7]. In 12 AATD patients followed up for at least 1 year, FEV_1 increased (mean, 54%), the quality of life was improved, and two patients were taken off oxygen therapy. During the 4-year follow-up, no significant deterioration was detected in lung function [7].

Finally, non-pulmonary issues, such as undernutrition and depression, also play a detrimental role in emphysema pathophysiology [2].

The Emphysematous Lung

The hallmark symptom of emphysema is breathlessness (dyspnea) on exercise (37% prevalence) [8]. Parenchymal destruction causes a decrease in the effective surface area of gas exchange and adjacent regions, leading to expiratory collapse of the small bronchioles and increase in airflow resistance and consequently dynamic hyperinflation. The impairment of expiratory airflow and the resulting air trapping produce dyspnea.

One of the most deleterious consequences of emphysema is the unusual lowering of the diaphragm, leading to respiratory pump dysfunction. Derangement of respiratory mechanics restricts chest wall compliance and further aggravates the function of respiratory muscles. In emphysema, static and dynamic hyperinflation greatly impacts quality of life and survival.

Small Airway Disease

The notion that the inflammatory process affecting small airways could be a prognostic indicator of functional response after LVRS finds support in the work of Kim et al. [9]. That study identified an important correlation between the absence of wall thickening in 2 mm airways and the functional response 6 months after LVRS.

Perera et al. [10] were the first to describe the behavior of inflammatory biological markers collected in the blood or in the airway as a means to diagnose COPD and consequently as a means of screening patients to initiate early treatment with antibiotics and corticosteroids. Interleukin-6 seems to play an important role as a marker of COPD.

Emphysema and small airway disease are the major determinants of chronic airflow obstruction in smokers. Quantitative CT (QCT) is the procedure of choice to study various combinations of these two types of structural changes, contributing to the recognition and description of COPD phenotypes [11].

Grydeland et al. studied the relationship between diffusing capacity of the lung for carbon monoxide (D_LCO) and airway wall thickness. Reduced levels of D_LCO have traditionally been linked to the emphysematous phenotype rather than the chronic bronchitis phenotype. In that study, a significant positive association was detected between CT-measured airway wall thickness and D_LCO in COPD patients. Associations were less convincing in the non-COPD group [12]. We foresee that small airway disease will soon be added as a criterion to select candidates for bronchoscopic emphysema treatments.

Lung Perfusion

Changes in vascular bed may anticipate pronounced alveolar wall destruction. A pig model of elastase-induced emphysema used single photon emission computed tomography (SPECT) to

show that vascular perfusion is reduced before the establishment of early emphysematous changes in lung parenchyma [13]. Blood flow is significantly diverted from inflamed lung. The decrease in both pulmonary and bronchial blood flow affects clearance of aerosol and noxious particles, contributing to inflammation. Abnormal lung perfusion may be a primary, rather than a secondary, phenomenon in the pathogenesis of emphysema [14].

Heterogeneity

Heterogeneity is among the most widely used parameters to assess LVR in emphysema patients, thanks to the NETT, which defined subgroups (phenotypes) based on emphysema heterogeneity. Patients with predominance of air trapping in upper lobes associated with low exercise tolerance were the best LVRS responders [15].

Heterogeneity in emphysema refers to the extent and spatial distribution of enlarged air spaces distal to the terminal bronchioles, accompanied by destruction of alveolar walls within the lung. Lung segmentation and densitometry measurements have been used extensively to quantify emphysema and determine the degree of heterogeneity. Visual scoring such as used in the NETT has significant interobserver variation, and CT-based analysis of the lung is more accurate to assess heterogeneity.

Using MDCT, emphysema can be quantified as the percentage of LAA ≤ −950 HU (or, depending on the study, −910HU) on inspiratory CT (LAA -950_I). In turn, air trapping is defined as the percentage of LAA ≤ −856 HU on expiratory CT (LAA -856_E). QCT assessments of inspiratory and expiratory LAA correlate with airflow obstruction measured by FEV_1 and FEV_1/FVC. These parameters increase in severity with increasing GOLD stage. In BLVR, heterogeneity index refers to the difference in % lung destruction between the lobe targeted for treatment and the ipsilateral lobe. Patients with high CT-measured heterogeneity index tend to respond better to EBV treatment [14].

In our experience, the best available method to assess heterogeneity and other aspects of the emphysematous lung is the Vida System™, which is based on thresholding to obtain approximate initial lung masks. The system relies on a validated segmentation algorithm to extract information regarding pulmonary lobes from CT images, producing a reliable three-dimensional model of the patient's lung (Figs. 32.1 and 32.2).

Density mask, defined as a given lung density (HU) at full inspiration, is a cornerstone in lung

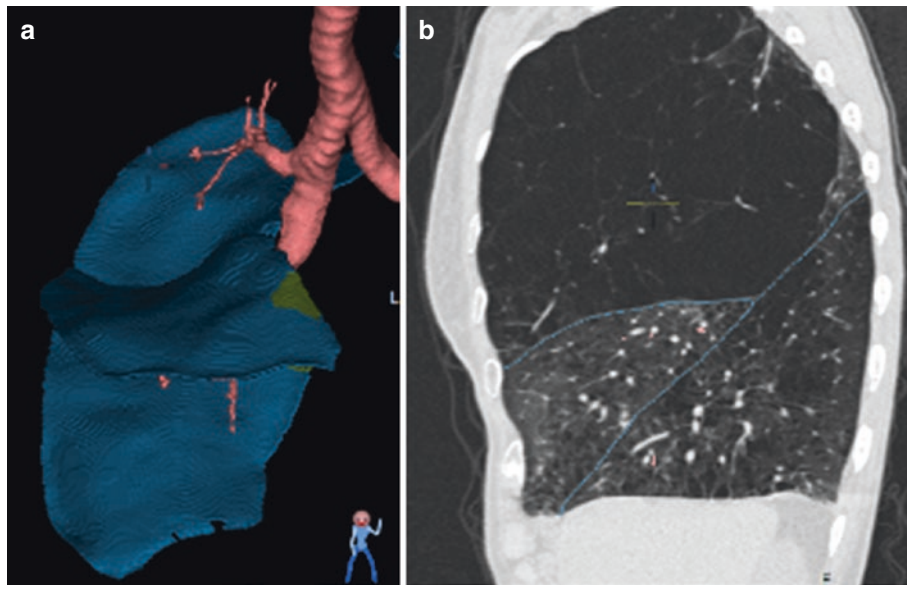
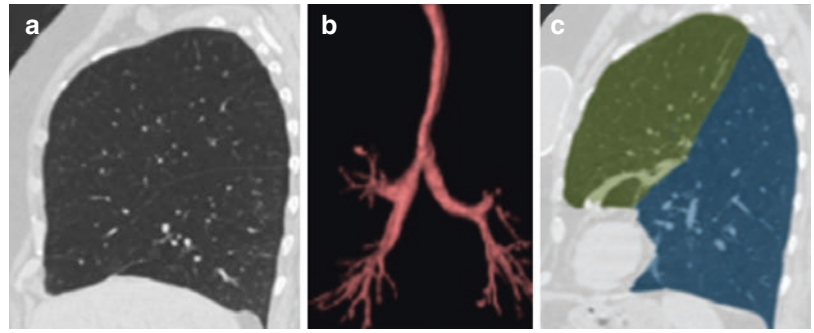


Fig. 32.1 Heterogeneity: remarkable RUL emphysema (gradient RUL vs. ML/RLL = 56.5 pp). Note fissure completeness (VIDA™ estimate, 99%). *ML* middle lobe, *RLL* right lower lobe, *RUL* right upper lobe



Left Lung	Volume (cc)	Emphysema at -950 HU
Upper lobe	854.37	35.60%
Lower lobe	1659.88	16.85%
Lung	2514.25	23.22%

Fig. 32.2 Heterogeneity: MDCT coupled with VIDA System™ and volumetry reports. (**a**) Pre-BLVR. (**b**) Airway study. (**c**) Post-BLVR; note upward shift in oblique fissure. Results: (1) Change in target lobe (LUL) volume: −1142 mL. (2) Change in left lung volume: −686 mL. (3) Change in nontarget lobe (LLL): +456 mL. *BLVR* bronchoscopic lung volume reduction, *LLL* left lower lobe, *LUL* left upper lobe, *MDCT* multidetector computed tomography

parenchyma analysis by MDCT. Density mask in 5 mm thin or thinner slices falls at approximately [14]:

- −950 HU for severe emphysema
- −910 HU for moderate emphysema
- −850 HU for mild emphysema

Collateral Ventilation and Fissure Integrity

Experienced interventional bronchoscopists treating emphysema patients with BLVR procedures agree that collateral ventilation is a cardinal issue determining treatment outcome. Atelectasis promotes more marked volume reduction, and therefore lobar exclusion is the treatment of choice in patients with negative collateral ventilation (Fig. 32.3).

In 2009, Aljuri and Freitag [16] introduced a new method to estimate collateral ventilation. The concepts described by these investigators have been employed to develop the Chartis™ Pulmonary Assessment System, which measures airway resistance and collateral ventilation in lung compartments. For that, a catheter with a compliant balloon component at the distal tip is inserted into the lung. The balloon is inflated and blocks the airway, so that the air flowing from the target compartment into the environment must pass through the Chartis catheter (Fig. 32.4).

The Chartis console displays airway flow, pressure, and resistance [16]. Collateral ventilation occurs through:

- Kohn pores (diameter 0.5 μm)—alveolar walls—require high pressure for air transport (196 cmH_2O).
- Communications of Lambert (diameter 30 μm)—distal bronchioles and alveoli.
- Martin pathway (diameter 80–150 μm)—between respiratory bronchioles and adjacent lung segments. This low-resistance pathway plays a major role in collateral ventilation airflow passage.

In patients with emphysema, in whom airway resistance is increased, collateral resistance is lower. This was demonstrated by Hogg et al. [17], who measured the resistance of CV in excised normal and emphysematous lungs. In normal lungs, the resistance of collateral channels was 260–330 cmH_2O (25–324 kPa), whereas this was 5–20 cmH_2O (0.5–2.0 kPa) in emphysematous lungs. Therefore, airflow is increased approximately 30 times through

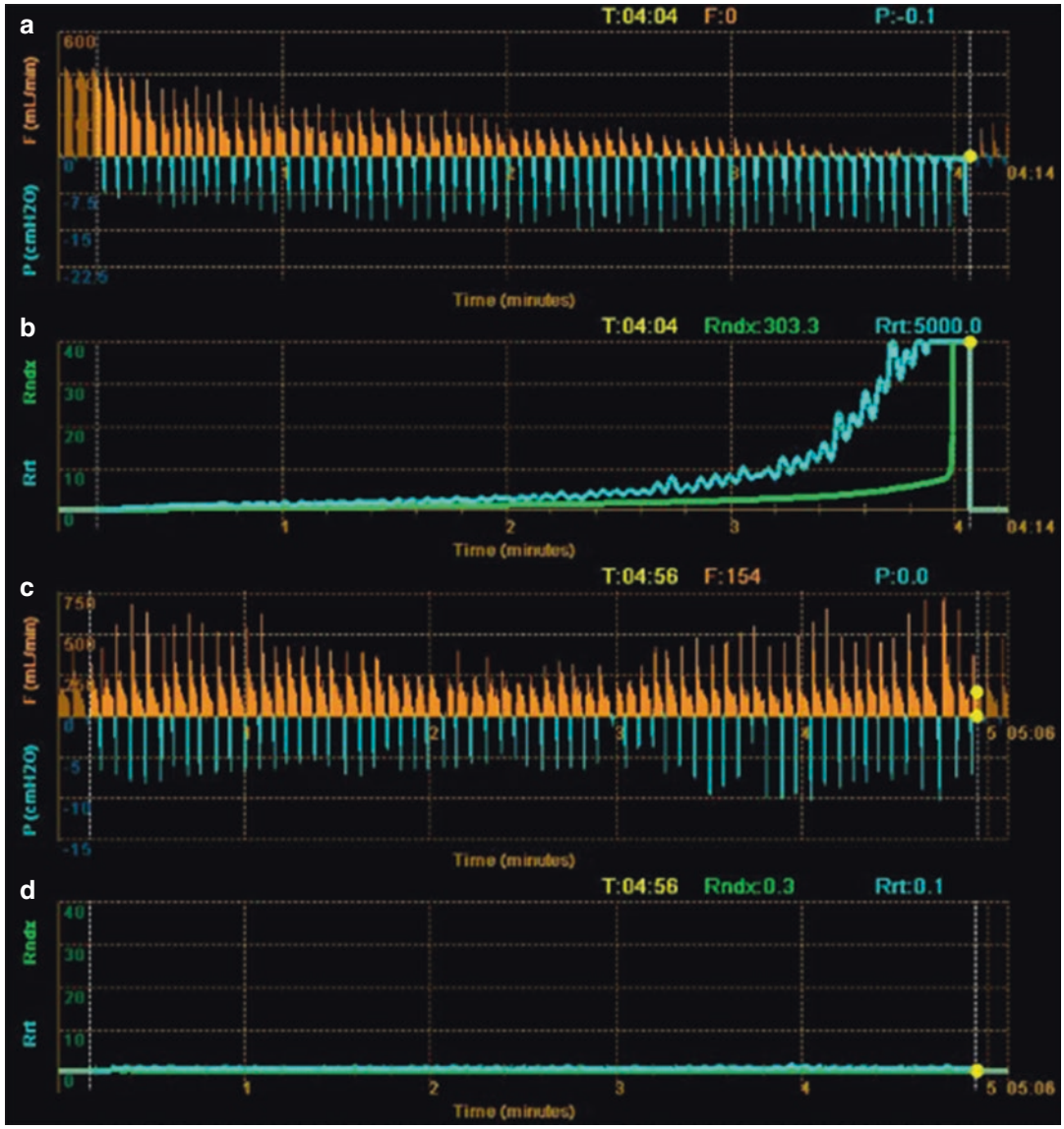


Fig. 32.3 (**a**) CV-negative: good candidate for BLVR as indicated by the *orange* curve, showing steady and continuous flow reduction through the Chartis™ catheter. *Blue* color signals a slight raise in negative pressure. (**b**) CV-negative: a peak in resistance occurs at the end of the third minute, indicating nonexistent interlobar airflow. (**c**) CV-positive: observe in *orange* a steady and continuous flow curve even when the Chartis™ system is closed, representing sustained interlobar airflow. (**d**) CV-positive: after 5 min the resistance curve is flat, indicating the absence of resistance. *BLVR* bronchoscopic lung volume reduction, *CV* collateral ventilation

collateral channels in an emphysematous vs. a normal lung [18].

Although collateral ventilation was initially thought to be strictly an intralobar phenomenon, interlobar ventilation (i.e., between the lobes) also occurs across incomplete lung fissures. Probably due to the same mechanism, the flow between different lobes is higher in patients with emphysema [17–19].

Fissure integrity has emerged as a focus of much interest for BLVR. In embryos, the visceral pleura is formed at around 7 weeks of gestational age, and invaginations start to separate the lobar bronchi. This gives rise to lobar fissures and the

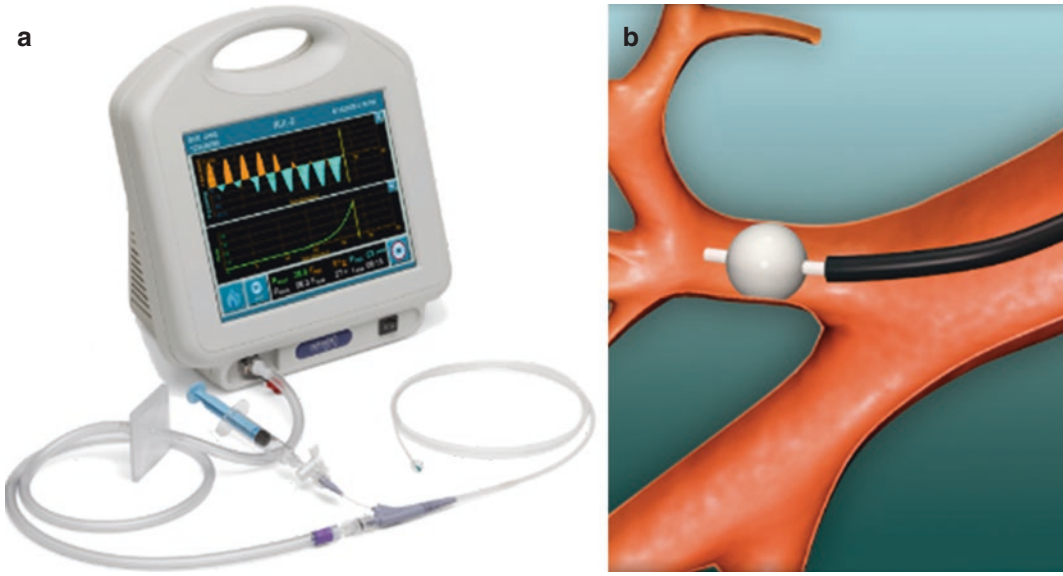


Fig. 32.4 (**a**) Chartis™ console displaying information of a patient with typical negative collateral ventilation curve, with catheter plugged into the console. (**b**) Chartis™ catheter in position, occluding RUL to provide physiographic measures after "lobar exclusion." *RUL* right upper lobe

formation of lung lobes. However, if the pleura fails to cover the entire lobe, it can be assumed that the fissures will be incomplete near the lung hilum [20]. The right major fissure has been shown to be more often incomplete (48 vs. 43% for the left-side major fissure 43%, $p < 0.05$). Minor fissures are convex superiorly with an anterolateral apex and have been reported to be incomplete in 63% of the cases [21].

In another study, Manoj et al. describe the variations in lung fissure patterns in the general population of India (Fig. 32.5). One hundred lungs were meticulously dissected (right lung, 50; left lung, 50). The number of fissures, whether complete, incomplete, or absent, and the presence of accessory fissures were noted. In the right lung, horizontal fissure was absent in four (8%) and incomplete in 14 (28%) cases. Oblique fissure was absent in two (4%) lungs and incomplete in seven (14%). Accessory fissures were present in 19 specimens (38%). In the left lung, the oblique fissure was absent in two (4%) lungs and was incomplete in 16 (18%) lungs. Accessory fissures were present in 16 (32%) [22].

Knowledge regarding the occurrence of fissure variability in a particular population might help radiologists and clinicians make a correct diagnosis and help surgeons plan, execute, and modify their surgical procedures. However, definitive studies regarding the role of fissure integrity in lung volume reduction following BLVR are still lacking.

Interlobar CV might be an important predictor of EBV treatment outcome, as BLVR therapy is based on complete atelectasis of a lobe. Most probably, incomplete fissures are responsible for interlobar collateral flow. There is no literature regarding the mechanism of CV in incomplete fissures between lobes. It can be assumed that the mechanism of collateral flow between lobes is the same as within a lobe. The collapse of emphysematous lobes, despite occlusion of their bronchi, is attributed to the low collateral resistance in emphysema. Collateral resistance is often less than airway resistance in these patients, and collateral channels frequently cross incomplete interlobar fissures [23]. Gas may thereby continue to enter these lung regions at rates exceeding their rate of absorption. A technique to predict which patients or which lobes have high collateral resistance and are likely to become atelectatic could guide patient selection and procedural planning [24].

Fig. 32.5 (**a**) Incomplete fissure of the left lung. (**b**) Absence of fissure in the left lung. (**c**) Absence of horizontal fissure in the right lung. (**d**) Incomplete oblique fissure in the right lung. (**e**) Incomplete fissure of the right lung. (**f**) Absence of fissure in the right lung (Reproduced with permission from the *Journal of Krishna Institute of Medical Sciences University* (JKIMSU) [22])

In a retrospective study [25], our group has shown that target lobe volume reduction is possible with lung fissure integrity ≥75%. Patients with fissure integrity >90% are likely to achieve a clinically relevant target lobe volume reduction with EBV treatment. Patients with fissure integrity between 75 and 90% should undergo further evaluation of interlobar ventilation (Chartis™), as previously noted [25–27]. The overall accuracy of a 75% fissure integrity cutoff point was 87.2% for a 350 mL reduction in target lobe volume. Patients with fissure integrity <75% are not likely to achieve any clinically relevant target lobe volume reduction with BLVR-EBV.

Heart

Lung hyperinflation leads to exercise intolerance and greatly hurts quality of life. Lung emphysema encompasses a broad vicious cycle in which social isolation, depression, limb weakness,

breathlessness, and a disturbed chest wall mechanics contribute to increase mortality. In a large 4-year follow-up study of patients with mild-to-severe emphysema, IC/TLC ≤ 0.25 was associated with a twofold increase in mortality vs. IC/TLC ≤ 0.25. We conclude that IC/TLC is an independent risk factor for mortality in subjects with chronic obstructive pulmonary disease. We propose that this ratio be considered in the assessment of patients with COPD [28].

In emphysema, heart performance is greatly compromised by lung hyperinflation. In 2010, Barr et al. [29], using MRI, showed that a 10% worsening of emphysema on CT scans was sufficient to reduce LV diastolic volume, LV mass, stroke volume, and cardiac output. The same was observed for the increase in airway obstruction (FEV_1/FVC).

Gerard Criner has recently proposed the notion of "Less Lung Means More Heart," shedding light on the contribution of the heart for the severity of symptoms and the loss of quality of life in lung emphysema [30].

Historical Aspects

The first endoscopic approach for emphysema treatment was proposed by Crenshaw. In 1966, that author described a technique in which diluted sodium hydroxide was bronchoscopically applied as sclerosing agent to promote retraction of emphysema bullae. Despite the marked improvement obtained with two patients, with one being able to resume work, there is no record of this experience having been pursued further [31].

Also pioneer was the work of Watanabe et al., who proposed the use of an endoscopically delivered cork-like device, the spigot. One of the major limitations of the method was the occurrence of obstructive pneumonia and pneumothorax, possibly resulting from hyperinflation due to collateral ventilation. Therefore, the Watanabe Spigot had limited clinical application. Other therapeutic options include fibrin sealant, extra anatomical airway, vapor, and coils [32].

Concerning lung volume reduction surgery (LVRS), the uncertainties related to the outcomes, and the high associated morbidity and mortality have limited the use of this major surgical procedure [24]. In the NETT, almost 30% of the participating patients faced major pulmonary complications, including the need for reintubation and tracheostomy and the need for ventilatory support for more than 2 days or pneumonia within 30 days of operation. In turn, about 20% of the sample developed cardiovascular problems, such as arrhythmia requiring chemical or electrophysiological treatment, myocardial infarction, or pulmonary embolus [33]. Advancing age, declining FEV_1, and declining D_LCO were predictors of major cardiac morbidity, as well as the use of oral corticosteroids at the time of surgery and non-upper lobe predominant pattern of emphysema. Conversely, there is good evidence that patients with upper lobe emphysema and poor exercise capacity benefit from LVRS [34].

It is well recognized that the NETT played a major role in advancing the development of minimally invasive endoscopic modalities such as BLVR. The framework of this prospective randomized clinical trial provided the foundation for the search of alternative methods of lung volume reduction that could produce clinically significant results and translate into improved lung function and exercise capacity.

In 2001, our team was invited to participate in a phase II trial set up by endobronchial valve manufacturer Emphasys Medical. We implanted the first EBV in the Americas in the morning of June 4, 2002 (Fig. 32.6).

This was a challenging premiere because treatment strategy in this 75-year-old male was right upper lobe (RUL) exclusion with three classic EBVs. Complete atelectasis was achieved almost immediately (Fig. 32.7).

After 48 h, minor chest pain and respiratory discomfort evolved to a large ipsilateral pneumothorax on chest X-ray requiring the insertion of a 32F chest tube. This measure however was unsuccessful in re-expanding the RUL, since a massive air leak indicated that a large bulla was probably torn apart. Removal of the valve located in the anterior segment (B3) naturally allowed pulmonary re-expansion, followed by an uneventful recovery (Fig. 32.8).

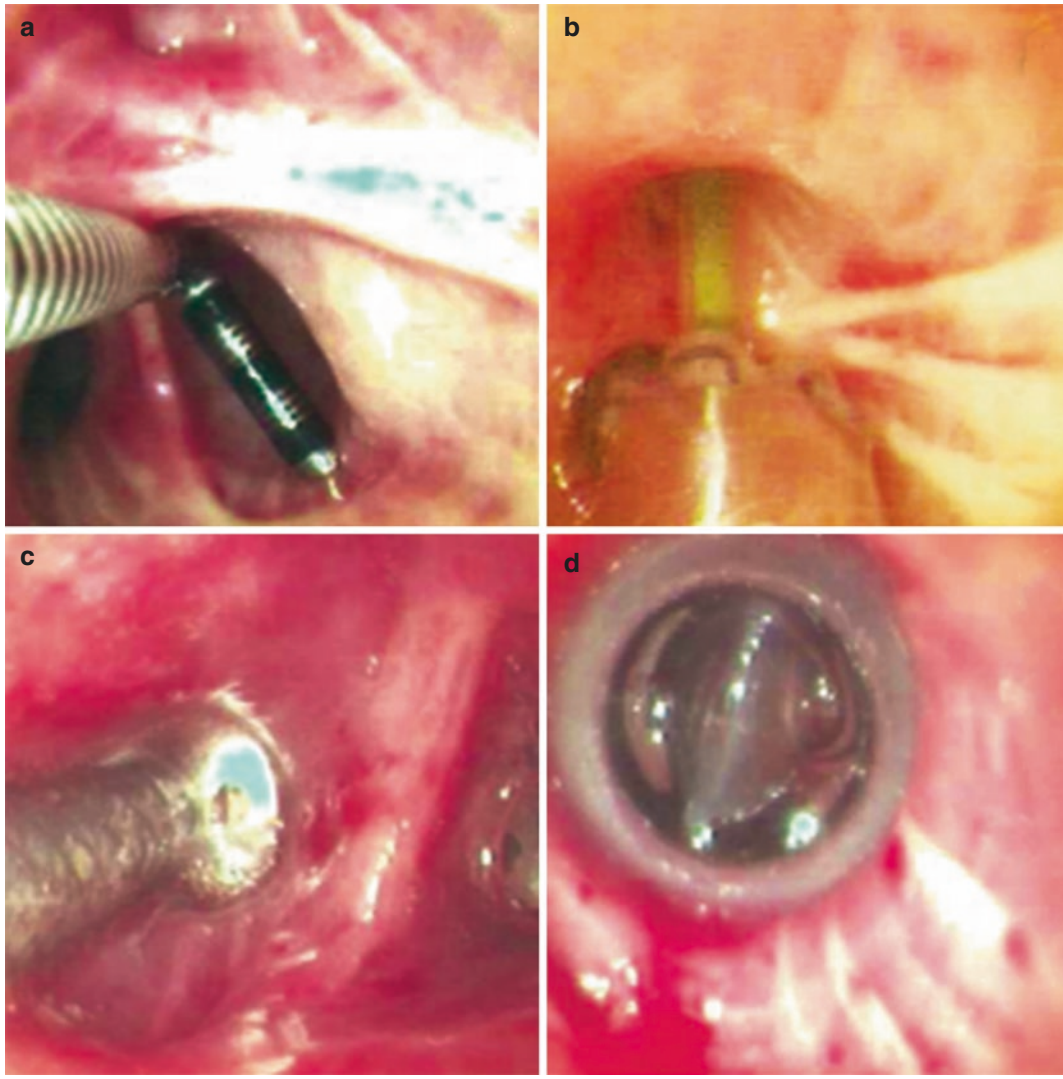


Fig. 32.6 Classic valve in 2002: first emphysema case treated with EBV in the Americas. (**a**) Guide wire with a meter tip to better select valve diameter. (**b**) Delivery system with guide wire and encapsulated valve. (**c**) Valve released into RUL-B3 seen from above through fiberoptic bronchoscope. (**d**) Valve snuggly in place

As part of this project, 19 patients were treated between June 2002 and October 2004. At that initial stage, we were able to show that treatment with EBV was safe and reversible, an advantage over other emerging bronchoscopic techniques. Nevertheless, it soon became clear that patient selection and the criteria to measure improvement required refinement.

Around 2004, classic EBV valves were replaced with a transcopic endobronchial valve model called Zephyr™. The transcopic model added elegance and fluency to the procedure; the classic EBV model was delivered through a comparatively clumsy system, using a guide wire and a delivery case that was passed through a large orotracheal tube. The flexible bronchoscope only provides a visual field from above. Implantation of the classic EBV required more technical dexterity and was difficult especially in upper lobe apical segments. However, the crucial disadvantage was a high incidence of granuloma formation close to the tip of the valve, which often obstructed the valve itself [35].

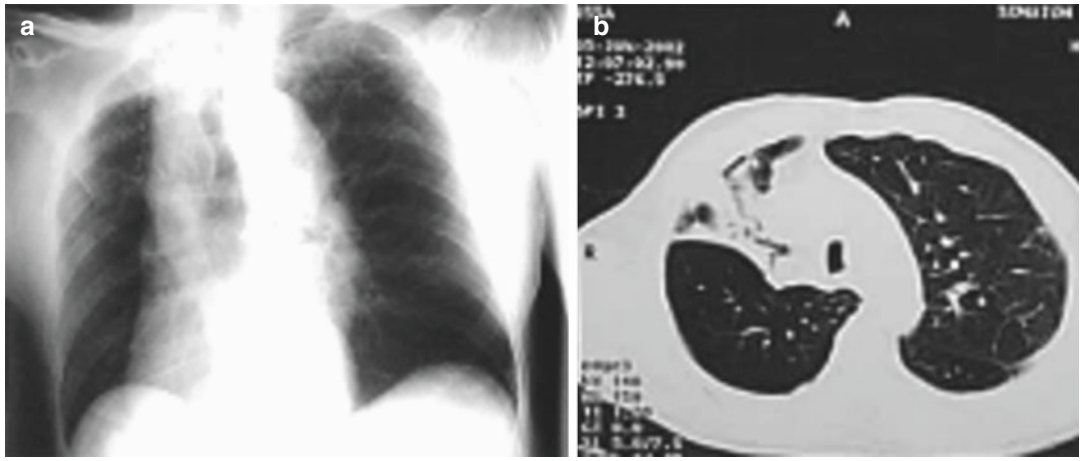


Fig. 32.7 Same patient shown in Fig. 32.6. Complete atelectasis detected in postoperative X-ray. (**a**) Control CT scan shows three well-positioned valves in right upper lobe (RUL). (**b**) Note lung volume reduction in right hemithorax and mediastinal shift. *CT* computed tomography, *RUL* right upper lobe

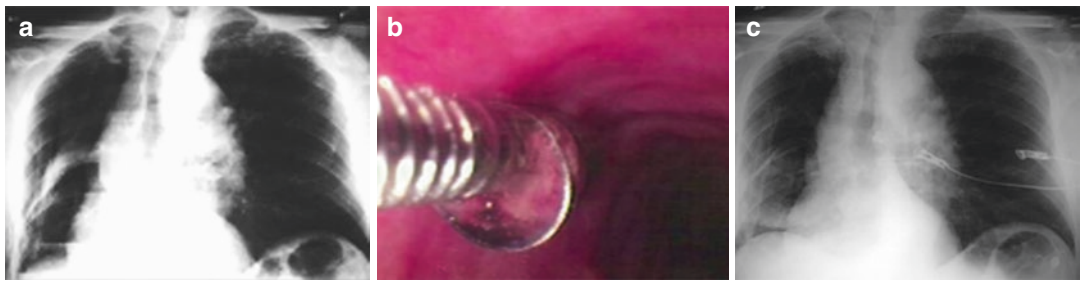


Fig. 32.8 (**a**) Large pneumothorax 48 h after BLVR. No response to chest tube insertion and moderate pleural effusion. (**b**) EBV being removed. (**c**) Full right lung expansion with simultaneous air leak discontinuation. *EBV* endobronchial valve, *BLVR* bronchoscopic lung volume reduction

In the early era of EBVs, there was some debate regarding the appropriateness of the name "bronchoscopic lung volume reduction surgery" as the best description for the procedure. We ourselves proposed the use of the term "transbronchoscopic pulmonary emphysema treatment" (TPET), based on the argument that the bronchoscope is only a means to deliver the treatment. The idea of TPET was also an attempt to prevent confusion with LVRS and an acknowledgment of the realization that volume reduction is often not obvious with BLVR. In this sense, it should also be noted that clinical improvement is often possible even in the absence of significant lung volume reduction. Nevertheless, the expression BLVR prevailed, and this is the current term used to describe the minimally invasive procedure through which EBVs are implanted in patients with emphysema [36–38].

Definition of the Procedure

Bronchoscopic lung volume reduction (BLVR) with one-way unidirectional EBVs is a minimally invasive, reversible treatment option that has been used to treat over 12,000 patients with emphysema around the world. Considering an average of three valves per patient, around 36,000 valves have been implanted in the world since 2004.[1] This is currently the most common BLVR modality.

[1]Personal communication, Narinder Shargill, vice-president, PulmonX™ Clinical and Regulatory Affairs

One-way endobronchial valves operate by blocking airflow into diseased portions of the lung in which parenchyma disruption causes air trapping. By doing that, the valves induce dependent volume reduction and redirect airflow to less diseased lung areas. Diaphragm repositioning and improved respiratory mechanics are expected to diminished dyspnea and restore to a certain extent the ability to perform simple tasks of daily living, such as taking a shower, getting dressed, or walking short distances. The recovered ability to perform activities of daily living improves patient disposition. Collateral ventilation still seems to be the main factor complicating the likelihood of success [4].

Description of the Equipment

- Zephyr endobronchial valves 4.0–4.0LP or 5.5 in diameter
- Delivery catheter
- Loader system
- Rat tooth grasping forceps (Fig. 32.9)

As previously mentioned, the new EBV design (Zephyr™) introduced improvements for implantation, with the valve being totally compressed and loaded in a catheter with a diameter that is sufficiently small to be passed through a 2.8 mm bronchoscope operative channel. Also, the new valve design provided protection for the valve mechanism itself, facilitating grasping with the removal

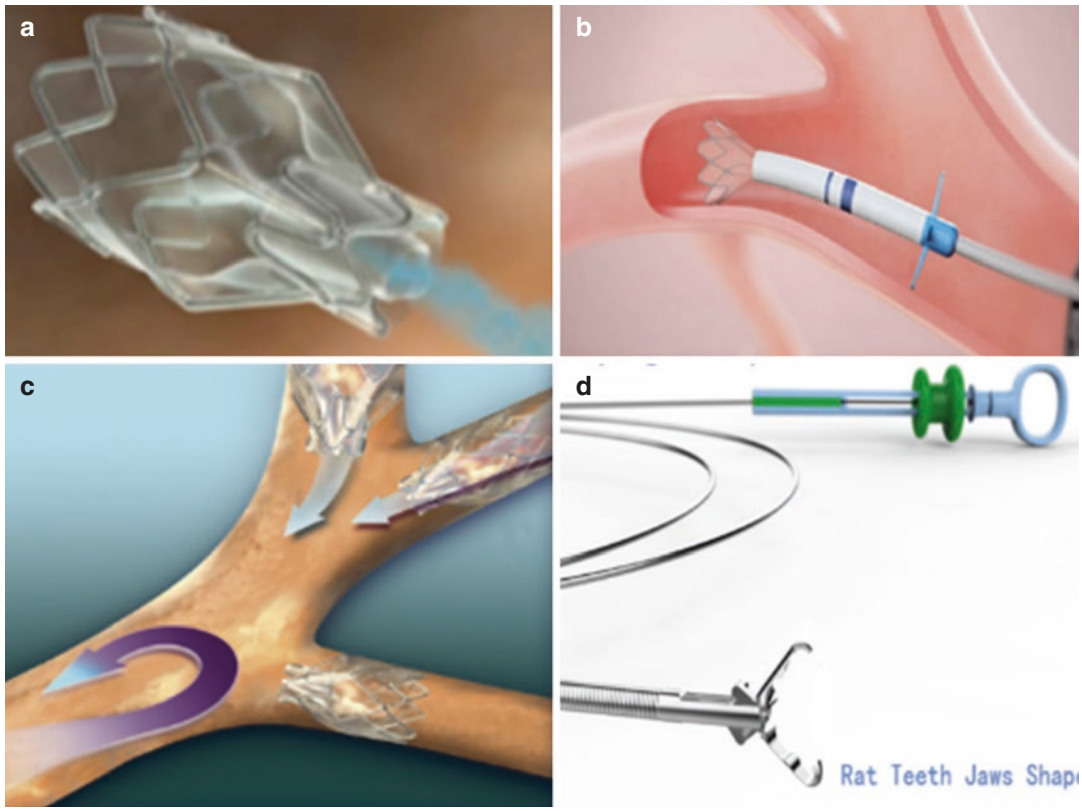


Fig. 32.9 (**a**) Zephyr™ one-way endobronchial valve. (**b**) Valve delivery system: *blue* marks must be aligned with the beginning of the bronchus (*black line*). (**c**) Simulation of LUL exclusion with three valves. (**d**) Rat tooth endoscopic grasp forceps used for valve removal as needed. *LUL* left upper lobe

forceps when required. Our group was able to maintain a strict follow-up scheme in second half of the phase II Emphasys Medical trial. Mandatory flexible bronchoscopies at 30, 90, 180, and 365 days following the procedure allowed us to verify a significant reduction in granuloma formation with the Zephyr™ valve. Reversibility of the procedure was also improved with the transcopic valve. We were able to safely remove a valve more than 5 years after implantation in one case.

The Zephyr™ is available in three sizes, 4.0, 4.0LP, and 5.5, each delivered by a specific catheter (Table 32.1). There are separate delivery catheters and loader systems for each valve size. Each system is color coded: blue for the 4.0 and 4.0LP systems and green for the 5.5 system.

The valves are built with a nitinol frame that provides structural support and is covered by a silicone layer that prevents the inclusion of material in the mucosa. One-way airflow is controlled through a duckbill tip. The new model mimics airflow flexibility, decreasing friction, minimizing granuloma formation, and reducing valve migration/dislodgment. In summary, the newer model can be delivered directly through a 2.8 bronchoscope channel, streamlining the procedure. Valve mounting has also been greatly simplified.

The Zephyr® 4.0-J EDC facilitates the introduction of valves in apical and intricate segmental or subsegmental bronchi, because the length in 4.0LP is 5.2 mm instead of 6.9 mm as normal 4.0 valve.

Rat tooth grasping forceps must be available to remove mismanaged valve delivery and positioning. For valve removal, the bronchoscope must be introduced through the mouth.

Table 32.1 Available diameters of endobronchial valves (Zephyr™)

Description	Airway diameter range (mm)	Delivery catheter
EBV-TS-4.0—Zephyr® 4.0 Endobronchial Valve	4.0–7.0	EDC-TS-4.0
EBV-TS-4.0-LP—Zephyr® 4.0-LP Endobronchial Valve	4.0–7.0	EDC-TS-4.0-J
EBV-TS-5.5—Zephyr® 5.5 Endobronchial Valve	5.5–8.5	EDC-TS-5.5

Operative Technique and Follow-Up

Planning

Our group has long relied on Volumetric Imaging Display and Analysis software (VIDA™ Diagnostics, Coralville, IA, USA), which reconstructs the tracheobronchial anatomy from CT scans. The current version of this semiautomated software is called Apollo™. The software provides accurate results, even though its use is limited by the need for an expert operator who is capable of interpreting the tracheobronchial tree and in some cases making the necessary arrangements to complete lung fissures (reconstruction data).

The VIDA/Apollo™ software provides information on which and where each valve must be delivered to perfectly seal the segmental or subsegmental bronchi. Valve sizes 4.0 and 4.0LP are indicated for bronchi with 4.0–7.0 mm diameter, whereas size 5.5 is indicated for bronchi with 5.5–8.5 mm in diameter. It is also important to select segments with at least 9 mm in length.

Nevertheless, the 4.0LP size was developed to block short bronchi, as is sometimes the case with B6.

In our experience, virtual bronchoscopy with VIDA™ software plays a major role in planning the endoscopic treatment, because (1) it reduces procedure duration, an important aspect for patients who are severely ill, as is frequently the case of emphysema patients, and (2) it pinpoints the exact sites for implantation and lets the interventional bronchoscopist become acquainted with the anatomy of each particular patient. Nevertheless, there is a gap in the literature concerning this topic.

Sedation

The procedure is performed with ECG monitoring, digital oximetry, and intravenous access. Almost all cases are performed using a laryngeal mask. Propofol-based sedation with spontaneous breathing is routine. Topical anesthesia with 5%

lidocaine gel in the oral cavity is used, as well as tracheobronchial instillation of 1% lidocaine via the video bronchoscope operative channel.

Antihypertensive medication and bronchodilators are routinely administered before the procedure. Anticoagulant use is interrupted immediately before the procedure (depending on the drug used). The use of acetylsalicylic acid and *Ginkgo biloba* is interrupted 5 days before the procedure.

Corticosteroid prophylaxis is used only in patients with history of bronchospasm. Antibiotics, usually quinolone, is given at the time of sedation and usually maintained for a week.

Operative Technique Advice

- Perform Chartis™ in most patients.
- Invariably check the flexible bronchoscope for integrity and correct response to forced upward and downward positioning.
- Apical and apical-posterior segments must be treated first in upper lobar exclusion.
- B6 tends to be shorter in some cases, and that is why the 4.0LP Zephyr™ model was developed.

Follow-Up

The patient is contacted 1 week after the procedure, then monthly during the first 3 months. After 90 days, a follow-up evaluation is carried out including CT scan for VIDA™ evaluation, pulmonary function tests, 6MWD, SGRQ for the assessment of quality of life, and other tests at the discretion of the team. Bronchoscopic revision is carried out at any time when a valve-related problem is suspected, or else in the presence of intense mucus production. In patients without atelectasis, if mucus is clogging the valve, bronchoscopic cleaning and aspiration is carried out. This procedure does not endanger valve positioning.

It should be noted that a CT scan acquired with the correct parameters for VIDA™ analysis is sufficient to confirm the correct functioning of the valves. After this 3-month follow-up, a similar 6-month follow-up is carried out, and after that the patient is reviewed yearly.

As with patients receiving other types of tracheobronchial stents, we firmly recommend that patients keep physiological hydration levels and employ N-methylcysteine for airway fluidification. Continuation of physical therapy after the procedure is mandatory. Exercise and well-balanced nutrition care are also important and should be emphasized for patients and family members.

Indications and Contraindications

In brief, the ideal candidate for BLVR with EBV has:

- Severe emphysema with no infectious abundant sputum or bronchospasm
- Heterogeneity gradient above 15 pp
- Fissure integrity ≥90%
- Fissure integrity ≥75–90 with negative CV (Chartis™)
- Age ≥35 years
- No smoking for ≥6 months
- Post BD FEV_1 <60% of predicted value
- TLC >100%
- RV >150%
- MMRC ≥1 (O–4)

Table 32.2 describes relative and absolute contraindications for valve treatment.

Table 32.2 Absolute and relative contraindications for valve treatment

Absolute contraindication	Relative contraindication
Recurrent infection and daily sputum production judged clinically significant	Bronchitis
Refractory bronchospasm	FEV_1 < 20%
Bronchiectasis	pCO_2 > 60 mm Hg
Uncontrolled hypertension	Multiple subpleural bullae in lobe adjacent to lobar exclusion
Comorbidity or neoplasia compromising survival	Giant bullae
Current smoking	Mean pulmonary artery pressure > 50 mm Hg

Brazilian Experience at a Glance

Since 2002, our group has treated 152 patients and performed 38 retreatments at our headquarters at Hospital Moinhos de Vento, Porto Alegre, and Hospital de Clínicas de Porto Alegre, Brazil (Fig. 32.10).

We have also performed procedures and trained physicians for EBV-BLVR in other Brazilian cities (Rio de Janeiro, São Paulo, Belém, Fortaleza, Goiânia, Blumenau, Belo Horizonte) and in other Latin American countries (Colombia, Argentina, Uruguay, and Paraguay). To date, we have implanted more than 550 endobronchial valves.

Having pioneered the first seven cases in the Americas, we contributed to the report by Wan et al. [39] regarding the first 98 patients submitted to BLVR in the world.

In addition to the usual criterion of selecting patients with severe emphysema, our patient selection algorithm is based on specific characteristics regarding lobe volume and fissure integrity (Fig. 32.11). Therefore, in clinical practice, we rely on the following criteria to select patients for RBV-BLVR:

- Heterogeneity ≥15 pp between lobes
- Collateral ventilation double check:
  - Fissure integrity according to HRCT fissure analysis by VIDA/Apollo™; fissure is considered complete if integrity ≥90%.
  - In the presence of fissure integrity between 75 and 90%, Chartis™ measurement of collateral ventilation flow is required.

Our group agrees with others in defining emphysematous tissue as parenchyma with density below −950 HU [40–42].

Fig. 32.10 Bronchoscopy suite at Hospital Moinhos de Vento, Porto Alegre, Brazil

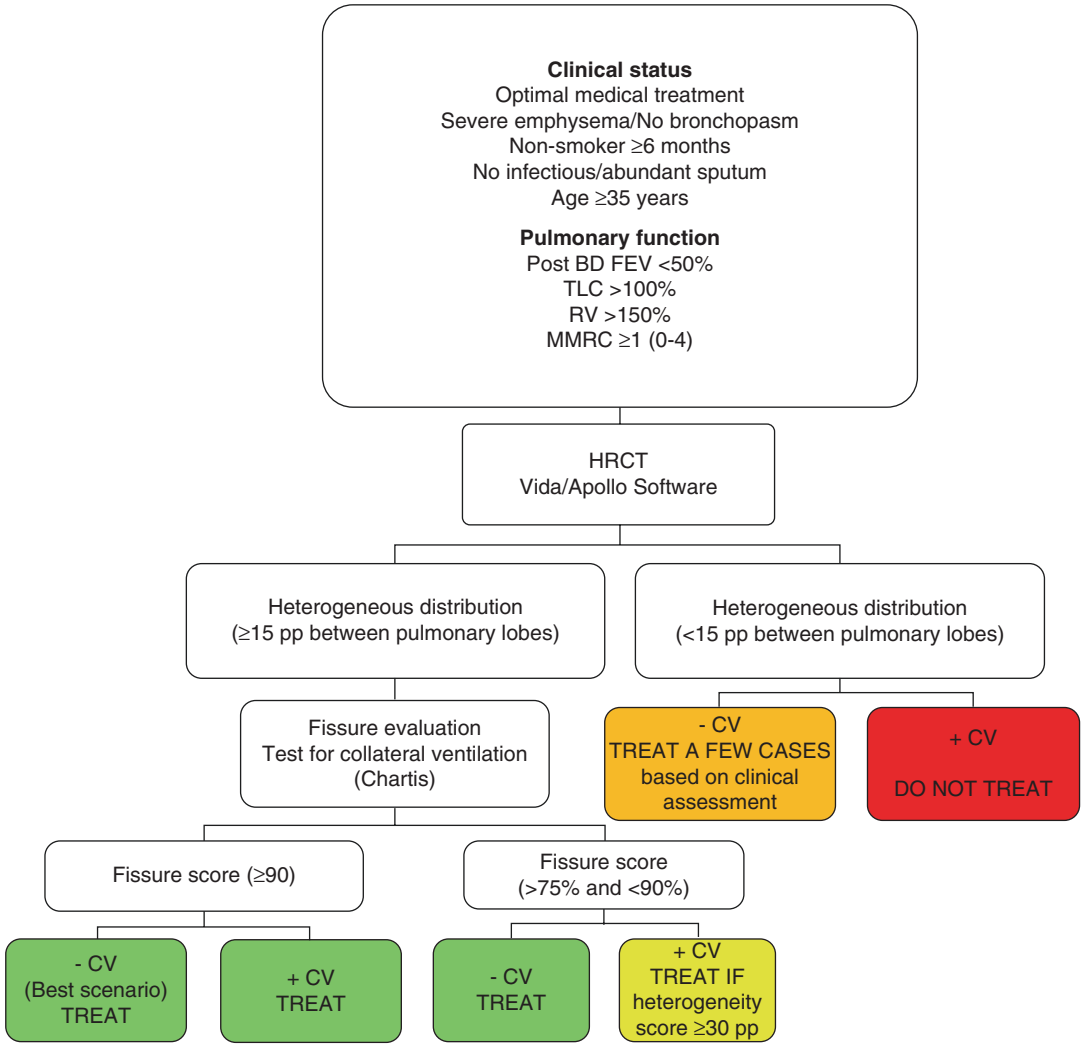


Fig. 32.11 Patient selection flowchart used by the Emphysema Treatment Group (Hospital Moinhos de Vento), Brazil, for EBV-BLVR. *BD* bronchodilator, *CV* collateral ventilation, *BLVR* bronchoscopic lung volume reduction, *EBV* endobronchial valve, *FEV* forced expiratory volume, *HRCT* high-resolution computed tomography, *MMRC* modified medical research council dyspnea scale, *pp* percent points, *RV* residual volume, *TLC* total lung capacity. Based on Shah and Herth [4]

We then determine the difference in percentage of emphysematous tissue between lobes to assign a heterogeneity score (HS). For example, if an upper lobe has 52% parenchymal tissue with density < −950 HU and a lower lobe has 25% parenchymal tissue with density < −950 HU, HS would be 27 percent points (pp). Also like others, we adopt an arbitrary cutoff point of 15 pp between the upper and lower lobe to define the minimum heterogeneity for BLVR. The right middle lobe is added to the untreated lobe for heterogeneity calculation [25, 43].

To illustrate our experience, we chose to describe three cases treated with Zephyr™ BLVR.

Case 1: LLL exclusion with two Zephyr™ 4.0 (LB6/LB8) + one Zephyr™ 5.5 (LB9/LB10) valves (Fig. 32.12)
Case 2: LUL exclusion (Fig. 32.13)
Case 3: RUL exclusion in 54-year-old male. MMRC 4; BODE 9 (Fig. 32.14)

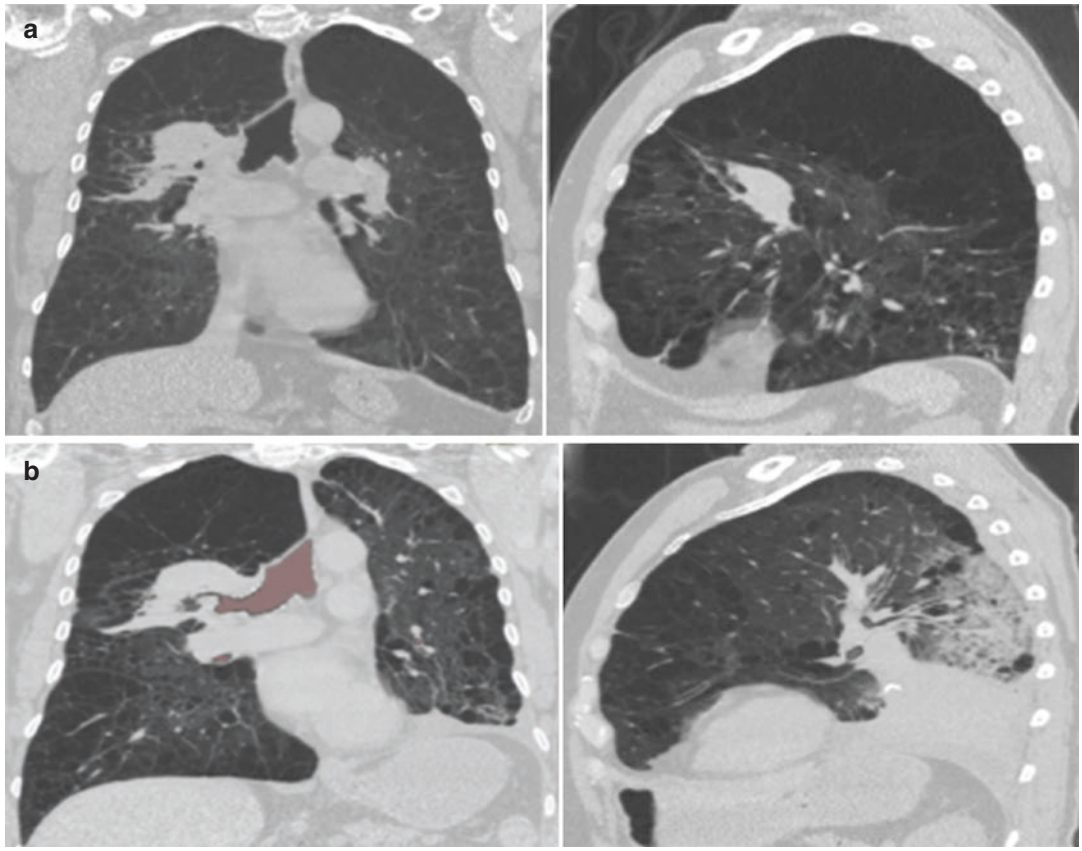


Fig. 32.12 (**a**) Baseline. (**b**) Five postoperative days. A 66-year-old lawyer, restricted to the home, requiring continuous oxygen therapy (4 L/min O_2) was treated with BLVR. The patient was able to resume work and had marked improvements in quality of life. Two years later, the patient died possibly as a result of pulmonary embolism. *BLVR* bronchoscopic lung volume reduction

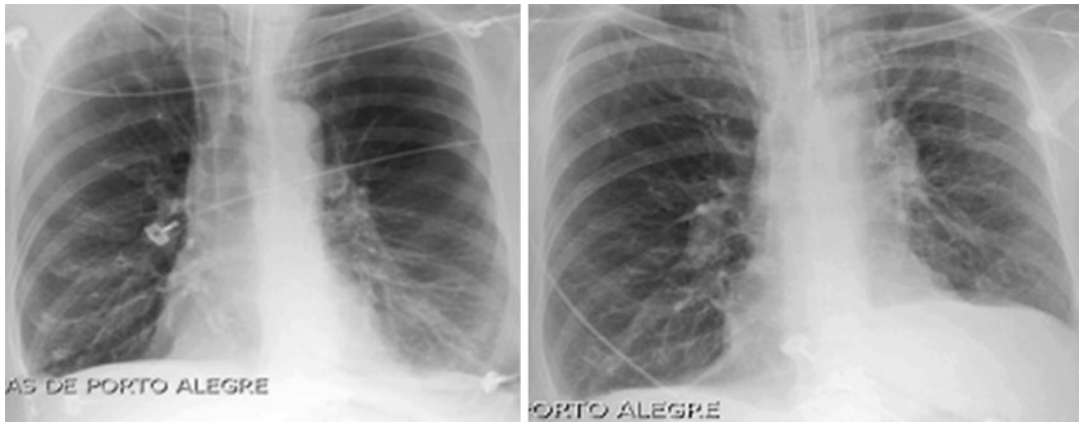


Fig. 32.13 LUL exclusion. Note significant reduction in LUL volume (−850 mL) in both coronal and sagittal views. We treated a 65-year-old female after 2 weeks of mechanical ventilation and tracheostomy in an ICU (pCO_2 114). Forty-eight hours after treatment with three Zephyr™ valves, she was weaned from mechanical ventilation and discharged from the ICU. *ICU* intensive care unit, *LUL* left upper lobe

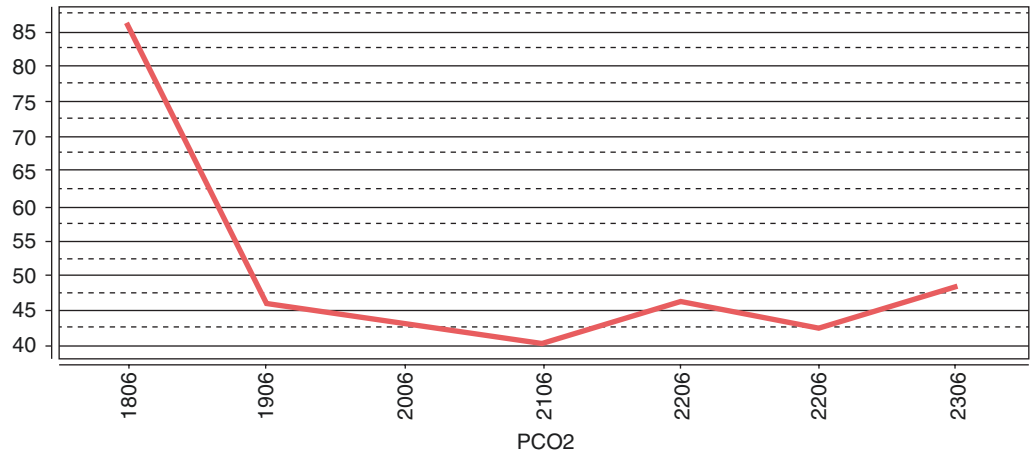


Fig. 32.13 (continued)

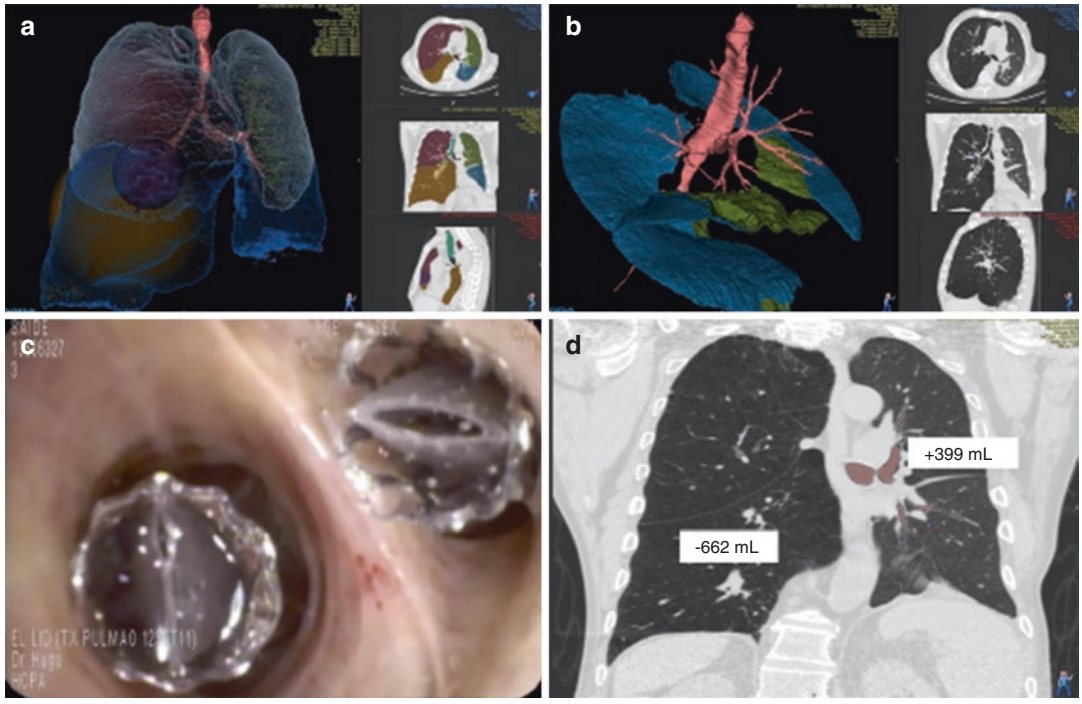


Fig. 32.14 Native lung hyperinflation 28 months after single lung (*left lung*) transplantation. RLL exclusion was achieved with one Zephyr™ 5.5 in RLL7 and one Zephyr™ 4.0 in RB6, with significant volume reduction (662 mL). (**a**, **b**) VIDA/Apollo volumetry and fissure analysis, (**c**) EBVs implanted in RLL7 and RB6, (**d**) MDCT coronal view showing beneficial volume reduction in RLL. *EBV* endobronchial valve, *RLL* right lower lobe, *MDCT* multidetector computed tomography

Evidence-Based Review

The literature on EBVs to treat emphysema has been largely limited to fairly preliminary results that agree regarding valve safety but are inconclusive in terms of clinical outcomes. In 2006, we reported the first long-term follow-up of patients treated with EBV-BLVR (up to 24 months). Our experience with 19 patients provided evidence of the safety and reversibility of EBV-BLVR while underscoring the need for improvement in outcome measures and patient selection [35].

Nevertheless, in the past 5 years, more robust studies have been published, including RCTs [43–46]. The results of these studies indicate that most patients feel better after EBV treatment. EBV treatment may act as a positive trigger to improve clinical status and quality of life. As previously stated, however [40], it is of paramount importance that EBV-BLVR be performed in centers specializing in COPD.

Four randomized controlled trials—VENT, EuroVENT, BeLieVeR-HIFi and STELVIO—have demonstrated the significant benefits of the Zephyr™ EBV in severe emphysema patients with heterogeneous disease [43, 44, 46]. One year after EBV treatment, pulmonary function, exercise capacity, and quality of life were significantly improved compared to baseline in patients with heterogeneous emphysema as well as in patients with homogeneous emphysema without interlobar collateral ventilation [47].

The LIBERATE Study (NCT01796392) is also currently recruiting participants in 23 sites: 18 in the United States, one in the Netherlands, two in the United Kingdom, and two in Brazil. It has as primary outcome measures, FEV_1, and as a secondary outcome measures, volume reduction of the treated area of the lung, SGRQ, and 6MWD at 1 year. Data show that the left lung is most frequently treated (70/90) and that the LUL is the excluded lobe in most cases (59/90). Pneumothorax and death rate are reported to be 25 and 3.4%, respectively. Most pneumothoraces are treated with chest tube insertion (20/32).

Even though clinical improvement may occur following EBV-BLVR even in the absence of atelectasis, we currently work with the aim of achieving a reduction of ≥350 mL in the treated lobe. For that, lobar exclusion must be performed. Volume reduction of ≥350 mL following Zephyr™ BLVR has been shown to result in objective improvement in FEV_1, 6MWT, RV, and SGRQ scores [45].

Evolving Selection Criteria

A review by Shah and Herth [4] has concluded that in unselected patients, only 20% are good responders to EBV treatment, whereas the ratio of responders increases to 75% when adequate selection criteria are applied. The heterogeneity parameter remains as a useful selection criterion for EBV-BLVR candidates and has been associated with greater likelihood of benefit. Among patients treated with EBV-BLVR, those in the high-heterogeneity subgroup had greater improvements in both FEV_1 and 6MWD than did patients with lower heterogeneity [44].

Perhaps the greatest advancement in the understanding of emphysema and the effectiveness of EBV-BLVR relates to the identification and acceptance of collateral ventilation as a crucial factor, directly linked to lung volume. Together, dynamic air trapping and the absence of collateral ventilation indicate the cases in which valve treatment is more likely to succeed.

A 6-month follow-up RCT testing Zephyr™ EBV versus standard medical care in 84 severe emphysema patients confirmed that negative collateral ventilation measured with the Chartis™ system helped select patients prone to clinically meaningful results. FEV_1 and 6MWD

improved 23% and 106 meters, respectively. The rate of responders was 63% and 87%, respectively. Pre-BLVR SGRQ was −4 points vs. −15 points (better) after EBV-BLVR, with a 79% responder rate [40].

Systems such as the Chartis™ have provided the opportunity for more objective patient selection, with more power to identify responders before the procedure. The system calculates airway resistance and measures CV in isolated lobes in the lung (Fig. 32.15).

In practical terms, when using the Chartis™, it is important to stretch the reading for at least 5 min, since deflation of the diseased lobe might take longer than that of a normal lung. Also, the catheter must be held still in the same position, or the exam will be compromised. The tip of the bronchoscope must be kept close to the transparent balloon catheter, which ensures a clear distal view and correct positioning.

Although collateral ventilation was first described as strictly intralobar, there is also an interlobar (between the lobes and across fissures) component in emphysema. Most probably, incomplete fissures are responsible for the interlobar collateral flow. There is no literature regarding the mechanism of collateral ventilation in incomplete fissures between lobes. It can be assumed that the mechanism is the same as within a lobe [20]. Collateral ventilation prevents absorptive atelectasis and thereby limits the improvement in lung mechanics [48]. In that sense, emphasis on fissure integrity and its role in

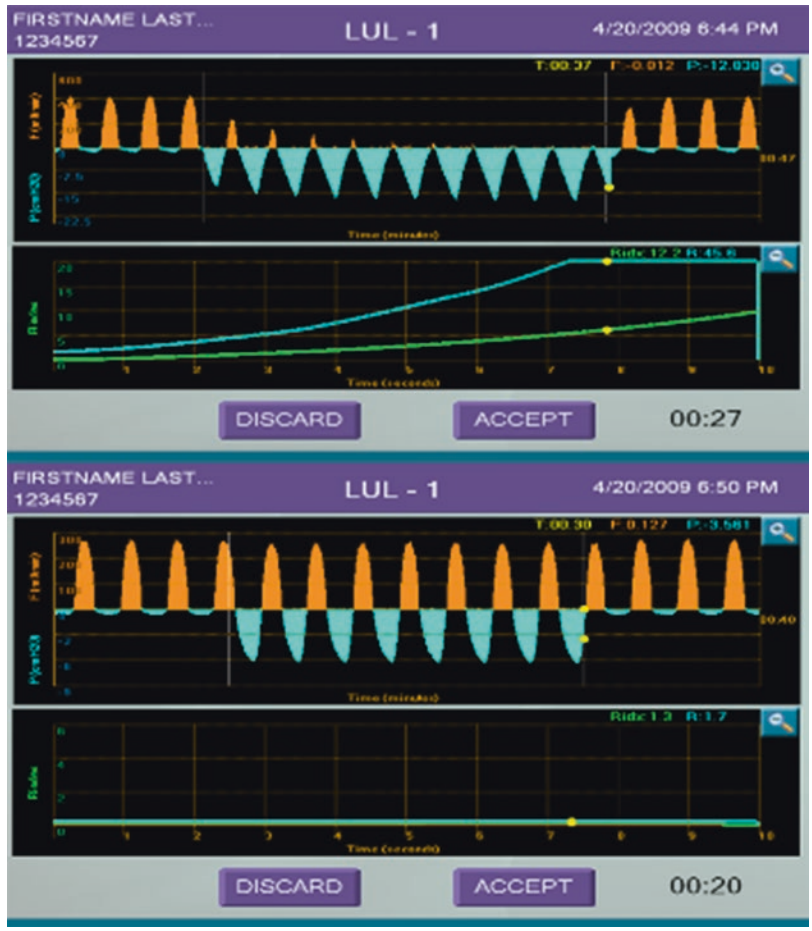


Fig. 32.15 Examples of negative (*top*) and positive collateral ventilation (*bottom*)

interlobar collateral ventilation is gaining attention [25].

Nevertheless, the role of small airway disease should not be neglected, since it may jeopardize the airflow through endobronchial segmental and/or subsegmental valves on expiration. Distal small airway collapse sustains air trapping more distally in the damaged lung parenchyma, preventing airflow through the EBV. In fact, this is possibly one of the main reasons for the failure of Chartis™ (no flow) in 10–20% of cases.

A good question is whether HRCT and Chartis™ measurement should always be used to define if a patient is a potential responder to EBVs. There are still a significant number of patients without LR response. Response rates of 65% were observed in patients with >90% fissure completeness [49].

Complications

An RCT including 362 patients in the treatment arm reported four deaths (1.1%) vs. one death in the control group (n = 183, 0.5%) within the first 90 days [4]. Considering only Zephyr™ valves, a composite of major events (death, respiratory failure, pneumonia distal to the valves' massive hemoptysis, pneumothorax, or prolonged air leak for more than a week) at 12 months was 10.3% for patients treated with valves versus 4.6% in the control group (p = 0.17). As expected, COPD exacerbation was the most common adverse effects [43, 44].

Pneumothorax

Pneumothorax is the main complication directly related to insertion of the valves [4]. Pneumothorax events tend to increase from 4–8 to 18–23% with lobar exclusion. This is possibly due to the rapid shift in lung volumes that causes rupture of parenchyma with pleural adhesions. Another reason for pneumothorax is barotrauma [50]. Our team has a rate of pneumothorax around 10–12%. This rate is lower than that reported by others but seems compatible with our observation of fewer patients achieving complete atelectasis. Thus, one of the main concerns of performing BLVR in patients with severe emphysema is pneumothorax feasibility. In properly selected patients, it is prudent to consider a 20% prevalence rate of pneumothorax. The median onset of pneumothorax after the BLVR has been reported to be 2 days [51]. Jarad has reported that all cases of pneumothorax in BLVR-treated patients occurred in the initial hours after implantation of EBVs [52]. Based on our experience, we recommend that patients, especially those who respond with quasi-immediate lobar atelectasis, should remain in the hospital for at least 5 days with minimal physical effort and daily radiologic monitoring.

Valve Dislodgement

EBV migration and dislodgment are infrequent (Fig. 32.16). The main reason for concern is the implantation of a valve whose diameter is too small, for example, if there was edema during Chartis™ measurements. Implanting long valves

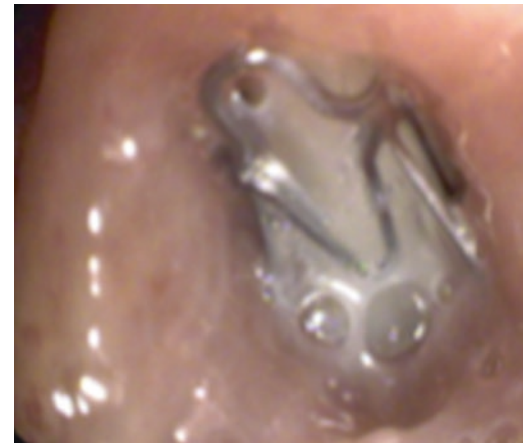


Fig. 32.16 Upward movement dislodgement (Zephyr™ 4.0) compressing the duckbill valve mechanism against the bronchial wall. Valve was removed and reinserted after 1 week. The picture shows local edema and inflammation

in a short bronchus is also a reason for concern. Dislodged valves must be removed and replaced with new valves [52]. Another advantage of using the VIDA/Apollo™ virtual bronchoscopy tool is the ability to calculate the better valve diameter and length.

A shorter version of the 4.0 mm Zephyr™ (4.0LP) has recently become commercially available. This shorter valve is very useful for implantation in B6 and has greatly facilitated manipulation in bronchi with less room than the average.

Bleeding

Granulation tissue can cause brisk and mild hemoptysis. Local measures using videofibrobronchoscopy usually solve these cases. Massive hemoptysis is a rare event, and valve removal is recommended in this situation (Fig. 32.17). Reinsertion of the valve a week later is enough to clear the problem. We had two cases of massive hemoptysis in 152 patients treated (plus 38 retreatments) with EBVs, representing 1.3% of the patients.

We suppose that one possible explanation is the fact that, after lobar exclusion, exaggerated distal negative pressure may induce mucosal bleeding in a few individuals. Patients with marked pulmonary hypertension could also be at risk because of the nature of the bronchial-pulmonary anastomosis in bronchial submucosa.

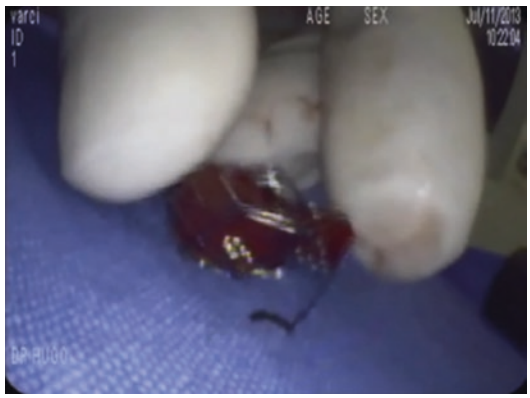


Fig. 32.17 Blood clot inside Zephyr™ 4.0 valve

COPD Exacerbation/Infection

COPD exacerbation occurs in up to 20% of patients following EBV-BLVR. One possible explanation for this is the occurrence of an inflammatory reaction triggered by the implantation of a foreign body. If that is the case, exacerbations may be linked to a systemic response with production of cytokines. In an attempt to prevent post-BLVR exacerbations or infection, prednisolone and antibiotics are prescribed prior and after the procedure.

In the future, cell therapy may play a role in modulating inflammatory processes in these patients.

Perspectives

Like LVRS, BLVR must reduce lung volume [4]. To overcome issues related to small airway disease or incomplete fissures, which prevent lung volume reduction, researchers must continue to create and develop solutions.

Handling Incomplete Fissures and Collateral Ventilation

AeriSeal Coupled with EBV

In the presence of incomplete fissures, the use of a liquid foam-based lung sealant system that functions at the small airway and alveolar levels (AeriSeal™) has been proposed. The AeriSeal™ foam is a proprietary polymer that is deployed via a catheter through the flexible bronchoscope operative channel. Within about 30 min of injection, the foam hardens to a rubbery consistency, blocking off the holes in the air sacs and sealing off the damaged regions of the lung. Over the course of several weeks, the air sacs deflate and the lung shrinks in size, clearing the way for the diaphragm to resume normal function. The main limitation of this therapy is an immune system inflammatory response with flu-like symptoms that resolves over the course of 2 or 3 days [53, 54].

It is known that MDCT associated with a resourceful software platform provides more pre-

cise analyses of imaging data for more objective insights, being capable to enable: (a) detailed visualization of interlobar fissures, (b) determination of lobar and segmental volumes, and (c) high-fidelity virtual bronchoscopy. Once this "anatomical map" showing emphysematous areas and areas lacking fissure integrity is available, it might be possible to use fibrin foam sealant for closure of interlobar collateral ventilation holes. In some patients, the association of induced fissure integrity by biologic foam sealant with valve implantation in segmental or subsegmental bronchi (third and fourth) might be effective. Of course, the maximization of benefits may invite a greater number of side effects, an aspect that deserves consideration.

New Spiracles

The hypothesis that ventilation of emphysematous lungs would be enhanced by communication with the parenchyma through holes in the pleural surface was tested by Choong et al. [55]. In that study, fresh human lungs obtained from patients with emphysema undergoing lung transplantation were ventilated through the bronchial tree or transpleurally via "a small hole communicating with the underlying parenchyma over which a flanged silicone tube had been cemented to the surface of the lung (spiracle)." The authors observed that passively expelled volumes at 20 s were 94% greater through spiracles than via airways. Following passive deflation from the airways, an average of 1.07 L of trapped gas volume was recoverable via spiracles.

Spiracle efficiency to ventilate some lung regions was far better than via bronchi. Because of the extensive collateral ventilation present in emphysematous lungs, direct communication with the lung parenchyma through nonanatomical pathways has the potential to improve the mechanics of breathing and hence ventilation [55].

Promoting expiratory airflow through an alternative transthoracic wall pathway may resolve air trapping in emphysematous lungs in which small airway disease prevents airflow through the bronchial tree. [56]. Airflow diversion is the concept behind this uncanny spiracle design. Novel technologically advances could be developed based on this concept.

Interlobar Fissurectomy

The basic idea underlying "fissurectomy" is to overcome the lack of integrity of interlobar fissures. Video-assisted thoracic dissection can be used for stapling incomplete interlobar fissures. For that, it is necessary to perform intrafissure dissection of the pulmonary artery. To ensure safety, it is crucial to position the endoscopic stapler anteriorly to the artery. The 3.5 mm staple load seems ideal, used alone or reinforced with bovine pericardial patch. Because the intrinsic anatomical characteristics of emphysema pose some tricky challenges, this minimally invasive operative procedure must be performed by an expert and experienced surgeon [57].

As we know, contemporary VATS developments currently allow patients submitted to lobectomy and mediastinal dissection to be discharged within 2 days postoperatively, with minimal discomfort or pain.

Cell Therapy

We hypothesized that the associated use of EBV with intrabronchial administration of mesenchymal stromal cells (MSCs) at the EBV site would decrease the inflammatory process, thus improving lung function and quality of life in patients with severe COPD. Three brazillian universities were involved in this project (Universidade Federal do Rio Grande do Sul, Universidade Federal do Rio de Janeiro, and PUC-Curitiba—NCT01872624). The results are currently being prepared for publication.

Ten patients were treated with EBV + MSCs (n = 10), and five patients were treated with EBV + saline (n = 5). All were monitored during 90 days. MSC delivery was not associated with toxicity, death, or serious adverse events. A decrease in levels of circulating C-reactive protein was observed at day 30 and 90 ($p < 0.0001$,

p = 0.0009, respectively) after MSCs administration.

These yet unpublished data sample will provide a basis for subsequent investigations using MSCs as concomitant therapy.

Sleep Medicine and Pulmonary Hypertension

Whether COPD or obstructive sleep apnea (OSA) interacts to increase the prevalence of both disorders in a given population is still not clear. However, it is understood that this association puts patients at risk for more nocturnal desaturations and potential complications, including pulmonary hypertension and heart rhythm disturbances. In smokers with OSA, increased gas trapping and emphysema as assessed by CT imaging are associated with a decreased apnea-hypopnea index [58].

Pulmonary vascular resistance and right ventricular remodeling have also been observed in patients with overlapping COPD and OSA, which could relate to higher risk for pulmonary hypertension in this population [59]. OSA is an established risk factor for recurrent atrial fibrillation. An elevated incidence of new-onset atrial fibrillation has been demonstrated in overlapping COPD and OSA patients [60]. Thus, OSA should be evaluated particularly in GOLD III and IV patients.

Despite an upper limit of normal of 20 mm Hg for pulmonary artery pressure (PAP), current guidelines define pulmonary hypertension (PH) as a mean PAP ≥25 mm Hg. Assessment of PAP requires right heart catheterization. In COPD, most hemodynamic studies involving a large number of subjects have been performed in patients with advanced disease (GOLD IV stage), who are candidates to either lung transplantation or LVRS. In this group, the prevalence of PH is very high, affecting more than one-third of patients [61].

In conclusion, much research is still necessary to help emphysema patients. Emphysema is a complex condition, and much remains to be learned regarding pathophysiology, COPD phenotypes, pulmonary vascular bed, interlobar airflow, exercise, nutrition, and other aspects including the quality of sleep. In addition to essential pathophysiological research, efforts must be made to devise interventions that underscore the biopsychosocial well-being of emphysema patients.

Disclosure AM and HGO are investigators in the PulmonX Endobronchial Valves Used in Treatment of Emphysema (LIBERATE Study) (NCT01796392); HGO acts as international specialist for PulmonX and is a consultant for VIDA Diagnostics.

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Bronchial Thermoplasty

33

Chase Hall, Adrian Shifren, Praveen Chenna, Alexander Chen, and Mario Castro

Introduction

Asthma is a chronic pulmonary disease characterized by recurrent episodes of bronchial hyperresponsiveness and airflow obstruction. During these episodes, patients experience coughing, wheezing, chest tightness, and dyspnea. The symptoms are typically reversible, either spontaneously or with treatment. These symptoms are the result of a number of pathophysiologic processes including airway remodeling characterized by airway epithelial injury, subepithelial fibrosis, excess mucus secretion, airway inflammation, and increased airway smooth muscle mass [1–3]. In a subgroup of patients with severe asthma, increased airway smooth muscle mass is thought to contribute considerably to persistent airflow obstruction that is difficult to manage, even with the maximal medical therapy [4]. Bronchial thermoplasty (BT) was developed to reduce airway smooth muscle mass in the treatment of severe persistent asthma.

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The Impact of Severe Asthma

Asthma is a major global health concern. Estimates suggest that almost 300 million people worldwide have asthma. In developed countries, the prevalence of asthma can exceed 15% [5]. While asthma is less prevalent in developing countries, the prevalence is increasing at an alarming rate [6]. Over 24 million people in the United States have asthma [7]. Poorly controlled asthma imposes a significant disease burden resulting in decreased quality of life, increased healthcare utilization, and significant economic burden [8]. There were nearly 13.6 million unscheduled physician office visits, 1.8 million emergency room visits, 450,000 hospitalizations, and 3600 deaths attributable to asthma in the United States in 2012 [7]. The estimated annual cost of asthma in the United States is approximately $56 billion, including $5.9 billion in indirect costs like lost work days, and $50.1 billion in direct costs such as medications and healthcare utilization [9].

Asthma is currently managed with the use of long-term controller medications, to achieve and maintain control of persistent asthma, and quick-relief medications to treat acute symptoms and exacerbations. Long-term controller medications include inhaled corticosteroids (ICS), long-acting β_2-agonists (LABA), muscarinic antagonists (LAMA), monoclonal antibodies (anti-immunoglobulin (Ig)E and anti-interleukin (IL)-5), and, in a subset of patients, chronic oral corticosteroids. Approximately 15–20% of asthmatic patients

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have severe persistent asthma, defined by the presence of persistent asthma symptoms despite treatment with the best available medications [4]. The most severe asthmatic patients have refractory asthma. These patients constitute approximately 5–10% of all asthmatic patients and are defined by a requirement for treatment with high-dose inhaled corticosteroids plus a second controller medication or the need for continuous or near continuous (> 50% of year) oral corticosteroids [10]. Patients with severe persistent asthma present the greatest burden to the healthcare system [11], with refractory asthmatics having the most concentrated healthcare utilization including intensive care unit stays [4].

Limitations of Current Therapeutic Interventions

Although the current treatment of severe asthma has improved the level of asthma control, refractory asthmatics do not achieve disease control and have recurrent exacerbations requiring systemic corticosteroids [4]. Chronic oral corticosteroid use is associated with undesirable side effects ranging from mild annoyances to serious, irreversible organ damage. These side effects occur more frequently with higher doses and more prolonged treatment and include immunosuppression, adrenal suppression, growth retardation, osteoporosis, skin thinning, hypertension, cataracts, glaucoma, muscle weakness, and increased risk of infection. Short-term side effects include stomach upset, headache, dizziness, anxiety, agitation, trouble sleeping, fluid retention, weight gain, high blood pressure, hypokalemia, elevated cholesterol, and vision changes. There is, therefore, a critical need for additional therapeutic options for patients with corticosteroid-dependent asthma.

More recently, several biologic agents that target specific subsets of patients with severe asthma are either approved for use or undergoing clinical trials. Omalizumab, a monoclonal antibody to IgE, is FDA approved and is appropriate for patients with a predominant allergic component and severe uncontrolled asthma [12]. The most recent biologic therapies are antibodies to IL-5, mepolizumab and reslizumab, that are best suited for severe uncontrolled asthmatic patients with a predominant eosinophilic component [12]. Over the past decade, BT has been developed as a novel device-based approach for the treatment of severe persistent and refractory asthma.

The Rationale for Bronchial Thermoplasty

In normal airways, smooth muscle offers support, enables mucus clearance, enhances cough, and promotes lymphatic flow [13]. Chronic asthma is associated with a pathologic increase in airway smooth muscle mass [2, 14]. This excess airway smooth muscle constricts in response to asthma triggers resulting in airway hyperresponsiveness, bronchospasm, and severely reduced airflow, leading to difficulty breathing during asthma exacerbations. Early investigations into mechanisms of airflow obstruction and airway resistance demonstrated that 75% of airway resistance occurs in the first 6–8 generations of airways, indicating that larger airways are critically important [15]. Therefore, physical reduction of the increased airway smooth muscle mass of asthmatic patients, even in larger airways, could have significant conceivable benefits [16]. By reducing the amount of airway muscle present, the potential for bronchoconstriction may be reduced. The benefits of such an intervention might include less severe bronchoconstriction during exacerbations with fewer symptoms of airflow obstruction and less variability of disease [17]. BT provides a new approach for treating severe persistent and refractory asthma through a reduction in this excess airway smooth muscle mass, with the goal of providing long-term relief of asthma symptoms and reducing exacerbations.

Indications and Contraindications for Bronchial Thermoplasty

BT is currently only indicated for the treatment of severe persistent asthma in patients over the age of 18 whose symptoms are not well controlled with inhaled corticosteroids (ICS) and long-acting beta-2-agonists (LABA) [Alair

Table 33.1 Inclusion and exclusion criteria for bronchial thermoplasty

Inclusion criteria	• Males or females age 18 or greater • Patient has asthma and remains uncontrolled despite using regular maintenance medication for past 12 months that includes: • Inhaled corticosteroid (ICS) at a dosage greater than 1000μg beclomethasone per day or equivalent, AND long acting ß2-agonist (LABA) at a dosage of ≥100μg per day Salmeterol or equivalent • Other asthma medications such as long acting muscarine antagonist (LAMA), leukotriene modifiers, or biologic therapy, are acceptable • Asthma confirmed by: (a) b-agonist reversibility of FEV1 ≥ 12 % following 360mcg albuterol OR (b) 20% fall in forced expiratory volume in 1 second (PC20-FEV1) after a challenge with methacholine ≤ 8 mg/ml if not receiving an inhaled corticosteroid (ICS) or ≤ 16 mg/ml if receiving an ICS • FEV1 ≥ 50% predicted pre-bronchodilator • Patient is a non-smoker for 1 year or greater (if former smoker, less than 10 pack-years total smoking history)
Exclusion criteria	• Asthma exacerbation (ED visit, hospitalization, course of increased systemic steroids, or urgent health care visit for asthma) during the prior four weeks • Asthma exacerbation requiring hospitalization during the prior six weeks. • Chronic oral steroid therapy greater than 30 mg per day • Respiratory tract infection within past 4 weeks • Patient has a known sensitivity to medications required to perform bronchoscopy (such as lidocaine, atropine and benzodiazepines) • Patient has bleeding diathesis, platelet dysfunction, and thrombocytopenia with platelet count less than 125,000/mm2 or known coagulopathy (INR > 1.5) • Patient uses an internal or external pacemaker, cardiac defibrillator, or other implantable electronic device • Patient has clinically significant cardiovascular disease, including myocardial infarction, angina, cardiac dysrhythmia, conduction defect, cardiomyopathy, aortic aneurysm, or stroke

package insert, Boston Scientific, Marlborough, MA]. Patients are deemed appropriate based on inclusion and exclusion criteria from previous and current clinical trials of BT and accepted treatment guidelines for asthma [17, 18]. Table 33.1 outlines important patient selection criteria.

The Bronchial Thermoplasty Apparatus

BT is performed using the Alair Bronchial Thermoplasty System® (Boston Scientific, Marlborough, MA). The system is composed of two principle components (Figs. 33.1 and 33.2):

1. The Alair Controller System, which includes a radiofrequency (RF) controller, a footswitch, and a patient return electrode
2. The Alair catheter, which includes an expandable 4-arm array and an actuator

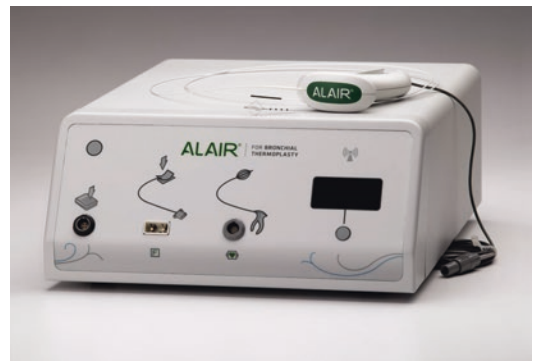

Fig. 33.1 The Alair radiofrequency controller with inputs for the footswitch (*right*), return electrode (*center*), and Alair catheter (*left*). The Alair catheter can be seen resting on the controller

The Alair catheter is a sterile, single-use device that is introduced into the airways through the working channel of an RF-compatible bronchoscope. The bronchoscope should ideally have an outer diameter of 4.9–5.2 mm and a working channel ≥2.0 mm [17]. The catheter has a distal 4-arm

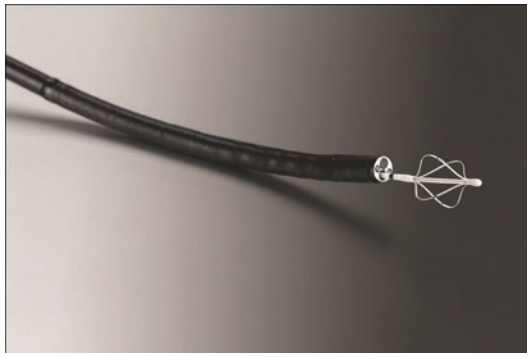

Fig. 33.2 The Alair catheter inserted through the working channel of the bronchoscope with the 4-arm array fully expanded

electrode wire array that expands to contact the airway wall when the proximal actuator is activated. The catheter is connected to the RF controller by a cable attached to its proximal end. The controller also has inputs for the footswitch and the patient return electrode. The footswitch allows the bronchoscopist to initiate delivery of RF energy. The return electrode completes the circuit, providing a pathway for the return of electrical current. This gel electrode is typically placed on the patient's chest or thigh. The RF controller delivers RF energy to the expanded 4-arm array in contact with the airway wall for a duration of 10 s. The RF controller utilizes sensory data from the catheter to limit current, power, voltage, time, and temperature of the RF energy delivered. This allows for the proper intensity and duration of RF energy to be applied while minimizing collateral airway damage. If the bronchoscopist determines that early termination of RF energy is needed, the footswitch can be pressed and released a second time to cease energy delivery [19]. The RF controller also safeguards against incorrect device setup. If any of the individual components are incorrectly connected, or the catheter electrodes fail to contact the airway wall, the device will not deliver RF energy.

Overview of the Bronchial Thermoplasty Technique

BT is performed under conscious sedation to a moderate level or general anesthesia. Visible airways distal to the main stem bronchi are treated by activation of the RF probe against nonoverlapping adjacent airway segments. Airways between 3 and 10 mm in diameter are systematically targeted, starting distally and moving proximally, being careful to avoid overlap with areas already treated [16, 19, 20]. Three sequential procedures are performed with a minimum interval of 3 weeks between each procedure. This allows for adequate healing of the airways between treatments and minimizes the likelihood of an asthma exacerbation [17]. Each treatment addresses a separate lobe, with the exception of the right middle lobe (RML). The RML remains untreated due to its narrow opening and the theoretical concern that inflammation related to the procedure may result in the development of RML syndrome [21]. However, recent experience suggests that the RML can be treated safely [22]. The right lower lobe is treated first, followed by the left lower lobe. Finally, both the right and left upper lobes are addressed in a single treatment. Each treatment takes approximately 45 min to 1 h to perform [16].

Pre-procedure Preparation

In order to facilitate successful BT, adequate pre-procedure preparation is essential. Pre-procedure preparations include (1) reassessing asthma stability and status on the day of each procedure; (2) administration of oral steroids (prednisone 50 mg daily) 3 days before, on the day of, and after each procedure; and (3) administration of inhaled bronchodilators, antisialagogues, anxiolytics, sedatives, and topical anesthetics to facilitate an uneventful procedure.

Clinical assessment of the patient on the day of the procedure is the first step in performing BT. The patient should have no contraindications to routine bronchoscopy. It is imperative to rule out current respiratory tract infections and ensure that the patient has not had a severe asthma exacerbation within 2 weeks of performing the procedure. Finally, the patient should be at baseline with respect to their asthma symptoms and pulmonary function testing performed on the day of the procedure by confirming that the patient's FEV_1 is within 15% of their baseline value [18, 23]. If any of the recommended criteria are not met, bronchoscopy should be postponed.

To reduce inflammation resulting from the application of thermal energy, patients are prescribed

oral corticosteroids (equivalent to 50 mg/day of prednisone) starting 3 days prior to the procedure, on the day of the procedure, and for one day following the procedure [17]. Patients on chronic oral steroids should be increased to the level used to treat their exacerbations. Antisialagogues are administered on the day of the procedure to reduce salivary and tracheobronchial secretions. At our institution, the antimuscarinic agent glycopyrrolate (0.2–0.4 mg IV/IM) is administered a minimum of 30 min prior to initiation of the procedure. Lastly, bronchodilators are administered prior to the procedure to help ameliorate bronchospasm. We make use of nebulized albuterol (2.5–5.0 mg), but albuterol may also be dispensed through a metered-dose inhaler (four to eight puffs) [24].

Maintaining adequate analgesia and proper sedation during BT is necessary because each procedure lasts for up to 1 h. At our institution sedation is accomplished with the combination of a short-acting benzodiazepine and a short-acting narcotic, specifically midazolam (Versed) and fentanyl (Sublimaze). Midazolam (1–2 mg IV initial bolus followed by repeated 1–2 mg IV doses) and fentanyl (50–100 mcg IV initial bolus followed by repeated 25–50 mcg IV doses) are administered alternately throughout the procedure. Sedation level is frequently reassessed during the procedure, and additional sedation is administered as needed. Benefits of this specific drug combination include familiarity with the drugs, rapid onset of action of both agents and their additive effects, convenient dose titration, and the ability to rapidly reverse either agent if needed [18]. Other agents including propofol have been utilized for sedation. Some centers have utilized general anesthesia administered with anesthesiologist assistance. Ultimately, the final decision on sedation is dependent on the physician performing the procedure and institution-specific guidelines.

In order to suppress the cough reflex during bronchoscopy, topical anesthetics are administered prior to and during the procedure. At our institution, anesthetization of the upper airway is achieved using 4 mL of 2% lidocaine nebulized through a mask prior to the procedure. Next, the posterior pharynx and laryngeal area are anesthetized with 5 mL of 1% lidocaine using a syringe with blunt-tip catheter directed over the back of the tongue. The bronchoscopy is initiated, and the bronchoscope is advanced to the level of the vocal cords, which are directly anesthetized with two to three 2 mL aliquots of 1% lidocaine delivered through the working channel of the bronchoscope. Finally, the trachea, carina, and each of the main stem bronchi are anesthetized with 2 mL aliquots of 1% lidocaine until the patient appears comfortable and exhibits minimal coughing. When the bronchoscope is advanced into the airway segments targeted for treatment, additional 2 mL aliquots of 1% lidocaine can be administered. During the procedure it may be necessary to administer additional targeted doses of lidocaine utilizing the intervals when the catheter is removed from the bronchoscope for suctioning. In our experience, the use of 1% lidocaine limits the potential for toxicity. While elevated levels of lidocaine have occurred, toxicity is rare. Lidocaine doses in the range of 400–600 mg (9 mg/kg) appear to be safe in asthmatic patients undergoing bronchoscopy as long as patients are monitored continuously for evidence of toxicity [25, 26]. Signs and symptoms of toxicity include lightheadedness, dizziness, headache, visual disturbances, metallic taste, muscular twitching, tremors, perioral tingling, auditory disturbances, seizures, or loss of consciousness [27].

Due to the length of the procedure and the level of sedation required, the use of an airway device may become necessary. An endotracheal tube (ET) can be used to maintain a patent airway and minimize the number of desaturations but runs the risk of irritating the asthmatic airways, potentially triggering bronchospasm. At our institution, a laryngeal mask airway (LMA) is used when performing BT. It does not enter the trachea, protects the upper airway, and provides comparable benefits to an ET tube. Ultimately the discretion of the bronchoscopist and their level of comfort with the various airway devices will determine which device is optimal.

Intra-procedural Technique

Pathway planning is performed at the beginning of each BT procedure. This is essential and guarantees that no targeted bronchopulmonary segments are missed during each procedure. It also ensures that each targeted segment is treated once, and only once, and that no overlapping ablations are performed. Pathway planning is accomplished by inspecting, identifying, and

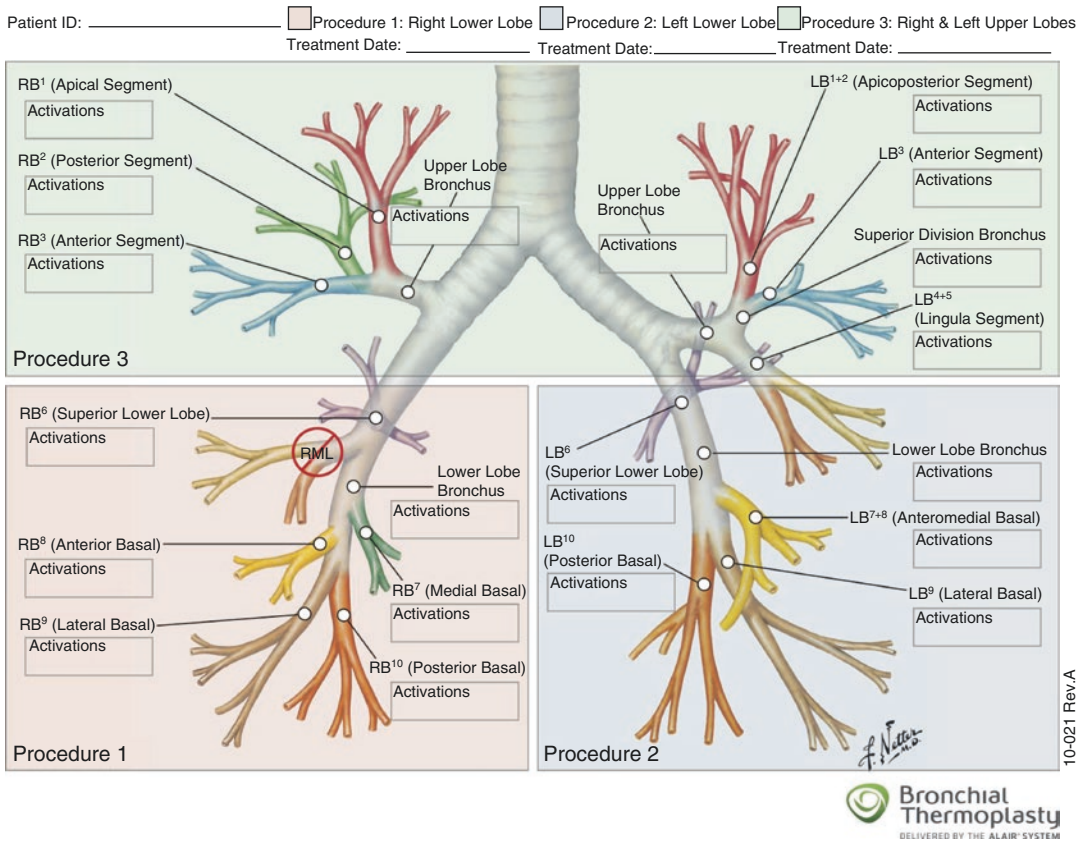

Fig. 33.3 Diagram of the tracheobronchial tree. The diagram can be used for mapping of the airways and thermoplasty planning prior to starting treatment. Activations performed during the procedure can be noted and recorded

mapping out the segments targeted for treatment. A systematic, methodical, and consistent approach is key, working from distal airways to proximal and from airway to airway across the lobe being treated to ensure that all accessible airways are identified and treated only once [17, 18]. Within each segment, subsegmental airways should also be identified and treated. We recommend moving from superior airways to those that are more inferior or from airways to the right of the field of view toward those to the left. Diagrams of the tracheobronchial tree can assist in both planning BT and documenting treated airway segments (Fig. 33.3).

Once planning is complete, RF ablation may be initiated. The bronchoscope is directed into the desired segment or subsegment of the lobe under visualization. The Alair catheter is deployed through the working channel of the bronchoscope into the targeted area under direct bronchoscopic visualization until the desired location is reached. The diameter of the non-expanded catheter is 1.5 mm and is used to determine the diameter of the targeted airways. Once the catheter tip is at the desired location, the actuator is gripped allowing the arms of the catheter array to expand into contact with the airway wall. The degree of pressure applied to the actuator is determined by visualization of the expanding array in more proximal airways, while resistance guides the bronchoscopist in more distal segments where visualization is not possible. Once all four electrode wires are firmly in contact with the airway wall (Fig. 33.4), the footswitch is depressed (activated) and released and RF energy is delivered automatically for approximately 10 s [17, 23]. The actuator is then released, partially collapsing the electrode array, and the catheter is retracted 5 mm proximally.

This distance corresponds to a set of black markings present on the distal end of the catheter just proximal to the electrode array. These markings guide withdrawal of the catheter during the BT ensuring that the electrode array is positioned adjacent to, but does not overlap, the previous activation site (Fig. 33.5). If contact with the airway walls is not adequate during an attempted activation, a different audible signal will be emitted from the RF controller notifying the bronchoscopist. In these instances, the array will need to be collapsed and the catheter will need to be repositioned prior to retreating that particular area. The airways are always treated from the smaller more distal subsegments all the way to the most proximal main lobar bronchi. The usual number of activations per treatment session varies, and the usual range for successful activations is between 50 and 100 per lobe.

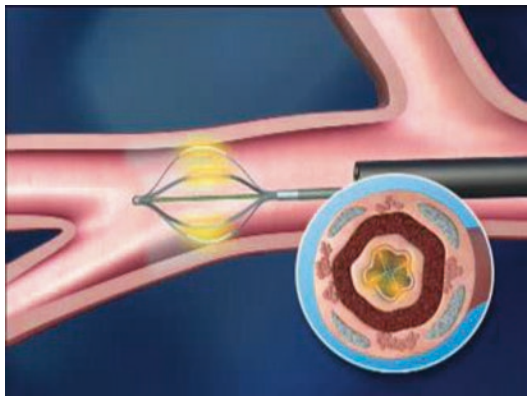

Fig. 33.4 Longitudinal and cross-sectional representation of an expanded Alair catheter making contact with the bronchial wall during activation

In our experience, and based on the manufacturer's recommendations, the following may assist when performing BT:

1. Be careful to ensure that the catheter does not kink or bend during insertion into the working channel of the bronchoscope as this can damage the catheter.
2. Avoid flexing the distal end of the bronchoscope when the catheter tip is in the working channel for the same reason.
3. Avoid deploying the catheter far beyond the view of the bronchoscope to ensure patient safety.

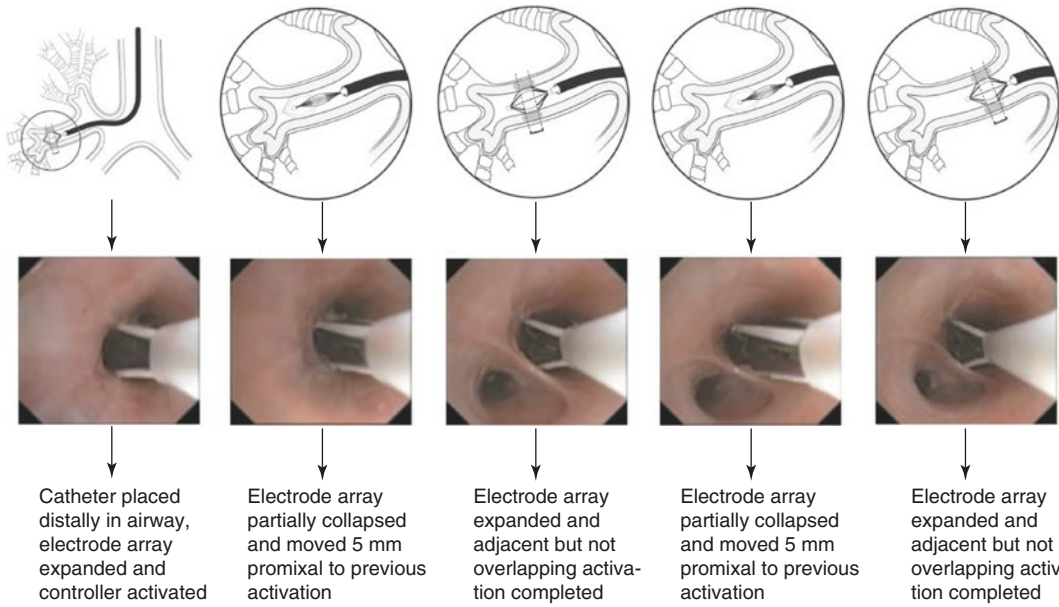

Fig. 33.5 Schematic and bronchoscopic views of the Alair catheter during sequential activations

4. Since most subsegments do not require full expansion of the catheter array for contact with the airway walls, avoid overexpanding the electrodes as this may cause inward deflection of the individual arms and loss of contact with the airway wall.
5. Accumulation of mucus or secretions in the airways or on the electrode array may require periodic catheter removal from the working channel for catheter cleaning and patient suctioning—at these times additional topical lidocaine can be administered to provide continued patient comfort.
6. The RF controller will automatically stop the RF signal if an abnormality is detected—if this happens repeatedly, the entire system should be checked for problems starting at the patient end and working backward to the controller [Alair package insert].

The technique for the second and third treatments is identical to the first with one important addition. Prior to initiating the second and third treatments, the lobe treated at the previous session must be inspected before starting pathway planning to evaluate for airway secretions or inflammation that may require suctioning or postponement of the current treatment.

Post-procedure Care

After BT is completed, normal post-bronchoscopy monitoring is performed, often in conjunction with institution-specific practice guidelines. Because of the increased doses of sedation required for the prolonged bronchoscopy, patients should be monitored for the presence of an intact gag reflex and tolerance for oral liquids on recovery from sedation. In addition, patients undergoing BT must have serial post-procedure FEV_1 tests performed after bronchodilator administration. In order to be discharged home, the post-procedure FEV_1 should be ≥80% of the pre-procedure *post-bronchodilator* value. Upon discharge, patients need to be advised of potential adverse events and reminded to take their remaining prophylactic steroid doses. Since patients undergoing BT have severe asthma, worsening of respiratory-related symptoms, including wheezing, dyspnea, chest discomfort, and cough, is not uncommon following the procedure [20, 28]. These typically occur within 1–2 days of treatment and resolve over 1 week with standard treatment with bronchodilators and systemic steroids. As a result, patients should be contacted at 24 h, 48 h, and 1 week post procedure to assess their respiratory status. Alternatively, very severe or labile asthmatics may be admitted overnight to the hospital for observation. Lastly, the patient should be assessed at a clinic visit 2–3 weeks after the procedure to determine whether they are stable for the next BT [23].

Possible Therapeutic Mechanisms of Bronchial Thermoplasty

The potential mechanisms of BT have been studied in a bovine tracheal smooth muscle model. Smooth muscle responsiveness is substantially reduced a few seconds after application of 60 °C heat and is eliminated by 5 min posttreatment [29]. The intervention appears to be dose-dependent, and the desired effect does not progress. The immediate loss of airway smooth muscle cell function in this model suggests that the high temperature disrupts actin-myosin interactions, possibly through denaturation of muscle motor proteins [29]. Identification of this airway smooth muscle target also introduces the possibility of other therapeutic interventions focusing on abolition of the smooth muscle spasm cascade [16, 29].

At least four clinical studies to date have demonstrated a significant reduction in airway smooth muscle in severe refractory asthmatic patients treated with BT [30–33]. The first study evaluated biopsies in ten patients 15 days before and 3 months after BT [33]. Following BT, smooth muscle decreased to 48.7–78.5%. Interestingly, a 50% decrease in smooth muscle was found in the RML which was not treated. Three subsequent studies, involving a total of 38 patients, have

demonstrated an approximately 50–60% reduction in smooth muscle mass following BT [30–32]. Furthermore, a decrease in nerve endings (9.5-positive nerves) [30], type I collagen [31], transforming growth factor-β1, CCL5, and eosinophils in BAL and an increase in tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) have been found following BT [32]. Lastly, whole transcriptome gene expression analysis in 15 patients before and after BT has demonstrated a significant decrease in genes associated with T-cell activation, neuron homeostasis, and eosinophilic inflammation, suggesting a systemic response to BT [34].

Preclinical and Non-asthmatic Evidence for Bronchial Thermoplasty

Animal studies in non-asthmatic dogs demonstrated that the application of thermal energy to airway walls attenuated methacholine responsiveness for up to 3 years posttreatment [19]. Degeneration or lack of bronchial wall smooth muscle was seen as early as 1 week following treatment, and the extent of the smooth muscle changes was inversely proportional to bronchial responsiveness**.** No evidence of smooth muscle regeneration was noted over the 3 years of study. Adverse effects in these animals included cough, airway edema, increased mucus production, and blanching of airway walls at the sites of catheter contact.

The first human study of BT was a feasibility study in individuals undergoing targeted lung resection for lung cancers [35]. Eight individuals underwent BT to visible airways within the areas of the lung selected for resection. BT was performed at 3–9 treatment sites per patient, 5–20 days prior to scheduled lung resection. There were no significant adverse events, and at the time of resection, bronchoscopy was generally unremarkable. Only airway narrowing, excess mucus, or linear blanching was noted. The treated lung tissue showed airway smooth muscle changes at approximately 50% of the treated areas [35].

Clinical Evidence for Bronchial Thermoplasty in Asthmatic Patients

Since 2005, numerous human studies of BT in mild to moderate asthmatics, and later moderate to severe refractory asthmatics, have been performed to identify appropriate candidates, adverse events, and expected outcomes with BT [24, 28, 35, 36].

The first study of BT in mild to moderate asthmatic patients was a prospective observational study of 16 patients at 2 centers in Canada. It was a single-arm study designed to evaluate the safety of BT [20]. Patients were pretreated with prednisone, either 30 or 50 mg, on the day before and the day of the procedure, and the three BT treatments were spaced 3 weeks apart. The right middle lobe remained untreated. There were no hospitalizations following the procedures. The most common post-procedure side effects were cough, bronchospasm, wheeze, or dyspnea. Symptoms commonly started 2 days after the procedure and resolved within 5 days of treatment [20]. Over 2 years of follow-up, the majority of adverse events were mild, and no severe events were felt to be procedure-related. Improvement in peak flow rates at 3 months posttreatment demonstrated the early effectiveness of the procedure when compared to baseline, but there was no significant change in peak flows at 2 years of follow-up. Symptom-free days also increased significantly 3 months post-procedure. A significant decrease in airway hyperresponsiveness (measured by methacholine challenge) was maintained at 3 months, 1 year, and 2 years following the procedure. BT in this study was associated with a high level of patient satisfaction 14–36 months after treatment [37]. In addition, annual CT of the chest demonstrated no parenchymal or airway changes related to the procedure. However, the small number of subjects and their relatively stable asthma status limited the findings of this study [13].

The Asthma Intervention Research (AIR) trial was a multicenter, prospective, randomized, controlled, non-blinded study to evaluate the effectiveness and safety of BT in subjects with

moderate to severe asthma [28]. All subjects (56 BT group and 56 control group) were on standard asthma care, requiring ICS (≥200 mcg beclomethasone equivalent) and LABA to maintain asthma control. All subjects demonstrated impairment with LABA withdrawal. Subjects were randomized to either BT plus ICS and LABA (BT group) or to ICS and LABA alone (controls). Treatments occurred in three sessions over 9 weeks and were followed by attempts to discontinue LABA at 3, 6, and 9 months post-procedure. Acute exacerbations on ICS alone were the primary study endpoint. Daily diaries documenting symptoms and rescue inhaler use and Asthma Quality of Life Questionnaire (AQLQ) and the Asthma Control Questionnaire (ACQ) were administered. Compared to the control group, the BT group experienced an increased number of adverse events during treatment period (up to 6 weeks after the last bronchoscopy). The events occurred largely within 1 day of BT and resolved on average 7 days after the onset. There were more hospitalizations in the BT group (four subjects required six hospitalizations) than in the control group (two hospitalizations) [28]. Reasons for hospitalization included asthma exacerbations, left lower lobe collapse, and pleurisy. Compared to control subjects, there was a significantly greater reduction in mild exacerbation rates at both 3 and 12 months in the BT-treated group (ten fewer mild asthma attacks per year). Severe exacerbations were lower in the BT-treated group compared to control subjects, but the difference did not achieve statistical significance. The BT group demonstrated significantly lower rescue medication use at 3 and 12 months (400 fewer rescue medication puffs). BT patients also had significant improvements in asthma control and quality of life (86 more asthma symptom-free days). Hospitalization rates for respiratory adverse events were low in the posttreatment period (between 6 and 52 weeks posttreatment) and did not differ between the two groups. The AIR study, however, was limited by its non-blinded design and a strong placebo effect in the control group and highlighted the need for a trial with a sham treatment arm [13].

The Research in Severe Asthma (RISA) trial was a multicenter, randomized, controlled clinical trial designed primarily to study the safety of BT in subjects with severe refractory asthma. Patients whose asthma was more severe than those in the AIR study were evaluated for procedure safety, changes in asthma symptoms, and daily medication use [24]. Subjects had to be symptomatic despite treatment with >750 mcg/day of fluticasone or equivalent and could also be taking oral corticosteroids (OCS) up to 30 mg prednisone/day. Thirty-two subjects were randomized to BT with ICS + LABA ± OCS ($n = 15$) or medical management with ICS + LABA ± OCS alone ($n = 17$). Following a 2-week run-in period, three BT treatments were performed 3 weeks apart. After treatment the study was divided into a 16-week corticosteroid-stable phase, followed by a 14-week corticosteroid wean phase, and finally a 16-week reduced corticosteroid extension phase. During the last 2 phases, attempts at decreasing oral steroid or ICS doses were made. During treatments there was a higher rate of hospitalization in the BT group (seven hospitalizations in four subjects) compared to controls (no hospitalizations). Reasons for hospitalization included asthma exacerbations and a partial left lower lobe collapse. However, during the 6-week posttreatment period, the BT group had a similar number of hospitalizations compared to controls and a lower number of hospitalizations when compared to baseline. During the corticosteroid-stable phase, the BT group demonstrated a significant reduction in rescue inhaler use (25 fewer puffs/week) and improvement in pre-bronchodilator FEV_1 (15.8% improvement). In addition, both AQLQ and ACQ scores improved. In the corticosteroid wean phase, all subjects in the BT group were able to initiate steroid weaning, while three subjects in the control group did not attempt steroid reduction at all. During the reduced corticosteroid extension phase, four of eight BT subjects were weaned completely off OCS through 52 weeks, compared to only one of seven control subjects. Although there was significant potential for placebo effect, BT-treated patients demonstrated significant improvement

in clinical asthma outcomes compared to the control group [24]. The study also demonstrated that BT could be safely performed in severe refractory asthmatic populations.

The most recent randomized controlled trial evaluating BT in severe asthmatics was the AIR2 trial [36]. AIR2 was a multinational, multicenter, randomized, double-blinded, and sham-controlled study. Sham procedures were identical to active procedures, and used an RF controller that provided audio and visual cues that mimicked the active controller, but did not deliver RF energy through the catheter. Neither subjects nor assessing physicians were aware of individual treatment assignments. AIR2 used a 2:1 randomization scheme (2 BT to 1 control subject) to randomize a total of 297 subjects (196 BT/101 sham) to 3 bronchoscopy procedures, separated by 3 weeks. All patients had severe asthma and were symptomatic despite management with ICS (>1000 μg/day beclomethasone or equivalent) and LABA (≥ 100 μg/day salmeterol or equivalent). The primary outcome was the difference in the change in AQLQ score between study groups from baseline measurements at 6, 9, and 12 months after the final BT treatment. During the treatment period, there was a higher rate of hospitalization for respiratory symptoms in the BT group (19 hospitalizations in 6 subjects) compared to controls (2 hospitalizations). Reasons for hospitalization included low $FEV_{1,}$ worsening asthma, segmental atelectasis, lower respiratory tract infections, an aspirated prosthetic tooth, and an episode of hemoptysis requiring bronchial artery embolization. Ten of the nineteen hospitalizations in the BT group occurred on the day of the procedure. However, in the 6-week posttreatment period, there was a significant 34% reduction in severe exacerbations in the BT group compared with the sham group. There was also a 66% reduction in days lost from work, school, or other daily activities due to asthma in the BT group.

The AIR2 BT group experienced improved quality of life compared to the sham group. This was demonstrated by a significant difference between the groups in average improvement in AQLQ score from baseline at 6, 9, and 12 months (posterior probability of superiority of 96.0%). To further determine the clinical significance of the data, the AQLQ data were categorized into the proportion of subjects in each group that achieved a significant and clinically meaningful improvement in AQLQ score of ≥0.5. While 64% of the sham group experienced improvements in AQLQ scores of ≥0.5, 79% of BT-treated subjects demonstrated the same. For the intention to treat population, the difference between the groups had a posterior probability of superiority of 99.6%, proving that the AQLQ score improvement in the BT group was superior to that in the sham group. However, the large percentage of sham subjects demonstrating improved AQLQ scores emphasizes the importance of the placebo effect in asthmatic populations.

During longer-term follow-up (>6 weeks after the last BT treatment), secondary endpoints also demonstrated clinically meaningful and statistically significant differences in favor of the BT group. These included reductions in asthma adverse events, emergency department visits for respiratory symptoms, and hospitalizations for respiratory symptoms. In addition, blinded evaluation of CT of the chest from 100 BT and 50 sham subjects did not reveal any parenchymal or airway changes related to the procedure. Overall, the AIR2 study demonstrated improved short- and long-term quality of life along with decreased healthcare utilization in severe refractory asthma treated with BT [36].

FDA Approval and Long-Term Follow-Up

In early 2010 the FDA approved the Alair Bronchial Thermoplasty System® for severe refractory asthma [Alair package insert,]. As part of the conditions of approval, the FDA required a post-approval study based on long-term follow-up of the AIR2 trial population. In addition, a second prospective, open-label, single-arm, multicenter, post-approval study (PAS2) is currently underway to assess the treatment effects and the short- and

long-term safety profiles of BT. Long-term follow-up data are available out to 5+ years from the lung cancer feasibility study [38], the AIR Extension Study [39], the RISA Extension Study [Asthmatx, Inc., personal communication], and the AIR2 trial. In AIR2 extension study, the average 5-year reduction in severe exacerbations and ED visits compared to the year prior to BT were 44% and 78%, respectively [40]. In addition, high-resolution CT images at 5 years demonstrated no structural abnormalities compared to baseline. These studies demonstrate the durability of the therapy without any obvious long-term structural consequences.

Future Directions

As with other new therapies for asthma, there is a need to identify which phenotypes will have an optimal response to BT with the fewest side effects. In an effort to elucidate which characteristics will predict a response to BT, 42 patients had baseline ACT, AQLQ, medication usage, demographic data, as well as pulmonary function testing analyzed and compared to repeat evaluation at periodic intervals for 12 months after BT [41]. In addition, baseline CT images were analyzed for wall area percentage and air trapping by automated software. A logistic regression model identified patients with a shorter duration of asthma and a higher number of severe exacerbations in the year prior to BT as potential responders. Prior studies have demonstrated that patients with severe asthma have heterogeneous ventilation defects that can be identified using hyperpolarized noble gas MRI [42, 43]. Currently, studies are ongoing utilizing this technology to identify high-yield targets for BT treatments, which may eliminate the need for multiple treatment sessions and associated complications [44].

Summary

In patients without significant contraindications to bronchoscopy, BT is a well-validated, FDA-approved therapeutic modality for the treatment of severe refractory asthma not well controlled on combination high-dose ICS and long-acting bronchodilator therapy. Clinical trials have demonstrated its efficacy and safety for improving quality of life, respiratory symptoms, and healthcare utilization in carefully selected patients with asthma. Patient selection is paramount and should be based on a careful evaluation by an asthma specialist. In addition, proper monitoring of patients both during and after the treatment period (up to 6 weeks after the last procedure) is mandatory. As experience with the procedure increases, we will further characterize the subsets of severe asthmatic patients obtaining maximal benefits from BT and, in doing so, improve outcomes while minimizing adverse events.

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Part VII

Interventional Bronchoscopy in Special Situations

Percutaneous Tracheostomy

34

Anthony W. Gray Jr.

Introduction and Definition of Procedure

The terms "tracheostomy" and "tracheotomy" refer to the creation of an opening in the trachea for the insertion of a tube. The procedure itself is sometimes referred to as a tracheotomy and the opening, a tracheostomy, though often the two terms are used interchangeably. The addition of the descriptor, "percutaneous," differentiates this technique from the previously standard surgical or "open" tracheostomy. This technique has transformed what was once a procedure performed almost exclusively in the operating room by surgeons alone, to one that can now be safely performed at the bedside by surgeons and internists alike.

History and Historical Perspective

The history of modern-day percutaneous tracheostomy is a relatively short one. At present, it is a procedure popularized by Dr. Ciaglia, a self-described "general thoracic surgeon," and published in 1985 [1]. The procedure of tracheostomy, however, has its roots dating back centuries ago, with descriptions found on Egyptian tablets dating before 3000 B.C. [2].

The term "percutaneous tracheotomy" was first described by Sheldon and Pudenz in 1957 [3] and "percutaneous tracheostomy" by Toye and Weinstein in 1969 [4]; however, these earlier descriptions of the procedure, initially using a slotted needle and cutting trochar and subsequently a modified Seldinger technique using a recessed cutting blade, did not gain popularity.

Inspired by Brantigan's description of cricothyroidotomy [5], Ciaglia drew inspiration for his newly described technique from the percutaneous nephrostomy Amplatz renal dilator set [1]. Ciaglia's serial dilation technique has undergone minor modifications over the past 27 years; however, the procedure remains after which the current technique is modeled.

Indications and Contraindications

The indications for percutaneous tracheostomy are similar to those for a conventional tracheostomy [6–8] and include:

(a) Bypassing unobstructed airway, whether secondary to trauma, foreign body, vocal cord paralysis, infection, or angioedema
(b) Removal of secretions from the distal tracheobronchial tree

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(c) Prolonged application of a mechanical ventilation or positive pressure ventilation (most common indication)
(d) Therapy for obstructive sleep apnea
(e) As an adjunct in preparation for head and neck surgery for temporary management of the airway in the perioperative period

Contraindications to percutaneous tracheostomy have changed over the years as more experience with the procedure is gained and published. The presence of an unstable cervical spine, a previous tracheostomy procedure, and the performance as an emergency procedure were, in years past, considered to be contraindications though there are numerous published reports (as well as personal experience) that have proven percutaneous tracheostomy a safe and acceptable procedure in these circumstances.

Anatomic abnormalities, such as significant thyromegaly, anterior neck mass, retrosternal location of appropriate tracheal rings, active infection at the proposed tracheostomy site, or unavoidable vascular structures, should be considered as present-day absolute contraindications.

While admittedly subjective, patients with "uncorrectable" coagulopathy, such as those with a prolonged prothrombin time/international normalized ratio, thrombocytopenia, or acquired defects of coagulation (patients with renal failure or those being treated with antiplatelet agents) should be considered as having a relative contraindication.

Similarly, one must proceed with great caution in patients receiving significant support to maintain adequate oxygenation and/or ventilation; perhaps waiting until survival from critical illness is more assured, and support somewhat reduced.

Description of the Equipment Needed

There are a number of different kits approved for placement of a percutaneous tracheostomy. Following Ciaglia's description of the multiple dilator technique in 1985 [1], several modifications have been proposed including a guidewire dilating forceps [9], a translaryngeal technique [10], a single-dilator technique [11], a rotational dilation technique [12], and finally a balloon dilation technique [13]. While there are no randomized, controlled trials comparing tracheostomies performed by the different techniques, a recent systematic, meta-analysis review of six different techniques was recently reviewed by Cabrini in 2012 [14]. The authors found that "overall, the different techniques and devices appeared largely equivalent" though there were minor differences favoring the single-dilator technique in comparison with the translaryngeal technique (fewer severe complications or need to convert to alternate technique) and also in comparison with the rotational dilation technique (fewer failures). Additionally, the single-dilator technique had fewer mild complications compared with the balloon dilation technique and was more expedient (1.5 vs. 4 min). Still, the meta-analysis lacks the strength of a randomized study, making the choice of technique operator dependent.

With these limitations in mind, the technique outlined within this review (below) describes the most commonly used method, the single-dilator technique.

Application Technique

As is true for the "open" or surgical technique, modeled after Chevalier Jackson's description in 1909 [15], there is no single, standard technique for performing a percutaneous tracheostomy, though, in general, there are many similarities among the various percutaneous techniques.

The procedure can be performed either at the bedside or in the operating room though most prefer to perform at the bedside. When performed at the bedside, the risks associated with transportation of patients outside of the ICU are minimized, specifically the risk of accidental extubation or removal of catheters, among others. Additionally, there is also evidence that transport out of an ICU is associated with an increased risk of ventilator-associated pneumonia [16].

In the intensive care unit, however, the proceduralist may not have the benefit of an experienced anesthesiologist who is dedicated to the induction and maintenance of adequate analgesia and anesthesia. Therefore, the operator must ensure patient comfort personally or by enlisting the help of an assistant for this purpose.

Another variation in the performance of percutaneous tracheostomy is the use of the flexible bronchoscope by a skilled assistant. While not required for a successful procedure, and not outlined in Ciaglia's initial description of the procedure, it is nonetheless strongly recommended for a number of safety reasons. First and foremost, the correct placement of the newly placed tracheostomy tube can be assured under direct vision, rather than by indirect methods, for example, with the presence of bilateral breath sounds, absence of gastric air insufflation, or with monitoring of exhaled tidal volumes. Real-time avoidance of complications during the procedure, such as inadvertent placement above the first tracheal ring or below the third tracheal ring, or puncture through the posterior tracheal wall, for example, can be prevented.

Pre-procedure Checklist

1. The team (Fig. 34.1):
   (a) Physician/proceduralist
   (b) A surgical assistant (or trainee)
   (c) Bronchoscopist
   (d) Anesthetist (unless this role is delegated to the bronchoscopist or managed by the proceduralist)
   (e) Nurse
   (f) Respiratory therapist
2. Monitoring, to include pulse oximetry, electrocardiography, and blood pressure recording.
3. Emergency backup equipment to include laryngoscope, airway exchanger, endotracheal tube, tracheostomy tube (one size smaller), laryngeal mask airway (or similar), and resuscitation bag. Based on airway assessment, emergency equipment may also include an anesthesiologist or individual who is skilled in airway management in the event that unplanned extubation occurs prior to securing the airway with the tracheostomy.
4. Flexible video bronchoscope, the purpose of which is to assist with endotracheal tube repositioning, surgical site verification, documentation of midline entry into the tracheal lumen, and confirmation of tracheostomy tube position. Additionally, specimens for culture can be performed at the time of the procedure (generally prior to performance of the percutaneous tracheostomy) and bronchial hygiene or removal of clot and debris post-procedure.
5. Appropriate procedural kit and components including appropriate sized tracheostomy tube (and backup tube to include a duplicate tracheostomy tube as well as a tube that is one size smaller) (Fig. 34.2).

The Procedure in Detail

1. Pre-oxygenate with $FiO_2 = 1.0$.
2. Administer intravenous sedation and analgesia.

Fig. 34.1 Percutaneous tracheostomy team

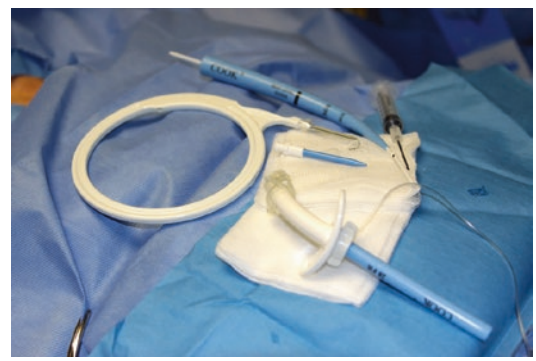

Fig. 34.2 Equipment needed

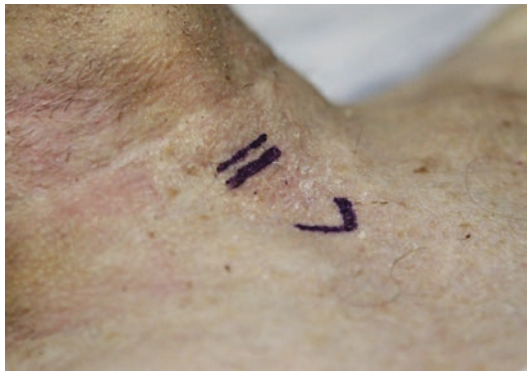

Fig. 34.3 Cricoid cartilage and sternal notch

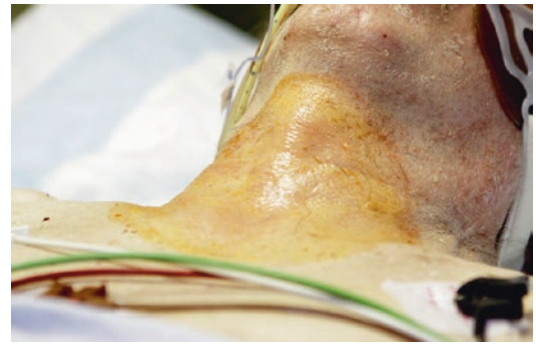

Fig. 34.4 Sterile preparation

3. Positioning of patient: appropriate height, bed maximally inflated if appropriate, the neck in neutral position or slightly hyperextended. Overdistention of the neck may distort the anatomy compared to the neck in a neutral position and lead to a less than optimal placement of the tracheostomy tube.
4. Identification of landmarks and surgical site (Fig. 34.3).
5. Chlorhexidine skin prep, sterile drape (Figs. 34.4 and 34.5).
6. Infiltration of the skin and subcutaneous tissues with local anesthesia (lidocaine 1% with epinephrine 1:100,000) (Fig. 34.6).
7. Skin incision. A 1.5–2.0 cm skin incision can be performed either in the vertical or horizontal plane. The benefit of performing a horizontal skin incision is primarily related to reduced scar formation post-decannulation, as this incision follows Langer's lines, once patient has improved and no longer is in need of a tracheostomy. The benefits of a vertical incision include avoidance of blood vessels, especially thyroidal vessels, as they approach the trachea laterally. Additionally, a vertical incision has the advantage of being extended either superiorly or inferiorly should either the initial incision location appear not to be above the first and second or second and third tracheal rings or, perhaps, an enlarged thyroid or crossing vessel be encountered; a modification of the placement of the tracheostomy can easily be accommodated by extending the vertical incision. The major disadvantage of a vertical incision is primarily related to the possibility of a larger scar post-decannulation; however, since the incision is generally of a fairly small size, that is, less than 2 cm, a

Fig. 34.5 Sterile drape

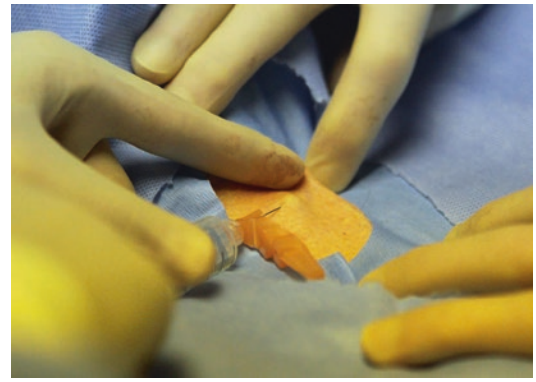

Fig. 34.6 One percent lidocaine with epinephrine injection

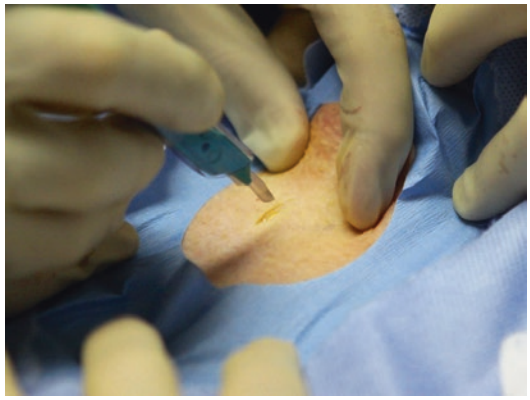

Fig. 34.7 Skin incision

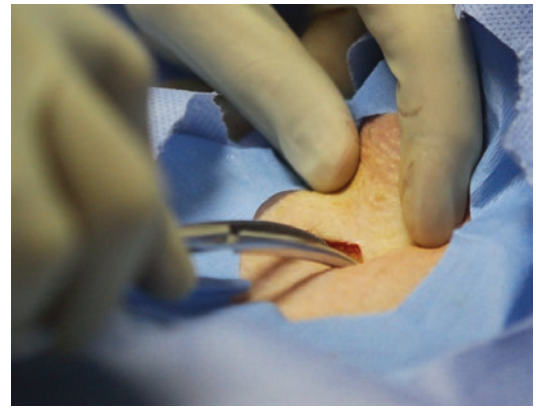

Fig. 34.9 Optional blunt dissection

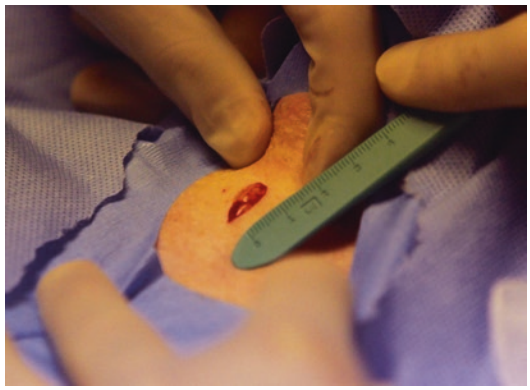

Fig. 34.8 One and a half to two centimeter incision

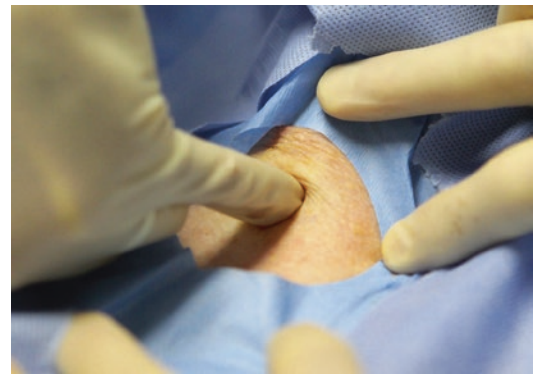

Fig. 34.10 Manual palpation

large surgical scar is generally not seen in either the horizontal or vertical approach.

When performing a vertical incision, the superior aspect should start at the inferior aspect of the cricoid cartilage (Figs. 34.7 and 34.8).

8. Following the skin incision, blunt dissection can be performed at the discretion of the proceduralist. Blunt dissection is often helpful in providing reassurance that appropriate tracheal landmarks are respected, that is, the cricoid cartilage and first and second tracheal rings. Blunt dissection is not necessary, however, in patients with thin necks or small distances between the skin surface and trachea. Dissection with electrocautery is to be discouraged given both the lack of adequate hemostasis that may be encountered when using deep electrocautery and the risk of fire given flammable skin prep and high oxygen concentrations used during the procedure. Manual palpation via the incision is then performed to confirm anatomic landmarks (Figs. 34.9 and 34.10).
9. Repositioning of the endotracheal tube. Following the skin incision, either with or without dissection, the bronchoscopist assists by advancing the flexible bronchoscope beyond the open end of the endotracheal tube as the proceduralist watches through the newly created incision for passage of the bright light of the bronchoscope, noted via transillumination. The ambient lights within the room may need to be dimmed or turned off to visualize the transilluminated light. Once this is done, the

bronchoscopist together with the proceduralist estimates the distance that the endotracheal tube must be withdrawn. The bronchoscopy assistant then partially deflates the cuff of the endotracheal tube (which has been previously unsecured), and together with the bronchoscope which is held in position just above the distal end of the endotracheal tube, that is, within the endotracheal tube, the bronchoscope and endotracheal tube are withdrawn *en bloc* under direct vision of the proceduralist, who is observing the position of the transilluminated light, to a level just above the appropriate previously identified position of the first and second or second and third tracheal rings. The endotracheal tube cuff is then reinflated and held in position by the bronchoscopy assistant.

Note: Throughout the procedure, titration of sedation and analgesia is performed based on sedation guidelines [17]. At the discretion of the proceduralist, and in conjunction with the bronchoscopist and team caring for the patient, the administration of a neuromuscular blocking agent can be considered.

10. Using a 14-gauge finder (catheter) needle attached to a fluid-filled syringe, the anterior trachea is punctured in the midline position between the first and second or second and third tracheal rings. The presence of air bubbles entering the fluid-filled syringe provides reassurance that the trachea has likely been entered. This is one of the most important parts of the procedure as it determines the final location of the tracheostomy tube. To assist in finding the appropriate midline location of the puncture site, the proceduralist should transfix the trachea between the thumb and either second or third fingers of the nondominant hand, superior to the planned insertion site (Figs. 34.11 and 34.12). The proceduralist should be standing on the same side of the patient as his/her dominant hand. That is, if the proceduralist is right-handed, he/she should be standing at the right side of the patient. The nondominant hand, then, is transfixing the trachea either just superior to the planned insertion site or higher at the level of the thyroid cartilage. By transfixing the trachea in this position, the proceduralist can enter the trachea midline between the two fingers that are being used to transfix the trachea, assuring a more likely occurrence that the finder needle will enter the trachea at the midline position. The cephalad position of the bronchoscope allows confirmation of appropriate positioning from within the airway with the exact positioning provided as the bronchoscopist describes the location based on the hands of a clock, for example, "the trachea has been entered at the 12 o'clock position." The proceduralist can also directly observe the video monitor if one is available. The optimal positioning of the puncture site is between

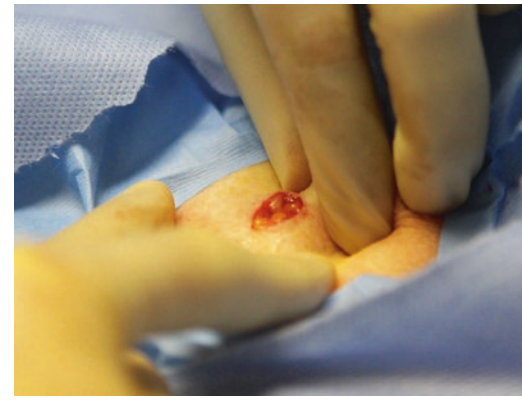

Fig. 34.11 Transfix trachea between index finger and thumb to prepare for central access

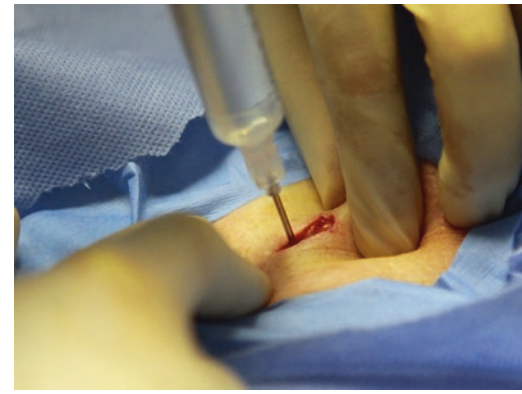

Fig. 34.12 Aspirate air with a fluid-filled syringe

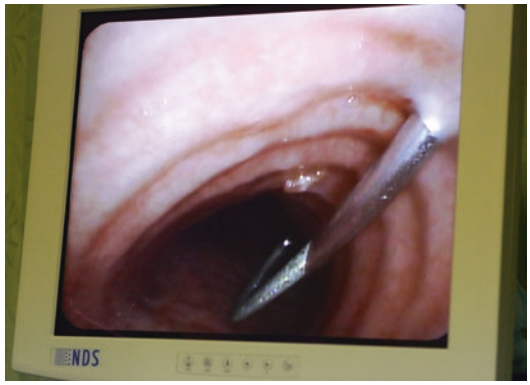

Fig. 34.13 Advance J-wire via finder needle

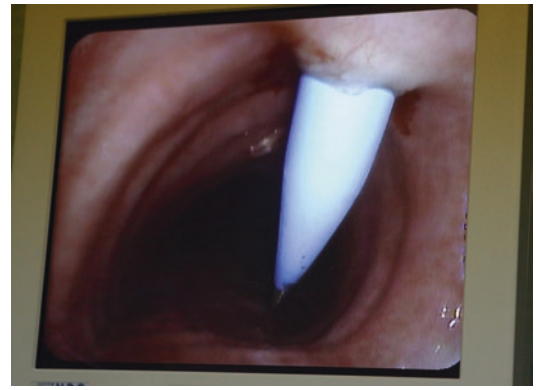

Fig. 34.14 Advance punch dilator

the 11 and 1 o'clock positions although a more lateral approach may be necessary based on anatomic considerations.

11. The fluid-filled syringe is removed and a J-tipped guidewire is advanced either through the finder needle or, if a catheter over needle approach is used, through the catheter after the needle has been withdrawn (Fig. 34.13).
12. A lubricated punch dilator is then advanced over the guidewire and into the trachea in a slight twisting motion. This allows for passage of the stiffening catheter, as described in the next step (Fig. 34.14).
13. The stiffening catheter is advanced over the guidewire to the skin surface.
14. The dilating catheter is then advanced over the stiffening catheter; its passage over or rather beyond the stiffening catheter is prevented by a small bulge near the distal end of the stiffening catheter. The stiffening catheter and dilating catheter can be preassembled and advanced over the guidewire as one unit to reduce the number of steps.
15. The dilating catheter, or catheters, is then held gently, similar to how one grasps a pen or pencil, and advanced over the guidewire into the airway (Figs. 34.15 and 34.16). Excessive force should be avoided when advancing dilating catheter as this often represents placement of the initial puncture through a tracheal cartilage. If this occurs, it is the preference of this author to reposition the puncture site, that is, repeating step 10 to ensure placement of the dilating catheter *between* tracheal rings. In this way, fracture of a tracheal ring, while not contraindicated, can be avoided. The dilating

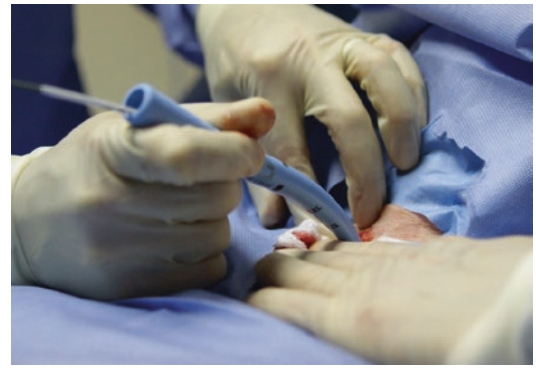

Fig. 34.15 Advance dilating catheter

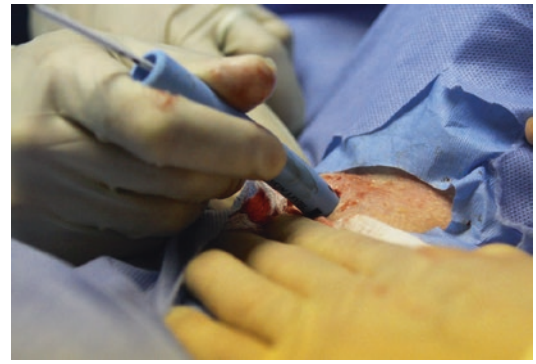

Fig. 34.16 Advance dilating catheter

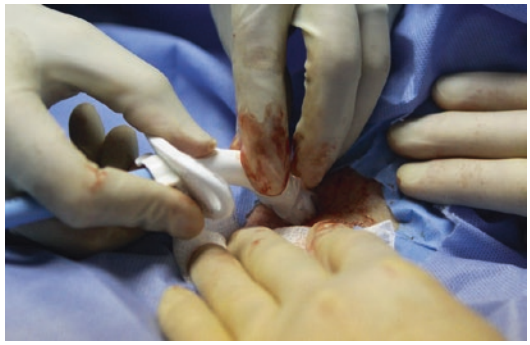

Fig. 34.17 Advance tracheostomy-obturator combination

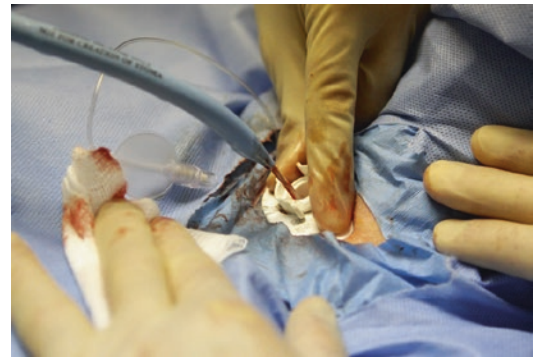

Fig. 34.18 Remove obturator-stiffening catheter-guidewire

catheter is advanced into the trachea gently and slowly up until the line of demarcation on the dilating catheter is at the same level of the skin surface. Less than full dilation may be preferable in patients in whom a smaller-sized tracheostomy tube is indicated and also in those patients in whom a coagulopathy is present or who are at a greater risk of post-procedural stomal bleeding.

16. The dilating catheter is then removed and replaced by the tracheostomy-obturator combination which is then advanced in a similar method as the dilating catheter (Fig. 34.17).
17. Bronchoscopic confirmation is then performed both from above the newly placed tracheostomy tube, that is, from the view from within the endotracheal tube, and also via the newly placed tracheostomy tube after the obturator-stiffening catheter-guidewire is removed en bloc (Figs. 34.18 and 34.19). The tracheostomy cuff is then inflated, and adequacy of returned tidal volumes provides another confirmation of appropriate positioning (Fig. 34.20). Following inspection, bronchial hygiene may be performed to ensure the absence of airway bleeding or removal of blood from the airway if necessary.

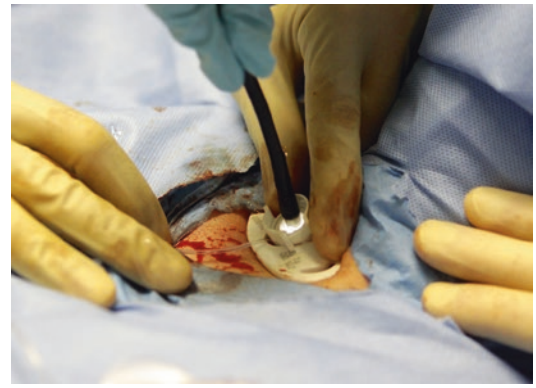

Fig. 34.19 Bronchoscopic confirmation

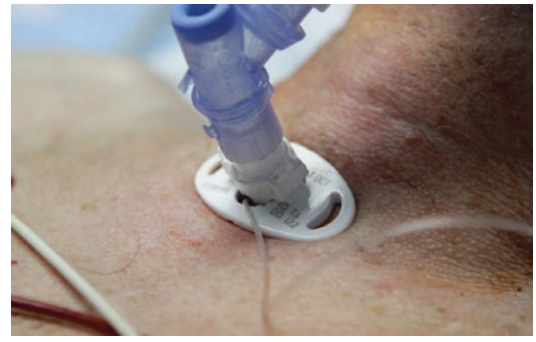

Fig. 34.20 Inflate cuff attach ventilator circuit

Evidence-Based Review

Complications: Comparison with Surgical Tracheostomy

There are numerous studies that have attempted to compare the complications of the percutaneous technique to the open technique. These are best summarized by Higgins and Punthakee in a meta-analysis designed primarily to compare complication rates using randomized or quasi-randomized clinical trials only [18]. Fifteen studies met criteria for analysis with 973 as the total number of patients included (490 in the percutaneous arm and 483 in open). Wound infection and unfavorable scarring favored the percutaneous route, while the risk of decannulation/obstruction favored the open route. There was no difference noted with respect to false passage, minor or major hemorrhage, subglottic stenosis, or death. Overall complication rate "trended" toward favoring the percutaneous route, mentioned here only because the p value *equaled* 0.05.

Specifically with regard to rates of infection, a recent meta-analysis using only randomized controlled trials again found no difference with regard to a number of different complications including bleeding, pneumothorax rate, and oxygen desaturation but, again, a statistically significantly reduced risk of post-procedural infection when compared with surgical tracheostomies [19]. This compares favorably with a large prospective, single-site non-randomized study of 640 trauma patients with more than 300 patients in each arm that also found a lower incidence of skin and soft tissue infections in the percutaneous arm (3.4% versus 7%, $p = 0.04$) [20].

Competence

Procedural competence is institution specific, and while there are no widely accepted guidelines for proof of competence, this author agrees with the American College of Chest Physicians recommendations which have been consistent over the past decade: a minimum of 20 procedures, performed in a well-supervised setting, is necessary to establish competency for trainees [21, 22]. Supporting this number is a well-conducted analysis of complication rates published by Massick [23] demonstrating a reduction in complication rate, and therefore an improved competency rate, after an initial cohort of 20 procedures.

Summary and Recommendations

The choice regarding which procedure to perform, that is, tracheostomy via the standard surgical route or by the percutaneous method, should not be guided by the desire to perform the least expensive or most expeditious or "newest" procedure; rather the skill and expertise of the operator and the right choice of the procedure for the individual patient—always respecting what is in the patient's best interest—should guide one's decision.

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Bronchoscopy Role in Interstitial Lung Disease

35

Maria Molina-Molina

Introduction

Interstitial lung disease (ILD) is a group of respiratory entities in which the main pathological alteration affects the interstitial alveolar structures but also can involve the small airways and the pulmonary vasculature [1]. Clinical, radiologic, and lung function presentations maybe common in several ILD [1]. Cytological evaluation and/or histological study are usually crucial to achieve the confident diagnostic and also to rule out other causes of interstitial lung pathology such as infections or cancer [1]. Surgical lung biopsy is usually too risky given the clinical, lung function or cardiovascular status and is only performed in 20–40% of cases [2]. Therefore, bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial lung biopsy (TBLB) is often the initial procedure of choice [2–4]. BAL and conventional TBLB may provide sufficient evidence to diagnose sarcoidosis, amyloidosis, hypersensitivity pneumonitis, eosinophilic pneumonias, organizing pneumonia, pulmonary Langerhans cell disease (histiocytosis X), Goodpasture's syndrome, lymphocytic interstitial pneumonia, some pneumoconioses, pulmonary lymphangioleiomyomatosis, and pulmonary alveolar proteinosis, as well as infections and neoplastic processes presenting with interstitial lung infiltrates [3, 4]. Since the introduction of transbronchial criobiopsy allowing a better preserved and bigger histological samples, the spectrum of entities diagnosed through bronchoscopy has broadened since almost all of histological patterns may be identified. When clinical information and HRCT findings are combined with BAL fluid analysis and/or transbronchial lung biopsy, a confident diagnosis may emerge that obviates the need for surgical lung biopsy [4]. However, some considerations should be made in order to take advantage from both procedures in ILD evaluation.

Bronchoalveolar Lavage (BAL)

BAL has gained wide acceptance as a safe method to obtain respiratory secretions for the examination of cellular and acellular components for both diagnostic and research purposes [5, 6]. Certainly, much data have been published over the past decades that demonstrate the utility of BAL to identify agents of respiratory infections and changes in the composition of the airspace environment associated with the presence of non-infectious parenchymal lung diseases. The introduction of high-resolution computed tomography

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(HRCT) at the end of the last century represented a revolutionary improvement in the diagnosis of specific forms of ILD and also a useful tool to decide the best place to obtain respiratory samples [6]. BAL is now routinely used as a tool to diagnose respiratory infections, study diffuse parenchymal lung diseases, and monitor the status of transplanted lung allografts [7]. Although the widespread use of BAL by pulmonologists, BAL cellular analysis, especially nucleated immune cell differential counts, may be underused in ILD diagnosis since its results differ from center to center and depend on multiple factors [8, 9]. BAL appearance and differential cell count should be interpreted appropriately and evaluated with an updated awareness of the potential diagnoses associated with each cellular pattern in order to provide useful diagnostic clues [7–9].

Technical Aspects of BAL Procedure

The usefulness of the BAL in ILD is only possible if (a) the bronchoscopist uses an appropriate technique to obtain the fluid; (b) the differential cell count is performed according to good clinical laboratory practice, by experienced personnel; and (c) cell count and evaluation is interpreted by an expert pathologist in interstitial lung diseases [6–8].

BAL technique through the fiber-optic bronchoscope is not difficult to perform, but it could reach best results if certain advices are followed [10–12]. To retrieve alveolar cells or cells from distal airspaces, a sufficient amount of isotonic saline should be instilled [12]. Proximal large airway secretions contamination should be avoided by maintaining the distal end of the bronchoscope in a wedged position in a segmental or subsegmental bronchus throughout the period of time required for the instillation and retrieval of saline aliquots [12]. Furthermore, aliquots should be aspirated immediately once the entire aliquot volume has been instilled. Many different BAL protocols have been published and consist of multiples aliquots: five or six aliquots of 20 mL each, three of 50 mL, or four of 60 mL [12, 13]. The first aliquot frequently represents bronchial airway cells and secretions, so it is recommended to keep it separate and just use it for microbiological analysis. The other aliquots should be pooled and used for cellular analysis [12, 13].

The right middle lobe and lingula of the left upper lobe have traditionally been used for lavage since they are easily accessible areas and allow good return of BAL fluid [10]. However, nowadays patients with ILD are routinely evaluated with chest HRCT images that are used to target areas of the lung that may be more representative of the disease process (ground glass attenuation, prominent nodularity, or fine reticulation) and that could increase the possibility to obtain relevant information (abnormal areas located proximal and peribronchial) [6].

If possible, the percentage of BAL fluid that is retrieved should be ≥30% of the instillation for a reliable cellular analysis [13]. An accurate cell count and evaluation of BAL require examination of at least more than 300 nucleated cells [6]. The presence of squamous epithelial cells suggests that oropharyngeal secretions have contaminated the BAL fluid. More than 5% of squamous or bronchial epithelial cells mean that the BAL sample is unsuitable for cell analysis. It is of key importance that the technicians handling the samples, analyzing the BAL slide preparations, and performing differential counts are adequately trained in proper identification of BAL cells [6]. Afterward, expert pulmonologists in ILD, familiar with BAL cell patterns, should interpret the BAL analysis results [8, 9].

BAL fluid obtained from healthy, never-smoking individuals contains a majority of alveolar macrophages (80–95%), some lymphocytes (5–12%), and very few neutrophils (<5%) or eosinophils (<1%) [4]. BAL cell count from smokers has a significantly increased total BAL cell amount, but the BAL differential cell count is similar than never-smokers or ex-smokers, except for a lower percentage of lymphocytes [4, 14]. Age can modify the total and differential BAL cell account. It seems that elderly subjects present more lymphocytes and neutrophils in their differential cell count and that the volume of retrieved fluid declines with advanced age [15]. However, a volume of instilled saline that range

from 100 to 250 mL appear to give similar cell differentials in individual patients with ILD [12]. When a bacterial infection is suspected during the study of diffuse lung infiltrates or coexist with noninfectious ILD, the first non-centrifuged aliquot of BAL should be examined for quantitative bacterial culture, including mycobacterial and fungal screening. If viral infection or intracellular bacteria (*Pneumocystis jirovecii*) are suspected, centrifuged BAL fluid enhances their detection through stains or viral nucleic acid probes [10].

ILD Cell Patterns and Diagnosis from BAL

A confident BAL cell evaluation, including differential cell count and other macro- or microscopic characteristics, the combination with clinical and imaging data provides relevant information that contributes significantly to the diagnosis of specific ILD (Table 35.1) [1, 5, 8, 16, 17]. Furthermore, cytopathological examination may rule out other causes of parenchymal lung diseases with a similar radiological pattern such as malignancies (bronchoalveolar and lymphangitic carcinoma) or infection (*P. jirovecii*) [18]. In the appropriate clinical and radiological setting, certain gross and cellular findings in BAL may help in the differential diagnosis for a specific ILD. Recent data suggest that predictive value of BAL for ILD diagnosis is very useful for some entities such as sarcoidosis (frequent and predominant peribronchial disorder), in contrast to rare forms of ILD or common forms that predominantly affect subpleural space (such as idiopathic pulmonary fibrosis—IPF) [19].

Table 35.1 BAL findings are important for the diagnosis of different interstitial lung diseases

Diagnostic	Bronchoalveolar lavage finding
Milky BAL fluid, PAS+	Pulmonary alveolar proteinosis
Bloody fluid	Diffuse alveolar hemorrhage
Eosinophils ≥25	Eosinophilic pneumonia
Lymphocytes ≥70%	Lymphoid interstitial pneumonia, nodular lymphoid hyperplasia, lymphoma
CD1a+ cells >4%	Pulmonary Langerhans cell histiocytosis
CD4/CD8 T-cell ratio > 3.5%	Sarcoidosis

BAL macroscopic appearance is very important. Retrieved BAL fluid that has milky or light brown appearance, with protein content that settles to the bottom of its container, clearly suggests pulmonary alveolar proteinosis (PAP) [20]. The diagnosis requires the confirmation through the positively staining with Schiff periodic acid (PAS+). In this case, whole-lung lavage is still considered the treatment for PAP, although there is no scientific evidence that supports the best protocol to perform it. On the other hand, a grossly bloody lavage fluid is suggestive of diffuse alveolar hemorrhage (DAH) when it increases in the sequentially retrieved BAL fluid aliquots [19]. Furthermore, alveolar macrophages can stain positively for hemosiderin if the BAL is performed 24–48 h after the onset of hemorrhage.

BAL lymphocytosis can be found in cryptogenic organizing pneumonia (COP), cellular nonspecific interstitial pneumonia (NSIP), hypersensitivity pneumonitis (HP), sarcoidosis, drug toxicity, and lymphoid interstitial pneumonia (LIP) [19]. When mast cells or plasma cells are also increased, the diagnosis of HP is more probable, although mast cells can be observed in sarcoidosis, drug reactions, ILD associated with collagen vascular disease, or COP [19]. A percentage of eosinophils higher than 25% is usually associated with eosinophilic lung disease, mainly acute eosinophilic pneumonia [21]. Neutrophil predominance is usually due to infection or acute lung injury, although some IPF patients also present increased neutrophilic count, but to a lesser degree.

Some morphological changes in alveolar macrophages are also important: cytoplasmic inclusions are suggestive of viral infection, and vacuolated cytoplasm with positive staining for fat can be observed in chronic aspiration pneumonitis, asbestos bodies in asbestos disease, dust particles in other pneumoconiosis, and phagocyted red blood cells in DAH [19].

BAL differential cell count utility in a patient with ILD that presents a usual interstitial

pneumonia (UIP) pattern in the thoracic HRCT is limited. It mainly helps identifying other non-IPF entities that can also present the same radiological findings. An increased lymphocyte cell count in BAL would suggest the possibility of chronic HP, fibrotic NSIP, or other diagnoses associated with BAL lymphocytosis [2, 3, 22, 23]. Therefore, no fiber-optic bronchoscopy is required for IPF diagnosis. However, if clinical or epidemiological data suggest other UIP non-IPF, BAL could help in the differential diagnosis, and it may help to identify some chronic HP [22, 23].

Flow cytometric analysis can improve the performance of BAL in some instances, mainly when the ILD differential diagnosis includes sarcoidosis, pulmonary Langerhans cell histiocytosis, and lymphoid malignancy [1, 19, 24]. However, due to the high cost of this procedure, flow cytometry is only used for the evaluation of CD4+/CD8+ cell ratio [19].

Alterations in BAL lymphocyte subsets have been widely examined, especially for sarcoidosis [1, 25]. Conventionally, a high CD4+/CD8+ T-lymphocyte ratio associated with BAL lymphocytosis is suggestive of sarcoidosis. However, elderly subjects can also present elevated CD4+/CD8+ ratio, so age is a variable to consider for appropriate interpretation [16]. Recent data have demonstrated that the presence of a CD4+/CD8+ ratio of ≥3.5 is relatively specific for sarcoidosis [19, 25]. However, the sensitivity of this ratio is low since many patients do not have an elevated ratio or may even have a low one [19]. On the other hand, a decreased CD4+/CD8+ ratio has been observed in HP, drug toxicity, COP, and eosinophilic diseases [4, 19]. Therefore, the efficacy of this ratio is low for other ILD different from sarcoidosis.

The diagnosis of pulmonary Langerhans cell histiocytosis can be supported by the presence of more than 4% CD1+ cells in BAL, which is more frequent in early stages of the disease [26]. These cells can be seen by means of immunohistochemistry or flow cytometry. Both techniques are also useful to identify monoclonal lymphocyte populations in the differential diagnosis of lymphoid diseases.

Finally, BAL cell analysis early in the study of an acute ILD, such as acute interstitial pneumonia, eosinophilic pneumonia, DAH, acute HP, acute COP, drug toxicity, or acute exacerbation of an underlying ILD, may help in their diagnosis [4, 19]. The study of BAL fluid can reveal infection or hemorrhage, large numbers of eosinophils (eosinophilic pneumonia), an increase of lymphocytes (acute HP and drug toxicity), or plasma cells (acute HP). Careful consideration of the respiratory and clinical status should be evaluated before performing BAL, since worsening in those parameters are not unusual and have been reported after this procedure [3, 5].

Some centers use less amount of instillation while performing BAL in acute disease, with good results. A risk-benefit analysis is in order, in a patient-to-patient bases [3].

Transbronchial Lung Biopsy (TBLB)

Some ILD are associated with typical histopathologic features that can be distinctive even in small lung biopsy specimens. Progressive ILD where the pathologic diagnosis is based on the recognition of different patterns and stages of the condition requires a surgical lung biopsy, whereas in most granulomatous pneumonias, conventional transbronchial biopsies may be enough to achieve a confident diagnosis. For many other ILDs, there is not enough evidence to make recommendations, but the possibility of bigger and better transbronchial samples using cryoprobes has brought new possibilities.

The main utility of the TBLB in ILD is based on the possibility of making a specific diagnosis avoiding a surgical lung biopsy. Bronchoscopy can be done as an outpatient procedure, usually with minimal morbidity and mortality [27, 28]. Recently, a new system for obtaining samples through fiber-optic bronchoscopy has been developed: the cryoprobe. It is a device with a distal fast frozen probe that removes tissue samples. This new technique was initially used for the diagnosis of lung cancer, but during the last years, it has been found to be a safe method to study interstitial lung diseases (ILD) (Fig. 35.1).

Classically, TBLB has been an appropriate first biopsy procedure in patients with bronchocentric

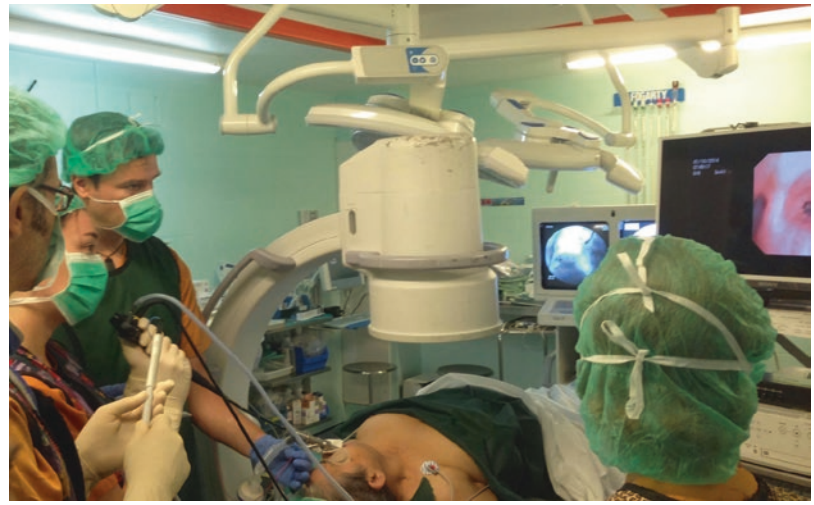

Fig. 35.1 Technical support required performing safe transbronchial cryobiopsies

ILD, especially sarcoidosis, lymphangitis, infection, and the less frequent proteinosis, Wegener granulomatosis, Langerhans cell histiocytosis, and lymphangioleiomyomatosis (LAM) [29]. In other ILD, the combination of clinical, radiological, and BAL data can provide information for more specific diagnostic: cryptogenic organizing pneumonia, acute interstitial pneumonitis, eosinophilic pneumonia, hemosiderosis, and acute interstitial pneumonia [29–33] (Table 35.2). Currently, with the introduction of cryoprobes and the progressive improvement in the procedure of transbronchial cryobiopsies, with better samples and conditions to decrease the incidence of bleeding and pneumothorax, almost all ILDs can be diagnosed in the appropriate multidisciplinary expert approach [34–40]. However, we advise against performing TBLB in isolated subpleural lesions because the imbalance of risk-benefit since there is a high risk of pneumothorax [4].

The efficacy of TBLB in the diagnosis of ILD depends in part on the differential diagnosis that is done after careful evaluation of clinical and radiological findings [29–33]. UIP cannot be accurately diagnosed by conventional TBTB, since its histological pattern cannot be determined by this technique due to two main reasons: (a) the "subpleural" space is quite impossible to be evaluated, and (b) the size of the tissue sample obtained through TBLB is not

Table 35.2 ILDs that may be diagnosed by transbronchial cryobiopsy

ILDs that can be confidently diagnosed through transbronchial cryobiopsy, with high probability	IIP; COP, DIP-BR/ILD, LIP Sarcoidosis and other granulomatous diseases Acute and subacute HP Pneumoconiosis PAP, hemosiderosis, eosinophilic pneumonias, lipoid pneumonia Langerhans disease
ILDs that can be diagnosed (low probability) or in which the cryobiopsy can help in the final diagnostic approach	IIP; NSIP, AIP, peribronchial fibrosis IPF[a] Chronic HP Induced drug interstitial disease Vasculitis, alveolar microlithiasis SRIF LAM

ILD interstitial lung disease, *IIP* idiopathic interstitial pneumonia, *COP* cryptogenic organizing pneumonia, *DIP* desquamative interstitial pneumonia, *RB/ILD* respiratory bronchiolitis associated with interstitial lung disease, *LIP* lymphoid interstitial pneumonia, *HP* hypersensitivity pneumonia, *PAP* pulmonary alveolar proteinosis, *NSIP* nonspecific interstitial pneumonia, *AIP* acute interstitial pneumonia, *IPF* idiopathic pulmonary fibrosis, *SRIF* smoking-related interstitial fibrosis, *LAM* lymphangioleiomyomatosis

[a]Only in the context of an expert multidisciplinary team and with a trained and experienced team for performing distal transbronchial cryobiopsy

enough to appreciate all the changes required to define this condition [29, 34]. A description of "interstitial pneumonitis and fibrosis" on a transbronchial lung biopsy is nonspecific and does not mean UIP [4]. However, Poletti V et al. have described the possibility of finding a UIP pattern through transbronchial cryobiopsies [39, 40]. They achieved subpleural lung samples in which all UIP histological criteria were met [39]. However, the proportion of pneumothorax was similar to the ratio of IPF diagnosis (around 30% of cases).

In contrast, the flexible bronchoscope is the main source of diagnosis in sarcoidosis. A high degree of diagnostic accuracy is achieved if more than four samples are taken. The distribution of granulomas along pulmonary lymphatic routes is frequent, and also bronchial lesions can be sampled directly with the cupped forceps. It has been shown that TBLB samples can detect granulomas even when radiological findings fail to reveal lung parenchymal disease [35]. Some cystic interstitial lung diseases can also be diagnosed by TBLB. Langerhans cell histiocytosis is an airway-centered disease, and TBLB can identify the typical histological lesion. The performance of immunohistochemical stains for Langerhans cells (S100 protein and CD1a) is not required when histological findings are characteristic. On the other hand, in LAM immunohistochemical staining may be useful even if definite lesions are not seen [31, 36]. LAM cells are eosinophilic on hematoxylin-eosin-stained sections, and HMB-45 immunohistochemical stains confirm the diagnosis.

Some studies that evaluate the diagnostic yield of transbronchial cryobiopsy in ILDs show a range of 74–98% that is even higher after reviewed by a multidisciplinary team [38]. So, the probability to achieve an accurate diagnosis for non-IPF ILDs seems to be higher by transbronchial cryobiopsy than by conventional forceps. However, only the results of the ongoing multicentric international studies evaluating both types of forceps will demonstrate if this new variant of TBLB is better than the conventional one or when is better to perform one or the other (both types requires different technical support).

Technical Advises for TBLB in ILD

Another determinant for the utility of TBLB in ILD is the technical procedure [29]. Biopsies from two different segments from the same lung can be obtained, but biopsy specimens from both lungs are contraindicated. After introducing the bronchoscope until a segmental bronchus, the forceps is distally introduced.

In conventional TBLB, the patient is asked to inhale and the forceps are opened. The patient is then asked to exhale, and, at end-expiration, the forceps jaws are closed. If the patient experiences pain at this point, the forceps is opened and withdrawn because the only pain-sensitive structure in the area is the visceral pleura. Approximately four to six biopsies are the ideal number for pathologists, although this number of samples is not always possible due to many reasons.

In TBL cryobiopsies, the patient requires deep sedation to avoid cough, an endotracheal tube to protect the upper airway (rigid or semi-rigid), fluoroscopic guidance to better decide the area for TBLB and to decrease the risk of pneumothorax, and a balloon for selective bronchial blockade in case of bleeding. Ideally, the procedure requires two bronchoscopists and nurses, anesthesiologist, and the adequate installations to perform the procedure in a safe manner. Around two to four biopsies are required for better diagnostic yield in most cases.

The main complication of TBLB is bleeding, mainly for those performed through cryoprobes, which is the primary limiting factor in obtaining more or larger biopsy samples. Less frequent complications are pneumothorax, hypoxemia, or cardiac arrhythmias during the procedure. Although less common, pneumothorax may induce important deterioration in lung fibrosis. Pneumothorax occurs almost 100% of the times in TBL cryobiopsies if the evaluation of the pleural-subpleural area is the objective (as for UIP) [39]. Usually, fluoroscopic guidance is effectively used to reduce the rate of pneumothorax.

Conventional TBLB is a safe procedure that does not require general anesthesia, with an overall mortality of 0.1%, and can be performed as an outpatient procedure. Bleeding occurs to some degree in virtually all TBB procedures and in

some cases can be substantial. Bleeding is a major concern because of the limited options available to manage excessive bleeding through the flexible bronchoscope. The suction channel is millimetric, and the volume of blood that can be suctioned is limited, also visibility is impaired as blood obscures the lens. Moreover, because the entire tracheobronchial tree is only about 150 mL in volume, a relatively small amount of blood can produce major problems with oxygenation [29].

TBL cryobiopsies present a variable probability of pneumothorax (mean of 12%) and bleeding (mean of 39%), with higher severity (grade 2–4) [38]. However, the fact of performing this procedure under an endotracheal tube and the possibility of controlling the bleeding through angioplasty balloon selectively located in the distal bronchi allow decreasing morbidity and mortality if this complication arises.

TBLB is contraindicated in the presence of bleeding abnormalities. An international normalized ratio (INR) greater than 1.5 is an absolute contraindication. When oral anticoagulation therapy is taken, it should be withheld for at least 4 days or until INR is <1.5 [29]. Fresh frozen plasma can be administered to reverse oral anticoagulant therapy more quickly. TBLB is also contraindicated if the platelet count is less than 50,000/μL. The platelet count can improve quickly with platelet transfusions prior to the procedure. There are insufficient data on antiplatelet agents such as clopidogrel, but some bronchoscopists require withholding treatment with this agent at least 1 week before the procedure. Finally, arterial pulmonary hypertension, which is quite usual in advanced stages of some ILD, may increase the risk of fatal bleeding.

Functional respiratory test and oxygen saturation should be evaluated prior a TBLB, since it is not recommended in severe hypoxemia, DLCO <30% or FVC < 50% [3]. There are some contraindications inherent to fiber-optic endoscopic procedure that of course also apply, such as uncontrolled cardiac arrhythmias, unstable angina, or high intracranial pressure. There is few information about TBLB performed in patients on mechanical ventilation, but it is known that there is a higher risk for pneumothorax [29].

Future Directions

The pathogenesis of different ILDs has been better understood thanks to continuous research on transbronchial samples [41–49]. Recently, it has been known that gene and protein expression patterns could identify key molecules involved in different ILDs [41–49]. These specific protein findings could provide relevant information for clinical diagnosis of ILDs and also target for effective therapies. Protein synthesis is determined by genetic and metabolic factors that may be the clue to some ILD development. Different technologies such as DNA and protein microarrays are useful to identify gene and protein expression patterns. The improvement in the world of genomic-proteomic approach may increase the utility of BAL for ILD diagnosis, management, monitoring disease activity, and assessing the effect of therapeutic interventions [47]. Recent investigations based on protein profile examination in BAL have demonstrated differences between IPF and other fibrotic lung diseases such as HP or fibrosis associated to connective tissue disease or other ILDs such as sarcoidosis [45–47].

Technical advances may also improve the utility of TBLB. The main limitation of TBLB using regular forceps is the small sample size. Recently, the cryoprobes have increased the diagnostic yield of ILDs through bronchoscopy (Figs. 35.2, 35.3, and 35.4). Bleeding, usually mild, and pneumothorax represent the most important potential complications that can be encountered. This procedure allows the evaluation of larger-sized samples, less artifacted, and better-preserved architecture than the samples taken by forceps, increasing the diagnostic yield [44–46] (Fig. 35.5). Clinical studies are ongoing to validate the usefulness of this new tool for ILD diagnosis and the potential benefit compared with surgical lung biopsies and conventional TBLB. Furthermore, many case reports have shown that it could be a valuable and safe method in some ILD cases with respiratory failure in which there was no benefit of conventional TBLB.

Fig. 35.2 ErbeKrio (Erbe Elektromedizin, Tubingen, Germany). Equipment for cryotherapy

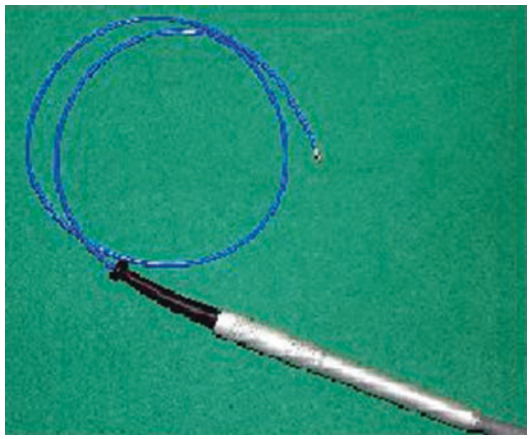

Fig. 35.3 Cryoprobe

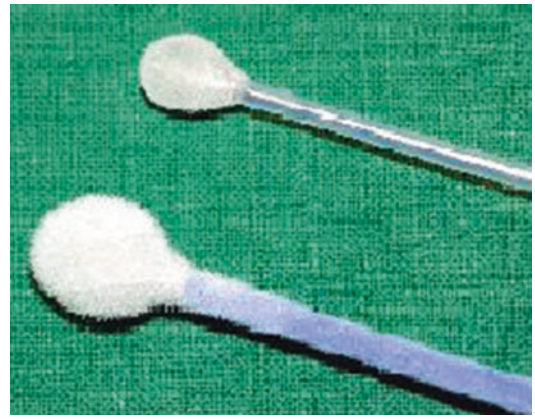

Fig. 35.4 Defrozen and frozen cryoprobe

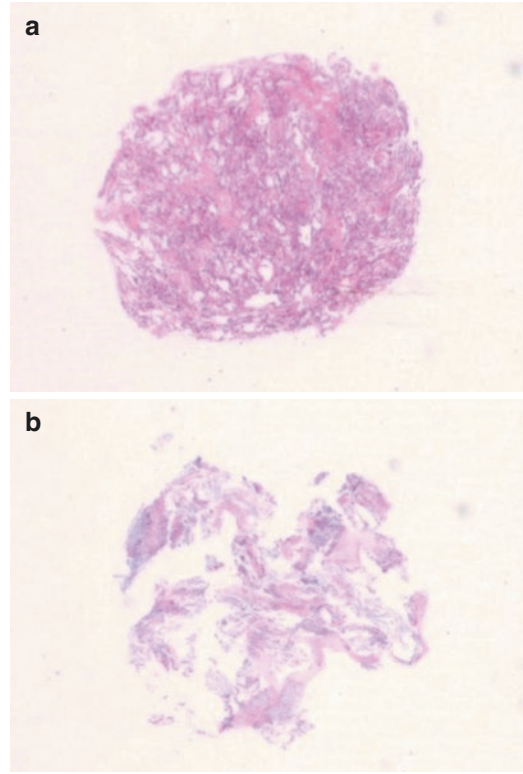

Fig. 35.5 (**a** and **b**) Transbronchial lung biopsy using a cryoprobe allows the histological evaluation of bigger samples, with less artifacts, and better-preserved architecture (**a**) than samples taken by conventional forceps (**b**)

Summary and Recommendations

The number of recognizable cito-histopathologic reaction patterns in ILDs is limited, and their morphological specificity in the diagnosis of ILDs is variable.

BAL should be considered in all patients with suspected infection, malignancy, and some ILDs in which it may be diagnostic. The utility of BAL in ILD diagnosis depends on different factors: expertise obtaining, analyzing, and interpreting the results are the main ones. When diagnosis is uncertain after clinical assessment and HRCT scanning, typical BAL cellular profiles may provide important clues in some ILD such as sarcoidosis or HP. However, BAL is not a diagnostic tool in patients with clinical features and HRCT pattern typical of IPF. In this situation, BAL mainly helps to support other entities with similar presentation, such as HP or NSIP.

Some biopsy specimens may provide specific clues that are diagnostic of the underlying disease, whereas others reveal only nonspecific abnormalities. Transbronchial biopsy is a powerful tool for diagnosis of specific ILD when matched with appropriate expectations on the part of clinicians, radiologist, and pathologists.

HCTR images are essential for choosing the best place to biopsy and to help in the final diagnosis. TBLB is the initial procedure of choice in those patients in which small samples may be diagnostic, particularly if the disease has a tendency for bronchocentric involvement, and, when possible, BAL and TBLB should be performed before the initiation of any treatment. Conventional TBLB is not recommended in IPF or other ILD with UIP radiological pattern.

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Foreign Bodies in the Airway: Endoscopic Methods

36

Michael Simoff and Harmeet Bedi

Abbreviations

APC	Argon plasma coagulation
ARDS	Acute respiratory distress syndrome
CT	Computed tomography
ED	Emergency department
EGCR	Esophagoglottal closure reflex
FB	Foreign body
GPA	Granulomatosis with polyangiitis
LES	Lower esophageal sphincter
Nd:YAG	Neodymium-doped yttrium aluminum garnet
NSC	National Safety Council
PDT	Photodynamic therapy
PGCR	Pharyngoglottal closure reflex
UES	Upper esophageal sphincter

Introduction

Airway foreign body (FB) aspiration is defined by the presence of foreign material anywhere in the glottis and/or tracheobronchial tree, with or without airflow obstruction. One cannot discuss FB retrieval without mentioning the birth of interventional pulmonology (IP) and its pioneers. On March 30, 1897, Gustav Killian performed the first FB retrieval from the right mainstem bronchus of a farmer who had aspirated a small piece of pork bone while eating vegetable soup [1]. This event marks the beginning of bronchoscopy and IP with Gustav Killian identified as the "Father of Bronchoscopy."

The first FB retrieval performed in the United States was at Massachusetts General Hospital by Algernon Coolidge in 1898. Chevalier Jackson, following in Gustav Killian's footsteps, continued to advance the technique of bronchoesophagoscopy and developed various instruments, including the first illuminating bronchoscope. For his work, he is credited as "Father of American Bronchoesophagology." Like Dr. Killian, he was a renowned otolaryngologist. His collection of over 2000 foreign bodies that he retrieved over his career is still on display at the Mütter Museum in Philadelphia, Pennsylvania (USA).

Historically, the mortality related to foreign bodies in the nineteenth century was estimated to be 23%; however, this changed profoundly with the advent of bronchoscopy with literature now suggesting a mortality rate less than 1% [2, 3]. Over the past century, further advances in medicine and diagnostic and therapeutic bronchoscopy have drastically improved the morbidity and mortality attributed to this condition. In this

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chapter, we will review various clinical aspects of airway FB aspiration and retrieval, including diagnostic and therapeutic techniques and considerations.

Anatomy and Physiology of Swallowing

Upper Airway Embryological Development and Anatomy

The development of the aerodigestive organs begins with the primitive foregut [4–7]. From onset, the glottal folds are present which represent the future vocal cords. Around the sixth to seventh weeks during gestation, development of the epiglottis, aryepiglottic folds, false vocal cords, and laryngeal ventricles begins. The epiglottis arises from the hypobranchial eminence, which is also the precursor for the development of the tongue. The separation of these structures occurs around the seventh week. Eventually the larynx is formed as a result of the primitive foregut folding upon itself to create the laryngotracheal bud, which divides, and is responsible for the creation of the bronchopulmonary segments in the future. The fourth and sixth pharyngeal arches are responsible for the development of the laryngeal muscles and are innervated by branches of cranial nerve X. The intrinsic muscles of the larynx are supplied by the recurrent laryngeal nerve, while the superior laryngeal nerve supplies constrictors of the pharynx, cricothyroid, and levator veli palatini. Other supraglottic structures such as the pharyngeal walls, posterior one-third of the tongue, and stylopharyngeus muscle are all supplied by the glossopharyngeal nerve. This nerve also provides sensory fibers to the mucosa of the oropharynx and palatine tonsils.

The esophagus is a muscular tubular structure that consists of two muscle layers: an inner circular layer and a longitudinal outer layer [8, 9]. The proximal esophagus is striated muscle, while the distal esophagus consists of smooth muscle. The upper esophageal sphincter (UES) forms the anatomic boundary where a zone of high pressure is generated between the pharynx and esophagus. Pressure in this zone is generated primarily by the cricopharyngeus muscle, as well as the cervical esophagus and inferior pharyngeal constrictor. The UES receives innervation from the vagus nerve branches (pharyngoesophageal, superior laryngeal, and recurrent laryngeal nerves), the glossopharyngeal nerve, and the sympathetic branches of the cervical cranial ganglion.

Functional Physiology of Swallowing

The pharyngoesophageal interface is responsible for facilitating airway protection, deglutition with safe transport of proximal esophageal contents, and clearance of volume during swallowing and emesis. The laryngeal structures are responsible for accommodating the following three functions: phonation, ventilation, and airway protection. Swallowing is a complex series of motions that requires very coordinated voluntary and involuntary movements of the oropharynx, larynx, and esophagus. Swallowing can be divided into three different phases based upon the relationship of the food bolus and anatomical structure: oral, pharyngeal, and esophageal [10–12].

Oral Phase: The oral phase can further be divided into the preparatory and early transfer phases. The preparatory phase consists of various oral movements such as chewing, suckling, and masticating. The aim of this phase is to break down food and mix it with saliva with the eventual goal of making a food bolus that can easily and safely be transported. The transfer phase initiates once a decision to swallow has been made. At this point, the tongue contracts against the hard palate which leads to a squeezing motion that moves the bolus toward the oropharynx through a chute created by the posterior tongue. Subsequently, the soft palate contracts superiorly to protect the nasopharynx from nasal regurgitation. Finally, the posterior tongue contracts against the palate, and there is contraction of the posterior pharyngeal wall which allows the food bolus to pass in a one-way direction toward the pharynx [13–15].

Pharyngeal Phase: At the start of this phase, the nasopharynx is sealed off by the soft palate

and the oropharynx is sealed off by the tongue pressing against the palate. Pharyngeal constrictor muscles contract in a top to down motion to propel the bolus distally. Airway protection mechanisms are of the utmost importance during this phase as this is the time where airway aspiration is most likely to occur. The opening to the trachea is protected by vocal cord closure, which is supplemented by arytenoid closure. Additionally, the epiglottis then swings down to cover and protect the laryngeal vestibule. During the pharyngeal phase, the hyoid bone moves the larynx superiorly and anteriorly. The suprahyoid and thyrohyoid muscle contractions facilitate the movement of the hyoid bone. This mechanism helps move the larynx to a position that is distant from the path of the bolus. Finally, the UES is moved upward by facilitation of the widening and shortening of the pharynx. This motion decreases the distance the bolus has to transfer and allows the esophagus to be an open position to accept the bolus. The estimated time for transfer of a bolus through the pharynx is 1 s, with an approximate speed of 40 cm/s [16, 17].

Esophageal Phase: Once the bolus enters the esophagus through an open and relaxed UES, a series of peristaltic waves occur to transport the bolus down the esophagus. There is an initial wave of relaxation that occurs at the location of the bolus, which is followed by a wave of contraction that propels the bolus distally. When in an upright position, gravity can assist in this movement. While a liquid bolus can move distally with just gravity, a solid requires peristaltic motion to advance it toward the stomach. As the bolus is propelled, the lower esophageal sphincter (LES) relaxes and allows for passage into the stomach. The estimated travel time through the esophagus is approximately 5–6 s.

Upper Airway Protective Reflexes

Through the entire complex and well-coordinated process of swallowing, the human body has incorporated many involuntary mechanisms to protect the lungs from aspiration from birth until the end of life. The neuromuscular interface of these reflexes is so robust that its protective nature works within the space shared by laryngeal and esophageal structures [7, 18].

Laryngeal Adductor Reflex: This reflex represents the best line of defense against pulmonary aspiration. Contraction of the lateral cricoarytenoid and interarytenoid muscle leads to adduction of the anterior and posterior aspects of the vocal cords, respectively. The vocalis and thyroarytenoid muscles, which make up the laryngeal tensors, assist with vocal cord closure during various physical activities. As already mentioned, additional protection is provided by descent of the epiglottis, arytenoid adduction, and laryngeal elevation.

Esophagoglottal Closure Reflex (EGCR): It is important to recognize that aspiration does not have to necessarily occur with anterograde movement of contents. Retrograde movement of gastric contents is a major cause of aspiration, especially in the elderly population. There are various causes of retrograde movement such as reflux, belching, regurgitation, and vomiting. The major stimulus for the EGCR is dilation and distention of the esophagus. The vagus nerve is responsible for the afferent innervation and impulse resultant from stretch of the esophagus. Impulses from this reflex result in efferent output to the glottal structures via the recurrent laryngeal nerve. Stimulation leads to vocal cord adduction.

Pharyngoglottal Closure Reflex (PGCR): It has been demonstrated that exposure of the pharynx to different quantities of instilled water leads to vocal cord adduction [19]. This adduction has a linear relationship to the amount of water instilled. There is also evidence that the elderly require significantly larger amounts of fluid volume to obtain PGCR in comparison to younger individuals. Similarly, larger volumes are required for stimulation in smokers compared to nonsmokers [20].

Upper Esophageal Sphincter (UES): As mentioned above, the UES is the zone of pressure generated at the junction of the pharynx and esophagus, primarily influenced by the cricopharyngeus muscle. The pharyngeal constrictors and proximal esophagus also act as

adjunct muscles in generating tone. The UES is an additional safety measure in preventing retrograde movement of gastric and esophageal contents. It is mainly stimulated during esophageal distention and gastric reflux, especially when gastric contents reach the distal esophagus.

Epidemiology

Aspiration can occur at any age but is most commonly found in young children and in the elderly. There tends to be a bimodal distribution for airway FB-associated death with peak incidences at less than 1 year of age and greater than 75 years of age. According to the National Safety Council (NSC) in 2013, 4800 people died from choking, and of this, 2700 people were older than 75 years of age. The odds of dying from choking from inhalation and ingestion of food in the United States are approximately 1 in 3408. Choking and suffocation related to FB aspiration also accounts for a great proportion of pediatric emergency department (ED) visits on an annual basis. According to the Centers for Disease Control and Prevention, ED visits for nonfatal injuries related to foreign bodies accounted for 221,117 visits in 2012 for children less than 10 years of age. Overall, FB aspiration was the fourth leading cause of ED visits for children less than 5 years of age.

There does appear to be a gender bias with males being affected approximately twice as much as females [3, 21, 22]. While data is sparse in regard to the impact of geographical and cultural factors on FB aspiration in children, there appears to be some relationship between the primary language spoken at home and the incidence of aspiration events [23]. In one study, children from non-English-speaking households had significant higher incidence of foreign body aspiration, especially with nuts, compared to English-speaking households. As the language spoken in a household is a surrogate marker for cultural background differences, this relationship may be more indicative of dietary differences that exist among different ethnic groups (i.e., promotion of culture-specific diets with increased presence of nuts).

Types of Foreign Bodies

Any object or material that can fit in the oral cavity has the potential to cause airway obstruction. The most commonly aspirated foreign bodies are nuts, seeds, bones, and dental-related objects [3, 21, 24]. Foreign bodies can be divided into the following categories: organic, inorganic, mineral, and miscellaneous.

Organic

As airway aspiration is usually a by-product of malfunction of airway reflex mechanisms, one can expect aspiration of edibles to be the most likely offender. Organic material is responsible for the majority of airway FB aspiration cases. The most frequent types of organic aspirations result from nuts and seeds. The most common type of nut aspirated is usually peanuts (Fig. 36.1) but can also be other varieties including walnuts, almonds, and pistachios. Seeds from sunflowers and watermelons are frequently responsible, in regard to seeds. Other types of aspirated organic material include popcorn, fruits, vegetables, and cereals.

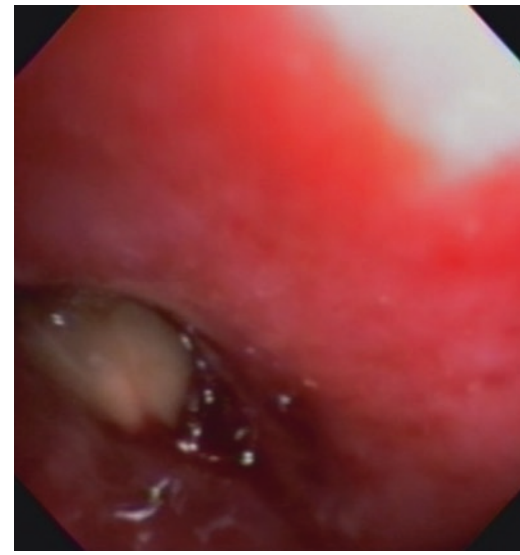

Fig. 36.1 Peanut identified in the left mainstem bronchus

Inorganic

Inorganic material can further be divided into metallic and plastic materials. Metallic foreign bodies that are often implicated include different types of pins and coins. Other aspirated metallic foreign bodies include nails (Fig. 36.2), jewelry, metallic crowns, coins, and even wiring from undergarments (Fig. 36.3). In regard to plastic foreign bodies, other objects that are responsible included medical-related devices such as broken endotracheal and tracheostomy tubes, nasopharyngeal airways, intubating introducers, and drug delivery devices such as inhalers and inhaler caps. Thumbtacks (Fig. 36.4), plastic toys, and pen caps are also commonly implicated [23, 24].

Dental-related appliances usually account for the most frequently aspirated objects after organic matter. Examples of dental-related appliances include bridges, porcelain or metal crowns (Fig. 36.5), mouth guards, dentures, and fillings. There have even been reports of aspiration of dentistry tools during procedures [25].

Mineral

Aspiration of teeth compromises the majority of cases under mineral-related foreign bodies (Fig. 36.6). This can occur in relation to trauma, impaired airway reflexes (i.e., neurological disease), and during impaired states of consciousness (i.e., sleep, alcohol/drug intoxication, anesthesia, etc.). Bones from meats and fish are also not uncommonly aspirated. Another mineral is glass, which can be from broken glass pipe fragments (used for inhalation of illicit drugs) and from motor vehicle accidents with shattered glass. It is important to understand that even endogenous substances can act as foreign bodies when they produce airflow obstruction with or without gas exchange abnormalities. As an example, broncholiths that have eroded into the intraluminal can act as foreign bodies (Fig. 36.7).

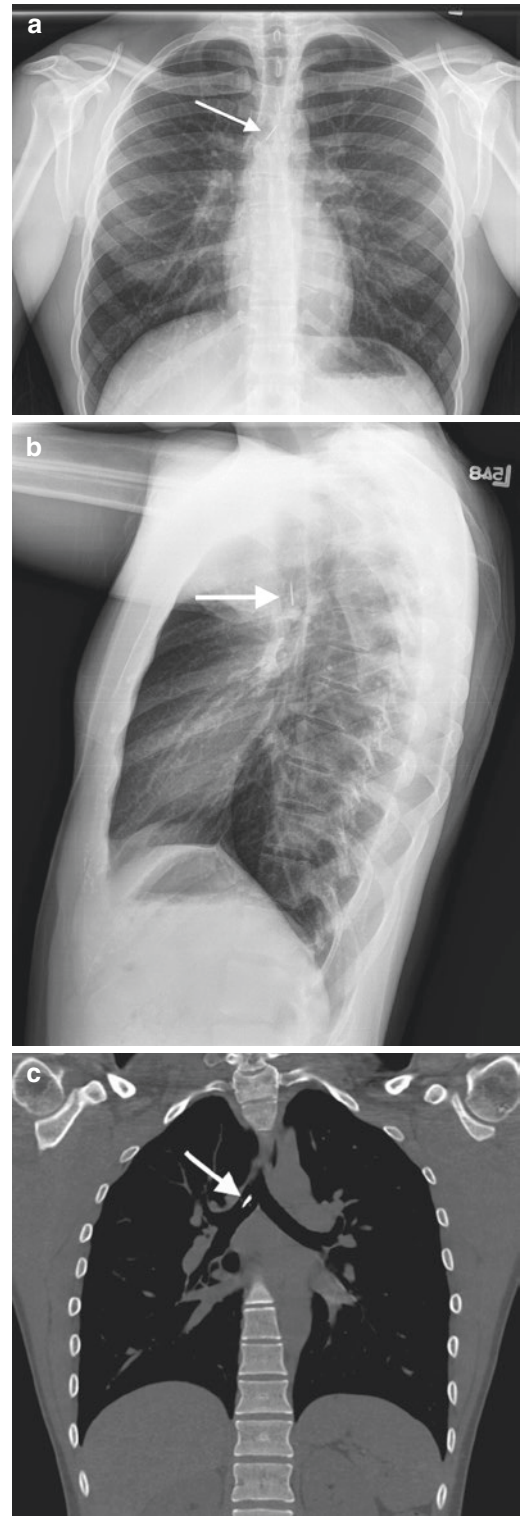

Fig. 36.2 Metal nail aspirated into the distal trachea. *White arrow* points to the nail in each radiologic study. (**a**) Posterior-anterior chest plain film. (**b**) Lateral chest plain film. (**c**) Coronal CT chest

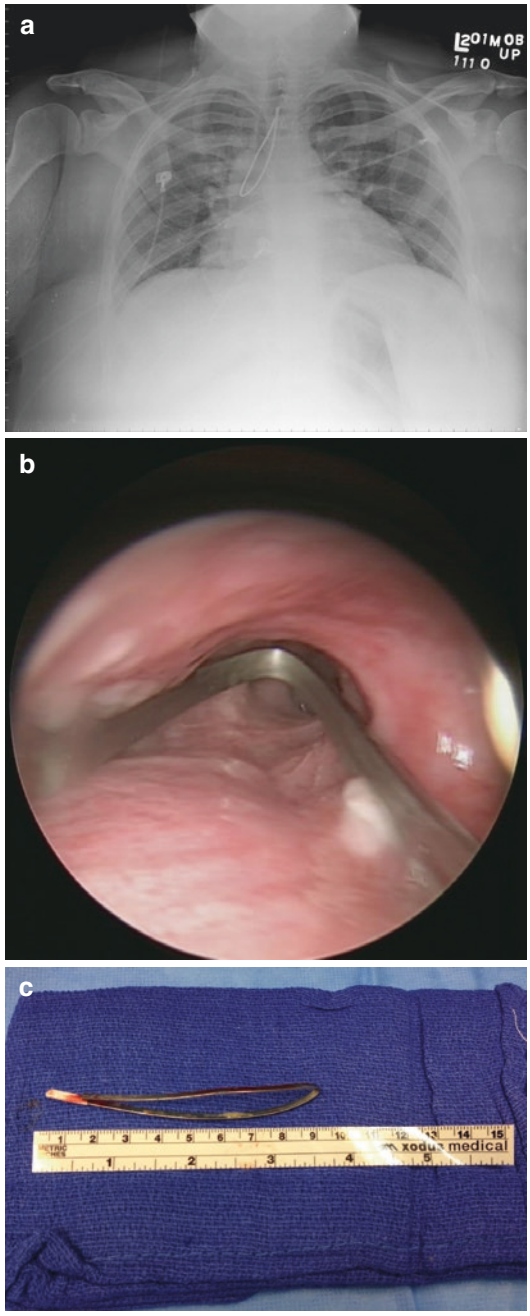

Fig. 36.3 Wire from women's bra aspirated into the trachea and right mainstem bronchus. (**a**) Posterior-anterior chest plain film. (**b**) Bra wiring seen in right mainstem bronchus and bronchus intermedius. (**c**) Bra wiring visualized after bronchoscopic removal

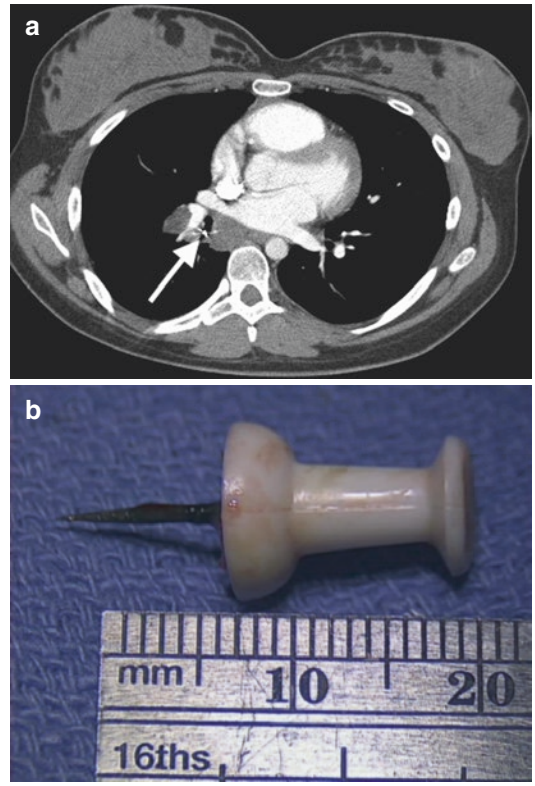

Fig. 36.4 A thumbtack aspirated by a patient. (**a**) Axial CT scan with *white arrow* pointing to thumbtack in the right lower lobe bronchus. (**b**) Thumbtack after bronchoscopic retrieval

Miscellaneous

Pills and Capsules: There are various factors that promote the aspiration of pills and capsules including (but not limited to) the motion of placing them into the oral cavity, the state of airway reflexes in the subject (i.e. neurological disease, age, etc.), as well as the quantity and frequency of medication regiments which tend to be more prevalent in the elderly population. When evaluating pill aspiration, it is important to evaluate the obstructive properties of the implicated pill(s), as well as the early and late inflammatory potential of the pill(s). Technically any pill has the potential to be aspirated; however, there are well-known sequelae related to specific medications such as iron supplementation, potassium preparations, and activated charcoal.

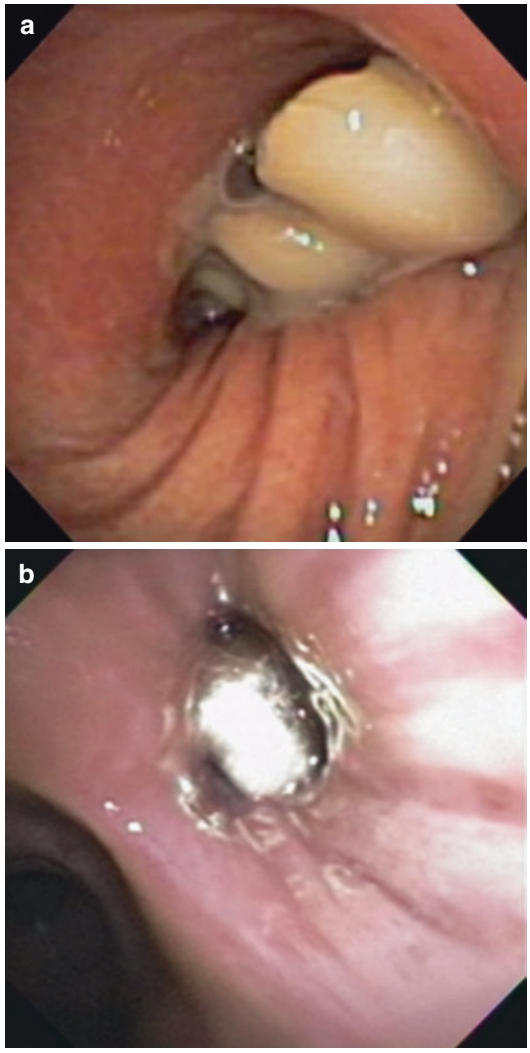

Fig. 36.5 Types of dental appliances aspirated into the airway. (**a**) Dental bridge. (**b**) Gold dental crown

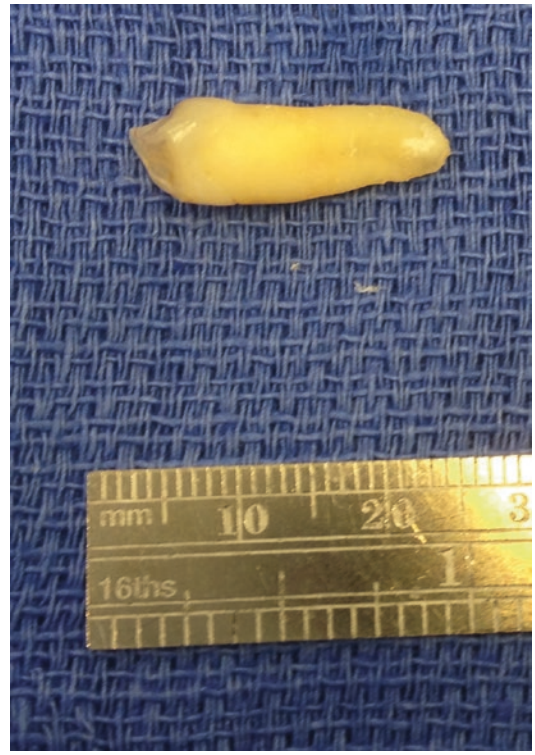

Fig. 36.6 Tooth that was aspirated and bronchoscopically retrieved

Iron pill aspiration is a well-recognized problem. Any medication containing ferrous sulfate ($FeSO_4$), when aspirated, has a caustic effect on the bronchial mucosa secondary to its acidic pH (usually <3), which leads to a local inflammatory cascade of effects including acute mucosal damage and, eventually, airway stenosis [26–28]. This can lead to the formation of granulomas and fibrosis. Further specifics of iron pill aspiration will be discussed in depth later in this chapter.

Potassium preparations are also very well associated with local inflammatory effects when aspirated. Of the potassium-based formulations, potassium chloride (KCL) is the most commonly aspirated preparation. Due to the hyperosmolar properties of KCL, it leads to mucosal irritation with additional erosive properties to the airway [29]. Similar to ferrous sulfate, late effects can result in airway stenosis. Enteric-coated KCL preparations take time to dissolve and may initially present with airway obstruction.

Activated charcoal is reported to be aspirated in approximately 2.3% of all patients receiving it for gastric emptying indications [30]. Although charcoal is biologically inert and nonabsorbable, it is immunogenic, which can cause a local inflammatory response within the airways. Bronchospasm, airway obstruction (due to inflammatory response), pneumonitis, and acute respiratory distress syndrome (ARDS) have all been reported with charcoal aspiration [29].

Other medications that are associated with similar inflammatory response include nortriptyline, metformin, pomegranate supplements, barium sulfate, and alendronate. While technically

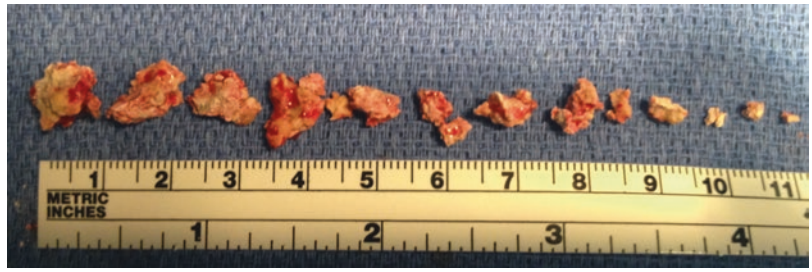

Fig. 36.7 Multiple broncholiths retrieved from a single patient

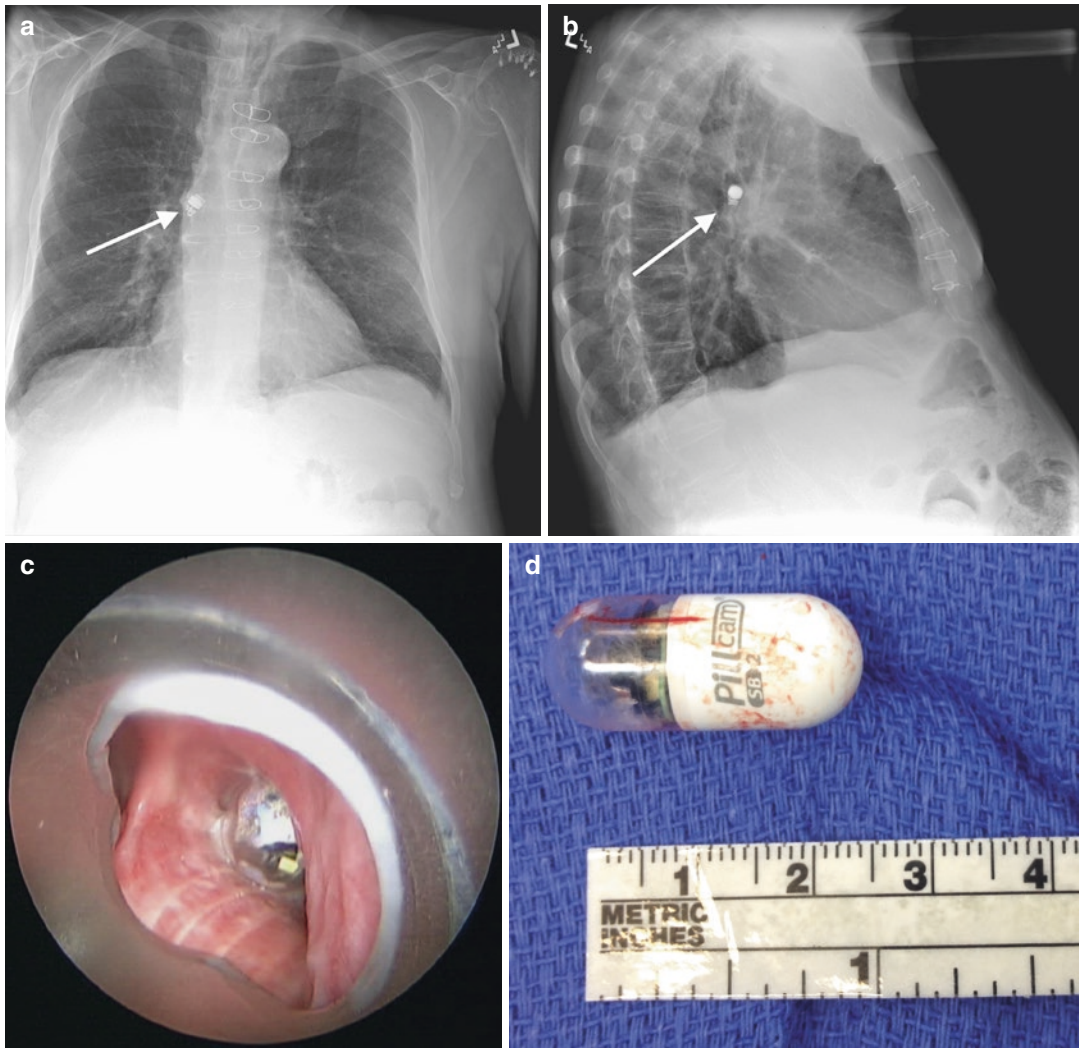

Fig. 36.8 An aspirated endoscopic capsule (pill camera). *White arrows* are pointing toward the capsule in the radiologic studies. (**a**) Posterior-anterior chest plain film. (**b**) Lateral chest plain film. (**c**) Bronchoscopic image of capsule in the right mainstem bronchus. (**d**) Endoscopic capsule after retrieval

not a medication (but are administered similar to oral medications), endoscopic capsules (pill camera) used in diagnostic gastrointestinal evaluation have also been aspirated into the airway [31]. As endoscopic capsules are inorganic, they do not dissolve and act more as obstructive foreign bodies (Fig. 36.8). While extremely rare, aspiration occurs more commonly in elderly patients, whom

may or may not have a history of swallowing dysfunction.

Stents: While airway stents are used in the treatment of airway obstruction, it is well known among bronchoscopists that stents have the ability to migrate. Airway stent migration rates have been reported between 4.6 and 17% [32, 33]. Migration of airway stents can occur due to inappropriate choice of stent in relation to airway size but can also be a result of successful treatment of the underlying etiology for stent requirement. For example, stents are deployed for the management of malignant central airway obstruction, and after successful treatment of tumor, there may be shrinkage or resolution of the initial malignant obstruction. The response to therapy may lead to stent migration because of the lack of airway support on the outer surface of the stent. Additionally, stents used for benign disease in conditions such as tracheal and bronchial stenosis, similar response to therapy, and/or excessive coughing may lead to inadvertent stent migration. Airway stents are also known to promote bronchial secretions with the risk of developing airway obstruction due to tenacious secretions. While secretions are not foreign bodies, airway stents obstructed with mucus present in a similar manner.

Esophageal stents have also been implicated in FB airway obstruction. Although, esophageal stent migrations are associated with distal esophageal/gastric migrations [34], there have been reports of acute airway obstruction from proximal migration of esophageal stents with occlusion of the glottis [35]. There have also been case reports of esophageal stents migrating through the posterior membrane of the trachea leading to severe acute airway obstruction and asphyxiation [36].

Photodynamic Therapy (PDT): PDT is a photoablative therapy used as an adjunct treatment of central airway malignant disease not amenable to further standard treatment options. Routine practice is to perform a follow-up bronchoscopy 48–72 h post-procedure to clear necrotic debris induced by the therapy. In some instances, this debris can slough off and can obstruct the central airways. There have been reports of acute airway obstruction in the immediate hours after completion of PDT [37]. Similar to other incidences, tumor slough is typically not thought of as a true FB, yet its clinical presentation mirrors that of other foreign bodies.

Other Miscellaneous Foreign Bodies: Other rare causes of FB aspiration include erosion of grafted rib material during tracheoplasty, endobronchial suture material from bronchial stumps status post lobectomy/pneumonectomy, and migrated gauze packing from nasal and oropharyngeal indications.

Clinical Presentation

Patients that aspirate an airway FB can have a wide array of presentations, ranging from asymptomatic to immediate death. Patients present with one of two conditions: acute or retained FB. Acute FBs represent those cases associated with minimal airway inflammation and are relatively early in the sequence of events, either immediately after the aspiration event or within hours/days. Retained FBs are those cases where the FB has initiated a significant airway inflammatory cascade with subsequent complications such as severe mucosal inflammation, granulation tissue, stenosis, or post-obstructive pneumonia (Fig. 36.9). Patients with such cases tend to have presented in a relatively delayed manner (i.e., weeks, months, or years later) or aspirated a FB known to be associated with mucosal inflammatory effects. While children commonly present in the acute time period, adults more commonly seek medical attention in a delayed manner [38].

Acute FB

Most patients in this population will seek and require medical attention in the immediate post-aspiration time period, often with a relatively inert FB. Patients will usually know exactly when the aspiration event occurred and what type of FB was aspirated. When the patient is unable provide history, witnesses may provide information regarding the event. Depending on the type of FB, the size, the location of FB impaction, and the time taken to reach medical services, presentation can range from coughing to acute

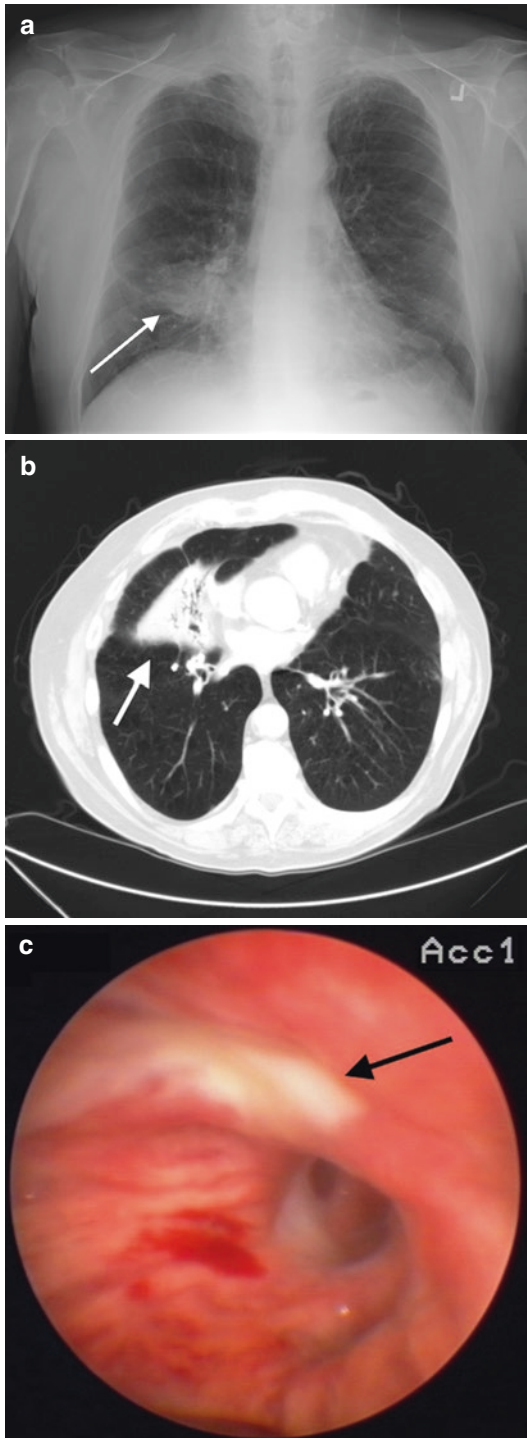

Fig. 36.9 Aspiration of vegetative matter leading to a retained foreign body presentation. *White arrows* are indicating air space consolidation in the right middle lobe. (**a**) Posterior-anterior chest plain film. (**b**) Axial CT chest. (**c**) Bronchoscopy demonstrating right middle lobe bronchus occluded by a calcified lesion and granulation tissue. Endobronchial biopsy of this lesion revealed retained vegetative debris with surrounding mild inflammation

asphyxiation and death. Acute asphyxiation, also known as café coronary, is more commonly found in children compared to adults. Usually in these cases, the laryngotracheal region is obstructed by a relatively large FB. While choking is the most frequent complaint on presentation, it is more common with children as opposed to adults [39].

As in most of the practice of medicine, history is our most important tool. Correctly identifying the risk factors, potential etiologies, and comorbidities will allow the interventional pulmonologist to plan their intervention carefully and completely to ensure that the best management plan is chosen for each patient. Physical examination findings will vary depending on the location of FB impaction. However, keep in mind, the initial symptoms are heavily reliant upon one's airway reflexes, and patients with blunted reflexes, from any cause, may not demonstrate these symptoms and/or findings.

When the laryngotracheal region is involved, choking, stridor, wheezing, dyspnea, and hoarseness of voice are commonly observed. Generally, inspiratory stridor occurs with obstruction of the larynx, while expiratory stridor occurs when the tracheobronchial tree is involved. As would be expected with an upper airway obstruction, cyanosis and/or cardiopulmonary decompensation can occur with prolonged hypoxia. Approximately one-third of patients with acute asphyxiation will have FB impaction at the level of the supraglottic region [40]. This said, the oral cavity must undergo a thorough evaluation in any presentation of aspiration to ensure that the FB or any remnants of it are not left behind.

With primary bronchial involvement, there is usually an initial choking event that is followed by dyspnea, wheezing, and usually coughing. Although less commonly, hemoptysis can also be a presenting symptom. More serious findings such as severe hypoxia can occur with complete mainstem bronchial obstruction. With more distal airway involvement, patients will usually have an initial choking event that is followed by a relatively symptom-free period. For such patients, the choking event may or not be followed by respiratory symptoms such as coughing, shortness of breath, or hemoptysis.

Retained FB

A retained FB presentation is more common in the adult population. Seeking medical attention not uncommonly can be delayed by weeks or even months and, in some cases, years later. The hallmark in this population usually encompasses patients seeking medical attention for persistent respiratory symptoms due to the complications which develop because of retained foreign bodies such as chronic cough, recurrent pulmonary infections, shortness of breath, fever of unknown origin, and hemoptysis. The most common presenting symptom is chronic cough. A subset of patients may have a FB discovered as a consequence of clinical evaluation for suspected lung cancer because of concerning findings during a diagnostic work-up (i.e., radiologic findings, advanced age, constitutional symptoms, etc.).

History is paramount to the successful management of any medical condition. As patients presenting with the symptoms of prolonged aspiration of a FB is not common in most practices, having a high index of suspicion is key to rapid diagnosis. The literature suggests that most adults with aspirations are unable to recall a choking episode in their history [21, 38]. This may be due to the size difference of foreign bodies in comparison to the adult airway, neurologic disease prevalence in this population, influence of medications and drugs, as well as adults in iatrogenic circumstances such as intensive care and anesthesia related. To complicate obtaining a thorough history further, it is well known that even when patients have a transient choking event that this is not uncommonly followed by a relatively asymptomatic period due to the distal migration of the FB. In addition to many adults' aversion to seeing a physician, this may lead many patients to delay seeking treatment until respiratory symptoms recur or become significantly bothersome.

Radiologic Findings

While the sensitivity of plain films for visualizing radiopaque foreign bodies is notoriously low and is approximately 4–21% in the pediatric and adult populations [41–46], it is reasonable to start with plain films of the neck and chest because of the its availability, ease of use, and cost. Associated radiographic changes for foreign bodies do tend to improve the sensitivity for plain films to above 70–85% [3, 22, 38, 47]. These include air trapping, atelectasis, volume loss with mediastinal shift, and air space opacities. In evaluating plain films, it is important to evaluate two different aspects: visualization of FB and radiographic changes related to foreign body presence/impaction. Patients with retained FBs may have additional findings such as persistent/recurrent air space disease, presence of a mass, and/or a pleural effusion. Visualization of foreign bodies is inherently dependent upon size and material. Most foreign bodies tend to be organic material which tends to be radiolucent, while inorganic metallic materials are radiopaque. Once again, it is important to emphasize that one must have high index of suspicion in evaluation of this population and to understand how FB size and properties may have effects on plain film appearance. Interestingly, normal chest films may be noted in approximately 9–37% of adults and children [38, 39, 44, 48]. If foreign body aspiration is of high concern and a normal plain film is encountered, computed tomography (CT) imaging should be obtained.

CT imaging of the chest and neck is considered to be the most sensitive method for imaging in suspected airway FB aspiration. CT imaging has many advantages over plain films such as the superior ability to define location, spatial relationship to important anatomic structures (i.e., vascular structures), and better definition of associated FB effects. Depending on the size of the FB, CT imaging also has the ability to identify radiolucent materials. Thin-slice CT imaging may be preferred for identification of smaller foreign bodies and debris. The detection for airway foreign bodies is much greater with CT imaging than plain films, and CT imaging has been reported to have a sensitivity of 100% in this regard [47–49]. Additionally, in situations like these, CT imaging has the benefit of providing useful information that can assist bronchoscopists in their therapeutic approach to FB retrieval. It is important to note that false positives can occur with CT imaging due to mucus impaction.

Bronchoscopy

Regardless of symptoms and radiology findings, bronchoscopy remains the gold standard for diagnosing FB aspiration. The decision to start with flexible versus rigid bronchoscopy will be discussed under the "Airway Management" section of this chapter. When performing flexible bronchoscopy, it is of the utmost priority to perform a detailed airway exam of not only the central and segmental airways but to also thoroughly assess the nasopharynx, oropharynx, and glottal structures. In examining the segmental airways, not only do the bronchopulmonary segments need to be evaluated, but complete examination of the most distal visible subsegments needs to be performed to ensure that there is no distal impaction or residual debris. This is particularly important in the evaluation of smaller foreign bodies such as nuts, seeds, and pills. Flexible bronchoscopy has the benefit of not only acting as a diagnostic tool but can also be used for therapeutic FB retrieval with various instruments that can be inserted through the working channel of the bronchoscope. Additionally, flexible bronchoscopy can also be used for procedure planning in preparation for rigid bronchoscopy.

Airway Management

Rigid vs. Flexible Bronchoscopy

Traditionally, the gold standard method for FB retrieval has been rigid bronchoscopy. This said, the decision to use rigid or flexible bronchoscopy depends significantly on institutional practices, stability of the patient, equipment availability, and operator experience. The success rates for rigid bronchoscopy in the retrieval of foreign bodies are reported between 95 and 100% [21, 22, 39], compared to flexible bronchoscopy which has reported rates of success between 61 and 90% [21, 38, 39]. In our practice, we avoid viewing rigid and flexible bronchoscopy as mutually exclusive techniques but more as valuable complimentary tools. Each patient is unique and their clinical presentation should guide the selection of the best method for FB retrieval. Patient safety should always outweigh the bronchoscopist's personal preference and equipment availability. If rigid bronchoscopy is required for safe retrieval of a FB, then arrangements should be made for this to occur, including the transfer of a patient to a specialized center.

Flexible bronchoscopy has the benefit of being able to be performed with moderate sedation with the ability to remove FBs from distal airways. When using flexible bronchoscopy, a therapeutic bronchoscope with a working channel of 2.8–3.2 mm is recommended to allow passage of all available retrieval instruments. When performing flexible bronchoscopy, avoid the transnasal route as the nasal passage may be too narrow to allow passage of the retrieved FB. In patients with upper airway/tracheal FBs, stridor, or respiratory failure, rigid bronchoscopy is the preferred tool because of its capability to protect the airway and maintain oxygenation and ventilation. Rigid bronchoscopy also allows the use of various specialty instruments that are designed for FB retrieval; in addition, it is easily used in combination with a flexible bronchoscope. In children, rigid bronchoscopy is almost always recommended as airway size limits ventilation when a flexible bronchoscope is independently used.

Retrieval Procedure

As in any therapeutic procedure, preparation is of the utmost importance prior to onset of procedure. Always ensure that all potential equipment, personnel, and medications are available. Anticipation of complications is the best preventive strategy for such circumstances. When a central airway obstruction (i.e., trachea) is encountered, particularly in an unstable patient, consider distal advancement of the FB to allow for improved ventilation. Many FBs will have induced airway injury or stimulated certain inflammatory pathways. Blood, pus, and other secretions will often cover and/or surround the FB. Clear visualization of the FB is a priority and allows examination of various characteristics of the FB and the airways surrounding it, such as size, proximity to surrounding airways, and

whether the FB is free-laying or adherent by granulation tissue and/or adhesions. Also, assess for the presence of surrounding inflammation, blood, and bleeding potential during FB manipulation. Topical epinephrine can be instilled in such circumstances to minimize bleeding.

Retained FBs have a higher potential for the development of associated granulation tissue and may require tissue resection in order to release the FB. Tissue debulking can be achieved mechanically or with ablative therapies (i.e., laser, argon plasma coagulation, cryotherapy, and electrocautery). Before using laser, argon plasma coagulation (APC) or electrocautery, one must consider if the involved FB has combustible properties and if the patient can tolerate an inspired fraction of oxygen less than 40%.

The choice of which instrument to use for retrieval will depend on whether retrieval is being achieved with rigid and/or flexible bronchoscopy, instrument availability, location of FB (i.e., central or distal), and FB qualities (i.e., hard, soft, smooth, rough, sharp, size, etc.). FB repositioning may introduce different options for retrieval and instrument selection, but this always increases the risk of the FB moving more distally and out of reach or further injury to the airway. Retrieval instruments and their respective advantages and disadvantages are discussed in the next section. After the FB has been secured with the selected instrument(s), care must be taken while pulling out to ensure that the path of least resistance is taken not only in the airways but also through a rigid scope or artificial airway. If the FB is too large for the rigid scope or artificial airway, the FB attached to the retrieval instrument and airway device (i.e., rigid scope or endotracheal tube) may need to be removed in an en bloc fashion. This also applies to cases where the FB was lost in the airway device. Occasionally, mucosal and vocal cord injury can occur during this process and bleeding may occur.

Once the FB is removed, distal airways must be assessed adequately to ensure there are not any additional foreign bodies or remnants that need removal. Also, assess the physical properties of the removed FB to identify if the FB was retrieved in a complete manner or if there is evidence of FB fracture suggesting the presence of retained pieces. In retained FB cases, there may be evidence of secretion retention and/or post-obstructive pneumonia, with expulsion of purulent secretions from the distal airways. Our practice is to perform airway washings, using 10 mL aliquots of normal saline instilled sequentially to remove small plugs which might have formed, assist with drainage of secretions, and ensure that no retained debris is left behind.

After completion of FB retrieval, perform a detailed airway exam in the region of the FB to assess for inflammation, granulation tissue, mucosal tear, and/or airway stenosis. Some of these injuries may need subsequent follow-up examinations to assess for progression.

Instruments

Grasping Forceps

Grasping forceps represent the mainstay of FB retrieval because of their versatility, ease of use, and variety. Forceps are available for both rigid and flexible approaches. There are two primary forceps mechanism designs: single and dual action. In single-action forceps, one jaw of the forceps is stationary and in a fixed position, while the other jaw is movable. In dual-action forceps, there are two movable jaws that open symmetrically away from each other (i.e., alligator jaw forceps). There are a variety of jaw surfaces available with variances in serration size, number, and arrangement. Additionally, there are available variances in surface area, shapes, presence of a needle, and fenestrations. Some examples of different available forceps designs include curved, needle, rat-tooth, V-shape, and shark-tooth. Forceps can also have different coatings, such as latex and rubber, which can help with enhancing grip of specific FBs. Some rigid forceps have the capability to rotate upon their axis, which can allow for an easier approach (Fig. 36.10). Rigid optical forceps are also available (Fig. 36.11). These forceps can be used in conjunction with a Hopkins telescope, which allows direct visualization when grasping FBs.

FB properties and location should determine the selection of forceps. The use of rigid forceps requires the FB to be directly in the pathway of

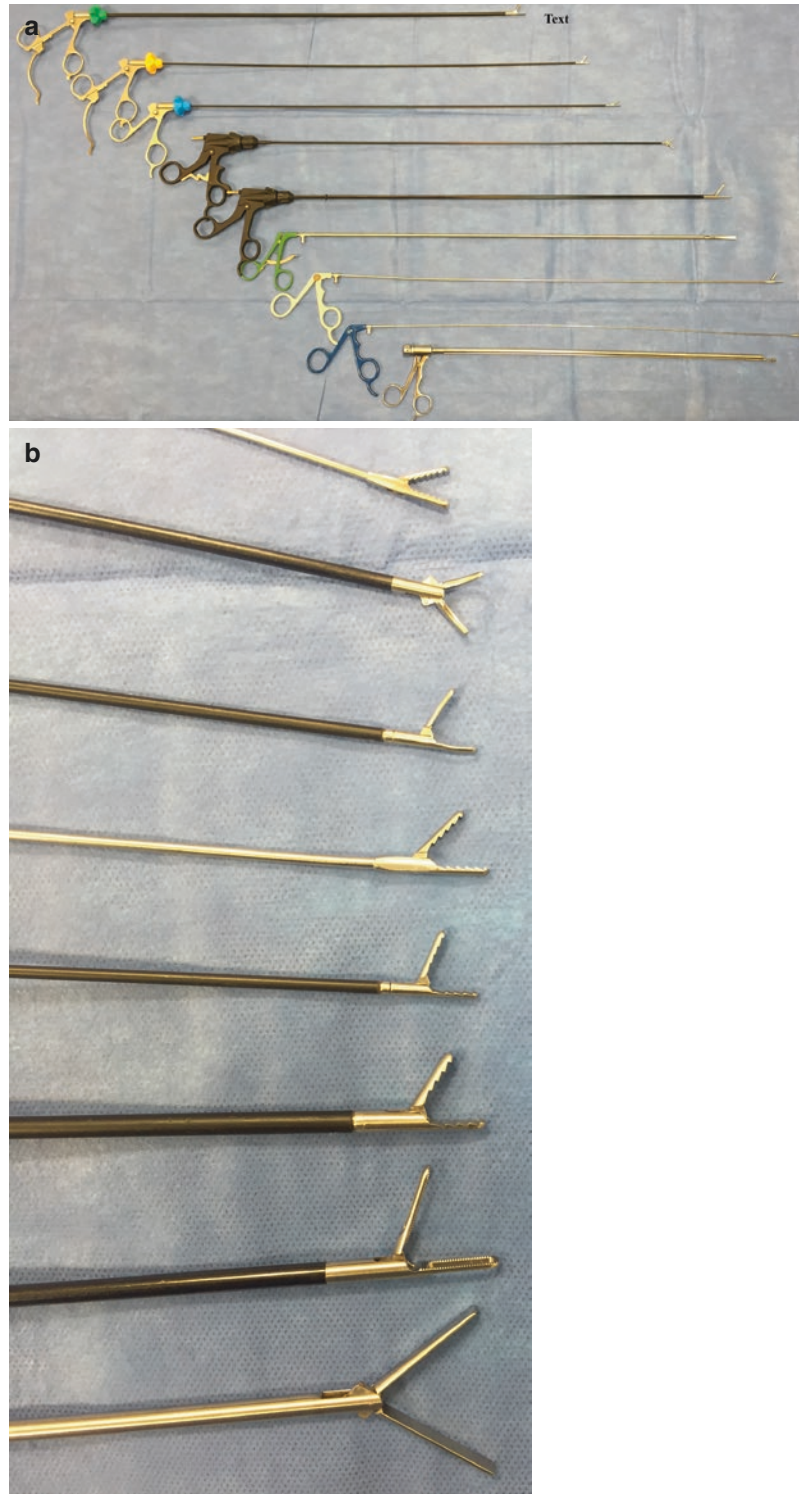

Fig. 36.10 Rigid forceps and graspers. (**a**) Variety of rigid forceps and graspers. (**b**) Close up of jaws of different forceps that can be used for removal of foreign bodies

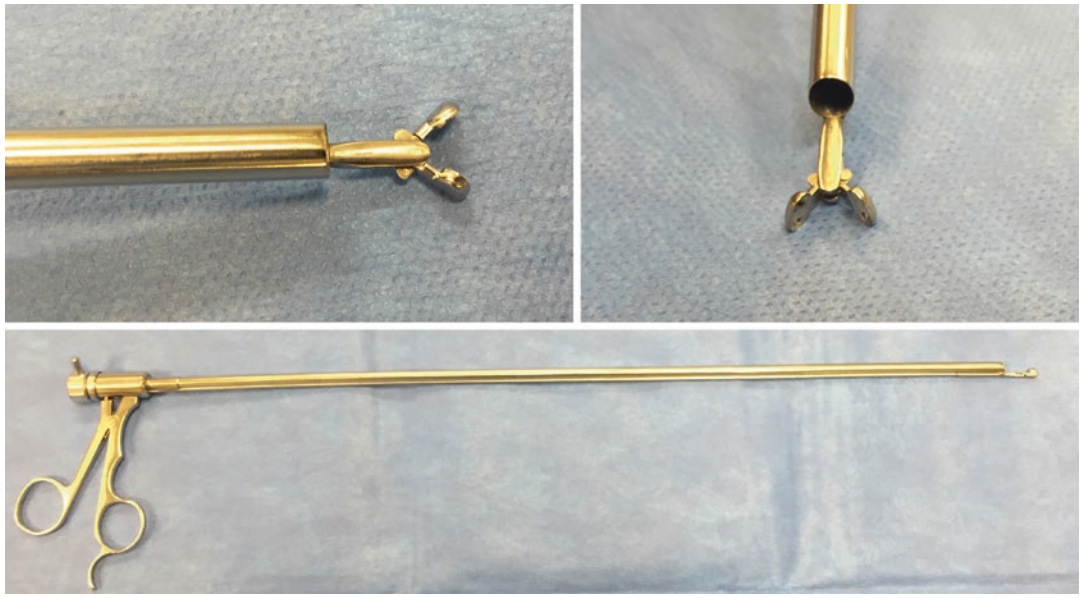

Fig. 36.11 Rigid optical forceps. These forceps work in conjunction with the Hopkins telescope and allow for direct visualization during use

the rigid tracheoscope/bronchoscope barrel. Distal FBs will often require a flexible bronchoscope and flexible forceps. When a FB is located in a confined space or is up against an airway wall, single-action forceps are considered initially because the space required for jaw opening is less than dual-action forceps. Rat-tooth forceps have a configuration where the teeth of the jaws interlace with each other when closing, which make these useful in retrieval of softer FBs. Objects with flat surfaces such as coins and certain dental appliances are better grasped with V-shape and shark-tooth forceps (known for having a firm grip).

While technically not forceps, multipronged graspers serve FB retrieval in a similar manner (Fig. 36.12). These graspers can have anywhere from three to five arms that open wide apart, usually to accommodate larger FBs. The tips of these arms come in different shapes, such as rings, to avoid mucosal trauma when opening them.

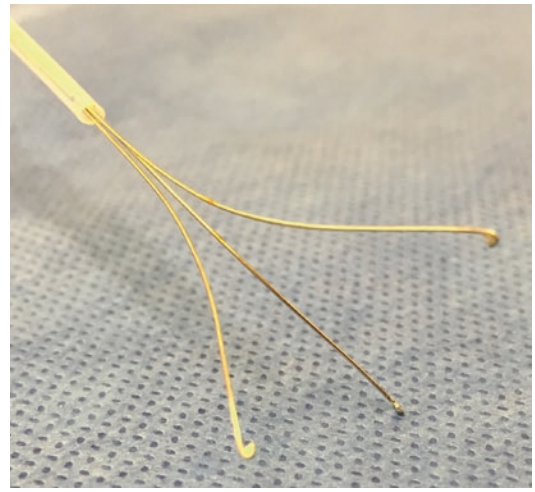

Fig. 36.12 Flexible three-pronged grasper

Baskets

Baskets are essentially complex snares that contain two or more wires that are in a loop formation and can be tightened in order to "capture" a FB (Fig. 36.13). The use of retrieval baskets originated in the field of gastroenterology, with it being the primary tool for removal of resected polyps. However, the use of baskets has spread to many other endoscopic and laparoscopic specialties for removal of various tissues and materials. While baskets are generally used in conjunction with flexible bronchoscopes, there are rigid varieties available. Baskets come in different sizes,

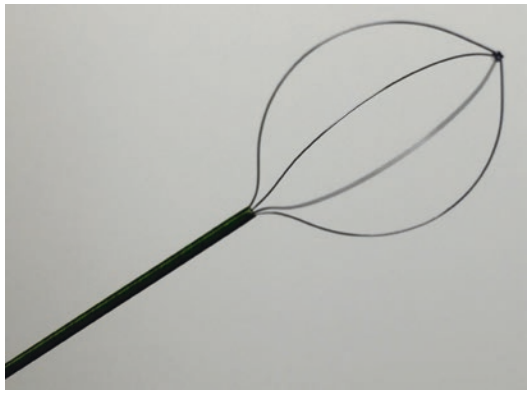

Fig. 36.13 Boston Scientific Zero Tip™ Airway Retrieval Basket (Spencer, Indiana, USA)

number of wire loops, stiffness, and different tips. Some baskets have nets built in to them to assist in retrieval of smaller material. Baskets are especially useful for airway FBs that are round or spherical in shape as well as those that are smooth. Caution should be used in FBs that are less solid or soft in nature, as retraction of wire loops can lead to unintended cutting of the FB into multiple smaller pieces.

Balloons

Balloons used for airway dilation, embolectomies, and bronchial blockage purposes can also be used to assist in the removal of FBs indirectly. For distal FBs that are "wedged" or in a confined space that won't allow for instrumentation, the use of a balloon can be considered. The technique involves passing a balloon distal to the FB and then inflating it. By slowly pulling the balloon proximally, the FB can often be dislodged and/or moved. The purpose of this maneuver is to allow for improved positioning of the FB giving the operator more retrieval options. Another use of a balloon is placing it distal to the FB to prevent migration into smaller airways during instrumentation. This technique usually requires the use of rigid bronchoscopy to control multiple tools within the airways. Keep in mind that balloons should be avoided with sharp FBs as the pulling/dislodgement can lead to mucosal injury in addition to balloon rupture. In addition, caution must be maintained when deciding to pass the balloon distal to the airway FB, as this maneuver does pose the risk of pushing the FB further into the airway.

Suction Instruments

Particularly when a FB is sitting more freely within an airway, there are various methods to utilize suction during FB retrieval. Most simply, this can be accomplished directly with the flexible bronchoscope's working channel and/or with the plastic or metal suction catheters used with rigid bronchoscopy. It is very important to acknowledge that despite its ease, this method does not allow for secure procurement of the FB during retrieval. Precautions must be taken during retrieval, especially when the bronchoscope is used trans-orally without an artificial airway. It is possible for the FB to become loose and detached from the bronchoscope at any number of levels (i.e., vocal cords, hypopharynx, pharynx, etc.). This may lead to the FB becoming obstructive in a more proximal or central location, such as the trachea, glottis, or supraglottic region. If such an event occurs in the upper airway and proximal to the vocal cords, direct laryngoscopy should be performed with the use of Magill forceps (Fig. 36.14) for retrieval of the lost FB. Loss of FB in the trachea could lead to cardiopulmonary decompensation and may require endotracheal intubation. In such cases, bronchoscopically advancing the FB distally into a main stem may allow for improved ventilation and further stabilization of the patient.

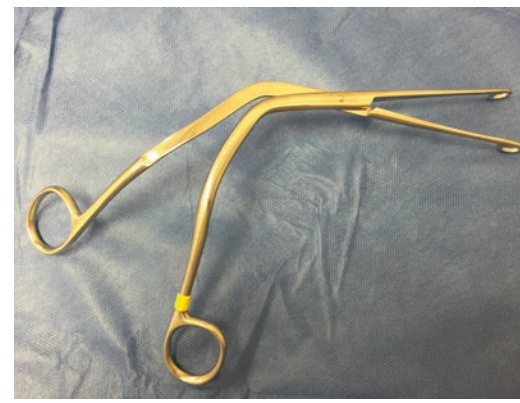

Fig. 36.14 Magill forceps

Rigid bronchoscopy allows for the use of large-caliber suction catheters. These catheters are specifically useful in suction of macerated and/or fragmented FBs such as medication pills and chewed edibles. Also, large-bore catheters are excellent for suctioning large volumes of blood, if massive hemoptysis occurs associated with the FB aspiration or its removal.

Ablative Therapies

While ablative therapies are routinely used for their tissue coagulative and destructive effects, they have a unique role in management of FBs. Granulation tissue is a common consequence of retained FBs and can make retrieval challenging. Ablative therapies such as laser, argon plasma coagulation (APC), and electrocautery are all effective tools in destroying granulation tissue and allowing easier access to the FB. Cryotherapy is unique in that in addition to its ablative effects, it can directly be used for FB retrieval. Below, we discuss in-depth aspects of cryotherapy, laser therapy, and electrocautery/APC.

Cryotherapy: Cryotherapy is traditionally used for its destructive properties in the treatment of obstructive airway lesions, but it is also a very useful tool in specific cases of FB retrieval. The extremely cold temperatures produced by cryotherapy allow organic FBs to freeze and attach to the probe. Often these FBs can be removed without much difficulty. It is important to remember that cryotherapy's usefulness is reliant upon the presence of liquid in the FB, which will subsequently transform into a more solid state with the application of cryotherapy and adhere it to the probe. Typically, it often requires freezing for 5–10 s to create the attachment. The operator must be very careful not to touch the airway wall while attempting to remove the FB, as the probe will stick to the wall also.

Cryotherapy is also known for its use in the removal of blood clots and mucus plugs from obstructed airways. Because of their water content, blood and mucus are excellent candidates for cryotherapy and are efficiently removed when using this technique. Mucus and blood casts of the tracheobronchial tree can be removed in an en bloc manner with cryotherapy, but it requires freezing for 20–30 s. Similarly, ensure that the probe does not touch the airway wall during this maneuver.

Organic FBs such as vegetables, fruits, and meats (without bones) are excellent candidates for removal with cryotherapy. Medication pills are also often retrievable with cryotherapy. Objects without water content (i.e., metals, plastics, etc.) will rarely attach to the cryotherapy probe. Another technique reported in the literature that has been used in FBs without water content is instilling normal saline around the FB and then applying cryotherapy until ice forms around the object [50]. This allows for solidification of the normal saline and subsequent encasement of the FB. Cryotherapy can also be used in the resection of the associated granulation tissue caused by FBs.

Laser Therapy: Laser therapy has three potential uses in the management of FBs which are resection of granulation tissue, photocoagulation to minimize or treat bleeding, and intentional fracturing of FBs. As stated earlier, it is important to ensure that the FB in question is noncombustible and that the inspired fraction of oxygen concentration is less than 40%. Laser therapy can be performed with a variety of different types of lasers. Photodessication can be used to destroy granulation tissue obstructing the FB or attached to it when this tissue interferes with the removal of the FB. If mucosa in the vicinity is inflamed or demonstrates a significant bleeding potential during retrieval, photocoagulation techniques can be used to minimize mucosal bleeding prior to instrumentation. Laser has also been used to reduce the size of a FB, referring to a report of neodymium-doped yttrium aluminum garnet (Nd:YAG) being used to fracture a large broncholith into smaller fragments to allow retrieval [51]. In the GI literature, there is a case report of using laser to intentionally fracture a denture impacted in an esophagus to allow for successful retrieval [52].

Electrocautery and APC: Electrocautery and APC are not tools used in FB retrieval; however, they can be used for those situations where granulation tissue has grown around the FB, impeding retrieval. Before using, the bronchoscopist must know what the FB is and ensure that it is noncombustible. As in any case using thermal

energy, and the inspired fraction of oxygen, concentration must be reduced below 40% during use. Electrocautery and APC can be used to resect granulation tissue with or without the FB attached and provide coagulation effects to the affected mucosa, limiting bleeding which can negatively affect visualization.

Surgical Management

Surgical intervention should be used as a last resort measure. Bronchoscopic retrieval is considered to be first-line therapy as it is minimally invasive, safe, and highly effective. However, there are a few indications that may warrant surgical resection for retained FBs. For distally impacted FBs that are not amenable to FB retrieval or were unable to be retrieved successfully, thoracic surgery consultation should be sought for consideration of surgical resection. Another indication is for deeply embedded FBs. These FBs usually represent retained FBs that may have been aspirated months or years earlier and can be associated with intense inflammation, infection, excessive granulation tissue, or fibrosis. If bronchoscopic retrieval is unsuccessful or considered to be high risk for complications, surgical intervention should be considered.

Sharp foreign bodies may require surgical resection as they can be challenging to retrieve and pose risks such as mucosal tearing, airway perforation, and bleeding. Additionally, sharp FBs can be "wedged" or embedded into tissue, which can make retrieval more high risk. Surgery may be considered for FBs that have penetrated the airway wall and are in contact with mediastinal or hilar structures/vessels. Bronchoscopic retrieval may lead to undesired communications and/or bleeding. Regardless, if any doubts or concerns exist, a multidisciplinary approach should be used as it is very valuable to provide the best plan of action for each patient with such circumstances.

Complications

In the hands of experienced bronchoscopists, the complication rate for bronchoscopic intervention in children and adults is reported at less than 5%, with most studies indicating rates of less than 1%. Mortality from bronchoscopic FB retrieval is exceedingly rare and is reported as less than 0.1% [3, 21, 24, 39]. The most common complications associated with FB retrieval include mucosal injury, bleeding, and airway perforation. While extremely rare, perforation can lead to pneumothorax and/or pneumomediastinum. Perforations should be managed in a multidisciplinary fashion with interventional pulmonology, thoracic surgery, and/or otolaryngology involved.

Bleeding and Hemoptysis

When patients present with hemoptysis due to FB aspiration, rigid bronchoscopy should be the modality of choice for retrieval. Rigid bronchoscopy allows for superior visualization, stabilization of airway, and better instrumentation options for bleeding and retrieval simultaneously. Remember, minor hemoptysis associated with FB aspiration may foreshadow more significant bleeding that can occur during retrieval.

Excessive bleeding during retrieval will likely occur in the setting of FB-associated perforation of the pulmonary or bronchial arterial circulation. Massive intraoperative bleeding during flexible bronchoscopic retrieval should lead to aborting the retrieval and stabilizing the patient emergently. In these cases, airway securement is of the utmost importance, whether it is with endotracheal mainstem intubation, balloon blockade of the bleeding airway, or rigid bronchoscopy. Adjunct therapies such as placing the patient in the lateral decubitus position (on side of bleeding) or sedation/paralytics to control coughing can also be utilized. In sub-massive bleeding with relative patient stability, a bronchial blocker balloon may be used in conjunction with securing the airway.

For minor intra-procedure bleeding, topical epinephrine mixed with normal saline (1:10,000 concentration) can be instilled with 2 mL aliquots delivered over the affected area. Keep in mind to avoid topical epinephrine in patients that are elderly or a have history of arrhythmias, carcinoid tumors, and coronary artery disease. Laser

therapy, electrocautery, or APC can be used to photocoagulate mucosal irregularities when friable mucosa is observed or bleeding is expected, prior to proceeding with FB retrieval or afterward in the appropriate clinical situations. When bleeding originates from a FB in a distal segmental airway, consider wedging the bronchoscope in the affected airway for 2–5 min to promote clot formation. While, technically, clotting time for human blood ranges from 5 to 15 min [53] and bleeding time ranges from 1 to 3 min [54], our recommendations are to first wedge bronchoscope for 2 min and then reassess. If bleeding persists, then re-wedge for 5 min and then reassess. Another technique that can be utilized is wedging the bronchoscope into the affected airway and instilling iced saline, which promotes vasoconstriction and applies pressure to the airway mucosa to decrease bleeding.

Distal Airway Impaction

Smaller FBs have a tendency to migrate into segmental and sub-segmental airways. Impaction of these FBs can occur because of specific FB properties such as their texture and shape. Additionally, impaction may occur as a result of a weak cough reflex or anatomic variations, which may not be conducive to proximal movement of the FB. As always, care must be taken with retrieving sharp FBs. Prior to retrieval, it is important to assess the FB and its relationship to the airway to explain the cause of impaction. Always try to identify the point of maximal resistance and points of contact that may pose risks for airway trauma during retrieval.

Flexible bronchoscopy is best for these situations because of the ability to navigate and enter distal airways. We recommend using flexible bronchoscopy in combination with an artificial airway device such as endotracheal tube or rigid bronchoscope for these situations. Having a secure airway allows for easy exchange of different types of bronchoscopes (pediatric, diagnostic, and therapeutic scopes) and provides a safe environment for unexpected bleeding. Because flexible bronchoscopy is the only modality that can reach distal airways, flexible instruments are used via the working channel of the bronchoscope.

The aim of retrieval in these circumstances is to remove the FB in the path of least resistance with minimal injury to the airway wall and/or displace the FB to a location (i.e., central airway) where retrieval is more feasible. While each FB and patient presents with its unique challenges, the following represents general principles that should be considered during retrieval. Topical epinephrine (as previously described) is very useful in minimizing bleeding during the actual removal process. When feasible, the FB should be removed with protection over the sharp aspect of the FB and in a manner to prevent chances of dropping it. This can be achieved by grasping the FB from the sharp edge or by repositioning the FB with the aim of moving the sharp edge to the middle of the lumen. As mentioned earlier, distal positioning of a balloon and inflation can help pull impacted FBs proximally into more ideal retrieval location when it does not pose the risk of pushing the FB into a worse position during balloon placement. Pulling FBs too proximally is actually undesired, as the FB may move excessively while you are trying to grasp it with forceps. To achieve good control, there must be some resistance to the FB while grasping it. Preferably, you should place it up against a wall which can simplify this process. Remember that for simultaneous use of a balloon and flexible bronchoscope, rigid bronchoscopy is recommended. A distally placed balloon can also act as a safeguard to prevent further distal migration of the FB during manipulation and instrumentation, but you need to get it past the FB without dislodging it. The appropriate size balloon should be used also to minimize risk of over dilation of such relatively small-diameter airways which could lead to inadvertent tearing and bleeding.

A small-caliber bronchoscope can also be used as an instrument for retrieval. If the bronchoscope can be passed distally to the impacted FB, flexion of the distal end of the scope can be used to displace or move the FB proximally. This technique should not be used with any FB that may pose danger or damage to the scope. As stated earlier, if granulation tissue is contributing to the impaction, ablative techniques can be utilized to resect the tissue to detach or "loosen" the FB from the airway wall and allow retrieval.

Iron Pill Aspiration

In this section, we will discuss iron pill aspiration, as from our experience and from various case reports, it is well known to be associated with severe airway injury when aspirated. Iron supplementation comes in three different formulations: ferrous sulfate, ferrous gluconate, and ferrous fumarate. Ferrous sulfate is the most common preparation used by patients. Its caustic properties are a direct result of its acidic pH (<3) when dissolved [28] and mixed with bronchial secretions. Consequences of exposure to airway mucosa include intense acute and chronic inflammation, granuloma formation, and eventual fibrosis and bronchostenosis (Fig. 36.15). Radiologically, patients present with findings consistent with sequelae of retained FBs and airway obstruction such as recurrent pneumonias and atelectasis.

Interestingly, on bronchoscopic examination, iron pills are almost never visualized as they are known to rapidly disintegrate. Endobronchial biopsy of affected mucosa usually will show iron deposition when stained with Prussian blue stain with associated inflammation (acute and/or chronic). These findings have been reported even 1 year after the initial pill aspiration event [26]. Also, bronchial washings may demonstrate reactive epithelial cells and histiocytes which may stain positive for iron also. In the relatively acute period, bronchoscopic exam may yield a green-brown coating over the bronchial mucosa which represents necrotic debris [29]. A history of pill aspiration and intense bronchial inflammation should raise suspicion for iron formulation aspiration. In our experience, iron pill aspiration is notorious for its sequelae of bronchial inflammation and recurrent stenosis which is relatively difficult to manage.

Iron pill aspiration-related bronchostenosis behaves very similar to severe autoimmune inflammatory disorders such as granulomatosis with polyangiitis (GPA, formerly known as Wegener's disease) and sarcoidosis. Bronchostenosis can be severe to the point where lobar/segmental collapse may develop with/without post-obstructive pneumonia. In our practice, we treat iron pill-associated bronchostenosis with balloon bronchoplasty and resection of necrotic tissue. These cases always require surveillance bronchoscopies to assess for recurrent bronchostenosis, which is common, and need for repeat therapeutic interventions. There are case reports of topical mitomycin C, a chemotherapeutic agent, used in conjunction with balloon bronchoplasty and treatment of such bronchostenosis cases [26, 27]. Mitomycin can be applied with a concentration of 0.2 mg/mL to the affected area for a total duration of 5 min. In severe cases of recurrent airway obstruction, an airway stent may be considered. From our experience, iron pill-induced bronchostenosis does resolve but usually requires three to five interventions.

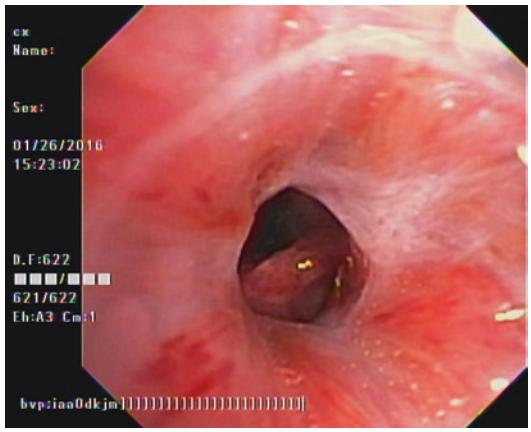

Fig. 36.15 Iron pill aspiration-induced bronchostenosis of the right lower lobe bronchus

Follow-Up and Sequelae

The majority of acute FB retrieval cases with minimal signs of airway injury do not require any subsequent diagnostic interventions (i.e., bronchoscopy, imaging, etc.). Associated mucosal inflammation from FB aspiration is common and is expected to resolve in a majority of cases. While literature is lacking, we recommend follow-up bronchoscopy in certain circumstances for acute FB cases. When severe airway inflammation, endobronchial obstruction from associated granulation tissue, or stenosis is encountered, it is our practice to perform a follow-up bronchoscopy 4–6 weeks later to assess for resolution

or progression of findings. It is important to recognize that severe inflammation from a relatively acute FB may foreshadow undesired sequelae to occur, similar to other benign inflammatory airway disorders.

Unlike acute FBs, chronic/retained FBs are almost always associated with inflammation, infection, granulation tissue, fibrosis, or some degree of stenosis. For these cases, our practice is to routinely perform a follow-up bronchoscopy 4–6 weeks after retrieval. Some of these cases may require further interventions similar to other benign airway disorders (i.e., balloon dilation, tissue resection, etc.). Subsequent follow-up bronchoscopies should be determined on a case-to-case basis. Patients with retained FBs in segmental or sub-segmental airways may have associated atelectasis and/or chronic regional changes (i.e., fibrosis, bronchiectasis, scarring, etc.). These changes do not require routine follow-up and should be assessed on a case-to-case basis.

Iatrogenic airway injury from retrieval should be followed up with a follow-up bronchoscopy on a case-to-case basis. Small mucosal injury/tears can occur during retrieval and may not require any further escalation. As mentioned above, larger tears and/or perforations may require intervention and should be followed up with a bronchoscopic exam and preferably in a multidisciplinary manner with thoracic surgery and/or otolaryngology consultation. If after FB retrieval the patient fails to improve as expected from a symptom standpoint or an infection occurs in the previous FB-involved region, one must consider if there is a retained FB that was not visualized during bronchoscopic retrieval. If there is any doubt, repeat CT imaging (preferably thin-cut, high-resolution) with a follow-up bronchoscopy to assess for retained fragments, additional FB presence, or subsequent unexpected changes in the airway from the initial FB.

Conclusion

While airway FB aspiration and retrieval are less commonly encountered and vary from center to center, it does, however, represent the origins of interventional pulmonology and bronchoscopy. In the hands of well-trained bronchoscopists, bronchoscopic FB retrieval represents the gold standard treatment for airway FBs. Rigid and/or flexible bronchoscopy combined with a vast arsenal of available instruments allows for various approaches and therapeutics not only for retrieval but for its associated complications.

Retained FBs are a very important subset of patients, as this population commonly presents with nonspecific respiratory complaints secondary to the FB-associated inflammatory cascade and its sequelae such as airway inflammation, granulation tissue, airway stenosis, and/or post-obstructive pneumonia. A high level of suspicion must be maintained to avoid misdiagnosis and/or delay in treatment. Clinical presentation, FB location, and/or presence of inflammatory sequelae should guide the bronchoscopist on the selection of the bronchoscopic approach (rigid and/or flexible bronchoscopy). Regardless, adequate training and knowledge is required not only to successfully perform bronchoscopic retrieval but to competently manage all possible complications. When encountering a high-risk patient or a complication from retrieval, a multidisciplinary approach involving interventional pulmonology, otolaryngology, and/or thoracic surgery should be applied to formulate the best plan of action for each patient.

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Interventional Pulmonology in the Intensive Care Unit

37

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Abbreviations

BF	Bronchofiberscope
BPF	Bronchopleural fistula
CAO	Central airway obstruction
DAC	Dynamic airway collapse
ECA	Expiratory collapse of the airway
EDAC	Excessive dynamic airway collapse
ETT	Endotracheal tube
ICU	Intensive care unit
MV	Mechanical ventilation
PAL	Prolonged airway leak
RB	Rigid bronchoscope
RMB	Right main stem bronchi
TBM	Tracheobronchomalacia
TM	Tracheomalacia
TT	Tracheostomy tube

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It is already well known that the pulmonologist plays a very important role in the Intensive Care Unit (ICU). More recently, the interventional pulmonologist has become very important in this area as well, where he/she is frequently requested to solve different situations, particularly those related to the airway and/or the pleura. Patients in the ICU are critically ill, and many procedures have to be performed at the bedside, to avoid the additional risks involved in transferring patients to the operating room.

The bronchoscopist usually is required to perform bronchoalveolar lavage (BAL) samples to help diagnosing a pulmonary infection or for transbronchial lung biopsy in a patient on mechanical ventilation (MV). Less frequently, a transbronchial needle aspiration is needed, or a patient with hemoptysis is evaluated. These procedures are almost exclusively diagnostic.

The most classic therapeutic intervention requested in the intensive care setting is the evaluation and treatment of persistent atelectasis. However, in the last few years, the role of the interventional pulmonologist in the ICU has broadened, and the number of procedures that the interventionists can perform has evolved. In this chapter we will review different situations that can require assistance from the interventional pulmonology team. We will limit our discussion to airway-related problems.

Unfortunately, for many of the recommendations made in this chapter, there is no literature backing up

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their benefits and or safety. Most of them are based in expert opinions and personal experience of the authors who have shared their own practice on particularly serious clinical scenarios. The application of different tools such as laser, argon plasma coagulation, or electrocautery has more than enough literature support, and when we apply those tools, we follow international recommendations.

Central Airway Obstruction (CAO)

Respiratory failure due to CAO is more frequently recognized than in the past. Various disorders can cause CAO, and different degrees of airway obstruction can be seen. First of all, this entity needs to be suspected; second it needs to be confirmed; and third a therapeutic measure must be offered. We will limit our discussion to the adult population, since airway obstruction in children is very different, both in etiology and clinical presentation [1].

Causes of CAO

CAO can be located at any of the three different segments of the major airway (Table 37.1).

CAO can develop gradually (i.e., progressively growing malignant tumors) or acutely (i.e., respiratory infections, where secretions totally occlude an already compromised tracheal lumen) and can be caused by benign or malignant conditions located inside or outside the airway lumen (Table 37.2).

Table 37.1 Obstruction in the airway—location

Location	Types
Larynx	Supraglottic Glottic, anterior or posterior Subglottic
Trachea	From carina to vocal cords
Bronchi	Only important if it affects both main stem bronchi

Table 37.2 Acute causes of CAO and their location in the airway

Location	Cause
LARYNX	
Laryngeal edema	Anaphylactic reactions [56] Angiotensin-converting enzyme inhibitors [57] Burns [58] Post-extubation [59] Epiglottitis [60]
Bilateral vocal cord palsy	Laryngeal dystonia Parkinson's disease [61] Shy-Drager [62] Laryngeal dyskinesia [63] Myasthenia gravis [64] Relapsing polychondritis [65] Rheumatoid arthritis [11] Foreign bodies [12] Recurrent nerve damage after thyroidectomy [66]
TRACHEA	
Extrinsic compression	Thyroid disease [13] • Benign intrathoracic or substernal goiter • Malignant tracheal ingrowth of thyroid carcinoma [66] • Tracheomalacia secondary to direct sustained compression produced by thyroid enlargement [67] Mediastinal bronchogenic cysts [14] Esophageal foreign body [15] Thymic cysts [16] Vascular causes • Arterial puncture [17] • Descending aortic dissection [68] • Rupture of the aorta [69]
Intrinsic obstruction	Primary tumors • Squamous cell carcinoma [70] • Adenoid cyst (cylindroma) [71] Metastatic tumors [72]: breast, renal, colon Benign tracheal stenosis (including subglottic stenosis) • Post-tracheostomy • Post-endotracheal intubation • Idiopathic (rarely of acute presentation)

The severity of symptoms depends on the pressure drop along the stenosis, which is directly proportional to the flow speed and inversely proportional to the radius of the stenosis [2, 3]. Symptoms at rest appear when the stenosis occludes more than 70% of the airway lumen. Since flow speed is inversely proportional to the length of the stricture, the same degree of stenosis is more symptomatic when the length of the obstruction is shorter.

Acute Central Airway Obstruction

Clinical Presentation

The usual clinical presentation is a patient admitted to the ICU in acute respiratory failure. Frequently patients have a history of progressive dyspnea, with or without a prior known condition (e.g., tracheal carcinoma), that suddenly worsens due to disease progression or to a new respiratory infection. The infection generates swelling of the already compromised mucosa triggering acute respiratory distress.

The main priority is to secure the airway through endotracheal intubation. Once the endotracheal tube (ETT) is in place and ventilation is assured, any required endoscopic intervention can be performed safely either in the ICU or the operating room.

We, as most of the authors, prefer the rigid bronchoscope (RB) to explore the airway in a patient with CAO. However, the flexible bronchoscope should also be available to help throughout the procedure.

In the event that the ETT cannot be progressed through the stenotic airway or if the patient cannot be intubated, RB should be immediately performed by a skilled bronchoscopist. In these severe situations, to obtain a secure airway is critical, and it should be done to save the patient's life.

RB serves two purposes:

1. Diagnostic: RB is the best method to identify the cause of obstruction.
2. Therapeutic: RB can be used to dilate or to resect an intrinsic airway mass and place an airway prosthesis to support the airway if necessary.

In some situations (stenosis located right below the subglottic segment), a tracheotomy is the preferable procedure to secure the airway.

Therapeutic Options to Relieve CAO

In order to decide which procedure is best to solve the acute CAO, the bronchoscopist has to consider three important factors: bronchoscopic findings (location, extension, and degree of airway damage), equipment availability, and preference of the operator.

Bronchoscopic findings are assessed during inspection of the airway with the flexible or rigid bronchoscope. If pure extrinsic compression without damage of the airway mucosa is found, dilatation with the RB followed by stent placement is a good therapeutic option.

When the obstruction is caused by a mass compromising the airway lumen, bronchoscopic dilatation is also an option, but removal either mechanical or with the aid of a coagulation instrument such as Nd-YAG laser, argon plasma coagulation, or electrocautery is preferred. After opening the airway, the need for a stent to help keeping it open has to be evaluated. Stent placement is not always necessary.

In mixed lesions, where there is some intrinsic and extrinsic component, therapeutic options can be combined to open the airway.

Treatment modalities vary from center to center, and airway lesions can be very different from patient to patient, so the choice of the best method for a given situation has to be taken case by case and according, as we said, to equipment availability and the experience of the endoscopist with each one of the techniques.

All interventional procedures involve a dedicated bronchoscopist and his/her trained team that includes an ICU nurse or scrub nurse and one assistant. Also, they are performed under general anesthesia, and an experienced anesthesiologist has to monitor the patient closely. When this procedure is done emergently in the ICU, an intensivist and a respiratory therapist are needed. All supporting personnel should be well trained and familiar with the procedure taking place.

Equipment Needed

All the following items are required to the procedure:

1. Equipment to perform rigid and flexible bronchoscopy (rigid tracheoscope, different sizes of rigid tubes for the trachea and bronchus, rigid lenses and accessories such as alligator forceps, biopsy forceps for rigid and flexible endoscopes, stents of different sizes, etc). A large bore suction catheter is necessary to clear the field of secretions and blood. Hemorrhage, dense secretions, bulky tumors, difficult anatomy, and inflammation [4] can all be factors that complicate the intubation with the RB.
2. When electrocautery is to be applied, a high-frequency electric generator and insulated probes will be necessary. Usually, the monopolar mode is suitable for endoscopic application, and a grounded plate must be attached to the patient.
3. When laser is available, laser-specific equipment will be necessary (specific laser fibers with matching protective glasses and gloves).
4. More than one type of stent should be available, with their different deployment devices and accessories.
5. The procedure is usually performed under total intravenous anesthesia. Jet ventilation is used as ventilatory support and connected through a side port of the rigid bronchoscope.

Endoscopic Techniques

Endoscopic Dilatation

Mechanical dilatation is usually the best approach to offer as a first therapeutic measure. Dilatation is achieved with the rigid bronchoscope. In the patient with ventilatory failure and without a secure airway sometimes a forceful dilatation is needed in order to solve the acute situation. However, it has to be avoided if not strictly necessary, and it should be performed by an experienced operator. Mucosal trauma has to be minimized since it is followed by disorganized healing and scarring. This leads to proliferation of fibrous tissue and restenosis usually takes place [5].

In emergent situations, when the lesion is visualized, the scope is advanced through the stenosis, and the beveled end is pushed through the lesion rotating the rigid tube at the same time. Compression of the lesion with the rigid tube usually is sufficient to avoid bleeding. The bronchofiberscope (BF) is then passed through the rigid instrument, and a quick toilette and inspection are performed.

When the patient is stabilized and oxygenation is appropriate, the scope is withdrawn, and an ETT is placed. The diameter of the ETT must be the biggest that can be passed through the stenosis. We have to bear in mind that if a flexible scope needs to be passed through the ETT, it is preferred to have a minimum of 8 mm of internal diameter. To calculate the external diameter of the ET tube, 2–4 mm is added to its internal diameter.

Balloon dilatation is not a good option in emergent situations and is preferable in benign stenosis that involves the main stem or the lobar bronchi [6]. It is usually performed with a mitral valve valvuloplasty balloon [7], esophageal balloons, or a Fogarty catheter.

Mechanical Removal

When endoscopic dilatation cannot be done or if it was not enough to open the airway, mechanical removal of the obstructing tissue may be attempted. It is recommended to flush some millimeters of diluted adrenalin or cooled saline solution before starting mechanical debridement with forceps, to lower the risk of hemorrhage after removal. After that, the surface can be coagulated with laser, electrocautery, or argon plasma coagulation in order to prevent bleeding or to complete the resection (see advantages and disadvantages of each one in Table 37.3) [8].

Table 37.3 Advantages and disadvantages of the different methods of reopening airway [8]

Type of treatment	Results	Complications
Mechanical removal	Immediate but short duration of effects	Bleeding
Electrocautery	Immediate and superficial	Perforation, bleeding, fire, and electric shock
Laser	Immediate and in-depth action	Perforation, bleeding, and fire

Electrocautery, Nd-YAG Laser, and Argon Plasma Coagulation

A more detailed description for these procedures is presented in a dedicated chapter of this book.

Since electrocautery is available in our center, it is our instrument of choice. The probe is directly applied to the tissue that needs to be removed, always in coagulation mode.

The observed damage produced by cautery to the tissue has a very good correlation with the histological damage. This is very important, and represents one of the main differences with laser therapy, where the immediate visualization does not correlate with histological damage, since laser acts much deeper (6 mm depth) than electrocautery whose action is superficial.

A ground plate has to be attached to the patient's back to avoid electric injury to both the patient and the endoscopist. If the plate is not used, electric current can travel directly to the operator since the RB is not insulated. The best way to avoid this event is to utilize bipolar probes through insulated BF [9].

Tips for Using Electrocautery

The electric current dissipates within the tissue, moving through it and generating heat that vaporizes the targeted lesion. When resistance is high, difficulty in the passage of electricity is met. This situation occurs in dry tissues and in the presence of detritus and blood.

The generated heat reaching different targets is proportional to the square of the intensity. If the electric current is duplicated, the heat obtained will increase four times. Before augmenting the electric power of the cautery, other causes of failure to dissolve tissues must be ruled out [10]. Always have in mind that the presence of blood and detritus dissipates the electric current, and the desired effect will not be achieved in those circumstances unless removal of debris cleans the field.

There is a significant risk of catching fire when cautery is applied with high fraction of inspired oxygen (FiO_2 over 0.4). Therefore, we recommend to keep FiO_2 at 21% (room air) while electrocautery is in use. A power setting of 50 W is sufficient for coagulation, achieving the desired effects and avoiding adverse events.

Stents (Prosthesis)

When obstruction is caused by pure extrinsic compression [11–17], stent placement after dilatation is literally the unique option.

The rigid bronchoscope is the best instrument to place an airway prosthesis. Selecting the best stent size can be very difficult in emergency situations [18]. Before placing the prosthesis, an appropriate lumen must be achieved, usually applying a quick dilatation maneuver with the rigid scope. When intrinsic obstruction is present, electrocautery or laser may be used to help resection. Stent diameter can be calculated based on the diameter of the scope that can overcome the stenosis. A tight fit is advisable to avoid migration. If the maneuver is successful, a second elective procedure can be performed after careful planning, for a most definite solution.

Stent type will depend on the preference of the operator and availability, but we recommend to use silicone stents [19–21]. Their main advantage in these situations is that they can be easily removed. However, in the presence of a malignant obstruction, a metallic is also acceptable.

Having proper aspiration is of utmost importance during interventional procedures. Rigid plastic catheters, passed through the lateral ports of specially designed bronchoscopes, provide insufficient aspiration in these critical cases. We prefer the rigid metallic aspiration cannula or the

use of the BF through the rigid instrument. A faster and more efficient procedure can be favored by having the BF connected to its own vacuum port and a different power light source than the one utilized for the RB, ready for use at all times during the treatment.

Once a good lumen is obtained, an ETT tube is placed, and the patient is connected to mechanical ventilation.

Sometimes in critical obstructions when a tracheal stent is not immediately available, a tracheostomy may be needed. The ETT tube can then be inserted through the tracheostomy and be positioned across the lesion or stricture. With the ultrathin-walled ETT, this procedure is easier than with the regular ETT, so greater lumen is achieved with the same size tube [22].

In one retrospective study [23], it was confirmed that bronchoscopic interventions not only could achieve immediate airway relief but also improve survival in advanced lung or esophageal cancer patients. The conditions associated with a better survival were treatment-naïve status, an intact proximal airway, and available post-procedural additional treatment.

Murgu et al. [24] published their experience with bronchoscopic resection in patients admitted to the ICU in acute respiratory failure that required mechanical ventilation due to CAO for inoperable non-small cell lung cancer. After the bronchoscopic resection, 9 of 12 patients (75%) were immediately extubated. An additional patient was extubated 8 days after the procedure. The authors conclude that if these findings are confirmed in prospective and multicentric studies, the model of admission of these patients to the ICU must be reviewed.

Post-Intubation or Post-Tracheostomy Stenosis

Acute respiratory failure developing from tracheal stenosis requires a different approach than when the failure is progressive. It usually presents in the setting of an elective extubation during weaning from mechanical ventilation.

The permanence of the ETT in the larynx may produce ulcers in the posterior aspect of the vocal cords, followed by edema, granulation tissue, and scar formation [25]. Similarly, its permanence inside the trachea produces, in the early phase, mucosal lesion and ulceration followed by cartilage destruction, granulation tissue, and scar formation, leading to the formation of a stenotic area. In severe cases, tracheal rings are exposed, infection takes place, and they soften, fragment, and disintegrate, leading to a variety of tracheal lesions. Later, they may be reabsorbed, and the tracheal mechanical support is lost, resulting in collapse of the compromised segment [22] and, as we will discuss later, ultimately ending up in tracheomalacia.

To minimize the injury produced by the endotracheal tube cuff, high-volume low-pressure cuffs have been replaced by low-pressure high-volume ones. These low-pressure cuffs have a large residual volume prior to inflation. When the cuff is inflated and the operator feels a resistance, an important overexpansion of it may already exist [23]. High inflation pressures interfere with the submucosal vascularization of the trachea, causing ischemia and necrosis. Infected secretions above the cuff contribute to tracheal damage (that is why it is so important to have a careful subglottic aspiration). When pressure generated by the ETT cuff exceeds the mucosal capillary perfusion pressure, usually 20–30 mmHg, tracheal injury occurs. It is very important to maintain a low pressure on the tracheal mucosa, so when a cuff pressure of 25 mmHg is reached and air leak persists, it is advisable to intubate the trachea with a bigger tube instead of inflating the cuff over that pressure [26].

The usual clinical scenario is a patient weaned from MV that develops acute respiratory distress with stridor and other signs of upper airway obstruction and must be re-intubated. After the emergency has been solved, the following inspection is advisable: the bronchoscopist, with the aid of an anesthesiologist if possible, introduces the BF through the ETT until reaching its distal end. Once in place, an assistant proceeds to slowly remove the ETT while the endoscopist is inspecting the airway as they go. Areas of malacia and

other lesions may be observed. Careful must be taken no to overpass the vocal cords level with the BF, since it may be necessary to intubate again and that can be easily performed over the bronchoscope. It is also very important to make an inspection of the airway proximal to the vocal cords. Once inspection through the ETT is completed, the BF can be introduced again via nasal route, while the patient is connected to mechanical ventilation. Most of the times no injury is found in the airway and extubation fails for important edema of the supraglottic area. A plan to proceed can be outlined after finishing this evaluation.

When a stenotic area is found, dilatation, electrocautery, or laser may be necessary, alone or in combination. When the only finding is edema, a trial of steroids is advisable. More complex lesions require a planned procedure, taking into account the type and extension of the affected area.

One very common cause of tracheal stenosis is granuloma formation. They develop from persistent inflammation, and they do not compromise the tracheal wall. Weblike stenosis, in turn, represents a different form of stenosis developed from fibrous tissue that produces a subtotal stenosis, also sparing the tracheal wall. Bottleneck stenosis consists on a localized collapse of the tracheal wall less than 5 cm in length. Weblike and bottleneck are referred as simple stenosis.

Complex stenoses are large, affecting more than 5 cm in length or six tracheal rings or localized in more than one segment of the tracheobronchial tree. Usually, only the bottleneck and the complex type are responsible for severe obstructions. A detailed classification and therapeutic strategies of stenosis may be found in Dumon and Diaz-Jimenez [27], and tracheal stenosis is also discussed elsewhere in this book.

If the stenosis is limited exclusively to the subglottic area, dilatation is the procedure of choice since subglottic stents, in our experience, are not useful. Sometimes the obstruction is produced by pure tracheo- or tracheobronchial malacia, and in these cases a stent may be deployed. We will discuss this entity in the next section.

Tracheobronchomalacia (TBM)

TBM can be a cause of CAO in the ICU. The most usual clinical setting is a patient that is already extubated and develops signs and symptoms of acute upper airway obstruction and requires reintubation, and during endoscopic inspection, TBM is found.

TBM is a confuse term, of unclear meaning for healthcare professionals, where a variety of different pathologies have been included [28]. Briefly, we will refer to the correct utilization of these different terms.

TBM is an expiratory collapse of the central airway due to softening of the airway cartilage. The airway lumen at bronchoscopic examination acquires a saber-sheath shape or the crescent-type shape. The first is produced by a collapse of the lateral walls of the trachea, and the second one by the collapse of the anterior wall [29]. Tracheal cartilages are always compromised. When the anterior and lateral walls are involved, it is called circumferential type.

Expiratory collapse of the airway (ECA) refers to the collapse of some part of the tracheal wall. It is generally produced by the anterior bulging of the posterior membranous tracheal wall during expiration that decreases tracheal lumen. This is entirely due to the laxity of the membranous portion. The cartilages are intact, and in this specific case, the ECA is called dynamic airway collapse (DAC). It may be normal when the reduction of the lumen is less than 50% at forced expiration. However some authors, including me, prefer the limit of 70% instead 50% TBM is also an ECA, but in this case the expiratory collapse is not produced by the laxity of the membranous wall of the trachea, but due to the softening of the tracheal cartilages [28, 29].

By consensus, when expiratory collapse is less than 50% of the tracheal lumen, it is considered normal. If it is 50% or higher, it is considered abnormal. As it was already referred it seems that a limit of 70% may be better.

DAC is frequently found in COPD and asthma patients. Some authors refer this normal collapse as DAC and reserve the term excessive dynamic airway collapse (EDAC) when it exceeds this value. We resume these terms in Table 37.4.

Table 37.4 Accurate meaning of the different terms for expiratory collapse of the airway

Term	Meaning	Normal or abnormal
Expiratory collapse of the airway **(ECA)**	Collapse of one or more tracheal wall during expiration	May be normal or not
Dynamic airway collapse **(DAC)**	Expiratory collapse of the posterior wall of the trachea due to laxity of the membranous wall	Abnormal if more than 50% (EECA). Normal if equal or LESS than 50% (or 70%)
Tracheobronchomalacia **(TBM)**	Expiratory collapse of the anterior or/and lateral walls of trachea and bronchi due to softening of cartilages	Abnormal
Tracheomalacia **(TM)**	Similar to TBM but compromises only trachea	Abnormal
Excessive expiratory collapse **(EECA)** (is the abnormal DAC)	Expiratory collapse that exceeds 50% of the lumen	Abnormal

Upon bronchoscopic examination, the pathologic findings may be of pure TBM, pure EDAC, or both. Stent placement can be indicated, with or without previous dilatation. A tracheobronchial or a tracheal stent may be deployed depending on the location of the lesion. These entities are usually diagnosed after patients are extubated since the ETT functions like a stent, precluding airway collapse.

If the patient has a tracheostomy in place, we prefer to use TRACOE tracheostomy tubes, which are available in different sizes and lengths. They have the advantage of producing a good sealing of the trachea, and migration is uncommon.

Prior to a stent placement, a conservative management can be tried applying NIPPV in the form of continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BiPAP) ventilation. There are no comparative studies showing which of the two assisted ventilation modes is better (CPAP or BiPAP); however, we adhere to Murgu SD, who argues that CPAP is preferable, since in patients with high respiratory rates and small tidal volumes, the different inspiratory and expiratory trigger sensitivities of BiPAP could result in patient-ventilator asynchrony [30].

Recently high-flow nasal therapy was proposed as a form to replace continuous positive airway pressure ventilation (high flow about 30 L/m). Some reports in recent literature emphasize this approach [31].

Sometimes, the affection is limited to a bronchus or a segment, and stenting it can solve the problem. It is possible that the same degree of collapse in health condition does not interfere with a normal life. Once surpassed the acute event, the stent can be removed [32].

In cases of pure tracheal compromise, referred as tracheomalacia (TM) or EDAC limited to the trachea, the distal tip of the tracheostomy tube needs to lie above the carina, in order to stent all the tracheal length. Appropriate placement can be assessed by BF.

In summary:

- TM, EDAC, and TBM in the ICU are generally caused by cartilage damage produced by ETT and tracheostomy tubes.
- Pure EDAC is seen especially in patients with comorbidities, such as COPD or asthma, who might have some prior degrees of ECA.
- Bi-level or continuous positive airway pressure (noninvasive ventilation) may temporarily help in these situations acting as pneumatic stents [33].
- Metallic stents are not indicated since they cannot be removed.
- A definitive solution has to be planned by a multidisciplinary team, in a case-by-case basis. Surgery may be useful in well-selected cases [34].

In addition to bronchoscopy, there are other diagnostic procedures that can help to evaluate these patients, but they are difficult to apply in the ICU (e.g., paired inspiratory/expiratory dynamic computed tomography or cine magnetic resonance imaging) [35, 36].

Tracheostomy Bleeding

Another frequent consultation from the ICU is the evaluation of bleeding through a tracheostomy. Most of the times, bleeding is scant and represents mucosal injury produced by the tip of the tracheostomy tube, forceful aspirations, or tracheobronchitis and has no consequences.

It is very important to consider the timing of bleeding. When it takes place the first days after a tracheostomy, usually a surgical complication is responsible: poor hemostasis, injury to a small vessel, or misplacement of the tracheostomy tube.

When it occurs after the first week, the usual findings are ulcers resulting from tracheostomy tube movement, forceful aspirations, or tracheobronchitis secondary to infection.

However, when a sudden massive hemorrhage occurs, a tracheo-arterial fistula must be suspected [37].

This dangerous complication has a mortality rate near 90% and can present as an early or late complication (after more than 4 weeks). There is no role for the bronchoscopist here, because during this particular massive bleeding no endoscopic procedure is useful.

Two different situations might lead to a fistula between the trachea and the innominate artery: the first one occurs when the surgical tracheostomy incision is performed in the lower trachea. That might occur in young people with good neck extension, when the sternal manubrium is used as the landmark, and the tracheostomy is placed below the fourth tracheal ring. The recommendation is to choose the cricoid cartilage as the landmark in order to avoid this complication, since it is easier to count down the rings appropriately. The tracheostomy must be placed in the second or third, and in rare cases the fourth ring is needed. Placement below the fourth tracheal ring increases the risk of eroding the innominate artery, and this location should then be avoided.

When massive bleeding occurs and this complication is suspected, the initial goals are to control the airway with an ETT and tamponade the bleeding site. At the same time, the ETT cuff must be hyperinflated, and if bleeding continues, the innominate artery has to be compressed against the posterior sternum. To achieve this, the tracheostomy incision has to be extended inferiorly, the pretracheal space dissected with the finger, and when the pulsatile artery is manually recognized, direct finger pressure against the back of the sternum is made. The patient must be taken to the operating room and the injury repaired through a partial sternotomy and suture (Fig. 37.1).

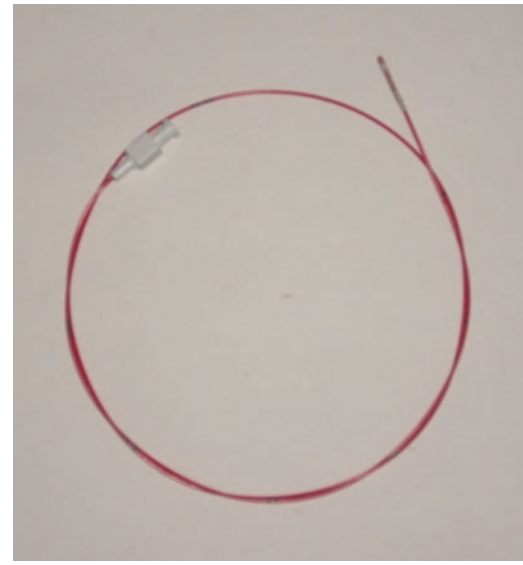

Fig. 37.1 Fogarty catheter used in massive bleeding to produce bronchial blockage in an attempt to stop bleeding. In its proximal end a hub is present, and in the distal end a balloon is inflated

The second situation occurs when a hyperinflated tracheostomy tube cuff erodes through the tracheal wall into the innominate artery. Since this point cannot be accessed through the neck, no finger compression will be possible at all. The bleeding might be controlled by hyperinflating the cuff to tamponade the bleeding site, while the patient is taken to the OR for repair [30]. This complication is avoided by limiting the cuff pressure to 20 mmHg. As in the first case, there is no role for the bronchoscopist in this setting.

Massive Hemoptysis or Life-Threatening Hemoptysis

Although there are several definitions of massive hemoptysis that consider the amount of blood expectorated in 24 h (ranging from 100 to 1000 mL), only the careful clinical evaluation at

the bedside allows to judge how severe is the hemoptysis. More frequent etiologies are:

- Bronchiectasis.
- Active or residual tuberculosis.
- Bronchogenic carcinoma.
- Carcinoid tumor.
- Endobronchial metastatic tumor: metastatic renal cell carcinoma is a particularly bleeding tumor.
- Pulmonary aspergilloma.
- Idiopathic hemoptysis: no evident cause is found.

Signs of severe hemoptysis are fast bleeding, presence of comorbidities (COPD, ischemic heart disease, renal failure) [31], the presence of bright red blood (indicating arterial bleeding), hemoptysis that does not slow down, and impending airway compromise.

In a chest X-ray, an obvious cause of hemoptysis can be observed such as a cavitated tumor. In this case the patient must be placed in the lateral decubitus with the side of the lesion down, feet elevated, and headboard lowered. CT scan is even more useful to find pulmonary causes of hemoptysis.

It is of utmost importance to maintain a patent airway. If the patient is in respiratory distress, he/she will have to be sedated and intubated. Another option is to proceed directly, under general anesthesia, to a rigid bronchoscopy. We prefer the RB to assess the airway in these cases, because the BF can have a weak suction (compared to the rigid) and the visibility can be very poor because of clots and bubbles. Almost all the times, a careful inspection with the rigid bronchoscope identifies the origin of bleeding.

Another very interesting modification is described, introducing the bronchoscope via nasal route with a snare catheter placed in its working channel. At the same time, the balloon is introduced by the other nostril. So the snare grasps the balloon and that way it can be left in place carried by the snare. Deflating it, the snare and bronchoscope are retired and the balloon can be left in place for about 2 or 3 days until evaluation of bleeding status [38].

Once the catheter is in place, and the hemorrhage has apparently ceased, the balloon is deflated three times a day during a brief period of time to verify that bleeding has really stopped. If bleeding continues, the catheter is left in place and the patient can be transferred for a definitive treatment to surgery for resection, or to hemodynamics to perform an arterial embolization.

The main problem placing these catheters arises when the flexible bronchoscope is withdrawn with the balloon occluding a bronchus, since the hub of the Fogarty has to be cut, resulting in balloon deflation (Fig. 37.2). To inflate the balloon again can be troublesome and time-consuming, and the blockade can be accidentally lost. To avoid these inconveniences, Freitag and colleagues [39] introduced in 1993 a new double-lumen, 2-mm outer diameter catheter with a proximal valve that can be detached and easily reconnected. The flexible bronchoscope can be thus retired detaching the valve and reapplying it once the bronchoscope has been taken out. Also, as the catheter has two lumens, it allows instilling saline through the second lumen while the balloon is inflated.

Some other reports describe other methods to treat massive hemoptysis. If saline lavage and adrenaline fail, a solution of fibrinogen-thrombin instilled through the working channel of the flexible bronchoscope can be utilized [40].

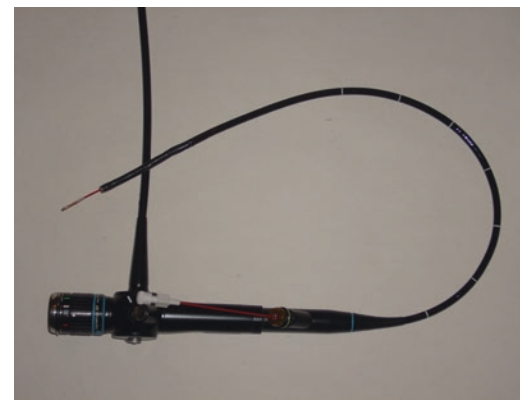

Fig. 37.2 Fogarty catheter passed through the working channel of the bronchofiberscope. When it is retired, the hub at the proximal end has to be cut off producing deflation of the balloon

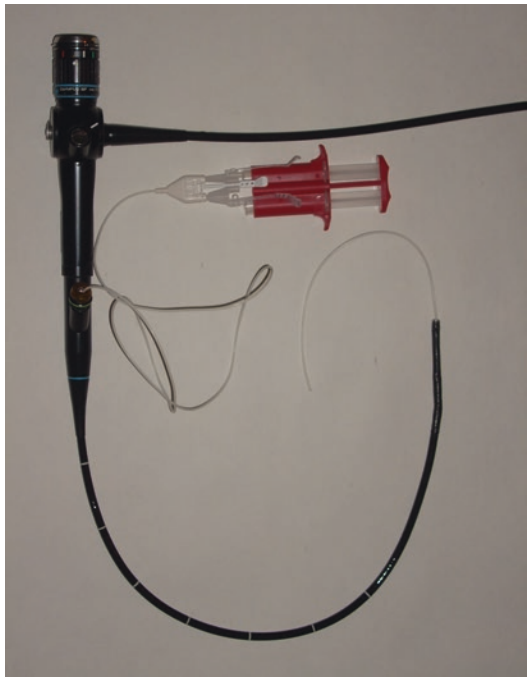

Fig. 37.3 Thrombin and fibrinogen solutions are injected simultaneously through this double-lumen catheter. They mix at the distal end to produce a hemostatic effect. It can be used to treat hemoptysis and bronchopleural fistulas

At our institution we prefer the use of fibrin glue-type products (Tissucol Duo Quick(R)). Two different solutions (fibrin solution and fibrinogen solution along with factor XII and plasminogen) are simultaneously injected through a double-lumen catheter. At the distal end, both solutions mix in at the selected bronchus and achieve a hemostatic effect (Fig. 37.3).

Valipour et al. [41] described good results with the use of oxidized regenerated cellulose, available in knitted fabric strip that they trim in four to ten fragments sized 30 × 40 mm (Surgicel(R)). These mesh layers are grasped with a biopsy forceps and pulled back into the operating channel of the BF leaving only a small piece in the visual field of the BF. When the bleeding site is identified, the flexible bronchoscope is moved out while pushing the forceps as far as possible deep in the bronchial tree.

Watanabe spigots have been used successfully for the occlusion of the bleeding bronchus as well. In a very interesting a report, a tunneled spigot with a 1 mm channel through its long axis can accommodate a guidewire and be introduced through the working channel of the bronchoscope and anchored where needed. When the scope is retired, it is reintroduced with a biopsy forceps that helps to leave the spigot in a satisfactory position [42].

In summary:

- Massive hemoptysis is an entity with a high mortality rate (up to 80%), and a rapid intervention is required.
- First, airway patency must be secured; second the bleeding source has to be identified; and third a therapeutic procedure has to be offered.
- The rigid bronchoscope is the instrument of choice in this setting, and again, the flexible instrument should be ready to be inserted through the RB in case of need.
- Electrocautery or laser equipment for coagulation must be available.
- Many procedures can be useful in massive hemoptysis, as described, but we have found that bronchial blockage by insertion of a Fogarty catheter occluding the bleeding bronchus is the most effective.

The Fogarty catheter should not be kept in place for more than 3 days. If bleeding continues, a definitive treatment (i.e., bronchial arterial embolization or pulmonary resection) has to be performed, or another kind of treatment can be attempted as described above (fibrin glue instillation or the use of oxidized regenerated cellulose).

Tracheoesophageal Fistula (TEF)

This is an infrequent but fearsome complication of prolonged airway intubation. The presence of an ETT may produce erosion of the membranous wall of the trachea, resulting in a TEF. High cuff pressures and endotracheal tube or tracheostomy tube movements are factors commonly involved in this complication. The presence of a nasogastric tube within the esophagus may also contribute to its development.

The most frequent predisposing factors are:

1. High cuff pressures
2. High airway pressures that result from a non-compliant lung, requiring high tidal volumes and high cuff pressure to avoid air leaks
3. Excessive motion of endotracheal or tracheostomy tubes

Others predisposing factors are [43]:

1. Prolonged intubation
2. Respiratory infections
3. Steroids
4. Hypotension
5. Insulin-dependent diabetes
6. Advanced age

The single most important measure to avoid this complication is to regularly check the ETT cuff pressure and maintain it between 20 and 25 mmHg. Other preventive actions are:

1. Fixing properly the endotracheal tube and if a prolonged intubation is anticipated, consider nasotracheal intubation that assure less movement of the tube or proceed directly to tracheostomy.
2. Maintain the head of the patient in a neutral position, as hyperextension produces close contact between the cuff and the tube with the posterior wall of the trachea, while flexion can injury the anterior wall.
3. Prompt and appropriate treatment of infections.
4. Maintain a stable hemodynamic status.

TEF is suspected on a ventilated patient that requires higher tidal volumes to maintain adequate ventilation, combined with higher pressure in the ETT cuff to avoid leaks. The amount of airway secretions increase markedly, as saliva empties in the airway. Accordingly to the size of the defect, pCO_2 increases, since part of the delivered tidal volume is lost through the tracheal defect and hypoventilation takes place.

To confirm TEF in a ventilated patient is troublesome, due to the fact that a barium esophagogram cannot be performed. The instillation of methylene blue diluted in saline into the esophagus will appear in the tracheal secretions or around the tracheostomy. An interesting approach is to analyze the inspired fraction of oxygen set in the ventilator and the oxygen fraction in the gastric air (it can be obtained by aspirating air by the nasogastric or the gastrostomy tube). If there is a relative coincidence between both measurements, the diagnosis is almost confirmed. To rule out swallowed air, it is useful to take a sample of room air close to the patient's mouth.

The definitive diagnosis requires flexible bronchoscopy with or without an esophagoscopy. Bronchoscopy can be done through the ETT or the tracheostomy tube as well. It allows visualization of the fistula at the membranous portion of the trachea.

Outcomes of various treatments are discouraging in patients on mechanical ventilation, and mortality is very high. Deflation of the cuff may be attempted to alleviate esophagus trauma; combined with high-frequency jet ventilation, a decrease in the mean airway pressure and volume loss can be achieved. If the fistula is identified, placement of an endotracheal tube with the cuff inflated below the lesion may be attempted. Success is not always possible and depends on fistula location.

If the patient can be appropriately ventilated and oxygenation can be maintained without air leakage through the fistula, a definitive therapeutic approach can be offered. Surgery is considered the best treatment, but is not always possible. It involves separating the trachea from the esophagus and closing the esophageal defect. Many times a segmental tracheal resection is needed to fix the tracheal orifice, and a muscle flap should be placed in between the trachea and the esophagus [44]. This approach requires the patient to be extubated as soon as possible after surgery, as there is a significant increase in the rate of failure if positive-pressure ventilation continues after surgical repair.

Frequently, the poor medical condition of these patients precludes surgery. In these cases an endoscopic approach may be attempted.

There are several reports of different methods applied, but the majority are anecdotic.

A single stent (tracheal or esophageal) or even better a double stenting (trachea and esophagus) may be tried. We prefer the use of a Dumon stent for the trachea. However, since it does not produce a hermetic seal of the tracheal wall affected, it must be accompanied by the insertion of an esophageal stent.

Freitag and colleagues [45] recommend the tracheobronchial dynamic stent, since it's slightly concave and the flexible posterior silicon portion adapts better to the convexity of the already placed esophageal prosthesis.

If we only insert an esophageal prosthesis, the positive-pressure ventilation oftentimes will cause displacement of the esophageal stent since the tracheal wall defect has not been solved and/or the displacement of the stent within the tracheal lumen. On the other hand, if we only place a tracheal stent, the sealing wall will be not optimal whereby saliva will penetrate in the tracheal lumen. For those reasons, a double stenting is recommended.

As we referred previously, stenting a patient on mechanical ventilation is not easy, and sometimes results are discouraging. These maneuvers must be performed fast and only by a skilled bronchoscopist. If the procedure was tolerated and successful, the next problem is the coexistence of a tracheobronchial stent and the ETT or tracheostomy tube. Before the procedure, careful attention must be paid to the selection of proper-sized tubes and stents since they have to adapt perfectly to the inner diameter of the prosthesis. In our experience this is a very difficult matter to resolve.

The instillation of fibrin glue in the fistulous orifice is another possibility [38]. This might work only in patients with very small defects.

Another option is to apply silver nitrate on the mucosa surrounding the fistula, with a bronchial brush. Dehydrated alcohol injected circumferentially around the orifice (2.5–5 mL) may be added [46]. It is assumed that the inflammatory and profibrotic response produced around the fistula might lead to its closure. Like the fibrin glue, it only might be applied in very small fistulas, less than 5 mm in diameter.

Bronchopleural Fistula (BPF) and Prolonged Air Leak (PAL)

BPF is a communication between the trachea or bronchi and the pleural space. BPF can complicate major pulmonary resections such as pneumonectomy, lobectomy, or segmentectomy, due to healing failure of the bronchial stump. It is more common after a right pneumonectomy than any other lung resection. Risk factors for the development of BPF are residual tumor in the bronchial closure, a large bronchial stump, preoperative radiotherapy, an active infection in the resected lung, and the need of mechanical ventilation in the postoperative period. BPF is always associated with empyema as the secretions of the major airways contaminate the pleural space. For this reason a drainage procedure of the pleural space is the most important part in BPF treatment.

Although unusual, BPF is a severe complication with high morbidity and mortality and most of the times requires surgery with some kind of muscle flap to be repaired. To develop this condition, a patient has to have undergone at least a segmentectomy, but it generally represents a complication of a major lung surgery or chest trauma.

BPF needs to be differentiated from prolonged air leaks (PALs). PALs are one of the most common complications of lung resection surgery and involve a communication between lung parenchyma (alveoli) and the pleural space. PALs are defined as an air leak lasting more than 7 days. PALs are much less morbid than BPFs, they do not contaminate the pleural space, and most of the times the treatment is drainage of the pleural space, time, and patience. Although more benign, PALs are a common cause of prolonged hospitalization.

When the bronchoscopist is called from the ICU to evaluate a patient with an air leak, the most important information to request is whether or not the patient had a lung resection surgery. If that is the case, PAL will be the most likely cause. However, if the patient has been on the ventilator for a prolonged period of time and especially if the ventilator volume

needed was high, BPF should be then suspected. Clinical clues that point at BPF are increasing amount of air leaking from the chest tube, purulent drainage from the tube, or a new pneumothorax.

If the patient did not have lung surgery and is on mechanical ventilation, barotrauma will be the most likely cause. The physiopathology of barotrauma is similar to that of postoperative PAL: overdistention of the alveoli caused by high tidal volumes that damages somewhere the surface of the lung and an air leak is produced. Barotrauma is treated as PALs: placement of chest tube for pleural drainage. According to location barotrauma can present as pneumothorax, pneumomediastinum, pneumopericardium, pulmonary interstitial emphysema, subcutaneous emphysema, or BPF (only in patients with prior lung surgery, for the reasons discussed earlier). Recently, clinicians refer to volutrauma to make reference to the pernicious action caused by overdistention of the alveoli produced by high tidal volumes. The evidence is not clear in differentiating which factor is responsible for the alveolar rupture: peak inspiratory pressure, mean airway pressure, or peak alveolar distending volume. Animal models, in fact, favor the volume overdistention theory.

There are several potential causes of barotrauma in patients on MV [47].

When pneumothorax appears few hours after the initiation of MV, the most likely cause is previous trauma from overinflation produced by manual, mouth-to-mouth ventilation or some other resuscitation maneuvers. Pierson calls this "pseudobarotrauma," that is, external trauma to the lung produced by a central line placement, a laceration during intubation, or injury from a bronchoscopic procedure.

However, much more often, extraalveolar air is a consequence of overdistention, resulting in a pressure gradient between the alveoli and the surrounding tissues (bronchovascular sheets), leading to alveolar rupture. This rupture is rare in the presence of normal lungs, but it can occur in patients with lung disease such as COPD or ARDS.

Diagnosis

When BPF is suspected in the mechanically ventilated patient, inspection bronchoscopy is indicated to visualize the bronchial stump. Bronchoscopic findings can range from a very tiny bubbling observed over the bronchial closure when it is flushed with saline through the bronchoscope to a bigger opening and necrotic tissue at the stump area. When the orifice is small, less than 6 mm or only bubbling is seen at the stump area with no recognizable orifice, a bronchoscopic procedure can be attempted in order to seal the BPF.

If no orifice or bubbling is seen at the bronchial stump, the diagnosis is prolonged air leak from the alveoli, the most common cause of air leak after lung resection.

Most of the times, PALs from alveolar leaks seal off by themselves. A chest tube should be placed for pleural drainage. However, when sealing is delayed, more often in the postoperative patient that has required mechanical ventilation for a prolonged period, there are some bronchoscopic maneuvers that can be of help. A selective occlusion maneuver can be used to identify the lung segment causing the alveolar leak. Fogarty balloon catheters of 5, 4 or 3F are used to occlude the airway from the more proximal to the more distal segment until the air leak stops. The air leak might not stop when there is significant collateral ventilation, and in these cases the procedure will not be useful to detect the site leaking. If a lung segment is identified as the source of the air leak, a bronchoscopic approach might be tried.

Treatment

There are some general measures that can be taken to reduce the air leak from a BPF or from an alveolar leak:

- Reduce the tidal volume in the ventilator: in a patient with high risk for developing volutrauma, the effective tidal volume should not be more than 6 mL/kg.

- Minimize inspiratory phase by:
  - Decreasing the inspiratory/expiratory ratio, setting a high inspiratory flow rate, about 70–100 L/min
  - Maintaining an inspiratory/expiratory ratio to about 0.3
- Chest tubes under water seal (no active suction or minimal suction to maintain lung expansion).
- Pressure support ventilation and synchronized intermittent mandatory ventilation are the preferred ventilation modes. High-frequency ventilation may be useful in patients with large air leaks.
- Extubate the patient as soon as possible.
- Treat aggressively bronchial obstruction.

The first measure is to have drained the pleural space, by placing a chest tube. It is recommended to apply the least possible suction to maintain the lung expanded. Antibiotics are started as well as enteral or parenteral feedings.

Surgery is the best option for the treatment of BPF. However, it involves transferring the patient to the operating room, reopening the chest, empyema drainage, lung decortication, BPF closure, and placement of a muscle flap to repair the bronchial stump. A serratus muscle flap can be used as it serves not only to provide vascularization to the bronchial stump but also to fill in the pleural space. Intercostal muscle flaps can also be used, but they do not provide as much vascularization to the stump and are not that useful in filling in the pleural space. In high-risk patients with small orifices, bronchoscopic treatment can be an option when spontaneous closure seems unlikely.

Several sealants have been used through BF to close a BPF. Regardless of the one applied, there are several considerations. If the orifice is visualized, the area to be treated must be washed and cleaned from secretions. Once the segmental bronchi leading to the air leak is identified by using a Fogarty balloon, a catheter should be advanced distally under direct vision after deflating the Fogarty balloon and then the sealant can be administered through the catheter.

Available sealants are:

- Fibrinogen-fibrin glue (Tissucol(R)): A double-lumen catheter needs to be used to apply this glue. Two milliliters of each compound is injected simultaneously through each one of the ports of the double-lumen catheter. They mix at the tip of the catheter forming the glue that blocks the leak. Once it is administered, apnea is necessary for 1–2 min to avoid disruption of the sealant [48] (Fig. 37.3).
- Tetracycline and blood clot: Martin et al. [42], described the successful BPF closure by instillation or tetracycline (0.5 g diluted in 25 mL of normal saline) through an inflated Fogarty catheter, followed by 10 mL of fresh non-heparinized autologous blood taken from the radial artery. The inflated Fogarty balloon is held in position during 10 min to allow clotting.
- Oxidized regenerated cellulose (Surgicel(R)): The technique was described in the section about massive hemoptysis [41, 49].
- Cerebral angiographic occlusion coils can be tried as well, deploying them as it is done for neurosurgery. Following coil placement, fibrinogen-fibrin glue may be also applied. The instillation of 1 mL of cyanoacrylate after the coils are deployed has been also described [50].
- Silver nitrate: As described in the tracheoesophageal fistula section, silver nitrate can be of help treating BPF.
- Cyanoacrylate glue is an agent that polymerizes in solid material when in contact with body fluids. After injection it acts as a plug and then induces an inflammatory response, followed by fibrosis and mucosal proliferation with closure of the fistula.
- Ethanol can be applied alone or in combination with another sealant. Before injection, it is convenient to use a cytology brush to scratch the mucosa of the fistulous orifice. Then, the absolute alcohol is applied as a submucosal injection, in aliquots of 0.1 mL via transbronchial needle, until the edematous surrounding tissue closes the fistula. More than one application might be needed. Ethanol

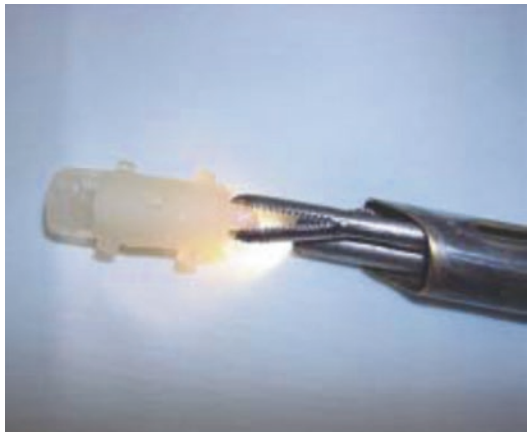

Fig. 37.4 Forceps grasping a spigot used through the rigid bronchoscope to seal a bronchopleural fistula or to block an air leak

treatment should be applied only if the BPF can be seen and may be effective in fistulas smaller than 3 mm [51].

- Spigots: Watanabe [52] developed radiopaque silicone spigots for the treatment of BPF and PAL. The spigot is placed through the rigid bronchoscope with grasping forceps, advancing until it occludes the BPF area. This method is preferred by many endoscopists (Fig. 37.4)
- Stents: Based on the same rationale as the spigots, airway prostheses sometimes are useful to occlude a fistulous orifice when it is visible at bronchoscopic examination. Our experience in the treatment of BPF utilizing Dumon stents is not conclusive. Usually the air leaks diminish, but do not cease completely. We have used a specially manufactured Y-stent (Stenning Company(R)) occlusive on the right arm, to treat a BPF after a right pneumonectomy. The result was not optimal, because the stent did not adapt properly to the stump surface.
- Emphasys valves: These valves are used for bronchoscopic treatment of emphysema. They work through a mechanism that closes during inspiration and opens during expiration, allowing deflation of the lung and mobilizing distal secretions. Their application for BPF can be of help in selected patients [53, 54].
- Neodymium-doped YAG laser may be used to produce mucosal erosion of the bronchial orifice when it is visualized, causing inflammation and ultimately resulting in healing.
- Some authors report good results applying laser to treat these lesions, but we do not recommend it, based on the potential damage that laser can exert, that may result in increasing the fistulous orifice.
- Amplatzer device: This device was originally designed for transcatheter closure of interauricular communication. It is a double nitinol disk that can be deployed bronchoscopically over a guide wire through the fistulous orifice. After the right placement, the device acts as a cuff link, occluding the fistula. It may be useful only in visible BPFs [55].

Surgery is the best therapeutic approach to patients with BPFs, but in high-risk patients, an endoscopic approach can be offered first, since it is generally well tolerated and it does not exclude a subsequent surgical approach if the bronchoscopic treatment fails. Selection of the appropriate endoscopic procedure to treat BPFs should be decided case by case in a multidisciplinary fashion, depending on personal experience and availability.

Brand names and manufacturing companies mentioned:

Tissucol Duo Quick	**Baxter Immuno**
Surgicel and Surgicel Fibrillar	**Johnson & Johnson's Ethicon**
Arndt Endobronchial Blocker Set	**Cook Company**

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Hemoptysis, Endoscopic Management

38

Rosa Cordovilla

Introduction

Hemoptysis is the expectoration of blood from the lower respiratory tract. Bleeding from the upper airway is excluded from this definition.

Causes of hemoptysis are wide and varied, as well as the amount, ranging from hemoptoic expectoration (sputum stained with blood streaks) to massive or life-threatening hemoptysis (expectoration of fresh blood in important quantities).

Life-threatening hemoptysis is defined as that hemoptysis that poses risks to life for the patient. This risk is determined by the total volume of bleeding, its velocity, and the patient's cardiopulmonary reserve [1]. In all hemoptysis and in most cases of hemoptysis, it is necessary to try to obtain both its anatomical location and etiological identification. In this sense, bronchoscopy and multidetector chest CT scan (MDCT) are complementary examinations, each with concrete advantages depending on the different clinical situations.

Bronchoscopy is indicated in order to locate the bleeding site, identifying the cause and controlling bleeding, even temporarily. Arteriography is also a very good method, since it allows to diagnose the bleeding area and treat it with embolization of bleeding vessels if possible.

Life-threatening hemoptysis thus requires two important steps to consider: first, bleeding control and location of the bleeding area and second definitive treatment of its cause.

We will define the role of bronchoscopy in both diagnosis and management of hemoptysis.

Definition

Hemoptysis is defined as the expectoration of blood from the lower respiratory tract. Bleeding from the upper airway is excluded from this definition.

In most cases the amount of bleeding is slight, the patient has hemoptoic expectoration (sputum staining with blood streaks) and hemoptysis is self-limited. In other cases the amount is higher (evident hemoptysis) or may even present massive hemoptysis (expectoration of fresh blood in important quantities).

Massive hemoptysis usually refers to the expectoration of large amounts of blood and/or the rapidity of this bleeding. The amount of expectorated blood in 24 h is usually used to differentiate between massive and non-massive hemoptysis. However, this definition varies widely in the literature, with values ranging from an expectorated blood volume of 100–600 mL, during a period of

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time that is also variable. Difficulty is even higher considering that hemoptysis is difficult to quantify: it could be both overestimated and underestimated by patients. Underestimation may occur when part of the blood is retained in the tracheobronchial tree.

It is therefore preferable to use the term threatening hemoptysis, defined as that which poses a risk to the life of the patient; this risk is determined by the total volume of bleeding, its velocity, and the patient's cardiopulmonary reserve [1]. As risk indicators, the amount of hemoptysis (greater than 100 mL) and the presence of airway obstruction, respiratory failure, and hemodynamic instability should be considered [2]. Asphyxia due to clot formation along with cardiocirculatory collapse is usually the cause of death, not exsanguination. Mortality of untreated threatening hemoptysis is high, greater than 50% [3], so it is very important the immediate assessment of the patient and identification of the causes of bleeding in order to start an appropriate treatment and avoid a fatal outcome.

Etiology of Hemoptysis

The causes of hemoptysis are multiple and varied.

Before detailing, it is important to know the system of vascularization of the lung.

Vascular Origin of Hemoptysis

There are two systems by which blood reaches the lungs: pulmonary arteries and bronchial arteries. The pulmonary arteries conform a low pressure system that contains all cardiac output and are responsible for gas exchange. The bronchial arteries are part of the systemic circulation and have greater pressure and much less flow; the irrigation of the bronchi and the visceral pleura depends on them. Despite its lower contribution to pulmonary blood flow, the bronchial arteries are the source of most hemoptysis. Sometimes other systemic nonbronchial arteries may be the source of hemoptysis. In a much lower percentage, the bleeding comes from the pulmonary arteries or from the pulmonary microcirculation [4].

The vessels of the bronchial network causing bleeding are usually neoformed, usually secondary to an inflammatory disease (bronchiectasis, sarcoidosis, lung abscess, tuberculosis, etc.). The walls of these vessels are surrounded by smooth muscle fibers capable of contracting, both physically and pharmacologically. Arterial embolization is also an effective method to eliminate this neovascularization. However, the pulmonary artery network is not capable of generating a vasospasm as potent as the bronchial vessels, since its walls are thin and do not contract. Therefore, the physical and pharmacological means have only a slight effect on them. The most frequent cause of hemorrhage is ulceration of the vessel wall caused by a destructive process of the lung parenchyma (pulmonary neoplasia, bacterial necrotizing pneumonia, mycetoma). In these cases, the cessation of bleeding is usually due to the temporary sealing by a clot whose dissolution or progression of the tear can lead to a relapse with greater hemorrhage [5]. Unfortunately, it is not always feasible to differentiate the vascular network originating the hemorrhage.

Etiology

The condition producing hemoptysis can affect the airway, lung parenchyma, or pulmonary vessels. Although they vary according to the population studied, the most frequent causes of hemoptysis are bronchiectasis, chronic bronchitis, and bronchogenic carcinoma [6].

1. Pathology of the airway (Table 38.1)

   Pathology of the airway is the most frequent cause of hemoptysis and includes:
   - Inflammatory diseases: bronchiectasis and chronic bronchitis
   - Neoplasms: bronchogenic carcinoma, carcinoid tumor, and endobronchial metastasis
   - Fistulas between the tracheobronchial tree and blood vessels, especially in the case of thoracic aorta aneurysms
   - Foreign bodies and trauma
   - Dieulafoy disease of the bronchi (presence of an abnormal bronchial artery, contiguous to the bronchial mucosa) [7, 8]

Table 38.1 Airway pathology

Inflammatory diseases: bronchiectasis and chronic bronchitis
Neoplasms: bronchogenic carcinoma, carcinoid tumor, endobronchial metastases
Bronchovascular fistula: thoracic aortic aneurysms
Foreign bodies, trauma
Dieulafoy disease of the bronchi (presence of an abnormal bronchial artery, contiguous to the bronchial mucosa) [7, 8]

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Table 38.2 Lung parenchyma conditions

Infections: pneumonia, tuberculosis, lung abscess, fungal infections, (aspergilloma)
Inflammatory or immunological diseases (diffuse alveolar hemorrhage): Goodpasture syndrome, systemic lupus erythematosus (SLE), granulomatous polyangiitis (Wegener), microscopic polyarteritis
Coagulopathies: thrombopenia, anticoagulant or antiaggregant drugs
Procedure complications: transbronchial lung biopsy, fine needle aspiration
Miscellaneous: cocaine inhalation, catamenial hemoptysis, antiangiogenic drugs (bevacizumab)

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2. Pathology of the pulmonary parenchyma (Table 38.2)

   Bleeding originating from the lung parenchyma is usually due to:
   - Infections: pneumonia, tuberculosis, lung abscess, and fungal infections, mainly aspergilloma
   - Inflammatory or immunological diseases leading to diffuse alveolar hemorrhage: Goodpasture syndrome, systemic lupus erythematosus (SLE), granulomatous polyangiitis (Wegener), and microscopic polyarteritis
   - Coagulopathies: thrombopenia and administration of anticoagulant or antiaggregant drugs
   - Complications of certain techniques: transbronchial biopsy and fine needle aspiration
   - Miscellaneous: cocaine inhalation, catamenial hemoptysis, and treatment with bevacizumab (vascular endothelial-derived growth factor inhibitor, VEGF).

Table 38.3 Lung vasculature conditions

Same causes as that originating in lung parenchyma
Intrinsic pathology or pulmonary vasculature: pulmonary embolism, arteriovenous malformation, aneurysms and pseudoaneurysms
Increased pulmonary capillary pressure: mitral stenosis, left heart failure
Iatrogenic: perforation of the pulmonary artery after a Swan-Ganz catheter placement [9]

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3. Pathology of the pulmonary vasculature (Table 38.3)

   Hemoptysis caused by diseases of the pulmonary arteries [8] may appear due to the same causes as those originating in the pulmonary parenchyma: intrinsic to the pulmonary vasculature conditions (pulmonary embolism, arteriovenous malformations) and increased pulmonary capillary pressure (mitral stenosis, pulmonary artery perforation originated by a Swan-Ganz catheter placement) [9]

4. Idiopathic or cryptogenic hemoptysis

   Up to 10–30% of cases, it is not possible to establish an etiological diagnosis of hemoptysis following bronchoscopy and chest CT scan [6, 10], and the patient is considered to have idiopathic or cryptogenic hemoptysis. Most of these patients are smokers and hemoptysis is usually due to inflammation of the bronchial wall produced by tobacco, rather than to an unspecified cause, known as tobacco-related hemoptysis [11]. Idiopathic hemoptysis is also related to chronic or acute bronchial inflammation, occult bronchiectasis, inactive tuberculosis, vascular pulmonary malformations, and coagulation disorders [12].

   It is likely that with the use of MDCT, the proportion of cryptogenic hemoptysis will be reduced [11].

Bronchoscopy in Hemoptysis

Bronchoscopy plays a key role in the diagnosis and management of hemoptysis.

It allows confirmation in doubtful cases, location of the bleeding point or, at least, location of the affected lung, and the determination of the cause if the lesion is visible or accessible to endoscopic examination. It also allows the isolation of the hemorrhagic segment or lobe to avoid the spreading of blood to the bronchial tree and reduce the risk of suffocation. In this sense performing rigid bronchoscopy complemented by flexible bronchoscopy carries a great advantage. In cases where a rigid bronchoscope is not at hand, flexible bronchoscopy as the only endoscopic procedure can also be very useful. It can be performed at the bedside and allows selective intubation or bronchial balloon blockade, as well as the application of local therapies. It can contribute, even temporarily, to control bleeding and the application of more definitive treatments such as embolization of bronchial arteries or even, in selected cases, surgical treatment (Figs. 38.1 and 38.2) [13].

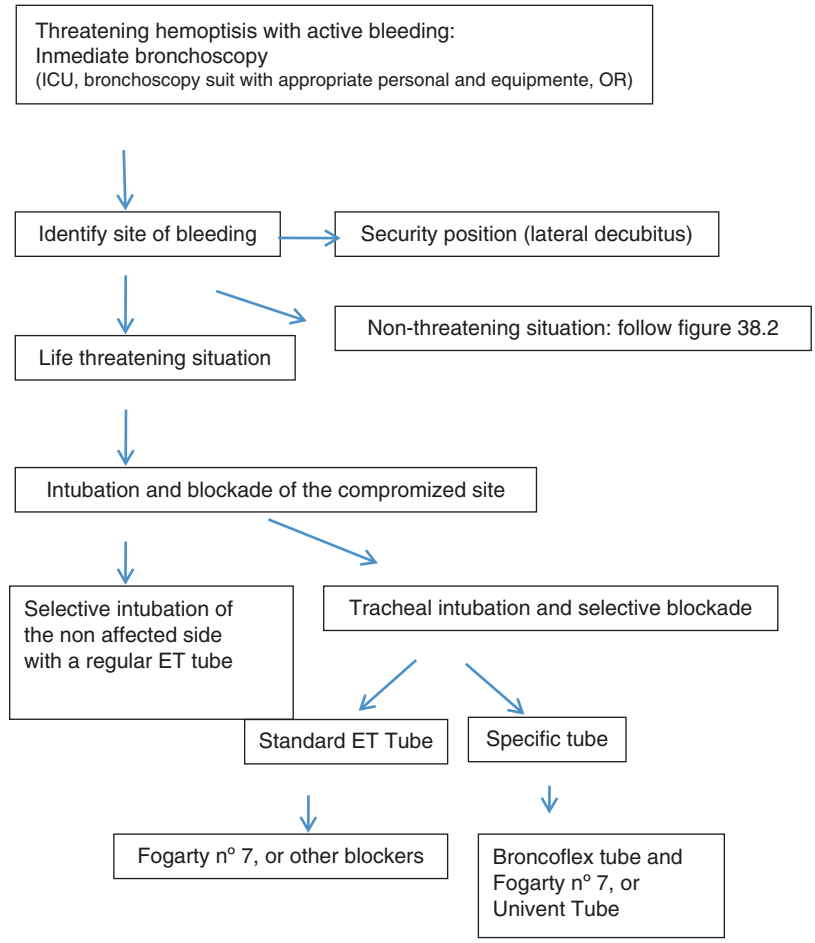

Fig. 38.1 Algorithm for bronchoscopy in threatening hemoptysis. With permission. Original Source: Cordovilla R, Bollo de Miguel E, Nuñez Ares A, Cosano Povedano FJ, Herráez Ortega I, Jiménez Merchán R. Diagnosis and treatment of hemoptysis. Arch Bronconeumol. 2016;52(7):368–377.

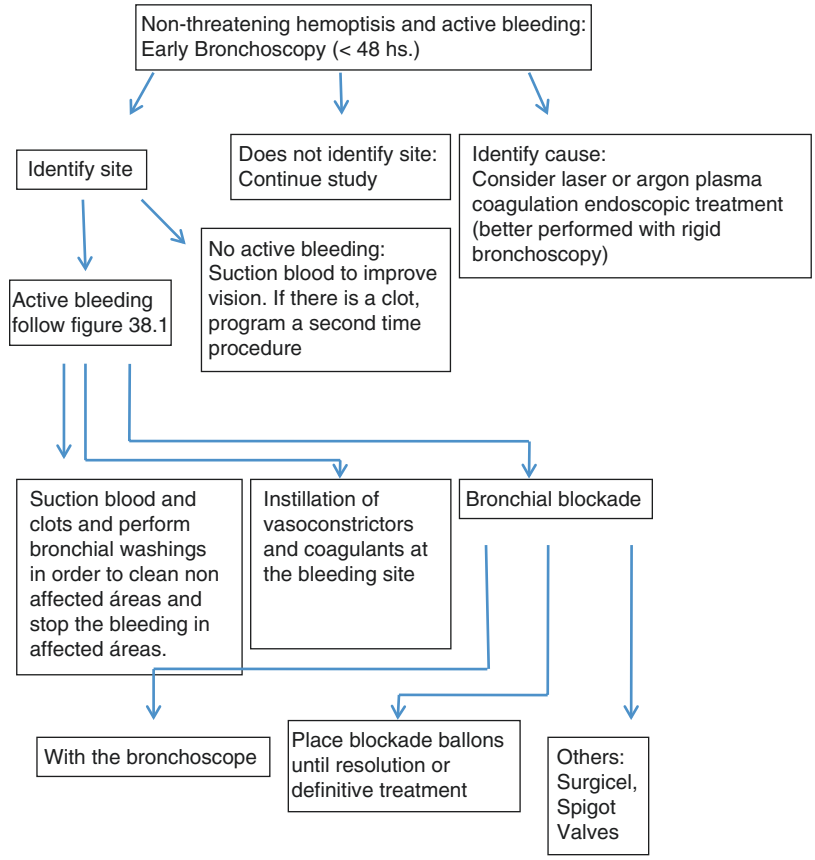

Fig. 38.2 Nonthreatening hemoptysis algorithm. With permission. Original Source: Cordovilla R, Bollo de Miguel E, Nuñez Ares A, Cosano Povedano FJ, Herráez Ortega I, Jiménez Merchán R. Diagnosis and treatment of hemoptysis. Arch Bronconeumol. 2016;52(7):368–377. Copyright © 2016 SEPAR. Published by Elsevier España, S.L.U. All rights reserved

Diagnostic Bronchoscopy

In the event of severe hemoptysis, diagnostic bronchoscopy can help in many ways:

1. Confirmation of hemoptysis and exclusion of pseudohemoptysis

   Although the clinical history, the characteristics of the episode, and the initial physical examination may suggest the digestive or respiratory origin of the bleeding, sometimes the aspiration of at least part of digestive bleeding content causes cough and can simulate a true hemoptysis (pseudohemoptysis) which requires an ENT examination, a high digestive endoscopy or bronchofibroscopy to differentiate.

2. Diagnostic of at least the side of bleeding, in anticipation to specific treatment

   Although imaging studies (chest CT scan) can identify the origin of bleeding and its cause sometimes with a superior performance than bronchoscopy [14, 15], this is still necessary. It should be indicated early, especially in massive or life-threatening hemoptysis. Bronchoscopy reveals or confirms the origin of bleeding, especially if it is performed within 48 h of the onset of the episode and in cases of significant bleeding in 73–93% of cases of massive hemoptysis [14, 16].

   In the case of threatening hemoptysis, it is advisable to perform bronchoscopy as soon as possible if the patient is unstable and once the

patient has been intubated [17, 18]. Endoscopy through the ET tube is safer since the airway is secure and the endoscope can be withdrawn every time oxygenation worsens or the working channel is occluded by clots.

Rigid bronchoscopy can be used for the diagnosis and initial evaluation of threatening hemoptysis, but the flexible bronchoscope has some advantages to it such as the ability to reach the distal airway more easily. It can be used in the setting more suitable for the patient: ICU, shock room, bronchoscopy room, etc., without the additional delays of having to transfer the patient to the OR to undergo rigid bronchoscopy, or the radiology room to perform angiotomography.

Bronchoscopy also proves its value in those cases of non-revealing radiological studies or those that show bilateral or non-localizing abnormalities. In any case, even in those nonthreatening episodes, it provides useful information in the event that bleeding increases dangerously in a sudden and unpredictable manner.

Location of the bleeding site requires direct visualization of active bleeding, which determines with certainty one bronchus or the responsible bronchial area. The most frequent endoscopic finding is hematic remains and

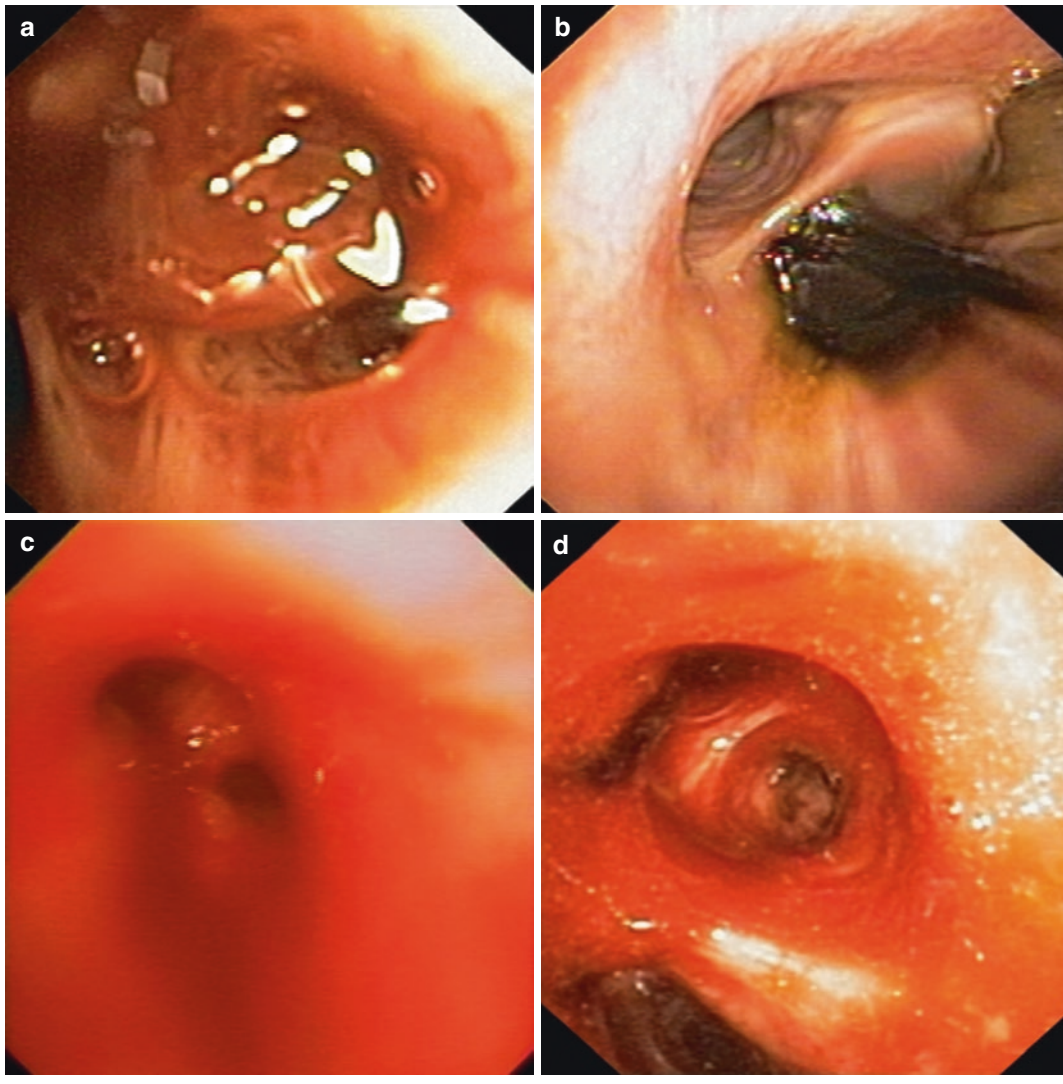

Fig. 38.3 (**a**) Right superior bronchial lobe clot. (**b**) Right inferior bronchial clot. (**c** and **d**) Active bleeding

clots (Fig. 38.3). Locating blood clots does not guarantee the origin of the bleeding. However, a combination of findings such as a great number of clots adhering to a particular bronchus can suggest, together with the imaging techniques, the responsible area. Blood remains should be aspirated through repeated small bronchial washes, in order to improve permeability and allow diagnostic examination of the underlying territory. However, in the presence of fresh clots adhering, it is not advisable to aspirate them given the risk of further bleeding. Subsequently, bronchoscopy can be repeated to evaluate whether they can be removed with a smaller risk of rebleeding.

A cryoprobe can be used for the removal of an adherent clot. In order to do that, a cryoprobe is placed in the center of the clot and freezing activated during 3–4 s. The clot will adhere to the end of the probe and extracted en bloc with the bronchoscope just like a foreign body would do. This procedure should be done through an ET tube or through a rigid bronchoscope in order to have complete control of the airway in the event of bleeding (Figs. 38.4 and 38.5).

3. Causal diagnosis, in case of accessible bronchial lesions

Bronchoscopy allows us to perform an endobronchial inspection and evaluate mucosal changes: hypertrophic or malformed capillary vascular network, areas of inflammatory or infiltrative mucosal thickening, bronchial stenosis, endobronchial tumors, antracosis or antracoestenosis, broncholiths, etc. (Fig. 38.6). In many cases, the changes are nonspecific and, therefore, nondiagnostic [19].

In addition to the visual examination, flexible bronchoscopy allows collection of samples for cytohistological and microbiological studies: bronchial lavage and bronchoalveolar lavage in the presence of suspected alveolar hemorrhage and biopsies and/or bronchial brushing in the presence of lesions suspected of malignancy. In the case of highly vascular lesions, some authors recommend local instillation of 1–2 mL of adrenaline 1:20,000 dilution, to reduce the risk of further bleeding, although clinical evidence is low [20].

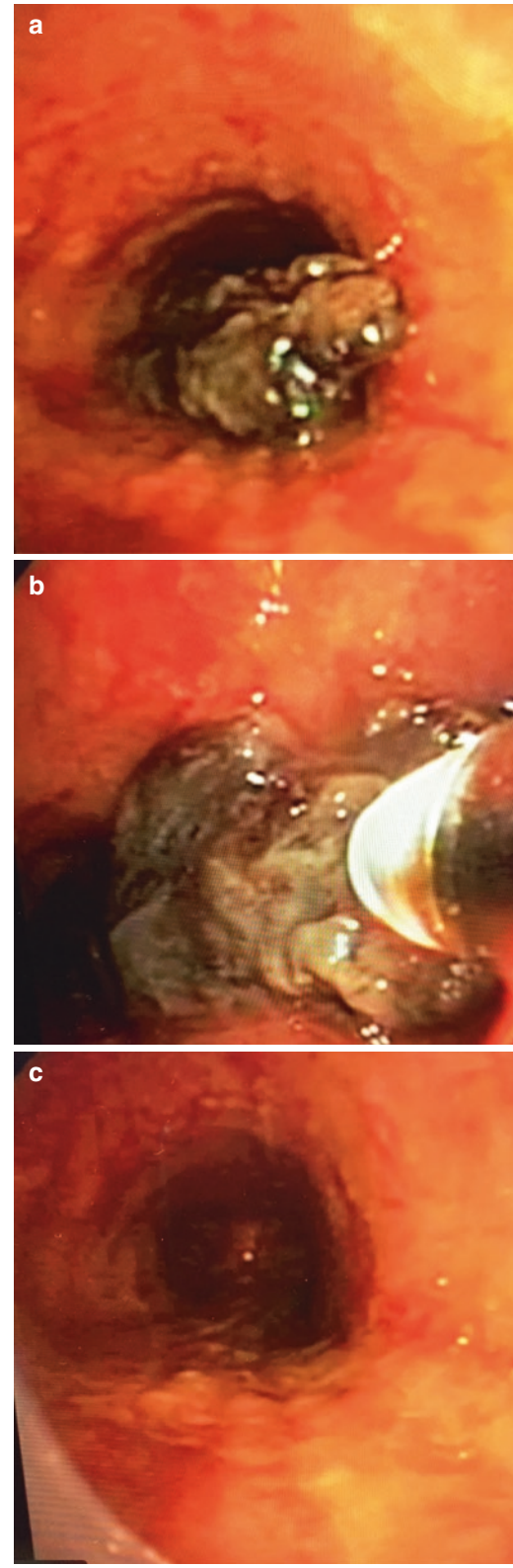

Fig. 38.4 (**a**) Tracheal clot. (**b**) Cryoprobe extraction. (**c**) After extraction

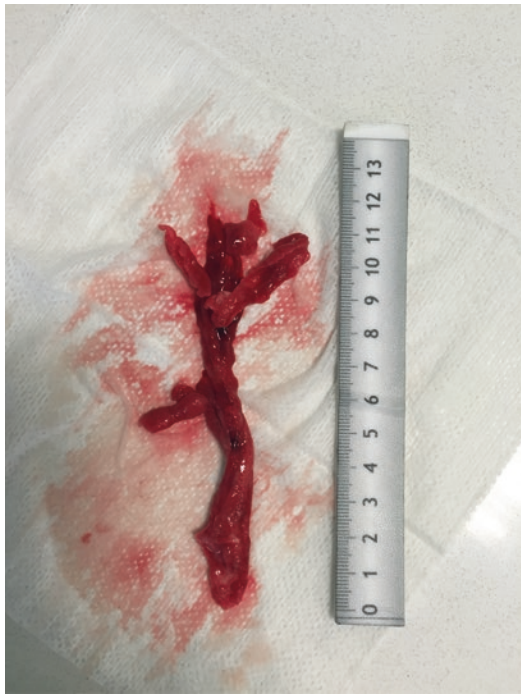

Fig. 38.5 Right bronchial tree clot

Bronchoscopy also plays a very important role in nonthreatening hemoptysis with no apparent radiological alteration.

The existence of a normal chest X-ray in the context of hemoptysis does not exclude the possibility of malignancy or other underlying pathology [4, 12, 21, 22]. The probability of malignancy in patients with hemoptysis and normal chest X-ray is low but may reach up to 10% in patients over the age of 40, with a history of smoking [23], even in patients with mild hemoptysis [24].

Bronchoscopy can detect an endobronchial lesion in 5% of patients with mild hemoptysis and normal chest X-ray [25], and HRCT detects bronchiectasis in up to 70% of cases of severe hemoptysis and normal chest X-rays [14]. Therefore, depending on the type of hemoptysis, bronchoscopy can be performed before or after the complementary radiological tests:

1. Hemoptoic expectoration: If there are no risk factors for cancer, bronchoscopy is indicated

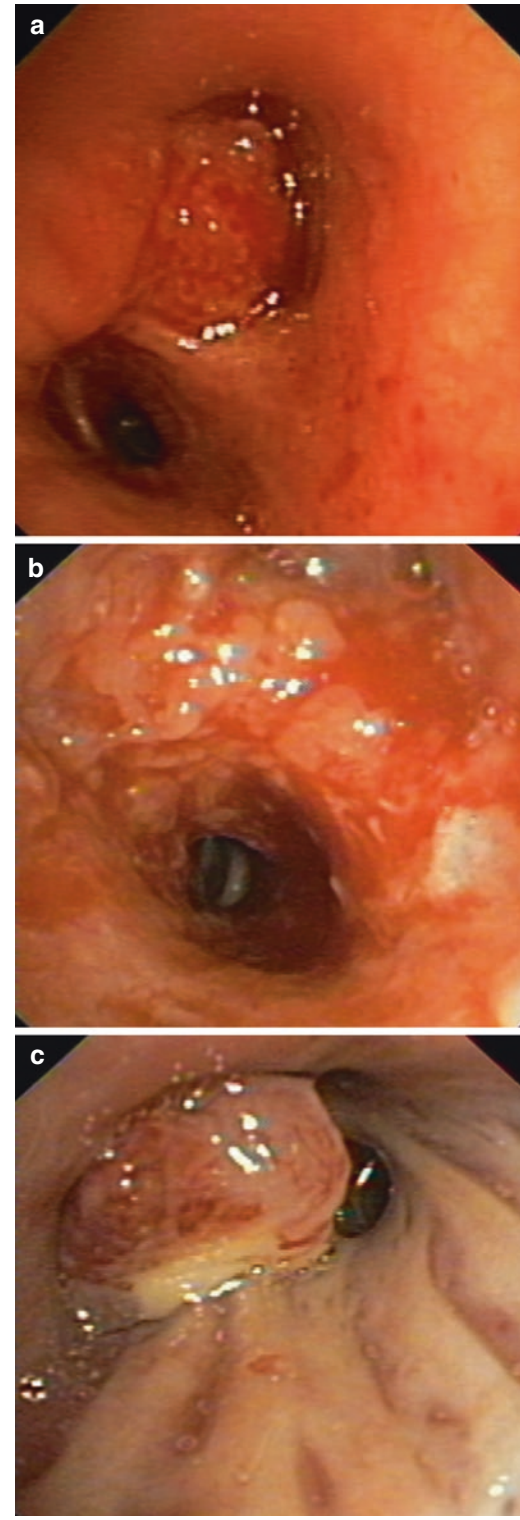

Fig. 38.6 (**a**) Vascular lesion right superior bronchus. (**b**) Tumoral infiltration at right B6. (**c**) Endobronchial mass right superior bronchus

when these episodes are recurrent, or when the amount of bleeding increases [25]. In the case of patients with recurrent hemoptysis, the first step is to perform a chest CT scan (HRCT or MDCTD) as it may be useful to select the most cost-effective endoscopic technique for diagnosis (flexible bronchoscopy or endobronchial ultrasound) [7, 14, 26, 27].

2. Evident hemoptysis: If there is no known cause, a bronchoscopy is necessary, especially in patients with risk factors for malignancy. However, depending on the stability of the patient, it may be advisable to perform a chest CT scan first. The combined use of bronchoscopy and MDCT increases the diagnostic yield for locating the bleeding site [14].

If the patient has a normal CT scan, bronchoscopy can diagnose the cause of bleeding in up to 16% of the cases. This percentage increases up to 37% when clinical history is also taken into account [23]. If bronchoscopy does not reveal changes, the patient is considered to have cryptogenic hemoptysis. A combination of CT and negative bronchoscopy has a very low probability of malignancy (1%) after a 6-month follow-up [28].

Therapeutic Bronchoscopy

Therapeutic bronchoscopy is specifically indicated to eliminate, at least transiently, a risk situation generally in the context of massive or threatening hemoptysis. Therefore, it is an urgent action applied in combination with other life-support measures, which seek to recover and keep the patient clinically stable. Diagnosis can then be completed with imaging techniques if the status of the patient allows and apply definitive treatment. Bronchial, systemic, and/or pulmonary embolization or surgical embolization can be used according to the situation. Generally, first evaluation of the patient should be oriented to estimate the severity of the condition and decide which treatment is most convenient and where it will take place.

Hemoptoic sputum does not require hospitalization, but evident and life-threatening hemoptysis does. In the latter case, admission to the ICU is warranted. Next, a quick and accurate diagnosis should be performed in order to locate the place of bleeding and determine its cause simultaneously.

The objectives of treatment are:

- Secure the airway.
- Maintain adequate oxygenation.
- Achieve hemodynamic stability.
- Locate and stop bleeding.
- Identify and treat the cause of hemoptysis.

Management of the patient during hospital admission includes a series of general measures:

1. Rest in bed in lateral decubitus, the affected side down, with the intention of protecting the airway and avoid aspiration of blood in the unaffected lung.
2. Control of clinical parameters (blood pressure, heart rate and respiratory rate, oxygen saturation) and quantification of hemoptysis.
3. Supplemental oxygen supply if necessary.
4. Control of cough by administering antitussives, avoiding respiratory physiotherapy techniques.
5. Empirical antibiotic treatment, useful in hemoptysis associated with respiratory infections and, in general, to prevent further complications.
6. Nothing per oral, to avoid aspiration to the airway, and to allow the performance of urgent tests like bronchoscopy, CT or arteriography.
7. Establishment of large-caliber venous access for fluid administration, availability of a blood reserve, and, if necessary, transfusion of packed red blood cells.
8. Antifibrinolytic agents: aminocaproic acid and tranexamic acid (AT) administration. They act by inhibiting the process of dissolution of the clot with the consequent reduction of hemorrhage. A Cochrane review [29] identifies two clinical trials evaluating the use of AT (Amchafibrin®), both orally and intravenously. The results indicate that they

may reduce the duration of bleeding, but the number of studies is limited and there is insufficient evidence for this recommendation. However, a review of published patient series concludes that although a recommendation cannot be given with strong evidence, TA can reduce both duration and volume of the bleeding, with a low risk of short-term thromboembolic disease [30]. The recommended dose is 500 mg–1 g intravenously two or three times per day, or 1–1.5 g two to three times a day.

Aminocaproic acid (Caproamin®) has been used in isolated case series, as intracavitary instillation in aspergillomas [31, 32].

Protection of the Airway

If there is severe respiratory failure or risk of suffocation (large and rapid bleeding), orotracheal intubation is required, preferably with a thick tube (8–9 mm) to facilitate diagnostic and interventional bronchoscopy [33].

In addition, bronchial blockade may be necessary to control bleeding in order to preserve ventilation of the healthy lung [15, 34]. There are several options to accomplish this (Table 38.4):

1. Perform the blockage with the orotracheal tube itself. This is possible in bleeding from the right bronchial tree, since the left main bronchus can be selectively intubated with the aid of the bronchoscope, so that the pneumatic balloon of the tube completely isolates the left lung. It should be taken into account that in tall patients, the tube may not be long enough to adequately reach the main bronchus.
2. Use independent bronchial blockers that are placed through a conventional tube:
   2.1. Fogarty inflatable balloon catheter (n° 7 or higher). This inflatable balloon is introduced parallel to the bronchoscope and it is placed at the selected location under direct vision. This maneuver can be facilitated by rotating the head to the opposite side, in a similar way than left main bronchus intubation with the rigid bronchoscope, and bringing the end of the tube closer to the tracheal carina. This device cannot be securely anchored

Table 38.4 Methods to control hemoptysis

1. Bronchial block with flexible bronchoscope and sustained aspiration to collapse the compromised segment and prevent bleeding
2. Orotracheal tube placed in the left main bronchus for bleeding of the right bronchial tree
3. Especial orotracheal tube (a) Torque Control Blocker Univent® (b) Broncoflex® (c) Double lumen tube
4. Independent bronchial blockers (a) Fogarty® Olympus (B5-2C® y B7-2C®) occlusion balloon (b) Olympus Multi-3V Plus B-V232P-A® balloon, a 190-cm-long catheter that can be insufflated up to 15 mm diameter. It is introduced through a 2.9 mm working channel, placed and insufflated, and then clamped and cut out without deflating the balloon, and finally the bronchoscope is removed (c) Arndt ® catheter (d) E-Z blocker®, "Y" shaped catheter with two balloons that can be insufflated separately (e) Cohen Flexitip®
5. Instillation of cold saline (4 °C) in 50 mL aliquots
6. Instillation of hemostatic drugs (a) Vasoconstrictors – Diluted adrenaline (1:20,000) in 1 mL aliquots – Derivatives of antidiuretic hormone such as terlipressin or ornipressin (b) Tranexamic acid undiluted on the bleeding site, with an initial dose of 500 mg (c) Fibrinogen-thrombin (Tissucol®)
7. Other bronchial blockade systems that have been successfully used in case series (a) Regenerated oxidized cellulose mesh (Surgicel®) (b) Endobronchial valves (c) Silicone plugs (Watanabe Spigots®)
8. In endoscopically visible bleeding tumors, some coagulative therapies can be applied (a) Laser photocoagulation (Nd:YAG, Nd:YAP, diode laser) (b) Argon plasma coagulation

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during long periods of time, but it may allow to block completely the bleeding site with enough time for a clot to form and adhere [33]. The introduction of the catheter independently of the bronchoscope instead of through its working channel allows continuous suctioning and improved vision.

2.2. Arndt endobronchial blocker® catheter (Fig. 38.7). It can be inserted transiently attached to the end of the bronchoscope to be transported to its location (size n° [7–9]). It has a transparent head of three ports: one to fix the catheter of the blocking balloon, another for the introduction of the bronchoscope, and the third one for the connection to the respirator.

2.3. EZ-Blocker®. It is a catheter Y-shaped at its distal end, to facilitate anchorage at the tracheal carina, and two balloons that can be inflated separately.

2.4. Cohen Flexitip Endobronchial®. It is a balloon catheter curved at its distal end to facilitate placement.

3. Perform intubation and blockage with a special orotracheal tube:

3.1. Torque Control Blocker Univent Tube®, which has a bronchial blocker that prolongs the tube itself, designed to occlude any major bronchi with the tube located inside the trachea (Fig. 38.8).

3.2. Broncoflex Tub®. This particular tube has a catheter on the outside, through which a Fogarty or similar tool can be inserted, and also provides an external fixation system. Its advantage is that it fully preserves the internal gauge of the tube and facilitates the location of the balloon in any of the main bronchi by rotating the orotracheal tube on its major axis.

3.3. Double-lumen tube: this particular tube allows the blockade of the bleeding site performing selective intubation. Given its reduced caliber, it is not possible to

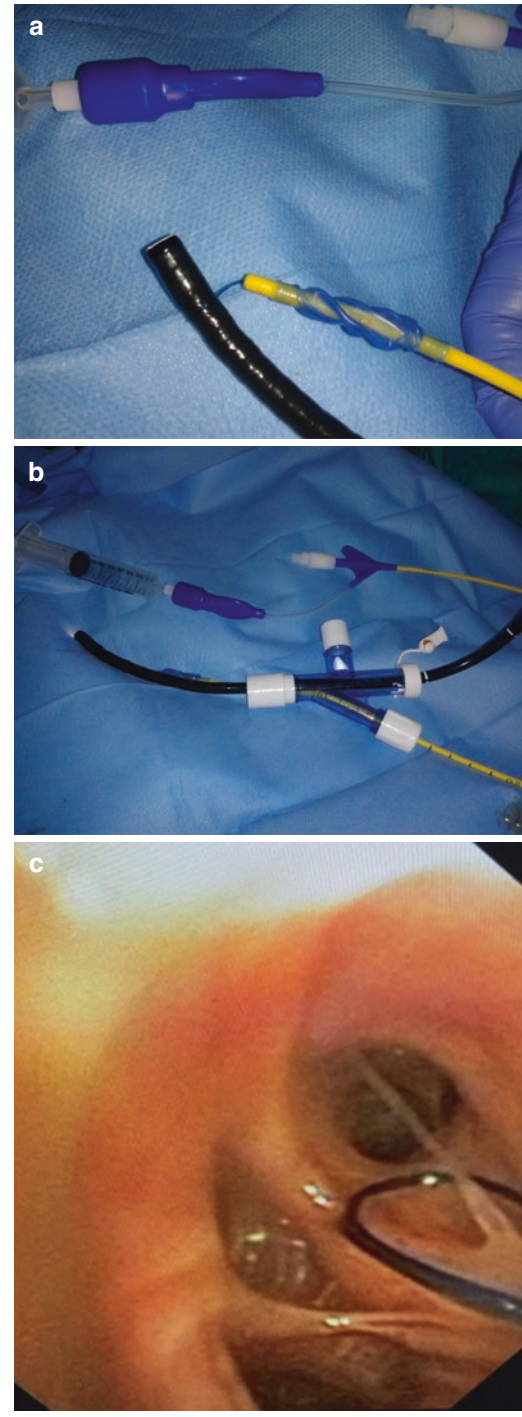

Fig. 38.7 Arndt catheter. (**a**) Catheter fixed at the distal end of the flexible bronchoscope. (**b**) Flexible bronchoscope introduced through the three-headed piece. (**c**) Catheter placed at the selected site

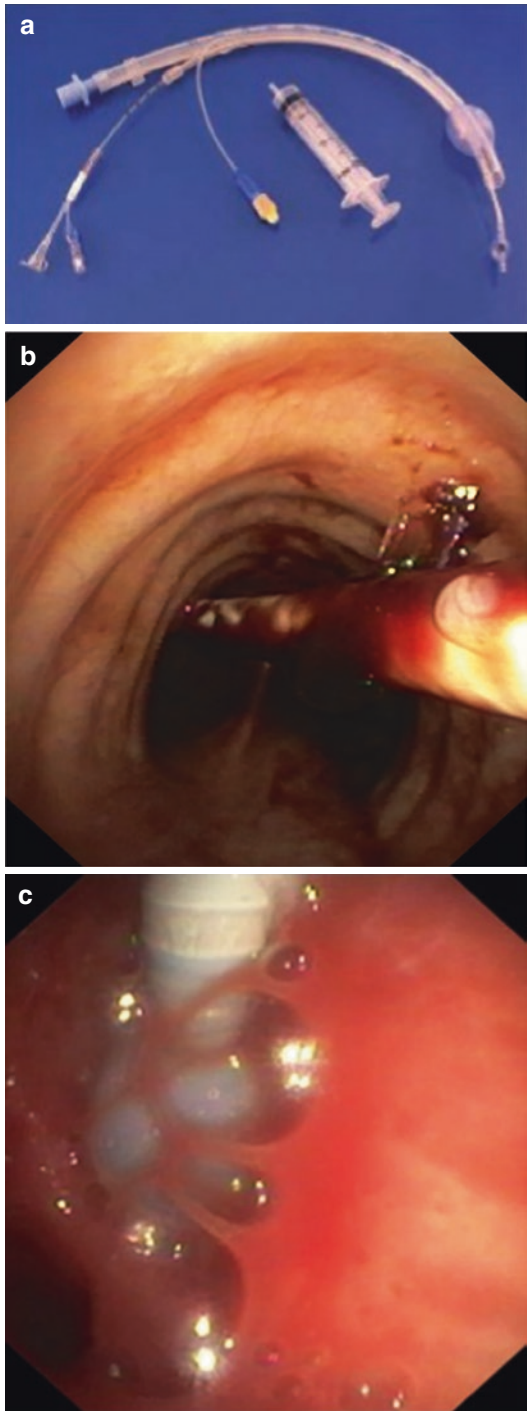

Fig. 38.8 (**a**) Univent tube. (**b**) Univent tube at the trachea, after hemoptysis. (**c**) Inflated balloon at the level of the bleeding bronchus

introduce the standard bronchoscope through it, and it is also difficult to anchor since the bleeding site is not directly visible.

Therapeutic Bronchoscopy

In our experience, flexible bronchoscopy is the first procedure indicated when a patient presents with life-threatened hemoptysis and hemodynamic instability. It can be performed in the intensive care setting or any other critical area. When a rigid bronchoscope is available, it is advisable to intubate with the rigid tube and through it introduce the flexible endoscope. They can complement each other taking advantage of both instruments:

- Ventilate the patient properly.
- Ensure airway permeability by aspiration of blood and clots with large-caliber probes.
- Perform direct hemostasis on bleeding areas, pressing with the external wall of the distal end of the rigid bronchoscope or by the application of vasoconstrictors or endobronchial coagulant therapies.
- Access the distal bronchial tree.

Therefore, the rigid bronchoscope supplemented with the flexible bronchoscope is the most complete and safe procedure in life-threatening hemoptysis [34, 35]. However, flexible bronchoscopy remains the most used procedure in these cases, given its broad availability. Rigid bronchoscopy is less available, it requires a special training that not many pulmonary physicians have, and it has to be used in the operating room under general anesthesia or conscious sedation. That implies moving an unstable patient, a risk that may not be affordable in a life-threatening situation.

Once the origin of the bleeding has been identified, if a lung blockade is not necessary, local measures can be applied. Their clinical efficacy is limited, as well as the published evidence.

In addition to the methods described above, other interventional procedures can be performed:

1. Bronchial blockade with the flexible bronchoscope and sustained aspiration in order to cause segmental collapse and stop the bleeding.
2. Selective bronchial blockage through the working channel of the bronchoscope:
   2.1. Fogarty n° 5 (5 Fr.) [36] or a similar type of balloon catheter (Olympus B5-2C® and B7-2C® balloon).
   2.2. Longer catheters such as the Olympus Multi-3V Plus B-V232P-A® balloon catheter. This one is a 190 cm catheter that can be inserted through a working channel of 2.8 mm and insufflated up to 15 mm in diameter. Without deflating the balloon, it can be clamped and cut to stay in place and finally removing the bronchoscope.
3. Selective bronchial blockade using a guide wire: a guide is inserted through the working channel to the chosen bronchus, and after removal of the bronchoscope, a balloon catheter is placed through the guide. Although this procedure is technically more complicated, it allows the balloon catheter to be located and the bronchoscope removed [37].

   The balloon can be inflated for up to 24–48 h to allow clot formation, although it can be maintained in the airway for up to several days. To prevent mucosal ischemia, it is necessary to deflate it periodically, at least three times a day [36], always under endoscopic vision in order to re-inflate immediately if bleeding persists. If the patient does not bleed again after several hours, the catheter balloon is withdrawn.
4. Washing of the bronchus with cold saline serum (4 °C) using aliquots of 50 mL until bleeding is suppressed, without exceeding 500 mL total volume [38]. The mechanism of action is local vasoconstriction although there are no controlled studies that demonstrate its effectiveness [39].
5. Instillation of hemostatic drugs:
   5.1. Vasoconstrictors: adrenaline diluted to 1: 20,000 and applied through the working channel in 1 mL aliquots. Its effect has not been compared in controlled trials and only clinical experience supports its use. In order to minimize its cardiovascular effects in patients at risk, it has been suggested to substitute it for some antidiuretic hormone derivatives such as terlipressin or ornipressin, although reports are anecdotic [40, 41].
   5.2. Tranexamic acid can be instilled undiluted on the bleeding site, with an initial dose of 500 mg [42, 43].
   5.3. Fibrinogen-thrombin (Tissucol®). It has been used in two case series in hemoptysis cases that could not be controlled which other endoscopic procedures [44].

   Topical hemostatics are not useful in fast and severe hemoptysis, since the blood washes out the hemostatic agent diminishing of abolishing its efficacy.
6. Other bronchial blockade systems that have been used successfully in case series:
   6.1. Regenerated oxidized cellulose mesh (Surgicel®). A report by Valipour et al. [45] describes how fragments of this hemostatic and resorbable mesh were introduced into the segmental or subsegmental bronchi causing the hemorrhage to stop. They were previously introduced through the working channel of a standard bronchoscope by pulling them with a flat blade forceps. Once the bleeding site was located, they were pushed into the segmental bronchus with the same forceps. In total, four–ten fragments of 3 × 4 cm were introduced, until hemostasis was achieved. As it was a resorbable material, it was not necessary to extract it later, and the absence of bronchial sequelae was later verified.
   6.2. Endobronchial valves, designed for endoscopic volume reduction and used for other purposes such as persistent air leakage or

bronchopleural fistula. Isolated cases of their application in the treatment of hemoptysis have also been described [46].

6.3. Silicone plugs (Watanabe spigots) [47, 48]. Initially introduced by Watanabe for endoscopic treatment of bronchopleural fistulas, they have demonstrated their efficacy in the transient tamponade of hemorrhagic segmental bronchi. The insertion and removal is performed by apprehending them with a biopsy forceps and transporting them at the end of the bronchofibroscope.

7. Laser coagulation: in cases of accessible, endoscopically visible tumor causing bleeding:

7.1. Laser photocoagulation (Nd: YAG, Nd: YAP, diode laser): the efficacy in stopping bleeding ranges from 60 to 74%, although a reduction is achieved in up to 94% of cases [49, 50]. If the bleeding is important, results are not so favorable [51]. Laser can be effective causing photocoagulation in depth. Very good results have been reported when applied on bleeding endobronchial tumors [49], but little is achieved on severe hemoptysis caused by laser application itself. In this context, the results have not been so favorable [51]. In fact, in highly vascular tumors causing severe hemoptysis, there is a tendency to avoid laser treatments unless an obstruction can be solved with the treatment, and the risks are justify.

7.2. Electrocoagulation with argon plasma. Argon plasma is an electrocoagulant method that does not require tissue contact and acts rapidly superficially. It is less effective than laser in coagulating in depth, and mechanical debridement is more difficult. But it can be very effective, at least transiently, in mucosal lesions whenever cough can be effectively inhibited and there is no significant active bleeding at the time of application. In that case, free blood is coagulated and the treatment does not reach the actual site of bleeding. Increasing the argon flow can facilitate its effect, risking the possibility of gas embolism. In a series of patients with endobronchial lesions responsible for active bleeding, argon plasma coagulation immediately stopped bleeding in 100% of cases (Fig. 38.9)[52].

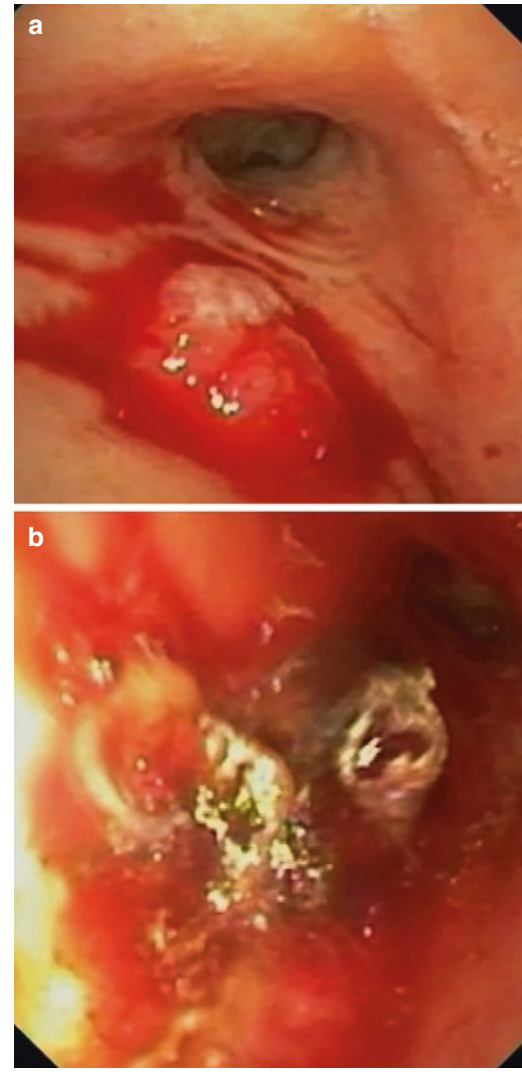

Fig. 38.9 (**a**) Endobronchial lesion with bleeding in left main broncus. (**b**) Endobronchial lesion after argon plasma treatment

Summary

Hemoptysis is defined as the expectoration of blood from the lower respiratory tract. In most cases the amount of bleeding is slight, the patient

has hemoptoic sputum (sputum staining with blood streaks), and hemoptysis is self-limited. In other cases the amount is more important (evident hemoptysis) or may even present as massive hemoptysis (expectoration of fresh blood in important quantities). However, it is preferable to use the term threatening hemoptysis, defined as the one that poses a risk to life for the patient.

The causes of hemoptysis are multiple and varied. The disease causing hemoptysis can affect the airway, lung parenchyma, or pulmonary vessels. Although they vary according to the population studied, the most frequent causes of hemoptysis are bronchiectasis, chronic bronchitis, and bronchogenic carcinoma. On most occasions bleeding comes from the bronchial arteries, sometimes other systemic non-bronchial arteries may be the source of hemoptysis. In a much lower percentage, the bleeding comes from the pulmonary arteries or from the pulmonary microcirculation.

Bronchoscopy plays a key role in the diagnosis and management of hemoptysis. It allows confirmation in doubtful cases, location of the bleeding point or, at least, location of the affected lung, and the determination of the cause in lesions accessible to it. It can allow the isolation of the hemorrhagic segment or lobe to avoid flooding the non-affecting bronchial tree and reduce the risk of suffocation, by selective intubation or bronchial blockade with balloon, as well as the application of local therapies that contribute to control the bleeding.

Recommendations

1. In all patients with hemoptysis, a bronchoscopy is indicated unless the patient no longer has active bleeding and the cause of hemoptysis is known or when hemoptoic expectoration is self-limited in a patient without risk factors for lung cancer.
2. The first objective of bronchoscopy is to confirm hemoptysis and assess its severity and location.
3. Bronchoscopy should be performed during active bleeding within the first 24–48 h.
4. In threatening hemoptysis bronchoscopy should be performed immediately in order to control bleeding.
5. Location of the source of bleeding requires visualization to determine the bronchus or responsible bronchial area with certainty.
6. In the presence of a fresh clot, its immediate withdrawal should not be performed. It is preferable a subsequent examination to reduce the risk of rebleeding.
7. Previous instillation with 1: 20,000 epinephrine in vascularized endobronchial lesions may be effective in diminishing bleeding.
8. The use of tranexamic acid is recommended to reduce the duration and volume of bleeding in threatening hemoptysis.
9. Intubation in patients with threatening hemoptysis should be performed with endotracheal tubes of 8 mm or larger.

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Part VIII

Interventions in Pulmonary Medicine: History and Future Perspectives

History of Bronchoscopy: The Evolution of Interventional Pulmonology

39

Tanmay S. Panchabhai, Michael Ghobrial, and Atul C. Mehta

The era of bronchoscopy began in 1876 with Gustav Killian inserting an esophagoscope into a farmer's airway to remove a piece of a pork bone. Today that procedure of bronchoscopy has evolved into a super-specialty of interventional pulmonology. Several innovators, scientists, and physicians have made invaluable contribution in bringing the procedure of bronchoscopy to its current eminence. Flexible bronchoscopy has opened the doors for number of minimally invasive procedures improving the welfare of our patients. Interventional pulmonologists and the thoracic surgeons are teaming up to expand and exploit the boundaries of bronchoscopy to innovate safe and cost-effective diagnostic and therapeutic modalities. Today there remains no single pulmonary ailment that cannot be either diagnosed, palliated, or cured with the help of a bronchoscope. In this chapter we describe the odyssey of bronchoscopy, highlighting its historical milestones and current status, and make humble predictions on the future potentials.

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"The Glottiscope" (1807)

The honor of being father of "endoscopy" belongs to Philipp **Bozzini** [1, 2], who revealed the very precursor of all endoscopes in 1807. He managed to deliver candle light into the bodily cavities through his invention of "light conductor" [Lichtleiter]. Speculums of various sizes and design were created based on the cavities to be examined, embarking in the era of endoscopy. The "glottiscope" invented in 1828 by **Benjamin Guy Babington,** for the first time, allowed inspection and ability to visualize the laryngeal areas which were earlier not amenable to direct examination [2]. He carried this out by attaching a mirror to a tube to allow the reflection of light and images.

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"The Esophagoscope" (1895)

A Spanish music teacher and singer, Manuel Garcia, took it upon himself to try to look at the "voice box" of his students in an attempt to see how voice is produced. This indeed was the first-known attempt to visualize the larynx, which he accomplished by using a dental mirror [3]. However, **Alfred Kirstein** (1895, Germany) was the first to report direct visualization of the vocal cords and proximal large airways, using an esophagoscope. He called this process autoscopy (i.e., examining the airways without a mirror) [4, 5].

"Rigid Bronchoscopy": From the Era of Gustav Killian (1876–) and Chevalier Jackson (1904–)

Gustav Killian is regarded as the father of modern-day bronchoscopy (Fig. 39.1). He was born in Freiberg, Germany, and was an otolaryngologist. He examined the trachea and the main bronchi of a volunteer, using a laryngoscope, and was later able to remove a pork bone and three other foreign bodies from the main bronchi (Fig. 39.2). This incident was described later by his assistant O. Kollofrath as follows: "*On March 30th of this year I had the honor to assist my admired principal, Prof. Killian, in extraction of a piece of bone from the right bronchus. This case is of such peculiarity with respect to its diagnostic and therapeutic importance that a more extensive description seems justified*" [5, 6]. This memorable experience led Killian to coin the term "directe bronkoscopie."

A direct ocular mechanism consisting of an illumination and suction tubing attached to a rigid bronchoscope was developed by a Philadelphia-based otolaryngologist, **Chevalier Jackson** (1904) (Figs. 39.3, 39.4 and 39.5). This is considered to be the precursor of the modern-day rigid bronchoscopes. Dr. Jackson became renowned in his time for extracting aspirated or swallowed foreign bodies from children and adults. He kept meticulous records of every object he removed to help other doctors learn his techniques. The Mütter Museum in Philadelphia displays 2374 objects recovered by Dr. Jackson during his 75-year-long career. He conducted numerous hands-on training courses which were instrumental in increasing the acceptance of bronchoscopy. The Pan-American Association of Otolaryngology and the International Bronchoesophagology Society were founded by Dr. Jackson. In 1907, he published the first systematic textbook on bronchoesophagology and dedicated it to Killian, the "father of bronchoscopy" [7]. Notable mention for other contributors who provided their valuable service in developing the field of bronchoscopy is as follows: **Edwin Broyles** who developed an optical telescope with forward viewing, **Paul H. Holinger** for bronchoscopic photography,

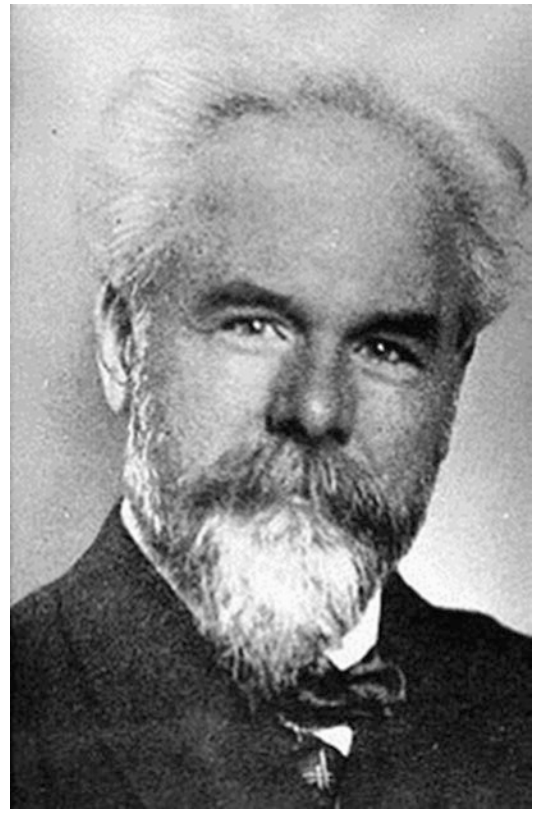

Fig. 39.1 Gustav Killian—the father of bronchoscopy

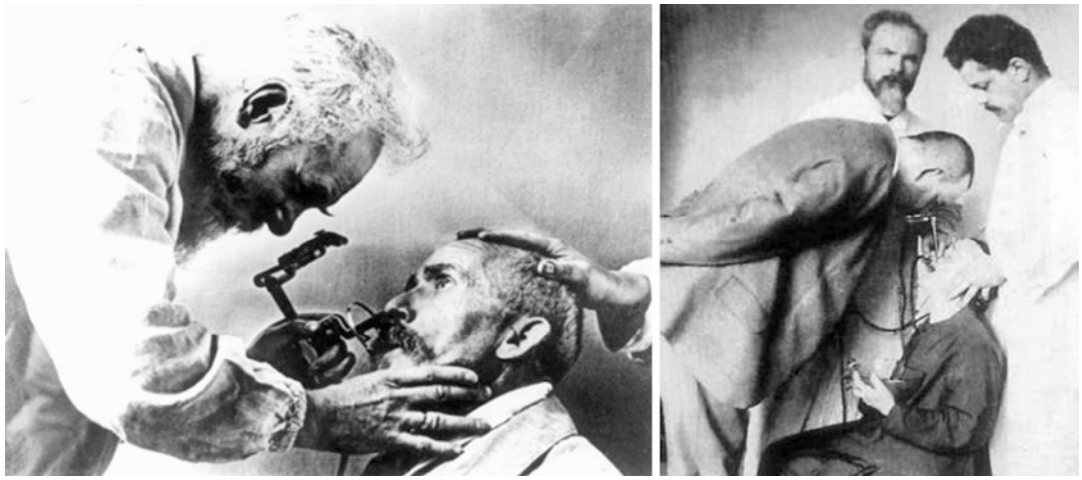

Fig. 39.2 Gustav Killian performing bronchoscopy

Fig. 39.3 Chevalier Jackson—the father of American bronchoesophagology

Neel and Sanderson for endobronchial cryotherapy, **Laforet** for the use of a CO2 laser on the trachea in 1976, and **Hooper and Jackson** for endobronchial electrosurgery in 1985 [8].

Fig. 39.4 The first illuminated rigid bronchoscope introduced by Chevalier Jackson

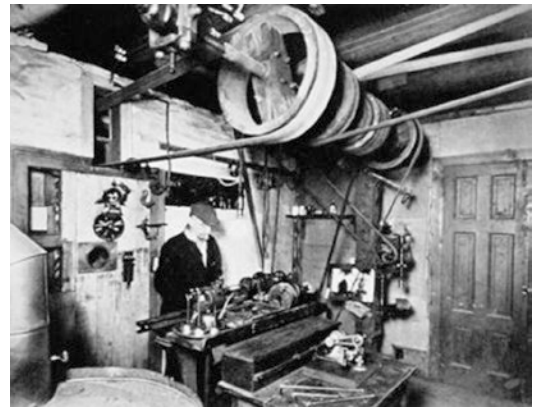

Fig. 39.5 Chevalier Jackson working in a watermill to construct rigid bronchoscope

The Rigid Bronchoscope (1897–)

Killian's descriptions regarding bronchoscopic examination of the proximal airways were critical in providing inspiration to his coworkers **Von Eiken, Brunings, Seiffert,** and **Albrecht** who worked on further development of the rigid bronchoscope. **Storz and Wolf** became the two pivotal companies that introduced newer technologies and newer versions of the rigid bronchoscope. On the other hand, the development of rigid bronchoscopy in the United States was brought about by **Chevalier Jackson** with his instrument maker, **George Pilling**. The next task at hand was the development of telescopic optics for bronchoscopy. This was accomplished by **E. Broyles**, who had trained under the mentorship of Dr. Jackson (1940). He then also went on to introduce the optical forceps in 1948 followed by fiber illumination techniques in 1962. The use of rigid bronchoscopy had declined since creation of the flexible bronchoscope until special tools for stent placement and neodymium-doped yttrium aluminum garnet (Nd:YAG) laser application was invented by **J.-F. Dumon**. The use of rigid bronchoscopy has since regained prominence, particularly for advanced therapeutic bronchoscopy [8].

The Flexible Bronchoscope (1968–)

The potential of fiber-optic imaging in bronchoscopy was first recognized by **Shigeto Ikeda** (1962), a thoracic surgeon at the National Cancer Center in Japan (Fig. 39.6). He approached the Machida Corporation to develop a flexible bronchoscope with a diameter of less than 6 mm. In 1964, the prototype device was developed, which since then has undergone numerous revisions. In 1966, the first useful device was presented at Copenhagen in 1966. This device comprising over 15,000 glass fibers was the first modern-day fiber-optic bronchoscope [9].

After the optical technology was incorporated, the next round of modifications involved the adoption of a working channel. This Machida flexible bronchoscope became available in 1968, which is known as the year of the "second revolution" in bronchoscopy. Researchers further revised the bronchoscope to make it more maneuverable at the tip that allows U-turn angulation for entry into the upper lobes. Olympus first came out with its model in 1970 with better imaging capabilities as well as ease of handling [9].

The first video bronchoscope developed by Asahi Pentax Corporation (1967) also involved significant contributions from **Shigeto Ikeda** [9]. Today, video bronchoscopy is an integral part of the practice of chest medicine as most ailments of the airways can be diagnosed, palliated, or sometimes cured by use of the flexible bronchoscope. Although removal of foreign bodies from the endobronchial tree was the initial application for the rigid bronchoscope,

Fig. 39.6 Shigeto Ikeda with flexible bronchoscope

currently the majority of foreign bodies, even in the pediatric age group, are successfully removed with the flexible bronchoscope in a relatively noninvasive fashion [10].

Transbronchial Lung Biopsy (1972) (Fig. 39.7)

Howard Anderson recognized the potential of accessing and sampling the lung parenchyma through the bronchoscope for histological analysis. After gaining some animal data with initial experiments, they reported their experience in obtaining bronchoscopic biopsies using a flexible forceps in 13 patients [11]. A subsequent larger series was published by **Anderson and Fontana** reporting data on 450 patients [12]. All biopsies performed by Anderson and colleagues were done using a flexible forceps passed through a rigid bronchoscope. These forceps were 60 cm in length and 7F in circumference. They also explained how they would engage a tiny peripheral bronchial carina with moderate pressure to obtain a small biopsy of the lung without causing a pneumothorax from pleural rupture. The rate of pneumothorax was 19% in the first 150 patients and 11% in the next 300 patients [12]. Though this technique of lung biopsy was developed and utilized through the rigid bronchoscope, it is now standard of care to use a flexible bronchoscope for this sampling procedure. Transbronchial lung biopsies are standard of care in the diagnostic work-up of a variety of lung diseases and are an inherent part of caring for lung transplant recipients [13, 14].

Flexible Transbronchial Needle Aspiration (1978–)

The idea of transbronchial needle aspiration (TBNA) through the rigid bronchoscope was first proposed by **Eduardo Schieppati** (1958). He proposed that this technique can be accomplished by passing a needle through a rigid bronchoscope to

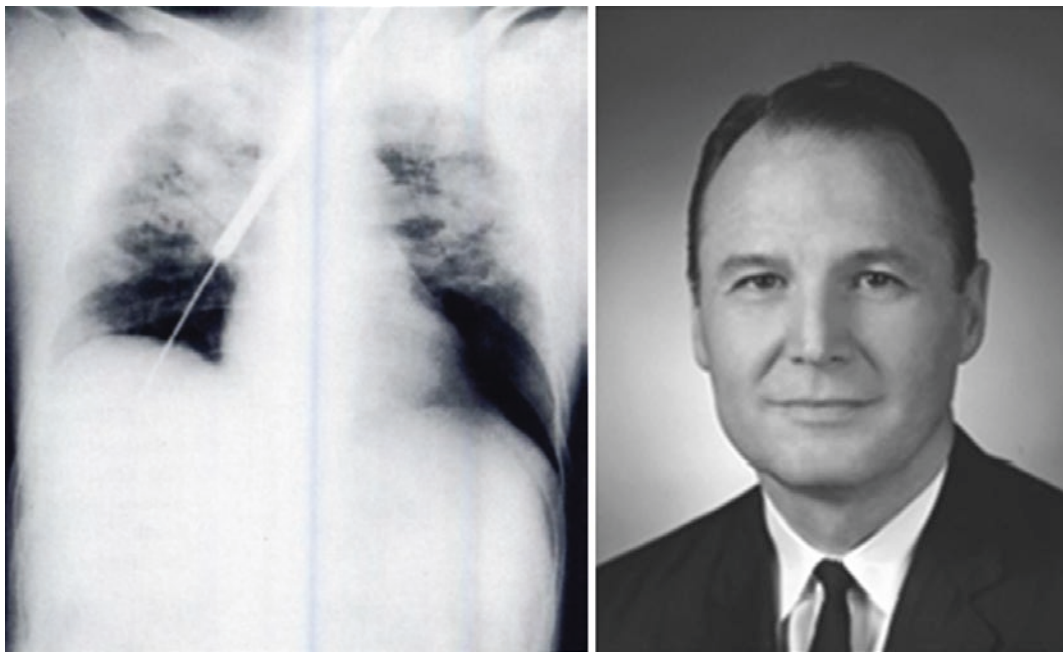

Fig. 39.7 Howard Anderson—inventor of the transbronchial biopsy

Fig. 39.8 Ko-Pen Wang—the inventor of the flexible TBNA

puncture the main carina and sample mediastinal lymph nodes [15]. This concept was furthered by the work of **Oho and colleagues** [16]. The first report of sampling paratracheal tumors and masses was published in 1978 by **Ko-Pen Wang** (Fig. 39.8) [17]. He successfully accomplished this technique via flexible bronchoscopy. He then further refined the technique by introducing a needle for histological specimen collection to help in diagnosing benign pathologies [18, 19]. Conventional TBNA (C-TBNA) which was commonly used in the 1980s and 1990s has paved the way for the development of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) which uses ultrasound technology via a probe at the apex of the scope to perform TBNA under direct visualization with ultrasonic images.

Laser Therapy (1981–)

The technique of delivering laser light with a wavelength of 1064 nm via a flexible quartz filament was reported by **Lucien Toty and colleagues** in 1981. They first reported the use of this Nd:YAG laser in the airways through a rigid bronchoscope [20]. This laser beam had the potential to coagulate or vaporize endobronchial lesions and abnormalities. The technique of using laser photo resection in patients with either malignant or benign lesions of the airway was further refined by **J.-F. Dumon** who also played a vital role in developing the techniques of airway stenting. He is considered the father of interventional pulmonology, and he propagated the use of endobronchial use of laser to bronchoscopists worldwide.

Endobronchial Argon Plasma Coagulation (APC) (1994–)

The year 1994 saw a newer mode of electrosurgical, noncontact, thermal ablation technique by using ionized argon gas (argon plasma). This pioneering modality was introduced by **Grund and colleagues** [21]. With this technique, 102 patients were treated endoscopically in 189 sessions with APC in the upper and lower gastrointestinal tract as well as in the respiratory system. Lesions treated were mainly malignant and benign tumors, diffuse hemorrhages of various origins and sites, tissue overgrowth after stent implantation, tissue remnants after endoscopic resections, and the conditioning of fistulas prior to fibrin sealing. APC was easy and effective in all cases via flexible bronchoscopy with minimal technical or other complications over standard electrocoagulation. Endobronchial APC currently offers the simplicity and low cost of an electrocoagulator with the noncontact approach of an Nd:YAG laser. The noncontact feature of APC allows rapid coagulation with minimal manipulation and mechanical trauma to the target tissue [22].

Endobronchial Stents (1990–)

The very first stent implantation was accomplished by **Trendelenburg and Bond** for the treatment of central airway strictures [23, 24]. This technique has made rapid progress since 1965.

Montgomery designed the first T-tube with an external side limb made of silicone for tracheal

stenosis [25]. **J.-F. Dumon** achieved a major breakthrough in airway stenting when he introduced a dedicated tracheobronchial prosthesis. This stent has a unique external surface with studs to preserve mucociliary action [26]. Since most pulmonologists in the United States are not trained in rigid bronchoscopy for stent placement, the utility of such stents has been limited. On the other hand, flexible bronchoscopy to place metallic stents is relatively easy but results in a significant amount of granulation tissue. This tissue reaction makes removal of these stents very challenging including possibility of airway laceration. Thus, their role is limited mainly to malignant processes, and they are the treatment of choice for bronchial dehiscence, especially after lung transplantation [27]. **The ideal stent** is one that is "easy to insert and remove, can be customized to fit the dimensions and shape of a stricture, reestablishes luminal patency by resisting compressive forces but is sufficiently elastic to conform to airway contours without causing ischemia or erosion into adjacent structures, is not prone to migration, biocompatible, nonirritating, and does not precipitate infection, promote granulation tissue, nor interferes with airway ciliary action necessary to clear secretions, and that is affordable" [28].

That ideal stent does not yet exist [28]. At present, highly specialized technology including three-dimensional printing with advanced radiographics is being employed to device stents specific for each patient's individual airway anatomy [29].

Bronchoscopy in Lung Transplantation (1992–)

Since 1986 when the first lung transplant was performed, about 50,000 transplants have been performed in the United States for end-stage lung diseases. The most common complications post-lung transplant are infection and rejection. Both these broad diagnostic categories cannot be narrowed upon without flexible bronchoscopy. Hence, the success of lung transplantation, however, cannot be imagined without the use of the flexible bronchoscope. This argument is supported by the study by **Trulock and colleagues** where they found a surprisingly high incidence of acute rejection in asymptomatic lung transplant recipients undergoing transbronchial biopsy [30]. The sensitivity of transbronchial lung biopsy was estimated at 72% for the diagnosis of acute rejection and 91% for the diagnosis of cytomegalovirus pneumonia. Surveillance bronchoscopy is performed in the first year after transplant in many lung transplant programs because the incidence of acute rejection resulting in graft dysfunction is highest in this period. Some others perform flexible bronchoscopy with transbronchial biopsies only when clinically indicated (i.e., drop in lung function or new radiographic abnormalities). Nevertheless, both approaches aim to detect subclinical, clinical acute cellular rejection and antibody-mediated rejection. Flexible bronchoscopy is also crucial in the diagnosis and management of airway complications after lung transplantation [31].

Radial Probe Ultrasound (1992–) (Fig. 39.9)

C-TBNA demonstrated the ability to access and sample mediastinal lymph nodes. However, the anatomy of the bronchial tree and associated vasculature makes direct visualization of structures quiet important, especially in the paratracheal regions and the hila. Ultrasound technology has made it possible to noninvasively assess most regions of the body. This concept led investigators to pursue real-time target visualization at the time of sampling. It was the pioneering work of **Heinrich Becker** that brought to fore the immense potential of applying ultrasound technology to the endobronchial region. This led to the development of EBUS of endobronchial ultrasound to guide sampling of mediastinal lymph nodes and parenchymal lesions [32]. **Hurter and Hanrath** first reported the usefulness of radial probe EBUS (RP-EBUS) in 74 patients with central lesions and 26 patients with parenchymal lesions in consecutive procedures [33]. Although RP-EBUS continues to play a pivotal role in the diagnosis of peripheral pulmonary lesions, a major limitation of RP-EBUS, however, is that after localizing the lesion, sampling is still performed in a blind fashion. Investigators have however worked on other technologies to localize pulmonary masses and use real-time

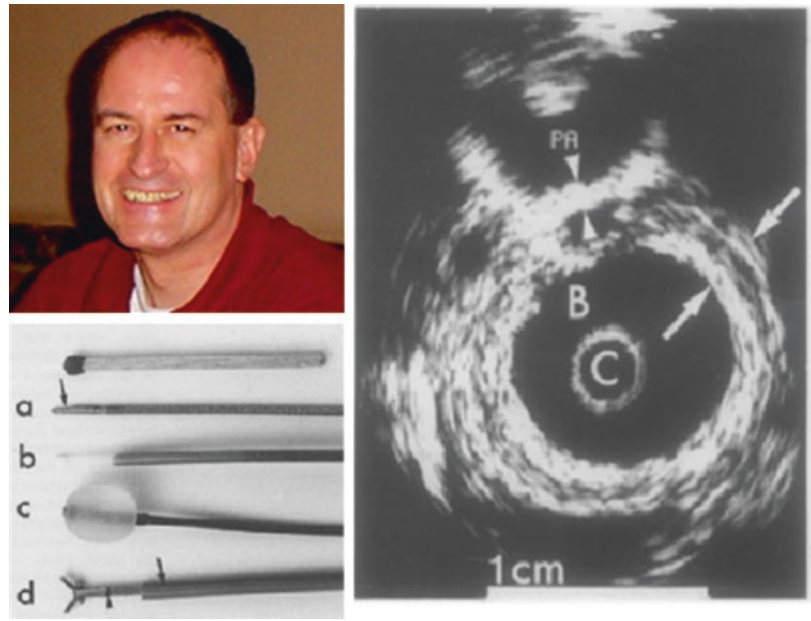

Fig. 39.9 Heinrich Becker—promoter of the radial probe EBUS

sampling in addition to RP-EBUS. This limitation has paved the way for the development of the convex probe EBUS [34].

Convex Probe Endobronchial Ultrasound (2004–)

Convex probe ultrasound was developed as an attempt to utilize real-time ultrasound technology to sample mediastinal lymph nodes and lung lesions. The distal end of the EBUS bronchoscope has a larger diameter than a flexible bronchoscope, with an angulated forward view at a 30 degree inclination (Fig. 39.10). This is necessary for imaging the lymph nodes and lung lesions and anchoring the scope to the airway while the needle comes out of a slightly proximal opening. The field of bronchoscopy imported the concept of linear probe ultrasound endoscopes from gastroenterology, after they were developed to sample paraesophageal lesions under real-time guidance. **Pedersen and colleagues** first described the usefulness of linear EBUS in sampling mediastinal lesions in 1996 [35]. **Kazuhiro Yasufuku and colleagues**

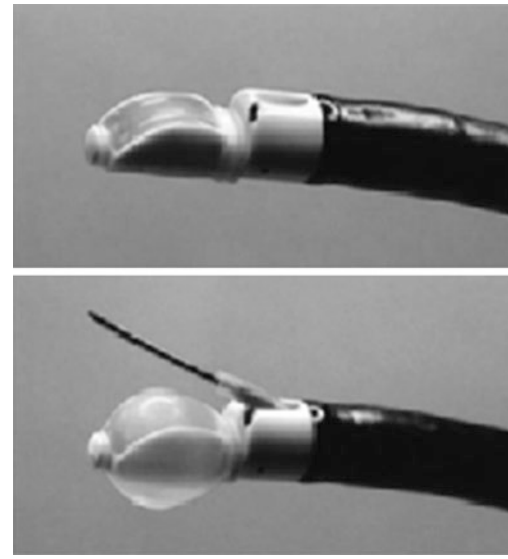

Fig. 39.10 Convex probe EBUS

(Fig. 39.11) first demonstrated the high diagnostic yield of the convex probe EBUS (CP-EBUS) in sampling mediastinal lesions [36]. Both studies reported a sensitivity of 96% and specificity of 100% for distinguishing between malignant and

Fig. 39.11 Kazuhiro Yasufuku

nonmalignant lesions [37]. Currently, CP-EBUS has become standard of care for diagnosis and staging of lung cancer as well as the diagnostic work-up of sarcoidosis and interstitial lung diseases [38, 39]. As shown in the granuloma trial, CP-EBUS-TBNA alone has been shown to have a high diagnostic yield for sarcoidosis. The yield is even higher when transbronchial lung biopsies are performed to complement it [40]. Thus, CP-EBUS has almost replaced surgical mediastinoscopy with a less invasive option.

Electromagnetic Navigation (2003–)

Although the problem of proximal lymph nodes and lung lesions has been solved by the development of RP-EBUS, accessing peripheral lung parenchymal lesions which are closer to the distal endobronchial tree still poses significant challenges. Electromagnetic navigation (EMN) is a technology that has been in continuous evolution since the late 1990s. This concept of navigating the bronchial tree or "GPS of the lung" originated in **Stephen Solomon's** animal laboratory [41]. The technique was refined and applied for the first time in humans by **Yehuda Schwarz and colleagues** in 2006 [42]. This technique involves a sensor and a computer-integrated magnetic field generator, which, when coupled with a three-dimensional map created by computerized tomography, helps to visualize small peripheral nodules. This three-dimensional map essentially is used to create a pathway all the way from the proximal bronchus to the distal bronchus in <1 cm (10 mm) proximity to the lung mass and nodule to be sampled. EMN has now been widely studied, and **Gildea and colleagues** described their yield of 74% and 100% with navigational bronchoscopy for sampling peripheral lesions and lymph nodes with a mean size of 22.8 ± 12.6 mm and 28.1 ± 12.8 mm, respectively [43]. Other factors and adjunct technologies that increase the yield of EMN are concomitant RP-EBUS, guided sheath techniques, multidimensional fluoroscopy, and rapid onsite cytology evaluation (ROSE). With the results of the National Lung Screening Trial, navigational bronchoscopy coupled with a staging procedure using CP-EBUS is currently the main procedures adopted for the diagnosis and staging of peripheral lung nodules [44].

Bronchial Thermoplasty (2006–)

Using heat to induce structural changes in the airway wall and hence decrease airway reactivity is the basic principle of bronchial thermoplasty (BT). The Alair system from Boston Scientific uses a radiofrequency controller with a treatment catheter to deliver 18 W of heat at each treatment site. Preliminary investigations in dogs showed that application of thermal energy to the airway decreased airway hyperresponsiveness and replaced smooth muscle with connective tissue with no evidence of scarring at 3 years [45].

After early investigations testing the usefulness of BT in human subjects, **Gerard Cox and colleagues** established the safety of BT in 16 human subjects over a 2-year period with improvements in symptom-free days, and morning and evening peak flow rates, and without significant complications [46, 47].

The safety of BT and duration of its effects in patients with asthma in terms of decreased emergency room visits and acute exacerbations have been demonstrated in a large multicenter study [48].

Bronchoscopic Lung Volume Reduction (2003)

The National Emphysema Treatment Trial (NETT) proved the beneficial effects of surgical lung volume reduction in carefully selected patients with emphysema [49]. As LVRS is a major surgery with postsurgical mortality and morbidity, significant interest was generated in the possibility of endobronchial lung volume reduction using minimally invasive techniques. **Tudor Toma** introduced the concept of endobronchial volume reduction using one-way valves in 2003 [50]. Since then two different types of endobronchial valves, Zephyr (Pulmonx Inc.) and IBV (Spiration Inc.), have undergone multiple safety and efficacy trials [51, 52].

The utility of endobronchial valves (EBVs) remains experimental in the United States. However, one major spin-off of the technology has been the application of EBVs to the management of bronchopleural fistula. Researchers have clearly shown that EBVs help heal these fistulas, thereby eliminating the need for surgical thoracic procedures [53]. It is also worth noting that the role of endobronchial coils in reestablishing elastic recoil of the lungs in patients with emphysema is being studied in a large international, multicenter trial [54].

Endobronchial Microwave Therapy (2004–)

Microwave coagulation refers to the electromagnetic wave with wavelengths ranging from 1 m to 1 mm or with frequencies between 300 MHz and 300 GHz, which fall in between the high-frequency electric-argon plasma and laser coagulation techniques.

It is a fairly safe procedure because it induces no tissue vaporization and requires no oxygen during the operation. In addition, it has an appreciable treatment depth. It has been used to treat the trachea blockage condition caused by benign and malignant tumors within the airway, intima hyperplasia of tuberculosis, polyps, granulomas, and other complications.

Bronchoscopic microwave tissue coagulation (MTC) and diathermy (MD) therapy were performed on 37 patients with severe tracheal stenosis at least two times. The effective rate immediately after treatment was 100% in all cases. After 1 month, the rate remained 100% in patients with benign diseases, but it dropped to 67% in patients with malignant tumors [55].

Endoscopic Doppler Optical Coherence Tomography and Autofluorescence Imaging: DOCT-AFI System (2014–) [56]

Autofluorescence imaging (AFI) can provide biochemical information of tissue by visualizing fluorescent tissue components such as collagen and elastin. AFI has been implemented in commercial bronchoscopes for wide-field imaging in central airway. When illuminated by blue light, normal central airway tissue emits green autofluorescence (AF), while cancerous tissue is known to have a markedly reduced and redshifted AF signal due to the breakdown of extracellular matrix components as well as increased absorption by blood [57].

Owing to this contrast mechanism, AFI is up to six times more sensitive compared to white-light bronchoscopy in detecting intraepithelial neoplastic lesions [58, 59]. This increased sensitivity comes at the cost of reduced specificity as inflammation and chronic bronchitis can also lead to reduced AF.

Optical coherence tomography (OCT) can visualize significantly finer tissue structures compared to RP-EBUS with 1–2 mm imaging depth penetration into tissue.

This imaging technique can offer both structural and functional information for the localization and management of pulmonary nodules.

This technology is relatively safe and feasible for the evaluation of pulmonary nodules. AFI can readily identify the vasculature pattern and suspicious areas along centimeter-long airway segments. Once identified, closer examination of OCT can verify if the site is appropriate for biopsy collection. Thus, DOCT-AFI may increase the ability to identify and locate pulmonary nodules and improve the safety of biopsy collection [60].

American Association for Bronchology and Interventional Pulmonology (AABIP) and Journal of Bronchology and Interventional Pulmonology (JOBIP) (1992–)

AABIP was founded in 1992 by a small group of dedicated bronchoscopists with the goal of advancing the field of bronchoscopy and interventional pulmonology. The AABIP has successfully helped develop training and education programs in interventional pulmonology. The training programs in interventional pulmonology now work with the national residency matching program (NRMP). In addition, board certification has now been established for the specialty of interventional pulmonology that has further strengthened this subspecialty within the domains of pulmonary medicine.

JOBIP, the flagship publication of the society, was accepted in Index Medicus in 2011. This was a major boost to the research output and recognition of interventional pulmonology around the world [61, 62].

In this chapter and other articles, we have attempted to give the readers a brief glimpse of the development of modern-day bronchoscopes and the innovation and creativity that went into building this present-day science and technology (Fig. 39.12) [63]. These techniques have revolutionized the diagnosis and management of a variety of lung diseases and advances continue to be made therein [63].

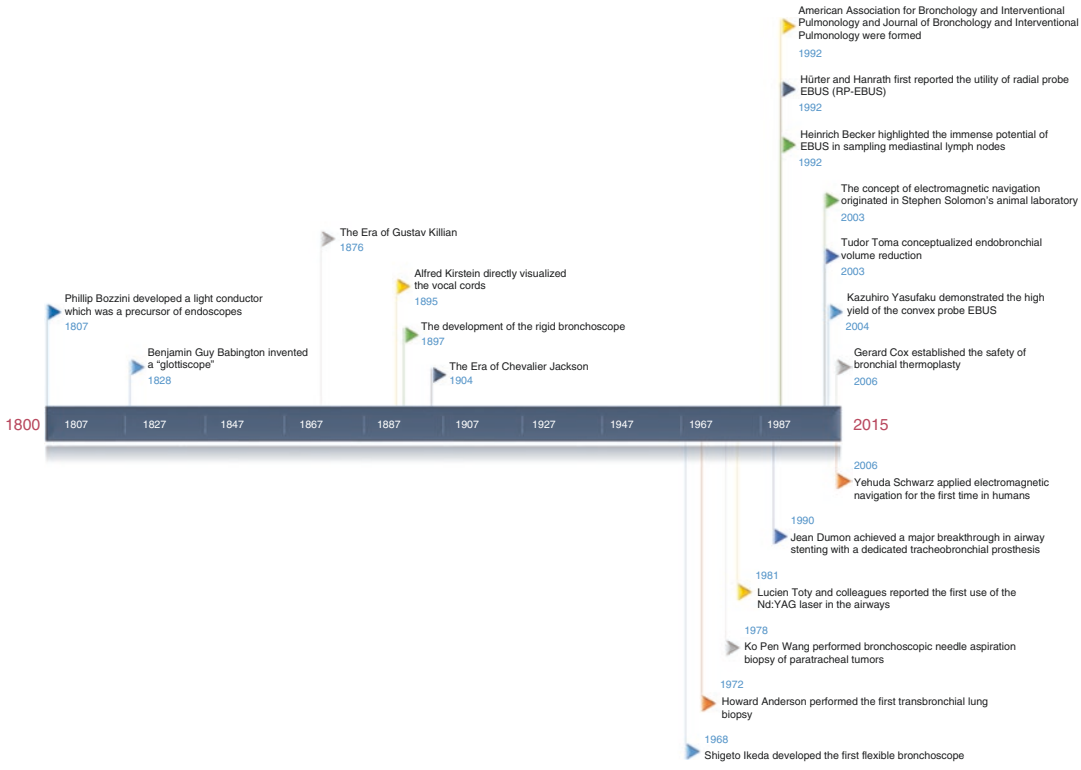

Fig. 39.12 Timeline of innovation is bronchoscopy (adopted with permission from reference [63])

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Bronchoscopy and Interventional Pulmonology

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Reflections on the Past, the Present, and the Future

Udaya B. S. Prakash

Introduction

The clinical application of bronchoscopy has been available for over a century [1]. In its infancy at the tail end of nineteenth century, the technique was used on an infrequent basis. As it has matured over the years, bronchoscopy is now frequently utilized to diagnose and treat a vast range of pulmonary disorders. Significant advances in the instrumentation, techniques, and ever-increasing indications over the past century have established bronchoscopy as an essential tool not only in the practice of pulmonary medicine but also in critical care medicine, thoracic surgery, rhinolaryngology, and pediatric pulmonology. Currently, bronchoscopy is perhaps the most commonly employed minimally invasive diagnostic procedure in pulmonary diseases.

The ever-expanding indications and the specialized tools required to manage certain clinical conditions now require advanced training and practice before the clinical application can begin. Several of these techniques are inherently time-consuming and call for well-developed skills beyond that required in standard or "routine" bronchoscopy procedures. To denote these aspects of bronchoscopy practice, the term "interventional pulmonology" is being used more frequently. This area encompasses not only bronchoscopy but also minimally invasive procedures to diagnose and treat the disorders of the pleural space and percutaneous tracheostomy. Some experts believe that esophageal ultrasound-guided needle aspiration of lymph nodes in lung cancer staging be considered under the term interventional pulmonology. In this chapter, the term bronchoscopy-interventional pulmonology (B-IP) will apply to procedures performed by the pulmonary specialists.

As the vast field of medicine and medical research continues to expand at a rapid pace, it is natural to wonder and contemplate what the distant future holds in the B-IP field. Before one embarks on this speculative endeavor, it is essential to trace back the origins of this field and acknowledge the remarkable contributions made by our predecessors and the trials and tribulations they encountered.

The Past

Interest in the Airways

The references to the study of the human airways and their diseases have been attributed

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from Hippocrates (460–370 BC) to subsequent generations of scientists through the successive centuries. Concerted efforts to study the human tracheobronchial tree based on scientific principles began in the early part of the nineteenth century. The inquisitiveness of medical practitioners to examine the internal cavities led to development of early instruments which were basically made of metallic tubular instruments. Subsequently, polished mirror plates were used to take advantage of the external sunlight for inspection.

In 1807, the German army surgeon Philipp Bozzini developed the *lichtleiter* or "light conductor," precursor of the endoscope for examination of bodily orifices [2]. Neither Bozzini's paper nor his inventions, the lichtleiter described as "The Magic Lantern in the Human Body," were taken seriously by his peers. During Bozzini's short life, others continued their work to visualize the larynx with the help of various lighting devices. Benjamin Guy Babington, a British physician is credited by some for the invention, in 1828, of the "glottiscope," the precursor of the laryngoscope [3]. Manuel Garcia, a Spanish music teacher, singer, and vocal pedagogue is also credited for being the first to perform laryngoscopy [4, 5]. The next subsequent developments in endoscopy did not appear for at least two decades following Bozzini's death in 1809 at the age of 36 years from typhus.

Advent of the Endoscope

In 1828, Horace Green demonstrated that the larynx could tolerate the presence of a foreign object without endangering the life of patient [6]. Green became quite adept at catheterizing the larynx and trachea. He subsequently inserted a gum elastic catheter through the larynx and into the lower bronchi. When Green presented his technique and results of his work at the Surgical Society of New York in 1847, the technique was condemned as "an anatomical impossibility and an unwarranted innovation in practical medicine." As a result, Green was subsequently expelled from the society [7]. Several decades later, Green's technique and clinical usefulness were universally approved. In 1867, Johnson used a laryngoscope to extract a penny coin impacted in the throat of a child [8].

Kirstein, Killian, Jackson, and Protégés

Alfred Kirstein of Germany is credited for the first direct visualization of the vocal cords in 1895, using a modified esophagoscope which he named the *autoscope* [9]. In 1897, Gustav Killian (1860–1921) of Freiburg used the Kirstein laryngoscope to examine the trachea and main stem bronchi of a hospital janitor [10]. In the same year, Killian used an esophagoscope to extract a bone from the right main stem bronchus of a 63-year-old farmer [11]. One year later, Killian extracted tracheobronchial foreign bodies in three patients and coined the word "directe bronkoscopie" to describe the procedure [12]. In 1898, Algernon Coolidge of Harvard Medical School used an open urethroscope, a head mirror, and reflected sunlight to remove a hard-rubber cannula from the right main bronchus [1]. Subsequently, several clinicians took up the procedure, and almost all procedures involved removal of aspirated foreign bodies [13–15]. As Gustav Killian was instrumental in introducing the technique, he is generally considered the father of bronchoscopy.

In the 1920s, Chevalier Jackson, a laryngologist from Philadelphia, made several modifications to the rigid bronchoscope. Because of his many innovations and contributions to the field of bronchoesophagology, he came to be known as the father of American bronchoesophagology. Jackson and his protégés popularized bronchoscopy and modified the rigid bronchoscope [1]. One of Jackson's students, the British laryngologist Victor Negus, modified one of Jackson's endoscopes, subsequently known as the "Negus bronchoscope." Chevalier Jackson and his son Chevalier Lawrence Jackson, also a laryngologist and better known as C. L. Jackson, wrote several books on bronchoscopy and esophagoscopy [16]. C. L. Jackson further popularized bronchoesophagology by founding the Pan

American Association of Otolaryngology and the International Bronchoesophagological Society.

For the next five decades, the rigid bronchoscope and the esophagoscope and their many modifications reigned supreme in the exploration of the airways and the esophagus. Over the years, several newer developments were incorporated into the rigid bronchoscope. In 1904, Chevalier Jackson had introduced a bronchoscope with a small light at the distal end. Edwin Boyles, another Jackson protégé, developed the optical telescope with forward and angle viewing which permitted inspections of the upper as well as lower lobes of the lung. Paul H. Holinger introduced bronchoscopic photography to document the visual findings [17]. Other developments included instruments for pediatric patients, better lighting and illumination techniques, photographic documentation, and improved anesthetic drugs. The rigid bronchoscopy practice quickly spread to other countries including Japan.

Among the main indications for bronchoscopy, airway foreign body topped the list [16]. The bronchoscope was primarily used as a therapeutic instrument to remove airway foreign bodies, treat atelectasis, drain of post-tonsillectomy pulmonary suppuration, and treat bronchitis, asthma, and pneumonia. The Mayo Clinic records indicate that in 1943, of the 436 rigid bronchoscopes performed, the main indication was the foreign body [18]. In 1965, Howard Andersen of the Mayo Clinic employed the rigid bronchoscope and a biopsy forceps to obtain lung parenchymal samples in patients with diffuse lung disease [19]. Andersen termed this technique "transbronchoscopic lung biopsy." A report of 450 cases in 1972 documented the safety of transbronchoscopic lung biopsy using the rigid bronchoscope [20]. However, these advancements in technology could not address the rigid bronchoscope's difficulty in the visualization of the upper lobe bronchi.

Fiberoptics and Shigeto Ikeda

The ability to convert the light rays from their natural predisposition to travel in straight lines to bend them with the fiberoptic technology had its origins in the early 1800s. The physical properties of glass fibers were first described by John Tyndall in 1872. The rod and lens fiberoptic lighting technique was adopted as cold light source for the rigid bronchoscopes in 1963 [21, 22]. Further refinements by countless investigators eventually culminated in the development of a clinically useable fiberoptic system. In 1957, Basil Hirschowitz at the University of Michigan presented the first gastrofiberscope at the Gastroscopic Society of America [23, 24].

Shigeto Ikeda of Tokyo, Japan, was responsible for developing and introducing the flexible fiberoptic bronchoscope into clinical practice in 1968 [25, 26]. In 1970, the first Olympus model became commercially available. Ikeda traveled widely and disseminated the technique and popularized it. As a result, the flexible fiberoptic bronchoscope moved rapidly into clinical practice and revolutionized the practice of pulmonology. The ability to reach and visualize the distal bronchial tree in all segments of all lobes permitted the diagnosis of endobronchial lesions and other abnormalities. Ancillary instruments that could be introduced into the working channel enabled the bronchoscopist to obtain brushings and biopsies of not only the endobronchial lesions but also the lung parenchyma. Simultaneous use of real-time fluoroscopy made it possible to more precisely direct the instruments to the lesion in question. Special cameras to capture both still and video images were developed to complement the system. Within a brief period after its introduction into clinical practice, the flexible bronchoscope became an important aspect of pulmonary practice.

Professor Ikeda continued his work to develop newer techniques and instruments. His work eventually led to the development of the flexible video bronchoscope in the late 1980s. The main difference between the fiberoptic bronchoscope and the video bronchoscope is the mode of capture and transmission of the bronchoscopic images. With fiberoptic system, the images are directly carried by the fiberoptic bundles through the bronchoscope to the objective lens and then viewed by the examiner. The video bronchoscope

uses a charged-couple device (CCD) to capture the digital images which are transmitted to a processor and then projected on to a larger video screen. This has resulted in our ability to capture still and video images with far greater resolution for documentation and educational purposes. Smaller diameter bronchoscopes are available to examine pediatric patients with respiratory disorder. Further refinements in the ancillary instruments have improved specimen collection from the respiratory tract. At present, over 95% of all bronchoscopies are performed with the flexible bronchoscope. Ikeda who introduced the flexible bronchoscope continued to work on improvements in and modifications to the flexible bronchoscope until his death on December 25, 2001 [27]. His legacy continues, carried on by countless number of bronchoscopists from around the world who benefited from his invention in the management of thousands of patients with respiratory disorders.

Revival of the Rigid Bronchoscope and Dumon

The continued improvements in flexible bronchoscopy and associated equipment vastly increased the indications for bronchoscopy. As the popularity of the flexible bronchoscope grew, it became universally accepted as the instrument of choice for airway diagnostics. Nevertheless, thoracic surgeons and laryngologists continued to use the rigid bronchoscope for procedures involving the major airways and for the extraction of airway foreign bodies. Several pulmonologists continued to use the standard rigid bronchoscope for traditional indications such as extraction of airway foreign bodies and dilatation of major airway stenosis. Jean Francois Dumon of Marseilles foresaw the need for better rigid bronchoscopes and associated ancillary equipment for the treatment of airway lesions such as obstructing tumors and benign stenosis of trachea and main bronchi. Dumon developed and modified many aspects of the rigid bronchoscope and peripheral equipment. In 1981, Dumon and colleagues reported on the use of YAG laser to treat tracheal lesions [28, 29]. Over the next decade, Dumon developed a newer type of rigid bronchoscope and stent insertion instrument [30]. Many specialists in B-IP became interested in the rigid bronchoscopy technique and its application in clinical medicine. As a result, the rigid bronchoscope regained its importance in the treatment of major airway lesions. A variety of silicone and metal stents have been developed to relieve airway stenosis from benign as well as malignant processes.

The Present

As the past innovations and applications of bronchoscopic techniques have gradually and imperceptibly melded into the present, the current practice wisely utilizes all clinically available and applicable techniques from the past and present to manage a variety of respiratory disorders. This view is reflected by the leading specialists in their excellent rendition of the current status of B-IP in the preceding chapters of this volume. Therefore, this part of this chapter will not dwell on the technical and other details and the nuances of the current practice. However, a few brief summarizing paragraphs might be in order to summarize the current status.

Diagnostic Procedures

In the realm of diagnostic bronchoscopy, the standard indication, namely, the visualization of the airways for suspected and unexpected abnormalities, remains among the main indications for bronchoscopy. Collection of bronchial secretions, washings, and bronchoalveolar lavage for cytologic analysis and culture of pathogenic organisms continues to maintain its importance, especially in immunocompromised patients with pulmonary abnormalities. The standard procedures used are well described in the preceding pages. To summarize, these include visualization and documentation, collection of bronchial secretions and bronchoalveolar lavage for cultures, cytology, quantitation of cells and cell types,

quantitation of hemosiderin- or lipid-laden macrophages, and brushing and biopsy of endobronchial as well as pulmonary parenchymal lesions, bronchoscopic ultrasound-guided needle aspiration of thoracic lymph nodes and masses, electromagnetic navigation to obtain tissue from nodular parenchymal lesions, and many other miscellaneous indications.

Therapeutic Bronchoscopy

Therapeutic bronchoscopy plays a major role in the critically ill patients with respiratory manifestations. The primary indication is the retention of airway secretions, mucous plugs, blood, or blood clots. The flexible bronchoscope is very capable of clearing airways of these obstructing materials. The bronchoscope is now an essential part of the equipment in the intensive and critical care units. Other well-known therapeutic indications for bronchoscopy include airway foreign bodies. The availability of small diameter bronchoscopes has permitted flexible bronchoscopic extraction of foreign bodies from the pediatric airways. Uncommon indications include treatment of airway fistulae, drainage of lung abscess and cysts, etc.

Bronchoscopy in Lung Cancer

A major role for the bronchoscope is in the diagnosis and treatment of lung cancer. As described in the preceding chapters, fluorescence bronchoscopy is used from time to time in patients suspected of having cancer of the airway mucosa. This technique permits localization of the lesion to obtain biopsies and in the follow-up of patients with persistent cellular atypia or other suspicious cytologic abnormalities. Optical coherence tomography is another technique used for detailed analysis of epithelial surface abnormalities in the airways. Narrow band imaging is yet another method to analyze abnormal mucosal surface. More recent encouraging developments in the diagnosis and treatment of lung cancer are the techniques available to isolate the molecular genetic variations among different histologic types of lung cancers. This advance has led to the development of newer chemotherapeutic agents targeted to treat specific type of lung cancer.

Bronchoscopic ultrasound-guided sampling of abnormal mediastinal and hilar lymph nodes now allows proper staging of lung cancer. The ability to stage lung cancer with the help of the flexible bronchoscope has significantly obviated the need for mediastinoscopy and video-assisted thoracoscopic surgery for staging purposes. It is essential to note that the role of computed tomography and positron emission tomography are important in guiding the bronchoscopist to the abnormal or suspicious areas for biopsy.

Fluoroscopy-guided bronchoscopic brushing and biopsy of peripheral nodular lesions has been in use since the advent of the flexible bronchoscope. During the past decade, electromagnetic navigation technique to localize and biopsy peripheral lesions is used in several medical centers. Another technique is the virtual bronchoscopic navigational bronchoscopy. This system uses the CT-developed virtual images of the airways to guide the biopsy forceps to the peripheral lesion.

Bronchoscopy techniques offer an important role in the treatment of patients with primary and metastatic malignancies. Many patients with an endobronchial component of the neoplasm present with hemoptysis, increasing dyspnea caused by luminal obstruction, post-obstructive atelectasis with pneumonia, and extrinsic compression of the airway lumen. Control of hemoptysis from a visible bleeding source in the airway lumen can be treated with simple aspiration of blood and repeated iced-saline irrigation. Other methods to stop the hemorrhage include bronchoscopic cauterization of the bleeding point, argon plasma coagulation (APC), cryotherapy, and laser coagulation [31]. Luminal obstruction is more likely to cause dyspnea and respiratory distress if the tumor involves trachea or the main bronchi. In such situations, the techniques mentioned above can remove the obstruction and improve luminal air flow. Mechanical debridement is also an option.

Patients with respiratory symptoms caused by airway obstruction from the endobronchial

component of the cancer can be relieved of the dyspnea with the bronchoscopic use of a variety of techniques. In the early 1980s, Jean Francois Dumon of Marseille, France, showed that bronchoscopic laser ablation of airway lesions can successfully relieve dyspnea as well as significant endobronchial hemorrhage. Subsequently, Dumon developed silicone stents for insertion in the airways to maintain a patent lumen after laser resection of the lesion [30]. To facilitate the laser resection and placement of airway stents, Dumon modified the rigid bronchoscope and developed a series of rigid bronchoscopes and ancillary instruments.

In addition to the techniques mentioned above, other techniques used include mechanical debridement, balloon dilatation, brachytherapy, and photodynamic therapy [32–35]. An overwhelming majority of these procedures are used for palliative purposes in patients with advanced or inoperable airway malignancies. The success of these procedures depends on the expertise of the operator, equipment available, and their optimal use.

Interventional Pulmonology

What is "interventional pulmonology?" My *PubMed* review of the medical journals and periodicals published in English language revealed that the term was first used in 1997 by Witt and colleagues [36]. It is unclear if the term was used in books published at an earlier date. Initially, interventional pulmonology referred to all aspects of bronchoscopy, especially the more invasive procedures such as rigid bronchoscopy, laser resections, airway dilatational procedures, and stent insertion, etc. Currently, all these and any pleural procedure performed by a nonsurgeon and percutaneous tracheostomy are included under the term interventional pulmonology.

Currently, involvement of the interventional pulmonologists has increased in the management of pleural disorders. Thoracentesis, pleural biopsy, placement of indwelling tunneled pleural catheters to treat recurrent benign and malignant pleural effusion, chylothorax, pneumothorax, trapped lung, pleuroscopy, and pleurodesis are among the procedures being performed [37–39]. The term "medical thoracoscopy" has been used to describe thoracoscopy performed by nonsurgeons and without subjecting the patient to tracheal intubation and general anesthesia [40–42]. Another procedure included in the interventional pulmonology is the percutaneous tracheostomy in patients who are expected to require prolonged mechanical ventilation. The current trend indicates that an increasing number of interventional pulmonologists will be performing these procedures.

Bronchoscopic lung volume reduction to treat emphysema has undergone multiple trials and is currently being used in many European countries [43–45]. The current status of this technique is such that that further work and innovations are required to convince the majority of pulmonologists to consider this in suitable patients. Several chapters in this volume describe the various techniques available and the details of the indications, technique, and the results of clinical studies.

Bronchoscopic thermoplasty is a technique developed to treat patients with refractory asthma [46–48]. While it is approved for clinical use in the United States, the technique has not been universally accepted by asthma specialists. Better definition of indications and long-term results will determine if this procedure will gain significant popularity.

The Future

While it is hazardous to guess and predict what the future holds for B-IP, it is safe to surmise that the prospect for B-IP is very promising. The medical science is advancing rapidly, and the advances will determine the indications and for B-IP. As outlined above, the continued technical advances in B-IP have altered the indications and role for the procedures. Newer diseases or increasing prevalence of well-known diseases may bring about important and new indications

for B-IP. Advances in technology are another reason for increased use of B-IP procedures. On the other hand, advances in nontechnical diagnostic methods can decrease or entirely eliminate the need for B-IP procedures. Newer therapeutics to treat nonpulmonary disorders can result in respiratory complications which in turn would require B-IP procedures for the diagnosis and treatment of such complications.

Changing Role of Bronchoscopy and Interventional Pulmonology

A further reflection on the above brings to mind some examples from the past three decades. An excellent example is the discovery of acquired immunodeficiency syndrome (AIDS) in the early 1980s. As clinicians quickly recognized, the lung involvement was common in AIDS and the etiologies of these were unknown. Very soon, bronchoalveolar lavage became very important in the diagnosis of lung infiltrates in these patients. The procedure remains an important tool in the management of patients with AIDS. Another group of patients who benefit from B-IP procedures are those who are immunosuppressed because of chemotherapy or medications administered to prevent tissue rejection following organ transplantations. The number of such patients is likely to increase as more and more organ transplants are performed. Major airway stenosis in lung transplant recipients may require frequent bronchoscopic evaluations.

Newer Technology

The prevalence of asthma as well as the proportion of patients with asthma refractory to aggressive medical therapy has increased. This has been the impetus for the consideration and development of bronchial thermoplasty. Advanced emphysema is another condition that is associated with significant mortality and morbidity. Medical therapy has limited role in alleviating the severe dyspnea and hypoxia in the affected persons. As the surgical lung volume reduction has been associated with high mortality and morbidity, less invasive procedures such as bronchoscopic lung volume reduction have been introduced in clinical practice. As of this date, it is difficult to be certain whether these two procedures will be generally accepted and frequently used.

Lung cancer will continue to be a major condition encountered by pulmonary physicians. Better understanding of genetic mutations in cancer cells has led to targeted chemotherapy in certain histologic types of lung cancer. The general expectation is that improved understanding of the basic abnormalities in genetic mutations may lead to so-called individualized medicine. It is easy to infer that the role of B-IP procedures will increase in the management of patients with lung cancer.

Lessons from the Past and Present

The past history of B-IP shows that some techniques languished for considerable length of time before being accepted by the majority of specialists in B-IP. Bronchoscopic needle aspiration/biopsy is such an example. After the bronchoscopic ultrasound-guided needle aspiration technique and technology became reliable in securing optimal tissue samples from affected lymph nodes, the technique has assumed a very important and essential tool in the nonsurgical staging of lung cancer. Further improvements may increase the indication for the technique. On the other hand, several techniques have yet to gain universal acceptance and widespread use, with only a few medical centers and interested specialists in B-IP using them. These include electromagnetic navigation, virtual bronchoscopic navigation, confocal bronchoscopy, optical coherence tomography, and several miscellaneous techniques. It is important to recognize that many of these require expensive equipment and extensive training. These are major considerations in determining the extent of usage.

Several of the B-IP techniques have established their valuable role in clinical pulmonology. Because of the very nature of the technique, expense, and the limited indications and the limited number of patients who might benefit from their deployment, these techniques are limited to a smaller number of medical centers and B-IP specialists. Included in among these are rigid bronchoscopy, airway debridement, laser bronchoscopy, airway stent insertion, medical thoracoscopy, indwelling tunneled pleural catheters, management of complex conditions of major airways, and percutaneous tracheostomy.

The indications for B-IP have significantly decreased following the introduction of improved diagnostic methods in associated procedures in pulmonology. A classic example is the universal availability of high-resolution computed tomography. Based on clinical information and chest CT images, it is now possible to confidently diagnose several interstitial lung diseases and avoid bronchoalveolar lavage and bronchoscopic lung biopsy. Examples of such disorders include idiopathic pulmonary fibrosis/usual interstitial pneumonitis, nonspecific interstitial pneumonitis, lymphangioleiomyomatosis, Langerhans cell granuloma, pulmonary alveolar proteinosis, and certain cases of sarcoidosis. Advances in serologic testing and other tests have obviated the need for bronchoscopic lung biopsy. Previously, lung biopsies were considered essential for the histologic diagnosis of granulomatosis with polyangiitis (also known as Wegener's granulomatosis). Currently, however, biopsy has been replaced by the reliable antineutrophil antibody testing (ANCA). While the advent of video-assisted thoracoscopic surgery (VATS) decreased the number of bronchoscopic lung biopsies, the improvements in bronchoscopic ultrasound guidance have decreased the need for surgical mediastinoscopy. If and when newer and less invasive tests become available for clinical use, the need for B-IP procedures may diminish. These considerations imply that multitude of factors may increase or decrease the need for B-IP procedures. Simultaneously, it is essential to recognize that the competing tests and procedures can also assume complimentary roles.

Education

Proper initial training and ongoing training including didactic and hands-on practice is required to enable the specialist in B-IP to provide optimal care to the patients. The increase in the number of different procedures performed by the specialists in B-IP had led to the establishment of dedicated training programs in B-IP. Ongoing training programs and refresher courses have increased in numbers. All professional respiratory organizations have established on-hands workshops and training programs in B-IP. A major advance is the introduction of simulation centers where the novices as well as experts are trained and retrained in techniques using mannequins or animal models. In this volume, a chapter is dedicated to the discussion on the various modes of teaching and training. The World Association for Bronchology and Interventional Pulmonology and national associations dedicated to the dissemination B-IP continue to provide guidance and training in B-IP procedures, and this activity will continue and expand.

Summary

It is likely that the importance of B-IP will increase in the future. The caveat that accompanies this statement is that a multitude of factors will increase or decrease the need for and the importance of B-IP procedures in the future. It is essential to concurrently recognize that the newer nonpulmonary tests and procedures do not compete with B-IP procedures but are complimentary. As the number of indications increase and newer instruments and techniques become available, more and more training becomes imperative. Even now, in some major medical centers with large number of specialists in B-IP, not every procedure can be performed by each and every B-IP specialist. Subgroups of specialists have dedicated themselves to the practice of certain B-IP procedures.

Further reflections on the history of B-IP and current practice and trend provide ample evidence to state with confidence that the field of bronchoscopy and interventional pulmonology will remain dynamic.

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