



SYLLABUS
IDKD

Diseases of the Heart, Chest & Breast 2011-2014

*Diagnostic Imaging and
Interventional Techniques*

Editors

J. Hodler
G.K. von Schulthess
Ch.L. Zollikofer



Diseases of the Heart and Chest, Including Breast 2011-2014
Diagnostic Imaging and Interventional Techniques

J. Hodler • G.K. von Schulthess • Ch.L. Zollikofer (Eds)

DISEASES OF THE HEART AND CHEST, INCLUDING BREAST 2011-2014

DIAGNOSTIC IMAGING AND INTERVENTIONAL TECHNIQUES

**43rd International Diagnostic Course
in Davos (IDKD)
*Davos, April 3-8, 2011***

including the
Nuclear Medicine Satellite Course "Diamond"
Davos, April 2-3, 2011

Pediatric Radiology Satellite Course "Kangaroo"
Davos, April 2-3, 2011

Breast Imaging Satellite Course
Davos, April 2-3, 2011

and Additional IDKD Courses 2011-2014

presented by the Foundation for the
Advancement of Education in Medical Radiology, Zurich

Editors

J. HODLER
Radiology,
University Hospital,
Zurich, Switzerland

G. K. VON SCHULTHESS
Nuclear Medicine,
University Hospital,
Zurich, Switzerland

CH. L. ZOLLIKOFER
Kilchberg/Zurich, Switzerland

ISBN 978-88-470-1937-9

e-ISBN 978-88-470-1938-6

DOI 10.1007/978-88-470-1938-6

Springer Milan Dordrecht Heidelberg London New York

Library of Congress Control Number: 2011922274

© Springer-Verlag Italia 2011

This work is subject to copyright. All rights are reserved, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, re-use of illustrations, recitation, broadcasting, reproduction on microfilms or in other ways, and storage in data banks. Duplication of this publication or parts thereof is only permitted under the provisions of the Italian Copyright Law in its current version, and permission for use must always be obtained from Springer. Violations are liable for prosecution under the Italian Copyright Law.

The use of general descriptive names, registered names, trademarks, etc., in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

Product liability: The publisher cannot guarantee the accuracy of any information about dosage and application contained in this book. In every individual case the user must check such information by consulting the relevant literature.

Cover design: Simona Colombo, Milan, Italy
Typesetting: C & G di Cerri e Galassi, Cremona, Italy
Printing and binding: Grafiche Porpora, Segrate (MI), Italy
Printed in Italy

Springer-Verlag Italia S.r.l., Via Decembrio 28, 20137 Milan
Springer is a part of Springer Science+Business Media (www.springer.com)

Preface

The International Diagnostic Course in Davos (IDKD) with its interactive courses and plenary lectures offers a unique learning experience for radiologists in training as well as for experienced radiologists and clinicians.

The IDKD has been able to attract the best available teachers mainly from North America and Europe for a long time. IDKD courses are focused on organ systems and diseases rather than on imaging modalities. The current courses provide an update on the current state of the art and the latest developments in diagnostic imaging of the chest, the heart and the breast. There are also insights into pertinent image-guided interventions.

The syllabus represents a condensed version of the contents of the course. It can be used to prepare the individual workshops. It also obviates the need to take notes during the workshops. Last but not least, the IDKD course syllabus is a valuable, systematic and up-to-date textbook provided by world's experts which is of interest to any reader interested in the topic even without having visited the courses.

Additional information can be found on the IDKD website: www.idkd.org

J. Hodler
G.K. von Schulthess
Ch.L. Zollikofer

Table of Contents

Workshops

Current Concepts in Diagnosis and Staging of Lung Cancer	3
José S. Vilar, Jeremy J. Erasmus	
CT Diagnosis and Management of Focal Lung Disease	13
Ioannis Vlahos, Heber MacMahon	
Plain-Film and CT Evaluation of the Adult Mediastinum and Hilum: Pitfalls vs. Disease	19
Sanjeev Bhalla, José Cáceres	
Current Approach to Chronic and Acute Airway Diseases	26
Philippe A. Grenier, Tomas Franquet	
Understanding Diffuse Lung Disease in Children: Rationale for a New Classification System	34
Alan S. Brody	
CT Evaluation of Pediatric Chest in Routine Practice	39
Marilyn J. Siegel	
Imaging of the Chest in the Newborn and Young Infant	47
Janet L. Strife, Veronica Donoghue	
Modern Diagnosis in the Evaluation of Pulmonary Vascular Disease	55
Martine Remy-Jardin, Gerald F. Abbott	
Imaging of Pulmonary Infections	60
Philip Goodman, Helmut Prosch, Daniela Kienzl, Christian J. Herold	
Imaging the Intensive Care Patient	66
Lawrence R. Goodman	
Imaging the Chest Trauma Patient	70
Robert A. Novelline	
Missed Lung Lesions	76
Nigel Howarth, Denis Tack	
Plain Film and HRCT Diagnosis of Interstitial Lung Disease	83
Sujal R. Desai	
HRCT of the Interstitial Lung Diseases: What, Why, and How To	87
Mario Maffessanti, Giorgia Dalpiaz	
A Systematic Approach to Chest X-Ray Analysis, I	96
Jeffrey S. Klein	

A Systematic Approach to Chest X-Ray Analysis, II	99
Katarina Malagari	
Diseases of the Chest Wall, Pleura, and Diaphragm	102
Johny A. Verschakelen, Peter Vock	
Pulmonary Manifestations of Systemic Diseases	108
David A. Lynch, Cornelia Schaefer-Prokop	
Three- and Four-Dimensional Imaging in Acute Aortic Syndrome	117
Dominik Fleischmann, Anne S. Chin, D. Craig Miller	
Clinical Applications of 3D Imaging in Thoracic Vascular Pathology: Pulmonary Vascular Applications	127
Mathias Prokop	
Morphologic Cardiac and Pericardiac Imaging with CT and MRI for the Chest Radiologist	136
Albert De Roos, Didier Revel	
Cardiac Function Imaging for the Chest Radiologist: Computed Tomography	142
Stephan Achenbach	
Cardiovascular Magnetic Resonance	151
Dudley J. Pennell	
The Atherosclerotic Process and Its Relationship to Coronary Blood Flow	162
Dominique Delbeke, Philipp A. Kaufmann	
Imaging Congenital Cardiovascular Disease	168
Lawrence M. Buxt, Lauren M. Sena	
Interventional Techniques in the Thorax of Adults	177
Dierk Vorwerk	
Imaging Breast Disease: Mammography and Breast Ultrasound	184
Edward A. Sickles, Rahel A. Kubik-Huch, Markus Müller-Schimpfle	



Nuclear Medicine Satellite Course “Diamond”

Lymphoma: Differential Diagnosis of Mediastinal Masses and Response	193
Dominique Delbeke	
Myocardial Perfusion Imaging with SPECT-CT	199
Philipp A. Kaufmann	
Staging, Restaging and Response Evaluation of Non-Small-Cell Lung Cancer	203
Jeremy J. Erasmus	
Lung Scintigraphy in Pulmonary Embolism	211
Giuliano Mariani, Laura Bruselli	
PET Imaging in Cardiovascular Disease	217
Markus Schwaiger, Sibylle I. Ziegler, Stephan G. Nekolla	
PET-CT Evaluation of the Pleura and Chest Wall	223
Hans C. Steinert	



Pediatric Satellite Course “Kangaroo”

Abnormal Chest in Children: Other than Pneumonia and Heart Disease	227
Veronica Donoghue	
Pulmonary Infections in Children	231
Silvia Cacaci, Catherine Owens	
Imaging Vascular Anomalies of the Pediatric Chest: Rings, Slings, and Other Things	237
Alan S. Brody	
Airway Obstruction in Children	243
Janet L. Strife	

Breast Imaging Satellite Course

Microcalcifications of the Breast: An Approach to Radiologic Classification	251
Markus Müller-Schimpfle	
Mammography: Asymmetries, Masses, and Architectural Distortion	255
Edward A. Sickles	
Ultrasound of the Breast, Including Interventions: An Update	259
Alexander Munding	
MRI of the Breast: Technique, Indications and BI-RADS Classification	267
Rahel A. Kubik-Huch	

Appendix: Full Color Figures	273

List of Contributors

- Abbott G.F., 55
Achenbach S., 142
Bhalla S., 19
Boxt L.M., 168
Brody A.S., 34, 237
Bruselli L., 211
Cacaci S., 231
Cáceres J., 19
Chin A.S., 117
Dalpiaz G., 87
De Roos A., 136
Delbeke D., 162, 193
Desai S.R., 83
Donoghue V., 47, 227
Erasmus J.J., 3, 203
Fleischmann D., 117
Franquet T., 26
Goodman L.R., 66
Goodman P., 60
Grenier P.A., 26
Herold C.J., 60
Howarth N., 76
Kaufmann P.A., 162, 199
Kienzl D., 60
Klein J.S., 96
Kubik-Huch R.A., 184, 267
Lynch D.A., 108
MacMahon H., 13
Maffessanti M., 87
Malagari K., 99
Mariani G., 211
Miller D.C., 117
Müller-Schimpfle M., 184, 251
Mundinger A., 259
Nekolla S.G., 217
Novelline R.A., 70
Owens C., 231
Pennell D.J., 151
Prokop M., 127
Prosch H., 60
Remy-Jardin M., 55
Revel D., 136
Schaefer-Prokop C., 108
Schwaiger M., 217
Sena L.M., 168
Sickles E.A., 184, 255
Siegel M.J., 39
Steinert H.C., 223
Strife J.L., 47, 243
Tack D., 76
Verschakelen J.A., 102
Vilar J.S., 3
Vlahos I., 13
Vock P., 102
Vorwerk D., 177
Ziegler S.I., 217

WORKSHOPS

Current Concepts in Diagnosis and Staging of Lung Cancer

José S. Vilar¹, Jeremy J. Erasmus²

¹ Hospital Universitario Dr. Peset, Valencia, Spain

² Division of Diagnostic Imaging, MD Anderson Cancer Center, Houston, TX, USA

Introduction

The main issues related to thoracic imaging in evaluating patients with lung cancer are: detection, characterization, staging, treatment assessment, and monitoring for tumor recurrence after treatment. In this chapter we review the diagnosis and staging of non-small-cell lung cancer (NSCLC) with an emphasis on the seventh edition of the tumor node metastasis (TNM) staging system. The advantages and proper use of imaging techniques are stressed, especially in relation to the specific situation of the patient and the needs of the clinician.

Detection of Lung Cancer

Radiologic manifestations of NSCLC can be divided into five major patterns: pulmonary nodule or mass, multiple pulmonary nodules, obstructive phenomena, parenchymal opacities, and lymphadenopathy. These abnormalities can be asymptomatic or can manifest clinically.

1. Preclinical detection: The most common finding related to an asymptomatic patient with NSCLC is the solitary pulmonary nodule (SPN), defined as a single intraparenchymal lesion <3 cm in diameter that is not associated with atelectasis or lymphadenopathy (Fig. 1 a, b). When the lesion is >3 cm, it is defined as a mass. SPNs

are detected serendipitously on chest radiographs or computed tomography (CT) but can also be detected by screening programs for lung cancer. The chance of a pulmonary nodule being a cancer is directly related to the prevalence of the disease, (pretest probability) and thus is much higher in high-risk groups such as heavy cigarette smokers.

2. Clinical manifestations of NSCLC: Local clinical manifestations such as chest pain and hemoptysis are related to invasion of the airways, lung, chest wall, and mediastinum. Invasion or narrowing of an airway by an endobronchial lesion or extrinsic compression gives rise to atelectasis and pneumonitis. Distant disease (metastases) can manifest with symptoms related to the organ involved and less frequently as a paraneoplastic syndrome.

Role of Imaging in Detecting Lung Cancer

The role of imaging is to detect NSCLC at an early stage. Chest radiographs have limitations and may miss small lesions, especially in blind areas such as the upper lobes, the retrosternal region, and behind the heart (Fig. 2) [1]. CT detects more nodules, but some can be overlooked due to small size, low density, or location near other parenchymal abnormalities or in the lower lobes. Post-processing and especially maximum intensity projection (MIP) images can improve nodule detection [2].

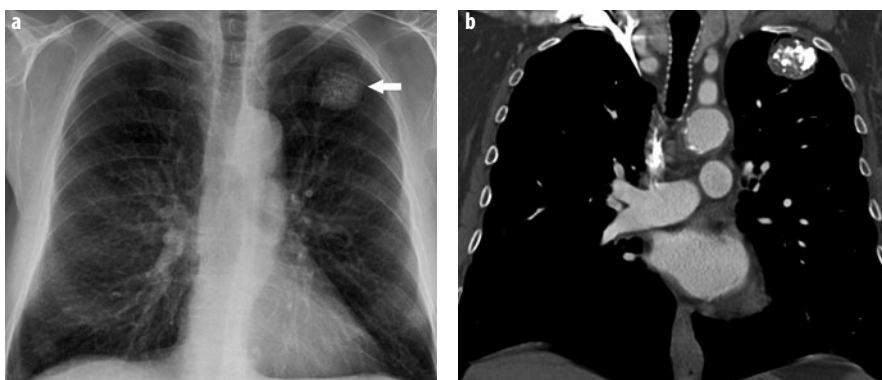


Fig. 1 a, b. Hamartoma in a 48-year-old man: **a** Chest radiograph shows a 2-cm pulmonary nodule in the left upper lobe (arrow). Note punctate calcification. **b** Coronal computed tomography reveals multiple “popcorn” calcifications in the nodule

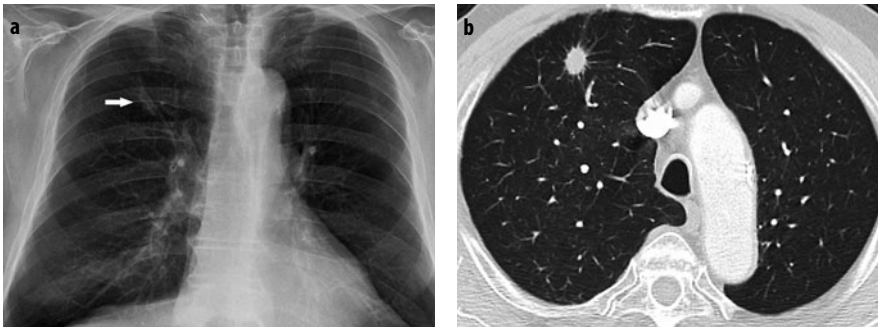


Fig. 2 a, b. Epidermoid carcinoma: **a** Chest radiograph shows a subtle focal opacity (arrow) of uncertain location and etiology. **b** Computed tomography reveals a right upper lobe nodule with irregular spiculated borders. Note spiculation is typical for primary lung malignancy

Detecting lung cancer can be incidental, by screening, or when the lesion has caused symptoms. Low-dose CT is more sensitive than chest radiographs for detecting early lung cancer.

Characterization of a Pulmonary Nodule

Previous chest radiographs or CT, if available, may suffice in characterizing a nodule as benign if there is stability in size for >2 years. However, occasionally, nodules can remain stable for >2 years due to very slow growth rates and ultimately prove to be indolent neoplasms, especially in cases of adenocarcinomas. Absence of prior studies or signs of radiologic change are indications for CT evaluation in order to better characterize an SPN. Growth, density, size, morphology, and contrast uptake are the main parameters of an SPN that should be analyzed with CT. Positron emission tomography (PET) can provide useful information about the metabolic behavior of the nodule.

Growth

Growth can be estimated by evaluating consecutive studies. Extremely rapid and or very slow duplication times are generally inconsistent with malignancy. Volume-doubling times (approximately a 25% increase in diameter) between 20 and 400 days have been reported with NSCLC. Volume doubling times <20-30 days are suggestive of an infectious or inflammatory etiology but can occur with lymphoma or rapidly growing metastases, whereas doubling times >400 days are usually associated with benign lesions [2-5].

Density

The presence of fat in a pulmonary nodule or mass indicates benignity, usually a hamartoma or, less frequently, lipoid aspiration pneumonia. Characteristic patterns of benign calcification are central (involving >10% of cross-sectional area of nodule), diffuse, and laminated and are usually indicative of prior granulomatous disease. Popcorn-type calcification is typically due to the chondroid tissue in pulmonary hamartomas (Fig. 1) but can be seen in carcinoid tumors. The presence of calcium

does not exclude the diagnosis of cancer and has been reported to occur in up to 6% of lung cancers. Generally, this calcification is amorphous, or if focal, is not central in location or forms only a small portion of the nodule. Central calcification or >50% of calcification of a nodule indicates benignity [6]. Nonsolid or partly solid nodules are more often malignant, being most commonly adenocarcinomas with bronchioloalveolar features or true bronchioloalveolar cell carcinomas [7].

Morphology

Signs of malignancy are irregular and spiculated margins and the presence of an air bronchogram. This latter sign is more frequently associated with adenocarcinomas and bronchioloalveolar cell carcinomas (Fig. 3) [8].

Contrast Uptake

Due to neovascularity, malignant nodules typically demonstrate more intense enhancement than benign nodules. The absence of significant lung nodule enhancement



Fig. 3. Bronchioloalveolar cell carcinoma: Chest computed tomography shows a left lower lobe nodule with a small branching air bronchogram

on CT has a strong negative predictive value. Using a threshold increase of 15 HU, contrast-enhanced CT has a sensitivity of 98%, and a specificity of 58% for malignancy [9]. False positive results can occur with active infectious or inflammatory lesions. Similar results can be obtained with contrast enhanced MRI [10].

Positron Emission Tomography

PET using the radiopharmaceutical [^{18}F]-2-deoxy-D-glucose (FDG), a D-glucose analog labeled with fluorine-18, compliments conventional radiologic assessment of an SPN. The reported sensitivity and specificity of PET for malignant pulmonary lesions is 97% and 78%, respectively. The spatial resolution of PET scanners is in the range of 6 mm; therefore, smaller lesions should not be evaluated with PET imaging. False negative results for malignancy include slow-growing cancers, especially bronchioloalveolar carcinomas and carcinoid tumors. False positive results are most commonly caused by infections and inflammatory processes, including Wegener's granulomatosis, sarcoidosis, organizing pneumonia, amyloid, and rheumatoid nodules [11].

Pulmonary nodules can be characterized according to growth, density, morphology, contrast uptake, and metabolic activity. Standard imaging protocols based on the pretest probability (risk) should be used to rule out malignancy (Table 1).

Staging of Lung Cancer

The anatomic extent of disease in a patient with NSCLC is a prognostic indicator and also determines appropriate treatment. Clinical staging of lung cancer has improved due to the improved capacity of new imaging techniques

to define anatomy and tissue abnormalities. Despite this, many cases are either over- or understaged [12]. The problem with improper staging is that treatment may be suboptimal or inappropriate. Surgical resection is typically performed in patients with limited disease. However, because surgical resection is associated with morbidity and mortality, an important role of radiologic staging is to avoid unnecessary resection. A careful description of the imaging findings, especially tumor size and extension, are of primary importance for the surgeon and radiation oncologist as well as for monitoring therapy. T staging is typically performed with CT and/or magnetic resonance imaging (MRI) [13]. PET/CT has an increasing role in staging, particularly for detecting nodal (N staging) and distant metastasis (M staging). The newly adopted seventh edition of the TNM staging system allows a more precise definition of tumor stage and consequently the most appropriate treatment. Accordingly, it is important for radiologists to be aware of the implemented modifications in the manual [14].

T Staging

The T status defines the size, location, and extent of the primary tumor (Table 1). There are numerous changes to the T descriptor in the seventh edition of the TNM classification of lung cancer that are based on differences in survival. The classification combines the T descriptors with the N and M descriptors into subsets or stages that have similar treatment options and prognoses. However, it is important to realize that although a T4 descriptor generally precludes resection, patients with cardiac, tracheal, and vertebral-body invasion are designated in the seventh edition staging system as being potentially resectable in the absence of N2 and/or N3 disease.

The following parameters must be analyzed regarding T staging: (1) size, (2) location, (3) extension.

1. Tumor size: Tumor size is a determinant for T staging and essential to define surgical and radiotherapy strategies as well as to evaluate response to treatment. In the seventh edition of the TNM classification, size is a significant parameter related to survival. T1 is now subclassified as T1a (<2 cm) or T1b (>2 cm to <3 cm); T2 is now subclassified as T2a (>3 cm to <5 cm or T2 by other factor and <5 cm) or T2b (>5 cm to <7 cm); tumors previously classified as T2 >7 cm are reclassified as T3. Size is usually measured on CT or MRI. On CT, lung window settings should be used, as mediastinal windowing may underestimate the size. Volumetric assessment may, in the future, replace the actual Response Evaluation Criteria In Solid Tumors (RECIST) that use the largest diameter of the lesion.
2. Tumor location: Tumor location is important in that it provides information to surgeons and radiation oncologists that can affect therapeutic management. For instance, centrally located tumors close to the spinal cord impose radiation dose-volume constraints, and deter-

Table 1. Follow-up protocols for pulmonary nodules (from [3])

Nodule size (mm)	Low-risk individuals	High-risk individuals
<4	No follow-up	Follow-up at 12 months; if no change, no further follow-up
>4-6	Follow-up at 12 months; if no change, no further follow-up	Follow-up CT at 6-12 months; if no change, follow-up at 18-24 months
>6-8	Follow-up at 6-12 months then at 12-24 months if no change	Follow-up CT at 3-6 months; if no change, follow-up at 9-12 months and then at 24 months if no change continues
>8	Follow-up at 3, 9, and 24 months, dynamic PET-CT and/or biopsy	

CT, computed tomography; PET, positron emission tomography

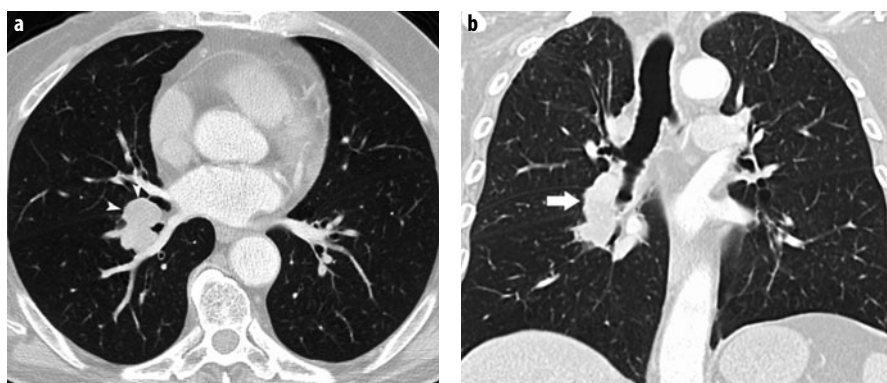


Fig. 4 a, b. Epidermoid carcinoma: **a** Axial computed tomography (CT) shows a lobular mass in the lower lobe with extension through the major fissure (arrowheads). **b** Coronal CT shows extension of the mass through the major fissure (arrow)

mining tumor margins is important as they can affect radiotherapy delivery. This is especially important with the increasing use of conformal radiation therapy, a technique that uses multiple radiation beams to generate dose distributions that conform tightly to target volumes. The relation of the tumor to a fissure must be reported, as it may imply a change in surgical technique (pneumonectomy instead of lobectomy) when there is evidence that the lesion crosses the fissure (Fig. 4). The proximity to a main pulmonary artery can also involve a change in surgical approach [15].

3. Tumor extension: Patterns of tumor propagation can be divided into local and distant extension. Local extension is included in the T staging, whereas distant metastases relate to the M staging. In the new staging system, pleura involvement has been upgraded from T4 to M1a, whereas additional pulmonary nodules in the same lobe are classified as T3 instead of T4, and nodules in other lobes are T4 instead of M1. The determination of the degree of pleural, chest-wall, and mediastinal invasion, as well as central airways, pulmonary veins, and artery involvement, is also important not only to radiation oncologists but to surgeons evaluating the tumor for resectability. For instance, pulmonary artery involvement may require a pneumonectomy rather than a lobectomy in order to obtain clear surgical margins. Additionally, involvement of the origin of the lobar bronchus or main bronchus may require a sleeve resection or pneumonectomy. Thoracic wall invasion does not preclude surgery but must be reported to the surgeon to ensure appropriate surgical resection, typically en bloc resection of the chest wall.

Role of Imaging in T Staging

CT and MRI have limitations in evaluating chest-wall and mediastinal invasion (Fig. 5) by NSCLC. However, MRI is particularly useful in evaluating cardiac invasion and assessing superior sulcus tumors. In these tumors, MRI provides information about the degree of involvement of the brachial plexus, subclavian vessels, and vertebral bodies (Fig. 6) [14]. Importantly, absolute contraindications to



Fig. 5. Non-small-cell lung cancer with chest-wall invasion. Chest computed tomography shows invasion of the chest wall disrupting the extrapleural fat

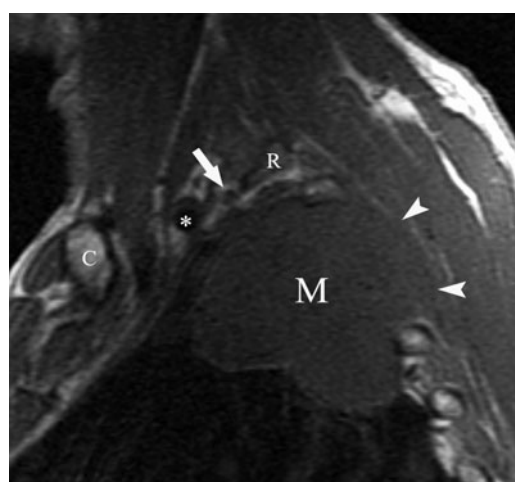


Fig. 6. Superior sulcus tumor in a 62-year-old man presenting with periscapular pain and numbness. Sagittal T1-weighted magnetic resonance shows a mass (M) in the right upper lobe. The lowest portion (T1 nerve root) of the brachial plexus (arrow) is not involved by the tumor. There is extension of the mass into the soft tissues of the thorax posteriorly (arrowheads) associated with destruction of the adjacent rib. C clavicle, R first rib, *subclavian artery

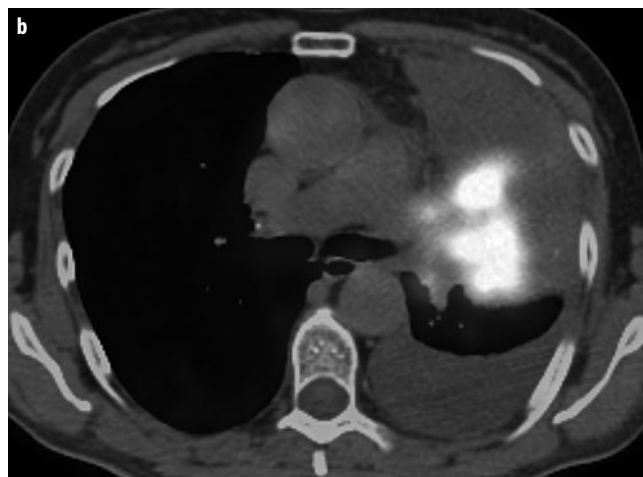
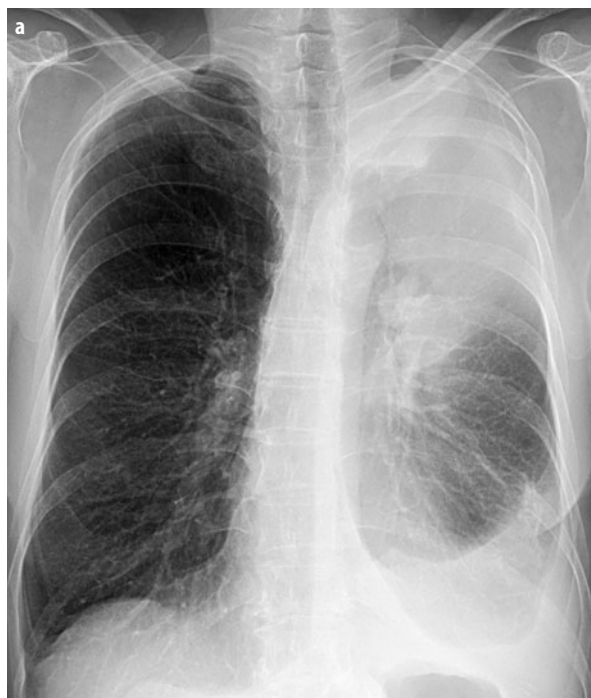


Fig. 7 a, b. Non-small-cell lung cancer with complete atelectasis of the left upper lobe. **a** Chest radiograph shows a left perihilar mass and complete atelectasis of the left upper lobe. Note left pleural effusion. **b** Fused positron emission tomography computed tomography (PET-CT) shows the [^{18}F]-2-deoxy-D-glucose-avid left upper lobe tumor and the distal atelectatic lung. Note PET-CT can assist the radiation oncologist in radiation treatment planning by delineating the primary tumor (for color reproduction see p 273)

surgery (invasion of the brachial plexus roots or trunks above the T1 level; invasion >50% of a vertebral body; invasion of the esophagus or trachea) are often accurately assessed by MRI [15, 16].

PET/CT can be useful in T staging in some situations. For instance, when there is distal atelectasis and the tumor cannot be separated from the atelectatic lung on CT, PET images can usually distinguish both atelectasis and tumor. Gerbaudo et al. reported a higher FDG uptake in atelectatic lung but always lower than the tumor (Fig. 7) [17]. Another indication for PET/CT is suspected pleural metastases when they are not well depicted on CT (Fig. 8) [18]. Also, the reported indication of PET/CT in lung cancer is localization of the most adequate area for biopsy, thus avoiding negative samples due to necrosis.

T staging has been modified in the seventh edition of the TNM staging system. Tumor size, location, and extension are the fundamental T-staging parameters. The radiologist must have a thorough knowledge of the anatomic implications of the T stage in relation to surgery, radiotherapy, and chemotherapy. CT and MRI play a fundamental role in T staging. PET/CT is an additional tool in some specific situations.

N Staging

The presence and location of nodal metastasis are of major importance in determining management and prognosis in patients with NSCLC. To enable a consis-

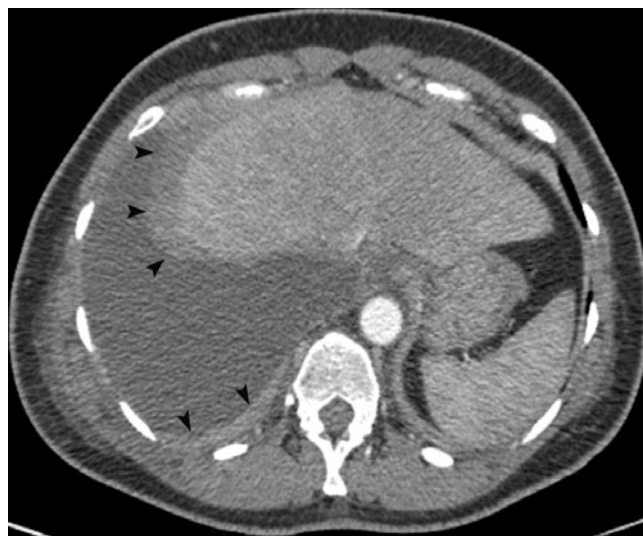


Fig. 8. Malignant pleural effusion in a 52-year-old woman with non-small-cell lung cancer. Contrast computed tomography shows enhancement and thickening of the pleura due to metastases (arrowheads)

tent and standardized description of N status, nodal stations are defined by the American Thoracic Society. The N descriptors in the seventh edition of the TNM classification of lung cancer have been maintained, as there is no significant survival difference in analysis by station (Fig. 9) [19, 20]. However, lymph node stations are now grouped together in six zones in the current N1 and N2 patient subsets for further evaluation. Zones are

 International Association for the Study of Lung Cancer TNM Descriptors	
T – Primary Tumour	
TX	Primary tumour cannot be assessed, or tumour proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)
T1a	Tumour 2 cm or less in greatest dimension ¹
T1b	Tumour more than 2 cm but not more than 3 cm in greatest dimension
T2	Tumour more than 3 cm but not more than 7 cm; or tumour with <i>any</i> of the following features ² :
	• Involves main bronchus, 2 cm or more distal to the carina
	• Invades visceral pleura
	• Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a	Tumour more than 3 cm but not more than 5 cm in greatest dimension
T2b	Tumour more than 5 cm but not more than 7 cm in greatest dimension
T3	Tumour more than 7 cm or one that directly invades any of the following: chest wall (including superior sulcus tumours), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumour in the main bronchus less than 2 cm distal to the carina ¹ but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumour nodule(s) in the same lobe as the primary.
T4	Tumour of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina; separate tumour nodule(s) in a different ipsilateral lobe to that of the primary.
N – Regional Lymph Nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
M – Distant Metastasis	
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumour nodule(s) in a contralateral lobe; tumour with pleural nodules or malignant pleural or pericardial effusion ³
M1b	Distant metastasis

Notes:

¹The uncommon superficial spreading tumour of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1a.

²T2 tumours with these features are classified T2a if 5 cm or less or if size cannot be determined, and T2b if greater than 5 cm but not larger than 7 cm.

³Most pleural (pericardial) effusions with lung cancer are due to tumour. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumour, and the fluid is non-bloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumour, the effusion should be excluded as a staging element and the patient should be classified as M0.

Fig. 9. Descriptions of malignant lung tumors, nodes, and metastases for classification purposes. Reprinted with permission courtesy of the International Association for the Study of Lung Cancer. Copyright 2009 IASLC (for color reproduction see p 273)

defined as peripheral (stations 12, 13, 14), or hila (stations 10, 11) for N1; and upper mediastinal (stations 1, 2, 3, 4), lower mediastinal (stations 8, 9), aortopulmonary (stations 5, 6), and subcarinal (station 7) for N2 nodes (Fig. 10) [19, 20].

Because surgical resection and potential use of adjuvant therapy are dependent on the patient's N descriptor, detecting nodal metastases is important. In this regard, ipsilateral peribronchial or hilum (N1) nodes are usually resectable, and the presence of mediastinal adenopathy has a major impact on resectability. Specifically, ipsilateral mediastinal or subcarinal adenopathy (N2) may be resectable (usually after induction chemotherapy), whereas contralateral mediastinal adenopathy and scalene or supraclavicular adenopathy (N3) are unresectable. Detecting nodal metastases is also important to the radiation oncologist, as incorporation of these nodes into the radiation treatment plan is imperative for appropriate treatment.

Role of Imaging in N Staging

In the imaging evaluation of nodal metastasis, size is the only criterion used to diagnose nodal metastases, with nodes >10 mm in short-axis diameter considered abnormal.

Chest radiographs are neither sensitive nor specific in evaluating nodal metastases. CT and MRI are better in this regard, but because enlarged nodes can be hyperplastic and small nodes can contain metastases, the accuracy of CT and MR imaging in detecting metastases to hilar and mediastinal nodes is not optimal [21]. PET using [¹⁸F]-FDG can improve the detection rate of nodal metastases (Fig. 11). In a recent meta-analysis (17 studies, 833 patients) comparing PET and CT in nodal staging in patients with NSCLC, sensitivity and specificity of FDG-PET for detecting mediastinal lymph node metastases ranged from 66% to 100% (overall 83%) and from 81% to 100% (overall 92%), respectively, compared with sensitivity and specificity of CT of 20-81% (overall 59%) and 44-100% (overall 78%), respectively [22]. Improved sensitivity (89%), specificity (94%), and accuracy (93%) of regional lymph node staging has been reported using integrated PET/CT scanners that allow acquisition of coregistered, spatially matched, functional and morphologic data [23]. Current recommendations for FDG-PET imaging are that it should be performed in patients with no CT findings of nodal metastatic disease to corroborate CT findings when there are no distant metastasis (M0) or to redirect nodal sampling by identifying an otherwise undetected site of metastasis.

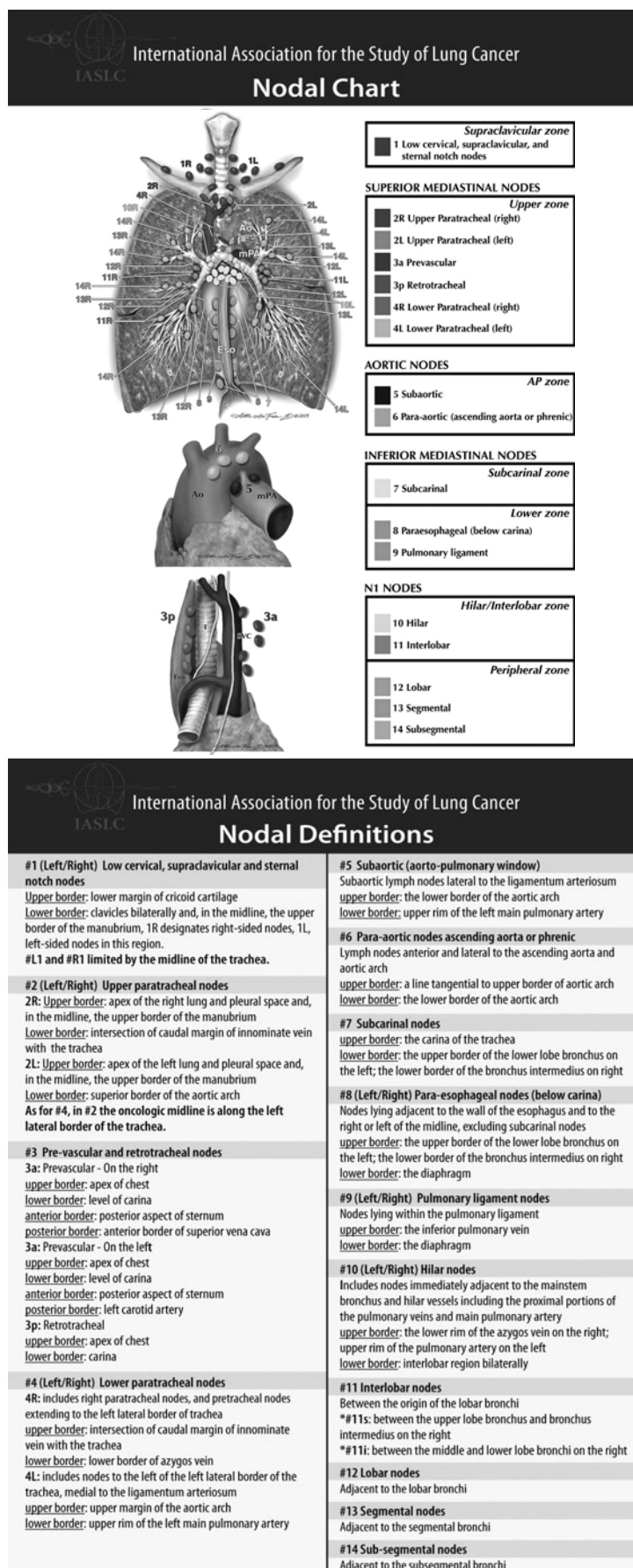


Fig. 10. Positions and descriptions of malignant lung nodes. Reprinted with permission courtesy of the International Association for the Study of Lung Cancer. Copyright 2009 IASLC and © 2008 Aletta Ann Frazier (for color reproduction see p 273)



Fig. 11 a-c. Nodal metastasis in a 78-year-old man with non-small-cell lung cancer. **a, b** Chest computed tomography (CT) shows a large left lower lobe mass and a normal-sized (short axis diameter <1 cm) right lower paratracheal lymph node (*arrow in b*). **c** Fused positron emission tomography CT (PET-CT) reveals increased [^{18}F]-2-deoxy-D-glucose uptake in the right paratracheal node. Mediastinoscopy confirmed nodal metastasis. Note that because N3 (contralateral mediastinal) nodal metastasis is nonresectable, the patient was treated palliatively (for color reproduction see p 273)

N staging has not been modified in the seventh edition of the TNM staging system. The location of nodal metastasis is of major importance in determining management. Ipsilateral hilar (N1) nodes are resectable, ipsilateral mediastinal or subcarinal adenopathy (N2) may be resectable (usually after induction chemotherapy), and contralateral mediastinal adenopathy and scalene or supraclavicular adenopathy (N3) are unresectable.

M Staging

Patients with NSCLC commonly have metastases to the lung, adrenals, liver, brain, bones, and extrathoracic lymph nodes at presentation. There are numerous changes to the M descriptor in the seventh edition of the TNM classification that are based on differences in survival (Table 1). The M1 descriptor is now subclassified into M1a (additional nodules in the contralateral lung) and M1b (distant metastases outside the lung and pleura) [23]. Additionally, the current M descriptor is modified to reclassify pleural metastases (malignant pleural effusions, pleural nodules) from T4 to M1a (Fig. 12) [24].

Role of Imaging in M Staging

Detecting metastases is important to determine whether the patient will be a candidate for surgical resection or will receive palliative radiation and chemotherapy. For instance, the diagnosis of a malignant pleural effusion or pleural metastases is important in patient management because these metastases preclude surgical resection. However, although patients with NSCLC commonly have metastases at presentation, the role of imaging in detecting these metastases is not clearly defined. Usually, chest CT that includes the adrenal glands is performed to detect metastases. The imaging performed to detect occult metastases to other organs, such as the brain and bones, is more variable and is discussed below. Generally, CT is the primarily modality used to diagnosis and characterize intra-abdominal lesions, and a confident diagnosis of



Fig. 12. Malignant pleural effusion in an 86-year-old woman with non-small-cell lung cancer. Coronal positron emission tomography computed tomography (PET-CT) shows a large left pleural effusion and diffuse [^{18}F]-2-deoxy-D-glucose (FDG)-avid pleural metastasis (*arrowheads*). Note enlarged and FDG-avid mediastinal nodal metastasis (*asterisk*) (for color reproduction see p 273)

benignity or malignancy is frequently possible. For instance, if an adrenal mass contains fat or has an attenuation value <10 Hounsfield units (HU) on a noncontrast CT scan, the mass can be considered benign without the need for MR imaging or biopsy [25]. Routine CT or MR imaging of the central nervous system has also been advocated,

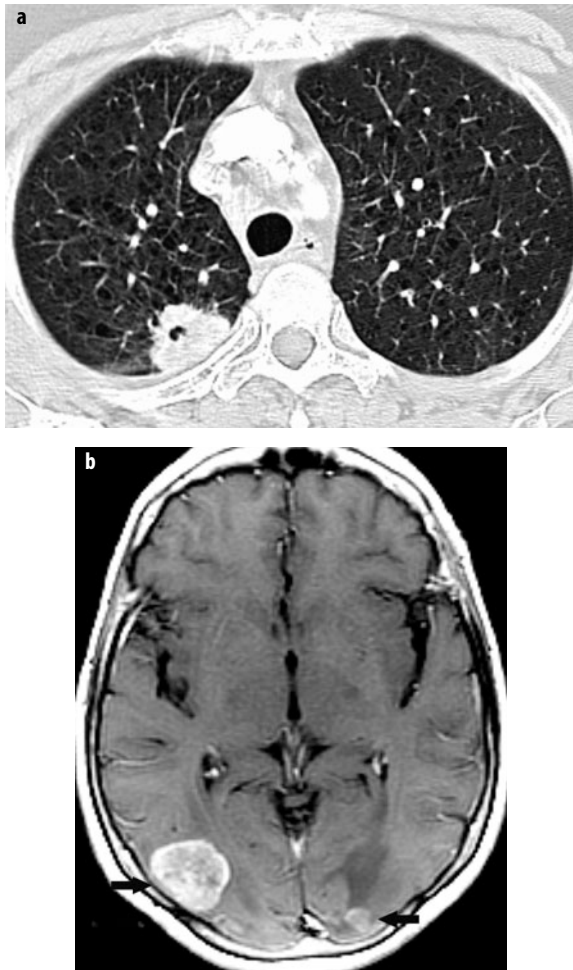


Fig. 13 a, b. Brain metastases in a 63-year-old woman with non-small-cell lung cancer who presented with cough, headache, hypertension, and abnormal gait. **a** Chest computed tomography (CT) shows a cavitary mass in the right upper lobe. **b** Contrast brain CT shows bilateral metastases and peritumoral edema (arrows)

because up to 18% of patients with NSCLC have brain metastases at presentation (Fig. 13). However, these metastases are usually associated with neurologic signs and symptoms, and if the patient is asymptomatic, imaging of the brain is frequently not performed. Similarly, imaging rarely reveals occult skeletal metastases and therefore bone radiographs, technetium 99mTc (technetium)-labeled methylene diphosphonate bone scintigraphy, and MRI are usually only performed if the patient has focal bone pain or an elevated alkaline phosphatase level.

Because NSCLC staging performed on the basis of symptoms, laboratory findings, and conventional radiologic imaging can be inaccurate, whole-body PET using FDG is being used to improve staging accuracy. FDG-PET has a higher sensitivity and specificity than CT in detecting metastases to the adrenal glands, bones, and extrathoracic lymph nodes. Whole-body PET imaging stages intra- and extrathoracic disease in a single study and is useful for detecting occult extrathoracic metastases (Fig. 14) [26, 27].



Fig. 14 a-c. Adrenal and intramuscular metastases in a 49-year-old woman with non-small-cell lung cancer presenting with right leg mass and pain. **a** Chest radiograph shows a large right upper lobe mass. **b** Computed tomography (CT) shows a right adrenal nodule and large heterogeneous left adrenal mass (arrows). **c** Coronal whole-body fused positron emission tomography CT (PET-CT) shows increased [^{18}F]-2-deoxy-D-glucose uptake in primary right upper lobe malignancy (M), bilateral adrenal metastases (asterisks), and intramuscular metastasis in the right thigh (arrow) (for color reproduction see p 273)

It is important to note that the incidence occult metastases detection has been reported to increase as T and N staging descriptors increase, i.e., 7.5% in early stage disease to 24% in advanced disease [28]. Two recent studies of patients with NSCLC considered resectable by standard conventional imaging showed that PET imaging prevented nontherapeutic surgery in one in five patients [25, 26]. However, a randomized controlled trial of the role of PET in early stage lung cancer (>90% of patients with T1-2N0) showed that distant metastases were rarely detected (<2.5%), although PET improved staging accuracy and led to more age-specific therapy [29].

M staging has been modified in the seventh edition of the TNM staging system. M1 descriptor is now subclassified into M1a (additional nodules in the contralateral lung, malignant pleural effusions, pleural nodules) and M1b (distant metastases outside the lung and pleura). M disease precludes resection in most cases. CT is usually used to detect metastases. PET is useful for detecting occult nodal and extrathoracic metastases and improves staging accuracy.

References

- Shah PK, Austin JH, White CS et al (2003) Missed non small cell lung cancers: radiographic findings of potentially resectable lesions evident only in retrospect. *Radiology* 226:235-241
- Girvin F, Ko JP (2008) Pulmonary nodules: detection, assessment, and CAD. *AJR Am J Roentgenol* 191:1057-1069
- MacMahon H, Austin JH, Gamsu G et al (2005) Guidelines for management of small pulmonary nodules detected on CT scans: a statement from the Fleischner Society. *Radiology* 237:395-400
- Nathan MH, Collins VP, Adams RA (1962) Differentiation of benign and malignant pulmonary nodules by growth rate. *Radiology* 79:221-232
- Beigelman-Aubry C, Hill C, Grenier PA (2007) Management of incidentally discovered pulmonary nodule. *Eur Radiol* 17:449-466
- Mahoney MC, Shipley RT, Corcoran HL, Dickson BA (1990) CT demonstration of calcification in carcinoma of the lung. *AJR Am J Roentgenol* 154:255-258
- Henschke CI, Yankelevitz DF, Mirtcheva R et al (2002) CT screening for lung cancer: frequency and significance of part-solid and nonsolid nodules. *AJR Am J Roentgenol* 178:1053-1057
- Kui M, Templeton PA, White CS et al (1996) Evaluation of the air bronchogram sign on CT in solitary pulmonary lesions. *J Comput Assist Tomogr* 20:983-986
- Swensen SJ, Silverstein MD, Ilstrup DM et al (1997) The probability of malignancy in solitary pulmonary nodules: application to small radiologically indeterminate nodules. *Arch Intern Med* 157:849-855
- Schaefer JS, Vollmar J, Schick F et al (2004) Solitary pulmonary nodules: dynamic contrast-enhanced MR imaging – perfusion differences in malignant and benign lesions. *Radiology* 232:544-553
- Gould MK, Maclean CC, Kuschner WG et al (2001) Accuracy of positron emission tomography for diagnosis of pulmonary nodules and mass lesions: a meta-analysis. *JAMA* 285:914-924
- Cetinkaya E, Turna A, Yildiz P et al (2002) Comparison of clinical and surgical-pathologic staging of the patients with non-small cell lung carcinoma. *Eur J Cardiothorac Surg* 6:1000-1005
- Maziak DE, Darling GE, Inculet RI et al (2009) Positron emission tomography in staging early lung cancer. *Ann Intern Med* 151:221-228
- Goldstraw P, Crowley JJ (2006) The International Association for the Study of Lung Cancer: International Staging Project on Lung Cancer. *J Thorac Oncol* 1:281-286
- Munden R, Swisher S, Stevens C, Stewart D (2005) Imaging of the patient with non-small cell lung cancer. *Radiology* 237:803-818
- Bruzzi J, Komaki R, Walsh GL et al (2008) Imaging of non-small cell lung cancer of the superior sulcus: Part 2: initial staging and assessment of resectability and therapeutic response. *RadioGraphics* 28:561-572
- Gerbaudo VH, Julius B (2007) Anatomic-metabolic characteristics of atelectasis in F-18 FDG-PET/CT imaging. *Eur J Radiol* 64:401-405
- Schaffler GJ, Wolf G, Schoellnast H et al (2004) Non small cell lung cancer: evaluation of pleural abnormalities on CT scans with 18F FDG PET. *Radiology* 231:858-865
- Rusch VW, Crowley J, Giroux DJ et al (2007) The IASLC Lung Cancer Staging Project: proposals for the revision of the N descriptors in the forthcoming seventh edition of the TNM classification for lung cancer. *J Thorac Oncol* 2:603-612
- Peter Goldstraw (ed) (2009) The IASLC Staging Reference Card in Thoracic Oncology. Editorial Rx Press, Orange Park, FL
- McCloud TC, Bourgouin PM, Greenberg RW et al (1992) Bronchogenic carcinoma: analysis of staging in the mediastinum with CT by correlative lymph node mapping and sampling. *Radiology* 182:319-323
- Birim O, Kappetein AP, Stijnen T, Bogers AJ (2005) Meta-analysis of positron emission tomographic and computed tomographic imaging in detecting mediastinal lymph node metastases in nonsmall cell lung cancer. *Ann Thorac Surg* 79:375-382
- Antoch G, Statta J, Nemat AT et al (2003) Non-small cell lung cancer: dual-modality PET/CT in preoperative staging. *Radiology* 229:526-533
- Postmus PE, Brambilla E, Chansky K et al (2007) The IASLC Lung Cancer Staging Project: proposals for revision of the M descriptors in the forthcoming (seventh) edition of the TNM classification of lung cancer. *J Thorac Oncol* 2:686-693
- Mayo-Smith WW, Boland GW, Noto RB, Lee MJ (2001) State-of-the-art adrenal imaging. *Radiographics* 21:995-1012
- Reed CE, Harpole DH, Posther KE et al (2003) Results of the American College of Surgeons Oncology Group Z0050 trial: the utility of positron emission tomography in staging potentially operable non-small cell lung cancer. *J Thorac Cardiovasc Surg* 126:1943-1951
- van Tinteren H, Hoekstra OS, Smit EF et al (2002) Effectiveness of positron emission tomography in the preoperative assessment of patients with suspected non-small-cell lung cancer: the PLUS multicentre randomised trial. *Lancet* 359:1388-1393
- MacManus MP, Hicks RJ, Matthews JP et al (2001) High rate of detection of unsuspected distant metastases by PET in apparent stage III non-small-cell lung cancer: implications for radical radiation therapy. *Int J Radiat Oncol Biol Phys* 50:287-293
- Viney RC, Boyer MJ, King MT et al (2004) Randomized controlled trial of the role of positron emission tomography in the management of stage I and II non-small-cell lung cancer. *J Clin Oncol* 22:2357-2362

CT Diagnosis and Management of Focal Lung Disease

Ioannis Vlahos¹, Heber MacMahon²

¹ St. George's Hospital, London, UK

² University of Chicago, Chicago, IL, USA

Introduction

The diagnosis of focal pulmonary opacities remains challenging. Compared with chest radiography, computed tomography (CT), supplemented by thin-section or high-resolution CT (HRCT) imaging, enables better determination of the characteristics of individual lesions. Focal opacities can be broadly categorised as nodules, masses scars or focal parenchymal airspace disease.

Nodules, Masses and Scars

Nodules are characterised as spherical, well-defined opacities measuring <3 cm. In practice, ill-defined or irregular nodules are included in the category of nodules, although more appropriately these should be considered nodular opacities. CT offers better categorisation of nodules and masses by enabling evaluation of density and contour morphometry. In practice, CT densitometry is only part of the evaluation of these abnormalities, which might include specific CT techniques to determine enhancement (nodule enhancement studies, dual-energy CT), follow-up imaging to verify evolution, positron emission tomography (PET)-CT to assess physiological activity and ultimately fine-needle aspiration or biopsy.

Benign Solid Nodule Features

The principle application of CT with regard to a solitary pulmonary nodule is determining whether these have specific benign density characteristics that include the identification of intralesional calcification or fat. Identifying these materials is aided by the use of thin-section contiguous images (1-3 mm) through nodules of interest, preferably performed with a targeted reconstruction of the nodule itself (field of view 10-12 cm). Although bulk fat may be evident on visual inspection alone, fat measurements with this technique should be less than -30 to -40 HU and often are as low as -150 HU. Measurements should be performed using a suitably sized region of interest (ROI) that encompasses an area that is still within the nodule on the slice above and the slice below

the measured slice. This reduces the risk of an erroneously low measurement due to partial volume average effects of the adjacent low-density lung parenchyma. The use of pixel mapping to identify voxels with HU <0 is a technique that was more applicable to thicker-section CT to compensate for the partial volume average effects of more solid parts of the nodule and is no longer advocated in the era of isotropic data CT acquisition. There is no absolute HU measurement that confirms calcification, although measurements >200 are usually related to pixels occupied by calcific material. Visual comparison with other thoracic osseous structures is considered sufficient for determining the calcific nature of lesions.

Central, lamellated or popcorn-type calcification is diagnostic of a benign lesion. The presence of central or lamellated calcification is usually indicative of granulomatous disease (Fig. 1). The presence of fat or popcorn calcification is diagnostic of a pulmonary hamartoma (Fig. 2). It is important that the calcification's central location be confirmed on coronal or sagittal images, as the eccentric nature of calcification is often only noted in these planes. Eccentric calcification is most often also benign and related to granulomatous disease; however, occasionally, eccentric calcification may reflect a small granuloma that has become engulfed within an enlarging adjacent neoplasm. Dystrophic or stippled calcifications are well known to occur within carcinoid lesions, non-small-cell carcinoma and small-cell carcinoma lesions and hence are not a helpful discriminator between benign and malignant nodules.

Other morphological features associated with benign lesions include a polygonal, elongated (length: width ratio >2), elliptical, linear or plaque-like shape, particularly when related to fissures or pleural surfaces. Indeed, by definition, such lesions are not all strictly nodules and are best characterised as scars. Ellipsoid-shaped nodules in the upper lobes are occasionally due to benign intrapulmonary lymph nodes. These findings are reported with variable incidence by pathologists and similarly with variable incidence and confidence by radiologists. The confident accurate diagnosis of this entity requires an upper-lobe location and an elongated nodule aligning lengthwise along typical lymphatic locations, such as fissures or bronchi of the central axial interstitium.

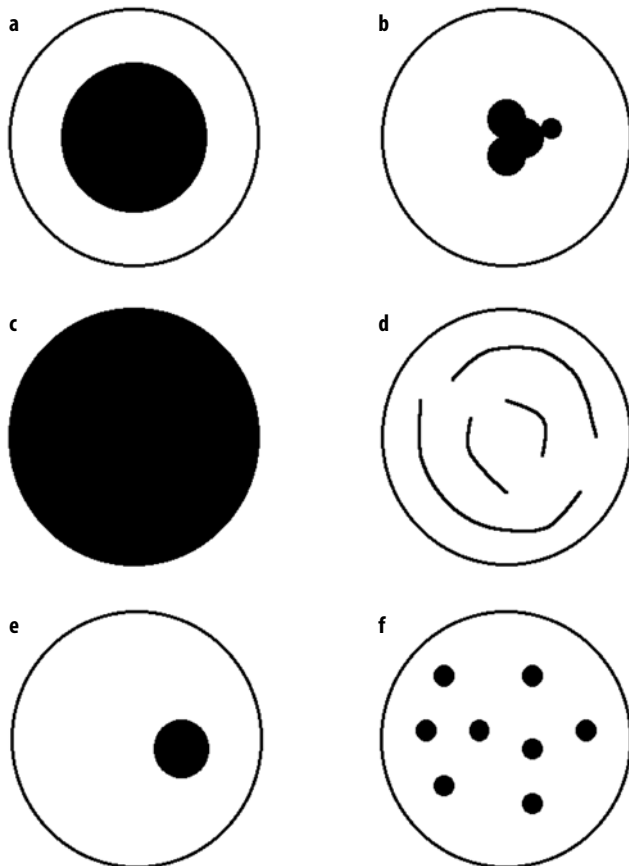


Fig. 1 a-f. Types of calcification. Benign: **a** central, **b** central multifocal, **c** uniform, **d** lamellar. Indeterminate: **e** eccentric, **f** stippled



Fig. 2. Pulmonary hamartoma. Intralesional fat and popcorn calcification

Malignant Solid Nodule Features

Specific features of malignancy are more common in larger nodules but relatively uncommon in nodules <1 cm. Spiculation, microlobulation, pleural tags, satellite nodules and the presence of a bronchus leading directly into

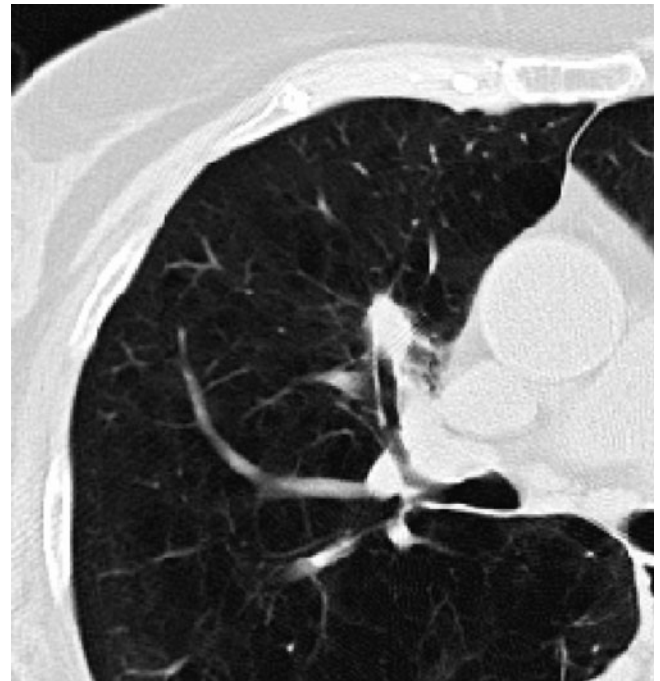


Fig. 3. Computed tomography bronchus sign; lung adenocarcinoma

a nodule (CT bronchus sign) (Fig. 3) are associated with a high probability of neoplastic disease, although occasionally, they are also seen in inflammatory or infectious diseases, including mycobacterial disease. The presence of cavitation can be seen in both neoplastic and benign infectious disease (including bacterial, mycobacterial and fungal) and inflammatory diseases (e.g. vasculitides, Langerhans cell histiocytosis). The appearance of thicker-walled cavities on chest radiographs has historically been described as a feature favouring neoplasia [1]. However, CT evaluation of nodule wall thickness or masses does not corroborate this earlier radiographic interpretation [2].

CT Nodule Enhancement Studies

Evaluating the physiology of a solid lung nodule may be of assistance in determining whether the lesion is benign or malignant. Nodule enhancement studies are performed using noncontrast acquisition at 120 kVp through the lesion, followed by repeated postcontrast acquisition at 1, 2, 3, 4 and 5 min. Adapted protocols that evaluate initial nodule enhancement to extract perfusion metrics have also been developed. A multicenter study by Swensen et al. demonstrated that nodules that enhance <15 HU are highly likely to be benign [3]. Nodules that enhance >15 HU can be benign or malignant. Important caveats to this study are that the ROI for evaluating nodule density before and after contrast should measure at least 70% of the lesion surface area and that the technique should not be applied to heterogeneous or cavitory lesions. For similar reasons, the technique may be falsely negative in

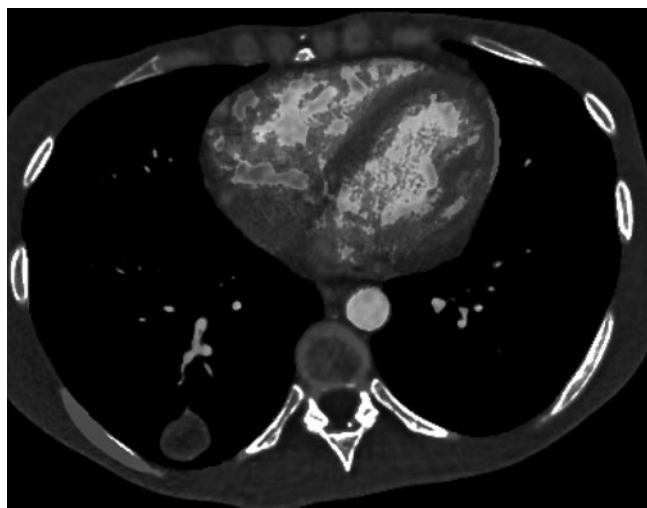


Fig. 4. Dual-energy computed tomography demonstrating peripheral enhancement of a pulmonary metastasis (for color reproduction see p 273)

mucin-rich lesions such as mucinous adenocarcinomas. The clinical value of nodule enhancement studies is in the very high negative predictive value (96%) of the test. However, in clinical practice, it is only a small fraction of benign cases that exhibits low-level enhancement, and so following the test, the vast majority of lesions remain indeterminate. Therefore, increasingly, PET-CT imaging is used as an alternative physiological assay of nodule activity, as this is more likely to alter the pretest probability of malignancy or benignity.

The introduction of dual-energy CT either by dual source or rapid kilovolt peak kVp switching technology has permitted the accurate determination of contrast enhancement without the need for pre-contrast images [4]. This may be helpful in determining lesion extent and enhancement pattern, perhaps as a surrogate enhancement marker before and after treatment (Fig. 4). However, it is unclear whether this technological evolution will permit better characterisation of benign from malignant disease. Certainly, implementation of nodule enhancement is problematic in that the original studies of this technique have all been performed at 120 kVp. As such appropriate thresholds for enhancement evaluation at other kilovolt peak values from 80 to 140 kVp have not been determined.

Indeterminate Solid Nodules

The majority of nodules are indeterminate on CT imaging, not demonstrating features that can be definitively ascribed as benign or malignant. In the Mayo screening series of >1,500 patients, >3,300 indeterminate noncalcified nodules were identified, the vast majority of which were small (≤ 4 mm) and benign [5]. Even in established smokers, the risk of malignancy in nodules of this size is <1% [6]. How to manage these patients has previously been a matter of great debate. Prior guidelines imposed

Table 1. New evidence-based guidelines for incidentally detected CT nodules from the Fleischner Society [7]

Nodule size	Low risk	High risk
≤ 4 mm	No FU	12-month FU No change→stop
>4-6 mm	12-month FU No change→stop	6- to 12- then 18- to 24-month FU No change→stop
>6-8 mm	6- to 12- then 18- to 24-month FU No change→stop	3- to 6-, 9- to 12-, then 24-month FU No change→stop
>8 mm	3, 9, 24 FU, or CT-PET, or biopsy	

FU, follow-up; *CT*, computed tomography; *PET*, positron emission tomography

that a 2-year stability was required to determine that a nodule was benign. Emerging experience from studies similar to the Mayo study suggest this is not essential. New evidence-based guidelines from the Fleischner Society have greatly transformed the management of such nodules [7]. It should be noted that these guidelines apply to the management of incidentally detected solid nodules and to patients >35 years without immune suppression and without known or suspected neoplasia. The guidelines vary according to whether patients are smokers (high risk) or nonsmokers (low risk) but significantly eliminate the need for follow-up of small nodules in low-risk patients and greatly reduce the frequency in other patients (Table 1). It is important to note that the guidelines do not apply to subsolid nodules or to patients with suspected neoplastic disease. In the former group, a more infrequent follow-up may be appropriate (see below); in the latter group, a more aggressive follow-up schedule or correlation with aspiration or PET may be indicated.

Role of Computer-Assisted Diagnosis

Computer-aided detection (CAD) improves the detection of pulmonary nodules, although sensitivity is known to be highly dependent upon lesion characteristics, including size, density and location. Technical parameters also affect sensitivity, including the thickness of evaluated CT images and vendor-specific issues related to CT algorithm optimisation to effect high detection rates with acceptable false positive detection rates. Most CAD systems are also accompanied by computer-aided diagnosis (CADx) features for evaluating pulmonary nodules. These systems may incorporate algorithms that can perform two- or three-dimensional analysis of focal lung opacity density and morphometry to determine the likelihood of malignancy, often quoted as a percentage probability of malignancy. Although such complex analysis has been documented to perform better across multiple cases than human readers, it is difficult to reliably implement such percentage probabilities in individual cases [8].

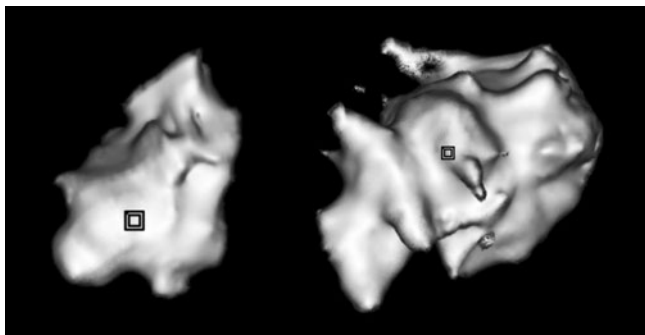


Fig. 5. Lung adenocarcinoma. Computer-aided 3D volumetric evaluation demonstrating asymmetric growth over an 11-month period (for color reproduction see p 273)

One of the most useful CADx tools is its ability to segment individual nodules, permitting a three-dimensional evaluation of lesion size and shape. Also, it can be coupled with follow-up examinations to determine volumetric growth. This is based on the observation that the doubling time of benign lesions is far longer than that of malignant lesions [9]. Volumetric evaluation of growth is also more reliable than reader-applied uni- or bidimensional measurements of size [10]. Moreover, volumetric evaluation may be more sensitive to detecting asymmetric growth, a feature limited to malignant lesions (Fig. 5). A commonly used threshold for solid-lesion volume doubling time is 400 days, although several authors advocate a more stringent threshold of 500 days [11-13]. This extended threshold is perhaps more prudent when the veracity of volumetric nodule evaluation is assessed. Although the accuracy and reproducibility of lung-nodule segmentation has been confirmed in artificial and porcine models, the reproducibility in vivo of human nodule measurements can vary by up to 15% by evaluating the same nodule in different phases of inspiration or by using different CT thickness data or software packages [13, 14]. Smaller changes may occur as a result of different reconstruction algorithms or dose variation. The presence or absence of intravenously administered contrast material appears to play a largely inconsequential role. Nonetheless, by ensuring a similar technique is employed on initial and follow-up examinations, lung-nodule volumetry shows great promise and may further reduce the need for follow-up examinations.

Subsolid Nodules

Subsolid nodules include lesions that are pure ground-glass opacities and lesions that are part solid with part ground-glass opacity. Lesions with these characteristics are well known to be associated with a higher prevalence of malignancy than are solid lesions, particularly when the lesion is a part solid and a part ground-glass opacity (Fig. 6) [15]. In particular, these lesions usually lie along the spectrum of disease that extends from the suspected malignant precursor lesion of atypical adenomatous hyperplasia (AAH) through to invasive adenocarcinoma.

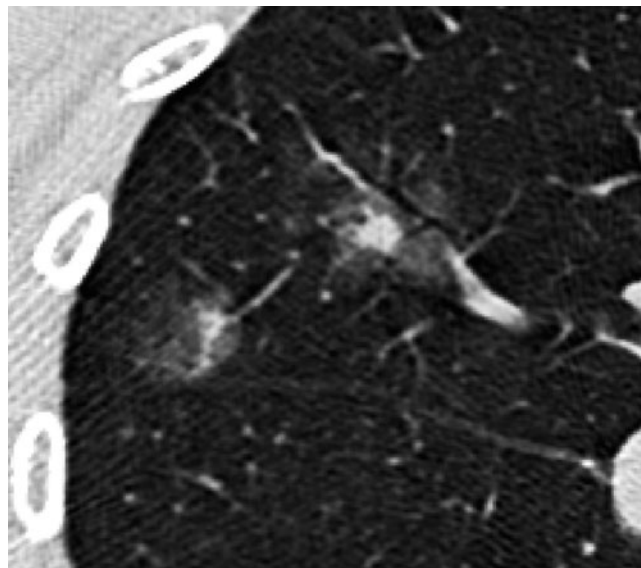


Fig. 6. Multifocal subsolid lesions. Mixed ground-glass opacity/solid-density lesions due to multifocal adenocarcinoma with bronchioloalveolar cell features

Aoki et al. demonstrated that AAH and the lower-stage lesions of bronchioloalveolar cell carcinoma (Noguchi subtype A, B, C) are associated with lesions that are nearly exclusively of a ground-glass nature. Conversely, the higher-grade lesions (Noguchi D, E, F) are associated with lesions that become progressively more reticular, demonstrate tractional bronchiolectasis and eventually increase in solid components [16, 17]. Lesions showing an exclusively ground-glass appearance or that have minimal solid components may grow very slowly. A comparison of mean volume doubling times in lung-cancer patients with solid, part-solid or pure ground-glass-appearing neoplastic lesions demonstrate a stepwise increase in CT-calculated volume-doubling times (158 vs 457 vs 853 days) [18]. Therefore, for subsolid lesions, the demonstration of 2-year stability may not be enough to ensure a benign nature. In these cases, an initial follow-up examination at 3 months may be performed to demonstrate that the lesion persists and is not inflammatory. Follow-up may then be performed at more prolonged time intervals (1-2 years). When comparing these irregular, ill-defined lesions, it can be difficult to measure incremental size, and evaluation should include comparison of comparable thin-section images and whether the ground-glass appearance or solid component geographically extends around more vessels or airways. It is also important to note that the natural evolution of these lesions includes transient reduction in size that may occur when there is histological alveolar collapse. The definitive determination that a lesion with ground-glass opacity is malignant can be problematic. Progressive incremental overall or solid-component size strongly favours malignancy. PET-CT imaging in these cases may be noncontributory, as it is often recognised that these

lesions may have low maximum standard uptake value (SUV_{max}) activity. Additionally, evaluation of predominantly ground-glass-opacity lesions by CT-guided fine needle aspiration or biopsy should be done with great caution. These results may be subject to significant sampling-error effects and are likely to vary significantly from the ultimate excision specimen. In particular, the extent of invasive adenocarcinoma can be significantly underestimated by percutaneous needle sampling, even if directed to the more solid components.

The optimal management of patients with single sub-solid lesions is a subject of some debate and controversy. It is well established that lesions with a greater percentage of ground-glass opacity are less likely to have nodal disease or higher stage and to have a better prognosis than lesions with a greater solid component, in which invasive adenocarcinoma likely predominates [19, 20]. In the absence of definitive guidelines regarding the management of these types of lesions, excellent interim guidelines have been published [21] that advocate more aggressive surgical management when a lesion exceeds 1 cm overall or when there is significant increase in the solid component. Conversely, it has been suggested that lesions with a pure ground-glass appearance measuring <5 mm are not followed, as they almost always reflect benign entities or atypical adenomatous hyperplasia. Managing patients with multiple lesions of varying density is more complex, especially as radiologically it is not always possible to determine the extent of neoplasia in multiple lesions with ground-glass opacities. Treatment strategies may include resection of initial lesions, with subsequent localised resection of progressive or recurrent lesions, although there is no standardised long-term data to support this approach. In part to address these complex issues of clinico-radiological management, it is anticipated that there is likely to be a further revision of the 2004 World Health Organisation (WHO) classification of adenocarcinoma moving away from the term bronchioloalveolar-cell carcinoma towards the concept of *adenocarcinoma in situ* and *minimally invasive adenocarcinoma*.

Focal Parenchymal Airspace Disease

There are a multitude of aetiologies that can result in focal air-space opacities. The majority will be multifocal and are infective in nature, with distinction of predisposing aetiologies impossible unless there are uncommon specific features present, e.g. ground-glass-appearing halo in invasive aspergillosis. The differential diagnosis may be narrowed by referring to a combination of radiological features, chronicity, progression, response to treatment and the patient's immune status. The presence of cavitation in airspace disease can be helpful in differential diagnosis, although the differential can again be broad, incorporating staphylococcal or gram negative bacterial infections, mycobacterial disease or fungal infection. Rounded pneumonia is more common in children

but also occurs in adults, usually due to *Streptococcus pneumoniae*. Appearances are mass-like without air bronchograms, a result of disease propagation through the collateral air-drift mechanisms of the pores of Kohn and the Canals of Lambert. Chronic focal consolidative opacity may be characterised by minor volume loss and tractional bronchiectasis, these features being more common in patients with chronic eosinophilic lung disease or organising pneumonia. The latter may also present with a reverse halo appearance, central ground-glass opacities and peripheral consolidation, although this appearance is not specific to organising pneumonia. Progressive focal airspace disease may reflect neoplastic disease, including bronchioloalveolar-cell carcinoma, lymphoma or, occasionally, mucinous metastases from gastrointestinal source primaries. Calcification may be present in mycobacterial disease and, occasionally, amyloidosis.

References

1. Woodring JH, Fried AM, Chuang VP (1980) Solitary cavities of the lung: diagnostic implications of cavity wall thickness. *AJR Am J Roentgenol* 135:1269-1271
2. Honda O, Tsubamoto M, Inoue A et al (2007) Pulmonary cavity nodules on computed tomography: differentiation of malignancy and benignancy. *J Comput Assist Tomogr* 31:943-949
3. Swensen SJ, Viggiano RW, Midthun DE et al (2000) Lung nodule enhancement at CT: multicenter study. *Radiology* 214:73-80
4. Chae EJ, Song JW, Seo JB et al (2008) Clinical utility of dual-energy CT in the evaluation of solitary pulmonary nodules: initial experience. *Radiology* 249:671-681
5. Swensen SJ, Jett JR, Hartman TE et al (2005) CT screening for lung cancer: five-year prospective experience. *Radiology* 235:259-265
6. Piyavisetpat N, Aquino SL, Hahn PF et al (2005) Small incidental pulmonary nodules: how useful is short-term interval CT follow-up? *J Thorac Imaging* 20:5-9
7. MacMahon H, Austin JH, Gamsu G et al (2005) Guidelines for management of small pulmonary nodules detected on CT scans: a statement from the Fleischner Society. *Radiology* 237:395-400
8. Li F, Aoyama M, Shiraishi J et al (2004) Radiologists' performance for differentiating benign from malignant lung nodules on high-resolution CT using computer-estimated likelihood of malignancy. *AJR Am J Roentgenol* 183:1209-1215
9. Yankelevitz DF, Reeves AP, Kostis et al (2000) Small pulmonary nodules: volumetrically determined growth rates based on CT evaluation. *Radiology* 217:251-256
10. Jennings SG, Winer-Muram HT, Tarver RD et al (2004) Lung tumor growth: assessment with CT—comparison of diameter and cross-sectional area with volume measurements. *Radiology* 231:866-871
11. Jennings SG, Winer-Muram HT, Tann M et al (2006) Distribution of stage I lung cancer growth rates determined with serial volumetric CT measurements. *Radiology* 241:554-563
12. Revel MP, Merlin A, Peyrard S et al (2006) Software volumetric evaluation of doubling times for differentiating benign versus malignant pulmonary nodules. *AJR Am J Roentgenol* 187:135-142
13. Honda O, Kawai M, Gyobu T et al (2009) Reproducibility of temporal volume change in CT of lung cancer: comparison of computer software and manual assessment. *Br J Radiol* 82:742-747
14. Bolte H, Riedel C, Müller-Hülsbeck S et al (2007) Precision of computer-aided volumetry of artificial small solid pul-

- monary nodules in ex vivo porcine lungs. *Br J Radiol* 80:414-421
15. Henschke CI, Yankelevitz DF, Mirtcheva R et al (2002) CT screening for lung cancer: frequency and significance of part-solid and nonsolid nodules. *AJR Am J Roentgenol* 178:1053-1057
 16. Aoki T, Nakata H, Watanabe H et al (2000) Evolution of peripheral lung adenocarcinomas: CT findings correlated with histology and tumor doubling time. *AJR Am J Roentgenol* 174:763-768
 17. Noguchi M, Morikawa A, Kawasaki M et al (1995) Small adenocarcinoma of the lung. Histologic characteristics and prognosis. *Cancer* 75:2844-2852
 18. Hasegawa, Sone S, Takashima SM et al (2000) Growth rate of small lung cancers detected on mass CT screening. *Br J Radiol* 73:1252-1259
 19. Kodama K, Higashiyama M, Yokouchi H et al (2001) Prognostic value of ground-glass opacity found in small lung adenocarcinoma on high-resolution CT scanning. *Lung Cancer* 33:17-25
 20. Higashiyama M, Kodama K, Yokouchi H et al (1999) Prognostic value of bronchiolo-alveolar carcinoma component of small lung adenocarcinoma. *Ann Thorac Surg* 68:2069-2073
 21. Godoy MC, Naidich DP (2009) Subsolid pulmonary nodules and the spectrum of peripheral adenocarcinomas of the lung: recommended interim guidelines for assessment and management. *Radiology* 253:606-622

Plain-Film and CT Evaluation of the Adult Mediastinum and Hilar: Pitfalls vs. Disease

Sanjeev Bhalla¹, José Cáceres²

¹ Mallinckrodt Institute of Radiology, Washington University School of Medicine, Barnes-Jewish Hospital, St. Louis, MO, USA

² Department of Diagnostic Radiology, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain

Introduction

Knowledge of the normal mediastinal anatomy and its variants is indispensable for proper interpretation of chest radiology. Mediastinal masses may be found incidentally in asymptomatic individuals, but they can also be symptomatic, depending on their size and location. Cross-sectional imaging with computed tomography (CT) and magnetic resonance (MR) imaging plays an important role in the nonsurgical evaluation of mediastinal lesions.

In this article, we review the anatomy and normal variants of mediastinal structures as well as the radiographic, CT, and MR appearances of some of the most common mediastinal diseases, with emphasis on those features that permit a focused differential diagnosis and help direct management.

Imaging Strategies in Mediastinal Diseases

Conventional Chest Radiography

Many mediastinal masses are incidentally discovered on routine chest examinations obtained for other reasons. Chest radiography is the first imaging modality used in those asymptomatic patients or when a mediastinal mass is suspected. The key to the chest radiograph is to determine whether the lesion is actually within the mediastinum or lung and to make an educated guess as to where the lesion is within the mediastinum. A lesion confined to the posterior mediastinum (paravertebral region) may be better evaluated by MR.

Computed Tomography

Computed tomography is currently the gold standard for the detection of mediastinal pathology. Initial non-enhanced contiguous slices should be obtained to demonstrate calcifications and hemorrhage. The injection of intravenous contrast will define the enhancement patterns of the lesions as well as their relationship with adjacent vascular and mediastinal structures.

Magnetic Resonance Imaging

Magnetic resonance has a complementary role in the evaluation of mediastinal masses. It is mainly used: (a) to solve unanswered questions after CT scan, (b) to assess mediastinal masses in patients allergic to iodinated contrast material, and (c) to better assess the relationship of the mediastinal mass with adjacent structures, e.g., the pericardium, heart cavities, spinal canal, and vessels. For this last reason, MR is usually preferred to CT for the assessment of masses of suspected neurogenic origin. Another indication for mediastinal MR is if the mediastinal mass is suspected to be a cyst (thymic, pericardial, foregut duplication, neuroenteric) and this suspicion cannot be confirmed by CT. With MR subtraction imaging (post-contrast image minus pre-contrast image) only enhanced structures are shown. Cysts should be invisible on these images.

Anatomic and Normal Variants Mimicking Mediastinal Pathology

Thymus

The thymus has a wide variation in appearances on cross-sectional imaging and its size and morphology are directly related with age [1]. Whereas relatively large in the neonate and young infant, after puberty, there is a gradual reduction of the thymus size due to a progressive replacement of the atrophied thymic follicles by adipose tissue. However, there is a broad variation in this involution and significant residual thymic tissue may be present in individuals over the age of 30.

Superior Pericardial Recess

The superior pericardial recess is a semicircular space surrounding the ascending aorta. The most superior extent of this recess is at the level of the innominate artery. On rare occasions, pericardial effusion within the superior pericardial recess can simulate a cystic mediastinal mass [2].

Lymph Nodes

The maximal diameter of normal lymph nodes ranges from 6 to 14 mm. However, the short axis of mediastinal nodes has been advocated as the most predictable measure of nodal enlargement; 1.0 cm is considered the upper limit of normal [3]. When mediastinal fat is scanty, the collapsed esophagus may be confused with a lymph-node mass on CT and MR.

Left Pulmonary Artery

On rare occasion, the main and left pulmonary arteries are positioned at an unusually high level with respect to the aortic arch, thereby mimicking a mediastinal mass on CT or plain-chest radiographs [4].

Pericardial Fat Pad

An enlarged pericardial fat pad, usually associated with obesity, exogenous steroid therapy, and Cushing syndrome, may mimic a cardiophrenic angle mediastinal mass.

Mediastinal Lipomatosis

An excess of mediastinal fat, which is a benign condition usually seen in obese patients or in patients under exogenous steroid use, results in significant mediastinal widening. Patients are asymptomatic and do not require therapy.

Classification of Mediastinal Masses

Classification of a mediastinal mass on CT and MR is based on two main features: location and attenuation/signal. Although sometimes artificial, the mediastinum can be classified into three compartments: (a) anterior, comprising the structures and tissue situated in front of a line drawn along the anterior border of the trachea and the posterior border of the heart; (b) middle, located between this line and the anterior aspect of the vertebral bodies; and (c) paravertebral, when a mass is situated predominantly in the potential space adjacent to a vertebral body [5].

The attenuations/signals of fat and fluid as well as high attenuation/signal (higher than muscle) may be of diagnostic help. A fat attenuation/signal may be seen in thymolipomas, germ-cell tumors, lipomatosis, fat pads, liposarcomas, extramedullary hematopoiesis, and esophageal fibrovascular polyps. A fluid attenuation/signal may be seen with foregut duplication cysts, germ-cell tumors, thymomas, lymphomas, necrotic tumors, lymphangiomas, pericardial cysts, and thymic cysts. High-attenuation/signal lesions include hemangiomas, Castleman's disease, goiter, paraganglioma, vascular abnormalities, and vascular metastases.

Anterior Mediastinum

The anterior mediastinum is the site of origin of the majority of mediastinal masses, including thymoma and other thymic disorders (cysts), lymphangioma, germ-cell neoplasms (mature teratomas and malignant germ-cell tumors), Hodgkin's disease and non-Hodgkin's lymphoma, and mesothelial cyst (pericardial) [5-8]. Residents and medical students sometimes like to use the mnemonic '3T's' to help with remembering thymoma, teratoma, and 'terrible' lymphoma. Though this can be helpful, it can also be misleading, as it allows one to forget the other thymic lesions that may be present in the anterior mediastinum (cysts, carcinoid, carcinoma) and that not all anterior germ-cell tumors are benign.

Thymoma

This is by far the most common primary tumor of the anterior mediastinum. Men and women are equally affected and most of the lesions occur in patients >40 years. Thymomas are rare in children and adolescents. Myasthenia gravis occurs in approximately 30-50% of patients with this tumor. Less commonly, patients may present with other parathymic syndromes, such as pure red cell aplasia or hypogammaglobulinemia. Radiologically, thymomas commonly manifest as well-defined, lobulated, homogeneous, or heterogeneous mediastinal masses usually located anterior to the aortic root. Punctate or curvilinear calcifications can be detected on conventional radiographs. In up to one third of cases, necrosis, hemorrhage, and/or cystic changes can be demonstrated on cross-sectional imaging studies (Fig. 1) [5]. Cross-sectional imaging does not reveal the malignant potential of a thymoma

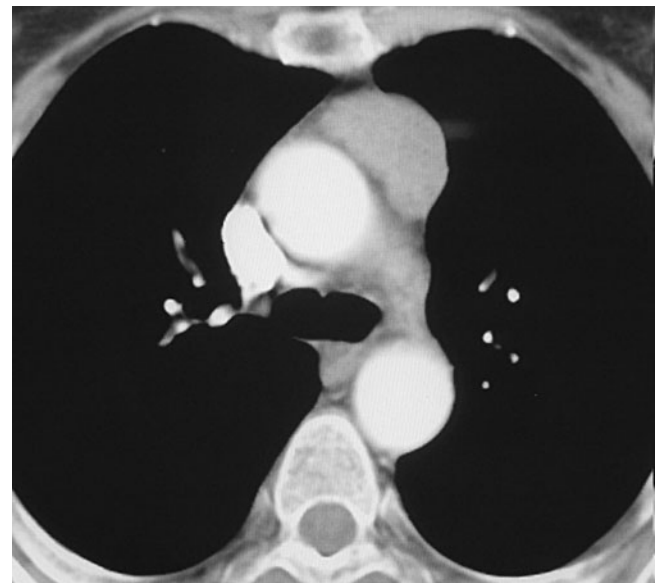


Fig. 1. Thymoma. CT shows a mass in the anterior mediastinum with uniform enhancement

unless pleural seeding is present. Therefore, the term 'invasive thymoma' is reserved for the visualization of an anterior mediastinal mass with pleural deposits.

Thymic Cysts

Thymic cysts represent approximately 3% of all anterior mediastinal masses and are most commonly found in children. They are generally considered developmental abnormalities caused by persistence of the thymopharyngeal duct. Radiologically, thymic cysts manifest as well-marginated, rounded masses that are characteristically located in the anterior superior mediastinum. On CT scans, they appear as sharply delineated masses with near-water attenuation. Thymic cysts are usually unilocular but some may be multiloculated, with occasional visualization of linear wall calcification. On MR, thymic cysts have a very high signal attenuation on T2-weighted images but variable signal intensity on T1-weighted images, depending on the degree of proteinaceous material or hemorrhage present [5, 6]. They should not enhance with gadolinium. Occasionally, multiple thymic cysts may be present in HIV patients and in those with Langerhans cell histiocytosis.

Lymphangioma

Lymphangiomas are rare, benign lesions of lymphatic origin, representing 0.7-4.5% of all mediastinal tumors [5, 6, 8]. Most patients are asymptomatic, but occasionally they have symptoms of compression or pain. In adults, lymphangiomas are more often found in the mediastinum, whereas in children, especially those <2 years of age, lymphangiomas are usually discovered as a mass in the neck or axilla. CT scanning typically shows a uniformly cystic lesion with an attenuation equal to or slightly higher than that of water and insinuating throughout multiple mediastinal compartments. On MR imaging, the cyst contents have increased signal intensity on T2-weighted images and can also have high signal intensity on T1-weighted images.

Germ-Cell Tumors

Most primary mediastinal germ-cell tumors are teratomas. These are a heterogeneous group of tumors that are derived from more than one germ-cell layer and thus contain different tissue types [9]. These tumors can be found in persons of any age, although they are most often detected in young adults. Teratomas account for 60-70% of mediastinal germ-cell tumors. Mature teratomas are by far the most frequent and occur more commonly in young women. Radiologically, such tumors manifest as a rounded or lobulated, well-defined, anterior mediastinal mass that usually protrudes to one side of the midline. The CT scan appearance of these lesions depends on the proportions of the various tissues of which they are composed. CT examination al-

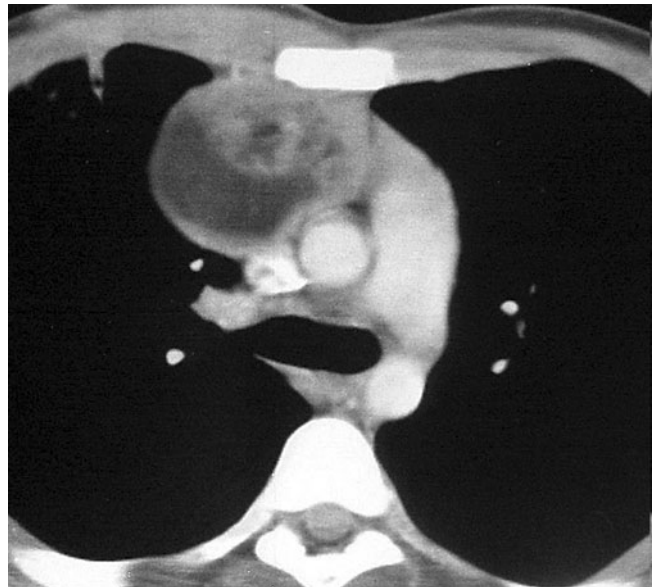


Fig. 2. Teratoma. CT shows an anterior mediastinal mass with a combination of fat and soft-tissue attenuation

lows a confident diagnosis of a mature teratoma when a combination of fluid, soft-tissue, calcium, and fat attenuation is present [5, 9] (Fig. 2).

Germ-cell tumors are frequently cystic, and mature teratomas do not need to contain fat. When the soft-tissue component is proportionally greater than the cystic components, malignant germ-cell tumor may be suspected. Seminoma is the most common primary mediastinal germ-cell tumor [5, 9].

Pericardial Cysts

These are believed to arise from the persistence of blind segments of the ventral parietal recesses of the pericardium. Seventy percent occur in the right cardiophrenic angle as a well-defined soft-tissue opacity on conventional chest radiograph [5, 7]. On CT, pericardial cysts typically manifest as well-circumscribed, unilocular, non-enhancing masses with low (near-water) attenuation contents. They are located adjacent to the cardiac border, typically changing shape as the patient changes position (Fig. 3). On MR, pericardial cysts have low-signal intensity on T1-weighted images, homogeneous high-signal intensity on T2-weighted images, and do not enhance [7]. Pericardial cysts not infrequently communicate with the pericardial space and, therefore, may change in size between two CT examinations.

Middle Mediastinum

The most common abnormalities of middle-posterior mediastinum are developmental anomalies of the aortic arch and aortic aneurysms, esophageal lesions and

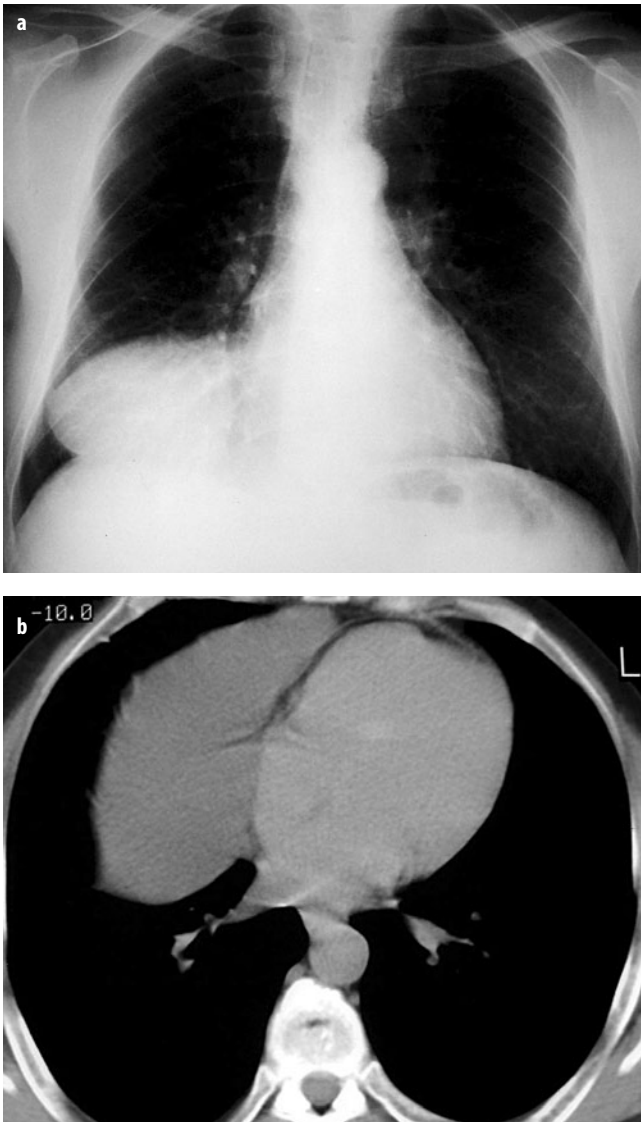


Fig. 3 a, b. Pericardial cyst. **a** Posteroanterior chest radiograph shows a well-defined mass in the right cardiophrenic space. **b** CT shows the typical appearance of a pericardial cyst. Note the change in shape with the change in the patient's position

developmental cysts (bronchogenic and enteric cyst) [5]. The predominant mass in the middle superior mediastinum is the intrathoracic goiter.

Mediastinal Goiter

Mediastinal goiter is one of the most common mediastinal abnormalities seen in daily practice [6]. Patients are usually asymptomatic but rarely may present with pain or symptoms related to tracheal compression.

Radiographically, mediastinal goiter appears as a sharply defined, smooth or lobulated mass that usually causes displacement and narrowing of the trachea. Coarse or ring-like calcifications are commonly associated with the lesion being visible on plain films. CT can show the

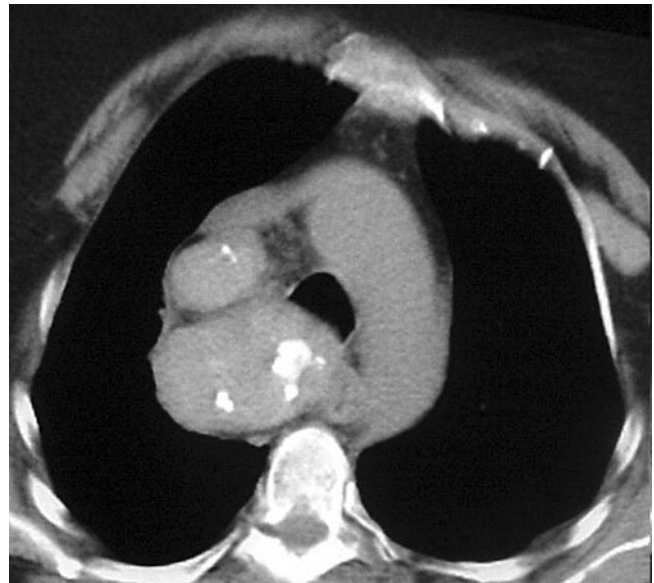


Fig. 4. Intrathoracic goiter. Middle mediastinal mass, posterior and lateral to the trachea. Note the typical coarse calcifications

extent of intrathoracic thyroid tissue and its connection with the thyroid gland (Fig. 4) [5, 6]. On CT, goiters should be heterogeneous in attenuation, with components that are of high attenuation. If the thyroid is enlarged and shows homogeneous low-attenuation, tumor infiltration should be suspected [7].

Developmental Cysts

Bronchogenic cyst is by far the most common form of foregut-duplication cysts, which result from abnormal ventral budding of the tracheobronchial tree. Bronchogenic cysts represent 50-60% of all mediastinal cysts. Approximately 80% occur in the paratracheal or subcarinal region, but they may also have an intrapulmonary location [6, 8]. On CT scanning, bronchogenic cysts are typically unilocular nonenhancing masses of water attenuation, intimately related to the airway. Calcification of the cyst wall can occur and sometimes the cyst's attenuation on CT can be higher because they may contain milk or calcium. On MR imaging, the cystic contents can exhibit low- or high-signal intensity on T1-weighted images and typically have homogeneous bright signal intensity on T2-weighted sequences [8] (Fig. 5). They should not enhance with gadolinium.

Enteric cysts are usually lined by alimentary epithelium. Esophageal duplication cysts comprise 10-15% of all alimentary-tract duplications and 60% are located adjacent to the lower esophagus [6, 8]. They can be found within or attached to the esophageal wall and rarely communicate with the esophageal lumen. On CT, esophageal duplication cysts appear as spherical nonenhancing intramural lesions with no esophageal communication, or sometimes showing a fibrous tract attached to the esophageal wall.

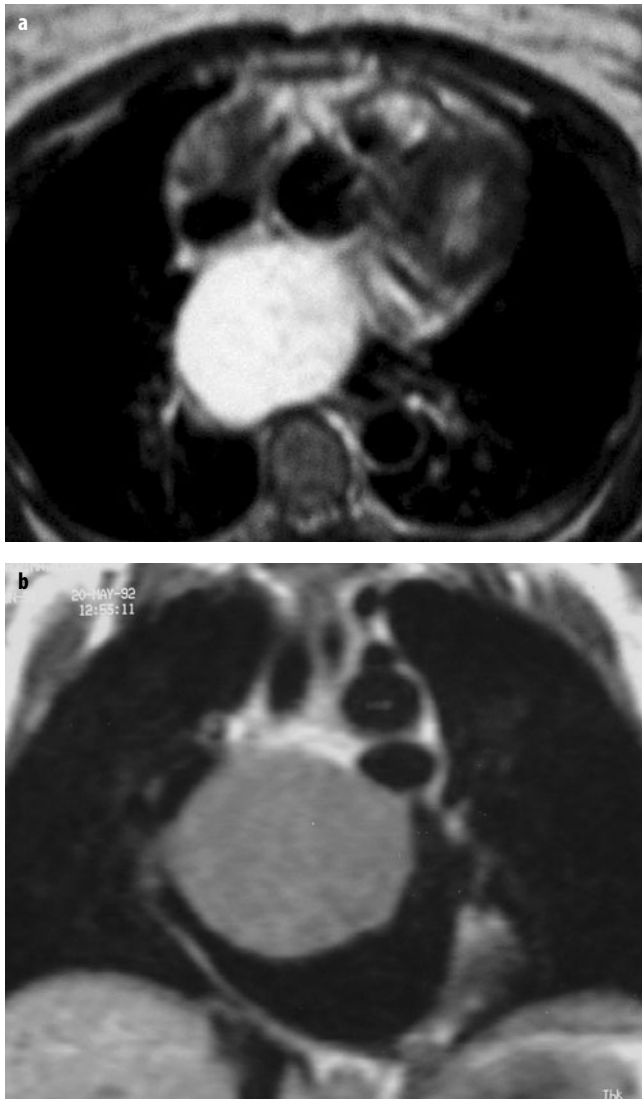


Fig. 5 a, b. Bronchogenic cyst. **a** T2-weighted transverse MRI shows a high-signal round mass in the middle mediastinum. **b** T1-weighted coronal view confirms the location of the mass and its liquid content

Often times, the foregut duplication cyst cannot be further classified as bronchogenic or enteric. No communication to the trachea, bronchi or esophagus is demonstrated. In these cases, one must wait for the final surgical pathology, although it may not be more revealing. If the cyst has become infected or bled, the lining may become indistinct and further classification is not possible.

Paravertebral Region

This region is bounded in the front by the anterior surface of the vertebral column and in the back by the chest wall. The most common abnormalities of the paravertebral region are neoplasms of neural tissue arising from

the peripheral nerves or sympathetic ganglia, infectious processes from the spine, bone and cartilage tumors, costovertebral traumatic lesions, and extramedullary hematopoiesis [6, 10].

Tumors of Neural Tissue

Neoplasms of neural tissue account for about 20% of all primary mediastinal neoplasms. Schwannoma, neurofibroma (plexiform and nonplexiform), and malignant schwannoma are tumors that arise from an intercostal nerve [6]. Their radiographic appearance consists of sharply defined round, smooth, or lobulated paraspinal masses. In 50% of cases they are associated with bone abnormalities, including expansion of the neural foramina, erosion of the vertebral bodies, and erosion and deformity of ribs [6]. Ganglioneuroma, ganglioneuroblastoma, and neuroblastoma are neural tumors arising from the sympathetic ganglia. They usually manifest radiographically as sharply defined oblong masses located along the anterolateral surface of the vertebral spine (Fig. 6). At times, a schwannoma can emulate a foregut duplication cyst (low-attenuating from the myelin). One must look for enhancement or bone-remodeling to help in the identification, as neither of these properties is routinely seen with duplication cysts.

Extramedullary Hematopoiesis

Extramedullary hematopoiesis is a rare disease that is usually associated with chronic hematologic diseases in which there is inadequate production or excessive destruction of blood cells [10]. Thalassemia and sickle-cell disease are the most common hematologic disorders associated with foci of extramedullary hematopoiesis in organs such as liver, spleen, and lymph nodes. Unilateral or bilateral masses of hematopoietic tissue can be occasionally found in the paravertebral region. The radiographic appearance consists of smooth and lobulated paravertebral masses situated in

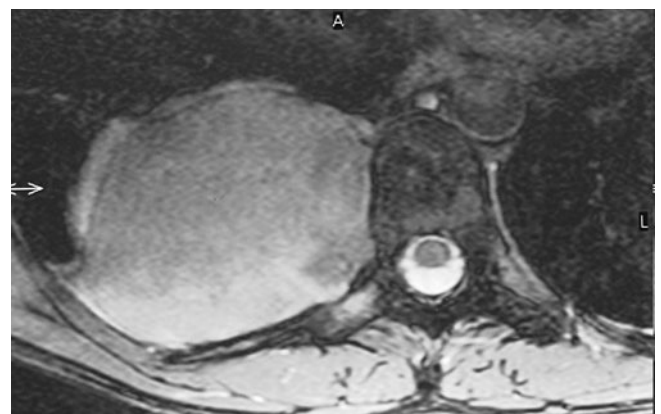


Fig. 6. Neurogenic tumor. T2-weighted transverse MRI shows a posterior mediastinal mass. Ganglioneuroma confirmed at surgery

the lower chest. On CT scans, they may have a large fatty component [10]. This uncommon disorder should be considered in the differential diagnosis of a paravertebral mass in a patient with severe chronic anemia.

Vascular Abnormalities

Vascular anomalies of the mediastinum can occasionally be confused with mediastinal masses on plain film. Cross-sectional imaging is helpful in diagnosing them but the clinician must be well-acquainted with these entities to avoid propagating the confusion.

Tortuous vessels are perhaps the most common mediastinal vascular abnormality confused with mass on chest radiography. The right innominate artery (causing a right paratracheal opacity) and the left superior intercostal vein are two of the more common enlarged, tortuous variants [11].

Anterior to the aortic arch in the para-aortic region, two venous anomalies are frequently encountered: the left-sided vena cava and partial anomalous return of the left upper lobe [12]. The former drains from the left brachiocephalic vein to the coronary sinus and may be present with a right-sided superior vena cava. The latter represents the most common form of isolated anomalous drainage. In this entity the left upper lobe drains into the left brachiocephalic vein. The key to distinguishing partial anomalous return of the left upper lobe from a left superior vena cava is that the former does not connect to the

coronary sinus, and no vessel is encountered anterior to the left mainstem bronchus. This is in distinction to the situation with a left superior vena cava, in which two vessels are encountered anterior to the left mainstem bronchus (the normal superior pulmonary vein and the left superior vena cava). Another venous anomaly is an azygos continuation of an interrupted inferior vena cava. In this condition, the azygos vein is responsible for all infrahepatic venous return. This entity should be suspected when the azygos vein is noticeably enlarged in a patient without superior vena cava thrombus or obstruction.

Aortic arch variations may also be encountered as an incidental mediastinal mass. They include double aortic arch, right arch with aberrant left subclavian artery, and left arch with aberrant right subclavian artery. Detailed analysis of the branching vessels should allow for accurate diagnosis.

Positron Emission Tomography and Mediastinal Masses

Fluoro-deoxyglucose positron emission tomography (FDG-PET) has not routinely been used in the primary evaluation of mediastinal masses. Instead, FDG-PET is often used as part of staging of lung cancers (to evaluate for mediastinal lymph node metastases or in the evaluation for metastases from a primary mediastinal mass).

Recently, however, as a result of increased availability FDG-PET has made inroads in the assessment of

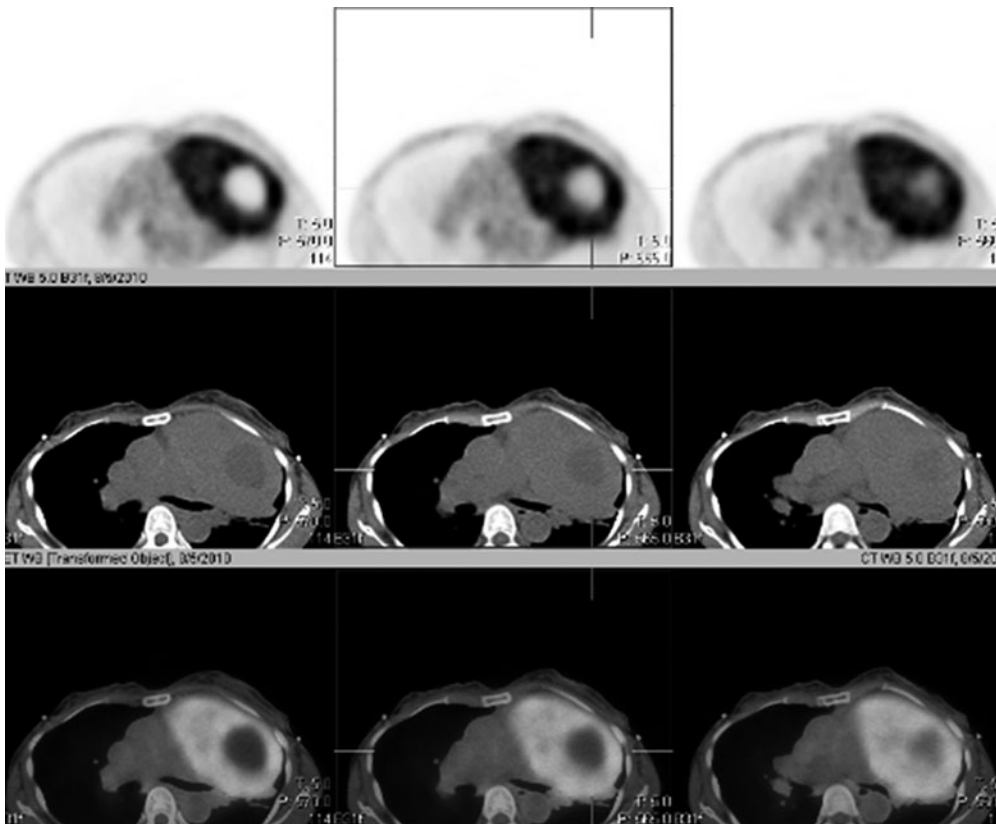


Fig. 7. Thymic carcinoma. FDG-PET-CT shows the marked increased uptake in an anterior mediastinal mass which was confirmed to be thymic carcinoma at surgery (for color reproduction see p 273)

mediastinal masses, especially anterior mediastinal masses [13]. Solid masses with marked increased uptake (standardised uptake value, SUV, max >5) are concerning for possible lymphoma or thymic carcinoma and should be biopsied prior to surgery (Fig. 7). If the lesion is small with marked increased uptake, a median sternotomy should be performed because of a higher chance of local invasion. When the solid lesion demonstrates lower uptake, a minimally invasive surgery can be performed without a biopsy as the lesion is likely to be a resectable thymoma.

Duplication cysts and thymic cysts should not demonstrate any uptake of FDG. Nerve sheath tumors, however, can be variable in their uptake of FDG. Benign lesions may be metabolically active. Granulomatous lymphadenopathy (as with sarcoidosis, mycobacterial and fungal infection) may also be markedly FDG-avid. The anatomic imaging, therefore, remains very important in generating an appropriate differential diagnosis.

Some recent work has evaluated the performance of FDG-PET at 2 time points to assess whether benign disease can be distinguished from malignant disease based on the change in SUV max. This has not, however, translated into an effective clinical practice.

References

1. Dixon AK, Hilton CJ, Williams GT (1984) Computed tomography and histological correlation of the thymic remnant. *Clin Radiol* 32:255-257
2. Winer-Muram HT, Gold RE (1980) Effusion in the superior pericardial recess simulating a mediastinal mass. *AJR Am J Roentgenol* 154:69-71
3. Quint LE, Glazer GM, Orringer MB et al (1986) Mediastinal lymph node detection and sizing at CT and autopsy. *AJR Am J Roentgenol* 147:469-472
4. Mencini RA, Proto AV (1982) The high left and main pulmonary arteries: a CT pitfall. *J Comput Assist Tomogr* 6:452-459
5. Strollo DC, Rosado de Christenson ML, Jett JR (1997) Primary mediastinal tumors. Part I. Tumors of anterior mediastinum. *Chest* 112:511-522
6. Strollo DC, Rosado de Christenson ML, Jett JR (1997) Primary mediastinal tumors. Part II. Tumors of the middle and posterior mediastinum. *Chest* 112:1344-1357
7. Kim HC, Han MH, Kim KH (2003) Primary thyroid lymphoma: CT findings. *Eur J Radiol* 46:233-239
8. Müller NL, Fraser RS, Colman NC, Paré PD (2001) Radiologic diagnosis of diseases of the chest. WB Saunders, Philadelphia, PA
9. Rosado de Christenson ML, Templeton PA, Moran CA (1992) Mediastinal germ-cell tumors: radiologic and pathologic correlation. *Radiographics* 12:1013-1030
10. Long JA Jr, Doppman JL, Nienhuis AW (1980) Computed tomographic studies of extramedullary hematopoiesis. *J Comput Assist Tomogr* 4:67-70
11. Cole TJ, Henry DA, Jolles H, Proto AV (1995) Normal and abnormal vascular structures that simulate neoplasms on chest radiographs: clues to the diagnosis. *Radiographics* 15:867-891
12. Dillon EH, Camputaro C (1993) Partial anomalous pulmonary venous drainage of the left upper lobe vs. duplication of the superior vena cava: distinction based on CT findings. *AJR Am J Roentgenol* 160:375-379
13. Luzzi L, Campione A, Gorla A et al (2009) Role of fluorine-FDG-PET/CT in the preoperative assessment of anterior mediastinal masses. *Eur J Cardiothorac Surg* 36:475-479

Current Approach to Chronic and Acute Airway Diseases

Philippe A. Grenier¹, Tomas Franquet²

¹ Department of Radiology, University Pierre & Marie Curie – Hospital Pitié-Salpêtrière, Paris, France

² Department of Radiology, Hospital de St. Pau, Barcelona, Spain

Introduction

Multidetector computed tomography (MDCT) using thin collimation during a single breath hold has become the best imaging technique for assessing airway diseases. Volumetric high-resolution data sets provide precise morphologic evaluation of both proximal and distal airways [1]. The different CT patterns and their main causes are reported in Tables 1-5. The different diseases involving the airways, which are presented in this course, include neoplastic and nonneoplastic tracheobronchial diseases, bronchiectasis and small airway diseases, asthma, and chronic obstructive pulmonary disease (COPD).

Table 1. Endoluminal opacity

- Benign tracheobronchial neoplasm
- Malignant primary tracheobronchial neoplasms
- Bronchial metastasis
- Mucous secretions
- Foreign body
- Broncholithiasis

Table 2. Multinodular appearance of the inner surface of the airway

- Wegener granulomatosis
- Tracheobronchial metastases (hematogenous spread)
- Laryngotracheobronchial papillomatosis
- Adenoid cystic carcinoma (multicentric)
- Tracheobronchial amyloidosis
- Tracheobronchopathia osteochondroplastica (TO)

Table 3. Focal tracheobronchial narrowing

- Posttraumatic strictures
- Postinfectious stenoses (e.g., tuberculosis)
- Tracheobronchial neoplasms (primary and secondary malignant)
- Wegener granulomatosis
- Sarcoidosis
- Inflammatory bowel disease
- Extrinsic compression

Table 4. Diffuse tracheobronchial wall thickening

- Infectious tracheobronchitis (tuberculosis, aspergillosis)
- Relapsing polychondritis^a
- Tracheobronchial amyloidosis
- Tracheobronchopathia osteochondroplastica^a
- Tracheobronchitis associated with ulcerative colitis

^a Calcific deposits

Table 5. Tracheobronchial dehiscence, fistula and diverticula

- Tracheal or bronchial rupture
- Bronchial dehiscence occurring after lung transplantation
- Tracheal diverticula (tracheocele)
- Accessory cardiac bronchus
- Multiple tracheobronchial diverticula (COPD)
- Nodobronchial and nodo-broncho-esophageal fistulas
- Tracheoesophageal fistulas
- Bronchopleural fistulas

COPD, chronic obstructive pulmonary disease

CT Acquisition and Postprocessing Techniques

MDCT acquisition is performed at full suspended inspiration over the entire lungs using thin collimation (0.6-1.5 mm) without contrast material. The axial images are reconstructed with overlapping and thin slice thickness (0.8-1.5 mm). Complementary MDCT acquisition at full continuous expiration using low-dose (120 kV to 20-40 mA) is often recommended and particularly appreciated for assessing tracheobronchial collapsibility and expiratory air trapping [2]. Interpretation is done at the workstation. Visualization of the overlapped thin axial images sequentially in cine mode allows the bronchial divisions to be followed from the segmental origin to the distal bronchial lumens down to the smallest bronchi, which can be identified on thin-section images. Moving and swiveling through the volume is helpful for selecting the plane displaying better distribution of airway abnormality and is highly recommended. Multiplanar reformation of variable thicknesses created on the selecting planes may be completed by intensity projection techniques. The application of minimum intensity projection is appreci-

ated to visualize airway dilatation, diverticula, and fistulas and facilitate assessing the presence and extent of expiratory air trapping. Maximum intensity projection is appreciated when displaying mucoid impactions seen in dilated bronchi or for displaying small centrilobular nodular linear opacities (tree-in-bud sign) expressing infectious bronchiolitis. Volume-rendering techniques (CT bronchography) consist of segmentation of the lumen-wall interface of the airways. This technique has proven to be of particular interest in diagnosing mild changes in airway caliber and understanding complex tracheobronchial abnormalities. Virtual bronchoscopy provides an internal rendering of the tracheobronchial inner surface. It is appreciated to detect inner nodulation expressing granulomatous or tumoral lesions in proximal airways.

Tracheobronchial Tumors

MDCT plays a key role in depicting tracheobronchial tumors and assessing tumor extent within the lumen, airway wall, and surrounding structures before treatment planning. Lesions larger than 5 mm within the airways are usually detected using CT due to the natural contrast between luminal and soft tissue density of the lesions [3-5].

Primary Malignant Tumors

Primary malignant tumors are rare in the trachea compared with laryngeal or bronchial cancers. The most frequent histological types are squamous cell carcinoma and adenoid cystic carcinoma.

Adenoid Cystic Carcinoma (Sialadenoid Tumor)

Adenoid cystic carcinoma is a low-grade malignancy that is not associated with cigarette smoking. It occurs in patients in their forties and shows no sex predilection. In the central airways, it has a propensity to infiltrate the airways walls, with submucosal extension manifesting as a sessile, polypoid, annular, or diffuse infiltration. The inner surface is smooth and regular. An extraluminal growth, visible on CT scan, is a common feature.

Squamous Cell Carcinoma

Squamous cell carcinoma is the most frequent primary malignancy of the trachea affecting predominantly men between 50 and 60 years of age. It is strongly associated with cigarette smoking. The tumor appears on CT as a polypoid intraluminal mass or an eccentric irregular wall thickening presenting an irregular surface. The tumor has a tendency to spread to adjacent mediastinal lymph nodes with an extension into the mediastinum.

Carcinoid Tumor

Carcinoid tumor is a low-grade, malignant, neuroendocrine neoplasm representing 1-2% of primary lung

tumors. It appears on CT scan as a well-circumscribed polypoid mass that protrudes into the airway lumen. Segmental or lobar atelectasis and obstructive pneumonitis, as well as foci of calcifications, are present in 30% of cases. Marked homogeneous early contrast enhancement of an endobronchial nodule consistent with the high vascularity of this tumor may be present.

Mucoepidermoid Carcinoma

Mucoepidermoid carcinoma is a rare tumor that originates from the minor salivary glands lining the tracheobronchial tree, occurs in young patients (<40 years old), and mainly affects the segmental bronchi creating airway obstruction. CT appearance is an endobronchial mass smoothly oval or lobulated containing some punctuate calcifications with variable contrast enhancement.

Lymphoma of the Trachea

Lymphoma of the trachea is rare and is usually related to mucosa-associated lymphoid tissue. CT appearance is nonspecific.

Secondary Tracheobronchial Malignancy

Direct invasion of the central airways by neoplasms of the thyroid, esophagus, lung, or larynx is much more frequent than hematogenous metastases. CT demonstrates the primary neoplasm and its extension by contiguity to the main airways (endoluminal mass, cartilage destruction, and tracheobronchialesophageal fistula). Many cancers have the potential to metastasize to the trachea and bronchi. Endotracheal or endobronchial metastases appear as endotracheal nodules or eccentric thickening of the airway wall or soft tissue density with contrast enhancement.

Benign Tracheobronchial Neoplasms

Benign tracheobronchial neoplasms represent less than 2% of lung neoplasms. CT shows endoluminal masses that are confined within the tracheobronchial lumen without evidence of surrounding structure involvement. They tend to be demarcated, round, and <2 cm in diameter. Because they originate in the mucosa or submucosa, the overlying epithelium is usually intact, resulting in a smooth appearance of the tumor surface in the airway lumen. Histology includes mainly hamartomas, lipomas, leiomyomas, fibromas, chondromas, and schwannomas. Endobronchial hamartomas represent 30% of intrathoracic hamartomas. The presence of fat with or without calcification is diagnostic.

Laryngotracheobronchial papillomatosis is a neoplastic disease caused by human papillomavirus infection usually acquired at birth from an infected mother. The lesion arises in the larynx and spreads by seeding from the upper airway to the trachea and proximal bronchi in

around 50% of cases. Exceptionally (1%), the infections spread into the lung parenchyma. In such cases, there are multiple lung nodules and cavitary and cystic lesions in the parenchyma.

Nonneoplastic Tracheobronchial Disorders

Here we describe ten nonneoplastic tracheobronchial disorders [3, 5, 6].

Posttraumatic Stenoses

Posttraumatic tracheal strictures are usually secondary to damage from a cuffed endotracheal or tracheostomy tube or to external neck trauma. The lesions consist of granulation tissue which develops a dense mucosal and submucosal fibrosis associated with distortion of cartilage plates. The two principal sites of stenosis following intubation or tracheostomy tube are at the stroma or the endotracheal or tracheostomy tube balloon level. The size of narrowing is usually well visualized at CT. The narrowing is often concentric with regular soft tissue thickening. Postintubation stenosis extends for several centimeters and typically involves the trachea above the thoracic inlet level. Posttracheostomy stenosis typically begins 1-1.5 cm distal of the inferior margin of the tracheostomy stoma and involves 1.5-2.5 cm of the tracheal wall. Multiplanar reformations are particularly helpful in defining accurately stenosis site, length, and degree on longitudinal images. Focal and circumferential narrowing may produce a characteristic hourglass configuration. Less commonly, the tracheal or bronchial stenosis may present as a thin membrane or granulation tissue protruding into the airway lumen. In select cases, the degree of stenosis may also be assessed by use of virtual bronchoscopy.

Infectious Diseases

A number of infections, both acute and more often chronic, may affect the trachea and proximal bronchi, resulting in both focal and diffuse airway disease. Subsequent fibrosis may result in localized airway narrowing. The most common causes of infectious tracheobronchitis are bacterial tracheitis in immunocompromised patients, tuberculosis, rhinoscleroma (*Klebsiella rhinoscleromatis*), and necrotizing invasive aspergillosis. On CT, the extent of irregular and circumferential tracheobronchial narrowing is clearly demonstrated, and in some patients an accompanying mediastinitis (opacification of the mediastinal fat) is evident. In active disease, the narrowed trachea and frequently one or the other main bronchus have an irregularly thickened wall. In the fibrotic or healed phase, the airway is narrowed but has a smooth and normal wall thickness. Occasionally, due to the presence of chronic fibrous or granulomatous hilitis/mediastinitis, tuberculous infection of the trachea and/or proximal bronchi may mimic malignant tumor of the airways on CT scans.

Wegener Granulomatosis

Involvement of the large airways is a common manifestation of Wegener granulomatosis. Inflammatory lesions may be present with or without subglottic or bronchial stenosis, ulcerations, or pseudotumors. Radiologic manifestations include thickening of the subglottic region and proximal trachea, with a smooth, symmetric, or asymmetric narrowing over variable length. The tracheal ring may present thickening and calcification. Cartilaginous erosion and ulcerations also may be seen, as may stenosis on any main, lobar or segmental bronchus. Nodular or polypoid lesions may be seen on the inner contour of the airway lumen.

Relapsing Polychondritis

Relapsing polychondritis is a rare systemic disease of autoimmune pathogenesis that affects cartilage at various sites, including ears, nose, joints, and tracheobronchial tree. Histologically, the acute inflammatory infiltrate present in the cartilages and perichondrial tissue induces progressive dissolution and fragmentation of the cartilage followed by fibrosis. Symmetric subglottic stenosis is the most frequent manifestation in the chest. As the disease progresses, the distal trachea and bronchi may be involved. CT scans show smooth thickening of the airway wall associated with more or less diffuse narrowing. In the early stage, the posterior wall of the trachea is spared, but in advanced disease, circumferential wall thickening occurs. The trachea may become flaccid, with considerable collapse at expiration. Gross destruction of the cartilaginous rings with fibrosis may cause stenosis.

Amyloidosis

Amyloid deposition in the trachea and bronchi may be seen in association with systemic amyloidosis or as an isolated manifestation. As a result, the amyloid forms either multifocal or diffuse submucosal plaques or masses. The overlying mucosa is usually intact. Dystrophic calcification or ossification is frequently present. CT scans show focal or, more commonly, diffuse airway wall thickening and lumen narrowing. Calcification may be seen. Proximal bronchi narrowing can lead to distal atelectasis, bronchiectasis, or both, and obstructive pneumonia.

Tracheobronchopathia Osteochondroplastica

Tracheobronchopathia osteochondroplastica (TO) is a rare disorder characterized by the presence of multiple cartilaginous nodules and bony submucosal nodules on the inner surface of the trachea and proximal airways. TO affects men more frequently than it does women, and most patients are older than 50 years of age. Histologically, the nodules contain heterotopic bone, cartilage, and calcified acellular protein matrix. The overlying bronchial mucosa is normal, and because it contains no cartilage, the tracheal posterior wall is spared. On CT, tracheal cartilages

are thickened and show irregular calcifications. Nodules may protrude from the anterior and lateral walls into the lumen; they usually show foci of calcification.

Saber-Sheath Trachea

Characterized by diffuse narrowing involving the intrathoracic trachea, the saber-sheath entity is almost always associated with COPD. The lesion's pathogenesis is obscure, but probably it is an acquired deformity related to the abnormal pattern and magnitude of intrathoracic pressure changes in COPD. On radiographs and CT, the condition is easily recognized by the internal side-to-side diameter of the trachea, which is decreased to half or less than the corresponding sagittal diameter. The narrowing usually affects the entire intrathoracic trachea, with an abrupt return to normal caliber at the thoracic inlet. The trachea usually shows a smooth inner margin but occasionally has a nodular contour. Calcification of the tracheal cartilage is frequently evident.

Tracheobronchomegaly (Mounier-Kuhn Disease)

Tracheobronchomegaly manifests as a marked dilatation of the trachea and mainstem bronchi. It is often associated with tracheal diverticulosis, recurrent lower respiratory tract infection, and bronchiectasis. Atrophy affects the elastic and muscular elements of both the cartilaginous and membranous parts of the trachea. The diagnosis is based on radiologic findings. The immediately subglottic trachea has a normal diameter, but it expands as it passes to the carina, and this dilatation often continues into the major bronchi. The atrophic mucosa prolapses between cartilage rings and gives the trachea a characteristically corrugated outline. Corrugations may become exaggerated to form sacculations or diverticula. On CT, a tracheal diameter >3 cm (measured 2 cm above the aortic arch) and diameter of 2.4 and 2.3 cm for the right and left bronchi, respectively, are diagnosing criteria. Additional findings include tracheal scalloping or diverticula (especially along the posterior membranous tracheal wall).

Tracheobronchomalacia

Resulting from weakened tracheal cartilages, tracheobronchomalacia may be seen in association with a number of disorders, including tracheobronchomegaly, COPD, diffuse tracheal inflammation such as relapsing polychondritis, and following trauma [7, 8]. Dynamic expiratory MDCT may offer a feasible alternative to bronchoscopy in patients with suspected tracheobronchomalacia. Dynamic expiratory CT may show complete collapse or collapse of $>70\%$ of the airway lumen. Central tracheobronchial tree involvement may be diffuse or focal. The reduced airway may have an oval or crescentic shape, which is due to the bowing of posterior membranous wall. The increase in compliance is due to the loss of integrity of the wall's structural components and is

particularly associated with damaged or destroyed cartilages. The coronal diameter of the trachea becomes significantly larger than the sagittal diameter, producing a lunate configuration to the trachea.

Broncholithiasis

In broncholithiasis, peribronchial calcified nodal disease erodes into or distorts an adjacent bronchus. The underlying abnormality is usually granulomatous lymphadenitis caused by mycobacterium tuberculosis or fungi such as histoplasma capsulatum. A few cases have been reported with silicosis. Calcified material in a bronchial lumen or bronchial distortion by peribronchial disease results in airway obstruction. This leads to collapse, obstructive pneumonitis, mucoid impaction, or bronchiectasis. Symptoms include cough, hemoptysis, recurrent episodes of fever, and purulent sputum. Broncholithiasis is recognized at CT by the presence of a calcified endobronchial or peribronchial lymph node associated with bronchopulmonary complication due to obstruction in the absence of an associated soft tissue mass.

Tracheobronchial Fistula and Dehiscence

Multidetector MDCT with thin collimation is the most accurate technique to identify peripheral bronchopleural fistula that are most commonly caused by necrotizing pneumonia or secondary to traumatic lesions [1, 5]. Nodobronchial and nodobronchoesophageal fistulas that are most commonly caused by mycobacterium tuberculosis infection are depicted by the presence of gas in cavitated hila or mediastinal lymphadenopathy adjacent to the airways. Tracheal diverticula and tracheobronchoesophageal fistula may also be diagnosed even in adults. Malignant neoplasia, particularly esophageal, is the most common cause of tracheoesophageal fistula in adults. Occasionally, congenital fistulas first manifest in adults. Infection and trauma are the most frequent nonmalignant causes. MDCT has a high degree of sensitivity and specificity for depicting bronchial dehiscence occurring after lung transplantation. Bronchial dehiscence is seen as a bronchial wall defect associated with extraluminal air collections. Congenital anomaly of the bronchial tree may mimic bronchial dehiscence – the accessory cardiac bronchus characterized by a large blind outpouching arising from the middle part of the right intermediate bronchus [9]. Although typically asymptomatic, this anomaly may serve as a potential reservoir for retained secretions, leading to chronic inflammation and hypervascularity that in turn lead to recurrent episodes of aspiration pneumonitis or hemoptysis.

Bronchiectasis

Bronchiectasis is a chronic condition characterized by local, irreversible bronchi dilatation and is usually associated

Table 6. Specific causes of disseminated bronchiectasis

Acute, chronic, or recurrent infections
– Genetic abnormalities
– Cystic fibrosis
– Dyskinetic cilia syndrome
– Young's syndrome
– William-Campbell syndrome
– Mounier-Kuhn syndrome (tracheobronchomegaly)
– Immunodeficiency syndromes
– Yellow nail syndrome
– Alpha-1-antitrypsin deficiency
Noninfectious inflammatory diseases
– Allergic bronchopulmonary aspergillosis
– Asthma
– Systemic diseases (rheumatoid arthritis, Sjögren syndrome, inflammatory bowel diseases)
– Posttransplantation bronchiolitis obliterans

with inflammation. Despite its decreased prevalence in developed countries, bronchiectasis remains an important cause of hemoptysis and chronic sputum production. Although the causes of bronchiectasis are numerous (Table 6), there are three mechanisms by which dilatation can develop: bronchial obstruction, bronchial wall damage, and parenchymal fibrosis. In the first two mechanisms, the common factor is the combination of mucus plugging and bacterial colonization. Cytokines and enzymes released by inflammatory cells plus toxins from the bacteria result in a vicious cycle of increasing airway wall damage, mucous retention, and bacterial proliferation. In parenchymal fibrosis, bronchi dilatation is caused by maturation and retraction of fibrous tissue located in the parenchyma adjacent to an airway (traction bronchiectasis).

Pathology

Pathologically, bronchiectasis has been classified into three subtypes, reflecting increasing disease severity: (1) cylindrical, characterized by relatively uniform airway dilatation; (2) varicose, characterized by nonuniform and somewhat serpiginous dilatation; and (3) cystic. As the extent and degree of airway dilatation increase, the lung parenchyma distal to the affected airway shows increasing collapse of fibrosis.

CT Findings

CT findings of bronchial dilatation include lack of bronchial lumina tapering (the cardinal sign of bronchiectasis), internal diameter bronchi greater than that of the adjacent pulmonary artery (signet-ring sign), visualization of bronchi within 1 cm of the costal pleura or abutting the mediastinal pleura, and mucus-filled dilated bronchi [5]. In varicose bronchiectasis, the bronchial lumen assumes a beaded configuration. Cystic bronchiectasis is seen as a string of cysts caused by sectioning of irregular dilated bronchi along their lengths, or a cluster of cysts caused by

multiple dilated bronchi lying adjacent to each other. Cyst clusters are most frequently seen in atelectatic lobe. Air-fluid levels, caused by retained secretion, may be present in the dependent portion of the dilated bronchi. Secretion accumulation within bronchiectatic airways is generally easily recognizable as lobulated glove-finger, V- or Y-shaped densities. CT may show a completely collapsed lobe containing bronchiectatic airways. Subtle degrees of volume loss may be seen in lobes in relatively early disease.

Associated CT findings of bronchiolitis are seen in about 70% of patients with bronchiectasis. These abnormalities are very common in patients with severe bronchiectasis and can even precede the development of bronchiectasis. The obstructive defect found during pulmonary tests in patients with bronchiectasis is the consequence of an obstructive involvement of the peripheral airways (obliterative bronchiolitis). The extent and severity of bronchiectasis and bronchial wall thickening correlate with pulmonary function test findings of airflow obstruction. In patients with bronchiectasis, bronchial wall thickening, as well as the extent of decreased lung attenuation, remains the strongest determinants of airflow obstruction [10, 11]. In addition, bronchial wall thickening on baseline CT correlates with functional deterioration over time [12].

MDCT with thin collimation is the highly recommended technique to assess the presence and extent of bronchiectasis [13]. Several studies have demonstrated that multiplanar reformations increase bronchiectasis detection rate, readers' confidence as to bronchiectasis distribution, and improved agreement between observers as to the diagnosis of bronchiectasis [14–16].

The reliability of CT for distinguishing among the causes of bronchiectasis is somewhat controversial. An underlying cause is found in fewer than half of patients, and CT features alone do not usually allow a confident distinction between idiopathic bronchiectasis versus a known cause.

Small-Airway Diseases

Although visualizing normal bronchioles is impaired by spatial resolution limitations of thin-section CT, these airways may become directly visible when bronchiolar wall inflammation and accompanying exudate develop. On the other hand, bronchiolar changes can be too small to be visible directly but can cause indirect signs that suggest small-airways involvement. Obstruction of the bronchioles actually may induce regional underventilation, leading to reflex vasoconstriction; and expiratory air trapping, both being depictable on CT images [5, 17, 18]. Four different CT patterns can express small-airway pathology.

Small Centrilobular Nodular and Branching Linear Opacities (Tree-in-Bud Sign)

Tree-in-bud sign is created by focal or multifocal areas of small centrilobular nodular and branching linear opacities.

It reflects abnormal bronchiolar wall thickening, dilatation of bronchiolar lumen filled with mucous or pus, and is often associated with peribronchiolar inflammation [19]. The tree-in-bud sign is characteristic of acute or chronic infectious bronchiolitis. It can also be seen in diffuse pan-bronchiolitis and diffuse aspiration bronchiolitis.

Poorly Defined Centrilobular Nodular Ground-Glass Opacities

Poorly defined centrilobular nodular ground-glass opacity reflects the presence of peribronchiolar inflammation in the absence of airway filling with secretion. When nodule distribution is diffuse and homogeneous, the pattern is suggestive of bronchiolar disease or vascular entities. Bronchiolar entities include respiratory bronchiolitis, bronchiolitis associated with hypersensitivity pneumonitis, and follicular bronchiolitis.

Decreased Lung Attenuation and Mosaic Perfusion

Areas of decreased lung attenuation associated with vessels of decreased caliber observed in bronchiolar disease reflect bronchiolar obstruction resulting in decreased perfusion. In acute bronchiolar obstruction, this decrease represents a physiologic reflex of hypoxic vasoconstriction, but in the chronic state there is vascular remodeling and the reduced caliber becomes irreversible. The lung areas of decreased attenuation related to decreased perfusion can be patchy or widespread in distribution. They are poorly defined, or sharply demarcated giving a geographical outline, representing a collection of affected secondary pulmonary lobules. Blood-flow redistribution to the normally ventilated areas causes increased attenuation of lung parenchyma in these areas. In patchwork, the combination of abnormal areas of low attenuation and normal lung or less diseased areas that either appear normal in attenuation or hyperattenuated, increases the appearance of mosaic attenuation. Because the vessels running in the abnormal hypoattenuated areas are reduced in caliber and vessels running in normal areas are increased in size, the mosaic pattern is called mosaic perfusion. This pattern is accentuated on expiratory CT because the low-attenuation areas show air trapping. The air is trapped, and the cross-sectional area of the affected parts of the lung does not decrease in size on expiratory CT. Usually, the regional inhomogeneity of lung density seen at end inspiration on thin-section CT scans is accentuated on sections obtained at the end of or during expiration because the high-attenuation areas increase in density and the low-attenuation areas remain unchanged. In a more global involvement of the small airways, the lack of regional homogeneity of lung attenuation is difficult to perceive on inspiratory scans and, as a result, mosaic perfusion becomes visible only on expiratory scans. In patients with particularly severe and widespread small-airways involvement, the patchy distribution of hypoattenuation and mosaic pattern is lost. Inspiratory scans appear with an apparent uniformity of decreased attenuation in the lungs, and scans taken at end expiration may appear unre-

Table 7. Causes of, and association with, obliterative (constrictive) bronchiolitis

– Postinfection
– Childhood viral infection (adenovirus, respiratory syncytial virus, influenza, parainfluenza)
– Adulthood and childhood infections (<i>Mycoplasma pneumoniae</i> , <i>Pneumocystis carinii</i> in AIDS patients, endobronchial spread of tuberculosis, bacterial bronchiolar infection)
– Postinhalation (toxic fume and gases)
– Diffuse aspiration bronchiolitis (chronic occult aspiration in the elderly, patients with dysphagia)
– Connective tissue disorders (rheumatoid arthritis, Sjögren syndrome)
– Allograft recipients (bone-marrow transplant, heart-lung or lung transplant)
– Drugs (penicillamine, lomustine)
– Ulcerative colitis
– Other conditions
– Bronchiectasis
– Cystic fibrosis
– Hypersensitivity pneumonitis
– Microcarcinoid tumorlets (neuroendocrine cell hyperplasia)
– Sauropus androgynus ingestion
– Idiopathic

markable. In these patients, the most striking features are paucity of pulmonary vessels and lack of change of the cross-sectional areas of the lung at comparable levels on inspiratory and expiratory scans.

Mosaic perfusion is seen in patients who have obliterative bronchiolitis, bronchiolitis associated with hypersensitivity pneumonitis, as well as in asthma and COPD. Obliterative bronchiolitis, characterized by submucosal circumferential fibrosis along the central axis of terminal bronchioles, is the result of a variety of causes and, rarely, is idiopathic (Table 7). Bronchial wall thickening and bronchiectasis, both central and peripheral, are also commonly present. The mosaic perfusion pattern may also be seen in patients with chronic thromboembolic disease; however, in this condition, a frank dilatation of proximal pulmonary arteries within the hyperattenuated areas and extensive areas of hypoattenuation and hypoperfusion are almost always present.

Expiratory Air Trapping

Lobular areas of air trapping may appear on expiratory CT scans, whereas there is no lung attenuation abnormality depicted on inspiratory CT scans. These areas are commonly well demarcated, reflecting the geometry of individual or joined lobules. Even if these lobular areas of air trapping may be present in dependent parts of the lung on expiratory CT scans of normal individuals, the presence in nondependent parts of the lung or coalescence of these images that extend to an area equal to or greater than one segment in dependent parts of the lung has to be considered abnormal. It may be seen in smokers and patients with asthma, obliterative bronchiolitis, bronchiolitis associated with hypersensitivity pneumonitis, and sarcoidosis.

Asthma

Asthma is a chronic inflammatory condition responsible for airway hyperresponsiveness to several stimuli and causes episodes of wheezing, coughing, and breathlessness due to airflow obstruction, which is reversible either spontaneously or after bronchodilatation. Over time, this inflammatory disorder induces structural changes in airways (fibrosis, smooth-muscle hypertrophy and hyperplasia, and neovessel formation), which lead to persistent airflow limitation [3, 20]. The main clinical indication for imaging in asthmatic patients is to identify diseases that may mimic asthma clinically, particularly hypersensitive pneumonitis, obliterative bronchiolitis, and tracheal or carinal obstruction by neoplastic or nonneoplastic tracheal disorders. In asthma, when CT is performed, abnormalities on bronchi may be depicted. Mucoid impactions and linear bands, reflecting subsegmental or segmental atelectasis, are reversible on follow-up. Bronchial wall thickening is commonly present and has been demonstrated to correlate with clinical severity and duration of asthma and the degree of airflow obstruction [21]. It also correlates with pathologic measures of remodelling from bronchial biopsies [22]. Bronchiectasis may also be present, and its prevalence is associated with an increased severity of asthma.

In patients with persistent moderate asthma, mosaic perfusion reflects remodelling in the small airways. The extent of expiratory air trapping does not change after inhalation of salbutamol [23]. On the other hand, in patients with mild or moderate uncontrolled asthma, corticosteroid inhalation decreases the extent of air trapping, suggesting that CT may be a new outcome related to control of the disease [24].

Airway Disease in COPD

COPD is regarded as slow and progressive airway obstructive disorders [25, 26] resulting from an exaggerated inflammatory response to cigarette smoke that ultimately destroy lung parenchyma (emphysema) and induce irreversible reduction in the small airway caliber (obstructive bronchiolitis). Both emphysema, due to loss of alveolar attachments and decrease of elastic recoil, and airway wall remodelling with peribronchiolar fibrosis, are responsible for airflow limitation. This explains why individuals having the same degree of severity of functional impairment may present on CT scans with different morphologic appearances. Some people have extensive emphysema, whereas others with the same degree of airflow limitation have no or little emphysema, suggesting small-airway remodelling. These differences in morphologic appearances suggest differences in pathophysiology and genomic profile. CT may help define the different phenotypes of COPD for better stratification of patients in clinical trials and ultimately for a more personalized treatment. Airway disease phenotypes of COPD include abnormalities on the small and large airways. Small

centrilobular nodules and ground-glass attenuation predominant in the upper lobes reflect inflammatory changes in and around the bronchioles (respiratory bronchiolitis), which are reversible after smoking cessation and steroid treatment. Mosaic perfusion and respiratory air trapping reflect obstructive bronchiolitis and definite remodelling on the small airways.

Saber-sheath trachea occurs specifically in COPD. Bronchial wall thickening and irregularities are frequently present. Bronchial wall thickening quantitatively assessed on CT scans may provide an estimate of small-airway remodelling in the absence of extensive emphysema [27]. Bronchial wall thickness is one of the strongest determinants of forced expiratory volume in 1 s (FEV1) in COPD patients [28]. In cigarette smokers, bronchial wall thickness is related to lung function (FEV1) [29]. Bronchial diverticula, seen as small amounts of air collection in the walls of the main and lobar bronchi, represent dilated ducts of mucous glands, which are fused, creating herniation through and between the smooth-muscle bundles of the bronchial walls. They are frequently observed in smokers, particularly in heavier smokers with a history of coughing, with more severe functional impairment, greater extent of emphysema, and more severe bronchial wall thickening [30]. Because of cartilage deficit, evidence of moderate tubular bronchiectasis, primarily in the lower lobes, is common. Bronchiectasis is often associated with more severe COPD exacerbations, lower airway bacterial colonization, and increased sputum inflammatory markers. However, the presence of bilateral varicose and cystic bronchiectasis in patients with panlobular emphysema should lead to the diagnosis of alpha-1-antitrypsin deficiency. Cartilage deficiency in COPD may also induce prominent collapse of airway lumen (mostly in the lower lobes where the deficit is prominent) at expiration, contributing to airflow limitation. Tracheomalacia may also occur.

References

1. Grenier PA, Beigelman-Aubry C, Fetita C et al (2002) New frontiers in CT imaging of airway disease. *Eur Radiol* 12:1022-1044
2. Beigelman-Aubry C, Brillet PY, Grenier PA (2009) Multidetector CT of the airways: Technique and normal results. *Radiol Clin North Am* 47:185-201
3. Boiselle PM, Lynch DA (2008) CT of the airways. Humana, New York, NY
4. Ferretti GR, Bithigoff C, Righini CA et al (2009) Imaging of tumors of the trachea and central bronchi. *Radiol Clin North Am* 47:227-241
5. Naidich DP, Webb WR, Grenier PA et al (2005) Imaging of the airways. Functional and radiological correlations. Lippincott Williams & Wilkins, Philadelphia, PA
6. Grenier PA, Beigelman-Aubry C, Brillet PY (2009) Nonneoplastic tracheal and bronchial stenoses. *Radiol Clin North Am* 47:243-260
7. Baroni RH, Feller-Kopman D, Nishino M et al (2005) Tracheomalacia: comparison between end-expiratory and dynamic expiratory CT for evaluation of central airway collapse. *Radiology* 235:635-641

8. Lee EY, Litmanovich D, Boiselle PM (2009) Multidetector CT evaluation of tracheobronchomalacia. *Radiol Clin North Am* 47:261-269
9. Desir A, Ghaye B (2009) Congenital abnormalities of intrathoracic airways. *Radiol Clin North Am* 47:203-225
10. Roberts HR, Wells AU, Milne DG et al (2005). Airflow obstruction in bronchiectasis: correlation between computed tomography features and pulmonary function tests. *Thorax* 55:198-204
11. Ooi GC, Khong PL, Chang-Yeung M et al (2002) High-resolution CT quantification of bronchiectasis: clinical and functional correlation. *Radiology* 225:663-672
12. Sheehan RE, Wells AU, Copley SJ et al (2002) Comparison of serial computed tomography and functional change in bronchiectasis. *Eur Respir J* 20:581-587
13. Dodd JD, Souza CA, Müller NL (2006) Conventional high-resolution CT versus helical high-resolution MDCT in the detection of bronchiectasis. *AJR Am J Roentgenol* 187:414-420
14. Chooi WK, Matthews S, Bull MJ et al (2003) Multislice helical CT: the value of multiplanar image reconstruction in assessment of the bronchi and small airways disease. *Br J Radiol* 76:536-540
15. Remy-Jardin M, Amara A, Campistron P et al (2003) Diagnosis of bronchiectasis with multislice spiral CT: accuracy of 3-mm-thick structured sections. *Eur Radiol* 13:1165-1171
16. Sung YM, Lee KS, CA YI (2003) Additional coronal images using low-milliamperage multidetector-row computed tomography: effectiveness in the diagnosis of bronchiectasis. *J Comput Assist Tomogr* 27:490-495
17. Franquet T, Müller NL (2003) Disorders of the small airways: high-resolution computed tomographic features. *Semin Respir Crit Care Med* 24:437-444
18. Pipavath SNJ, Stern EJ (2009) Imaging of small airway disease (SAD). *Radiol Clin North Am* 47:307-316
19. Franquet T, Müller NL, Oikonomou A, Flint JD (2004) Aspergillus infection of the airways: computed tomography and pathologic findings. *J Comput Assist Tomogr* 28:10-16
20. Woods AQ, Lynch DA (2009) Asthma: an imaging update. *Radiol Clin North Am* 47:317-329
21. Niimi A, Matsumoto H, Amitani R et al (2000) Airway wall thickness in asthma assessed by computed tomography. Relations to clinical indices. *Am J Respir Crit Care Med* 162:1518-1523
22. Aysola RS, Hoffman EA, Gierada D et al (2008) Airway remodeling measured by multidetector CT is increased in severe asthma and correlates with pathology. *Chest* 134:1183-1191
23. Laurent F, Latrabe V, Raherison C et al (2000) Functional significance of air trapping detected in moderate asthma. *Eur Radiol* 10:1404-1410
24. Tunon-de-Lara JM, Laurent F, Giraud V et al (2007) Air trapping in mild and moderate asthma: effect of inhaled corticosteroids. *J Allergy Clin Immunol* 119:583-590
25. Ley-Zaporozhan J, Kauczor HU (2009) Imaging of airways: chronic obstructive pulmonary disease. *Radiol Clin North Am* 47:331-342
26. Brillet PY, Fetita CI, Saragaglia A et al (2008) Investigation of airway using MDCT for visual and quantitative assessment in COPD patients. *Int J Chron Obstruct Pulm Dis* 3:97-107
27. Nakano Y, Wong JC, de Jong PA et al (2005) The prediction of small airway dimensions using computed tomography. *Am J Respir Crit Care Med* 171:142-146
28. Aziz ZA, Wells AU, Desai SR et al (2005) Functional impairment in emphysema: contribution of airway abnormalities and distribution of parenchymal disease. *AJR Am J Roentgenol* 185:1509-1515
29. Berger P, Perot V, Desbarats P et al (2005) Airway wall thickness in cigarette smokers: quantitative thin-section CT assessment. *Radiology* 235:1055-1064
30. Sverzellati N, Ingegnoli A, Calabro E et al (2010) Bronchial diverticula in smokers on thin-section CT. *Eur Radiol* 20:88-94

Understanding Diffuse Lung Disease in Children: Rationale for a New Classification System

Alan S. Brody

Department of Radiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Introduction

Recent efforts to improve our understanding of diffuse lung disease in children are leading to new knowledge of this diverse group of diseases and a greater ability to care for these patients [1]. For adult patients, collaboration between societies resulted in a classification system that has formed the basis for understanding and further investigating these diseases for the past decade [2]. No such system is used for children with such diseases. The adult system has been applied to children, but with limited success. This is not surprising, as there are marked differences between diffuse lung disease in adults and in children.

In this text, with few exceptions, the term diffuse lung disease is used to describe this diverse group of diseases. Although inaccurate, as many diseases included in this category involve pulmonary spaces other than the interstitium, the term interstitial lung disease, or ILD, is widespread and unlikely to be replaced. Thus, the term diffuse lung disease is used in this text as an equivalent term to ILD, or in children, chILD.

Diffuse lung disease is more common in adults than in children, with an incidence of approximately 700 per million in adults [3] and of 4 per million in children [4]. In adults, usual interstitial pneumonia (UIP) is the dominant form of diffuse lung disease, accounting for up to one third of cases. In children, UIP is almost never seen, and no single form dominates childhood diffuse lung disease. In addition, there are unique entities seen in children (described below) that do not fit into the histologic classification of adult diffuse lung disease. Through collaborative efforts by pathologists, clinicians and imagers, a different approach to diffuse lung diseases in children has developed. This new understanding begins by including in the definition of chILD all children with a presentation consistent with diffuse lung disease, rather than by the presence of specific pathologic findings. These children are recognised by the presence of chILD syndrome, a constellation of findings seen in most children with diffuse lung disease. These findings include the presence of respiratory symptoms for >1 month with: (1) symptoms (cough, dyspnea, exercise intolerance), (2) signs (crackles, tachypnea, retractions), (3) hypoxaemia, (4) diffuse parenchymal abnormality on

chest radiograph or computed tomography (CT), and (5) restrictive or obstructive lung function. Other causes or respiratory symptoms should be excluded, such as bronchopulmonary dysplasia, heart disease, malignancy, aspiration and cystic fibrosis [5]. More than 90% of children diagnosed with diffuse lung disease will have three or more of the components listed.

The different diseases affecting children with chILD syndrome are organized by a new classification scheme that divides these diseases into seven categories [6, 7] (Table 1). These are the primary references for the cate-

Table 1. Classification scheme for diffuse lung disease in children

Disease category	Description
Diffuse developmental disorders	Acinar dysplasia, congenital alveolar dysplasia, alveolar capillary dysplasia with misalignment of the pulmonary veins
Growth abnormalities	Pulmonary hypoplasia, chronic neonatal lung disease (BPD), related to chromosomal disorders, congenital heart disease
Specific disorders of unknown etiology	Neuroendocrine cell hyperplasia of infancy (chronic bronchiolitis of infancy); pulmonary interstitial glycogenosis (infantile cellular interstitial pneumonia)
Surfactant dysfunction mutations	<i>SP-B</i> , <i>SP-C</i> , <i>ABCA3</i> , other genetic mutations
Disorders of the normal host	Infectious and postinfectious processes related to environmental agents, aspiration, eosinophilic pneumonia
Disorders related to systemic disease processes	Immune-mediated disorders, acquired PAP, pulmonary haemorrhage syndromes, storage disease, sarcoidosis, Langerhans cell histiocytosis, malignant infiltrates
Disorders of the immunocompromised host	Opportunistic infections related to therapeutic intervention, related to solid organ, lung and bone marrow transplantation and rejection syndromes
Disorders masquerading as ILD	Arterial, venous, lymphatic disorders; congestive changes related to cardiac dysfunction
Unclassified	End-stage lung disease, inadequate biopsy, insufficient clinical information

BPD, bronchopulmonary dysplasia; *SP-B*, surfactant B moiety; *SP-C*, surfactant C moiety; *ABCA3*, adenosine-triphosphate-binding cassette A3; *PAP*, pulmonary alveolar proteinosis

gory descriptions later in this chapter. Unlike the adult classification that is based on pathologic appearance, this system is based on the etiology of the disease process. In this system, a specimen with the pathologic appearance of pulmonary alveolar proteinosis and one with the appearance of nonspecific interstitial pneumonia are classified in the same category if in both cases the etiology of the appearance is a surfactant dysfunction mutation. The majority of this chapter describes the different entities that make up childhood diffuse lung disease, with an emphasis on diseases seen primarily in children.

CT and Lung Biopsy Technique

Chest radiographs are usually the first imaging study performed in these children. Plain radiographs often provide useful information and are rarely normal, but they are neither sensitive nor specific enough to eliminate the need for a CT scan [8]. The goal when performing CT for diffuse lung disease in children is to provide the necessary image quality to make the diagnosis with the least risk to the child. The primary risks are the risk of sedation or anaesthesia and of radiation exposure. Authors disagree on the need for lung-volume control in children who are too young to cooperate with breathing instructions. Long et al. pointed out that both improved image quality and true inspiratory and expiratory images improve diagnostic quality and can be performed without general anaesthesia or intubation [9]. Lucaya et al. found that imaging during quiet breathing and the use of decubitus positioning allows sufficient image quality for diagnostic purposes [10, 11]. There is broad agreement that atelectasis markedly limits interpretation of chest CT for diffuse lung disease in children, and that a very low radiation dose technique can be used for these examinations.

High-resolution CT (HRCT) is the most commonly used method for evaluating childhood diffuse lung disease. Obtaining thin axial sections at intervals decreases radiation dose several times compared with volumetric imaging. 1-mm (approximately) sections at 5-mm intervals can be used in very young children. In older children, 1-mm sections at 10-mm intervals should be used. Expiratory images can be obtained with a lower dose technique than the inspiratory series. No more than one expiratory slice for each two inspiratory slices should be obtained. The fastest scan time available should be used. There is no benefit to reducing kilovolt peak rather than milliamperage, unless the milliamperage lower limit has been reached. Intravenously administered contrast medium is not required.

Lung biopsy for diffuse lung disease requires a surgical lung biopsy in almost all cases. Imagers will likely be involved in selecting a biopsy site. It is often useful to obtain biopsies from two sites and is not uncommon for a biopsy obtained in an area of normal-appearing lung to be of equal or greater value than the biopsy from the abnormal area. It has been observed that biopsies from the tip of the lingula or right middle lobe frequently

underestimate the disease present elsewhere, and these sites should be avoided. Guidelines for obtaining and handling paediatric lung biopsies have recently been published [12].

The remainder of this manuscript reviews the seven categories of diffuse lung disease in children and some of the corresponding processes.

Diffuse Developmental Disorders

These are congenital structural diseases of the lung that impede the gas-exchanging function of the lung. These disorders include acinar dysplasia, congenital alveolar dysplasia, and alveolar capillary dysplasia with misalignment of the pulmonary veins (ADMPV). ADMPV is representative of this group. In ADMPV, the pulmonary veins parallel the pulmonary arteries rather than travelling in their normal position in the interlobular septae. Few capillaries are found at the alveolar surface, limiting gas exchange. Children with diffuse developmental disorders usually die within a matter of days, although rarely they may live for up to several months. Due to the severity of their lung disease, imaging in these children is usually limited to portable chest radiographs. CT scanning is rarely indicated, as transport to the CT scanner is a high-risk procedure, and no specific features have been reported on CT scanning to allow a specific diagnosis. Chest radiographs are nonspecific, usually showing a diffuse ground-glass appearance. Lung volumes are often high without ventilator support, which may distinguish these children from children with hyaline membrane disease.

Growth Abnormalities

These are alveolar growth disorders that result when alveoli cannot grow normally in the developing lung. This disturbance can be due to prenatal or postnatal insult as well as genetic conditions. In a review of children <2 years old with chILD, alveolar growth disorders were found in approximately one fourth. Associated conditions included pulmonary hypoplasia, chronic neonatal lung disease [bronchopulmonary dysplasia (BPD)], chromosomal disorders such as trisomy 21 and congenital heart disease. Potter's syndrome – pulmonary hypoplasia due to prenatal renal insufficiency and oligohydramnios – is likely the alveolar growth disorder most familiar to imagers. Hypoplasia and disordered structure are key pathologic findings in this group, but it is important to understand that hypoplasia does not always refer to a decrease in the size of an affected system. Hypoplasia can also manifest as simplification of structure with normal or increased size. When abnormal growth limits the number of alveoli, those alveoli that are present may increase in size. This increase is frequently seen unevenly distributed through the lungs. The peripheral alveoli are particularly prone to enlargement in growth disorders.

These children usually have respiratory abnormalities from birth. Respiratory compromise may improve slowly or worsen over time, likely depending on the degree of alveolar abnormality and the ability of the child to grow new alveoli. Alveoli continue to develop through approximately age 8, so future growth is likely a more important factor than the initial severity of respiratory disease. Features suggesting an alveolar growth disorder on CT scanning include areas of ground-glass opacity, peripheral cysts and disordered architecture of the secondary pulmonary lobule. The lobular changes include variable size and shape of the normally homogeneously sized and regularly polygonal lobule, as well as the presence of lobules with abnormal attenuation, particularly decreased attenuation.

Specific Disorders of Unknown Etiology

As noted above, there are disorders seen in children with diffuse lung disease that are not seen in adults. Two conditions with a specific pathologic appearance and unknown etiology are pulmonary interstitial glycogenosis (PIG) and neuroendocrine cell hyperplasia of infancy (NEHI). Pulmonary interstitial glycogenosis is characterised pathologically by a marked cellular infiltration of the alveolar septae by cells containing glycogen [13]. These cells stain with vimentin. Two important clinical features are seen in children with PIG. First, this disorder seems to be limited to the first 6 months of life. In a few children who have had serial biopsies, the findings of PIG have cleared as the children grew older. Second, PIG is often highly responsive to corticosteroid treatment. Anecdotal information suggests that a lack of response to pulse steroids should raise concern that PIG is not the complete diagnosis. PIG is commonly, possibly overwhelmingly, seen in association with alveolar growth disorders. This association has limited descriptions of the imaging appearance of “pure” PIG. There are published reports of the CT appearance, but these are based on extremely limited series, and the likelihood that the reported findings reflect changes due to alveolar growth disorder as well as PIG limit the value of these reports [14]. Ground-glass opacity has been suggested as a frequent finding on CT.

NEHI is a disorder of unknown etiology with very characteristic clinical and imaging presentations in addition to specific pathologic criteria [15]. NEHI pathology is characterised by the presence of increased numbers of neuroendocrine cells in the epithelium of the peripheral airways. Neuroendocrine bodies, focal collections of neuroendocrine cells, are also increased [16]. Detection of these cells requires special staining with Bombesin. This is not a standard stain, so it is important to notify the pathology department if NEHI is suspected. This is one of the few diseases that can reliably be diagnosed without the need for a lung biopsy. If both the imaging and clinical presentations are typical for NEHI, referral centres for childhood diffuse lung disease may not perform a lung biopsy on these children.

Children with NEHI rarely present in the newborn period, and most present later in the first year of life. The typical presenting symptom is tachypnea, and evaluation reveals hypoxia. Auscultation may reveal crackles, but the chest is usually quiet. These children do not wheeze. In older children, failure to thrive may be seen. In some cases, a history of a viral pneumonia will be elicited. In many cases, an inciting infection seems to have exacerbated pre-existing respiratory symptoms [15].

The appearance of NEHI on chest radiographs is non-specific. Hyperinflation is usually present, and there is often ill-defined central and perihilar opacity. No features distinguish it from viral or reactive airways disease. The appearance on CT scanning, however, is strikingly consistent and highly specific. In a review of 24 cases of pathologically proven NEHI and six control cases of other diffuse lung diseases, 75% of NEHI patients had a characteristic CT appearance [17]. Geographic ground-glass opacity is present in the paramediastinal lung and disproportionately involving the right middle lobe and lingula. Diffuse air trapping affecting both the areas of ground-glass opacity and the lower-attenuation areas is usually present. No other features of diffuse lung disease are seen, and there is no bronchiectasis, peribronchial thickening or other airway abnormality.

Surfactant Dysfunction Mutations

Abnormalities of surfactant are an important cause of diffuse lung disease in children. Three specific genetic abnormalities directly affecting the formation and transport of surfactant are more common: (1) abnormality of the surfactant B moiety (SPB), (2) the surfactant C moiety (SPC) and (3) abnormality of the adenosine triphosphate (ATP)-binding cassette A3 (ABCA3) [18]. Two further disorders associated with abnormal surfactant function are lysinuric acid intolerance and defective thyroid transcription factor 1 (TTF1).

SPB and ATPA3 are transmitted as autosomal recessive disorders. SPC has dominant transmission with variable penetrance. SPB causes early and severe respiratory dysfunction. ABCA3 can present early or later, and SPC usually presents later. The disease in these children is due to accumulation of abnormal protein in the alveoli and deficient surfactant function. Unlike surfactant deficiency in premature infants, children do not respond to exogenous surfactant administration.

The histology of surfactant dysfunction varies, particularly with age. In newborns the pathologic appearance is that of pulmonary alveolar proteinosis. Over time, the appearance changes, so that biopsy specimens obtained after the neonatal period may no longer show the appearance of pulmonary alveolar proteinosis, but rather, other patterns, including chronic pneumonitis of infancy, desquamative interstitial pneumonitis or nonspecific interstitial pneumonitis. Infants with SPB are usually too ill to be transported to the CT scanner, and very few CT scans have been

performed. Chest radiographs show diffuse ground-glass opacity, without definite features to distinguish it from hyaline membrane disease. CT scans in children with SPC and ABCA3 initially show features of alveolar proteinosis, with ground-glass opacity and septal thickening producing the crazy-paving appearance. In older children, there is a marked change in the appearance of the lungs, as parenchymal damage becomes the predominant feature. The initial diffuse crazy-paving appearance is replaced by a heterogeneous and variable appearance. Features described in older children with ABCA3 include ground-glass opacity, septal thickening, parenchymal cysts and pectus excavatum [19].

Disorders of the Normal Host

These are processes affecting previously healthy children and include infectious and postinfectious processes, environmental agents, aspiration and eosinophilic pneumonia. Common community-acquired infections are unlikely to be seen in children with history and symptoms suggesting diffuse lung disease. Mycobacterial disease and histoplasma infection are most common. In patients with mycobacterial disease, *Mycobacterium tuberculosis* is more common than atypical mycobacteria. Bronchiolitis obliterans is believed to frequently represent a postinfectious complication, often of a viral pneumonia [20]. Bronchiolitis obliterans is a pathologic diagnosis characterised by airway fibrosis with luminal narrowing or obliteration. The interval between acute infection and the onset of symptomatic bronchiolitis obliterans is variable and may be as short as several months. Hypersensitivity pneumonitis usually follows a large exposure to an environmental antigen. Many antigens can produce hypersensitivity pneumonia, with thermophilic actinomyces and avian antigens being two common agents. Aspiration injury is common but difficult to diagnose either noninvasively or pathologically. In most cases, diagnosis should be suspected by history and symptoms, but aspiration may be unsuspected and present as suspected diffuse lung disease. The presence of bronchiectasis more marked on the right than left, and right-sided tree-in-bud opacities, should raise the possibility of aspiration.

On chest radiographs, bronchiolitis obliterans has a variable appearance, with asymmetric hyperlucency probably being the most common. On CT scanning, mosaic attenuation is seen on inspiratory images. Vessels in the low-attenuation areas are attenuated, and expiratory images confirm air trapping in the low-attenuation areas. Large and small airway disease is usually present, so bronchiectasis is commonly seen. Bronchiolitis obliterans has a very characteristic appearance on CT scanning, and in the correct setting, lung biopsies are not always performed in these children. Hypersensitivity pneumonitis is characterised by acute ground-glass attenuation, which may show reticulation or heterogeneity suggesting confluent ground-glass nodules. Findings may be subtle, and subacutely, centrilobular nodules are a predominant finding [21].

Disorders Related to Systemic Disease Processes

This is a large and diffuse group of diseases that may affect primarily or only the lung. Immune-mediated causes include capillaritis and rheumatologic or collagen vascular disease [22]. Rarely, lung disease may precede other evidence of systemic lupus erythematosus by up to 6 months. Secondary pulmonary alveolar proteinosis, sarcoid and storage diseases may present with respiratory symptoms. Unsuspected cystic fibrosis may be seen. In rheumatologic/collagen vascular disease pathology is characterised by involvement of multiple compartments: the interstitium, vessels, airways and pleura. Histologic patterns include nonspecific interstitial pneumonia (NSIP), lymphoid hyperplasia and vasculopathy. The histologic pattern does not discriminate between the different disorders.

The imaging appearance of these diseases is as varied as the different diseases, with few CT appearances that strongly suggest a specific etiology. In children with collagen vascular disease, particularly mixed connective tissue disease, CT findings of geographic peripheral areas of ground-glass and reticular opacity may be seen. In our experience, these chest CT findings are accompanied by pulmonary function test abnormalities, but respiratory symptoms may be minimal and may not have been appreciated. Both respiratory status and CT abnormalities may progress slowly or remain stable over several years.

Disorders of the Immunocompromised Host

Infections are the most common disorders in this group. As more aggressive infections will not usually present as suspected diffuse lung disease, infections are usually atypical, and opportunistic infections such as pneumocystis jiroveci. Immunocompromise is more commonly due to therapeutic intervention, either bone marrow or organ transplantation or chemotherapy for malignancies. Immunodeficiency syndromes include chronic granulomatous disease and common variable immunodeficiency. In transplant patients, additional disorders related to complications of transplantation include rejection, graft vs. host disease and posttransplant lymphoproliferative disorder. Lung biopsy is usually required in this group of patients if diagnosis cannot be made by other methods. CT scan findings are nonspecific but may be useful to narrow the differential diagnosis and to choose appropriate sites for lung biopsy.

Disorders Masquerading as Diffuse Lung Disease

In this classification of diffuse lung disease, patients are included if they present as possible diffuse lung disease. No pathologic criteria are used to limit the conditions that may be found in these children. With this classification,

children will be included who do not have diffuse lung disease. These masqueraders should be kept in mind and clinical data sought that may suggest an alternative diagnosis. In their review of 187 children <2 years old, Deutsch and colleagues found six such cases [6]. Pulmonary oedema is probably the most common entity in this group when an acute presentation of diffuse lung disease is suspected. Other aetiologies include lymphatic abnormalities, such as lymphangiectasia and congenital heart disease, particularly with left-sided obstructive lesions.

Unclassified

Not all lung biopsies provide adequate tissue to allow a diagnosis to be reached. Lung biopsies of end-stage lung disease may not suggest which of many possible aetiologies resulted in the fibrotic scarring and lung destruction seen in end-stage lung disease. In addition, the lung biopsy specimen may be inadequate, particularly if a single specimen is obtained that includes only the very superficial subpleural lung. If no airways or larger vessels are included, it may not be possible to suggest a diagnosis.

Conclusion

Diffuse lung disorders are a rare but important cause of childhood lung disease. Recent work has improved our ability to identify these disorders and in many cases to suggest appropriate care. For the imager, the new classification scheme provides an organization that can promote better understanding and future research.

References

1. Haran Jogeessvaran K, Owens CM (2010) Chronic diseases of lung parenchyma in children: the role of imaging. *Pediatr Radiol* 40:850-858
2. ATS/ERS (2002) American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. *Am J Respir Crit Care Med* 165:277-304
3. Coultas DB, Zumwalt RE, Black WC, Sobonya RE (1994) The epidemiology of interstitial lung diseases. *Am J Respir Crit Care Med* 150:967-972
4. Dinwiddie R, Sharief N, Crawford O (2002) Idiopathic interstitial pneumonitis in children: a national survey in the United Kingdom and Ireland. *Pediatr Pulmonol* 34:23-29
5. Fan LL, Kozinetz CA, Wojtczak HA et al (1997) Diagnostic value of transbronchial, thoracoscopic, and open lung biopsy in immunocompetent children with chronic interstitial lung disease. *J Pediatr* 131:565-569
6. Deutsch GH, Young LR, Deterding RR et al, for the ChILD Research Cooperative (2007) Diffuse lung disease in young children: application of a novel classification scheme. *Am J Respir Crit Care Med* 176:1120-1128
7. Langston C, Dishop MK (2009) Diffuse lung disease in infancy: a proposed classification applied to 259 diagnostic biopsies. *Pediatr Dev Pathol* 12:421-437
8. Copley SJ, Coren M, Nicholson AG et al (2000) Diagnostic accuracy of thin-section CT and chest radiography of pediatric interstitial lung disease. *AJR Am J Roentgenol* 174:549-554
9. Long FR, Castile RG, Brody AS et al (1999) Lungs in infants and young children: improved thin-section CT with a noninvasive controlled-ventilation technique – initial experience. *Radiology* 212:588-593
10. Lucaya J, García-Peña P, Herrera L et al (2000) Expiratory chest CT in children. *AJR Am J Roentgenol* 174:235-241
11. Garcia-Pena P, Lucaya J (2004) HRCT in children: technique and indications. *Eur Radiol* 14(Suppl 4):L13-L30
12. Langston C, Patterson K, Dishop MK et al (2006) A protocol for the handling of tissue obtained by operative lung biopsy: recommendations of the chILD pathology co-operative group. *Pediatr Dev Pathol* 9:173-180
13. Canakis AM, Cutz E, Manson D, O'Brodovich H (2002) Pulmonary interstitial glycogenosis: a new variant of neonatal interstitial lung disease. *Am J Respir Crit Care Med* 165:1557-1565
14. Deutsch GH, Young LR (2010) Pulmonary interstitial glycogenosis: words of caution. *Pediatr Radiol* 40:1471-1475
15. Deterding RR, Pye C, Fan LL, Langston C (2005) Persistent tachypnea of infancy is associated with neuroendocrine cell hyperplasia. *Pediatr Pulmonol* 40:157-165
16. Young LR, Brody AS, Inge TH et al (2010) Neuroendocrine cell distribution and frequency distinguish neuroendocrine cell hyperplasia of infancy from other pulmonary disorders. *Chest* doi: 10.1378/chest.10-1304
17. Brody AS, Guillerman RP, Hay TC et al (2010) Neuroendocrine cell hyperplasia of infancy: diagnosis with high-resolution CT. *AJR Am J Roentgenol* 194:238-244
18. Hamvas A, Mallinckrodt E (2010) Evaluation and management of inherited disorders of surfactant metabolism. *Chin Med J (Engl)* 123:2943-2947
19. Doan ML, Guillerman RP, Dishop MK et al (2008) Clinical, radiological and pathological features of ABCA3 mutations in children. *Thorax* 63:366-373
20. Fischer GB, Sarria EE, Mattiello R et al (2010) Post infectious bronchiolitis obliterans in children. *Paediatr Respir Rev* 11:233-239
21. Silva CI, Churg A, Muller NL (2007) Hypersensitivity pneumonitis: spectrum of high-resolution CT and pathologic findings. *AJR Am J Roentgenol* 188:334-344
22. Lynch DA (2009) Lung disease related to collagen vascular disease. *J Thorac Imaging* 24:299-309

CT Evaluation of Pediatric Chest in Routine Practice

Marilyn J. Siegel

Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, MO, USA

Introduction

This chapter reviews the applications of computed tomography (CT) in the evaluation of common chest problems in children, in particular, mediastinal masses and congenital lung anomalies. Normal anatomy and anatomic variants and CT techniques are also discussed.

Techniques

The following parameters need to be determined prior to data acquisition: section collimation, pitch (travel distance of the scan table per 360° rotation of the X-ray tube divided by the collimation), tube voltage (kVp), tube current (mA), and rotation time. For conventional CT scans (evaluation of nonvascular pathology), parameters include section collimation 0.6-1.25 mm and pitch 1.0-1.5. For CT angiography, collimation is 0.6-0.75 mm and pitch 1.0-1.5. Tube current and voltage are adapted to the patient's dimensions [1, 2]. Postprocessing reconstruction parameters include slice thickness and interval. Slice thickness and reconstruction intervals usually range between 3 and 5 mm. Thinner (1- to 2-mm) reconstructions are advantageous for evaluating small structures and vessels.

Nearly all CT examinations of the chest are performed with the intravenous administration of contrast material (2 ml/kg, not to exceed 4 ml/kg, or 100 ml). Intravenously administered contrast agent is given via a power injector when a 22-gauge or larger cannula can be placed in an antecubital vein. Flow rates are 1.5-2.0 ml/s for a 22-gauge catheter and 3.0-4.0 ml/s for a 20-gauge catheter. A hand injection is used when intravenous access is through a peripheral access line in the dorsum of the hand or foot [3, 4]. For conventional CT examinations (evaluation of mass, adenopathy, abscess, trauma), the scan delay time is 25-30 s after the onset of contrast administration. CT angiography is best performed with a bolus tracking method. A default time of 12-15 s is used if the automated triggering fails. Studies are reviewed with volume imaging (multiplanar, maximum intensity, or volume rendered) [5].

CT examinations are performed with breath-holding at suspended inspiration in cooperative patients, usually children older than 5 years of age. Scans are obtained during quiet respiration in sedated children and in those who are unable to cooperate with breath-holding instructions.

Normal Anatomy

In infants and young children (<5 years of age), the thymus appears quadrilateral on CT, with convex or straight lateral margins (Fig. 1). In older children, the thymus gradually assumes a triangular or arrowhead configuration with straight or concave margins, and by 15 years of age, it is triangular in nearly all individuals (Fig. 2) [1, 2, 6]. In prepubertal children, the thymus is homogeneous, with an attenuation value equal to that of chest-wall musculature. In adolescents, the thymus may be heterogeneous, containing areas of fat deposition. Occasionally, the thymus extends either cranially above the brachiocephalic vessels or into the posterior thorax [6, 7].

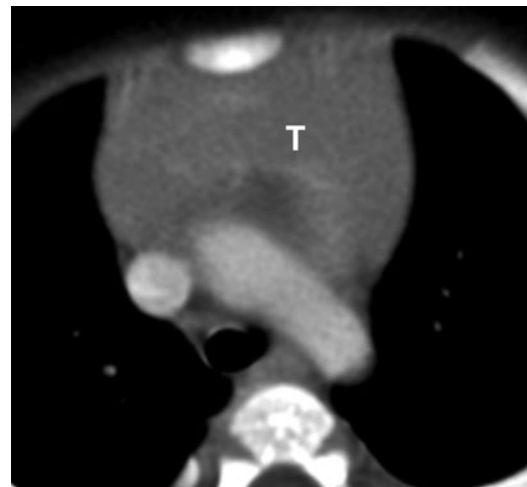


Fig. 1. Normal computed tomography appearance of the thymus (T) in a 6-month-old boy. The thymus is quadrilateral in shape, with slightly convex lateral borders and a wide retrosternal component. Thymus attenuation is equal to that of chest-wall musculature

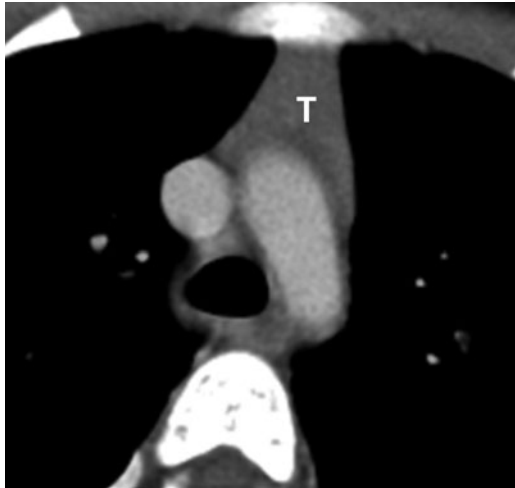


Fig. 2. Normal computed tomography appearance of the thymus (*T*) in a 6-year-old boy. The thymus has assumed a triangular shape with straight borders

There are no well-established data concerning size of normal lymph nodes in infants and young children. Mediastinal lymph nodes generally are not seen on CT prior to puberty. In adolescents, small normal nodes (not exceeding 1 cm in widest dimension) occasionally can be identified.

The azygoesophageal recess is dextroconvex in children younger than 6 years of age, straight in children between 5 and 12 years of age, and concave in adolescents and adults [8]. Recognizing the normal dextroconvex appearance is important so that it is not mistaken for lymphadenopathy.

Nonvascular Mediastinal Masses

The differential diagnosis of a mediastinal mass is based on identifying its location (anterior, middle, or posterior mediastinum) and attenuation (soft tissue, fat, fluid, enhancing) [9].

Anterior Mediastinal Masses

Soft Tissue Attenuation

Lymphoma is the most common anterior mediastinal mass in children, with Hodgkin's lymphoma occurring three to four times more frequently than non-Hodgkin's lymphoma [10]. Lymphomatous masses in Hodgkin's disease are most common in the anterior mediastinum and reflect lymphadenopathy or infiltration and enlargement of the thymus, whereas non-Hodgkin's lymphoma predominantly affects lymph nodes. The enlarged thymus has a quadrilateral shape with convex, lobular, lateral borders (Fig. 3). On CT, attenuation of the lymphomatous organ is equal to that of soft tissue. Calcifications or cystic areas, due to ischemic necrosis consequent to rapid tumor growth, can be seen within the tumor. Lymphadenopathy from lymphoma has varied appearances, ranging from mildly enlarged nodes in a single

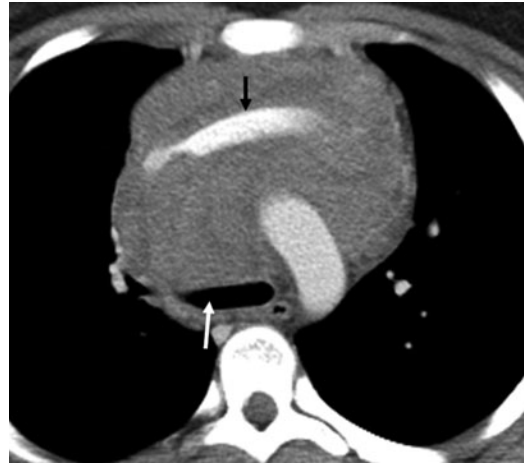


Fig. 3. Thymic Hodgkin's disease, thymic infiltration in a 14-year-old girl. A large soft tissue mass with biconvex borders fills the anterior mediastinum, encasing the brachiocephalic vein (*black arrow*) and compressing the trachea (*white arrow*)

area to large conglomerate soft tissue masses in multiple regions. Thymic enlargement and lymphadenopathy show minimal if any enhancement after intravenous administration of contrast medium. Additional findings include airway narrowing and compression of vascular structures.

Thymic hyperplasia is another cause of thymic enlargement. In childhood, thymic hyperplasia is most often "rebound" hyperplasia associated with chemotherapy, particularly therapy with corticosteroids. Rebound hyperplasia may be observed during the course of chemotherapy or after therapy completion. The mechanism of hyperplasia is believed to be initial depletion of lymphocytes from the cortical portion of the gland due to high serum levels of glucocorticoids, followed by repopulation of the cortical lymphocytes when cortisone levels return to normal. On CT, hyperplasia appears as diffuse enlargement of the thymus, with preservation of the normal triangular shape (Fig. 4).



Fig. 4. Rebound thymic hyperplasia in a 14-year-old girl receiving chemotherapy for osteosarcoma. The thymus (*T*) is diffusely enlarged but maintains a triangular configuration

The attenuation value is similar to that of the normal organ and also of the tumor. The absence of other active disease and a gradual decrease in thymus size on serial CT scans supports the diagnosis of rebound hyperplasia as the cause of thymic enlargement.

Thymomas account for <5% of all mediastinal tumors in children. Nearly all thymomas are benign and occur sporadically. Benign thymomas appear as well-defined soft tissue attenuation masses bulging the lateral thymic margin.

Fat Attenuation

Germ-cell tumors are the second most common cause of an anterior mediastinal mass in children and the most common cause of a fat-containing lesion. Approximately 90% are benign. On CT, benign teratoma is a well-defined, thick-walled cystic mass containing a variable admixture of water, calcium, fat, and soft tissue [1, 2, 11, 12] (Fig. 5). Low-attenuation fluid components predominate.

Malignant teratomas tend to have irregular or nodular walls and a predominance of soft tissue attenuation components. They also may show pulmonary and/or liver metastases and chest wall invasion. The most common nonteratomatous germ-cell tumors in the pediatric population are choriocarcinoma, embryonal cancer, and yolk-sac cancer. Nonteratomatous malignant tumors typically are heterogeneous, soft tissue masses containing large areas of necrosis (Fig. 6). They may contain areas of calcification and may invade locally and infiltrate adjacent fat planes.

Thymolipoma is an infrequent fat-containing thymic tumor. At CT, it appears as a heterogeneous mass containing fat and soft tissue elements. Calcifications are absent. Thymolipoma does not compress or invade adjacent structures [13].

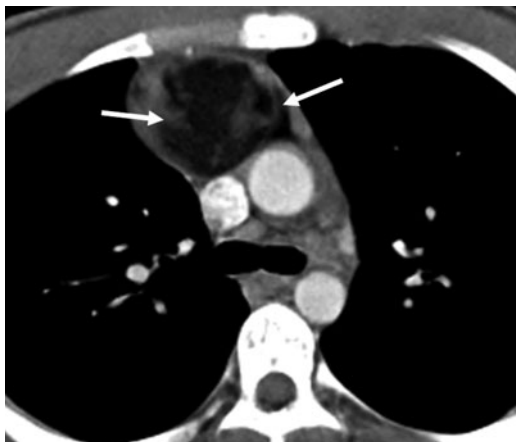


Fig. 5. Benign teratoma in an 18-year-old girl. A large, well-circumscribed, heterogeneous mass (arrows) containing a predominance of fat occupies the right lobe of the thymus



Fig. 6. Choriocarcinoma in a 19-year-old man. Computed tomography scan shows a predominantly low-attenuation mass with a thick, irregular wall and internal septations. Multiple pulmonary metastases are noted in the left lung (Case courtesy of Eduardo Villanueva, Santiago, Chile)

Fluid Attenuation

Lymphangiomas are developmental tumors of the lymphatic system and are almost always inferior extensions of cervical lymphangiomas [1, 2]. At CT, they appear as nonenhancing, thin-walled, multiloculated masses with near-water attenuation (Fig. 7). The presence of contrast enhancement of the wall or internal septations suggests superimposed infection or a hemangiomatous component.

Thymic cysts usually are congenital lesions resulting from persistence of the thymopharyngeal duct, but they can occur after thoracotomy. Typically, they are thin-walled, homogeneous masses of near-water attenuation on CT. The attenuation value may be higher than that of simple cysts when the contents are proteinaceous or hemorrhagic rather than serous.

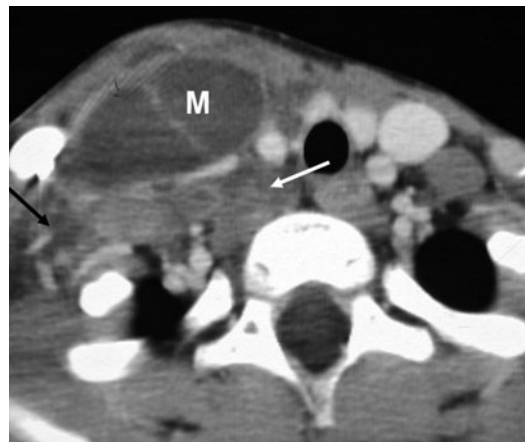


Fig. 7. Cystic hygroma in a 6-month-old girl. A septated low-attenuation mass (M) infiltrates the superior mediastinum (white arrow) and right axilla (black arrow)

Middle Mediastinal Masses

Frequent causes of middle mediastinal masses are lymph-node enlargement and congenital foregut cysts and lymphadenopathy [1, 2]. Foregut cysts in the middle mediastinum are classified as bronchogenic or enteric [14]. Bronchogenic cysts are lined by respiratory epithelium, and most are located in the subcarinal or right paratracheal area. Enteric cysts are lined by gastrointestinal mucosa and are located in a paraspinal position in the middle to posterior mediastinum. CT findings are a well-defined, round, nonenhancing mass of near-water attenuation, reflecting serous contents (Fig. 8). Air or an air-fluid level can be present when communication between cyst and bronchial tree or gastrointestinal tract develops.

Mediastinal lymphadenopathy is usually caused by lymphoma or granulomatous disease. On CT, adenopathy can appear as discrete, round, soft tissue masses or as a single soft tissue mass with poorly defined margins (Fig. 9).

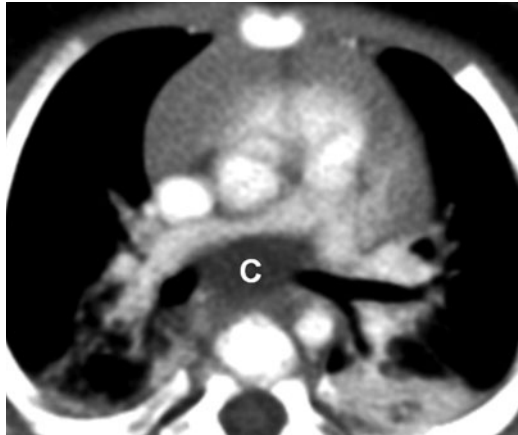


Fig. 8. Duplication cyst in a 2-year-old girl. Contrast-enhanced computed tomography shows a homogeneous, water-density cyst (C) with imperceptible walls in the right infrahilar area (middle mediastinum). There also is bibasilar atelectasis

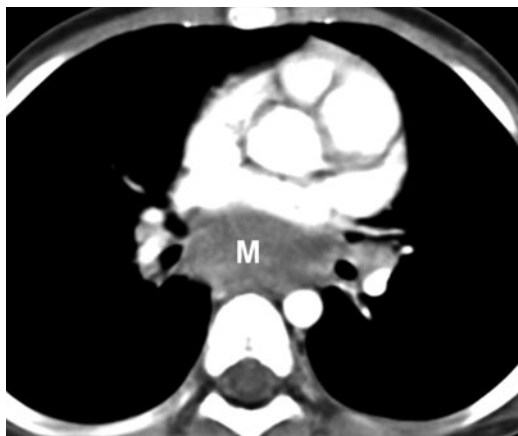


Fig. 9. Middle mediastinal adenopathy in a 5-year-old boy with histoplasmosis. Axial computed tomography shows a bulky soft tissue mass (M) of coalesced lymph nodes in the subcarinal area. Adenopathy is also present in the left hilum

Calcification within lymph nodes suggests old healed granulomatous disease. Areas of low attenuation suggest tuberculosis or fungal infection.

Posterior Mediastinal Masses

Posterior mediastinal masses are of neural origin in approximately 95% of cases and may arise from sympathetic ganglion cells (neuroblastoma, ganglioneuroblastoma, or ganglioneuroma) or from nerve sheaths (neurofibroma or schwannoma).

On CT, ganglion-cell tumors appear as paraspinal masses extending over the length of several vertebral bodies. They are fusiform in shape, of soft tissue density, and can contain calcifications (Fig. 10). Nerve-root tumors tend to be smaller, spherical, and occur near the junction of a vertebral body with an adjacent rib. Both types of tumors may cause pressure erosion of a rib and invade the spinal canal.

Vascular Mediastinal Masses

Congenital abnormalities of the aorta and its branches and aneurysms can cause a mass or mediastinal widening on plain chest radiography.

Aortic Arch

The right arch with aberrant left subclavian artery and the double arch are common congenital anomalies of the aorta that produce an abnormal mediastinum on plain chest radiography [15]. The double arch is characterized by two arches that surround the trachea and esophagus [15-17]. The arches arise from a single ascending aorta and reunite to form a single descending aorta after giving rise to the subclavian and carotid arteries. The right arch component of a double-arch anomaly usually is more cephalad and larger than the left-arch component. Both aortic arches usually are patent, but occasionally, the left arch is



Fig. 10. Neuroblastoma in a 2-year-old girl. Axial computed tomography shows a large right paraspinal soft tissue mass (M). There is minimal extension into the spinal canal

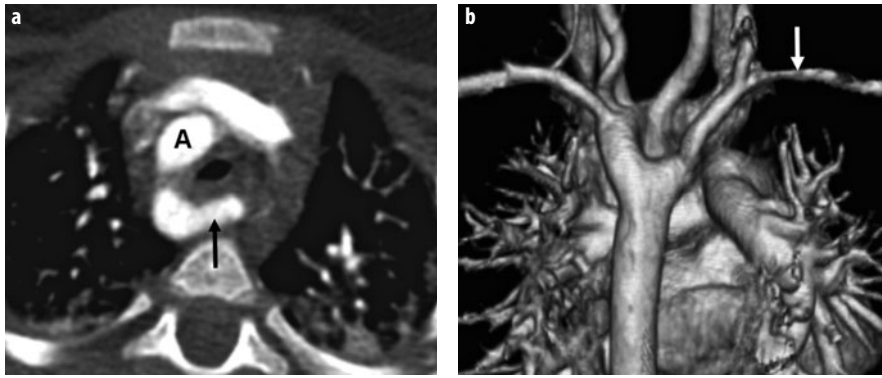


Fig. 11 a, b. Right aortic arch with aberrant left subclavian artery. **a** Axial computed tomography scan demonstrates a right aortic arch (*A*) with the aberrant left subclavian artery (*arrow*) crossing the mediastinum posteriorly. **b** Coronal 3D reconstruction: the left subclavian artery (*arrow*) is the last vessel arising from the aorta (for color reproduction see p 273)

atretic. Treatment is surgical division of the smaller arch. Following surgery, some patients may have persistent airway obstruction related to tracheomalacia as a result of long-standing extrinsic airway compression.

In the right arch with aberrant subclavian artery, the subclavian artery arises as the last branch from the aortic arch and traverses the mediastinum behind the esophagus to reach the left arm [15-17] (Fig. 11). The vascular ring is completed by the ligamentum arteriosum. Airway compression may be due to a tight ligamentum arteriosum or a Kommerell diverticulum. In symptomatic patients, treatment is surgical division of the ductus or ligamentum.

There are two main types of right arch: that with aberrant left subclavian artery and that with mirror-image branching. The latter anomaly is not a true vascular ring and is almost always associated with congenital heart disease [15-17].

Aneurysm of the thoracic aorta is another cause of a vascular mediastinal mass. Marfan syndrome is the most common cause of aneurysms in children. Less commonly, infection and trauma are causes of aneurysm. In Marfan syndrome, aneurysms are fusiform in configuration. Mycotic and traumatic aneurysms are typically saccular in appearance [17].

Congenital Pulmonary Lesions

Congenital lung anomalies include a variety of conditions involving the pulmonary parenchyma, the pulmonary vasculature, or a combination of both [18, 19]. CT is performed to confirm the diagnosis and to determine its extent in patients in whom surgery is contemplated.

Anomalies with Normal Vasculature

Congenital lobar emphysema, cystic adenomatoid malformation, and bronchial atresia are anomalies resulting from abnormal bronchial development.

Congenital lobar emphysema is characterized by hyperinflation of a lobe [18, 19]. Bronchial obstruction, resulting from primary cartilage deficiency or dysplasia, is believed to be the cause of the overinflated lobe. The af-

ected patient usually presents in the first 6 months of life with respiratory distress. CT shows a hyperinflated, low-attenuation lobe with pulmonary vascular pruning, atelectasis of ipsilateral adjacent lobes, and mediastinal shift into the opposite hemithorax (Fig. 12). The left upper lobe is involved in about 45% of cases, the right middle lobe in 30%, the right upper lobe in 20%, and two lobes in 5%.

Cystic adenomatoid malformation is a mass of disorganized pulmonary tissue that has a normal communication with the bronchial tree and normal vascular supply and drainage. The cause is believed to be an overgrowth of distal bronchiolar structures resulting in formation of a cystic mass. Symptoms of respiratory distress usually occur soon after birth. Type I (50% of cases) contains a single or multiple large cysts (>2 mm in diameter); type II (41%) contains multiple small cysts (1-10 mm in diameter); type III (9%) is a solid lesion to visual inspection but contains microscopic cysts [20, 21]. The anomaly occurs with equal frequency in both lungs, although there is slight upper lobe predominance. CT findings of cystic adenomatoid malformation are multiple, thin-walled, air-filled cysts of variable size, expanding a lobe or lobes and



Fig. 12. Congenital lobar emphysema in a neonate. Computed tomography through the upper thorax shows a hyperinflated left upper lobe, mediastinal shift to the right, and atelectatic right upper lobe

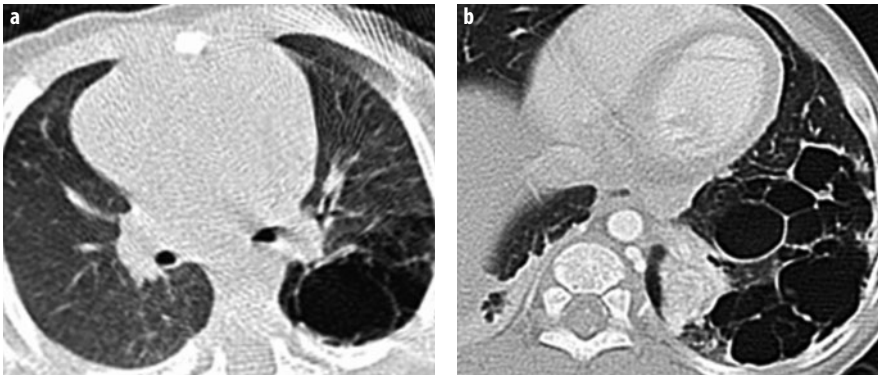


Fig. 13 a, b. Cystic adenomatoid malformation. **a** Type I lesion in a neonate: a multilocular mass in the left lower lobe contains a dominant large cyst. **b** Type II malformation in a 6-month-old boy: computed tomography shows a complex mass in the left lower lobe containing multiple small cysts, which ranged in size from 3 mm to 1 cm

displacing the mediastinum to the opposite hemithorax (Fig. 13). A higher attenuation or thick walls may be seen when cyst contents are infected or hemorrhagic. Air-fluid levels occasionally can be seen within the cysts.

Segmental bronchial atresia results from abnormal development of a segmental or subsegmental bronchus. The bronchus distal to the atretic segment is patent and contains impacted mucus, whereas the lung beyond the obstruction is air-filled and overaerated as a result of collateral air drift via the pores of Kohn. It rarely causes symptoms and is usually discovered on chest radiographs performed for other indications. The CT features of bronchial atresia include a dilated, mucoid-filled, segmental or subsegmental bronchus surrounded by hyperinflated (oligemic) lung [22] (Fig. 14).

Anomalies with Abnormal Vasculature

Sequestration, hypogenetic lung syndrome, and arteriovenous malformation (AVM) are congenital anomalies with abnormal vasculature.

Bronchopulmonary sequestration is a congenital mass of pulmonary tissue that has no normal connection with the tracheobronchial tree and is supplied by an anomalous artery, usually arising from the descending aorta. When the sequestered lung is confined within normal visceral pleura and has venous drainage to the pulmonary veins, it is termed intralobar or congenital. The sequestered lung is termed extralobar or acquired when it has its own pleura and venous drainage to systemic veins [23, 24]. Contrast-enhanced CT demonstrates opacification of the anomalous vessel immediately following enhancement of the descending thoracic aorta (Figs. 15 and 16) [25-27]. CT appearance of the pulmonary parenchyma includes an area of consolidated lung (pneumonia), abscess formation, and a round or pyramidal mass-like lesion.

Hypogenetic lung syndrome, also known as venolobar syndrome and scimitar syndrome, is characterized by a small right lung, ipsilateral mediastinal displacement, a corresponding small pulmonary artery, and occasionally partial anomalous pulmonary venous return from the right lung (Fig. 17) [28]. The anomalous venous return is



Fig. 14. Bronchial atresia in a 15-year-old girl. Computed tomography shows an ovoid soft tissue nodule (arrow) in the right lower lobe. The nodule is surrounded by an over-aerated lung from collateral air drift



Fig. 15. Intralobar sequestration in a 10-year-old girl with recurrent left lower lobe pneumonia. Computed tomography demonstrates the anomalous arterial supply (arrow) arising from the thoracic aorta and supplying the sequestered lung (S)

most often to the inferior vena cava, but it may be to a portal vein, hepatic vein, or right atrium. Other associated anomalies include systemic arterial supply to the hypogenetic lung, accessory diaphragm, and horseshoe



Fig. 16. Extralobar pulmonary sequestration in a 2-week-old girl with a left paraspinal mass on chest radiography. Coronal computed tomography shows the anomalous vein (*white arrow*) draining the left lower-lobe sequestration (*S*). The vein drains into the portal vein (*black arrow*)

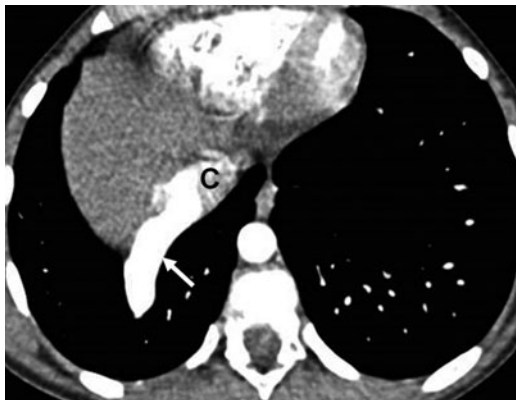


Fig. 17. Scimitar syndrome. Axial computed tomography scan at the level of the cardiac ventricles shows the anomalous vein (*arrow*) entering the intrahepatic inferior vena cava (*C*). Note that the right hemithorax is smaller than the left and that there is shift of the heart to the right

lung. In horseshoe lung, the posterobasal segments of both lungs are fused behind the pericardial sac.

Pulmonary AVM is characterized by direct communication between a pulmonary artery and vein without an intervening capillary bed [29]. It is usually supplied by one artery and drained by one vein, although multiple feeding arteries and draining veins may be present. Most are associated with Osler-Weber-Rendu syndrome (hereditary hemorrhagic telangiectasia). On lung windows, AVMs can appear as a well-defined, smooth, round or tubular ground-glass nodule representing a single vascular sac or as a lobulated or serpiginous mass representing a tangle of dilated tortuous vessels. Most are located subpleurally or peripherally. Contrast-enhanced CT shows the

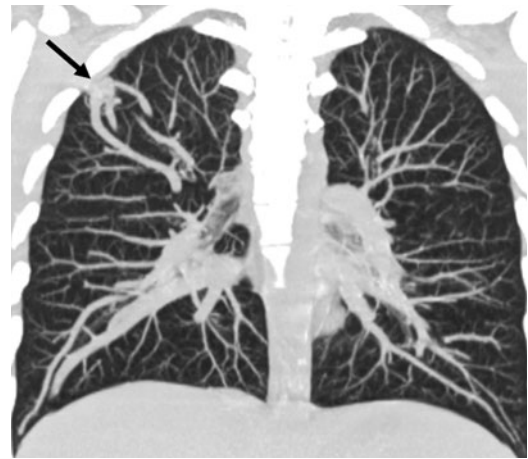


Fig. 18. Pulmonary arteriovenous malformation. Coronal maximum intensity projection computed tomography (CT) shows a subpleural arteriovenous malformation (AVM) (*arrow*) with its feeding artery and draining vein. AVMs can be reliably diagnosed on CT based on their morphology

dilated feeding arteries, draining veins, and interposed nidus of vessels. Maximum-intensity projection (MIP) and 3D reconstructions are helpful in precisely depicting architecture, size, and number of malformations and feeding arteries and draining veins [29] (Fig. 18).

References

1. Siegel MJ (2006) Pediatric applications. In: Lee KTL, Sagel SS, Stanley RJ, Heiken JP (eds) *Computed body tomography with MRI correlation*, 4th edn. Lippincott Williams & Wilkins, Philadelphia, PA, pp 1727-1791
2. Siegel MJ (2008) Mediastinum. In: Siegel MJ (ed) *Pediatric body CT*, 2nd edn. Lippincott Williams & Wilkins, Philadelphia, PA, pp 33-67
3. Rigsby CK, Gasber E, Seshadri R et al (2007) Safety and efficacy of pressure-limited power injection of iodinated contrast medium through central lines in children. *AJR Am J Roentgenol* 188:726-732
4. Siegel MJ (2003) CT angiography: optimizing contrast use in pediatric patients. *Applied Radiol* 2003:S38-S46
5. Fishman EK, Ney DR, Heath DG et al (2006) Volume rendering versus maximum intensity projection in CT angiography: what works best, when, and why. *RadioGraphics* 26:905-922
6. Nishino M, Askiku SK, Kocher ON et al (2006) The thymus: a comprehensive review. *RadioGraphics* 26:335-348
7. Krysta MM, Gorecki WJ, Miezynski WH (1998) Thymic tissue manifesting as a posterior mediastinal mass in two children. *J Pediatr Surg* 33:632-634
8. Miller FH, Fitzgerald SW, Donaldson JS (1993) CT of the azygoesophageal recess in infants and children. *RadioGraphics* 13:623-634
9. Franco A, Mody NS, Meza MP (2005) Imaging evaluation of pediatric mediastinal masses. *Radiol Clin North Am* 43:325-353
10. Hudson MM, Onciu M, Donaldson SS (2006) Hodgkin lymphoma. In: Pizzo PA, Poplack DG (eds) *Principles and practice of pediatric oncology*. Lippincott Williams & Wilkins, Philadelphia, PA, pp 695-721
11. Quillin SP, Siegel MJ (1992) CT features of benign and malignant teratomas in children. *J Comput Assist Tomogr* 16:723-726

12. Rosado-de-Christenson ML, Templeton PA, Moran CA (1992) Mediastinal germ cell tumors: radiologic and pathologic correlation. *RadioGraphics* 12:1013-1030
13. Rosado-de-Christenson ML, Pugatch RD, Moran CA, Galobardes J (1994) Thymolipoma: analysis of 27 cases. *Radiology* 193:121-126
14. Tsuchiya T, Mori K, Ichikawa T et al (2003) Bronchopulmonary foregut malformation diagnosed by three-dimensional CT. *Pediatr Radiol* 33:887-889
15. Hernanz-Schulman M (2005) Vascular rings: a practical approach to imaging diagnosis. *Pediatr Radiol* 35:961-979
16. Siegel MJ (2011) Vascular rings and slings. In: Ho VB, Reddy GP (eds) *Cardiovascular imaging*. Elsevier, St. Louis, MO, pp 542-548
17. Siegel MJ (2008) Great vessels. In: Siegel MJ (ed) *Pediatric body CT*, 2nd ed. Lippincott Williams & Wilkins, Philadelphia, PA, pp 121-144
18. Daltro P, Fricke B, Kuroki L et al (2002) CT of congenital lung lesions in pediatric patients. *AJR Am J Roentgenol* 183:1497-1506
19. Siegel MJ (2008) Lung, pleural and chest wall. In: Siegel MJ (ed) *Pediatric body CT*, 2nd ed. Lippincott Williams & Wilkins, Philadelphia, PA, pp 69-120
20. Kim WS, Lee KS, Kim IO et al (1997) Congenital cystic adenomatoid malformation of the lung: CT-pathologic correlation. *AJR Am J Roentgenol* 168:47-53
21. Rosado-de-Christenson ML, Stocker JT (1991) Congenital cystic adenomatoid malformation. *RadioGraphics* 11:865-886
22. Al-Nakshabandi N, Lingawi S, Muller NL (2000) Congenital bronchial atresia. *Can Assoc Radiol* 51:47-48
23. Frazier AA, Rosado de Christenson ML, Stocker JT et al (1997) Intralobar sequestration: radiologic-pathologic correlation. *RadioGraphics* 17:725-745
24. Rosado-de-Christenson ML, Frazier AA, Stocker JT, Templeton PA (1993) Extralobar sequestration: radiologic-pathologic correlation. *RadioGraphics* 13:425-441
25. Franco J, Aliaga R, Domingo ML, Plaza P (1998) Diagnosis of pulmonary sequestration by spiral CT angiography. *Thorax* 53:1089-1092
26. Ko SF, Ng SH, Lee TY et al (2000). Noninvasive imaging of bronchopulmonary sequestration. *AJR Am J Roentgenol* 175: 1005-1012
27. Lee E, Siegel MJ, Foglia R (2004) Evaluation of angioarchitecture of pulmonary sequestration in pediatric patients using 3D MDCT angiography. *AJR Am J Roentgenol* 183: 183-188
28. Konen E, Raviv-Zilka L, Cohen RA et al (2003) Congenital pulmonary venolobar syndrome: spectrum of helical CT findings with emphasis on computerized reformatting. *RadioGraphics* 23:1175-1184
29. Hoffman LV, Kuszyk BS, Mitchell SE et al (2000) Angioarchitecture of pulmonary arteriovenous malformation: characterization using volume-rendered 3D CT angiography. *Cardiovasc Intervent Radiol* 23:165-170

Imaging of the Chest in the Newborn and Young Infant

Janet L. Strife¹, Veronica Donoghue²

¹ Radiology Department, Cincinnati Children's Hospital, University of Cincinnati, Cincinnati, OH, USA

² Radiology Department, Children's University Hospital, Dublin, Ireland

Introduction

Throughout the world, chest imaging is the most commonly interpreted study in infants and young child. The chest radiograph is not particularly difficult to interpret, as most images fall into predictable patterns of disease, which are different than in the adult patient. This chapter suggests an approach to imaging the normal chest radiograph and provides a framework for learning about dis-

eases in the neonate. Broadly speaking, it divides neonatal disease into medical disease, such as hyaline membrane disease or meconium aspiration; and lung lesions/surgical diseases, which are primarily lung masses or congenital anomalies (Fig. 1) [1, 2]. Although chest masses and congenital malformations are rare, imaging descriptions are presented to enhance understanding of the natural history, current treatments, and/or outcomes of those lesions.

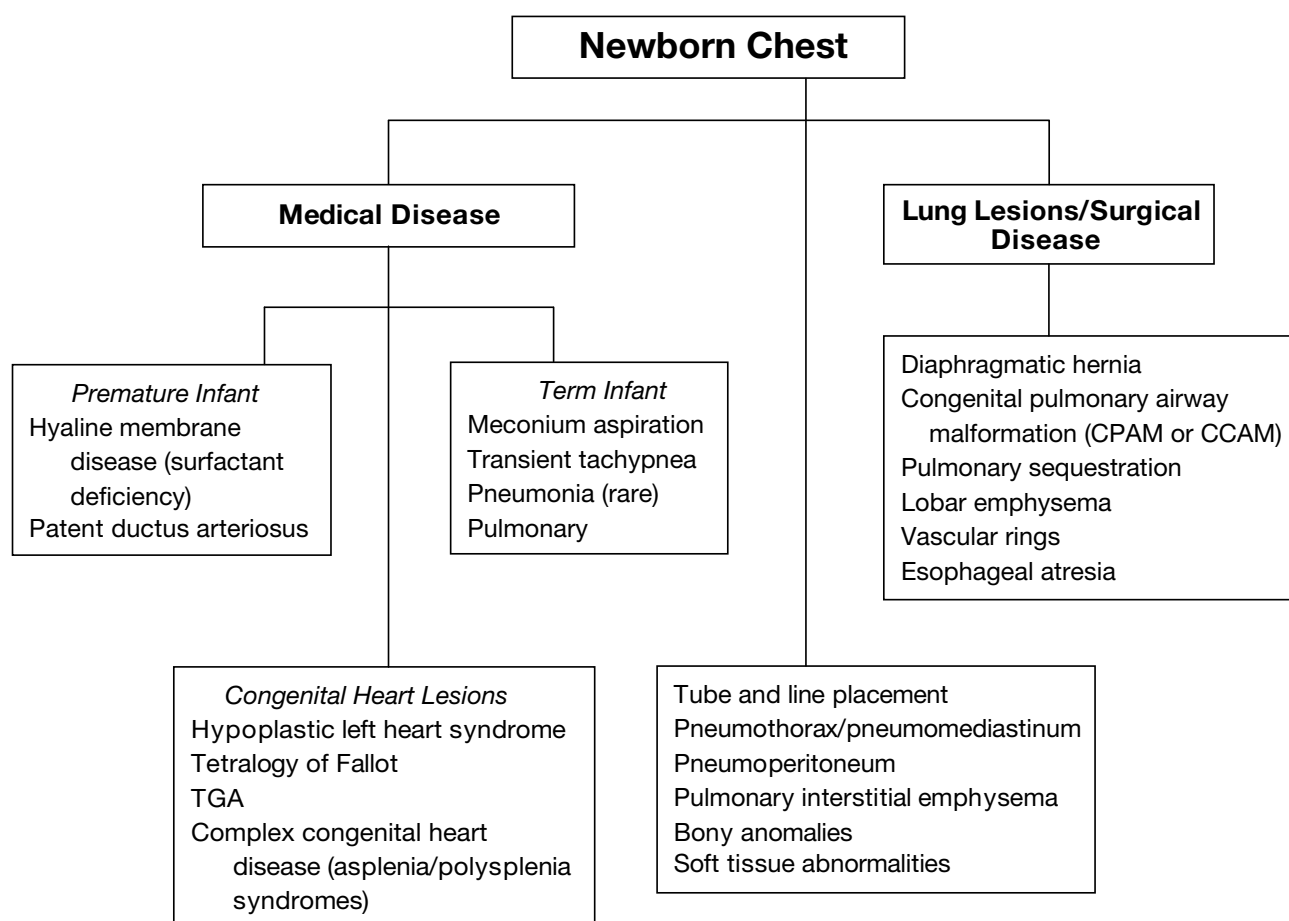


Fig. 1. Neonatal chest diseases: medical, and lung lesions/surgical diseases

The spectrum of diseases that affect the neonates' chest has significant overlap in radiographic and clinical appearance, and it is helpful to always look at the lines and catheters first, know the infant's gestational age, and ideally have an exchange of information between the neonatologist and the radiologist. The main disease entities are medical diseases, such as respiratory distress syndrome (RDS)/hyaline membrane disease (HMD), chronic lung disease [bronchopulmonary dysplasia (BPD)], meconium aspiration syndrome (MAS), neonatal pneumonia, and transient tachypnea of the newborn. Surgical diseases are usually congenital lung lesions, chest-wall lesions, or congenital anomalies, and many are recognized antenatally. There has been an increase in knowledge and understanding of pre- and postnatal imaging and management that continues to evolve and enhance our knowledge of the natural history, complications, and issues relating to long-term survival in these children.

Lines, Tubes, and Catheters

Endotracheal Tube Position

In intubated infants and children, the best way to find the tip of the endotracheal tube (ET) is to find the tracheal bifurcation and then identify the position of the tip relative to the carina. A low tube position relative to the carina can quickly cause contralateral lung collapse and an increase in respiratory effort. Occasionally, esophageal intubation is performed, and can be recognized by the ET being external to the trachea, air in the esophagus, marked stomach overdistention, and increased lung density. It is surprising that esophageal intubation goes undetected. Inflatable cuffs are not used in infants and children and thus movement of the ET tip changes with head position. If the head/neck is extended, the tube moves proximally. If the neck is flexed, the tip moves distally in the trachea. The ideal position is between the thoracic inlet (near the medial clavicles or first thoracic vertebral body) and the carina. Referencing the tip of the ET tube relative to the vertebral bodies should be discouraged, as the angle of the radiographic beam may alter the apparent tip projection.

Enteric Tubes

Nasogastric and orogastric tubes should be positioned so that the tip projects into the expected region of the stomach. Enteric tubes are often placed into the small bowel for feeding purposes. Ideally, these tubes should follow a course that corresponds to the normal positioning of the stomach, pylorus, duodenum, and proximal jejunum, with the duodenal-jejunal junction in the left upper quadrant of the abdomen, roughly at the same level as the pylorus. However, enteric tubes may cause a straightening of their course, mimicking the positioning of midgut malrotation. In some instances in these infants, tube-tip position may need to be confirmed using contrast material injection.

Central Venous Lines

The correct position of lines, including peripherally inserted central catheters (PICC), is not standardized and differs institutionally. Catheter tips sometimes seem "to change", which could be attributed to the beam angle of the portable radiograph as well as catheter motion. The catheters are very small, and if the tip is in the right atrium (RA) and the image is taken in systole, the tip moves, motion blurs the tip, and there is a false impression that the catheter tip is in the superior vena cava (SVC) [3]. Many neonatologists prefer to have the tip situated within the SVC, or near the junction with the RA, which is at the same level as the right mainstem bronchus.

Umbilical Arterial Catheters

The umbilical arterial catheter (UAC) enters at the umbilicus, extends inferiorly in the umbilical artery, enters one of the iliac vessels and ascends in the aorta. There are two commonly used practices for UAC placement. Both are meant to minimize the potential for developing thromboembolic propagation into the main aortic branches. The "high-line" position is intrathoracic, near the T4-9 level; and the "low-line" position is below the renal arteries at or just below the third lumbar vertebral body.

Umbilical Venous Catheters

The umbilical venous catheter (UVC) pathway enters the umbilicus, advances through the liver in the umbilical vein, enters the left portal vein, crosses the ductus venosus, and enters the RA. Most consider the preferred tip position to be at the inferior vena cava (IVC) and RA junction (IVC/RA junction). When the catheter extends more superiorly, a statement should be made in the report as to where the tip resides, i.e., in the RA, right ventricle (RV), pulmonary artery, or across the foramen ovale into the left atrium (LA) or pulmonary veins, or in the SVC into the neck, etc.

Respiratory Distress Syndrome

Pulmonary disease of the newborn is also called RDS, HMD, or surfactant deficiency. RDS is a manifestation of pulmonary immaturity and a primary disease of premature infants. The incidence and severity are inversely related to gestational age, and extraordinarily preterm infants of 23-28 weeks have more severe disease than the older preterm infant. It is important to remember that the premature infant's entire body is immature and that they have multiple interrelated problems. RDS remains the leading cause of death in live-born infants, and boys are affected almost twice as often as girls.

The pathophysiology of RDS is the result of anatomic pulmonary immaturity and surfactant deficiency. Type 2 alveolar cells begin to produce surfactant at 24-28 weeks

gestational age. Surfactant absence results in a cascade of events, with alveolar instability, collapse, capillary leak, necrotic cells, and hyaline membrane formation. These alter the ability for gas exchange, causing hypoxia, pulmonary hypertension, and right-to-left shunting at the ductus. Normally, type 2 pneumocytes provide sufficient surfactant and coat the alveolar surfaces, decreasing surface tension and allowing alveoli to maintain acinar distention. Glucocorticoids accelerate lung maturation, and sometimes mothers are given exogenous steroids if a premature delivery is expected. Intrauterine stress such as maternal sepsis can cause an increase in maternal steroids, which may cross the placenta and contribute to cell maturation in alveolar lining and surfactant production. Clinically, most premature infants are symptomatic soon after birth, with grunting, nasal flaring, retractions, tachypnea, and cyanosis.

The initial radiographic appearance can be normal or show low lung volumes or bilateral diffuse granular-appearing opacities, representing collapsed alveoli. As the large bronchi do not collapse, there may be bilateral air bronchograms. Subsequent chest radiographs are variable, partially related to different treatment protocols, gestational age, and surfactant delivery. Surfactant is administered via nebulizer or with a catheter via the ET. It may be administered prophylactically at birth in premature infants at risk or when the infant becomes symptomatic. The radiographic appearance changes, as surfactant delivery may not be distributed evenly throughout the lungs, creating alternating patterns of distention and collapsed acini, which may appear as focal areas of collapse with some overdistention and lucencies, which may mimic pulmonary interstitial emphysema. Early treatment with repeated doses of surfactant has significantly improved early management of these infants, and high-frequency ventilation has also been employed to reduce the incidence of barotrauma. The degree of pulmonary inflation is used to adjust mean airway pressure, and radiographs may be used to ideally project the dome of the diaphragm over the eighth to tenth posterior ribs.

In the premature infant, the rigid, noncompliant lungs and associated hypoxia and acidosis often result in persistent pulmonary hypertension, and if ventilatory pressures are increased, air block may occur, leading to pulmonary interstitial emphysema (PIE), pneumomediastinum, pneumothorax, and – less commonly – pneumopericardium. It is normal to have relative pulmonary hypertension at birth, and slowly the pressure decreases. In full-term infants, the duct closes, but in premature infants, it persists and may remain open. When the pressure in the pulmonary arteries is decreased, the infant may shunt left to right across the ductus. Treatment with indomethacin (by inhibiting prostaglandin production) may produce ductal closure but at the increased risk of inducing gastrointestinal perforation.

Sudden diffuse opacification of the lungs in RDS may be seen in a variety of circumstances, including patent ductus arteriosus, a significant decrease in the ventilatory

settings, central mucous plugs of the trachea or ET, change in percent of oxygen, or changes in ventilation rate. Less commonly, diffuse pulmonary hemorrhage is a cause. Sudden catastrophic intracranial hemorrhage may produce central nervous system (CNS)-mediated edema.

Bronchopulmonary Dysplasia: Chronic Lung Disease in the Premature Infant

Chronic lung disease, or bronchopulmonary dysplasia (BPD), is a common complication of prematurity with significant morbidity. It is most common in infants <1,000 gm and in those <32 weeks gestational age. The appearance is variable and relates to gestational age, intrauterine lung development, surfactant delivery, treatment protocols, sepsis, pulmonary hypertension, hemorrhage, etc. Since Northway's original description of BPD in 1967 [4], many changes have occurred in the management and outcome of children with RDS. Much has been learned about the specific toxic effects of oxygen and assisted ventilation. Babies of much lower gestational age and birth weight with BPD are now surviving, particularly since the advent of high-frequency ventilation and surfactant use. The likelihood of developing BPD or retinopathy of prematurity and their severity in any particular baby has diminished with successful attempts at keeping inspired oxygen at or below 60%, keeping ventilatory pressures and rate as low as possible, and extubating as soon as possible. Infants at greatest risk for chronic lung disease are the profoundly premature, who require longer courses of assisted ventilation at greater pressures and rate and higher inspired oxygen concentration. Infants with air-leak phenomenon (pulmonary interstitial emphysema, pneumothorax, pneumomediastinum, pneumopericardium) also usually require prolonged treatment with higher oxygen concentration. It is rare to see the development of the classic four stages of BPD as described by Northway [5]. Radiographic findings in BPD demonstrate progression of hazy densities through the lung, focal areas of hyperinflation, coarse lung markings, focal or diffuse bubble-like lucencies, and asymmetric aeration. Reticulonodular densities and band-like opacities develop. Most premature infants have prolonged respiratory support, are prone to infections, and are at high risk for viral and bacterial pneumonia throughout early childhood.

High-resolution computed tomography (HRCT) has contributed to our understanding of the chest radiograph of older BPD survivors [6, 7]. One study in adults demonstrated abnormal radiologic findings, including linear opacities, in 87%, and 58% demonstrated subpleural opacities in the lower lobes [6]. Other findings include regional air trapping, coarse linear opacities, and focal areas of subsegmental atelectasis with regional hypertrophy and thickened intralobular septa. In follow-up CT studies of children with chronic lung disease who were born <30 weeks' gestation, findings include triangular pleural-based densities attributed to pseudofissures and relative decrease in size and number of vessels in these areas.

Air Leaks

Although air leaks can occur at any age, they are frequently seen in infants. The term is used to describe rupture of the alveolus or lung interstitium, which – depending on the leakage site – causes PIE, pneumomediastinum, and pneumothorax. Air can also dissect into the soft tissues of the neck as well as extend retroperitoneally. Air leak is attributed to an increase in alveolar pressure and subsequent rupture. Premature infants are frequently mechanically ventilated and are at increased risk.

Pulmonary Interstitial Emphysema

PIE is air within the pulmonary interstitium and lymphatics usually secondary to barotrauma. It is characterized by tubular lucencies that do not conform to the air within the bronchus, and usually the air extends to the pleural surface. It can be diffuse or localized; it can appear centrally and peripherally and is characterized by overdistention of the alveoli, with rupture and dissection of air into the interstitial tissues and lymphatics. The patient's lungs become poorly compliant, and there is interference with gas exchange and increase in ventilatory requirements. The linear lucencies are usually seen extending peripherally in a perivascular distribution pattern. Occasionally, PIE acts like a mass, and there is significant shift of the lung or collapse of the associated lung. Chest CT is occasionally used to evaluating problematic infants with persistent PIE [8] and has a typical appearance that consists of dot-like structures within air-filled cysts, which are thought to represent the bronchovascular bundles surrounded by interstitial gas.

Pneumomediastinum

Pneumomediastinum occurs when air dissects into the mediastinum. It is usually seen in the anterior mediastinum and can elevate the thymus toward the apical portion of the lungs. It can be seen in asymptomatic infants and resolve spontaneously. In infants with RDS, it may be part of PIE or pneumothorax, usually reflecting difficulty related to pulmonary hypertension and ventilation.

Pneumothorax

In infants, pneumothoraces can be identified both medially and laterally, and commonly the medial pneumothorax is missed. It is important to identify a tension pneumothorax as its presence is life threatening due to significant shift of the mediastinum and decrease in ventilation and systemic venous return to the heart. Occasionally, skin folds may be mistaken for pneumothoraces; however, lung markings are usually seen distal to the discrete linear density. If it is uncertain whether the infant has a pneumomediastinum or pneumothorax, decubitus films or cross-table lateral chest images are helpful; however, the two entities may coexist.

Meconium Aspiration Syndrome

Meconium aspiration syndrome (MAS) is secondary to in utero stress, with resultant intrapartum or intrauterine meconium aspiration. It most commonly occurs in babies who are postmature or small for gestational age, or in infants who have intrauterine stress. Although there is meconium staining of the amniotic fluid in approximately 10-15% of live births, meconium below the level of the vocal cords is only seen in 1-5% of newborns.

Radiographic findings in MAS vary, in part secondary to aspiration severity. The tenacious meconium often causes both medium- and small-airway obstruction, causing focal areas of atelectasis alternating with areas of overinflation. The meconium is an irritant to bronchial mucosa and may cause a chemical pneumonia, which increases the risk for subsequent gram-negative bacterial infection. Surfactant dysfunction also plays a role. Hypoxia usually results, with all factors combining to produce pulmonary hypertension, referred to as persistent fetal circulation (PFC). Pneumothorax is seen in 5-20%, and pleural effusions are noted in approximately 10%.

The use of extracorporeal membrane oxygenation (ECMO) has markedly decreased as a treatment modality for these patients, which is partially related MAS prevention strategies, high-frequency ventilation, surfactant use, and improved understanding of the disease. Meconium is the result of in utero stress, and its presence in the trachea and lung are not the entire cause of MAS. ECMO, which bypasses the lungs, allows pulmonary inflation to be at a minimum while maintaining physiologic levels of oxygen tension and saturation. While on ECMO, the chest radiograph appears nearly airless. The most critical factor in weaning the patient from ECMO is not simply improved pulmonary mechanics but reduced pulmonary vascular pressure to below systemic pressure.

Neonatal Pneumonia

Neonatal pneumonia is seen in <1% of live-born infants, and premature infants are at increased risk. Infections may be acquired in utero, during labor, at delivery, or shortly after birth. The major risk factor for intrauterine development of pneumonia is prolonged rupture of the membranes, particularly if labor is active during this period. Some organisms, particularly viruses, may cross the placenta. Group B streptococcus infections are the most common cause of pneumonia in the newborn, with an incidence of 3/1,000 live births, and are acquired in utero or during labor and delivery. Both clinically and radiographically, it may be difficult to distinguish this infection from RDS. Radiographic findings include bilateral granular opacities or irregular patchy infiltrates and usually low lung volumes. The presence of pleural effusions is a helpful marker, as they are unusual in RDS and much more common (25-67%) in B hemolytic streptococcal pneumonia. Infections with other bacterial or viral organisms may

produce radiographic findings identical to those described in group B streptococcal infections. HMD and neonatal pneumonia frequently coexist. There have been several infants reported [9] with late-onset right-sided diaphragmatic hernia in association with neonatal pneumonia.

Chlamydia pneumonia is caused by a bacterial-like intracellular parasite, *Chlamydia trachomatis* [10], which is acquired from the mother by direct contact during vaginal delivery. This organism is widely distributed, having been identified in the vagina of up to 13% of women tested. Infected infants become symptomatic, with conjunctivitis, the most common manifestation, usually appearing around 5-14 days of life. Pneumonia develops in a smaller percentage, appearing between 2 weeks and 3 months of age, and is associated with peripheral eosinophilia. The average age of onset is 6 weeks. Therefore, *Chlamydia* is somewhat unusual in the neonatal age group. Radiographic findings may range from a purely interstitial process to a focal alveolar infiltrate, and the disease is bilateral.

Transient Tachypnea of the Newborn

Transient tachypnea of the newborn is a self-limiting disease and is seen in infants born by cesarean section or those who have a precipitous delivery. Infants present with tachypnea, possible oxygen requirement, and appear healthy. It is thought to be related to retained fetal lung liquid. Under normal circumstances, fetal lung fluid is cleared from the lungs at or shortly after birth via the tracheobronchial system (30%), the interstitial lymphatics (30%), and the capillaries (40%). The radiographs of the chest suggest a diffuse, mildly coarsened, interstitial pattern similar to pulmonary edema or an irregular opacification. A pleural effusion is a common accompaniment. A transient, slight cardiac enlargement may occur. The hallmark of this process is a relatively benign clinical course (i.e., tachypnea), and follow-up radiographs are rarely needed. If done, however, they demonstrate rapid clearing (1-2 days) of the infiltrates. The cause had been postulated that there is a lack of normal “vaginal squeeze” on the infant chest during caesarean delivery and that the tachypnea is therefore related to retained fetal lung fluid. More recently it has been shown that the process is more complex and related to osmotic gradients created by active solute transport by the alveolar epithelial cells, which usually begin in utero, and these can be disrupted [11].

Congenital Lymphangiectasia

Babies with congenital lymphangiectasia may present with symptoms of tachypnea. It can be associated with many syndromes, such as Turner, Noonan, Ehlers Danlos, and others. The lungs may be initially normal or reveal a coarse interstitial infiltrate secondary to the distended and abnormally draining lymphatics. Pleural effusions may be present. A particularly large pleural ef-

fusion should suggest this diagnosis or may be related to a traumatic chylous or hemorrhagic effusion. The presence of a chylous effusion without a history of trauma is suggestive of congenital lymphangiectasia, although isolated chylous effusions do occur. Radiographs of the chest may look similar to total anomalous venous return with obstruction, although the clinical presentation is quite different.

Congenital Heart Disease

Increasingly, the diagnosis of congenital heart disease is made in utero with prenatal ultrasound. As the fetus is nourished by oxygenated maternal placental blood flow, many fetuses with complex and severe cardiac anomalies thrive in utero. Echocardiography at birth is the fundamental noninvasive imaging modality to detect congenital heart lesions and can be used with relative ease to provide excellent spatial and functional information. It is the primary modality for diagnosis of heart lesions. Just as intrathoracic masses are detected on fetal ultrasound and/or magnetic resonance imaging (MRI), congenital heart anomalies and/or cardiac masses can be recognized. Fetal cardiac tumors include teratomas, rhabdoid tumors, and fibromas [12].

On chest radiographs, it is always helpful to look for clues of congenital or acquired heart disease; however, it is not useful for making a specific diagnosis. In previous years, radiologists would try to remember heart lesions based on pulmonary flow, which was categorized as increased, decreased, or normal. However, most radiologists cannot accurately assess pulmonary flow [13]. This is even more challenging in infants, as there is ductal shunting that may increase or decrease flow, adding to confusion. Once operated upon, the classification based on pulmonary flow is no longer useful [14]. What is important in the newborn? Evaluating the abdomen for situs anomalies can suggest the diagnosis of polysplenia or asplenia, and these infants have complex heart lesions and abnormal patterns of systemic and pulmonary venous return. If there is a right aortic arch, then tetralogy of Fallot, pulmonary atresia, or double-outlet RV could be considered. If the heart is massively enlarged or “wall to wall” in the chest [15], it suggests Ebstein anomaly, pulmonary atresia with intact septum, pericardial effusion, or cardiac tumor. Cardiac rhabdomyoma is the most common primary pediatric tumor of the heart, and although benign, its position within critical areas in the heart can lead to outlet obstruction or arrhythmias. In the newborn, a variety of entities cause big hearts and are not related to congenital heart disease, such as infants of diabetic mothers who have septal hypertrophy, arrhythmias (which can be seen in mothers with lupus), vein of Galen aneurysm, hemangioendothelioma of the liver, marked anemia, and polycythemia. Many other congenital lesions of the heart can have a normal appearance, such as initial radiographs in hypoplastic left heart syndrome.

Abnormalities of the Lung Bud and Vascular Development

Congenital cystic lung disease comprises a broad spectrum of rare but clinically significant developmental abnormalities. In a recent, retrospective review of 193 fetuses imaged between 18-35 weeks' gestation, 170 infants had cystic adenomatoid malformation (CCAM), 14 pulmonary sequestration, and ten fetuses congenital high airway obstruction lesions (CHAOS) [16].

The routine use of fetal imaging has led to frequent prenatal diagnosis of lung lesions and provided new insight into the natural history of many malformations. Some advocate that embryologic insult generally correlates with lesion type and histopathology manifested, differing only in gestational age at which obstruction occurs [17]. There are changing concepts as it becomes clear that these lesions tend not to be "static" and that many appear to be hybrid or coexistent with other congenital lesions. Dramatic changes in lesion size or characteristics have been identified both in utero and postnatally [17-20].

One of the determinant factors of outcome is the degree of pulmonary hypoplasia associated with the lesion. Large lung lesions may lead to hydrops fetalis, which is thought to arise from compression of the IVC, which compromises venous return. Increased intrathoracic pressure or mass effect may cause polyhydramnios secondary to compression of the esophagus and the inability of the fetus to swallow.

Congenital Pulmonary Airway Malformations; Cystic Adenomatoid Malformation

New terminology has emerged, and the previous CCAM terminology is now congenital pulmonary airway malformation (CPAM). The renaming of this lesion was suggested because some lesions are not cystic and others are not hamartomatous. Cysts may communicate with each other but seldom with the airway. It involves a lobe or part of a lobe, and in the majority of cases, bilateral lesions are rare. Stocker originally classified CCAM into three histological types [21], but the classification has been expanded even further and, more recently, type 0 to type 4 has been suggested:

- Type 1: Multiple cysts >2 cm in diameter. This is the commonest form and accounts for approximately 60-70% of abnormalities.
- Type 2: Cysts >2 cm in diameter.
- Type 3: Bulky lesions, more solid in appearance, with microcysts; extremely rare.
- Type 4: Large cyst lined by alveolar-type cells.

CCAM of the lung is frequently diagnosed in utero and has a variable natural history. Approximately 40% of infants may develop hydrops, which is associated with a poor prognosis, yet 15% of lesions will regress in size [18]. Overall, >50% become smaller on sequential obstetric sonograms [22]. Prenatal studies have demonstrated that hydropic fetuses have a poor outcome with high

fatality rate [17], but some of those that survive require substantial ventilatory support due to respiratory insufficiency. Criteria have been suggested to attempt to track growth and regression during gestation by measuring the cystic adenomatoid volume (volume of an ellipse) and dividing it by head circumference to correct for differences in gestational age. This is called the chest/volume/ratio (CVR). If the CVR is ≥ 1.6 at presentation, there is an 80% chance of hydrops developing [23].

At birth, chest radiograph usually shows an opaque mass that, if large, may cause mediastinal shift. On the initial image in the newborn, if it lies adjacent to the hemidiaphragm, it may be difficult to distinguish from a congenital diaphragmatic hernia. With time, the cysts become air-filled.

CT is superior to chest radiograph in showing residual lesions. The development of infection and delayed onset of malignancy, in particular, rhabdomyosarcoma and pulmonary blastoma, have been reported in patients with CPAM. Nevertheless, the need for surgery and its timing is controversial in asymptomatic patients.

Pulmonary sequestration may be associated with CPAM, and both conditions are probably in a spectrum of related lung abnormalities [24, 25]. Both CCAM and pulmonary sequestration are associated with other anomalies. In particular, infants with type 2 CCAM have an increased incidence of cardiac, renal, and chromosomal anomalies. Pulmonary sequestration is associated with cardiac anomalies, diaphragmatic hernias, and gastric duplication [26].

Intralobar and Extralobar Pulmonary Sequestration

Intralobar and extralobar pulmonary sequestration is due to a segment of lung parenchyma that lacks a connection with the tracheobronchial tree and the blood supply originates from a systemic artery. Many of these malformations are diagnosed in utero, and a substantial number become smaller on sequential exams [22]. Intralobar sequestration occurs in 75% of all sequestrations and is located in the left lower lobe 70% of the time. The blood supply is usually from the thoracic aorta. In neonates, sequestrations large enough to cause respiratory distress are usually extralobar [27]. They are separate from the lung and have their own pleural covering and their own systemic artery, which usually arises from the abdominal aorta and courses through the diaphragm to supply the lesion. On histological examination, there may be features of immature lung parenchyma or a hamartomatous type of lesion similar to CCAM. They can be hybrid lesions [24] and are seen with CCAM. Ultrasonography with Doppler examination may show the soft tissue mass and its blood supply preoperatively; however, CT or MRI also can be useful to locate the anomalous systemic blood supply to the lungs and determine the size or access coexisting lesions.

Congenital Lobar Emphysema

Focal areas of bronchomalacia, kinks, webs, mucosal folds, and crossing vessels have all been implicated in the

etiology of congenital lobar emphysema. Fetal imaging has demonstrated focal areas of hyperinflation, and many times these appear to resolve. If it is a focal large airway abnormality where the lobe is enlarged and overdistended [22], lobar emphysema may be present. If chest radiography is performed very early, the overdistended lobe may be fluid-filled. Once the fluid is reabsorbed, the lobe appears hyperlucent and overdistended. There may be atelectasis of the adjoining lobes and mediastinal shift to the contralateral side. Chest CT scan shows a similar appearance. The upper lobes are most commonly involved, with the left more often than the right.

Bronchial Atresia

Bronchial atresia is another overinflation lesion, which is characterized by overdistention of a lung segment that does not connect with a bronchus. Initially, it may be dense in appearance but eventually fills with air through collateral air flow. At the base of the bronchi, there is a round or elliptical mass, with overdistention of the lung distally. The cysts mass is thought to represent inspissated and trapped fluid.

Bronchogenic Cysts

Bronchogenic cysts occur secondarily to abnormal budding of the tracheal bronchial tree during development and are most common in the middle mediastinum (65-90% of cases). They may also occur in the lungs, usually centrally and solitarily, and may compress the distal trachea or bronchi. As with sequestration, they may become infected and appear as well-defined soft tissue attenuation or cystic air-fluid-containing masses. The children may present with an acute history of pneumonia or wheezing if the cysts cause tracheal compression, or they may be an incidental findings. The one major reason to get a follow-up chest radiograph in a child with round pneumonia is to evaluate whether healing has occurred or the mass persists. Mass size can vary considerably and cysts are usually surgically removed.

Congenital High Airway Obstruction Lesions

CHAOS is a condition recognized in fetal imaging in which the lungs are obstructed due to laryngeal atresia or high midline mass in the neck, throat, tongue, or face that obstructs the trachea or airway. Oligohydramnios may be related to lack of pulmonary drainage and esophageal compression by lungs that are overexpanded and somewhat everted. The heart is central, the diaphragm everted, lungs are echogenic, and ascites may be present. Whereas these lesions were once always fatal, there has been occasional survival following ex-utero intrapartum therapy (EXIT). At caesarean section, tracheal cannulation is done, which provides access to the airway prior to delivery. Even after the tracheal obstruction is removed, the lung does not function normally, as it was not exposed to growth factors in the amniotic fluid during fetal life.

Pulmonary Hypoplasia

Pulmonary hypoplasia may be secondary to oligohydramnios – for example, in Potter sequence – and usually is diagnosed in utero, although it occasionally can be seen in delivered babies who have unusual facies, who are near-term with multiple pneumothoraces, and who show difficulty in ventilation. These infants may also have ascites. Unilateral pulmonary hypoplasia as an isolated lesion usually occurs on the right, with varying degrees of lung hypoplasia, and is associated with a small or absent pulmonary artery with mediastinal shift to the affected side. This latter abnormality does not usually present in the neonatal period.

Congenital Diaphragmatic Hernia (Bochdalek Type)

Congenital diaphragmatic hernia results from a defect in the posterior diaphragm, most commonly on the left side, as a result of failure of closure, the pleuroperitoneal canal by the tenth week of gestation. The hernia may contain stomach, small bowel, colon, or liver. The fetal bowel migrates outside the abdominal cavity and returns by week 10-12 and moves into the chest if the diaphragm has not completely formed. The presence of bowel loops in the thorax results in hypoplasia of one or both lungs, which depends on the number of bowel loops present and the length of time the abnormality is present. It is associated with other congenital cardiac, genitourinary, CNS, and chromosomal abnormalities in 10-50% of infants. Direct intrauterine hernia repair was pioneered in the early 1990s [28]. Fetal tracheal ligation, known as PLUG (plug the lung until it grows), increases alveolar and vascular growth [29]. However, neither technique has found worldwide favor to date. The prognosis ultimately depends on the degree of pulmonary hypoplasia, which depends largely but not entirely on the size of the herniated contents and the timing of the event.

The presence of the stomach in the thorax is related to a poorer prognosis, as it indicates that the diaphragmatic defect is large. The chest radiograph initially shows opacification with significant mediastinal shift to the contralateral side. Over the subsequent hours, air is seen in the bowel loops. An abdominal radiograph should also be performed, which will show a scaphoid appearance due to absence of bowel loops from their normal location in the abdomen. This helps to differentiate the condition from congenital cystic adenomatoid malformation or a large pleural effusion. Right-sided diaphragmatic hernias may involve herniation of the liver or kidney in addition to bowel loops. Evaluating malposition of catheters related to the diaphragmatic hernia is sometimes helpful, such as the gastric tube and abnormal position of umbilical venous catheters if the liver is herniated. Initial therapy includes continuous deflation of the bowel loops by nasogastric suction, mechanical ventilation, and the use of nitric oxide to decrease pulmonary hypertension. If this

treatment is unsuccessful, the infant may be treated with ECMO. In the past, surgery to correct the diaphragmatic hernia was thought to be urgent, but currently, the surgical approach is delayed. These children have profound pulmonary hypertension, and there is increasing awareness of not injuring residual lung tissue from barotraumas. Following repair of the diaphragmatic defect, the chest radiograph shows the true volume of the underlying lungs. Frequently, there is a pneumothorax on the side of the large hernia, with subsequent fluid in the left hemithorax. There is increasing evidence that these children experience long-term effects of underdeveloped lung, with persistent pulmonary hypertension and sometimes cor pulmonale.

Conclusions

The chest radiograph remains the most common and most useful imaging tool in the diagnosis of conditions that contribute to respiratory distress in the newborn and young child, particularly in entities that cause lung parenchymal disease or have recognizable lung lesions. In the older child, infections are most common. A detailed clinical history should be obtained prior to interpretation. Many of the developmental lung-bud and vascular conditions, together with congenital diaphragmatic hernias, are now diagnosed antenatally, and the radiologist's role has changed to "monitoring" the course. International standardization of the definition of lung lesions, and sharing outcome data from different treatment protocols, is helpful, as patient outcome data and appropriate treatment protocols are still challenging. Imaging has certainly contributed new knowledge and understanding of many of the chest abnormalities presented in the newborn and young infant.

References

- Donoghue V (ed) (2008) Radiological imaging of the neonatal chest, 2nd edn. Springer-Verlag, Heidelberg
- Strife JL, Crotty EJ (2008) Neonatal chest imaging. In: Lucaya J, Strife JL (eds). Pediatric chest imaging, 2nd edn. Springer-Verlag, Heidelberg, p 448
- Singh S, Royal S, Hedlund G, Barnes G (1999) Central venous catheter motion: a pitfall in catheter localization on pediatric chest radiography. *AJR Am J Roentgenol* 172:803-808
- Northway WH Jr, Rosan RC, Porter DY (1967) Pulmonary disease following respirator therapy of hyaline-membrane disease. Bronchopulmonary dysplasia. *N Engl J Med* 276:357-368
- Northway WH Jr, Moss RB, Carlisle KB et al (1990) Late pulmonary sequelae of bronchopulmonary dysplasia. *N Engl J Med* 323:1793-1799
- Aukland SM, Halvorsen T, Fosse KR et al (2006) High-resolution CT of the chest in children and young adults who were born prematurely: findings in a population-based study. *AJR Am J Roentgenol* 187:1012-1018
- Howling SJ, Northway WH Jr, Hansell DM et al (2000) Pulmonary sequelae of bronchopulmonary dysplasia survivors: high-resolution CT findings. *AJR Am J Roentgenol* 174:1323-1326
- Donnelly LF, Lucaya J, Ozelame V et al (2003) CT findings and temporal course of persistent pulmonary interstitial emphysema in neonates: a multiinstitutional study. *AJR Am J Roentgenol* 180:1129-1133
- McCarten KM, Rosenberg HK, Borden ST, Mandell GA (1981) Delayed appearance of right diaphragmatic hernia associated with group B streptococcal infection in newborns. *Radiology* 139:385-389
- Schachter J (1978) Chlamydial infections (third of three parts). *N Engl J Med* 298:540-549
- Jain L, Eaton DC (2006) Physiology of fetal lung fluid clearance and the effect of labor. *Semin Perinatol* 30:34-43
- Avni FE, Massez A, Cassart M (2009) Tumours of the fetal body: a review. *Pediatr Radiol* 39:1147-1157
- Laya BF, Goske MJ, Morrison S et al (2006) The accuracy of chest radiographs in the detection of congenital heart disease and in the diagnosis of specific congenital cardiac lesions. *Pediatr Radiol* 36:677-681
- Strife JL (2006) Pediatric cardiac imaging: the beat goes on! *Pediatr Radiol* 36:578-580
- Donnelly LF, Gelfand KJ, Schwartz DC et al (1997) The "wall to wall" heart: massive cardiophrenic silhouette in newborns. *Appl Radiol* 26:23-28
- Cavoretto P, Molina F, Poggi S et al (2008) Prenatal diagnosis and outcome of echogenic fetal lung lesions. *Ultrasound Obstet Gynecol* 32:769-783
- Azizkhan RG, Crombleholme TM (2008) Congenital cystic lung disease: contemporary antenatal and postnatal management. *Pediatr Surg Int* 24:643-657
- Crombleholme TM, Coleman B, Hedrick H et al (2002) Cystic adenomatoid malformation volume ratio predicts outcome in prenatally diagnosed cystic adenomatoid malformation of the lung. *J Pediatr Surg* 37:331-338
- van Leeuwen K, Teitelbaum DH, Hirsch RB et al (1999) Prenatal diagnosis of congenital cystic adenomatoid malformation and its postnatal presentation, surgical indications, and natural history. *J Pediatr Surg* 34:794-798; discussion 798-799
- Winters WD, Effmann EL, Nghiem HV, Nyberg DA (1997) Disappearing fetal lung masses: importance of postnatal imaging studies. *Pediatr Radiol* 27:535-539
- Stocker JT, Madewell JE, Drake RM (1977) Congenital cystic adenomatoid malformation of the lung. Classification and morphologic spectrum. *Hum Pathol* 8:155-171
- Garel L (2008) Antenatal imaging of chest malformations. In: Donoghue V (ed) Radiological imaging of the neonatal chest, 2nd edn. Springer-Verlag, Heidelberg
- Sanders RC (2002) Cystic adenomatoid malformation of the lung (CCAM). In: Sanders RC (ed) Structural fetal abnormalities: the total picture. Mosby, St. Louis, MO, pp 193-195
- Cass DL, Crombleholme TM, Howell LJ et al (1997) Cystic lung lesions with systemic arterial blood supply: a hybrid of congenital cystic adenomatoid malformation and bronchopulmonary sequestration. *J Pediatr Surg* 32:986-990
- Samuel M, Burge DM (1999) Management of antenatally diagnosed pulmonary sequestration associated with congenital cystic adenomatoid malformation. *Thorax* 54:701-706
- Sohaey R, Zwiebel WJ (1996) The fetal thorax: noncardiac chest anomalies. *Semin Ultrasound CT MR* 17:34-50
- Schwartz DS, Reyes-Mugica M, Keller MS (1999) Imaging of surgical diseases of the newborn chest. Intrapleural mass lesions. *Radiol Clin North Am* 37:1067-1078
- Harrison MR, Adzick NS, Flake AW et al (1993) Correction of congenital diaphragmatic hernia in utero: VI. Hard-earned lessons. *J Pediatr Surg* 28:1411-1417; discussion 1417-1418
- Hedrick MH, Estes JM, Sullivan KM (1994) Plug the lung until it grows (PLUG): a new method to treat congenital diaphragmatic hernia in utero. *J Pediatr Surg* 29:612-617

Modern Diagnosis in the Evaluation of Pulmonary Vascular Disease

Martine Remy-Jardin¹, Gerald F. Abbott²

¹ Department of Cardiothoracic Imaging, Hospital Calmette, University Center of Lille, Lille, France

² Department of Imaging, Massachusetts General Hospital, Harvard University, Boston, MA, USA

Introduction

Among the various imaging modalities available in recent decades, computed tomography (CT) has remained the core technique for evaluating respiratory disorders. Over the last few years, this central position has been reinforced by the possibility of deriving morphological and functional information from the same data set. This approach is of major interest for evaluating pulmonary vascular diseases for three main reasons: (1) these disorders require optimal morphologic evaluation not only of the pulmonary vascular tree but also of surrounding structures, especially the lung parenchyma; (2) although we have currently reached an upper limit in terms of the resolution of morphology, CT has the ability to combine that high-quality morphologic imaging with perfusion imaging; and (3) it is mandatory to search for the cardiac consequences or causes of pulmonary vascular diseases, which requires a combination of high spatial and temporal resolution. Because all these complementary options are now available with CT, this course focuses on modern developments of CT applicable to evaluating pulmonary vascular diseases encountered in daily practice.

New Options for an Optimised Evaluation of Pulmonary Vessels on a Standard Chest CT Examination

Improved Temporal Resolution of Pulmonary CT Angiograms

The first prerequisite for high-quality chest imaging is high spatial resolution, which is necessary not only to detect subtle morphologic changes on lung images but is also very important for proper analysis of thoracic vessels on CT angiography (CTA). However, high spatial resolution is optimally employed when short overall examination times and high temporal resolution (i.e. short acquisition times of the individual axial image planes) are simultaneously available, thus enabling analysis of high-resolution images devoid of motion artefacts. The ongoing progress in development of multidetector-row CT (MDCT) technology has enabled radiologists to image the entire thorax with high spatial resolution in shorter periods of time. As a consequence,

patients are more frequently able to hold their breath during data acquisition, resulting in a dramatic decrease in respiratory motion artefacts. Shorter CT rotation times have enabled shorter acquisition times of image planes and significantly reduced cardiac motion artefacts, which not only alter image quality in the vicinity of cardiac cavities but may also produce pulsation artefacts at the level of systemic and pulmonary vessels, sometimes mimicking endovascular abnormalities. In order to image patients with the highest temporal resolution and shortest overall examination time, it is best to select the shortest rotation time available and the highest pitch, defined as the table feed per rotation divided by the nominal beam width at the isocenter. On 64-slice MDCT using a single X-ray source, rotation times vary between 0.30 and 0.40 s, resulting in a temporal resolution per image not better than half the rotation time, and the pitch values usually do not exceed 1.5 [1]. The introduction of dual-source 64-slice MDCT technology offers the possibility of improving CT conditions. When both tubes are operated at the same kilovoltage, the temporal resolution of each image is one quarter of the rotation time, each of the two detectors contributing 90° of data in parallel-ray geometry to each image plane [2]. Moreover, the second measurement system of dual-source CT allows for higher pitch modes than those available with single-source CT, without image distortions inside the field of view of the second detector. In a recent study, Tacelli et al. showed that this scanning mode provides CT angiographic examinations of excellent quality for thoracic applications in routine clinical practice, even for patients in poor clinical condition to tolerate chest examinations, including those referred for pulmonary vascular diseases such as acute pulmonary embolism (PE) [3] (Fig. 1).

Improved Morphological Evaluation of Peripheral Pulmonary Vessels

With the introduction of MDCT, CTA has reached the diagnostic capabilities previously acknowledged for pulmonary angiography and is now recognised as the gold standard for diagnosing acute PE [4]. The superiority of MDCT over single-slice CT results from the possibility of scanning the entire thorax with submillimetric collimation

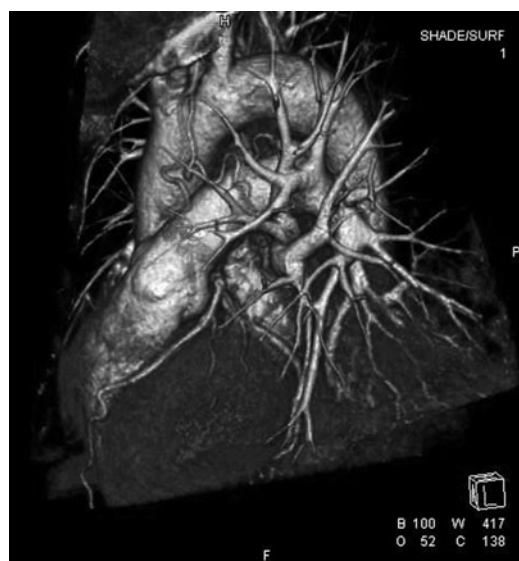


Fig. 1. Lateral view of the left hemithorax in a 51-year-old patient evaluated with a high pitch (3.2), high temporal resolution (75 ms) scanning mode (volume-rendered image). Note the sharpness of all pulmonary and systemic vessels in the volume scanned (data acquisition 0.79 s) (for color reproduction see p 273)

in short periods of time, which is particularly useful when evaluating dyspneic patients. These technological advances have been shown to improve the evaluation of peripheral pulmonary arteries and thus the accuracy of CT in the diagnostic workup of acute PE. In parallel, MDCT allows radiologists to scan patients at a low kilovoltage with two subsequent advantages, namely, the possibility of reducing contrast medium doses, and reducing the overall radiation dose delivered to patients. This is of particular importance to young female patients who may be exposed to substantial levels of radiation to breast tissue. In the specific context of acute PE, the latter concern is clinically relevant when keeping in mind the lower prevalence of acute PE, which has dropped from 33% on angiographic studies to <20% on CT/MDCT scans. To date, several studies have investigated the clinical benefits of low-kilovoltage techniques [i.e. 80-100 kV(p), vs 120-140 kV(p)], the parameters at which most CT angiograms are obtained. However, for obvious ethical reasons, these studies were based on the comparative analysis of different populations scanned with single-source CT [5-8]. The limitations of such comparisons include the lack of systematic adjustment for patient morphotype, cardiac haemodynamic conditions and underlying respiratory disease. When these factors cannot be strictly accounted for, they may interfere with the overall quality of pulmonary vascular enhancement. With the introduction of dual-source CT, it is now possible to scan patients with dual energy, each tube being set at a different kilovoltage. In addition to the possibility of evaluating lung perfusion with this technique, standard CT angiograms can also benefit from this scanning mode, which has been shown to improve the ability to analyse small-sized pulmonary arteries with 80 kV(p) settings [9].

Perfusion Imaging with Dual-Energy CT

Lung perfusion with dual-energy CT does not correspond to blood flow analysis per se, as it represents a measurement at one time point only, but it provides an iodine map of the lung microcirculation. Within normal lung parenchyma, the iodine content of the capillary bed can thus be assimilated to the parenchymographic phase of a conventional or digital angiogram. There are numerous parameters known to influence the iodine distribution within pulmonary capillaries. Some are technique-related, whereas others are due to the anatomical and/or physiological circumstances of data acquisition. Dual-energy CT angiographic examinations can be obtained using a scanning protocol similar to that utilized in routine clinical practice. The acquisitions are acquired from top to bottom of the chest with an injection protocol similar to that of a standard CT angiogram obtained with single energy on a 64-slice scanner. Two categories of images can be reconstructed, i.e. diagnostic and lung-perfusion scans. Diagnostic scans correspond to contiguous 1-mm-thick transverse CT scans generated from the raw spiral projection data of tube A and tube B (60% from the acquisition with tube A; 40% from the acquisition with tube B). Lung perfusion scans (i.e. images of the perfused blood volume of the lung parenchyma) are generated after determination of the iodine content of every voxel of the lung parenchyma on the separate 80- and 140-kV(p) images. They can be generated as gray-scale or color-coded images. All generated images can be displayed as transverse scans, complemented as needed by coronal and sagittal reformations. Even though a dual-energy acquisition does not correspond to true perfusion imaging, as it visualises only blood volume and not blood flow, several applications of this pulmonary micro-CTA have already been investigated within the current conditions of dual-energy CT [10].

Acute Pulmonary Embolism

Dual-energy CT can detect endoluminal clots on averaged images of tubes A and B as efficiently as can single-source CTA [11]. In this preliminary study, the authors also validated the detectability of perfusion defects beyond obstructive clots. Perfusion defects in the adjacent lung parenchyma have the typical perfusion territorial triangular shape well known from pulmonary angiographic, scintigraphic and magnetic resonance imaging (MRI) perfusion studies. Dual-energy CTA can help predict perfusion defects without directly identifying peripheral endoluminal clots that may be located in subsegmental or more distal pulmonary arterial branches (Fig. 2). Dual-energy CT can also help differentiate lung infarction from nonspecific peripheral lung consolidation, which sometimes mimics a so-called Hampton's hump.

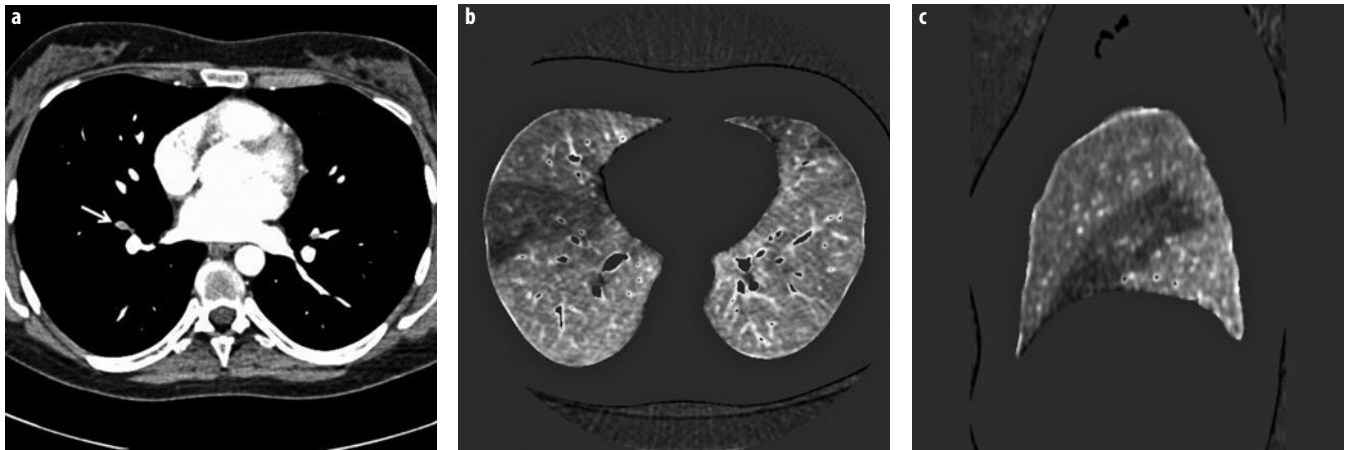


Fig. 2 a-c. Dual-energy chest computed tomography (CT) angiogram obtained in a 23-year-old woman suspected of acute pulmonary embolism. **a** Transverse CT scan (1-mm thick) obtained at the level of the left atrium (weighted averaged image from both tubes; 0.4 weighting factor). Note the presence of an obstructive clot at the level of the anterior segmental artery of the right lower lobe (*arrow*). **b** Perfusion scan (2-mm thick; transverse image) obtained at the level of the lower lobes showing a large perfusion defect in the anterior segment of the right lower lobe. **c** Perfusion scan (2-mm thick; sagittal image) obtained at the level of the right hemithorax, illustrating the extent of the right lower lobe perfusion defect

Chronic Pulmonary Embolism

Similar to the results achieved in acute PE, dual-energy CTA may depict perfusion defects distal to chronic clots. Three vascular characteristics of chronic PE may manifest on dual-energy CT imaging. First, chronic PE is responsible for a mosaic pattern of lung attenuation, characterised by areas of ground-glass attenuation, with enlarged vascular sections intermingled with areas of normal lung attenuation and smaller vascular sections. When present, these findings are highly suggestive of redistribution of blood flow, but they are not consistently demonstrated by conventional CT in chronic PE. In such circumstances, dual-energy CT has the potential to recognise ground-glass attenuation of vascular origin by means of high iodine content within the areas of ground-glass attenuation, thus enabling their distinction from ground-glass attenuation secondary to bronchioalveolar diseases [12]. Second, chronic PE can lead to the development of calcifications within partially or completely occlusive chronic clots as well as within pulmonary artery walls, when chronic PE is complicated by longstanding and/or severe pulmonary hypertension. Such calcifications can be detected by means of virtual noncontrast imaging, always accessible from dual-energy CT imaging. Third, the images generated at 80 kV can be used to improve visualisation of the systemic collateral supply present in chronic PE that originates from bronchial and nonbronchial systemic arteries.

Obstructive Airways Diseases

Alterations in pulmonary perfusion are present in numerous stages of smoking-related respiratory diseases.

Investigating endothelial dysfunction in pulmonary arteries of patients with mild chronic obstructive pulmonary disease (COPD), Peinado et al. showed that endothelial dysfunction of pulmonary arteries is already present in patients with mild COPD [13]. In these patients, as well as in smokers with normal lung function, some arteries show thickened intima, suggesting that tobacco consumption may play a critical role in the pathogenesis of pulmonary vascular abnormalities in COPD. Several structural changes in early stages of COPD have been described in experimental models, including proliferation of smooth-muscle fibres within peribronchiolar arterioles and collagen and elastin deposition in the thickened intima [14, 15]. In preliminary studies, Hoffman et al. [16] demonstrated an increased heterogeneity of local mean transit times of the contrast agent within pulmonary microvasculature of smokers with normal pulmonary function tests. More recently, Pansini et al. evaluated pulmonary lobar perfusion with dual-source, dual-energy CTA in COPD patients [17]. They observed that nonsmokers had no alterations in lung structure and a uniform distribution of iodine content within upper and lower lobes and between right and left lungs. Perfusion scans of emphysematous patients showed significantly lower iodine content within lung microcirculation of the upper lobes compared with smokers without emphysema and a significantly lower perfusion in the upper lung zones compared with lower lung zones, matching lung parenchymal destruction. These structural alterations are significant considerations in view of the epidemiologic burden represented by COPD, a disease expected to become the third leading cause of morbidity worldwide.

Are There Indications for ECG-Gated CTA Examinations when Exploring Pulmonary Vascular Diseases?

Depicting Pulmonary Hypertension

Although a pulmonary trunk (PT) diameter ≥ 33.2 mm has 95% sensitivity for pulmonary hypertension (PHT) diagnosis, the specificity of this measurement is only 58%, which is not sufficient for accurate PHT detection, especially in patients with mild PHT [18]. Moreover, no correlation has been found between the degree of PHT and PT diameter. Electrocardiograph (ECG)-gated MDCT acquisitions of the entire thorax enable the evaluation of new functional parameters in addition to the standard morphologic analysis of thoracic organs. In patients with PHT, right pulmonary artery distensibility has recently been reported as an accurate predictor for PHT on ECG-gated 64-slice MDCT scans of the chest [19]. Its diagnostic value was superior to that of the single measurement of PT diameter.

Assessing Right Ventricular Function

The introduction of fast rotation speed and dedicated cardiac reconstruction algorithms that exploit the multislice acquisition data scheme has allowed new possibilities for cardiac and thoracic imaging applications. The first method for ECG-gated examinations of the entire thorax was introduced by Flohr et al. with 4-slice MDCT technology [20]. The proposed technique offered extended volume coverage compared with standard ECG-gated spiral scanning, using reconstruction approaches for cardiac applications that provided more precise morphologic information at the level of major mediastinal vessels. Despite this improvement in image quality, the major impact of fast-scanning multislice CT technology was offered by 16-slice MDCT, which made possible the integration of cardiac functional information in a diagnostic CT scan of the chest. Three approaches were proposed: one investigating cardiac global function during a whole-chest multislice CT acquisition with a 16×1.5 mm collimation to ensure an acceptable breath-hold duration [21], one investigating a two-phase protocol to scan both the entire thorax and cardiac cavities with the highest spatial resolution [22] and the third evaluating a dedicated cardiac MDCT protocol to assess right ventricular function and mass [23]. Comparing ECG-gated 16-slice MDCT with equilibrium radionuclide ventriculography, these preliminary studies demonstrated the feasibility of such an approach in limited populations of hemodynamically stable patients and confirmed the accuracy of the CT estimation of right ventricular ejection fraction. The introduction of 64-slice scanners offered further improvement in this concept of integrating morphology and cardiac function. Investigating a study group of 133 patients with various respiratory disorders, Salem et al. reported that right and left ventricular function were obtainable in 93% of patients (124/133), whereas an imprecise segmentation of the right and left ventricular cavities was

the limiting factor for precise calculation of end-systolic and end-diastolic ventricular volumes in the remaining patients [24]. These results were achievable with lower dose-length-product (DLP) values than those recommended for standard non-ECG-gated examinations. This was possible by means of concurrent use of two dose modulation systems, namely, the adjustment of the milliampere setting for patient size and anatomical shape, and an ECG-controlled tube current. These results showed that the radiation dose issue was not a limiting factor for chest ECG-gated CT examinations inasmuch as the clinical relevance of such scanning conditions was fully justified.

References

1. Rogalla P, Kloeters C, Hein PA (2009) CT technology overview: 64-slice and beyond. *Radiol Clin North Am* 47:1-11
2. Petersilka M, Bruder H, Krauss B et al (2008). Technical principles of dual source CT. *Eur J Radiol* 68:362-368
3. Tacelli N, Remy-Jardin M, Flohr T et al (2010) Dual-source chest CT angiography with high temporal resolution and high pitch modes: evaluation of image quality in 140 patients. *Eur Radiol* 20:1188-1196
4. Remy-Jardin M, Pistolesi M, Goodman LR et al (2007) Management of suspected acute pulmonary embolism in the era of CT angiography: a statement from the Fleischner Society. *Radiology* 245:315-329
5. Holmquist F, Nyman U (2006) Eighty-peak kilovoltage 16-channel multidetector computed tomography and reduced contrast-medium doses tailored to body weight to diagnose pulmonary embolism in azotaemic patients. *Eur Radiol* 16:1165-1176
6. Sigal-Cinqualbre AB, Hennequin R, Abada H et al (2004) Low-kilovoltage multi-detector row chest CT in adults: feasibility and effect on image quality and iodine dose. *Radiology* 231:169-174
7. Schueller-Weidekamm C, Schaefer-Prokop CM, Weber M et al (2006) CT angiography of pulmonary arteries to detect pulmonary embolism: improvement of vascular enhancement with low kilovoltage settings. *Radiology* 241:899-907
8. Heyer CM, Mohr PS, Lemburg SP et al (2007) Image quality and radiation exposure at pulmonary CT angiography with 100- or 120-kVp protocol: prospective randomized study. *Radiology* 245:577-583
9. Gorgos AB, Remy-Jardin M, Duhamel A et al (2009) Evaluation of peripheral pulmonary arteries at 80 kV and at 140 kV: dual-energy computed tomography assessment in 51 patients. *J Comput Assist Tomogr* 33:981-986
10. Remy-Jardin M, Faivre JB, Pontana F et al (2010) Thoracic applications of dual energy. *Radiol Clin North Amer* 48:193-205
11. Pontana F, Faivre JB, Remy-Jardin M et al (2008) Lung perfusion with dual-energy multidetector-row CT (MDCT): Feasibility for the evaluation of acute pulmonary embolism in 117 consecutive patients. *Acad Radiol* 15:1494-1504
12. Pontana F, Remy-Jardin M, Duhamel A et al (2010) Lung perfusion with dual energy multidetector-row CT: can it help recognize ground glass opacities of vascular origin? *Acad Radiol* 17:587-594
13. Peinado VI, Barberà JA, Ramirez J et al (1988) Endothelial dysfunction in pulmonary arteries of patients with mild COPD. *Am J Physiol* 274:L908-L913
14. Yamato Y, Sun JP, Churg A et al (1997) Guinea pig pulmonary hypertension caused by cigarette smoke cannot be explained by capillary bed destruction. *J Appl Physiol* 82:1644-1653
15. Santos S, Peinado VI, Ramirez J et al (2002) Characterization of pulmonary vascular remodelling in smokers and patients with mild COPD. *Eur Respir J* 19:632-638

16. Hoffman EA, Simon BA, McLennan G (2006) A structural and functional assessment of the lung via multidetector-row computed tomography. *Proc Am Thorac Soc* 3:519-534
17. Pansini V, Remy-Jardin M, Faivre JB et al (2009) Assessment of lobar pulmonary perfusion in COPD patients: preliminary experience with dual-energy CT angiography. *Eur Radiol* 19:2834-2843
18. Edwards PD, Bull RK, Coulden R (1998) CT measurement of main pulmonary artery diameter. *Br J Radiol* 71:1018-1020
19. Revel MP, Faivre JB, Remy-Jardin M et al (2009) Pulmonary hypertension: ECG-gated 64-section CT angiographic evaluation of new functional parameters as diagnostic criteria. *Radiology* 250:558-566
20. Flohr T, Prokop M, Becker CR et al (2002) A retrospectively ECG-gated multislice spiral CT scan and reconstruction technique with suppression of heart pulsation artifacts for cardiothoracic imaging with extended volume coverage. *Eur Radiol* 12:1497-1503
21. Coche E, Vlassenbroeck A, Roelants V et al (2005) Evaluation of biventricular ejection fraction with ECG-gated 16-slice CT: preliminary findings in acute pulmonary embolism in comparison with radionuclide ventriculography. *Eur Radiol* 15:1432-1440
22. Delhay D, Remy-Jardin M, Teisseire A et al (2006) Estimation of right ventricular ejection fraction by multidetector row CT: comparison with equilibrium radionuclide ventriculography, Part I. *AJR Am J Roentgenol* 187:1597-1804
23. Kim TH, Ryu YH, Hur J et al (2005) Evaluation of right ventricular volume and mass using retrospective ECG-gated cardiac multidetector computed tomography: comparison with first-pass radionuclide angiography. *Eur Radiol* 15:1987-1993
24. Salem R, Remy-Jardin M, Delhay D et al (2006) Integrated cardiothoracic imaging with ECG-gated 64-slice multidetector-row CT: Initial findings in 133 patients. *Eur Radiol* 16:1973-1981

Imaging of Pulmonary Infections

Philip Goodman¹, Helmut Prosch², Daniela Kienzl², Christian J. Herold²

¹ Duke University Medical Center, Durham, NC, USA

² Department of Radiology, Vienna General Hospital, Medical University of Vienna, Vienna, Austria

Introduction

Pneumonia is one of the most frequent causes of morbidity and mortality throughout the world. It is the most prevalent community-acquired infection and the second most common nosocomial infectious disorder. Infections may occur in healthy people or individuals with concomitant intrapulmonary or extrathoracic diseases. Pneumonia may develop into a life-threatening condition, especially in immunocompromised patients, in children, and in the elderly.

In this contribution, the principles regarding epidemiology, pathogenesis, classification, and clinical and radiographic diagnoses of pneumonias are reviewed. Specific effort is directed toward formulating an integrated approach to the diagnosis of pneumonia that combines clinical and radiologic information. The course material focuses on: (1) community-acquired pneumonia (CAP); (2) nosocomial pneumonia (NP); and (3) pneumonia in immunocompromised patients.

Although the spectrum of organisms causing pneumonia differs between these groups of patients, and there is considerable overlap with regard to their radiologic features, there may be findings on chest imaging that help to narrow the differential diagnosis.

Community-Acquired Pneumonia

Pathogenesis

CAPs are acquired in the community and most often seen in the offices of general practitioners, private radiologists, and in the outpatient department or the emergency room of the hospitals. CAP primarily affects children (15-35 of 1,000 children per year) and elderly people (30-40 per 1,000 persons per year). The mode of transmission of CAP is usually person-to-person via water or mucus droplets laden with viruses or bacteria. The most frequent pathogens are Gram-positive bacteria, such as *Streptococcus pneumoniae* (*Pneumococcus*) and *Staphylococcus aureus*, and Gram-negative bacteria, such as *Haemophilus influenzae* and atypical bacteria, including *Mycoplasma*

pneumoniae, *Chlamydia pneumoniae*, and *Legionella pneumophila*. In addition, respiratory viruses, such as the influenza viruses, the human metapneumovirus (hMPV), the respiratory syncytial virus (RSV), the rhinovirus, parainfluenza viruses, adenoviruses, and corona viruses may also cause CAP. It appears from the literature that the spectrum of organisms varies according to patient demographics, temporal, geographic, and diagnostic factors.

In CAP, the patient's health and socioeconomic status have a certain impact on the spectrum of causative organisms. Normally healthy people are most likely to contract mycoplasma pneumonia or a mild form of pneumococcal pneumonia. Debilitated patients, alcoholics, and chronically ill people, however, more often present with severe pneumococcal pneumonia or infections caused by *H. influenzae*, *S. aureus*, or Gram-negative bacilli. *L. pneumophila* and *Chlamydia* infections are more common in patients with some form of mild immunologic compromise. Patients with poor oral hygiene and occasional loss of consciousness (epilepsy, alcoholism) may suffer from anaerobic pulmonary infections. In addition, in these patients, *Mycobacterium tuberculosis* infection is more prevalent compared with in healthy persons without risk factors. Recurrent pneumonia in outpatients usually indicates some sort of underlying problem, such as congenital or acquired immunologic disorder; airway abnormalities, such as chronic bronchitis, bronchiectasis, and bronchogenic carcinoma; cardiac problems (congestive heart failure); or systemic diseases, such as diabetes, chronic alcoholism, and intravenous drug abuse. Up to 10% of CAP are aspiration pneumonias caused by aspiration of colonized oropharyngeal or gastric contents. The most frequently isolated pathogens in aspiration pneumonia are Gram-negative bacteria. Aspiration pneumonia must be differentiated from aspiration pneumonitis, which is a chemical pneumonitis that results from the aspiration of noncolonized gastric contents (Mendelson's syndrome).

The definition of CAP has been challenged over the last few years, as the definition of CAP also includes patients from nursing homes, rehabilitation hospitals, and outpatient-based surgical centers who routinely receive

invasive medical treatment. As a consequence, the bacteriology and outcome of these patients is more similar to those of NPs. Therefore, it has been proposed that pneumonia in outpatients who were hospitalized for more than 2 days over the previous 3 months or who reside in nursing homes or extended-care facilities should be categorized as health-care-associated pneumonia (HCAP).

Clinical Diagnosis

Patients suffering from CAP usually present with fever, cough, dyspnea, sputum production, and pleuritic chest pain, as well as laboratory signs, such as leucocytosis. Because the clinical symptoms are nonspecific (most people who have fever and cough do not have pneumonia), the chest radiograph is one of the most important tools in the diagnosis of CAP. The radiographic identification of pulmonary opacities is, in the appropriate clinical setting, indicative of pneumonia. Conversely, a patient who has fever and cough but does not have radiographic evidence of pneumonia can be considered to be free of pneumonia. In CAP, the causative organism is frequently not identified, because noninvasive tests such as sputum cultures correctly identify the offending organism in only 50% of cases, and invasive procedures are rarely used in these patients.

Radiographic Diagnosis

In patients with CAP, the primary role of the radiologist is to detect or to exclude pneumonia. A second task for the radiologist is to aid the clinician in determining the etiologic diagnosis. Categorization of the causative organism is sometimes possible by integrating clinical and laboratory information with radiographic pattern recognition. A specific etiologic diagnosis, however, is difficult to establish due to the increasing spectrum of causative organisms and their overlapping radiographic features. In a prospective study of 359 adults with CAP, Fang and coauthors compared the radiographic, clinical, and laboratory features of patients with bacterial pneumonia (caused by *H. influenzae*, *S. pneumoniae*, *S. aureus*, and aerobic Gram-negative bacilli) with features from patients with atypical pneumonia (caused by *M. pneumoniae* and *Chlamydia* spp.). The authors found no features that could reliably differentiate these groups. Another group prospectively compared the clinical and radiologic features of CAP caused by *L. pneumophila* to those of patients with pneumococcal infections. The authors concluded that *Legionella* infection clinically as well as radiologically may look like a typical bacterial pneumonia.

The chest radiograph is the first-line tool in evaluating patients with suspected CAP. Computed tomography (CT) is reserved for assessing complications or for guiding further diagnostic procedures. It is definitely indicated in investigating patients with recurrent or persistent pulmonary opacifications.

Nosocomial Pneumonia

NPs develop in a hospital environment. The incidence of NP ranges from 0.5 to 5 cases per 100 admissions, but, in the subgroup of ventilated patients in an intensive care setting, may reach 7-41%. Mortality rates reported for hospital-acquired pneumonia range from 20% in multi-hospital studies to 50% or higher in single referral centers and university hospitals. Apparently, mortality is related to the causative agent, such that the prognosis associated with aerobic Gram-negative pneumonias is considerably worse than that associated with Gram-positive or viral agents.

Pathogenesis

NP develops from bacterial colonization of the oropharynx and aspiration of oropharyngeal secretions and gastrointestinal contents into the lungs. In addition, the microbial contamination of inserted tubes, lines, and catheters is an important pathogenetic factor. Less commonly, NP is the result of bacteremia originating from right-sided endocarditis or septic pelvic thrombophlebitis. Risk factors are either patient-related (underlying illness, previous surgery, prolonged hospital care) or iatrogenic (intravascular catheters, tracheal tubes, indwelling catheters, respirator equipment). Sources of infections are hospital personnel and patients with active infections. Most notably, the inappropriate use of broad-spectrum and prophylactic antibiotics is an additional and important factor leading to an increased susceptibility to hospital-acquired pneumonia. The majority of NPs are caused by Gram-negative bacilli, including *Pseudomonas aeruginosa*, *Klebsiella* spp., *Enterobacteriaceae* spp., *Escherichia coli*, *Serratia marcescens*, and *Proteus*. In addition, Gram-positive cocci, atypical bacteria such as *L. pneumophila*, and viruses such as the respiratory syncytial virus, may play a role.

Clinical Diagnosis

Compared with CAP, it may be difficult for the clinician to diagnose pneumonia in a hospitalized patient. The classical findings for pneumonia, such as new fever, new pulmonary opacification on chest radiographs, cough, sputum production, and elevated leucocyte count may not be present in the hospitalized patient with NP. If present, these symptoms may not necessarily be caused by pneumonia. Microbiologic evaluation of the patient with suspected NP (sputum, bronchoalveolar lavage) may or may not be helpful because of the difficulties in differentiating contamination from true infection. In addition, pulmonary disease in a hospital environment may be caused by more than one agent. Therefore, identifying a pulmonary infection, using various methods to obtain a specimen, and the value of isolating potential pathogens are matters of constant discussion in the clinical diagnosis of NP.

Radiographic Diagnosis

Because of the potential difficulties in the clinical diagnosis of pneumonia in the hospitalized patient, the radiologist has an important role in detecting and classifying suspected pneumonia. However, the radiographic diagnosis of a pulmonary opacity in suspected NP is not as straightforward as it is in patients with CAP. The radiographic diagnosis of a pneumonia may be hampered by preexisting disorders or concomitant lung disease, such as fibrosing alveolitis, lupus pneumonitis, hemorrhage or contusion, acquired respiratory distress syndrome (ARDS), tumor, atelectasis, and embolic infarcts. These disorders may obscure or alter the otherwise characteristic radiographic appearance of a pulmonary opacification and also render the etiologic approach using pattern recognition difficult.

The difficulties in diagnosing NP are nicely demonstrated in two studies. Winer-Muram et al. assessed the diagnostic accuracy of bedside chest radiography for pneumonia in ARDS patients. The overall diagnostic accuracy in these patients was only 42% because of false-negative and false-positive results originating from diffuse parenchymal areas of increased opacity that obscured the radiographic features of pneumonia. Wunderink et al. compared the premortem chest radiographic findings with pulmonary autopsy studies in ventilated patients with NP. No radiographic findings had a diagnostic efficiency greater than 68%. The only radiographic abnormality that correlated with pneumonia, correctly predicting 60% of pneumonias, was the presence of an air bronchogram.

CT is used more often when an NP is suspected than in patients with CAP to detect early morphologic signs of infection (for example, ground-glass densities). CT can also identify a pulmonary opacification in areas of pre-existent disease, detect complications such as empyema, and guide invasive diagnostic procedures, such as bronchoscopy or percutaneous biopsy, or thoracentesis.

Opportunistic Infections

Infectious agents that cause opportunistic pneumonia in humans include representatives from the classifications bacteria, virus, fungus, protozoa, and parasite. This chapter visits some of these pathogens and their appearance on chest film and CT. Usually, the chest radiograph will reveal the abnormality, but occasionally, the increased sensitivity of CT is necessary to see the pneumonia. Whereas the findings on chest imaging may not be totally pathognomonic of the underlying etiology of infection, they may be highly suggestive and will certainly lead to a reasonable differential diagnosis.

Human Immunodeficiency Syndrome

Since the first description of this disease and AIDS, *Pneumocystis jiroveci* (previously *carinii*) pneumonia (PCP) has been one of the most common complications.

PCP typically presents with increasing shortness of breath and may run a gradual or fulminant course. Chest films classically reveal a bilateral fine to medium reticulonodular pattern, generally bilateral but occasionally focal or unilateral. If the patient remains untreated, the radiograph progressively becomes more opaque and ultimately bilateral homogeneous opacities may be seen. Upper-lobe involvement was seen more commonly when inhaled pentamidine prophylactic therapy was used. The chest film may worsen within a few days of intravenous trimethoprim-sulfamethoxazole treatment secondary to overhydration and the production of pulmonary edema, but this can be treated with diuretics. Otherwise, with treatment, the radiographic course is one of steady improvement until by day 11, complete resolution may be seen. In approximately 10% of patients, pneumatoceles may develop. These are frequently in the upper lobes and will resolve within 2 months. However, they may also lead to pneumothorax, which can be extremely difficult to treat. Pneumothorax is seen in 5% of patients with PCP and AIDS. In about 10% of patients, the chest film may be normal. In some of these patients with normal radiographs, a CT scan will show the typical geographic appearance of ground-glass opacities associated with PCP. Lymphadenopathy and pleural effusions are not part of the PCP picture.

Cytomegalovirus may mimic the look of PCP on chest film, with diffuse bilateral fine to medium reticulonodular opacities. On CT, centrilobular nodules and ground-glass opacities are reported, and in a fairly large number of patients with CMV, the presence of discreet nodules, sometimes several centimeters in size, may help distinguish between these two entities.

Disseminated fungal infections, such as histoplasmosis and coccidiomycosis, generally produce bilateral, fairly symmetric, coarse, nodular opacities on chest radiographs. The nodules and occasionally reticular opacities are larger than those seen with PCP, and this may aid in distinguishing the processes.

Tuberculosis (TB) will appear differently depending on the patient's immune status. In patients with relatively normal CD-4 lymphocyte cell counts, TB will look much like it does in the general population. That is, with primary infection, patients will present with a homogeneous lobar opacity and ipsilateral hilar and/or mediastinal adenopathy. With postprimary infection, patients will present with apical and posterior upper-lobe and/or superior segment lower-lobe heterogeneous opacities with or without cavitation. In patients with low CD-4 cell counts and primary infection, the chest film may show homogeneous lobar opacities with adenopathy similar to immune competent hosts, but the chance of more adenopathy is present. With post primary disease, the organism disseminates more widely, creating a diffuse, coarse, nodular pattern on chest film similar to the pattern seen with fungal infections. Cavitation is not seen, as the body's response is weak, and well-formed granulomas and necrosis are not usually seen. If the organism is sensitive to appropriate therapy, then some resolution of the abnormal

findings on chest film should be observed within 1 week.

Ordinary bacterial infections occur with increased frequency in patients with HIV. They are perhaps being seen as a larger percentage of pulmonary infections in populations where antiretroviral therapy is available and in one Veteran's Administration (USA) cohort was seen more frequently than PCP as the initial pathogen. Common organisms are *S. pneumoniae*, *H. influenzae*, *S. aureus*, and *P. aeruginosa*. These usually appear as they do in normal hosts as homogeneous lobar opacities. Parapneumonic effusions may be present. The latter two organisms may present with some cavitation. They should begin to resolve within days of instituting antibacterial therapy, and complete resolution of abnormalities is seen in the majority of patients in about 2 weeks. Other bacterial etiologies, such as *Rhodococcus equi* and *Nocardia asteroides*, are less common and may present as nodules or masses with or without cavitation.

With the use of antiretroviral therapy, noninfectious etiologies of disease have become more prevalent, such as pulmonary hypertension and chronic obstructive pulmonary disease (COPD). Also, the immune reconstitution inflammatory syndrome occurring after antiretroviral treatment may cause confusing clinical and radiological findings.

Two neoplasms, related to infections, may also be seen in patients with AIDS and could cause confusion in generating a differential diagnosis. Non-Hodgkin's lymphoma (NHL) will produce well-defined nodules on chest films. The nodules range in size from about 1 cm to several centimeters in size. Solitary or multiple nodules may be noted. Lymphadenopathy and pleural effusions are also observed. The nodules have a tendency to grow extremely rapidly.

Whereas the nodules with NHL are very well defined, the nodules seen with Kaposi's sarcoma are not. This disease produces poorly marginated nodules that tend to coalesce. They tend to occur in the perihilar lung and lower lobes. On CT, the distribution is along bronchovascular pathways. In almost all cases of Kaposi's involvement in the lungs, cutaneous lesions will be seen. Pleural fluid is frequently seen as well.

Other Immune-Compromised Conditions

Increasing numbers of transplant procedures, both solid organ and bone marrow, have led to the widespread use of induced immunosuppression. Steroids are also being used with increased frequency for a number of medical conditions. With this, infectious complications in the setting of transplantation or steroid use have become a major problem. Whereas prophylactic treatment [with anti pneumocystis, cytomegalovirus (CMV), and occasionally fungal drugs] of these patients leads to some reduction in the number of infections, not all cases are prevented. The appearances on chest film of PCP and CMV will be similar to that in patients with HIV infection and are stated in the section above.

Other viral pathogens are also seen in this setting, including respiratory syncytial virus, parainfluenza virus, adenovirus, and influenza virus in lung transplant patients, and varicella-zoster, which may be seen in patients with lymphoma and those undergoing steroid therapy. On chest film, varicella pneumonia usually produces bilateral symmetric acinar opacities (nodules about 7-10 mm in diameter) that may coalesce as the disease worsens. CT shows similar-sized nodules and distribution as well as ground-glass opacities.

Among the fungal organisms seen with some regularity in this group of immunocompromised patients are *Cryptococcus* and *Aspergillus*. Other emerging agents include *Scedosporium apiospermum*, *Fusarium* spp., and *Mucorales* spp. *Cryptococcus* has numerous types of presentation on chest film. Perhaps most common is the appearance of well-defined nodules, usually solitary but sometimes multiple. If the nodules become masses, the margins may become indistinct. The nodules may cavitate. *Cryptococcus* may also manifest as a lobar pneumonia or diffuse heterogeneous reticulonodular opacities.

A. fumigatus is the usual species responsible for lung infections. The pattern of abnormality seen on chest film depends on the patient's immune status. In the setting of immunosuppression (neutropenia), the typical appearance is that of invasive aspergillosis. In this form of disease, the chest film initially demonstrates a poorly marginated area or areas of homogeneous opacity that may resemble ordinary bacterial pneumonia in appearance and distribution but is occasionally more round and distant from the subpleural lung than common community infections. In some cases, the disease is peripheral and wedge-shaped secondary to infarction caused by the angioinvasive obstruction of pulmonary vessels. In time, the lesions become more discreet and round, thus taking on the look of lung masses. As patients are treated and immune status improves, there may be cavitation within the masses with the formation of an air crescent. Wall thickness of the cavity is generally moderate. The air crescent is created by the contained necrotic debris within the cavity. On CT, initially, the areas of homogeneous opacity may have air bronchograms, and commonly, additional regions of involvement are identified. A halo sign may be observed, which is caused by ground-glass opacity that surrounds (frequently incompletely) a more opaque center of the lesion. The ground-glass portion is an area of hemorrhage and the central area is necrotic lung. The halo sign was thought to be pathognomonic of invasive aspergillosis but can be seen with other infections, neoplasms, and inflammatory diseases.

Take-Home Messages: Usefulness of Imaging Methods in Pulmonary Infections

Despite the increasing use of CT imaging for diagnosing chest disorders, plain film radiography is still the primary imaging modality for patients with suspected pneumonia. The presence of an appropriate lung opacity on a

chest radiograph is considered the gold standard for diagnosing pneumonia. Extensive knowledge of the radiographic appearances of pulmonary infections, their complications, and their course is essential in aiding the referring clinician and ultimately the patient. CT imaging is useful in patients with CAP and NP when there is an unresolving or complicated chest film and at times in immunocompromised patients with suspected pulmonary infections. CT can help differentiate infectious from non-infectious abnormalities. CT may detect empyema, cavitation, and lymphadenopathy when chest films cannot. CT should be performed in immunocompromised patients with a clinical suspicion of pneumonia when the chest film is normal. This is especially true when the early diagnosis of pneumonia is critical, as is the case with immunocompromised and severely ill patients.

To reiterate: No pattern of abnormality seen on chest films can be considered pathognomonic of a specific infection. However, the distribution and appearance of lung opacities, especially in conjunction with clinical information, should enable one to produce a useful, ordered list of most likely possibilities helpful to our clinical colleagues and, most importantly, the patients.

Suggested Reading

- Albaum MN, Hill LC, Murphy M (1996) Interobserver reliability of the chest radiograph in community-acquired pneumonia. *Chest* 110:343
- Aquino SL, Dunagan DP, Chiles C, Haponik EF (1998) Herpes simplex virus 1 pneumonia: patterns on CT scans and conventional chest radiographs. *J Comput Assist Tomogr* 22:795-800
- Aviram G, Boisselle PM. (2004) Imaging features of bacterial respiratory infections in AIDS. *Curr Opin Pulm Med* 10:183-188
- Bartlett JG, Dowell SF, Mandell LA et al (2000) Practice guidelines for the management of community-acquired pneumonia in adults. Infectious Diseases Society of America. *Clin Infect Dis* 31:347-382
- Basi SK, Marrie TJ, Huang JQ, Majumdar SR (2004) Patients admitted to hospital with suspected pneumonia and normal chest radiographs: epidemiology, microbiology, and outcomes. *Am J Med* 117:305
- Bierry G, Boileau J, Barnig C et al (2009) Thoracic manifestations of primary humoral immunodeficiency: a comprehensive review. *Radiographics* 29:1909-1920
- British Thoracic Society Standards of Care Committee (2001) BTS guidelines for the management of community acquired pneumonia in adults. *Thorax Suppl* 4:IV1-IV64.
- Carmona EM, Limper AH (2010) Update on the diagnosis and treatment of Pneumocystis pneumonia. *Ther Adv Respir Dis* 5:41-59
- Conee DJ (1999) Endemic fungal pneumonia in immunocompromised patients. *J Thorac Imaging* 14:1-8
- Connolly JE Jr, McAdams HP, Erasmus JJ et al (1999) Opportunistic fungal pneumonia. *J Thorac Imaging* 14:51-62
- Crothers K, Huang L, Goutlet JL et al (2010) HIV infection and risk for incident pulmonary diseases in the combination antiretroviral therapy era. *Am J Respir Crit Care Med* [Epub ahead of print]
- Donnelly LF (1999) Maximizing the usefulness of imaging in children with community-acquired pneumonia. *AJR Am J Roentgenol* 172:505-512
- Ellis SM (2004) The spectrum of tuberculosis and non-tuberculous mycobacterial infection. *Eur Radiol* 14(Suppl 3):E34-E42
- Escuissato DL, Gasparetto EL, Marchiori E et al (2005) Pulmonary infections after bone marrow transplantation: high-resolution CT findings in 111 patients. *AJR Am J Roentgenol* 185:608-615
- Fang GD, Fine M, Orloff J et al (1990) New and emerging etiologies for community-acquired pneumonia with implications for therapy. A prospective multicenter study of 359 cases. *Medicine (Baltimore)* 69:307-316
- Franquet T, Gimenez A, Hidalgo A (2004) Imaging of opportunistic fungal infections in immunocompromised patients. *Eur J Radiol* 51(2):130-138
- French MA (2009) Immune reconstitution inflammatory syndrome: a reappraisal. *Clin Infect Dis* 48:101-107
- Goodman P (2006) Radiographic assessment of HIV-related diseases. <http://hivinsite.ucsf.edu/InSite?page=Kb00#S4X>
- Goodman PC (2007) Pulmonary infection in adults. In: Grainger RG, Allison DJ, Dixon AK (eds) Grainger & Allison's diagnostic radiology: a textbook of medical imaging, 5th edn. Churchill Livingstone, London, New York
- Hansell DM, Armstrong P, Lynch DA, McAdams HP (2005) The immunocompromised patient. In: Rozenstein A (ed) Imaging of diseases of the chest, 4th edn. Elsevier Mosby, Philadelphia
- Herold CJ, Sailer JG (2004) Community-acquired pneumonia and nosocomial pneumonia. *Eur Radiol* 14:E2-E20
- Heussel CP, Kauczor HU, Ullmann AJ (2004) Pneumonia in neutropenic patients. *Eur Radiol* 14:256-271
- Huang L, Crothers K (2009) HIV-associated opportunistic pneumonias. *Respirology* 14:474-485
- Ibrahim EH, Traey L, Hill C (2002) The occurrence of ventilator-associated pneumonia in a community hospital: risk factors and clinical outcomes. *Radiology* 223:884
- Jeong YJ, Lee KS (2008) Pulmonary tuberculosis: up-to-date imaging and management. *AJR Am J Roentgenol* 191:834-844
- Johnstone J, Majumdar SR, Fox JD, Marrie TJ (2008) Viral infection in adults hospitalized with community-acquired pneumonia: prevalence, pathogens, and presentation. *Chest* 134:1141-1148
- Jung JJ, Kim H, Park SH et al (2001) CT differentiation of pneumonia-type bronchioloalveolar cell carcinoma and infectious pneumonia. *Br J Radiol* 74:490-494
- Kim EA, Lee KS, Primack SL et al (2002) Viral pneumonias in adults: radiologic and pathologic findings. *Radiographics* 22:S137.
- Kollef MH, Shorr A, Tabak YP et al (2005) Epidemiology and outcomes of health-care-associated pneumonia: results from a large US database of culture-positive pneumonia. *Chest* 128:3854-3862
- Krishnam MS, Suh RD, Tamasian A et al (2007) Postoperative complications of lung transplantation: radiologic findings along a time continuum. *RadioGraphics* 27:957-974
- Lacombe C, Lewin M, Monnier-Cholley L et al (2007) Imaging of thoracic pathology in patients with AIDS. *J Radiol* 88:1145-1154
- Leung AN (1999) Pulmonary tuberculosis: the essentials. *Radiology* 210:307-322
- Leung AN, Brauner MW, Gamsu G et al (1996) Pulmonary tuberculosis: comparison of CT findings in HIV-seropositive and HIV-seronegative patients. *Radiology* 198:687-691
- Lieberman D, Shvartzman P, Korsonsky I, Lieberman D (2003) Diagnosis of ambulatory community-acquired pneumonia. Comparison of clinical assessment versus chest X-ray. *Scand J Prim Health Care* 21:57-60
- Lim WS, Baudouin SV, George RC et al (2009) British Thoracic Society guidelines for the management of community acquired pneumonia in adults: update 2009. *Thorax* 64:1-55
- Mabie M, Wunderink RG (2003) Use and limitations of clinical and radiologic diagnosis of pneumonia. *Semin Respir Infect* 18:72-79
- Mandell LA, Bartlett JG, Dowell SF et al (2003) Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. *Clin Infect Dis* 37:1405-433

- Mandell LA, Wunderink RG, Anzueto A et al (2007) Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 44(Suppl 2):S27-S72
- Melbye H (2002) Community pneumonia – more help is needed to diagnose and assess severity. *Br J Gen Pract* 52:886-888
- Melbye H, Dale K (1992) Interobserver variability in the radiographic diagnosis of adult outpatient pneumonia. *Acta Radiol* 33:79-83
- Metlay JP, Fine MJ (2003) Testing strategies in the initial management of patients with community-acquired pneumonia. *Ann Intern Med* 138:109-118
- Metlay JP, Kapoor WN, Fine MJ (1997) Does this Patient have community-acquired pneumonia? Diagnosing pneumonia by history and physical examination. *JAMA* 278:1440-1445
- Mortensen EM, Copeland LA, Pugh MJ et al (2010) Diagnosis of pulmonary malignancy after hospitalization for pneumonia. *Am J Med* 123:66-71
- Niederman MS, Mandell LA, Anzueto A et al (2001) Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. *Am J Respir Crit Care Med* 163:1730-1754
- Primack SL, Hartmann TE, Lee KS, Mueller NL (1994) Pulmonary nodules and the CT halo sign. *Radiology* 190:513-515
- Reeders JWAJ, Goodman PC (2001) Differential radiological patterns in AIDS at a glance. In: Reeders JWAJ, Goodman PC (eds) *Radiology of AIDS*, Springer-Verlag, Heidelberg, pp 293-324
- Reittner P, Müller NL, Heyneman L et al (2000) Mycoplasma pneumoniae pneumonia: radiographic and high-resolution CT. Features in 28 patients. *AJR Am J Roentgenol* 174:37-41
- Remund KF, Best M, Egan JJ (2009) Infections relevant to lung transplantation. *Proc Am Thorac Soc* 6:94-100
- Reynolds JH, McDonald G, Alton H, Gordon SB (2010) Pneumonia in the immunocompetent patient. *Br J Radiol* 83:998-1009
- Shah RM, Wechsler R, Salazar AM, Spirn PW (1997) Early detection of pneumonia in febrile neutropenic patients: use of thin-section CT. *AJR Am J Roentgenol* 169:1347-1353
- Sharma S, Maycher B, Eschun G (2007) Radiological imaging in pneumonia: recent innovations. *Curr Opin Pulm Med* 13:159-69
- Sider L, Gabriel H, Curry DR, Pham MS (1993) Pattern recognition of the pulmonary manifestations of AIDS on CT scans. *Radiographics* 13:771-784
- Speets AM, Hoes AW, van der Graaf Y et al (2006) Chest radiography and pneumonia in primary care: diagnostic yield and consequences for patient management. *Eur Resp J* 28: 933-938
- Syrjala H, Broas M, Suramo I et al (1998) High-resolution computed tomography for the diagnosis of community-acquired pneumonia. *Clin Infect Dis* 27:358
- Vento S, Cainelli F, Temesgen Z (2008) Lung infections after cancer chemotherapy. *Lancet Oncol* 9:982-992
- Wagner AL, Szabunio M, Hazlett KS et al (1998) Radiologic manifestations of round pneumonia in adults. *AJR Am J Roentgenol* 170:723-726
- Winer-Muram HT, Rubin SA, Ellis JV et al (1993) Pneumonia and ARDS in patients receiving mechanical ventilation: diagnostic accuracy of chest radiograph. *Radiology* 188:479-485
- Wunderink RG, Woldenberg LS, Zeiss J et al (1992) The radiologic diagnosis of autopsy proven ventilator-associated pneumonia. *Chest* 101:458-463

Imaging the Intensive Care Patient

Lawrence R. Goodman

Department of Radiology, Medical College of Wisconsin/Froedtert Hospital, Milwaukee, WI, USA

Introduction

The intensive care patient presents a challenge to both the clinician and the radiologist. These patients may have more than one cardiopulmonary problem that may progress or regress – simultaneously or in opposite directions. Most cardiopulmonary problems are the results of disease originating in the thorax, but a significant number are secondary to disease beyond the thorax. The limited quality of portable radiographs adds to the diagnostic difficulty. Many cardiopulmonary problems appear radiographically similar [1]. Careful attention to the radiographic appearance for progression and regression of the abnormalities often leads to the correct diagnosis [2, 3]. Although not every intensive care patient requires computed tomography (CT), the liberal use of CT often results in a more rapid and more accurate diagnosis and direction for management.

Aspiration Pneumonitis

Although healthy people may aspirate small amounts of gastric or oral secretions into their lungs, these aspirations are usually clinically insignificant. Risk factors for

clinically significant aspiration include general anesthesia, neurological impairment, swallowing difficulties, and various esophageal diseases.

Toxic Fluid Aspiration

The prototype for toxic fluid aspiration is inhalation of gastric fluid with a pH <2.5 (Mendelson's syndrome) [4-6]. Within a matter of seconds, the aspirated acid crosses both the alveolar epithelium and the capillary endothelium, causing capillary permeability edema. Edema is visible within hours and usually progresses for the first 24 h (Fig. 1a). By 48-72 h, there is usually evidence of some clearing. Disease extent and severity depends on aspirate pH and volume. Depending on the severity of the pneumonitis, total clearing may take a week or more. Following massive aspiration, the pneumonitis may progress to acute respiratory distress syndrome (ARDS). Although the right lower lobe is most frequently affected, distribution is variable. CT often shows disease in the posterior segment of the upper lobes and the superior and posterior basal segments of the lower lobes.

Approximately a quarter of patients develop a secondary infection. This is usually evidenced by worsening

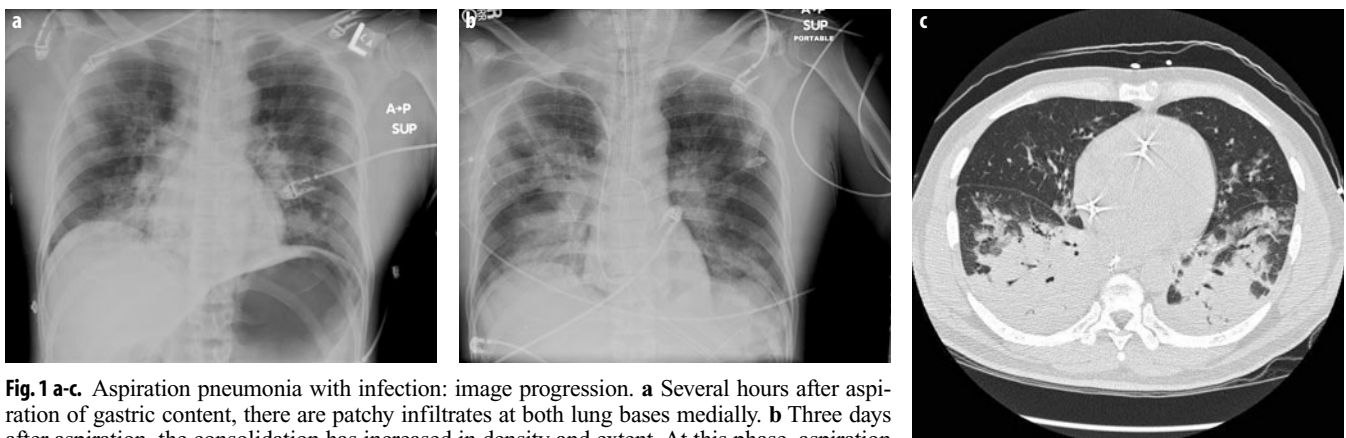


Fig. 1 a-c. Aspiration pneumonia with infection: image progression. **a** Several hours after aspiration of gastric content, there are patchy infiltrates at both lung bases medially. **b** Three days after aspiration, the consolidation has increased in density and extent. At this phase, aspiration pneumonitis should be improving. This suggests secondary infection. **c** Four days after aspiration, computed tomography reveals dense consolidation in the posterior and lateral basal segments of both lower lobes. This degree of consolidation is more than one usually sees with uncomplicated aspiration pneumonitis. There is no abscess. Cultures revealed mixed Gram positive (+) and Gram negative (–) organisms

consolidation 3-7 days after aspiration, when the radiograph should be improving (Fig. 1b). If the infection does not show evidence of clearing within a few days of antibiotic administration, an abscess or loculated empyema should be sought by X-ray or CT scan (Fig. 1c).

Neutral pH Gastric Contents

The aspiration of neutral pH gastric contents (food, blood, etc.) usually causes some tracheobronchial irritation but does not cause a chemical pneumonitis. The lungs may be normal or show consolidation due to flooding. Food particles or a clot may cause focal atelectasis. In general, with prompt removal of the aspirated material, the lung returns to normal rapidly. Impacted material may obstruct and cause infection or abscess behind it.

Infected Secretions

Infected secretions may be aspirated from the sinuses, the pharynx, or the intubated trachea. The radiographic appearance may vary from a focal indolent basilar consolidation not easily distinguished from atelectasis to rapidly progressing consolidation. Small inoculum of bacteria in relatively normal hosts may lead to abscesses manifesting days to weeks later.

Fistulas

Fistulas between the esophagus and bronchi or parenchyma are, fortunately, infrequent. These are usually due to esophageal injuries from trauma, radiation, or surgery. Esophageal infections, such as candida or tuberculosis, may fistulize the mediastinum or a lung. The appearance of air in the entire esophagus, pneumomediastinum, or pneumothorax may be the only clues that parenchymal or pleural disease is related to a fistula. CT and contrast-enhanced fluoroscopy of the esophagus are required for diagnosis.

Atelectasis

Atelectasis is a boring diagnosis to the radiologist, but it is important in patient management, as proper identification may prevent additional testing and unnecessary antibiotic administration and may encourage physical measures to reinflate the lung. Untreated atelectasis may become infected.

Alveolar collapse, rather than lung infection, is by far the most common cause of parenchymal opacification in the intensive care unit (ICU) [1]. Linear, subsegmental, or segmental opacification and volume loss usually present no diagnostic difficulty. Patchy airspace opacification, without obvious volume loss, is frequently confused with pneumonia or infarction. The absence of an air bronchogram in a lobe or segment indicates important mucous plugging. Primary atelectasis usually appears rapid-

ly and may change rapidly from film to film, especially following physical therapy. It should be suspected in any patient with recent abdominal or thoracic surgery, obtundation, thoracic trauma, or a neuromuscular disorder such as myasthenia gravis, and it may be associated with many more significant lung diseases (e.g., pulmonary embolism, pneumonia, etc.).

Atelectasis is most frequent in the dorsal, dependent segments. The gravitational force of the ventral lung diminishes aeration dorsally, and secretions tend to pool dorsally. Retrocardiac atelectasis is particularly difficult to evaluate through the opacity of the heart. Clues to diagnosis include loss of the diaphragmatic and descending aortic shadow, a homogeneous opacification behind the heart obscuring the pulmonary vessels, elevation of the left diaphragm, and depression of the left hilum. CT scans are considerably more sensitive for diagnosing dependent atelectasis or suggesting an alternative diagnosis.

Pneumonia

Even the most basic of pulmonary disease, pneumonia, is not easily diagnosed in the ICU patient [7-9]. Despite years of effort, pulmonologists have not developed reliable criteria for nosocomial pneumonia, so we as radiologists have no gold standard. The hallmarks of pneumonia, such as fever, pathogens in the sputum, altered white blood cell count, and X-ray evidence of consolidation may be present for multiple other reasons. A fever may be present from pneumonia, atelectasis, aspiration, or numerous extrathoracic causes. Pathogens in the sputum are almost universal following prolonged hospitalization. A heavy growth of pathogens plus bacteria within white blood cells on smear is required to document intrapulmonary infection. The best one can do radiographically is to try to separate atelectasis from pneumonia. Atelectasis tends to appear rapidly, change form film-to-film, and be focal. Pneumonia usually appears over several days, is progressive, and may be patchy and diffuse. Upper-lobe disease is more likely pneumonia than atelectasis.

Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) is a clinical syndrome of acute progressive respiratory failure characterized by severe hypoxia [partial pressure of oxygen in arterial blood/fractional inspiratory oxygen ($\text{PaO}_2/\text{FiO}_2$) <200 mmHg], bilateral pulmonary infiltrates, and no evidence of congestive heart failure. A similar syndrome with less severe hypoxia ($\text{PaO}_2/\text{FiO}_2$ <300 mmHg) is termed acute lung injury [10, 11]. As a general rule, ARDS becomes visible 1-3 days after the insult and progresses over the next several days (Fig. 2 a). The interstitial and ground-glass infiltrates are symmetrical and non-gravity dependent (Fig. 2 b, c). The heart and vessels are not enlarged. Published descriptions of ARDS are often

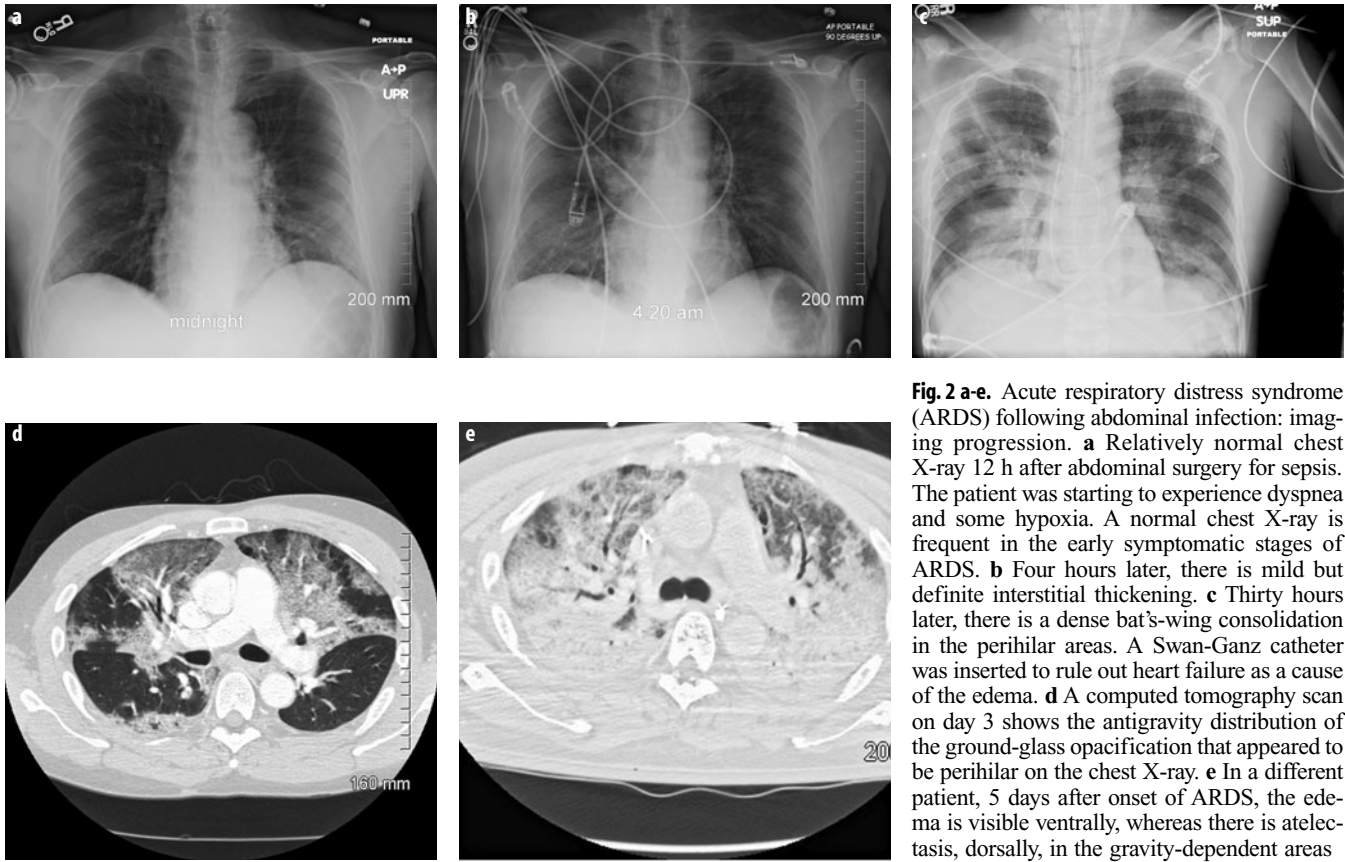


Fig. 2 a-e. Acute respiratory distress syndrome (ARDS) following abdominal infection: imaging progression. **a** Relatively normal chest X-ray 12 h after abdominal surgery for sepsis. The patient was starting to experience dyspnea and some hypoxia. A normal chest X-ray is frequent in the early symptomatic stages of ARDS. **b** Four hours later, there is mild but definite interstitial thickening. **c** Thirty hours later, there is a dense bat's-wing consolidation in the perihilar areas. A Swan-Ganz catheter was inserted to rule out heart failure as a cause of the edema. **d** A computed tomography scan on day 3 shows the antigravity distribution of the ground-glass opacification that appeared to be perihilar on the chest X-ray. **e** In a different patient, 5 days after onset of ARDS, the edema is visible ventrally, whereas there is atelectasis, dorsally, in the gravity-dependent areas

contradictory. We have analyzed over 70 CT scans on 33 ARDS patients imaged early and late in their disease [10]. In the early phase (<7 days), patients with ARDS due to extrapulmonary causes (sepsis, pancreatitis, etc.) tend to have symmetrical ground-glass opacification in a non-gravity-dependent distribution and gravity-dependent atelectasis (Fig. 2 d, e), whereas patients with ARDS due to lung disease (pneumonia, aspiration, etc.) tend to have asymmetrical airspace (1° disease) and ground-glass opacification (ARDS). Other studies have emphasized that there is overlap in appearance in a minority of patients [12]. Air bronchograms and small pleural effusions are almost universal. At 1-2 weeks, as the ARDS matures and becomes fibrotic, the CT distinctions blur. Radiographic improvement often lags behind clinical improvement.

Left Ventricular Failure

The usual radiographic and CT signs of left ventricular (LV) failure – cephalization, Kerley line, interstitial thickening, peribronchial cuffing, ground-glass opacification, and pleural effusions – are well known [13]. Less appreciated are the atypical appearances of pulmonary edema. In patients with underlying structural lung or vascular disease, such as emphysema, pulmonary embolus,

central tumor, etc., edema distribution is often atypical or asymmetrical. Patients with chronic obstructive pulmonary disease (COPD) with LV failure can be difficult to diagnose without reference to prior chest X-rays. Mitral valve insufficiency may cause a regurgitant jet to elevate pressures in the right upper lobe pulmonary veins, causing predominant right upper lobe edema. Prolonged decubitus positioning causes edema formation in the dependent lung. Neurogenic edema may be predominantly in the upper lobes.

Pulmonary Embolism

The clinical diagnosis of pulmonary embolism (PE) in the ICU is even more difficult than in other environments [14]. Bed rest, postoperative status, and many other conditions increase the risk of PE. There are no validated “prediction rules” for the ICU, and D-dimer is often elevated for reasons other than PE/deep-vein thrombosis (DVT) [15]. CT is the clear diagnostic test of choice, as ventilation/perfusion (V/Q) scans are usually indeterminate due to other lung diseases. Although venous thromboembolism prophylaxis helps, it is not perfect in preventing PE.

CT pulmonary angiography (CTPA) may be suboptimal due to patient cooperation issues, alteration in

cardiac output, and preexisting lung disease. Although CTPA is the most helpful diagnostic test, should it be negative in a high-probability patient and CT was of less than optimal quality, a false negative remains a distinct possibility. In such situations, the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED II) has suggested additional imaging (V/Q, repeat CT pulmonary angiography, lower-extremity imaging) to verify a negative diagnosis [15, 16]. We routinely do CT venography (CTV) following CTPA in ICU patients >40 years of age, as ICU patients are more prone to DVT, and a negative CTV adds confidence when the CTPA is suboptimal [16].

ICU patients are more likely to suffer from right ventricular (RV) strain after a large PE. Each CT should be checked for RV enlargement, intraventricular septum shift to the left, retrograde flow of contrast into the inferior vena cava (IVC), and enlargement of the central pulmonary arteries [17].

If the patient is clinically unstable, moving the patient for a CT scan is often not practical or safe. Transesophageal echocardiography (TEE) offers a reliable alternative for central PE [18]. If there is a high clinical probability, there is a visible PE, and there is a lower-extremity DVT, sensitivity and specificity approaches 100%. If two of three are positive, sensitivity and specificity are also very high (portable perfusion scanning is an alternative to bedside TEE). In either case, if doubt remains, CT should be performed when the patient is stable.

Pulmonary Insufficiency and the Normal Chest Radiograph

Potentially life-threatening pulmonary insufficiency may be present with a normal radiograph. In patients with central nervous system (CNS) disease, neuromuscular disorders, and most drug overdoses, the initial and subsequent radiographs remain normal unless a secondary complication develops. Patients with severe COPD or fibrosis frequently have potentially fatal pulmonary insufficiency with little or no radiographic evidence of an acute process. Subtle pulmonary edema is often difficult to detect radiographically without old radiographs for comparison. Large, life-threatening pulmonary emboli may frequently cause little or no acute change in the chest radiograph. In early ARDS, the chest X-ray is normal (Fig. 2a).

References

1. Goodman LR, Putman C (1992) Critical care imaging, 3rd edn. WB Saunders, Philadelphia, PA
2. Trotman-Dickenson B (2003) Radiology in the intensive care unit (part 2). *J Intensive Care Med* 18:239
3. Maffessanti M, Berlot G, Bortolotto P (1998) Chest roentgenology in the intensive care unit: an overview. *Eur Radiol* 8:69-78
4. Franquet T, Giménez A, Rosón N et al (2000) Aspiration diseases: findings, pitfalls, and differential diagnosis. *RadioGraphics* 20:673-685
5. Kim M, Lee KY, Lee KW et al (2008) MDCT evaluation of foreign bodies and liquid aspiration pneumonia in adults. *AJR Am J Roentgenol* 190:907-915
6. Shifrin RY, Choplin RH (1996) Aspiration in patients in critical care units. In: Goodman LR, Kuzo RS (eds) *Radiologic Clinics of North America: intensive care radiology*. WB Saunders, Philadelphia, PA, pp 83-96
7. Lipchik RJ, Kuzo RS (1996) Nosocomial pneumonia. In: Goodman LR, Kuzo RS (eds) *Radiologic Clinics of North America: intensive care radiology*. WB Saunders, Philadelphia, PA, pp 47-58
8. Winer-Muram HT, Steiner RM, Gurney JW et al (1998) Ventilator-associated pneumonia in patients with adult respiratory distress syndrome: CT evaluation. *Radiology* 208:193-199
9. Valencia M, Torres A (2009) Ventilator associated pneumonia. *Curr Opin Crit Care* 15:30-35
10. Goodman LR, Fumagalli R, Tagliabue P et al (1999) Adult respiratory distress syndrome due to pulmonary and extrapulmonary causes: computed tomographic, clinical and functional correlations. *Radiology* 213:545-552
11. Gattinoni L, Caironi P, Pelosi P, Goodman LR (2001) What has computed tomography taught us about the acute respiratory distress syndrome? *Am J Respir Crit Care Med* 164:1701-1711
12. Desai SR, Wells AU, Suntharalingam G et al (2001) Acute respiratory distress syndrome caused by pulmonary and extrapulmonary injury: a comparative CT study. *Radiology* 218:689-693
13. Goodman LR (1996) Congestive heart failure and adult respiratory distress syndrome. In: Goodman LR, Kuzo RS (eds) *Radiologic Clinics of North America: intensive care radiology*. WB Saunders, Philadelphia, PA, pp 33-46
14. Chan KP (2008) Pulmonary embolism in the intensive care unit. *Crit Care Med* 17:113-120
15. Stein PD, Fowler SE, Goodman LR et al (2006) Multidetector computed tomography for acute pulmonary embolism [PIOPED II]. *N Engl J Med* 354:2317-2327
16. Goodman LR, Sostman HD, Stein PD et al (2009) CT venography: a necessary adjunct to CT pulmonary angiography or a waste of time, money, and radiation? *Radiology* 250:327-330
17. Ghaye B, Ghuysen A, Bruyere P-J et al (2006) Can CT pulmonary angiography allow assessment of severity and prognosis in patients presenting with pulmonary embolism? What the radiologist needs to know. *Radiology* 26:23-39
18. Goldhaber SZ (2002) Echocardiography in the management of pulmonary embolism. *Ann Intern Med* 136:691-700

Imaging the Chest Trauma Patient

Robert A. Novelline

Department of Radiology, Massachusetts General Hospital, Boston, MA, USA

Introduction

Trauma is the third leading cause of death in the USA and the leading cause of death for those younger than 40 years of age. Approximately 25% of trauma deaths result from thoracic injuries. In the USA each year, >300,000 patients are hospitalized and >25,000 die as a consequence of chest trauma [1-3]. Blunt trauma accounts for 90% of chest trauma, and the most common cases of blunt trauma are motor vehicle collisions and falls [4, 5].

The imaging workup of patients with suspected thoracic injuries usually begins with a portable chest radiograph in the supine position taken on arrival at the emergency center. Many obvious thoracic injuries such as displaced rib fractures and large pneumothoraces and hemothoraces can be quickly detected with this exam. Also, the chest radiograph may confirm proper positioning of an endotracheal tube or nasogastric tube. Other conditions such as small pneumothoraces, small hemothoraces, lung laceration, aortic trauma, tracheobronchial injury, cardiac injury, diaphragm rupture, and thoracic spine injuries require further imaging with computed tomography (CT). Multidetector CT (MDCT) scanners can quickly and accurately diagnosis and display with axial, multiplanar, and volumetric images a wide variety of thoracic injuries. In the multiple-trauma patient, chest CT can be included as part of a single-acquisition total-body trauma scan, which also includes the patient's head, face, cervical spine, chest, abdomen, and pelvis, and when indicated clinically, the scan can be continued downward to include the entire lower extremities.

MDCT Protocol for Suspected Thoracic Injury

Chest CT scans for suspected thoracic trauma should be performed with intravenous administration of contrast material to demonstrate any sites of active bleeding and to opacify the heart, aorta, and thoracic blood vessels. Optimum arterial opacification may be obtained with an injection of 75-125 cc of 370-mg concentration at 3.0 cc/s, beginning scanning after a 30-s delay. Scans should be acquired at thin detector configurations so that high-quality multiplanar and volumetric reformations can be produced

from the thin axial images. Routine coronal and sagittal reformations of the chest are recommended on all chest-trauma patients, and optional volumetric (3D), maximal intensity projection (MIP), and curved plane reformations are recommended in positive cases to better show trauma pathology. A detector configuration of 4×1.25 mm is recommended for four-slice scanners and 16×1.25 mm for 16-slice scanners. Sixty-four-slice scanners acquire axial slices less than 1 mm (sub-mm) thick. These thin slices produce high-quality, routine, coronal and sagittal reformations on the CT scanner, and in positive cases, they transmit directly to a workstation for any indicated optional volumetric or other postprocessing requirements, such as 3D reformations of fractures and dislocations or CT arteriograms (CTAs) of vascular injuries. Thin slices are also reformatted to 2.5 or 5.0 mm viewing axial slices and transmitted to the Picture Archiving and Communication System (PACS), along with coronal and sagittal reformations for formal examination and interpretation. All axial and multiplanar images should be reviewed on soft tissue, lung, and bone windows.

Injuries of the Thoracic Skeleton

Skeletal thoracic injuries may be apparent on radiographic examination, but nearly all are better shown and more accurately diagnosed by CT. Upper-rib fractures occur with severe chest trauma and may be associated with injuries of the aorta, great vessels, and brachial plexus. Lower-rib fractures may be associated with injuries to the liver, spleen, and kidneys. Multiple fractures of the same rib involving three or more adjacent ribs may produce a flail segment of the chest wall with paradoxical motion during respiration, resulting in a "flail chest", with ventilatory compromise. Other common injuries of the thoracic skeleton include scapular and sternal fractures, sternoclavicular dislocation, and thoracic spine injuries. Serious morbidity and even death have been associated with posterior dislocation of the clavicle at the sternoclavicular joint, as the displaced clavicle head may impinge on or injure the trachea, esophagus, great vessels, or major nerves in the superior mediastinum. Sternoclavicular dislocation is visualized well on CT (Fig. 1).

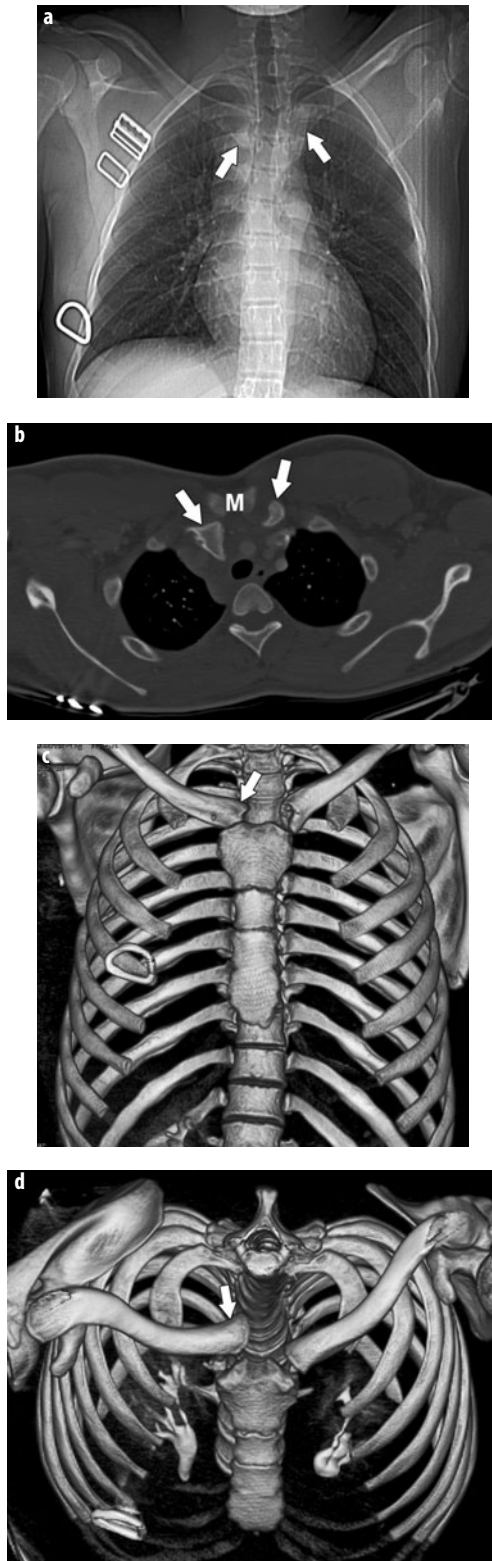


Fig. 1 a-d. Right posterior sternoclavicular dislocation: **a** Chest radiograph shows asymmetry of the clavicular heads (*arrows*). The right head of the clavicle is displaced inferiorly and medially. **b** Axial computed tomography (CT) scan at the level of the manubrium (*M*). The right head of the clavicle is dislocated posteriorly compared with the normally positioned left head. **c,d** Frontal and superior views of a volumetric (3D) CT reformation display the posteriorly displaced right clavicle (*arrows*) (for color reproduction see p 273)

Sternal fractures are usually not seen on the anteroposterior (AP) portable chest radiograph but are nearly all visible at CT, especially on sagittal reformations. CT also shows any associated retrosternal hematomas. Sternal fractures, however, show on lateral chest radiograph, which may not be possible in the acutely injured multiple-trauma patient. Sternal fractures have a high association with both aortic and cardiac injuries.

Fractures of the thoracic spine account for 15-30% of all spinal fractures. The most vulnerable segment of the thoracic spine is at the thoracoabdominal junction from T9 to T12. About 70% of thoracic spine fractures are visible on radiographs, but CT shows almost all of them. With the superior spatial resolution of MDCT technology, axial, coronal, and sagittal thoracic spine reformations obtained from the chest-trauma CT imaging protocol show more fractures than AP and lateral thoracic spine radiographs [6].

Pleural Manifestations of Trauma

Nonpenetrating trauma may be associated with hemothorax and pneumothorax. Blood can flow into the pleural space from injuries of the chest wall, diaphragm, lung, and mediastinal structures. CT can confirm a hemothorax when a pleural fluid collection in a trauma patient measures >35-40 HU. Air can enter the pleural space as a result of a lung or tracheobronchial injury or esophageal rupture. A pneumothorax may be seen in about 15-40% of patients with acute chest trauma [7]. Many small and even moderate-sized pneumothoraces not visible on supine chest radiograph are easily identified at CT. A pneumothorax seen at CT that cannot be identified on a supine chest radiograph is referred to as an "occult" pneumothorax. A persistent pneumothorax after chest-tube suction suggests either a malfunctioning chest tube or a bronchial injury. A tension pneumothorax is an emergency condition resulting from a lung or airway injury associated with a one-way accumulation of air within the pleural space. As intrapleural pressure rises, the mediastinal structures are compressed, decreasing venous return to the heart and leading to hemodynamic instability. Radiography and CT show mediastinal shift to the contralateral hemithorax, hyperexpansion of the ipsilateral thorax, and depression of the ipsilateral hemidiaphragm.

Pulmonary Contusion

Pulmonary contusion represents traumatic extravasation of blood and edema fluid into lung interstitium and air spaces as a result of small-vessel trauma without significant parenchymal disruption. The injury is caused by energy transmitted directly to the lung from a blow to the overlying chest wall. On radiographs, contusions appear

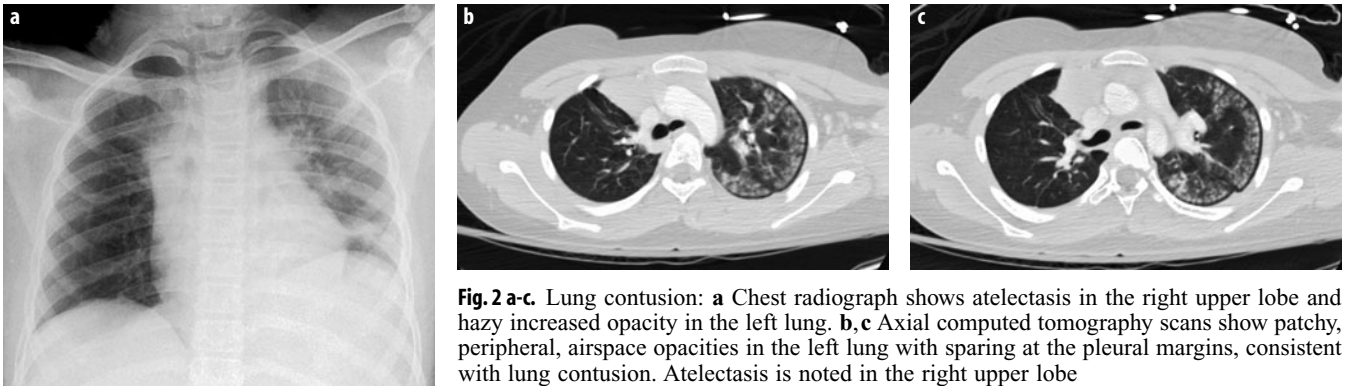


Fig. 2 a-c. Lung contusion: **a** Chest radiograph shows atelectasis in the right upper lobe and hazy increased opacity in the left lung. **b, c** Axial computed tomography scans show patchy, peripheral, airspace opacities in the left lung with sparing at the pleural margins, consistent with lung contusion. Atelectasis is noted in the right upper lobe

as patchy areas of consolidation that, if extensive, may show diffuse homogenous lung consolidation. Contusion may be absent on the initial chest radiograph but is usually evident within 6 h of injury and resolves rapidly, within 3-10 days [8]. CT (Fig. 2) shows peripheral, patchy, nonsegmental areas of consolidation often directly beneath the site of injury and often sparing 1-2 mm of the subpleural lung parenchyma. Opacities may be single or multiple, and both coup and contrecoup contusions may be identified. Contusion is often seen surrounding pulmonary lacerations. The nonsegmental distribution of opacities with lung contusion contrasts the bronchopulmonary, segmental distribution of opacities shown with aspiration – another common lung condition in trauma patients.

Pulmonary Laceration

Pulmonary lacerations are tears in the lung parenchyma that fill with air, blood, or both. When filled with air, these injuries are called traumatic pneumatoceles, and when filled with blood, they are referred to as traumatic hemothecles or lung hematomas. If both air and fluid are present, an air-fluid level may be identified. On chest radiographs, lacerations may initially be obscured by surrounding lung contusion but are revealed when the contusion clears, a few hours or days after the injury. However, acute lung lacerations are nearly always detected by CT. Because of the elastic recoil of lung parenchyma, lung lacerations at CT appear as spherical or ovoid airspaces containing air-fluid levels surrounded by varying amounts of lung contusion (Fig. 3).

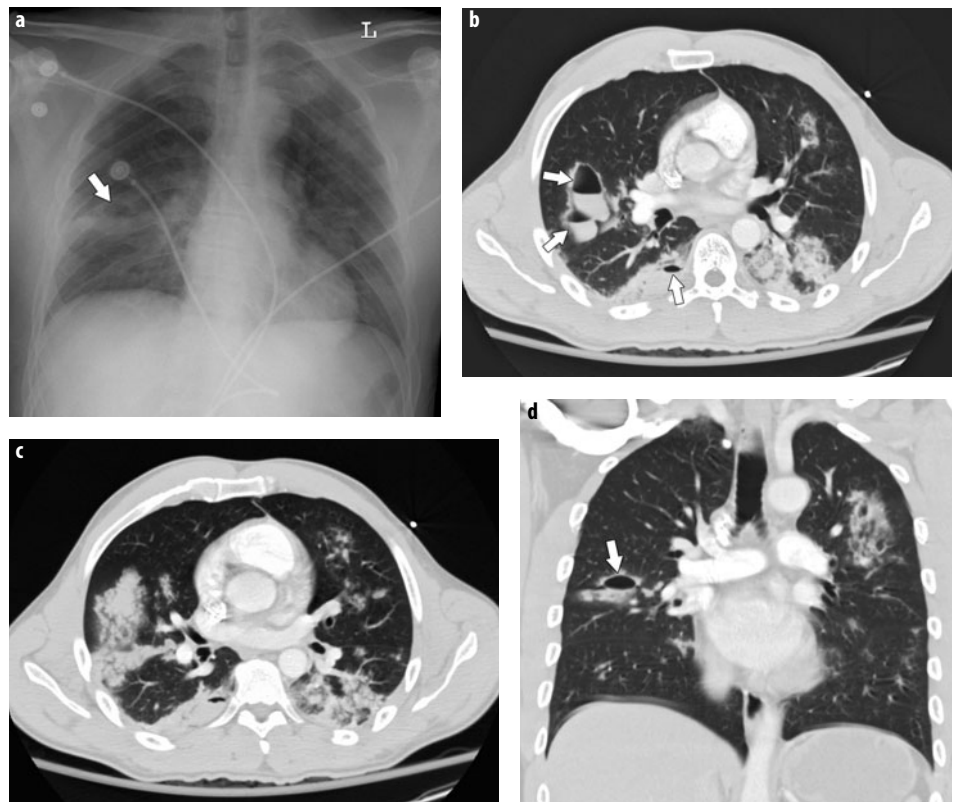


Fig. 3 a-d. Lung laceration: **a** Chest radiograph shows patchy airspace opacities in both lungs. Arrow indicates a possible right lung laceration. **b-d** Axial and coronal computed tomography scans show acute lung lacerations (arrows) appearing as spherical airspaces with air-fluid levels and surrounding contusion

Four types have been described with blunt trauma: compression rupture, compression shear, rib-penetration injury, and adhesion tears [5]. They may also result from penetrating trauma, most frequently from stab and gunshot wounds. Pulmonary lacerations are better shown and more extensively evaluated with CT than they are with radiographs. Unlike pulmonary contusions, lung lacerations may take weeks or months to heal and may result in residual lung scarring.

Traumatic Lung Herniation

Traumatic lung herniation is diagnosed when there is protrusion of lung tissue beyond the confines of the thoracic cage through a traumatically induced thoracic-wall defect, usually associated with rib and costochondral fractures. On chest radiographs, traumatic lung herniation may appear as a well-circumscribed collection of subcutaneous air. However, this appearance may only be seen if the radiograph is taken with a tangential view of the herniation. The condition is readily identified by CT, which can show the herniated lung protruding through a thoracic-wall defect (Fig. 4). Lung herniation does not usually resolve spontaneously, and a concern with this condition is positive pressure ventilation, which may result in lung incarceration and strangulation.

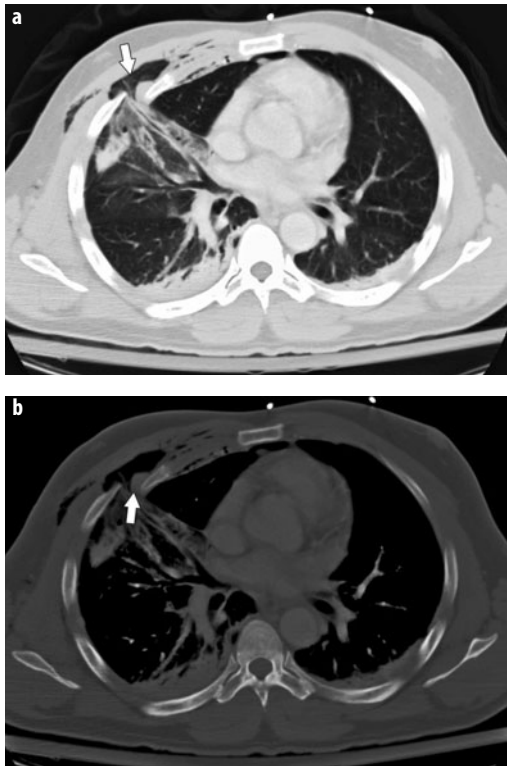


Fig. 4 a, b. Traumatic lung herniation: **a** Lung window computed tomography (CT) scan shows herniated lung (arrow) protruding beyond the thoracic cage. **b** Bone window CT scan at the same level shows the site of bony defect (arrow) in the thoracic cage

Tracheobronchial Injury

Tracheobronchial injuries are uncommon, and >80% occur within 2 cm of the carina [9]. There is an equal frequency of rupture of the left and right mainstem bronchi. The most common findings on chest radiographs are pneumomediastinum and subcutaneous emphysema; air leaks through the rupture and flows into the surrounding mediastinal soft tissues with subsequent dissection up into the neck. Large amounts of pneumomediastinum are easy to identify on plain radiographs; however, small amounts may not be visible on the initial portable chest radiograph. The majority of cases have an associated pneumothorax. The clinical observation characteristic of this condition is a pneumothorax that does not resolve with chest-tube suction due to continued leakage of air through the rupture. However, resolution of a pneumothorax after chest-tube placement does not exclude the diagnosis. Another pathognomonic finding is that of a “fallen lung,” which occurs when there is complete disruption of a main-stem bronchus. On the supine chest radiograph, the lung falls laterally and posteriorly; in the upright position, the lung falls inferiorly. This appearance contrasts with the usual situation in which a lung collapses toward the pulmonary hilus.

Other sign of tracheobronchial injury include a sharply angulated bronchus, bronchial discontinuity, or bronchial “cutoff.” Abnormalities of an endotracheal tube balloon may also be noted with tracheal injury. The balloon may appear overinflated or more spherical, as the balloon actually herniates through a vertical laceration of the trachea. All of these findings are better depicted at CT, which can show the actual tracheobronchial injury. In addition, CT shows more subtle secondary signs, such as smaller amounts of pneumomediastinum, than does the chest radiograph.

Esophageal Rupture

Esophageal injury is rare with blunt trauma and is far more common with penetrating or iatrogenic trauma. Blunt trauma may involve the upper thoracic esophagus or the lower esophagus just above the gastroesophageal junction. Radiographs of the chest may show pneumomediastinum and subcutaneous emphysema. CT may show focal air collections at the site of the tear or an esophageal wall hematoma. As lower injuries may rupture into the left pleural space, a left pneumothorax, left pleural fluid collection, or left lower lobe atelectasis may be seen. Diagnosis is usually confirmed by the demonstration of orally administered contrast material extravasation at injury site.

Aortic and Great-Vessel Injuries

Approximately 8,000 cases of thoracic aortic injury occur in the United States each year, and traumatic aortic rupture is responsible for 15-20% of all fatalities associated with

motor vehicle accidents [4]. Approximately 90% of patients with traumatic aortic rupture die before emergency treatment can be instituted. Most aortic injuries involve the junction of the posterior aortic arch and descending aorta, just distal to the origin of the left subclavian artery [5, 10]. The proposed mechanism of injury is rapid deceleration, resulting in differential forces on the proximal descending aorta between fixed and more mobile segments.

A normal chest radiograph has a high negative predictive value (98%) but a low positive predictive value for aortic injury [11]. The chest radiograph findings suggestive of aortic injury include mediastinal widening >8 cm, loss of the normal aortic arch, a left apical pleural cap, displacement of the nasogastric tube to the right, widened paraspinal lines, and loss of the descending aortic line. Most radiographic findings of aortic injury are nonspecific. The gold standard for aortic injury diagnosis was aortography; however, at most trauma centers today, aortography has been replaced by MDCT.

CT sensitivity is reported to be 92-100% and specificity 62-100% for detecting aortic injury [12-14]. CT findings (Fig. 5) include indirect signs, such as mediastinal hematoma surrounding the posterior aortic arch and proximal descending aorta, and direct signs of intimal tear/flap, aortic contour abnormality, thrombus protruding into the aortic lumen, false aneurysm formation, pseudocoarctation, and extravasation of intravenously administered contrast material. If only direct signs are utilized, sensitivity and negative predictive value remains

100% but specificity increases to 96% [14]. The accuracy of aortic trauma detection with CT has been improving in parallel with technologic improvements in CT scanning. Fast scanners decrease motion artifact and provide higher quality 2D and 3D reformations for diagnosis and surgical planning. Also, current-generation scanners can scan the chest with cardiac gating during diastole to eliminate aortic pulsatile motion artifacts that may be confused with an acute aortic injury. Patients with no direct evidence of aortic injury at CT and no mediastinal hematoma around the expected site of injury do not require further imaging workup to rule out aortic trauma.

Cardiac Injuries

Cardiac and pericardial injuries are uncommon with blunt thoracic trauma from severe blows to the anterior chest. They include cardiac contusion, cardiac rupture with cardiac laceration, pneumopericardium, hemopericardium, cardiac tamponade, and cardiac valve injury. Hemopericardium from a cardiac injury or cardiac rupture can quickly produce cardiac tamponade with hemodynamic compromise. Cardiomegaly is visible on plain chest radiographs; CT or cardiac ultrasound can confirm the presence of hemopericardium. However, CT may also show pneumopericardium with pericardial laceration, as well as extravasation of contrast material into the pericardium or mediastinum with cardiac laceration.

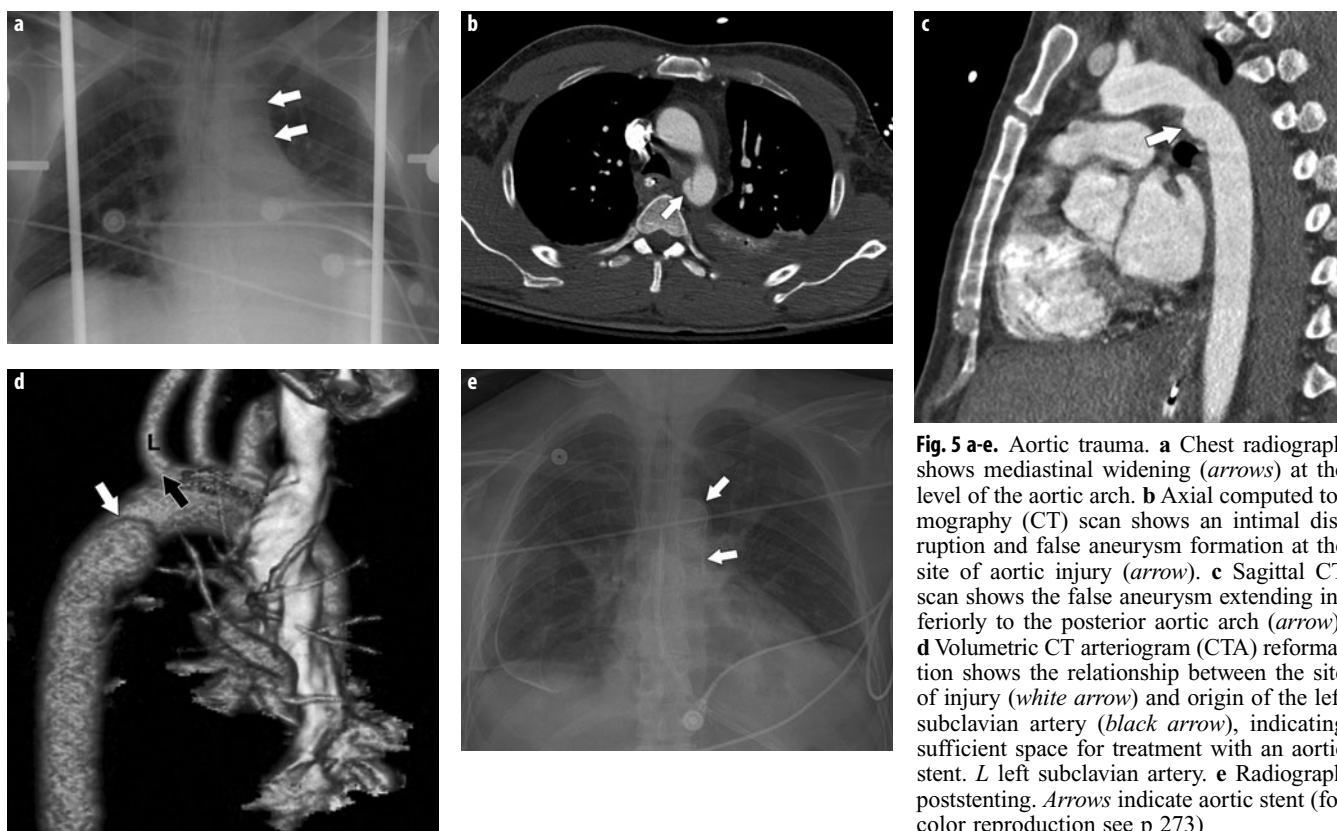


Fig. 5 a-e. Aortic trauma. **a** Chest radiograph shows mediastinal widening (arrows) at the level of the aortic arch. **b** Axial computed tomography (CT) scan shows an intimal disruption and false aneurysm formation at the site of aortic injury (arrow). **c** Sagittal CT scan shows the false aneurysm extending inferiorly to the posterior aortic arch (arrow). **d** Volumetric CT arteriogram (CTA) reformation shows the relationship between the site of injury (white arrow) and origin of the left subclavian artery (black arrow), indicating sufficient space for treatment with an aortic stent. *L* left subclavian artery. **e** Radiograph poststenting. Arrows indicate aortic stent (for color reproduction see p 273)

Diaphragmatic Injury

Diaphragmatic rupture is seen in about 5% of patients undergoing laparotomy or thoracotomy for trauma [15]. The postulated mechanism is a sudden increase in either intrathoracic or intra-abdominal pressure against a fixed diaphragm. Left-sided injuries are more common, having a reported left-to-right ratio of 3:1, with 4.5% having bilateral rupture [16].

The chest radiograph may show a hemothorax, a pneumothorax, loss of the visualized hemidiaphragm, apparent elevation of the hemidiaphragm, visualization of herniated abdominal organs into the thorax, and cephalad extension of a nasogastric tube into the thorax. MDCT axial scans combined with high-quality coronal and sagittal reformations depict both large and small ruptures of the diaphragm, in addition to any abdominal organs herniated across the rupture.

References

1. Kshetry VR, Bolman RM (1994) Chest trauma. Assessment, diagnosis, and management. *Clin Chest Med* 15:137-146
2. Blaisdell F, Trunkey D (1994) Trauma management III: Cervicothoracic trauma, 2nd edn. Thieme Medical Publishers, New York, NY
3. Mazurek A (1994) Pediatric injury patterns. *Int Anesthesiol Clin* 32:11-25
4. Groskin SA (1996) Selected topics in chest trauma. *Semin Ultrasound CT MR* 17:119-124
5. Collins J, Primack SL (2001) CT of nonpenetrating chest trauma. *Appl Radiol* 30:1-10
6. Rhea JT, Sheridan RL, Mullins ME, Novelline RA (2001) Can chest and abdominal CT eliminate the need for plain films of the spine? *Emerg Radiol* 8:99-104
7. Groskin SA (1996) Selected topics in chest trauma. *Semin Ultrasound CT MR* 17:119-141
8. Wiot JF (1975) The radiologic manifestations of blunt chest trauma. *JAMA* 231:500-503
9. Spencer JA, Rogers CE, Westaby S (1991) Clinico-radiological correlates in rupture of the major airways. *Clin Radiol* 43:371-376
10. Williams JS, Graff JA, Uku JM et al (1994) Aortic injury in vehicular trauma. *Ann Thorac Surg* 57:726-730
11. Mirvis SE, Bidwell JK, Buddemeyer EU et al (1987) Value of chest radiography in excluding traumatic aortic rupture. *Radiology* 163:487-493
12. Gavant ML, Menke PG, Fabian T et al (1995) Blunt traumatic aortic rupture: Detection with helical CT of the chest. *Radiology* 197:125-133
13. Mirvis SE, Shanmuganathan K, Miller BH et al (1996) Traumatic aortic injury: diagnosis with contrast-enhanced thoracic CT – Five-year experience at a major trauma center. *Radiology* 1200:413-422
14. Dyer DS, Moore EE, Mestek MF et al (1999) Can chest CT be used to exclude aortic injury? *Radiology* 213:195-202
15. Shah R, Sabanathan S, Mearns AJ et al (1995) Traumatic rupture of diaphragm. *Ann Thorac Surg* 60:1444-1449
16. Mueller CF, Pendarvis RW (1994) Traumatic injury of the diaphragm: report of seven cases and extensive literature review. *Emerg Radiol* 1:118-132

Missed Lung Lesions

Nigel Howarth¹, Denis Tack²

¹ Radiology Department, Clinique des Grangettes, Geneva, Switzerland

² Radiology Department, RHMS, Clinique Louis Caty, Brussels, Belgium

Introduction

Missed lung lesions are one of the most frequent causes of malpractice issues [1-3]. Chest radiography plays an important role in detecting and managing lung cancer, chronic airways disease, pneumonia and interstitial lung disease. Among all diagnostic tests, chest radiography is essential for confirming or excluding the diagnosis of most chest diseases. However, numerous lesions of a wide variety of disease processes affecting the thorax may be missed on a chest radiograph. For example, the frequency of missed lung carcinoma on chest radiographs can vary from 12% to 90%, depending on study design [4]. Despite the lack of convincing evidence that screening for lung cancer with the chest radiograph improves mortality rates, chest radiography is still requested for this purpose [5, 6]. The chest radiograph also helps narrow a differential diagnosis, helps direct additional diagnostic measures, and serves during follow-up. The diagnostic usefulness of the radiograph is maximized by the integrating radiological findings with clinical features of the individual patient [7]. In this chapter, we review the more important radiological principles regarding missed lung lesions in a variety of common chest diseases, with a special focus on how correlation with multidetector computed tomography (MDCT) of missed lung lesions can help improve interpretation of the plain chest radiograph.

Reasons for Missed Lung Lesions

Conditions contributing to missed lung lesions, especially carcinomas, have been extensively studied [1, 3, 4, 8-10]. Poor viewing conditions, hasty visual tracking, interruptions, inadequate image quality, and observer inexperience are amongst the most important issues [8, 9, 11-13]. Features of lesions themselves when nodules are being diagnosed, such as location, size, border characteristics, and conspicuity, also play a role [9, 11]. Missing lung nodules during initial reading of a chest radiograph is not uncommon. One estimate is that nearly 30% of lung nodules may be overlooked [14]. Missing a nodule that may represent malignancy will have adverse consequences on patient

management due essentially to delayed diagnosis, which may carry medicolegal implications. A number of authors have explored the reasons lesions are often overlooked [15-17]. Specific studies have focussed on size [18], contrast gradient [19], conspicuity [20] and anatomic noise [21].

A more recent study [22] examined the imaging features of non-small-cell lung carcinoma overlooked at digital chest radiography and compared general and thoracic radiologists' performance for lung carcinoma detection. Frontal and lateral chest radiographs from 30 consecutive patients with lung carcinoma overlooked during initial reading and 30 normal controls were submitted to two blinded thoracic radiologists and three blinded general radiologists for retrospective review. Location, size, histopathology, borders, presence of superimposed structures, and lesion opacity were recorded. Interobserver agreement was calculated, and detection performance between thoracic and general radiologists was compared. The average size of carcinomas missed by the thoracic radiologists was 18.1 mm (range 10-32 mm). The average size missed by general radiologists was 27.7 mm (range 12-60 mm). Seventy-one percent (5/7) of missed lesions were obscured by anatomical superimposition. Forty-three percent of lesions were located in the upper lobes and 63% were adenocarcinomas. Compared with general radiologists, the lesions missed by thoracic radiologists tended to be smaller but also had significantly lower CT density measurements and more commonly had an ill-defined margin. The clinical stage of the overlooked lesions did not differ between the two groups ($p = 0.480$). The authors concluded that size, location, conspicuity, and histopathology of lesions overlooked on digital chest radiography were similar to those missed on conventional film-screen techniques. Several other studies on the subject have led to similar conclusions (7, 18, 21).

Carcinoma detection on a chest radiograph remains difficult, with implications on patient management. Whereas overlooking chronic airways disease, pneumonia, and interstitial lung disease may not have the same potential medicolegal implications, the consequences for patient care could be critical. We propose to review how correlations with MDCT of missed lung lesions can help improve interpretation of the plain chest radiograph. During the

course of clinical work, when reporting chest CT, whenever available, every effort should be made to review previous chest radiographs and their reports, thereby providing one of the best learning tools for chest radiograph interpretation. A CT scan can be performed in patients with a negative chest radiograph when there is high clinical suspicion of chest disease. CT scan, especially high resolution CT (HRCT), is more sensitive than plain films for evaluating interstitial disease, bilateral disease, cavitation, empyema, and hilar adenopathy. CT is not generally recommended for routine use because data for its use in chronic airways disease and pneumonia are limited, the cost is high, and there is no evidence that outcome is improved. Thus, a chest radiograph is the preferred method for initial imaging, with CT scan reserved for further characterization (e.g., evaluating pattern and distribution and detecting of cavitation, adenopathy, mass lesions, or collections).

Many methods have been suggested for correct interpretation of the chest radiograph. There is no preferred scheme or recommended system. The clinical question should always be addressed. An inquisitive approach is always helpful, and being aware of the areas where mistakes are made is essential. Hidden abnormalities can thus be looked for. The difficult “hidden areas” which must be checked are the lung apex (superimposed over the heart), around each hilum, and below the diaphragm. Difficult areas, such as lesions at the lung apices or bases or lesions adjacent to or obscured by the hila or heart, are the focus of this review.

Specific Problems

To present a systematic approach, the review is divided into three sections representing specific problems: missed nodules, missed consolidation, and missed interstitial lung disease. In the case of a nodule or consolidation, the overlooked pathology may have been detected if special attention were paid to known difficult areas. The following examples show how a side-by-side comparison of chest radiograph and CT images improves our understanding of the overlooked lesion. There is no harm done by learning from one's mistakes!

Missed Nodules

1. Nodular lesions/tumors: Nodular lesions are frequently due to lung cancer, which may be primary or secondary. Lung cancer is probably one of the most common lung diseases that radiologists encounter in practice. Berbaum formulated the concept that perception is better if you know where to look and what to look for [23]. Our first example is that of a 53-year-old man who complained of pain in the right axilla for 4 months and underwent chest radiography. The posteroanterior and lateral radiographs were interpreted as showing normal findings (Fig. 1a, b). The subsequent MDCT shows a right superior sulcus mass with rib destruction. The coronal and sagittal reformats more precisely delineate the lesion (Fig. 1c, d). Needle biopsy

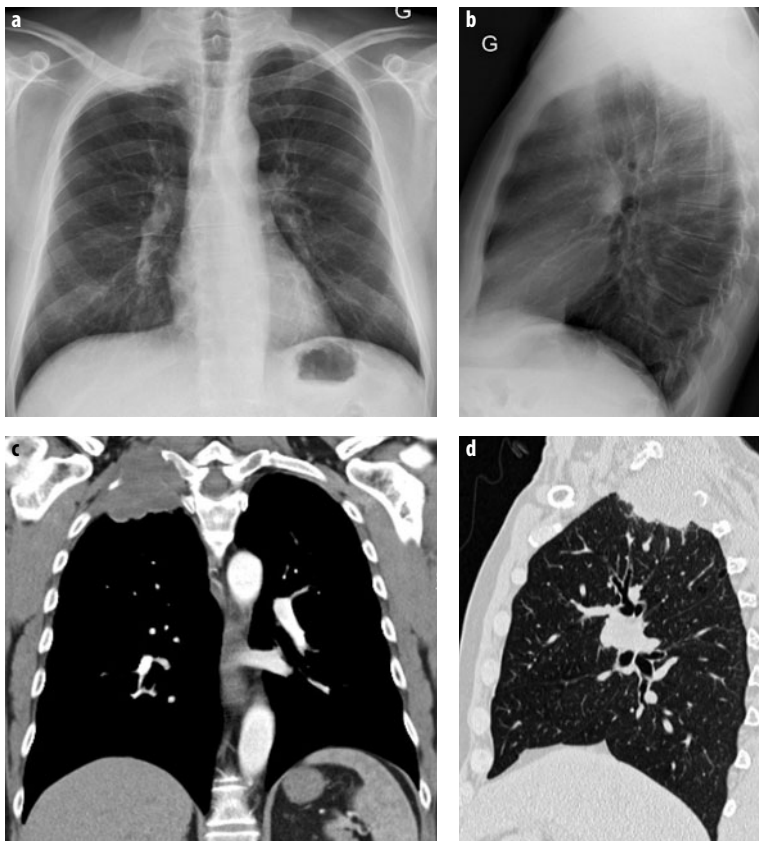


Fig. 1 a-d. A 53-year-old man who underwent chest radiography for pain in the right axilla: Posteroanterior (a) and lateral (b) radiographs interpreted as normal. With hindsight bias from multidetector computed tomography (MDCT), the right apical mass is obvious. c,d MDCT coronal and sagittal images with soft tissue and lung windows showing a right apical mass. G left

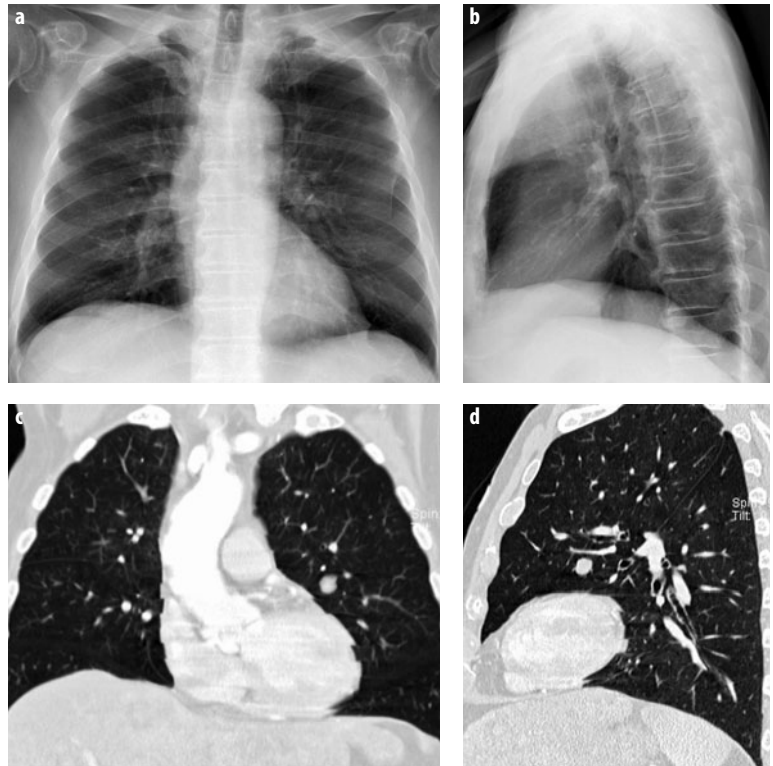


Fig. 2 a-d. A 77-year-old man with right upper quadrant pain: Posteroanterior (a) and lateral (b) radiographs interpreted as normal. With hindsight, the 13-mm nodule in the superior segment of the lingula can be seen. Coronal reformat from multidetector computed tomography (MDCT) (soft tissue window) shows a nodule in the lingula and multiple liver metastases. Coronal (c) and sagittal (d) reformats (lung window) show the position of the lingular nodule close to the hilum

established a diagnosis of bronchogenic carcinoma (adenocarcinoma). Hindsight bias [24] with the information available from the MDCT makes the initial lesion extremely obvious. Careful scrutiny of both apices is essential when reporting a frontal chest radiograph.

Radiologic errors can be divided into two types [25]: cognitive, in which an abnormality is seen but its nature is misinterpreted; and perceptual, the “miss”, in which a radiologic abnormality is not seen by the radiologist on initial interpretation. The perceptual type is estimated to account for approximately 80% of radiologic errors [26].

Our second patient is an example of the complexity of detecting a lung nodule close to the hilum. A 77-year-old man with known prostate cancer underwent chest radiography for right upper quadrant abdominal pain (Fig. 2a, b). The radiographs were reported as being normal. Subsequent MDCT revealed liver metastases as the cause of the abdominal pain, with a 13-mm lung nodule in the superior segment of the lingual. The coronal and sagittal reformats demonstrate the position of the nodule (Fig. 2c, d), which can be seen clearly with hindsight on the posteroanterior and lateral chest radiographs.

2. Nodular lesions/infections: Nodular lesions attributed to pulmonary infections are most often seen in nosocomial pneumonias and in immunocompromised patients. They may be caused by bacteria such as *Nocardia asteroides* and *Mycobacterium tuberculosis*, septic emboli, and fungi. *N. asteroides* causes single or nodu-

lar infiltrates with or without cavitation. Invasive pulmonary aspergillosis (IPA), *Mucor* spp, and *Cryptococcus neoformans* may present with single or multiple nodular infiltrates, which often progress to wedge-shaped areas of consolidation. Cavitation (the crescent sign) is common later in the course of the infiltrate. In the appropriate clinical setting, CT may aid in the diagnosis of IPA by demonstrating the so-called halo sign. Figure 3 shows a 43-year-old woman with fever after a bone marrow transplant. The posteroanterior radiograph was interpreted as normal (Fig. 3a). With hindsight, a subtle infiltrate can be seen at the left apex. Conspicuity is lessened by the overlying clavicle and first rib. Axial CT image (Fig. 3b) shows nodular consolidation with crescentic cavitation (the crescent sign) and surrounding ground-glass infiltrate (the halo sign). These characteristic findings of IPA are best identified on CT.

Missed Consolidation

Airspace disease: Airspace disease is usually caused by bacterial infections but can also be seen in viral, protozoal and fungal infections and malignancy, typically bronchioalveolar carcinoma [27]. Acute airspace pneumonia is characterized by a mostly homogeneous consolidation of lung parenchyma and well-defined borders, and does not typically respect segmental boundaries. An air bronchogram is very common. Progression to lobar consolidation may occur. As with lung nodules, whether consolidation is detected or missed on the plain chest

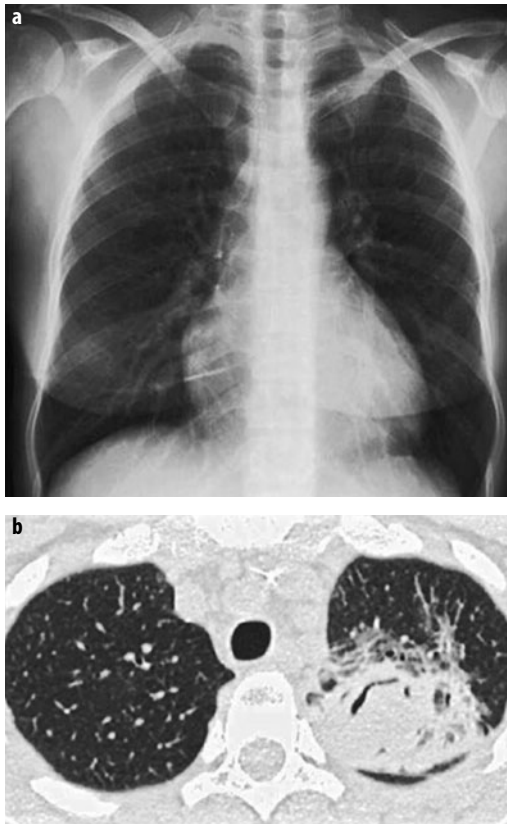


Fig. 3 a, b. A 43-year-old woman with fever after a bone marrow transplant: Posteroanterior radiograph interpreted as normal (**a**). With hindsight, a subtle infiltrate can be seen at the left apex. Conspicuity is lessened by the overlying clavicle and first rib. Also note the in-dwelling catheter from the left brachial vein to the superior vena cava. Axial computed tomography (lung window) shows nodular consolidation with crescentic cavitation (air-crescent sign) and surrounding ground-glass infiltrate (halo sign) (**b**)

radiograph may be determined by any combination of the same factors of size, density, location, and overlying structures. Location is a significant factor for missed consolidation [28]. Consolidation in the middle lobe and both lower lobes can be difficult to diagnose, especially when only the posteroanterior view is obtained. Figure 4 shows a 46-year-old woman with cough and right-sided chest pain. The posteroanterior radiograph was interpreted as normal (Fig. 4a). Due to a clinical suspicion of pulmonary embolism, MDCT was requested, showing consolidation in the anterior segment of the right lower lobe (Fig. 4b, c). The coronal and sagittal reformats demonstrate consolidation extent. There were no signs of pulmonary embolism on the contrast media study. A diagnosis of right lower lobe pneumonia was established, and the patient was treated successfully with antibiotics.

Chest radiography is the most frequently performed diagnostic investigation requested by general practitioners in Europe [29]. It is considered the gold standard for diagnosing pneumonia, which it does when an infiltrate is present. It can also differentiate pneumonia from other conditions that may present with similar symptoms, such as acute bronchitis. The results of the chest radiograph may occasionally suggest a specific etiology (example, e.g., a lung abscess) and identify a complication (empyema) or coexisting abnormalities (bronchiectasis, bronchial obstruction, interstitial lung disease). Chest radiography remains a valuable diagnostic tool in primary-care patients with a clinical suspicion of pneumonia to substantially reduce the number of patients misdiagnosed. MDCT imaging is useful in patients with community-acquired pneumonia when there is an unresolving or complicated chest radiograph, and at times in immunocompromised

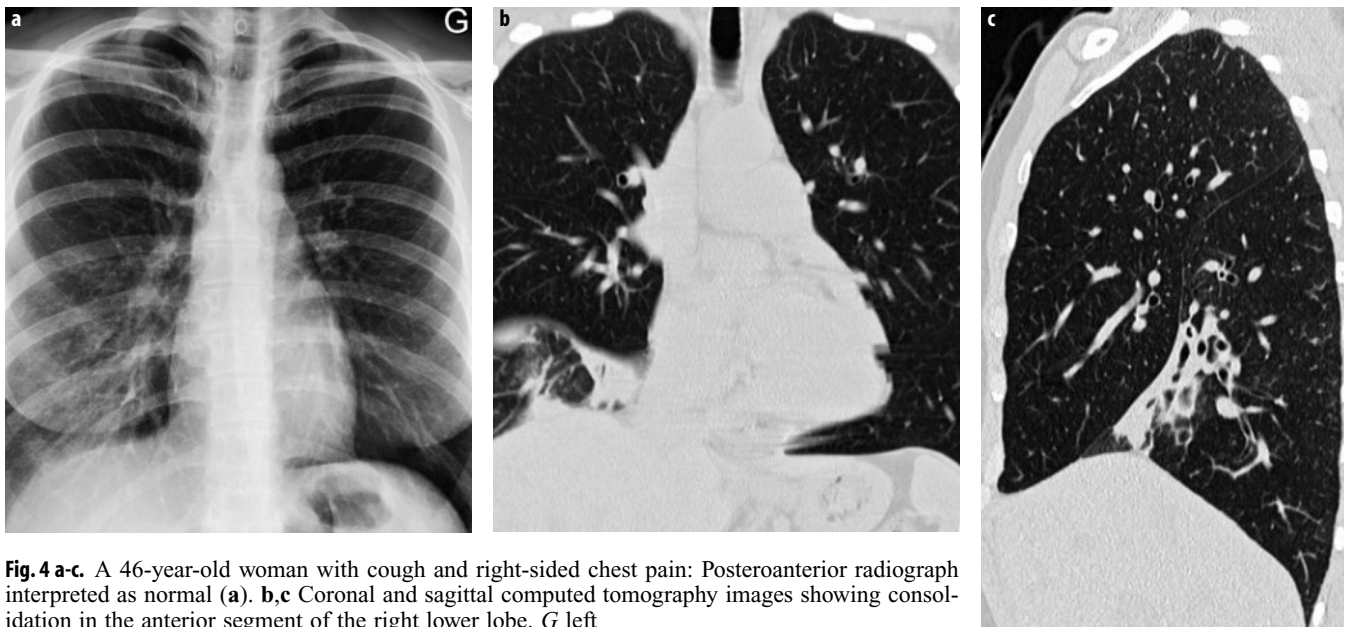


Fig. 4 a-c. A 46-year-old woman with cough and right-sided chest pain: Posteroanterior radiograph interpreted as normal (**a**). **b, c** Coronal and sagittal computed tomography images showing consolidation in the anterior segment of the right lower lobe. **G** left

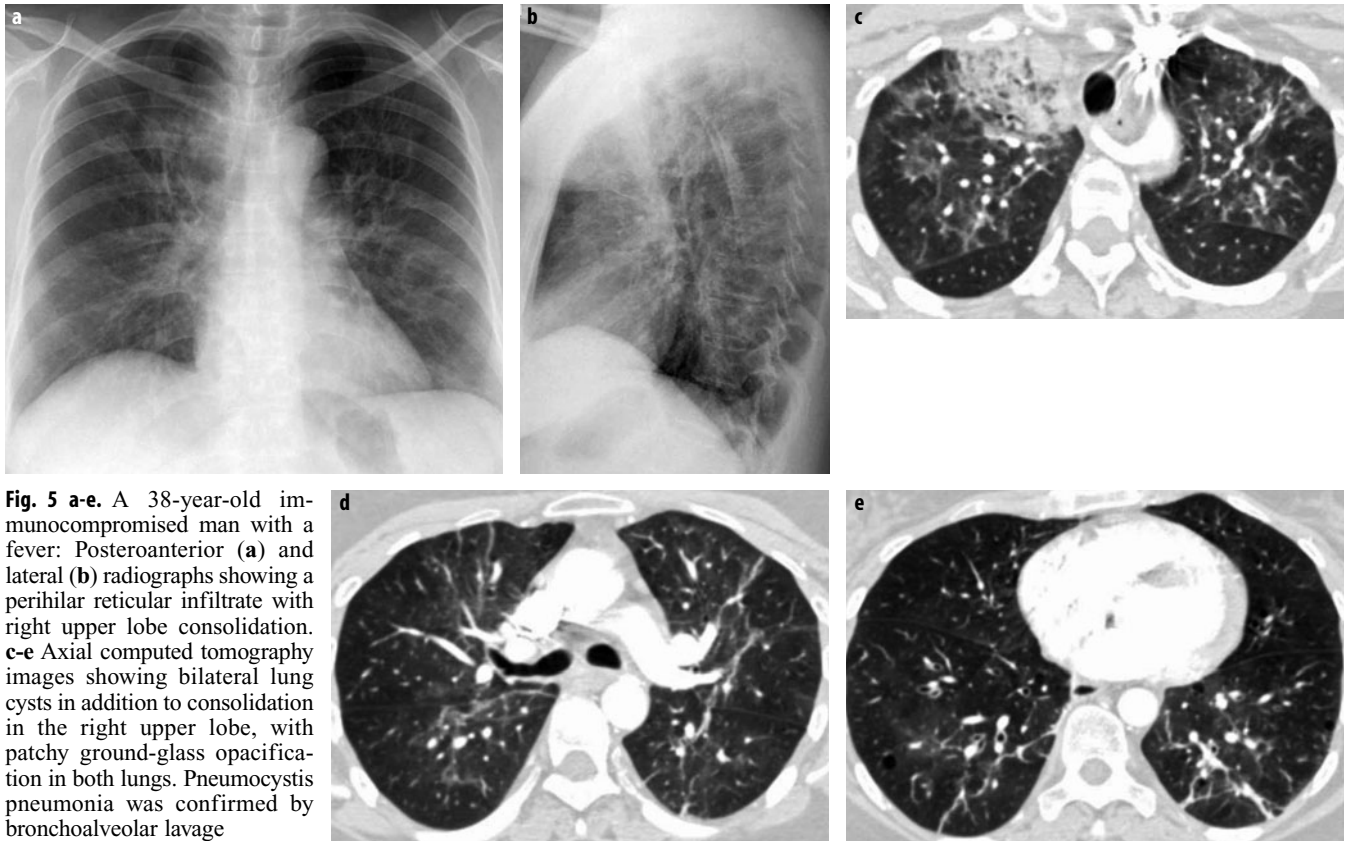


Fig. 5 a-e. A 38-year-old immunocompromised man with a fever: Posteroanterior (a) and lateral (b) radiographs showing a perihilar reticular infiltrate with right upper lobe consolidation. c-e Axial computed tomography images showing bilateral lung cysts in addition to consolidation in the right upper lobe, with patchy ground-glass opacification in both lungs. Pneumocystis pneumonia was confirmed by bronchoalveolar lavage

patients with suspected pulmonary infections. MDCT can help differentiate infectious from noninfectious abnormalities. It may detect empyema, cavitation, and lymphadenopathy when the chest radiograph cannot. MDCT should be performed in immunocompromised patients with a clinical suspicion of pneumonia when the chest radiograph is normal. This is especially true when the early diagnosis of pneumonia is critical, as is the case with immunocompromised and severely ill patients [30]. Figure 5 shows a 38-year-old immunocompromised man with a fever. The posteroanterior and lateral radiographs (Fig. 5a, b) were interpreted as showing a perihilar reticular infiltrate with right upper lobe consolidation. MDCT was requested to further characterize the infiltrate and revealed ground-glass opacification with bilateral lung cysts (Fig. 5c-e). Pneumocystis pneumonia was confirmed by bronchoalveolar lavage.

Missed Interstitial Lung Disease

Diffuse (interstitial or mixed alveolar-interstitial) lung disease: Diffuse lung disease presenting with widely distributed patchy infiltrates or interstitial reticular or nodular abnormalities can be produced by a number of disease entities. An attempt is usually made to separate the group of idiopathic interstitial pneumonias from known causes, such as infections, associated systemic disease, or drug use. The most common infectious organisms are

viruses and protozoa. In general, the etiology of an underlying pneumonia cannot be specifically diagnosed because the patterns overlap. It is beyond the aim of this chapter to discuss in detail the contribution of MDCT to the diagnosis of diffuse infiltrative lung disease. The development of HRCT has resulted in markedly improved diagnostic accuracy in acute and chronic diffuse infiltrative lung disease [31]. The chest radiograph remains the preliminary radiological investigation of patients with diffuse lung disease but is often nonspecific. Pattern recognition in diffuse lung disease has been the subject of controversy for many years. Extensive disease may be required before an appreciable change in radiographic density or an abnormal radiographic pattern can be detected on the plain chest radiograph. At least 10% of patients who are ultimately found to have biopsy-proven diffuse lung disease have an apparently normal chest radiograph. HRCT and now MDCT have become an integral component of the clinical investigation of patients with suspected or established interstitial lung disease. These techniques have had a major impact on clinical practice [32].

To end with a specific and striking example of the contribution of MDCT to patient management, Figure 6a shows the preoperative chest radiograph and subsequent MDCT (Fig. 6b-d) of a 45 year-old man with recently diagnosed renal cancer and no symptoms of chest disease. On axial CT (Fig. 6b), nodular ground-glass opacifica-

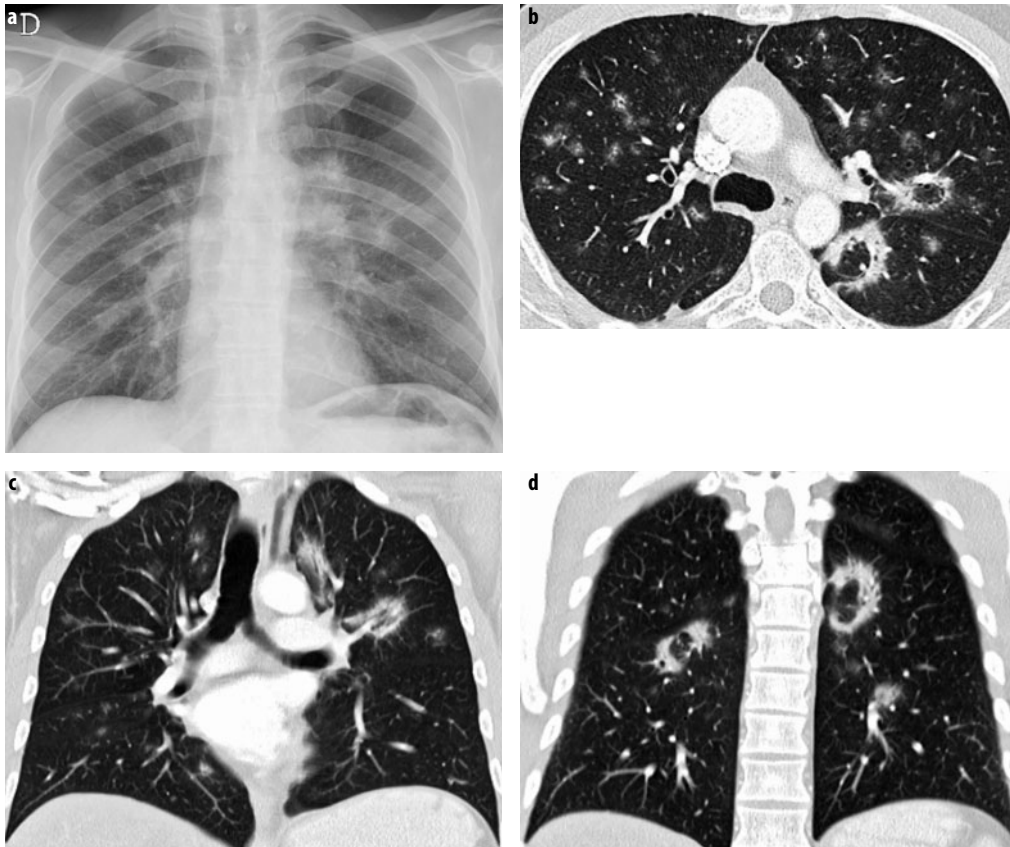


Fig. 6 a-d. A 45-year-old man with renal cancer and no chest symptoms: Preoperative posteroanterior radiograph showing bilateral, ill-defined, nodular ground-glass opacification (**a**). Axial computed tomography (CT) image shows nodular ground-glass opacification, with crescentic or ring-shaped opacities, representing an unusual CT feature encountered in organizing pneumonia. Coronal reformats show the CT feature more clearly, referred to as a reversed halo sign or atoll sign (**c-d**). *D* right

tion is seen, with crescentic or ring-shaped opacities, representing an unusual CT feature encountered in organizing pneumonia. The reformats (Fig. 6c, d) show this feature more clearly. It is referred to as a reversed halo sign or, atoll sign. Organizing pneumonia was confirmed by transthoracic needle biopsy of the largest lesion in the apical segment of the left lower lobe. After renal surgery and 6 months of corticosteroid therapy, the pulmonary infiltrates resolved completely.

Take-Home Messages

Despite the increasing use of CT imaging in the diagnosis of patients with chest disorders, chest radiography is still the primary imaging method in patients with suspected chest disease. The presence of an infiltrate on a chest radiograph is considered the gold standard for diagnosing pneumonia. Extensive knowledge of the radiographic appearance of pulmonary disorders is essential when diagnosing pulmonary disease. Chest radiography is also the imaging tool of choice for assessing the complications and in the follow-up of patients with pulmonary diseases.

MDCT plays an increasing role in diagnosing chest diseases, especially in patients with unresolving symptoms. CT aids in differentiating infectious and noninfectious disorders. The role of CT in suspected or proven chest disease can be summarized as follows:

1. CT is valuable in the early diagnosis of chest disease, especially in patient groups in which an early diagnosis is important (immunocompromised, critically ill);
2. CT may help characterize pulmonary disorders;
3. CT is an excellent tool in assessing complications of chest disease;
4. CT is required when investigating patients with a persistent or recurrent pulmonary infiltrate.

A side by side comparison between the chest radiograph and MDCT when confronted with a missed lung lesion is very instructive. The radiologist should be able to understand the reasons for missing certain lesions. By adopting the approach described above, cognitive and perceptual errors could both be reduced.

Acknowledgments. The authors thank Ms. Sophie Perrier for assistance in preparing the manuscript. Special thanks go to Prof. E. Coche, Prof. P.A. Gevenois, and Dr. B. Ghaye for providing help and material for the chapter.

References

1. Berlin L (1986) Malpractice and radiologists: an 11.5-year perspective. *AJR Am J Roentgenol* 147:1291-1298
2. Berlin L (1995) Malpractice and radiologists in Cook County, IL: trends in 20 years of litigation. *AJR Am J Roentgenol* 165:781-788
3. Potchen EJ, Bisesi MA (1990) When is it malpractice to miss lung cancer on chest radiographs? *Radiology* 175:29-32

4. Quekel LG, Kessels AG, Goei R et al (1999) Miss rate of lung cancer on the chest radiograph in clinical practice. *Chest* 115:720-724
5. Marcus PM (2001) Lung cancer screening: an update. *J Clin Oncol* 19:83S-86S
6. Melamed MR (2000) Lung cancer screening results in the National Cancer Institute New York study. *Cancer* 89:2356-2362
7. Aideyan UO, Berbaum K, Smith WL (1995) Influence of prior radiologic information on the interpretation of radiographic examinations. *Acad Radiol* 2:205-208
8. Carmody DP, Nodine CF, Kundel HL (1980) An analysis of perceptual and cognitive factors in radiographic interpretation. *Perception* 9:339-344
9. Austin JH, Romney BM, Goldsmith LS (1992) Missed bronchogenic carcinoma: radiographic findings in 27 patients with a potentially resectable lesion evident in retrospect. *Radiology* 182:115-122
10. Turkington PM, Kennan N, Greenstone MA (2002) Misinterpretation of the chest X-ray as a factor in the delayed diagnosis of lung cancer. *Postgrad Med J* 78:158-160
11. Woodring JH (1990) Pitfalls in the radiologic diagnosis of lung cancer. *AJR Am J Roentgenol* 154:1165-1175
12. Monnier-Cholley L, Arrive L, Porcel A et al (2001) Characteristics of missed lung cancer on chest radiographs: a French experience. *Eur Radiol* 11:597-605
13. Krupinski EA, Berger WG, Dallas WJ et al (2003) Searching for nodules: what features attract attention and influence detection? *Acad Radiol* 10:861-868
14. Samei E, Flynn MJ, Eyler WR (1999) Detection of subtle lung nodules: relative influence of quantum and anatomic noise on chest radiographs. *Radiology* 213:727-734
15. Kundel HL, Nodine CF, Krupinski EA (1989) Searching for lung nodules. Visual dwell indicates locations of false-positive and false-negative decisions. *Invest Radiol* 24:472-478
16. Samuel S, Kundel HL, Nodine CF et al (1995) Mechanism of satisfaction of search: eye position recordings in the reading of chest radiographs. *Radiology* 194:895-902
17. Quekel LG, Goei R, Kessels AG et al (2001) Detection of lung cancer on the chest radiograph: impact of previous films, clinical information, double reading, and dual reading. *J Clin Epidemiol* 54:1146-1150
18. Kelsey CA, Moseley RD, Brogdon BG et al (1977) Effect of size and position on chest lesion detection. *AJR Am J Roentgenol* 129:205-208
19. Kundel HL, Revesz G, Toto L (1979) Contrast gradient and the detection of lung nodules. *Invest Radiol* 14:18-22
20. Kundel HL (1975) Peripheral vision, structured noise and film reader error. *Radiology* 114:269-273
21. Kundel HL, Revesz G (1976) Lesion conspicuity, structured noise, and film reader error. *AJR Am J Roentgenol* 126:233-238
22. Wu M-H, Gotway MB, Lee TJ et al (2008) Features of non-small cell lung carcinomas overlooked at digital chest radiography. *Clin Radiol* 63:518-528
23. Berbaum KS (1995) Difficulty of judging retrospectively whether a diagnosis has been "missed". *Radiology* 194:582-583
24. Berlin L (2000) Hindsight bias. *AJR Am J Roentgenol* 175:597-601
25. Berlin L (2001) Defending the "missed" radiographic diagnosis. *AJR Am J Roentgenol* 176:317-322
26. Berlin L, Hendrix RW (1998) Perceptual errors and negligence. *AJR Am J Roentgenol* 170:863-867
27. Jung JI, Kim H, Park SH et al (2001) Differentiation of pneumonia-type bronchioloalveolar cell carcinoma and infectious pneumonia. *Br J Radiol* 74:490-494
28. Melbye H, Dale K (1992) Interobserver variability in the radiographic diagnosis of adult outpatient pneumonia. *Acta Radiol* 33:79-83
29. Woodhead M, Gialdroni Grassi G, Huchon GJ et al (1996) Use of investigations in lower respiratory tract infection in the community: a European survey. *Eur Respir J* 9:1596-1600
30. Heussel CP, Kauczor HU, Ullmann AJ (2004) Pneumonia in neutropenic patients. *Eur Radiol* 14:256-271
31. Webb WR, Müller NL, Naidich DP (2001) High-resolution CT of the lung, 3rd edn. Lippincott Williams & Wilkins, Philadelphia, PA
32. Epler GR, McLoud TC, Gaensler EA et al (1978) Normal chest roentgenograms in chronic diffuse infiltrative lung disease. *N Engl J Med* 298:934-939

Plain Film and HRCT Diagnosis of Interstitial Lung Disease

Sujal R. Desai

King's College London, King's Health Partners, Department of Radiology, King's College Hospital NHS Foundation Trust, London, UK

Introduction

The interstitial lung diseases (ILDs) are an important and challenging group of pulmonary disorders. The term ILD encompasses a range of disorders categorized by four broad groupings: granulomatous ILD (e.g., sarcoidosis), ILDs of known cause (e.g., drug-induced, connective-tissue-disease-related), idiopathic interstitial pneumonias, and a miscellaneous group [1, 2].

In patients with suspected ILD, a plain chest radiograph (CXR) will almost certainly be one of the initial tests requested by the physician. However, since the mid-1980s, there has been a growing reliance on the diagnostic capabilities of high-resolution computed tomography (HRCT), which continues to be a vital component of investigation. In some patients (where biopsy would previously have been mandatory), the diagnostic process has undergone a paradigm shift. The best example of this perhaps has been in usual interstitial pneumonia where the HRCT appearances may be characteristic enough for a confident and accurate radiological diagnosis to be made, obviating surgical biopsy [1, 3, 4]. Against this, it must be remembered that HRCT interpretation is not straightforward: there are well over 200 known ILDs manifesting as a surprisingly small number of histopathological patterns (e.g., fibrosis, consolidation, intra-alveolar hemorrhage), which, in turn, are reflected by a relatively small group of HRCT features. This is sometimes compounded by the occurrence of atypical CT features in some (otherwise well characterized) disorders and also changes in appearance that may occur over time [5, 6].

HRCT Technique

Two technical features are key to HRCT imaging: first, beam collimation is narrower than in conventional CT imaging (i.e., 1–2 mm versus 10 mm); second, a special mathematical high-spatial – frequency (bone) reconstruction algorithm is applied [7]. Reduced section thickness increases the likelihood that a small lesion will have dimensions comparable with the size of a voxel and improves spatial resolution significantly. The dedicated

reconstruction algorithm takes advantage of the intrinsically high contrast environment of the lung parenchyma so that the natural density differences between aerated lung and the interstitium are enhanced [7]. The conspicuity of vessels, small bronchi, and interlobular septa is increased compared with conventional (thick-section) CT images [8]. An important downside of high-frequency algorithms is the increased visibility of image noise. However, in practice, this rarely hampers radiological interpretation. Traditionally, HRCT image slices are interspaced – the logic being that in diffuse disease processes, the lungs only need to be sampled. It should be remembered, perhaps, that image interspacing in this way has the beneficial effect of reducing radiation dose [9]. The advent of multidetector CT (MDCT) machines means that HRCT can be, and has been, performed without image interspacing; the obvious drawback of noninterspaced (volume) HRCT imaging is increased radiation dose.

Plain CXR and HRCT in Interstitial Lung Diseases

Whereas CXR will almost always be requested, there are issues of sensitivity, specificity, and diagnostic accuracy (discussed below). By contrast, HRCT improves the detection of subtle parenchymal abnormalities: ground-glass opacification, small cystic air spaces, traction bronchiectasis/bronchiolectasis, and the irregular interfaces along pleural surfaces and bronchovascular structures are better appreciated at HRCT [10]. An important caveat is that in patients with nodular infiltrates, HRCT appearances can sometimes mislead: on thin-section images, the dimensions of nodules and pulmonary vessels may be comparable, making the distinction difficult [10]. This notwithstanding, the gamut of CT features that denotes interstitial lung disease is manageably small: a reticular pattern, thickening of interlobular septa, honeycombing, nodules, and ground-glass opacification are the common CT signs of interstitial disease [11].

Unlike CXR, HRCT depicts the macroscopic abnormalities seen by the pathologist. This was elegantly demonstrated in a study by Müller and colleagues who showed that CT features [in patients with usual intersti-

tial pneumonia/idiopathic pulmonary fibrosis (UIP/IPF)] reflected the histopathological changes [12]. A reticular pattern was seen in seven of nine patients and corresponded to areas of irregular fibrosis at microscopy. Not surprisingly, because there is no anatomical superimposition, HRCT sensitivity is superior to that of chest CXR. However, a more important issue than sensitivity is the confidence and accuracy with which diagnosis can be made. In a landmark study published by Mathieson and co-workers of 118 patients with a variety of biopsy-proven ILDs, experienced chest radiologists were independently asked to make up to three diagnosis on chest radiographs and CT [13]. For their first-choice diagnosis, readers were asked to assign a level of confidence. One important finding was that compared with CXR, a confident diagnosis was made nearly twice as often at HRCT. The second, and perhaps more striking, message was that when experienced radiologists were confident of the diagnosis, they were almost always correct [13]. In contrast, a confident diagnosis on CXR (only assigned in one quarter of cases) was associated with a significantly lower rate of correct diagnoses.

The results of subsequent studies have not always been so conclusive [14]. However, because of study design, the majority of these comparative investigations probably undervalue the true utility of HRCT [3]. Indeed, in many of these early studies, there was no recourse to pretest probabilities for observers and, therefore, do not accurately reflect clinical practice. Second, since the advent of HRCT, thoracic radiologists have become increasingly familiar with the spectrum and histopathological correlates of HRCT patterns: it seems highly likely that since the late 1980s (when the Mathieson study was published), there has been a proportionate increase in the confidence of experienced observers in making HRCT diagnoses. Some justification for this last statement comes from a series conducted in the early 1990s that addressed the clinically vexing issue of end-stage lung disease [15]. In that study, two experienced thoracic radiologists independently made correct first-choice diagnoses in just <90% of cases; nearly two thirds of these were made with high confidence. On first inspection, these data seem less than impressive. However, the results of open lung biopsy (the purported gold standard for diagnosing diffuse lung disease) are also often disappointing and, when considered in this context, the capabilities of HRCT can be put into perspective.

An Approach to CXR and HRCT Interpretation

A systematic approach to interpreting CXR and HRCT images in ILD is important. In this regard, the first question for the radiologist must be whether or not there is a real abnormality. It is important to establish this, and the question may not be as simple to answer as it might first appear. CXR and HRCT appearances may be entirely attributable to technical factors (e.g., related to a poor in-

spiratory effort, inadequate milliamperes, or regions of physiologically dependent atelectasis at CT) or normal anatomical variation. A failure to appreciate these factors will lead to overinterpretation and erroneous reports of disease. Making the distinction between normality and abnormality can also be difficult when there is apparently minimal disease or, conversely, where there is diffuse abnormality (e.g., widespread decreased attenuation or ground-glass opacification at HRCT).

Once the observer is satisfied that the visible abnormality is real, the next step is to establish the predominant radiological pattern or patterns. This is more readily achieved at HRCT. Nevertheless, the aim should be to identify the dominant pattern(s) using standard radiological terms [16]: the use of loose terminology (e.g., patchy opacification, parenchymal opacities) or descriptive terms in which there is an implied pathology (e.g., interstitial pattern or alveolitis) is misleading and should be discouraged. Making a note of the distribution of disease can be of considerable diagnostic value because certain ILDs have a predilection for certain zones. For instance, it is known that in the majority of patients with IPF, fibrosis is most prevalent in the mid to lower zones. This contrasts with fibrosis in patients with sarcoidosis, which typically has a predilection for the upper lobes. Similarly, an appreciation of the axial distribution of disease at HRCT should be made. Using the example of IPF and sarcoidosis again, the former is commonly peripheral (subpleural) whereas in the latter, disease tends may be central and bronchocentric. The presence or absence of ancillary radiological features may be important in suggesting or, indeed, excluding certain diagnoses: thus, the finding of pleural thickening or plaques (with or without calcification) may suggest a diagnosis of asbestos-related ILD and help to exclude IPF (in which pleural thickening is a rare finding). Lymph node enlargement may simply be reactive in patients with diffuse interstitial disease. However, coexistent symmetrical hilar nodal enlargement may suggest a diagnosis of sarcoidosis or occupational lung disease.

When the predominant radiological pattern or pattern is determined, the reader will be in a position to make a statement of the likely pathology. In this respect, knowledge of the relationships between HRCT appearances and the possible histopathological correlates is vital. Thus, in a patient with predominant consolidation, it is reasonable to conclude that the dominant pathology involves the air spaces, whereas with reticulation, the likely pathological process probably affects the interstitium. As a final step – and it is probably best that this is the last step after all the considerations above – the radiologist should be mindful of the clinical background. Specific clinical features that may be of importance in HRCT interpretation include basic demographic data (i.e., age, gender, ethnicity), smoking history, time course of the illness (i.e., over hours, days, weeks, months, years) and any relevant past medical history (prescribed or illicit drug use, occupation, travel).

HRCT Features in Selected ILDs

A working knowledge of the histopathological changes in various diseases allows the radiologist to understand and predict the findings on HRCT [17]. To illustrate the preceding statement, the following section briefly considers the HRCT appearances in three diseases with which a practicing thoracic radiologist will be relatively familiar.

IPF/UIP and Nonspecific Interstitial Pneumonia

The expected histopathological diagnosis in patients with the clinical entity of IPF is UIP [1]. At microscopy, there is temporally heterogeneous fibrosis intermingled with areas of unaffected lung parenchyma. Within areas of fibrosis, there is honeycombing and tractional dilatation of airways. The UIP pattern has a characteristic basal and subpleural predilection. Most of these features are reflected at HRCT. In the typical patient, the cardinal finding is a bilateral, roughly symmetrical, subpleural and basal reticular pattern with honeycombing [2, 12, 18-20]. There may be associated ground-glass opacification, but this is generally less extensive than the reticular pattern. Tractional dilatation of segmental and subsegmental airways (so-called traction bronchiectasis or bronchiolectasis) may be evident and might reflect more severe fibrosis [21]. The presence of these typical features will permit a confident and accurate HRCT diagnosis of UIP to be made by experienced radiologists, thereby obviating surgical biopsy [4]. However, it is important to stress that atypical CT features [sometimes overlapping with nonspecific interstitial pneumonia (NSIP)] will occur in around one third of patients [22], and in this group, biopsy confirmation of the diagnosis may be needed.

In NSIP, HRCT appearances can be more variable. However, many studies have shown that ground-glass opacification is the dominant finding [20, 23]. This is typically bilateral and symmetrical and most pronounced in the lower zones. Not infrequently, there is superimposed reticulation, and this may remain stable or increase in extent over time; indeed, on serial CT examination, a pattern similar to UIP may develop in patients with NSIP. Honeycombing tends to be a less conspicuous feature than it is in patients with the UIP pattern [24].

Organizing Pneumonia

Organizing pneumonia is a pattern of interstitial pneumonia that predominantly affects the air spaces. On pathological examination, there are polypoid plugs of loose granulation tissue in the air spaces (with or without intraluminal polyps extending into the airways) [20]. The lung architecture tends to be well preserved (in contrast to the other overtly fibrosing interstitial pneumonias), but there may be signs of organizing fibrosis in the air spaces. At HRCT, bilateral consolidation, generally in the lower zones, is the commonest finding. Disease may be

subpleural or even bronchocentric; a more distinctive pattern of perilobular consolidation has also been reported [25]. In some patients, there are linear opacities and there may be frank reticulation (denoting fibrosis).

Sarcoidosis

Noncaseating epithelioid-cell granulomata are the histopathological hallmark of sarcoidosis [26]. Granulomata have the tendency to distribute along the lymphatics. Thus, the lymphatic pathways that surround the axial interstitium that invest bronchovascular structures and those that exist subpleurally (including the subpleural lymphatics along the fissures) are typically involved. Not surprisingly, a nodular infiltrate (presumably reflecting conglomerate granulomata) with a propensity to involve the bronchovascular elements is a characteristic CT finding [27, 28]. Subpleural nodularity is also commonly seen. In the later stages of the disease, there may be obvious signs of established lung fibrosis with upper zone volume loss, parenchymal distortion, and traction bronchiectasis. Because of the bronchocentric nature of the disease, signs of small airways disease are seen at CT in some patients with sarcoidosis [29].

Hypersensitivity Pneumonitis

Exposure to a range of organic antigens will cause lung disease in some patients, probably due to an immunologically mediated response [26]. In the subacute stage, there is an interstitial infiltrate comprising lymphocytes and plasma cells with a propensity to involve the small airways (bronchioles). Scattered noncaseating granulomata may be seen. Predictably, at CT there is diffuse ground-glass opacification, ill-defined centrilobular nodules, and lobular areas of decreased attenuation on images performed at end expiration [30, 31]. The CT appearances in subacute hypersensitivity pneumonitis (HP) may be identical to those in patients with the entity of respiratory-bronchiolitis-associated interstitial lung disease (RBILD) [32]. However, consideration of the smoking history may help the differentiation: a history of smoking is the norm in the vast majority of patients with RBILD, whereas cigarette smoke appears to protect against the development of extrinsic allergic alveolitis.

References

1. King TE Jr, Costabel U, Cordier JF et al (2000) Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. *Am J Respir Crit Care Med* 161:646-664
2. Travis WD, King TE Jr, and the Multidisciplinary Core Panel (2002) American Thoracic Society/European Respiratory Society international multidisciplinary consensus classification of idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 165:277-304
3. Wells AU (1998) Clinical usefulness of high resolution computed tomography in cryptogenic fibrosing alveolitis. *Thorax* 53:1080-1087

4. Hunninghake GW, Zimmerman MB, Schwartz DA et al (2001) Utility of a lung biopsy for the diagnosis of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 164:193-196
5. Sverzellati N, Wells AU, Tomassetti S et al (2010) Biopsy-proved idiopathic pulmonary fibrosis: spectrum of nondiagnostic thin-section CT diagnoses. *Radiology* 254:957-964
6. Silva CI, Müller NL, Hansell DM et al (2008) Nonspecific interstitial pneumonia and idiopathic pulmonary fibrosis: changes in pattern and distribution of disease over time. *Radiology* 247:251-259
7. Mayo JR, Webb WR, Gould R et al (1987) High-resolution CT of the lungs: an optimal approach. *Radiology* 163:507-510
8. Murata K, Khan A, Rojas KA, Herman PG (1988) Optimization of computed tomography technique to demonstrate the fine structure of the lung. *Invest Radiol* 23:170-175
9. Mayo JR, Jackson SA, Müller NL (1993) High-resolution CT of the chest: radiation dose. *AJR Am J Roentgenol* 160:479-481
10. Remy-Jardin M, Remy J, Deffontaines C, Duhamel A (1991) Assessment of diffuse infiltrative lung disease: comparison of conventional CT and high-resolution CT. *Radiology* 181:157-162
11. Webb WR, Müller NL, Naidich DP (1996) HRCT findings of lung disease. In: Webb WR, Müller NL, Naidich DP, eds. *High-resolution CT of the lung*. Lippincott-Raven, Philadelphia, PA, pp 41-108
12. Müller NL, Miller RR, Webb WR et al (1986) Fibrosing alveolitis: CT-pathologic correlation. *Radiology* 160:585-588
13. Mathieson JR, Mayo JR, Staples CA, Müller NL (1989) Chronic diffuse infiltrative lung disease: comparison of diagnostic accuracy of CT and chest radiography. *Radiology* 171:111-116
14. Padley SPG, Hansell DM, Flower CDR, Jennings P (1991) Comparative accuracy of high resolution computed tomography and chest radiography in the diagnosis of chronic diffuse infiltrative lung disease. *Clin Radiol* 44:222-226
15. Primack SL, Hartman TE, Hansell DM, Müller NL (1993) End-stage lung disease: CT findings in 61 patients. *Radiology* 189:681-686
16. Hansell DM, Bankier AA, MacMahon H et al (2008) Fleischner society: glossary of terms for thoracic imaging. *Radiology* 246:697-722
17. Colby TV, Swensen SJ (1996) Anatomic distribution and histopathologic patterns in diffuse lung disease: correlation with HRCT. *J Thorac Imaging* 11:1-26
18. Müller NL, Miller RR (1990) Computed tomography of chronic diffuse infiltrative lung disease: part 1. *Am Rev Respir Dis* 142:1206-1215
19. Lynch DA (1996) Ground-glass attenuation on CT in patients with idiopathic pulmonary fibrosis. *Chest* 110:312-313
20. Lynch DA, Travis WD, Müller NL et al (2005) Idiopathic interstitial pneumonias: CT features. *Radiology* 236:10-21
21. Desai SR, Wells AU, Rubens MB et al (2003) Traction bronchiectasis in cryptogenic fibrosing alveolitis: associated computed tomographic features and physiological significance. *Eur Radiol* 13:1801-1808
22. Flaherty KR, Thwaite EL, Kazerooni EA et al (2003) Radiological versus histological diagnosis in UIP and NSIP: survival implications. *Thorax* 58:143-148
23. MacDonald SLS, Rubens MB, Hansell DM et al (2001) Nonspecific interstitial pneumonia and usual interstitial pneumonia: comparative appearances at and diagnostic accuracy of thin-section CT. *Radiology* 221:600-605
24. Elliot TL, Lynch DA, Newell JD et al (2005) High-resolution computed tomography features of nonspecific interstitial pneumonia and usual interstitial pneumonia. *J Comput Assist Tomogr* 29:339-345
25. Ujita M, Renzoni EA, Veeraraghavan S et al (2004) Organizing pneumonia: peribubular pattern at thin-section CT. *Radiology* 232:757-761
26. Colby TV, Carrington CB (1995) Interstitial lung disease. In: Thurlbeck WM, Churg AM, eds. *Pathology of the lung*. Thieme, New York, NY, pp 589-737
27. Lynch DA, Webb WR, Gamsu G et al (1989) Computed tomography in pulmonary sarcoidosis. *J Comput Assist Tomogr* 13:405-410
28. Brauner MW, Grenier P, Mompont D et al (1989) Pulmonary sarcoidosis: evaluation with high-resolution CT. *Radiology* 172:467-471
29. Hansell DM, Milne DG, Wilsher ML, Wells AU (1998) Pulmonary sarcoidosis: morphologic associations of airflow obstruction at thin-section CT. *Radiology* 209:697-704
30. Remy-Jardin M, Remy J, Wallaert B, Müller NL (1993) Subacute and chronic bird breeder hypersensitivity pneumonitis: sequential evaluation with CT and correlation with lung function tests and bronchoalveolar lavage. *Radiology* 189:111-118
31. Hansell DM, Wells AU, Padley SPG, Müller NL (1996) Hypersensitivity pneumonitis: correlation of individual CT patterns with functional abnormalities. *Radiology* 199:123-128
32. Desai SR, Ryan SM, Colby TV (2003) Smoking related interstitial lung diseases: histopathological and imaging perspectives. *Clin Radiol* 58:259-268

HRCT of the Interstitial Lung Diseases: What, Why, and How To

Mario Maffessanti¹, Giorgia Dalpiaz²

¹ Department of Radiology, University of Trieste, Ospedale di Cattinara, Trieste, Italy

² Department of Radiology, Ospedale Bellaria, Bologna, Italy

Introduction

Interstitial lung diseases comprise more than 100 entities in which the lung is more or less broadly involved by a diffuse disease, mostly – but not uniquely – nonneoplastic. A diffuse lung disease (DLD) is a pathologic process in which it is not possible to localize unambiguously the topographic site of onset. Interstitial should be considered a misnomer, because several diffuse entities involve uniquely or at least partially the alveolar spaces; however, the word is so deeply rooted in the collective imagination that it is widely used in the common practice.

For decades, the radiological diagnosis of these diseases has been confined to the chest radiograph (CXR), which is still on the spot in the beginning of the diagnostic process and during the follow-up. The introduction of high-resolution computed tomography (HRCT) in the mid-1980s made it evident that the CT technique has higher sensitivity and specificity than CXR, in particular when small lesions are the sole expression of disease at the lobular and sublobular level, so much so that it is well accepted that HRCT is indicated in the presence of an even normal CXR, when the patient has symptoms or abnormal pulmonary function tests, and when the CXR is positive but inconclusive or aspecific. Nowadays, there is probably no patient with suspected diffuse lung disorder that is not submitted for an HRCT study in the first assessment, if only for a more detailed and trustworthy definition of morphologic characteristics and extension of the underlying disease. The subsequent discussion consequently focuses solely on the CT aspects of interstitial lung disease.

The radiological appearance of each disease depends on the elementary lesions and their distribution throughout the lung. The beginning of the radiological process should be dedicated to verify the existence of a diffuse abnormality and in particular of the elements producing an increased absorption of the X-rays (opacities) or a reduced attenuation of them (hyperlucencies). If an abnormality is discovered, the subsequent step is dedicated to identifying its prevalent aspects, which in turn depend upon the underlying pathology. A further step is to localize the lesions in relation to both the lobular architecture (when possible) and the topographic distribution through-

out the lung. The lobular approach gives valuable information about the modalities of arrival/onset of the lesions and their spreading routes, whereas the topographic approach helps discriminate among diseases with similar morphological presentation (Table 1).

The two modalities are not mutually exclusive, and on the contrary, they strengthen each other through the concept of pattern. Pattern, in medical practice, is the ensemble of characteristic elements giving proof and name to a disease or to a family of diseases. In the DLD universe, basic radiological patterns play an important role in the beginning of the diagnostic assessment. However, two important caveats should be kept in mind when thinking in

Table 1. Lung predominance of miscellaneous diffuse lung diseases

Predominant location	Disease
Upper lung	Sarcoidosis
	Cystic Fibrosis
	RB and RB-ILD
	Centrilobular emphysema
	Hypersensitivity Pneumonitis
	Langerhans Cell Histiocytosis
	Pneumocystis jiroveci pneumonia
Lower lung	Silicosis and CWP
	Idiopathic UIP
	NSIP
	Asbestosis
	Desquamative Interstitial Pneumonia
	Cardiac edema
Central lung	Metastases
	Pulmonary hemorrhage
	Pulmonary alveolar proteinosis
	Renal edema
Peripheral lung	MALT lymphoma
	Idiopathic UIP
	NSIP
	Asbestosis
	Paraseptal emphysema
	Chronic eosinophilic pneumonia
	Organizing pneumonia

RB, respiratory bronchiolitis; *ILD*, interstitial lung disease; *CWP*, coal-workers pneumoconiosis; *MALT*, mucosa-associated lymphoid tissue; *UIP*, usual interstitial pneumonia; *NSIP*, nonspecific interstitial pneumonia

terms of patterns. First, a same disease may present with different patterns. This may result from its variable pathological expression in a given patient (e.g., a progressive systemic sclerosis may present histologically – hence radiologically – with an usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP), or even a diffuse alveolar damage pattern), from its temporal phase (e.g., a hypersensitivity pneumonitis may be investigated during an acute, subacute, or chronic stage) or from its natural progression (e.g., a NSIP may proceed from minimal changes to end-stage lung disease). Second, a same pattern may be present in several diseases (a classical model being the systemic collagen-vascular disorders). In addition, this evidence has to be expected because the lung has a limited number of reactions to different insults. These caveats are not an absolute limit to the pattern approach, but they emphasize the necessity of a tight integration of imaging with clinical presentation and pathology in arriving at a meaningful diagnosis for the patient. The importance of a multidisciplinary approach is widely recognized in the literature.

According to the literature and based on the personal experience, the distinction of six main radiological patterns is suggested. If more than one pattern is present in one patient, begin with the most prevalent one.

Septal Pattern

A septal pattern is present when thickening of perilobular interstitium and bronchovascular bundle both in the centrilobular core and at the central level are visible (Fig. 1). The final effect is of a regular network of white lines without signs of retraction or remodeling of pulmonary structures. Synonyms: regular linear pattern; linear pattern with preserved architecture.



Fig. 1. Septal pattern: Several perilobular septa and a thickened fissure are visible (*arrowheads*), together with a thickening of vessels and bronchial walls (*curved arrows*). There is also a tiny nodulation here and there, several hyperlucent lobules, and even a small consolidation to the *left*. However, the first pattern to deal with on this image in this patient should be the (prevalent) septal

Key Signs

Thickened Interlobular Septa (Interlobular Reticulation, Perilobular Reticulation)

White lines 1-2 cm long outlining the polygonal boundaries of secondary lobules; a few lines inside the lobule may be also visible. In normal conditions, the septa are not overtly recognizable, so such evidence points at an abnormality.

Centrilobular Peribronchovascular Thickening

Cuffing of the core structures of the lobule: The bronchiole becomes evident as a white ring adjacent to a dot of similar size (the centrilobular arteriole). Usually, the bronchiole is invisible under normal conditions. Compare always suspected areas with others that look normal in different lung regions.

Thickened Peribronchovascular Bundle

Increased artery size and bronchial-wall thickening are visible at a more central level. Vessel size and bronchial-wall thickness should be similar in corresponding regions of both lungs.

Subpleural Interstitial Thickening

White enveloping line simulating thickened pleura at the edges of the lung. This sign is often easier to identify at the fissural level, where two layers of subpleural interstitium coexist.

Pleural Effusion

Pleural effusion may be an additional finding in some septal disorders. When it is significant, compressive effects on the adjacent parenchyma may be present.

Subset Smooth

The interstitial compartments are thickened, with smooth profiles. The anatomy of the three interstitial compartments (perilobular, peribronchovascular, and subpleural) is visible without focal abnormalities. Coexisting patches of faint ground-glass opacity (GGO) are possible due to partial alveolar filling.

Diseases Presenting with Septal Pattern, Subset Smooth

Frequent:

- Interstitial hydrostatic pulmonary edema (PE)
- Lymphangitic carcinomatosis (LC)

Rare:

- Erdheim-Chester disease
- Venocclusive disease (VOD)

Subset Nodular

The interstitial compartments are thickened in nodular form (beaded appearance). The nodules are dense, with well-defined margins, embedded as they are inside thickened interlobular septa and interstitial lines. The septal pattern, subset nodular, differs from the nodular pattern, subset lymphatic in which the nodules are more or less individually seen along appropriate routes, which, however, are not thickened.

Diseases Presenting with Septal Pattern, Subset Nodular

Frequent:

- Lymphangitic carcinomatosis (LC)

Rare:

- Diffuse interstitial amyloidosis
- Lymphoid interstitial pneumonia (LIP)

Nodular Pattern

A nodular pattern is defined by the presence of multiple white, roundish, pulmonary opacities ranging in diameter from 2 to 10 mm (Fig. 2). Morphology and lobular distribution of the nodules depend on the route of arrival and the modality of spread.

Key Signs

Low-Density and Ill-Defined Margins (Nodular GGO)

With a snowflake aspect, sometimes tiny and hence difficult to recognize, these nodules may coalesce, resulting in the appearance of more or less extensive patchy GGO. They are commonly seen in patients with diseases primarily affecting small airways and surrounding areas.

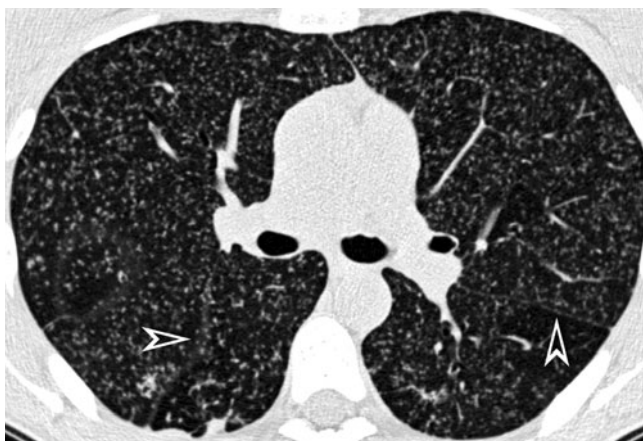


Fig. 2. Nodular pattern: Innumerable tiny nodules are randomly scattered throughout both lungs. Some of them also involve the fissures (arrowheads), however not insistently. A few relatively spared areas with less nodules show reduced vascularization [this was a miliary reactivation of an old tuberculosis (TB)]

High-Density and Well-Defined Margins

Of a solid aspect, like opaque beads, these nodules obscure the edges of vessels or other adjacent structures. Usually from diseases primarily affecting the interstitium, they may coalesce in larger opacities or pseudoplaques. Regular or lobulated contours and even shaggy profiles are possible in diseases with a fibrotic component.

Subset Lymphatic

Nodules avid of pleura and lymphatic routes. These nodules tend to concentrate in patches along the lymphatic routes: pleural boundaries and/or fissures, but also peribronchovascular interstitium as much as along vessels and bronchi. The nodules are more or less individually seen along appropriate routes that, however, are not intrinsically thickened. Purely interstitial, these nodules typically present high density and well-defined margins.

Diseases Presenting with Nodular Pattern, Subset Lymphatic

Frequent:

- Sarcoidosis

Rare:

- Interstitial amyloidosis
- Lymphoid interstitial pneumonia (LIP)
- Silicosis and coal-worker pneumoconiosis

Subset Random

Nodules indifferent to the pleura (at times in contact with the extremities of vascular structures: feeding-vessel sign). Random nodules present a quite homogeneous distribution here and there like sown seeds, also touching the pleural surfaces but without a consistent relationship with them. More frequently of high density and with well-defined margins, in specific conditions, they may show interaction with the surrounding parenchyma (halo sign) and cavitation.

Diseases Presenting with Nodular Pattern, Subset Random

Frequent:

- Hematogenous metastases
- Miliary tuberculosis (TB)

Rare:

- Miliary fungal infection

Subset Centrilobular

Nodules avid of pleura. A centrilobular distribution can be assumed when the nodules, patchily or randomly distributed, stop a certain distance from pleural surfaces and interlobular septa; thin black lines of normal lung are then visible along the latter. The diseases from inhaled substances typically show centrilobular nodules of low density and ill-defined margins. Nodules from focal

accumulation of cells, however, may present well-defined margins.

Diseases Presenting with Nodular Pattern, Subset Centrilobular

Frequent:

- Follicular bronchiolitis
- Respiratory bronchiolitis – interstitial lung disease (RB-ILD)
- Subacute hypersensitivity pneumonitis (HP)

Rare:

- Langerhans cell histiocytosis (LCH)
- Lymphoid interstitial pneumonia (LIP)

Fibrotic Pattern

A fibrotic pattern is present when signs of retraction and remodeling of thoracic structures at the lobular level and/or in larger portions of lung are present (Fig. 3). The final effect is an irregular network of white lines with distortion of the anatomical landmarks. Synonyms: irregular linear pattern; linear pattern with distorted architecture.

Key Signs

Irregular Reticulation (Irregular Linear Opacities)

These criss-crossing, not uniform, wavering white lines appear as if they were traced by an unsteady hand on the lung background.

Interlobular and Intralobular Reticulation

It could be imagined that one or more of these lines represent remnants of interlobular septa, but the visibility of

the latter is not the rule. On the contrary, the distortion due to fibrosis tends to reduce recognition of the lobular architecture. Small lines criss-crossing spaces of lobular size are called intralobular.

Traction Bronchiectasis and Bronchiolectasis

The bronchi are irregularly ectatic with thickened walls and winding or corkscrew appearance. In the periphery of the lung, the bronchioles may also be ectatic (therefore visible) with a same appearance (bronchiolectasis).

Parenchymal Bands

Long lines often connecting thickened septa. These lines marginate several lobules, but they may also represent focal scarring or linear atelectasis.

Fibrotic GGO

Usually inhomogeneous, this appears as a hazy opacification of the lung together with other signs of fibrosis. Traction bronchiolectasis and superimposing irregular reticulation are the discriminant features with a pure alveolar GGO.

Honeycombing and Microscopic Honeycombing

Small hyperlucent areas of variable size (from 2 mm to 1 cm) and shape, separated by well-defined thick walls crowded in an area where the lung architecture is lost. Honeycombing should be distinguished (not easy and not always possible) from roundish or elongated transparencies corresponding to ectatic bronchioles (microscopic honeycombing).

Interface Signs

Vessels enlarged with hairy margins and shaggy pleural lines connected with parenchymal linear irregularities. A secondary traction thickening of the extrapleural/mediastinal fat may be also obvious.

Signs of Volume Loss

Angulation and displacement of fissures, crowding of vessels and bronchi, mediastinal and diaphragmatic attraction toward the more affected lung. They are more evident in cases of advanced fibrosis when one or more lobes and even the entire lung are reduced in size.

Subset Usual Interstitial Pneumonia

Patchy areas of irregular reticulation and gross honeycombing with prominent signs of architectural distortion. Signs of retraction and remodeling of vessels, fissures, lobes, and pulmonary boundaries are common, especially in advanced cases. Bronchiectasis and microscopic

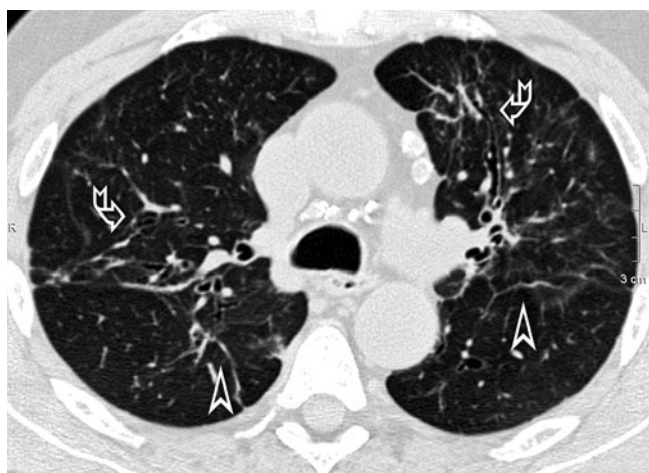


Fig. 3. Fibrotic pattern: There is evidence of an architectural reshaping of lung structures. In particular, there are winding and irregular interstitial lines (arrowheads) and evidence of ectatic bronchi with wall irregularities (curved arrows). These signs bear witness to a disease causing retraction and remodeling of pulmonary structures

honeycombing in connection with the pathologic areas are also characteristic. Some GGO is possible but less extensive than reticulation.

Diseases Presenting with Fibrotic Pattern, Subset UIP

Frequent:

- Idiopathic UIP [clinical idiopathic pulmonary fibrosis (IPF)]
- Collagen vascular diseases (CVD)
- Chronic hypersensitivity pneumonitis (HP)

Rare:

- Asbestosis
- Chronic drug toxicity
- Accelerated UIP and HP

Subset Nonspecific Interstitial Pneumonia

Quite homogeneous areas of GGO with or without irregular reticulation and traction bronchiectasis. The percentage of each component depends on proportions of inflammation and fibrosis. Attempts have been made to identify definite subgroups upon the extent of reticulation and traction bronchiectasis.

Diseases Presenting with Fibrotic Pattern, Subset NSIP

Frequent:

- Idiopathic fibrotic NSIP
- Collagen vascular diseases (CVD)
- Chronic drug toxicity

Rare:

- Acute exacerbation of NSIP.

Subset Tug-Of-War (TOW)

Irregular linear opacities stretching between the mediastinum and the thoracic boundaries. These lines bridge over variably involved bronchi, fissures and, more in general, anatomical structures and even pathological elements found on their way. The mediastinal profiles are variably stretched outward and the thoracic pleural profiles inward, hence the proposal for the name of this subset.

Diseases Presenting with Fibrotic Pattern, Subset Tug-Of-War

Frequent:

- Sarcoidosis

Rare:

- Berylliosis

Subset Bronchocentric

Traction and remodeling prevailing at the bronchial level. The extension of the fibrotic process varies from focal, concentrated on the bronchioli, to diffuse, along bronchiolar and bronchial sheaths. The direct evidence of the process depends upon its extent. When tiny, it is not

evident in itself, only indirectly from the effects on ventilation due to bronchial narrowing.

Diseases Presenting with Fibrotic Pattern, Subset Bronchocentric

Frequent:

- Constrictive bronchiolitis (CB)
- Langerhans cell histiocytosis (LCH)

Rare:

- Airway-centered interstitial fibrosis (ACIF)

Alveolar Pattern

An alveolar pattern is defined by the existence of more or less broad portions of lung more opaque than normal due to partial or complete alveolar filling (Fig. 4). With a few exceptions, the pulmonary architecture is overall preserved, and if signs of interstitial involvement are present, they are not prevalent.

Key Signs

Ground-Glass Opacity

Hazy increase of lung attenuation with preservation of bronchial and vascular margins. GGO may be caused by partial filling of airspaces, interstitial thickening, partial collapse of alveoli, increased capillary blood volume, or a combination of these – the common factor being the partial displacement of air.

Consolidation with or without Air Bronchogram

Intense increase in pulmonary attenuation that obscures the margins of vessels and airway walls. If air persists in

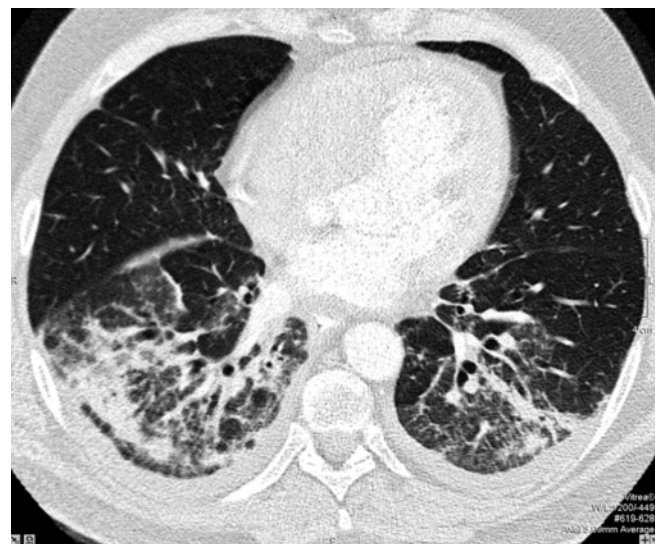


Fig. 4. Alveolar pattern: A mixed-densities mixture of ground-glass opacity and consolidation

lumen of the bronchi, lumen remains visible inside the opacity (air bronchogram). Consolidation is due to a complete filling of alveoli by any material (exudate, cells, or other disease product cause a similar radiological aspect), the common factor being the full displacement of air from alveoli.

Mixed Densities

GGO and consolidation may coexist in the same patient, creating an aspect of mixed densities. Opacities may also be intermingled with other evidence of alveoli and small airways involvement, as follows:

- *Crazy paving*: Smooth, fairly regular, network of white lines superimposed on a background of GGO, resembling shaped paving stones. These lines may represent thickened lobular interstitium but also purely alveolar material within the airspaces, bordering acini or secondary lobules.
- *Halo sign*: Central area of consolidation surrounded by a halo of GGO attenuation. This sign suggests that a disease might be pathologically active, with hemorrhage, inflammation, or tumor spread at its periphery.
- *Reversed halo sign*: Ring or crescent of dense consolidation surrounding a core of GGO. This often corresponds to patches of alveolar/septal inflammation and cellular debris surrounded by a rim of denser organizing pneumonia.
- *Perilobular pattern*: Poorly defined band-like opacities with arcade-like or polygonal appearance due to intra-alveolar material bordering the interlobular septa. These opacities have greater thickness and are less sharply defined than true interlobular thickening found in the septal pattern.
- *Tree-in-bud*: Centrilobular, dense-branching, linear structures originating from a single stalk and often ending in nodular form (thus resembling a budding tree) from bronchial pathology. The tree reflects the existence of luminal dilatation, bronchiolar wall thickening, and impaction; the buds are micronodular opacities due to concomitant filling of nearby alveoli or to infiltration of the centrilobular interstitium. Rarely, a tree-in-bud aspect may represent an intravascular pulmonary tumor embolism.

Subset Acute

Onset of respiratory symptoms dating back from days to a few weeks from the time of the diagnosis. Opacities are more often bilateral and diffuse, and they may change in appearance quite rapidly. With the exception of an underlying fibrotic disease being present, signs of distortion or remodeling of the pulmonary structures are not evident, at least in the early phases of disease. The opacities may appear with or without signs of small airways involvement. Signs of bronchial-wall involvement and peribronchial consolidation, poorly defined air-space nodules of acinar aspect, and lobular hyperinflation may coexist

and are peculiar signs of airborne diseases. The lobular hyperinflation is a consequence of reduced caliber of the bronchiolar lumen.

Diseases Presenting with Alveolar Pattern, Subset Acute

Frequent:

- Acute respiratory distress syndrome (ARDS)
- Acute drug toxicity
- Hydrostatic pulmonary edema (PE)
- Infectious diseases

Rare:

- Acceleration of fibrosing diseases
- Acute eosinophilic pneumonia (AEP)
- Acute interstitial pneumonia (AIP)
- Diffuse alveolar hemorrhage (DAH)

Subset Chronic

Onset of respiratory symptoms dating back from months to years from the time of diagnosis. Lesions may be bilateral but may also be unilateral. With a few exceptions, they tend to clear up slowly over time (unless they worsen and proceed toward fibrosis). Often arranged in patches of conspicuous size, they entertain tight relationships with the large airways, but participation of the small airways in the lobular area is also possible. Radiologically prevalent aspects are: (1) pure GGO, (2) mixed densities, (3) crazy paving, (4) tree-in-bud. The variety of chronic lung disorders may produce more multifaceted aspects than the acute forms. When present, they may be useful for narrowing the diagnostic choices.

Diseases Presenting with Alveolar Pattern, Subset Chronic

Frequent:

- Bronchioloalveolar carcinoma (BAC)
- Chronic eosinophilic pneumonia (CEP)
- Chronic drug toxicity
- Infectious and inflammatory diseases
- Organizing pneumonia (OP)
- Subacute hypersensitivity pneumonitis (HP)

Rare:

- Idiopathic cellular NSIP
- Collagen vascular diseases (CVD)
- Desquamative interstitial pneumonia (DIP)
- Lipoid pneumonia
- Mucosa-associated lymphoid tissue (MALT) lymphoma
- Pulmonary alveolar proteinosis (PAP)
- Respiratory bronchiolitis-interstitial lung disease (RB-ILD)

Dark Lung Pattern

A dark lung pattern is present when variable portions of pulmonary parenchyma show reduced attenuation to the X-rays and then are darker than normal (Fig. 5). Unlike

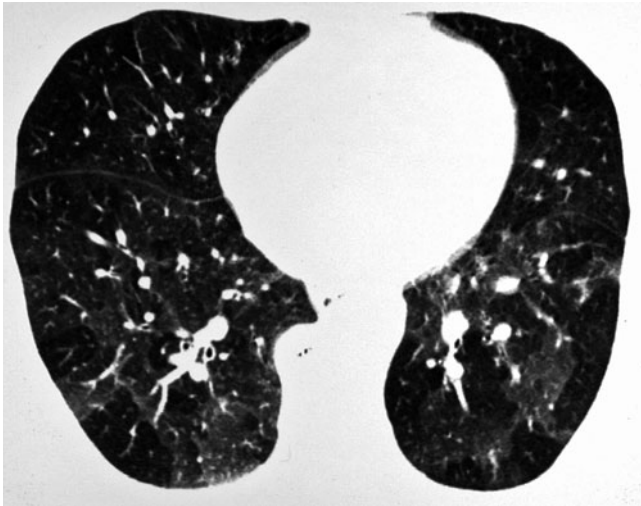


Fig. 5. Dark lung pattern: Extensive dark lung in the middle lobe and lingula, and patchy areas posteriorly. In the dark areas, there is a simplified vascularization; elsewhere, the vessels are normal or enlarged

the cystic pattern, the basic abnormality is not pure black but, rather, a dark grey. Vessels and bronchi are usually recognizable within the darkness. Synonyms: diffuse lucencies pattern; mosaic pattern.

Key Signs

Dark Areas, Patchy or Diffuse

The dark lung appears more black than normal and is associated with a simplification of the vascular tree. When patchy, the aspect is also called mosaic perfusion, either of vascular (vascular mosaic) or bronchial (bronchial mosaic) origin.

Vessels of Reduced Size and Number

The companion vessels in the unaffected regions, by contrast, may be enlarged. When the mosaic is produced, instead, by patchy areas of GGO, vessel size and number within different areas should be equal. Inside the areas of decreased attenuation, the vessels show no distortion.

With or without Expiratory Air Trapping

Expiratory air trapping may coexist presenting as homogeneous increase in density everywhere in the vascular mosaic, not in the dark areas in the bronchial mosaic. The differentiation between vascular or bronchial origin of a dark lung is achieved by repeating a number of CT expiratory scans.

Variable Extent of Dark Areas

From lobular size to an entire lung, depending on type and severity of the disease. In bronchial mosaic, hyperlucent

areas of lobular size with well-defined margins are common. In vascular mosaic, the areas of low attenuation are often larger and ill defined.

Signs of Bronchial Involvement

Some patients with dark lung from bronchial diseases show smooth thickening of bronchial walls and, occasionally, central and peripheral cylindrical or cystic bronchiectasis. Rarely, centrilobular branching linear densities and centrilobular nodules may also occur.

Diseases Presenting with Dark Lung Pattern

Frequent:

- Chronic pulmonary thromboembolism
- Constrictive bronchiolitis (bronchiolitis obliterans)

Rare:

- Diffuse interstitial pulmonary neuroendocrine cell hyperplasia (DIPNECH; Aguayo-Miller syndrome)
- Panlobular Emphysema
- Swyer-James syndrome

Cystic Pattern

A cystic pattern is present when multiple roundish, well-defined, air-containing spaces (black holes) are variably scattered throughout the pulmonary parenchyma (Fig. 6). These holes in the lung may be due to dilatation of bronchial structures, abnormal distension of alveolar spaces, focal destruction of lung parenchyma, or even cavitation of solid lesions. Synonyms: focal lucencies pattern; black holes pattern.

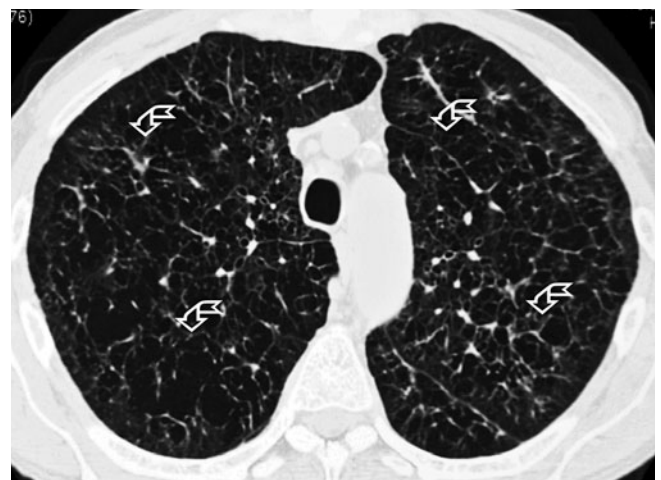


Fig. 6. Cystic pattern: Multiple black holes of various sizes extensively occupy quite haphazardly both lung fields. Several cystic spaces look like enlarged and coalesced lobular structures (curved arrows) containing lobular remnants. Some residual, relatively normal, lung is squeezed peripherally in the subpleural regions (this patient was a heavy smoker, with advanced centrilobular emphysema and possibly Langerhans cell histiocytosis)

Key Signs

With or Without Walls

White encircling rim of a thickness depending on the constituent elements (cells, fibrosis, etc.) and phase of disease may be present. Cysts without walls are usually the result of local destruction of lung parenchyma. Honeycombing is a cystic manifestation of advanced fibrotic conditions: small hyperlucent areas of variable size (from 2 mm to 1 cm) and shape separated by well-defined, thick walls.

Shape

Regular (usually secondary to check-valve mechanisms in the context of a normal parenchyma) or irregular (often due to fusion of several lesions and/or fibrotic phenomena). The shape of the cysts depends on the mechanism of their formation, the relationship with each other, and the concomitance of traction phenomena in the surrounding parenchyma.

Content

Cyst content should be black, because – by definition – it is pure air; however, when the cysts are due to destruction or necrosis of lung parenchyma, some opaque remnant may persist within the blackness. As a result, some cystic spaces may contain a small nodular opacity representing the centrilobular artery, and others may contain solid material due to their neoplastic nature or to a fungus ball. When infected, the lesions may contain air-fluid levels.

Distribution

Variable with the underlying disease, regional distribution is often useful in diagnosis. Multiplanar reconstructions (MPR) are particularly useful for providing a comprehensive assessment of the regional distribution of the cysts and minimum intensity projection (minIP) reformattening for quantifying them.

Diseases Presenting with Cystic Pattern

Frequent:

- Centrilobular emphysema
- Langerhans cell histiocytosis (LCH)
- Advanced CVD and drug toxicity (honeycombing)
- Advanced chronic HP (honeycombing)
- Advanced idiopathic UIP (clinical IPF) (honeycombing)

Rare:

- Asbestosis (honeycombing)
- Birt-Hogg-Dube (BHD) syndrome
- Cystic metastases
- Laryngotracheobronchial papillomatosis
- Lymphangioleiomyomatosis (LAM)
- Lymphoid interstitial pneumonia (LIP)
- Pneumocystis jirovecii pneumonia (inside GGO)

Suggested Reading

- American Thoracic Society; European Respiratory Society (2002) American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. *Am J Respir Crit Care Med* 165:277-304
- Beigelman-Aubry C, Hill C, Guibal A et al (2005) Multi-detector row CT and postprocessing techniques in the assessment of diffuse lung disease. *Radiographics* 25:1639-1652
- Chung MH, Edinburgh KJ, Webb EM et al (2001) Mixed infiltrative and obstructive disease on high-resolution CT: differential diagnosis and functional correlates in a consecutive series. *J Thorac Imaging* 16:69-75
- Churg A, Müller NL (2006) Cellular vs fibrosing interstitial pneumonias and prognosis: a practical classification of the idiopathic interstitial pneumonias and pathologically/radiologically similar conditions. *Chest* 130:1566-1570
- Collins J (2001) CT signs and patterns of lung disease. *Radiol Clin North Am* 39:1115-1135
- Flaherty KR, King TE Jr, Raghu G et al (2004) Idiopathic interstitial pneumonia: what is the effect of a multidisciplinary approach to diagnosis? *Am J Respir Crit Care Med* 170:904-910
- Gotway MB, Reddy GP, Webb WR et al (2005) High-resolution CT of the lung: patterns of disease and differential diagnoses. *Radiol Clin N Am* 43:513-542
- Hansell DM, Bankier AA, MacMahon H et al (2008) Fleischner Society: glossary of terms for thoracic imaging. *Radiology* 246:697-722
- Kim EA, Lee KS, Johkoh T et al (2002) Interstitial lung diseases associated with collagen vascular diseases: radiologic and histopathologic findings. *Radiographics* 22:S151-S165
- Koyama M, Johkoh T, Honda O et al (2003) Chronic cystic lung disease: diagnostic accuracy of high-resolution CT in 92 patients. *AJR Am J Roentgenol* 180:827-835
- Lee CH (2007) The crazy-paving sign. *Radiology* 243:905-906
- Lee KH, Lee JS, Lynch DA et al (2002) The radiologic differential diagnosis of diffuse lung diseases characterized by multiple cysts or cavities. *J Comput Assist Tomogr* 26:5-12
- Lynch DA (2008) Imaging of small airways disease and chronic obstructive pulmonary disease. *Clin Chest Med* 29:165-179
- Maffessanti M, Dalpiaz G (2006) Diffuse lung diseases: clinical features, pathology, HRCT. Springer-Verlag Italia, Milano
- Maffessanti M, Dalpiaz G (2011) Computed tomography of diffuse lung diseases and solitary pulmonary nodules. In: Leslie KO, Wick MR (eds) Practical pulmonary pathology. A diagnostic approach, 2nd edn. Churchill Livingstone (Elsevier), Philadelphia, PA (in press)
- Mueller-Mang C, Grosse C, Schmid K et al (2007) What every radiologist should know about idiopathic interstitial pneumonias. *Radiographics* 27:595-615
- Naidich DP, Müller NL, Krinsky GA et al (2007) Computed tomography and magnetic resonance of the thorax, 4th edn. Lippincott Williams & Wilkins, Philadelphia, PA
- Parrón M, Torres I, Pardo M et al (2008) The halo sign in computed tomography images: differential diagnosis and correlation with pathology findings. *Arch Bronconeumol* 44:386-392
- Pipavath SN, Stern EJ (2009) Imaging of small airway disease (SAD). *Radiol Clin North Am* 47:307-316
- Raoof S, Amchentsv A, Vlahos I et al (2006) Pictorial essay: multinodular disease: a high-resolution CT scan diagnostic algorithm. *Chest* 129:805-815
- Remy-Jardin M, Giraud F, Remy J et al (1993) Importance of ground-glass attenuation in chronic diffuse infiltrative lung disease: pathologic-CT correlation. *Radiology* 189(3):693-698

- Rice A, Nicholson AG (2009) The pathologist's approach to small airways disease. *Histopathology* 54:117-133
- Rossi SE, Erasmus JJ, Volpacchio Met al (2003) Crazy-paving pattern at thin-section CT of the lungs: radiologic-pathologic overview. *Radiographics* 23:1509-1519
- Rossi SE, Franquet T, Volpacchio M et al (2005) Tree-in-bud pattern at thin-section CT of the lungs: radiologic-pathologic overview. *Radiographics* 25:789-801
- Schoepf UJ (2006) Multidetector-row CT of the thorax. Springer-Verlag, Berlin Heidelberg
- Schwarz MI, King TEJ (eds) (1998) *Interstitial lung disease*, 3rd edn. BC Decker, Hamilton
- Silva CI, Müller NL (2009) Idiopathic interstitial pneumonias. *J Thorac Imaging* 24(4):260-273
- Stern EJ, Müller NL, Swensen SJ, Hartman TE (1995) CT mosaic pattern of lung attenuation: etiologies and terminology. *J Thorac Imaging* 10:294-297
- Webb WR (2006) Thin-section CT of the secondary pulmonary lobule: anatomy and the image – the 2004 Fleischner lecture. *Radiology* 239:322-338
- Webb WR, Müller NL, Naidich DP (2007) *High-resolution CT of the Lung*, 4th edn. Wolters Kluwer Health/Lippincott Williams & Wilkins, Philadelphia, PA

A Systematic Approach to Chest X-Ray Analysis, I

Jeffrey S. Klein

Department of Radiology, University of Vermont College of Medicine, Burlington, VT, USA

Introduction

This seminar will review the approach to commonly encountered chest radiographic (CR) abnormalities, with a focus on an approach to differential diagnosis and the use of ancillary imaging studies for specific characterisation of radiographic findings.

Artefacts on Chest Radiography

A number of artefacts can produce opacities on CR that need to be recognised, as they can simulate disease and lead to unnecessary clinical and radiographic evaluation. The advent of computed radiography has significantly reduced the incidence of artefacts related to under- or over-exposure of CR, but there remain a number of exposure, grid, plate and processing artefacts that can simulate or obscure disease [1]. In addition to technical artefacts seen in CR and direct radiography (DR) systems, overlying materials can produce opacities that simulate disease. These include monitoring and life-support devices, trauma boards and patient-related artefacts, including hair braids.

Parenchymal Lung Disease

Diseases Associated with Increased Lung Density

Interstitial Lung Disease

The radiographic detection of diffuse interstitial lung disease can be difficult, as the findings can be subtle despite the presence of symptoms. The earliest findings of interstitial disease are loss of vascular sharpness and increased lung density. The most common classification method for interstitial abnormalities is to divide changes into reticular, nodular and linear. Reticular lung disease is usually further subclassified as fine, medium or coarse, depending upon the size of the visible intervening lucencies. Fine reticular interstitial disease is also termed ground-glass opacity and generally reflects a process that results in incomplete alveolar filling or lining, and there-

Table 1. Ancillary findings in patients with interstitial lung disease (ILD) and the differential considerations

Finding(s)	Disease
Hilar lymph node enlargement	Sarcoidosis, lymphangitic carcinomatosis, viral pneumonia
Clavicular/bony erosions	Rheumatoid associated UIP
Pleural effusions	Infection, edema
Pleural plaques	Asbestosis
Hyperinflation	LCH, stage IV sarcoidosis, LAM/TS, emphysema with UIP
Oesophageal dilatation	Scleroderma associated UIP, recurrent aspiration
Conglomerate masses	Silicosis, sarcoidosis, talcosis
Basilar sparing	LCH, sarcoidosis
Basilar predominance	UIP, aspiration

UIP, usual interstitial pneumonia; LCH, Langerhans cell histiocytosis; LAM, lymphangioleiomyomatosis; TS, tuberous sclerosis

fore can reflect either interstitial or alveolar disease processes. As there are innumerable processes that can produce diffuse interstitial opacities, the differential diagnosis depends primarily on associated clinical and ancillary radiographic findings, as well as more specific characterisation of findings as seen on high-resolution computed tomography (CT) scan. In patients with acute interstitial abnormalities, the differential diagnosis is brief and primarily includes cardiac and infectious conditions. Table 1 lists the radiographic findings that when identified in association with interstitial opacities help limit the differential considerations [2].

Air-Space Disease

The findings of air-space disease are opacities that tend to obscure the underlying parenchyma, are often ill-defined and that tend to coalesce over time, and can produce lobar or segmental opacification with air bronchograms that de-silhouettes adjacent mediastinal structures and the diaphragms [3]. The approach to air-space disease is best considered by determining the distribution of opacities, as the finding is very nonspecific and simply

Table 2. Differential diagnosis of air-space disease

Finding(s)	Disease
Focal/segmental air-space opacification (ASO)	Pneumonia, contusion, infarct, lung cancer (BAC)
Lobar disease	Pneumonia, endogenous lipoid pneumonia, BAC
Patchy ASO	Infection, COP, BAC, metastases, emboli
Diffuse ASO	Oedema, haemorrhage, pneumonia
Perihilar ASO	Oedema, haemorrhage
Peripheral ASO	Eosinophilic pneumonia, ARDS, contusion
Rapidly changing/resolving ASO	Oedema, eosinophilic pneumonia, haemorrhage

BAC, bronchioloalveolar carcinoma; *COP*, cryptogenic organizing pneumonia; *ARDS*, acute respiratory distress syndrome

reflects the presence of material (blood, oedema fluid, inflammatory cells, tumor cells or proteinaceous material) within the alveoli. The differential diagnosis of air-space disease is shown in Table 2.

Solitary Pulmonary Nodule

The primary goal of the radiologist when identifying a focal opacity on CR is to determine whether the finding truly reflects a single pulmonary nodule (SPN). Identifying the opacity on orthogonal radiographic projections and methods of excluding abnormalities that may produce a nodular opacity on a single radiographic view, such as nipple shadows, skin lesions and bone islands or healing rib fractures, are excluded by comparison with prior CR and, when necessary, additional radiographic views and techniques, such as films with nipple markers, oblique or apical lordotic projections, dual-energy radiography, and – again, when necessary – chest fluoroscopy. Once a new or enlarging SPN has been identified, thin-section CT will almost invariably be necessary for further evaluation. For lesions that are not clearly benign based on density, morphology or absence of growth from prior radiologic studies, positron emission tomography (PET)-CT has high sensitivity and moderate specificity for SPN characterisation. CT nodule enhancement with iodinated contrast material can prove useful, particularly for lesions such as carcinoid tumors, that tend to have low metabolic activity and can therefore show false negative results on fluorodeoxyglucose (FDG)-PET. Definitive diagnosis with

Table 3. Differential diagnosis of the solitary pulmonary nodule

Granuloma
Bronchogenic carcinoma (adenocarcinoma most common)
Hamartoma
Solitary metastasis
Focal organizing pneumonia
Hematoma

image-guided biopsy or resection may be necessary for lesions that remain suspicious for malignancy [4]. The differential diagnosis of an SPN is shown in Table 3.

Mediastinal Mass

Mediastinal masses present either as asymptomatic masses (e.g. bronchogenic cyst) as a result of compression or invasion of adjacent mediastinal structures (intrathoracic thyroid goitre), or during investigation for possible malignancy (e.g. thymoma in patient with myasthenia gravis). Radiographically, a mediastinal mass is characterised by sharp demargination with obtuse borders with the adjacent lung and an incomplete border sign where it arises from the mediastinum. Whereas precise localisation in the past guided the specific imaging evaluation, presently, virtually all mediastinal abnormalities will undergo multidetector CT (MDCT) evaluation for localisation and characterisation of the mass [5, 6]. Common causes of mediastinal masses based upon the primary site of origin are detailed in Table 4.

Hilar Enlargement

Hilar disease, which may represent a number of conditions (Table 5), may be seen radiographically as increased hilar density, as a lobulated and enlarged hilar shadow or as a discrete hilar mass. CT with contrast enhancement will be necessary for further evaluation of suspected hilar disease.

Cardiac and Pericardial Disease

Although echocardiography has become the primary technique for evaluating cardiac and pericardial disease, CR

Table 4. Differential diagnosis of mediastinal masses

Superior	Anterior	Middle	Posterior
Thyroid goitre	Lymphoma	Bronchogenic carcinoma	Schwannoma
Lymphangioma	Thymic neoplasm	Lymph node enlargement/mass	Ganglion cell tumor
Lymphadenopathy	Germ cell neoplasm	Foregut cyst	Hiatal hernia
Parathyroid adenoma			Aortic aneurysm

Table 5. Etiologies of an enlarged hilum or hila

Unilateral	Bilateral
Bronchogenic carcinoma	Sarcoidosis
Infection (granulomatous)	Metastatic lymphadenopathy
Metastatic lymphadenopathy	Pulmonary hypertension
Bronchogenic cyst	Lymphoma
Valvular pulmonic stenosis (left)	Infection (granulomatous)

Table 6. Causes of an enlarged cardiomediastinal silhouette

Cardiomegaly
Pericardial effusion
Thymic enlargement (i.e. hyperplasia, thymolipoma)

can provide important information regarding the presence of cardiac or pericardial processes, which can present with symptoms that overlap with lung disease, including dyspnea and chest pain. CR findings of cardiac disease are primarily cardiac enlargement or an abnormal cardiac contour. Pericardial disease may manifest as an enlarged cardiomediastinal silhouette, pericardial calcification or a positive stripe sign, indicating the presence of pericardial effusion as seen on lateral CR. The causes of an enlarged cardiomediastinal silhouette are listed in Table 6.

Pleural Disease

Pleural disease may take one of several forms radiographically: pleural mass, focal or diffuse smooth or nodular thickening or calcification, or pneumothorax. Diffuse or lobulated pleural thickening usually reflects either as a multiloculated pleural fluid collection or primary or metastatic pleural malignancy, such as mesothelioma or metastatic adenocarcinoma. CT and sonography are useful in evaluating the characteristics of diffuse pleural thickening and distinguishing fibrosis from fluid or solid tumor [7]. The characteristics of a pleural mass are similar to those of a mediastinal mass: a sharply marginated peripheral opacity with obtuse margins and an incomplete border. The common etiologies of a pleural mass are listed in Table 7. The appearance of pleural air depends upon the amount of pleural air, patient position (i.e. upright vs supine) and the presence or absence of pleural adhesions.

Table 7. Differential diagnosis of a pleural mass

Loculated pleural effusion (pseudotumor)
Lipoma
Localized fibrous tumor of pleura
Metastatic lesion

Table 8. Common causes of a chest wall mass involving rib

Metastasis
Myeloma
Fibrous dysplasia
Eosinophilic granuloma
Enchondroma
Abscess
Chondrosarcoma

Chest-Wall Disease

Chest-wall lesions are recognised radiographically when they protrude from the skin surface and are thus outlined by air, or when associated with rib, vertebral, sternal, clavicular or scapular involvement. Most such patients present with chest-wall pain. Common causes of chest-wall masses with rib involvement are listed in Table 8 [8].

References

1. Cesar LJ, Schueler BA, Zink FE et al (2001) Artefacts found in computed radiography. *Br J Radiol* 74:195-202
2. Klein JS (2006) Diffuse lung disease. In: Brant and Helms (eds) *Fundamentals of diagnostic radiology*, 3rd edn. Lippincott Williams & Wilkins, Philadelphia, PA
3. Burgener FA (2008) Alveolar infiltrates and atelectasis. In: Burgener FA, Korman M, Pudas T (eds). *Differential diagnosis in conventional radiology*, 3rd edn. Thieme, New York, NY, pp 489-512
4. Klein JS, Braff S (2008) Imaging evaluation of the solitary pulmonary nodule. *Clin Chest Med* 29:15-38
5. Strollo DC, Rosado-de-Christenson ML, Jett JR (1997) Primary mediastinal tumors. Part I: Tumors of the anterior mediastinum. *Chest* 112:511-522
6. Strollo DC, Rosado-de-Christenson ML, Jett JR (1997) Primary mediastinal tumors: Part II. Tumors of the middle and posterior mediastinum. *Chest* 112:1344-1357
7. Helm EJ, Matin TN, Gleeson FV (2010) Imaging of the pleura. *J Magn Reson Imaging* 32:1275-1286
8. Jeung M-Y, Gangi A, Gasser B et al (1999) Imaging of chest wall disorders. *RadioGraphics* 19:617-637

A Systematic Approach to Chest X-Ray Analysis, II

Katerina Malagari

University of Athens, Athens, Greece

Introduction

The vast literature on techniques of X-ray interpretation confirms the difficulty of the subject, which comprises perception and interpretation of an abnormality. The pattern approach has many critics, and indeed, not all diagnostic problems can be solved with this approach simply because some findings may not be feasible to include within a specific pattern only. In this workshop, tips and tricks to increase diagnostic yield of chest X-rays are discussed.

Chest-Wall and Pleural Lesions

Chest-wall and pleural lesions most times display characteristics of extrathoracic extrapulmonary lesions, notably, well-defined margins, tapered borders when seen on edge and an incomplete border sign. The well-defined borders are formed by the interface of pleura with aerated lung, which may be compressed by the space-occupying effects of the lesion. When these borders are irregular and shaggy, it is an indication that the lung next to the lesion in question is either involved in the primary process (e.g. neoplastic or inflammatory) or that it is a primary pulmonary disease involving the subpleural structures also, namely, pleura and/or chest wall. The tapered borders are not seen when the lesion is seen en face. In the latter situation, an incomplete border sign may suggest the extrapulmonary nature of the abnormality.

Chest Wall

A definite sign suggesting that a lesion is, indeed, of the chest wall is bone destruction. This key observation suggests that the lesion is either a neoplastic or an inflammatory process. Actinomycosis is one of the aggressive granulomatous infections that involve chest wall, pleura and lung. Neoplastic diseases that cause bone destruction include metastasis, multiple myeloma, Ewing's tumour or metastatic neuroblastoma. Bone indentation may be caused by neurinomas and schwannomas.

Pleural Opacities

Pleural opacities present tapered borders when seen tangentially but otherwise have irregular shapes. Multiple pleural densities may represent loculated pleural effusions, metastatic disease (usually adenocarcinomas), primary pleural tumours (mesothelioma) or malignant thymoma with a lepidic growth pattern of pleural plaques. Pleural effusions have a very long differential diagnosis. It is important to perceive the abnormality and evaluate whether it is bilateral or unilateral and whether there is concomitant pericardial effusion. For this purpose, in addition to the X-ray evidence, an ultrasound of the costophrenic spaces and pericardium is vital in order to access whether there is an underlying systematic disease. Correlation with clinical history and the presence of cardiac enlargement, coexisting lung consolidation or hilar enlargement are key to narrowing the diagnostic differential in association with the results of pleural tap.

Diffuse Pleural Thickening

Diffuse pleural thickening is associated with prior infections [empyema, tuberculosis (TB)], neoplastic disease (mesothelioma, lymphoma), prior hemothorax, rheumatoid arthritis and systematic lupus erythematosus and asbestos exposure. Coexistent pleural calcification suggests prior trauma and hemothorax, empyema (particularly TB-associated) and asbestos exposure with pleural plaques, especially if calcification is juxtadiaphragmatic.

Diaphragmatic Elevation

When diaphragmatic evaluation is bilateral, it is usually the result of a shallow breath-hold due to obesity. If the radiograph has been taken at total lung capacity, it indicates inhibited diaphragmatic movement due to thoracic disease (restricting disease with small lung volumes), poor diaphragmatic motility (bilateral phrenic nerve damage) or subdiaphragmatic etiology, namely, ascites.

When the two diaphragms have a significant distance (more than 5 cm), then which one is abnormal must be determined (elevation or low position?). The radiological

search for thoracic etiology of the abnormal positions of the diaphragm includes looking for signs of pleural effusion, atelectasis, hypoplastic lung lobectomy or tumour near the course of the phrenic nerve. Abdominal disease such as subdiaphragmatic inflammatory processes or space-occupying lesions may also be the cause of an elevated hemidiaphragm. Finally, phrenic nerve paralysis, diaphragmatic eventration, diaphragmatic hernias or a hemidiaphragmatic rupture are local causes of diaphragmatic elevation. However, the most common intrathoracic cause of an elevated hemidiaphragm is the presence of subpulmonic pleural effusion, which can be recognised by the acute convexity of the dome of the hemidiaphragm on the right side and increased distance of the stomach fundus on the left side. An ultrasound will reveal the presence of even small amounts of fluid, and when ultrasound is not available, a lateral decubitus will confirm the diagnosis. An Alexander or sniff test with fluoroscopy or ultrasound will confirm abnormal movement of the diaphragm in cases of phrenic nerve paralysis.

Mediastinal Shift

Diagnosing mediastinal shift is obtained by identifying abnormal hemithorax. Loss of volume of one lung is usually associated with other dynamic signs, such as small or irregular position of the ipsilateral hilum. The latter may be the more subtle sign and, in fact, may be associated with a relatively oligemic lung compared with the contralateral side. Loss of volume may be attributed to atelectasis or hypoplastic lung. On the other hand, overexpansion of one hemithorax may be the cause of the mediastinal shift. Overexpansion (not attributed to an obvious space-occupying mass or cyst or a tension pneumothorax) can be associated with a large bulla, congenital lobar emphysema and, rarely, with air trapping. Swyer-James syndrome can be a cause of mediastinal shift if the involved lung is of considerable size or the bronchiolitis occurred during childhood.

Although there is localised air trapping in the involved lung, it is usually not overexpanded because in most cases, the underlying bronchiolitis obliterans occurred when the patient was young. Therefore, locally, the lung locally did not grow. The key observation in addition to air trapping is relative hyperlucency, oligemia and decreased size of the affected lobe or lung. With the advent of computed tomography (CT) these areas may be of segmental size. It must be noted that the complete algorithm for evaluating these types of abnormalities is beyond the scope of this workshop and abstract, and besides CT, bronchoscopy is necessary in these patients to exclude an endobronchial lesion. An unusual cause of a small hemithorax is an extended pleural thickening that prevents normal movement of the chest wall, lung and pleura and is identifiable on chest X-ray. A typical example is pleural thickening postempyema or TB and mesothelioma.

Mediastinum

Tips to increase perception of mediastinal abnormalities on chest radiographs include systematic observation of the aortopulmonary window, azygosophageal recess, retrotracheal area, supraaortic triangle and paraspinal lines. Any convexity of soft-tissue density that may be seen in the aortopulmonic window at the frontal radiograph is abnormal. This area normally contains mediastinal fat, the left pulmonic recess of the pericardium or, in some individuals, lung parenchyma [especially in chronic obstructive pulmonary disease (COPD)]. The ligamentum arteriosum and the recurrent laryngeal nerve normally cross this space. The most common space-occupying lesion in this area is enlarged lymph nodes. The azygosophageal recess is normally relatively hyperlucent to the right side, with a straight or convex interface with the right lung. Convex borders usually represent space-occupying lesions. The retrotracheal area in the lateral view should be relatively translucent. Otherwise, it may indicate a middle mediastinal mass.

Lung Opacities

Widespread airspace opacities with a perihilar distribution may be seen in high-pressure pulmonary oedema, alveolar proteinosis, pulmonary haemorrhage or inhalation of noxious gases. Timing and correlation with clinical information is highly suggestive of the correct diagnosis.

Atelectasis

Depending on the type and anatomical location of the atelectatic lung, increased lung density varies. More constant and characteristic signs of atelectasis are those that indicate volume loss – namely, altered size and position of the hila; displacement of fissures and pulmonary blood vessels. These are most important for recognising an atelectasis, as shift of the mediastinum or hemidiaphragm may be compensated by the overaeration and distension of the remaining aerating lung lobes.

Solitary Nodules

First, it is important to recognise solitary nodules. Perception is a major issue, and it is well known that even nodules larger than 1 cm may be missed, especially if in the parahilar, supraclavicular and retrocardiac areas of the lung. Calcifications within a nodule are only appreciated by CT, which can identify both presence and pattern of calcification, facilitating patient management. In addition, it must be noted that it is by no means justified today to assess nodule growth rate with chest radiographs. Cavitation or air bronchograms within a nodule may be seen on chest X-rays, but CT is absolutely essential for accurate evaluation. CT is also imperative to define whether the patient has one or multiple pulmonary

nodules. Multiple pulmonary nodules maybe malignant, benign (hamartomas, chondromas, papillomatous), infective, granulomatous noninfective, congenital or of miscellaneous origin, including amyloidosis.

Diffuse Parenchymal Disease

Septal-line thickening is identified as Kerley B, C, and A lines, also described as linear pattern. Septal-line thickening when of recent origin is most often attributable to pulmonary oedema and lymphangitis carcinomatosa. Although high-resolution CT (HRCT) can identify septal lines in patients with viral or mycoplasma pneumonia, pulmonary oedema should again be excluded from the diagnosis, even in the febrile patient. Interstitial pulmonary fibrosis and late-stage hemosiderosis may also cause this pattern. Diffuse small nodular opacities (military pattern) may be associated with military TB and non-TB granulomatous infections in the endemic areas. In the nonfebrile patient, a miliary pattern may be due to pneumoconiosis (notably, silicosis, siderosis, berylliosis and coal-workers' pneumoconiosis) or old

viral infections (e.g. varicella pneumonia), Langerhans cell histiocytosis, alveolar microlithiasis and, rarely, metastatic disease.

Suggested Reading

- Armstrong-Reed JC (1988) Chest radiology: patterns and differential diagnosis, 2nd edn. Year Book Medical, Philadelphia, PA
- Cotran RS, Kumar V, Robin FL (1989) Inflammation and repair. In: Pathologic basis of disease, 4th edn. WB Saunders, Philadelphia, PA, pp 39-86
- Feigin DS (1987) Radiology of the chest. In: Jacobs ER (eds) Medical imaging. A concise textbook. Igako Shoin, Tokyo, Chap 6, pp 83-112
- Felson B (1967) The roentgen diagnosis of disseminated pulmonary alveolar diseases. *Semin Roentgenol* 2:3-21
- Felson B (1973) Chest roentgenology. WB Saunders, Philadelphia, PA, pp 314-349
- Fraser RS, Muller NL, Colman N, Pare PD (1990) Fraser's and Pare's diagnosis of diseases of the chest. WB Saunders, Philadelphia, PA
- Heitzman ER (1984) The lung: radiologic-pathologic correlations, 2nd edn. Mosby, St. Louis, MO
- Wilson AG, Dee P, Hansell D (2005) Imaging of diseases of the chest. Mosby, St. Louis, MO

Diseases of the Chest Wall, Pleura, and Diaphragm

Johny A. Verschakelen¹, Peter Vock²

¹ Department of Radiology, University Hospitals Leuven, Leuven, Belgium

² Department of Radiology, University Hospital (Inselspital), Bern, Switzerland

Introduction

The chest wall, the pleura, and the diaphragm represent the outer boundaries of the chest cavity. Each can be affected by specific diseases, but abnormalities may also be related to changes in other structures both within and outside the chest. This chapter reviews the radiological signs of diseases that may involve these three compartments directly or indirectly.

Diseases of the Chest Wall

In contrast to the visceral organs (lung, mediastinum), the normal chest wall is symmetrical, which helps tiny changes overlaying the deeper structures to be detected on a radiograph. Except for skeletal disease, calcification, and emphysema, chest radiography often reveals non-specific signs, whereas sectional methods [ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI)] detect, characterize, and assess disease [1].

Specific Radiographic Patterns of Chest-Wall Disease

Radiographic appearance differs with the location of chest-wall lesions, specifically whether they are in an extrathoracic (exterior to the rib cage) or intrathoracic (extrapulmonary) location.

Extrathoracic Chest-Wall Disease

1. Soft-tissue emphysema: This disease is recognized on radiographs and, by its expansion through loose tissue, demonstrates the continuity between the chest wall, the neck, the mediastinum, and the abdominal wall.
2. Calcifications: Whether they are dystrophic or metastatic, calcifications are similarly well seen on X-ray films.
3. Soft-tissue swelling and tumors: These diseases must first be differentiated from asymmetries due to technical reasons, contralateral surgery (e.g., of the breast), and atrophy, such as seen in hemiplegia or just right/left-handedness; beyond a regionally increased absorption, they may cause specific signs that help

detection and differentiation from intrathoracic disease. Depending on the angle of projection, they often extend beyond the parietal pleura and may even bulge the skin. Medially, they are not limited by the mediastinum but may well continue over the midline. In case of pedunculation, analogous to the breast gland, they have a sharp, inferiorly convex lower but no recognizable upper contour. Smaller lesions, as with the nipples, may produce rounded shadows simulating lung nodules in one projection but usually no longer project into the lung on the orthogonal second view. Chest-wall tumors sometimes involve the skeleton, and bone changes will often be detected more easily with radiography (Fig. 1).

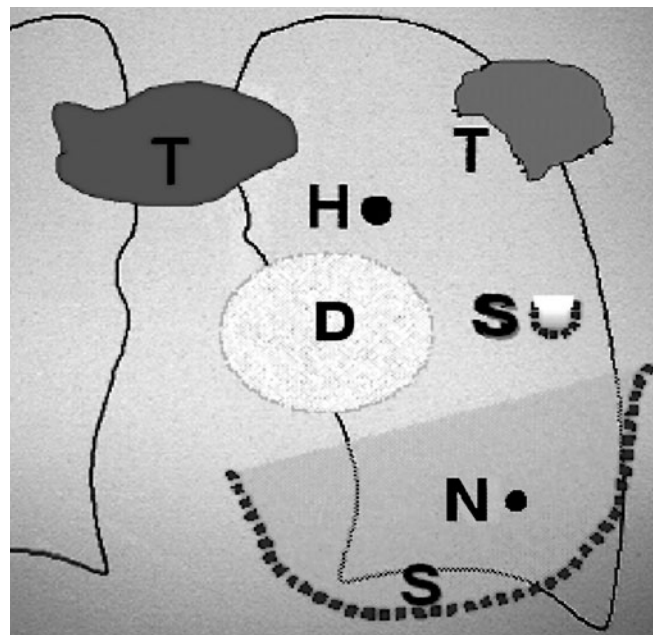


Fig. 1. Extrathoracic soft-tissue lesions. *T* opacities going beyond the parietal pleural border (inner rib contour), often mobile (e.g., skin fold, hematoma, tumor), *D* poorly margined density, *N/H* rounded opacities (often projecting on the lung in one plane) (e.g., nipple/skin tumor), *S* inferiorly rounded, superiorly not marginated, opacity (e.g., female breast, pedunculated skin tumor) (for color reproduction see p 273)

Intrathoracic Extrapulmonary Disease

1. Extrapulmonary lesions: When chest-wall lesions grow into the chest, they behave as extrapulmonary lesions. As with pleural disease, they are usually sharply margined, convex toward the hilum, have no air bronchogram, and form an obtuse angle with the adjacent normal pleura. Any skeletal pathology may also involve the chest wall.
2. Rib erosions: These are a unique and relatively specific sign found at the lower or upper contour. Concave osteolytic defects of 2-4 mm at the lower border are seen with enlarged intercostal collateral arteries but sometimes also with venous collaterals or nerve disease.

Congenital Disease of the Chest Wall

In soft tissues, Poland syndrome corresponds to an absence of the major pectoral muscle that is often accompanied by an absent breast gland and syndactyly, whereas polythelia means multiple nipples along the mammary crest. Lymphangioma and lymphangiohemangioma often extend from the neck to the chest wall and are best analyzed by CT or MRI. Hemolytic anaemia (thalassemia) may induce extramedullary hematopoiesis, causing paravertebral pseudotumors but of course also expansion of the ribs. There exists a large spectrum of anomalies of ribs, sternum (funnel chest, pigeon chest, defects), scapula, clavicle, and spine.

Inflammatory Disease of the Chest Wall

Noninfectious, mostly rheumatic, disorders often involve joints, cartilage, and soft tissues of the chest wall. Tietze syndrome and sternocostoclavicular hyperostosis deserve special mention. Chest-wall infection may arise through the skin (including wounds), extend from the lung and pleura (empyema necessitates) or the abdominal wall, or from hematogenous spread. Radiography – when the lung is not involved – shows the signs typical for extrapulmonary disease, whereas CT or MRI demonstrate the exact multicompartamental location and bone scintigraphy the distribution of inflammatory activity in the entire body. US helps guide diagnostic aspiration and drainage.

Trauma of the Chest Wall

Though not as critical as trauma to the visceral organs, injury to the bones and soft tissues of the chest wall is much more frequent. Chest instability may result both from vertebral fractures and multiple rib fractures (flail chest) and require surgical stabilization. Sternal fracture, diagnosed on lateral projections or CT, is often missed on supine radiographs.

Neoplasms of the Chest Wall

Primary Tumors

Primary tumors of the chest wall may be benign [2] or malignant [3] and arise in the skeleton (all types of chondrogenic neoplasms, angioma, Langerhans' cell histiocytosis, Ewing's and osteosarcoma, plasmocytoma) or the soft tissues (hemangioma, skin tumors, fibrous and neurogenic neoplasms). Radiographs show bony destruction, expansion and calcification and/or just the nonspecific signs of extrapulmonary lesions. CT or MRI localize, differentiate, and stage these neoplasms.

Secondary Tumors

Secondary tumors arise from hematogenous or lymphatic spread (in malignant lymphoma and organ tumors) or from continuous infiltration from the neighborhood, as most often seen in lung cancer and pleural mesothelioma. Again, cross-sectional imaging is required for staging, treatment planning, and follow-up.

Other Diseases of the Chest Wall

These include degenerative and metabolic disorders with sometimes typical manifestations, such as seen in diffuse idiopathic skeletal hyperostosis (DISH) or hyperparathyroidism (ruger jersey spine). Obstructive arterial and venous vascular disease often causes chest-wall collaterals. Iatrogenic disorders mainly include complications after surgery and insertion of central venous catheters or drains but also sequelae after therapeutic irradiation.

Diseases of the Pleura

The chest radiograph is still the most important and widely used means of demonstrating and following the progress of pleural disease, though US, CT, and MRI play a role in a number of specific situations [4, 5]. Grossly, pleural disease is manifest by the accumulation of fluid or air in the pleural space, by pleural thickening (with or without calcification), or by the presence of a pleural mass.

Pleural Effusion

All types of pleural effusion are radiographically identical, though historical, clinical, and other radiological features may help limit diagnostic possibilities. US, CT, and MRI can help specify the diagnosis [4, 5]. The goals of diagnostic imaging are: (1) to detect effusion and differentiation from other pathological pleural processes; (2) to detect underlying pulmonary, cardiac, mediastinal, or abdominal pathology; (3) when possible, to make a specific diagnosis.

A small amount of free fluid may be undetectable on an erect posteroanterior (PA) chest radiograph, as the

fluid tends initially to collect under the lower lobes. Such small subpulmonic effusions can be demonstrated by US or CT [4, 5]. Fluid can also loculate between visceral pleural layers in fissures or between visceral and parietal layers, usually against the chest wall. It is unusual for this to happen without some additional radiographic clue to the presence of pleural disease. Both US and CT can be used to distinguish loculated fluid from solid lesions. In addition, US, and CT in particular, can be used to characterize the morphology of pleural thickening that often accompanies a pleural effusion, distinguishing between malignant (nodular, with focal masses) and benign thickening, which is typically uniform. CT can also identify any underlying lung disease that might have provoked an effusion and it facilitates percutaneous aspiration and biopsy.

Pneumothorax

The diagnosis of pneumothorax is usually made with the chest radiograph, which also detects complications and predisposing conditions and helps in treatment management. Iatrogenic causes apart, the commonest type of pneumothorax in the adult is the so-called primary spontaneous pneumothorax, which is nearly always caused by the rupture of an apical pleural bleb. High-resolution computed tomography (HRCT) can be helpful to detect these abnormal apical airspaces which are not visible on the chest X-ray [6]. A large number of conditions predispose to the development of a secondary pneumothorax. Pneumothorax can be a complication of histiocytosis X, lymphangioleiomyomatosis, chronic obstructive pulmonary disease (COPD) and lung metastasis of an osteogenic sarcoma.

Visualization of a visceral pleural line (usually at the apex on an erect chest film) separated from the chest wall by a transradiant zone devoid of vessels is the typical sign of a pneumothorax. Interpretation can be difficult with avascular lung apices, as in bullous disease and when clothing or dressing artifacts create linear shadows, with tubes, and skin folds. Diagnosis is especially difficult in the supine position, when pleural air rises and collects anteriorly, particularly medially and basally, and may not extend far enough posteriorly to separate the lung from the chest wall at the apex or laterally. Signs that suggest a pneumothorax under these conditions are:

1. ipsilateral transradiancy, either generalized or hypochondrial;
2. a deep, finger-like costophrenic sulcus laterally;
3. a visible anterior costophrenic recess seen as an oblique line or interface in the hypochondrium;
4. a trans-radiant band parallel to the diaphragm and/or mediastinum with undue clarity of the mediastinal border;
5. visualization of the undersurface of the heart, and of the cardiac fat pads as rounded opacities suggesting masses; and
6. diaphragm depression: in case of doubt, a CT can be performed.

Pleural Thickening

Pleural thickening is common and usually represents the organized end stage of various active processes, such as infective and noninfective inflammation (including asbestos exposure and pneumothorax) and hemothorax. When generalized and gross, it is termed a fibrothorax and may cause significant ventilatory impairment. Radiologically, pleural thickening gives fixed shadowing of water density, most commonly located in the dependent parts of the pleural cavity. On US, benign pleural thickening produces a homogeneous echogenic layer just inside the chest wall. It is not reliably detected unless it is 1 cm or thicker. CT, on the other hand, is very sensitive at detecting pleural thickening, which is most easily assessed from the inside of the ribs, where there should normally be no soft-tissue opacity [7]. Pleural calcification is most commonly seen following asbestos exposure, empyema (usually tuberculous), and hemothorax.

Pleural Tumors

Localized tumoral thickening of the pleura can be a mass originating from the pleura itself, such as a fibrous tumor (localized mesothelioma) or a pleural lipoma but is more frequently a pleural metastasis usually from an adenocarcinoma. Plain radiographic findings of a fibrous tumor are a pleural-based, well-demarcated, rounded, and often slightly lobulated mass (2-20 cm in diameter), which may, because of pedunculation, show marked positional variation with changes in posture and respiration. They usually create an obtuse angle with the chest wall and may reach enormous sizes. CT findings are similar to those observed on plain radiography. It is a large, mobile mass, often heterogeneous because of necrosis and hemorrhage, frequently enhancing after contrast administration and rarely calcified. Malignant types are usually >10 cm and may invade the chest wall. Typically, these tumors show low signal intensity on both T1- and T2-weighted images, although tumors with intermediate to high signal intensity have been described [8]. Lipomas are asymptomatic benign tumors that are usually discovered incidentally on chest radiographs as sharply defined pleural masses. Diagnosis is easy with CT because this examination can delineate the pleural origin and the fatty composition. Pleural metastases are very often accompanied with pleural effusion, which can be the only finding on a chest radiograph. CT, MRI, and US are more sensitive at demonstrating pleural metastasis as the cause of the pleural effusion.

Diffuse tumoral thickening of the pleura can be caused by malignant mesothelioma or by pleural metastasis. Both entities are usually indistinguishable with imaging. Diffuse malignant mesothelioma presents on a chest radiograph as an irregular and nodular pleural thickening with or without associated pleural effusion. Tumor extension into the interlobar fissures, accompanying pleural effusion and invasion in the chest wall, are better

appreciated with CT. MRI may be superior to CT in determining disease extent because it allows better evaluation of the relationship of the tumor to the structures of the chest wall, the mediastinum, and the diaphragm [9, 10]. However, in most cases, CT and MRI provide similar information. Sonography may be a supplementary method for biopsy and surgery planning.

Diseases of the Diaphragm

The diaphragm is a thin, flat, musculotendinous structure that separates the thoracic cavity from the abdominal cavity and that, being a respiratory muscle, has an important role in respiration. Radiology of the diaphragm is difficult mainly because there is no imaging technique that can clearly and entirely visualize the diaphragm. On conventional chest film, the diaphragmatic muscle is only visible when air is present above and below it. US, CT, and MRI are the only imaging modalities that can visualize the diaphragm itself, although visualization is usually partial and dependent on the presence of pleural disease when using US and the presence of subdiaphragmatic fat when using CT and MRI [11-13].

Diaphragmatic Hernia

Bochdalek Hernia

Large Bochdalek hernias usually become evident in the neonatal period. Small asymptomatic Bochdalek hernias are sometimes an incidental finding in adults and can cause a smooth focal bulge seen on a lateral chest film centered approximately 4-5 cm anterior to either posterior diaphragmatic insertion. On CT, the diagnosis of Bochdalek hernia can be made when a soft-tissue mass (containing part of the liver, spleen, and even kidney) or – more frequently – a fatty mass is seen abutting the upper surface of the posteromedial aspect of a hemidiaphragm. This mass is in continuity with the subdiaphragmatic structures through a diaphragmatic defect presenting as a discontinuity of the soft-tissue line of the diaphragm.

Morgagni Hernia

The incidence of Morgagni hernia detected in the neonatal period, because of respiratory symptoms, is low. In older children and adults, Morgagni hernia is often an incidental finding, as there are mostly no symptoms. Although the weak area is caused by an embryonal failure of muscularization, the herniation of abdominal content to the thorax can be acquired. Increased intra-abdominal pressure due to severe effort, trauma, or obesity is probably responsible. On chest film, it presents as a varying-sized, rounded density in the right (or rarely left) anterior cardiophrenic angle, eventually containing gas shadows. Herniated liver can be identified on CT, MRI, or US.

Oesophageal Hiatus Hernia

In hiatal hernia, there is herniation of a part or, seldom, of the entire stomach or of another abdominal structure (fat, pancreas, pseudocyst) through the esophagus hiatus. Diagnosis can be made on conventional PA and lateral chest film and can be confirmed by a barium study. Hiatal hernias are often an incidental finding on CT [14].

Traumatic Diaphragmatic Rupture

Blunt trauma and penetrating wounds of the chest are the most frequent causes of traumatic diaphragmatic rupture. As diaphragmatic rupture is often associated with thoracic or abdominal injuries that require surgical treatment, the diagnosis is made during surgery in many cases. If surgery is not indicated, a diaphragmatic tear can be missed, especially when it is small and when there is no herniation of abdominal structures to the chest. As clinical symptoms are often very aspecific, and as missing a diaphragmatic rupture can have severe consequences when strangulation of herniated viscera occurs, special attention has to be given to small changes in the diaphragmatic contour or basal lung translucency when a conventional chest film of a patient with trauma to the lower chest or the pelvis is interpreted. Diagnosis is easier when a gas and fluid shadow is seen in the thorax. However radiological signs are very often aspecific and can be limited to a localized density in close relationship to the diaphragm. Chest film can even be completely normal [15, 16].

Barium studies can be helpful in making the correct diagnosis when an extrinsic narrowing occurs on the border of the stomach or bowel at the point where they pass the diaphragmatic tear. US can be diagnostic if both the diaphragm and the herniated organs can be visualized [17]. However, this technique is limited by the often-minimal visualization of the diaphragm itself, the tenderness over the upper abdomen and the presence of gas in herniated bowel. Multislice CT is superior because of its high image quality. CT signs of diaphragmatic rupture include discontinuity of the diaphragm, with direct visualization of the diaphragmatic injury (absent diaphragm sign) sometimes associated with inward curling of the torn hemidiaphragm (dangling diaphragm sign); herniation of abdominal organs with liver, bowel or stomach in contact with the posterior ribs (dependent viscera sign), thickening of the crus (thick crus sign), constriction of the stomach or bowel (collar sign), mushroom-like mass in the right hemithorax where the herniated liver is constricted by the tear (hump sign), linear lucency across the liver along the torn edges of the hemidiaphragm (band sign), active arterial extravasation of contrast material near the diaphragm, and in case of a penetrating diaphragmatic injury, depiction of a missile or puncturing instrument trajectory [18-20]. When the rupture is missed at the time of the trauma and the patient has recovered from the associated lesions, a latent phase of diaphragmatic rupture can occur. Symptoms and signs are then

caused by recurrent herniation of abdominal structures through the diaphragmatic defect and are again often aspecific. CT and MRI can be helpful in detecting these missed tears [21].

Tumors of the Diaphragm

Tumors of the diaphragm are rare lesions that are often difficult to assess and classify both clinically and roentgenographically. They are usually well defined and may mimic an elevated diaphragm or part of it, a focal eventration, or herniation. Malignant tumors are more frequent than benign tumors and can be primary or – most frequently – secondary. One should think about malignancy when a pleural effusion is accompanying the diaphragmatic change or when the patient has symptoms. CT and MRI can be helpful in providing a specific diagnosis [22]. CT attenuation values can be used to diagnose lipoma or cystic tumors. Visualization of an interrupted diaphragmatic soft-tissue line can be helpful to differentiate herniation of fat from lipoma. Visualization of the peridiaphragmatic area in frontal or sagittal views with spiral and multidetector CT or MRI can also give additional information.

Eventration

Eventration of the diaphragm is defined as an abnormally high or elevated position of one leaf of the intact diaphragm as a result of paralysis, aplasia, or atrophy of varying degrees of muscle fibers. In the area of eventration, the normal diaphragmatic muscle fibers are replaced by a thin layer of connective tissue and a few scattered muscle fibers. Eventration can be congenital, resulting from failure of proper muscularization of part or the entire diaphragmatic leaf. Eventration can also be acquired and is then the result of long-lasting paralysis causing atrophy and scarring of the diaphragmatic muscle. On conventional chest X-ray, partial eventration presents as a semicircular or semioval homogeneous shadow of soft-tissue density arising from the diaphragm that becomes more prominent on deep inspiration. CT, US, and MRI can be helpful to differentiate this entity from pleural, mediastinal and pericardial tumors or cysts. Differentiation with herniation and diaphragmatic paralysis can be difficult [23, 24].

Paralysis of the Diaphragm

The most common cause of unilateral paralysis of the diaphragm is involvement of the phrenic nerve by tumor, but paralysis can be caused by any lesion somewhere on the “respiratory chain” from the brain to the diaphragm (trauma, irradiation, poliomyelitis, cervical-disc degeneration). Sometimes, no cause is found. Fluoroscopy is the initial imaging tool for evaluating diaphragmatic dysfunction. However, in experienced hands, US is also valuable for studying and monitoring diaphragmatic movement [25]. Four signs indicate diaphragmatic paralysis:

1. elevation of the diaphragm above the normal range;
2. diminished, absent, or paradoxical movement on inspiration;
3. mediastinal shift on inspiration;
4. paradoxical movement during sniffing.

All these signs need not be present simultaneously, but paradoxical movement during sniffing is generally considered as the sine qua non of diaphragmatic paralysis. Paralysis of both hemidiaphragms is mostly associated with chronic neuromuscular disease and causes severe clinical disability. It may not be recognized by fluoroscopic examination, for passive descent of the diaphragm may occur with inspiration. Paralysis of the diaphragm can also be focal. The small paralysed area of the diaphragmatic muscle will bulge into the chest when the surrounding normal muscles are contracting. Differential diagnosis with eventration can be difficult or even impossible.

Other Causes of Diaphragmatic Dysfunction and Displacement

Other causes of diaphragmatic dysfunction are diaphragmatic fatigue, hiccups, and diaphragmatic flutter. The role of radiology in the diagnosis and follow-up of these diseases is limited. Local irritation of the diaphragm can also cause diaphragmatic dysfunction (decreased motion or even paralysis). Peridiaphragmatic inflammation or infections, such as lower-lobe pneumonia or subdiaphragmatic abscess, are the most common causes. The diaphragmatic function usually returns after the inflammatory condition resolves. Fluoroscopy and US show decreased movement and often-paradoxical motion. CT and US can be helpful for diagnosing peridiaphragmatic disease.

Mechanical forces can also be responsible for diaphragmatic displacement. The diaphragm can be pushed upward by abdominal structures, i.e., when abdominal pressure on the diaphragm increases. This is seen, for example, in supine body position, in obese patients, during pregnancy, and in the event of abnormal abdominal extension (abdominal mass, intestinal obstruction, ascites). On the other hand, the diaphragm can be pulled upward by changes in the chest causing volume loss (pulmonary fibrosis, atelectasis of the lung or part of the lung).

A pneumothorax, a large free or encapsulated pleural effusion or a large mass originating from the lung or pleura, can be responsible for a unilateral downward displacement of the diaphragm, whereas severe pulmonary emphysema is typically responsible for bilateral depression of the diaphragm.

References

1. Jeung MY, Gangi A, Gasser B et al (1999) Imaging of chest wall disorders. *Radiographics* 19:617-637
2. Tateishi U, Gladish GW, Kusumoto M et al (2003) Chest wall tumors: radiologic findings and pathologic correlation. Part 1. Benign tumors. *Radiographics* 23:1477-1490

3. Tateishi U, Gladish GW, Kusumoto M et al (2003) Chest wall tumors: radiologic findings and pathologic correlation. Part 2. Malignant tumors. *Radiographics* 23:1491-1508
4. McLoud TC, Flower CDR (1991) Imaging the pleura: sonography CT, and MR imaging. *AJR Am J Roentgenol* 156:1145-1153
5. Muller NL (1993) Imaging of the pleura. *Radiology* 186:297-309
6. Lesur O, Delorme N, Fromaget JM et al (1990) Computed tomography in the etiologic assessment of idiopathic spontaneous pneumothorax. *Chest* 98:341-347
7. Roach HD, Davies GJ, Attanoos R et al (2002) Asbestos: when the dust settles – an imaging review of asbestos-related disease *Radiographics* 22:S167-S184
8. Padovani B, Mouroux J, Raffaelli C et al (1996) Benign fibrous mesothelioma of the pleura: MR study and pathologic correlation. *Eur Radiol* 6:425-428
9. Lorigan JG, Libshitz HI (1989) MR imaging of malignant pleural mesothelioma. *J Comput Assist Tomogr* 13:617-620
10. Wang ZJ, Reddy GP, Gotway MB et al (2004) Malignant pleural mesothelioma: evaluation with CT, MR imaging, and PET. *Radiographics* 24:105-119
11. Gierada DS, Slone RM, Fleishman MJ (1998) Imaging evaluation of the diaphragm. *Chest Surg Clin N Am* 8(2):237-280
12. Verschakelen JA, Marchal G, Verbeken E et al (1989) Sonographic appearance of the diaphragm in the presence of pleural disease: a cadaver study. *J Clin Ultrasound* 17:222-227
13. Brink JA, Heiken JP, Semenkovich J et al (1994) Abnormalities of the diaphragm and adjacent structures: findings on multiplanar spiral CT scans. *AJR Am J Roentgenol* 163:307-310
14. Eren S, Çiri F (2005) Diaphragmatic hernia: diagnostic approaches with review of the literature. *Eur J Radiol* 54:448-459
15. Eren S, Kantarci M, Okur A (2006) Imaging of diaphragmatic rupture after trauma. *Clin Radiol* 61:467-477
16. Iochum S, Ludig T, Walter F (2002) Imaging of diaphragmatic injury: a diagnostic challenge? *RadioGraphics* 22:S103-S118
17. Walz M, David A, Schmitz J et al (1993) Value of ultrasound diagnosis after blunt chest trauma. *Intensiv Notfallbehandlung* 18:74-79
18. Mirvis SE, Shanmuganathan K (2007) Imaging hemidiaphragmatic injury. *Eur Radiol* 17:1411-1421
19. Desser TS, Edwards B, Hunt S et al (2010) The dangling diaphragm sign: sensitivity and comparison with existing CT signs of blunt traumatic diaphragmatic rupture. *Emerg Radiol* 17:37-44
20. Bodanapally UK, Shanmuganathan K, Mirvis SE et al (2009) MDCT diagnosis of penetrating diaphragm injury. *Eur Radiol* 19:1875-1881
21. Sattler S, Canty TG Jr, Mulligan MS et al (2002) Chronic traumatic and congenital diaphragmatic hernias: presentation and surgical management. *Can Respir J* 9:135-139
22. Schwartz EE, Wechsler RJ (1989) Diaphragmatic and paradiaphragmatic tumors and pseudotumors. *J Thorac Imaging* 4:19-28
23. Eren S, Ceviz N, Alper F (2004) Congenital diaphragmatic eventration as a cause of anterior mediastinal mass in the children: imaging modalities and literature review. *Eur J Radiol* 51:85-90
24. Deslauriers J (1998). Eventration of the diaphragm. *Chest Surg Clin N Am* 8:315-330
25. Bih LI, Wu YT, Tsai SJ et al (2004) Comparison of ultrasonographic renal excursion to fluoroscopic diaphragmatic excursion for the assessment of diaphragmatic function in patients with high cervical cord injury. *Arch Phys Med Rehabil* 85:65-69

Pulmonary Manifestations of Systemic Diseases

David A. Lynch¹, Cornelia Schaefer-Prokop²

¹ Department of Radiology, National Jewish Health, Denver, CO, USA

² Department of Radiology, Meander Medical Center, Amersfoort, Netherlands

Introduction

Lung involvement in systemic disease may be a manifestation of the underlying pathological process, a complication of the underlying disease or related to treatment. Lung pathology is dominant in certain diseases, such as sarcoidosis or Wegener's granulomatosis, but may be only rarely present, for example, in Henoch-Schönlein purpura. Lung involvement has a profound effect on prognosis and may be challenging to accurately diagnose. Imaging often plays a central part when lung involvement is suspected clinically. In the following, we focus on the more common entities that frequently develop pulmonary abnormalities, such as sarcoidosis, connective tissue diseases, vasculitis and inflammatory bowel disease. Rare pulmonary manifestations of tuberous sclerosis and lymphangioleiomyomatosis, Erdheim-Chester disease, storage diseases (Gaucher, Niemann Pick) or systemic amyloidosis as well as manifestations within neoplastic diseases (e.g. lymphoma) are not considered in this chapter. Langerhans cell histiocytosis shows pulmonary involvement associated with a systemic manifestation only in children but not in adults.

Pulmonary Sarcoidosis

Sarcoidosis is a systemic disorder of unknown origin. It is characterised by noncaseating epithelioid cell granulomas in multiple organs, but morbidity and mortality are closely related to pulmonary manifestation, which occur in >90% of patients. Computed tomographic (CT) appearance of pulmonary sarcoidosis varies greatly and is known to masquerade many other diffuse infiltrative lung diseases.

The histology of pulmonary sarcoidosis consists of noncaseating granulomas with a rim of lymphocytes and fibroblasts in a perilymphatic distribution, which may resolve or cause fibrosis. The disease may occur at any age, but mostly affects individuals between 20 and 40 years of age and only rarely occurs in over 65 years of age. The prognosis is mostly good, with disease resolution occurring in <2 years and mortality rates between 1% and 5%.

Staging (Siltzbach classification) is based on chest X-ray (CXR) findings (percentages indicate the proportion of disease stage at diagnosis):

- Stage 0 normal chest radiograph (5-10%);
- Stage I bilateral hilar and paratracheal lymphadenopathy (50%);
- Stage II lymphadenopathy and nodular opacities (25-30%);
- Stage III nodular opacities without lymphadenopathy or signs of fibrosis (10-12%);
- Stage IV fibrosis (5-25% during course of disease).

Pulmonary findings include small, well-defined nodules in a characteristic perilymphatic distribution in relation to the subpleural surface, adjacent to the major fissures, along thickened interlobular septa and adjacent to vessels in the lobular core. The nodules may be evenly distributed throughout both lungs, with predominance of the upper and middle lung zones. However, they may also be clustered in the perihilar and peribronchovascular regions, with relative sparing of the lung periphery, or they may be grouped in small areas. Confluence of granulomas results in larger nodules (1-4 cm, nodular sarcoid, galaxy sign) or ill-defined opacities (ground-glass opacities or consolidations up to 10 cm, alveolar sarcoidosis). Lymphadenopathy is seen in up to 50% on CT, with calcifications (eggshell or with an amorphous cloudlike pattern).

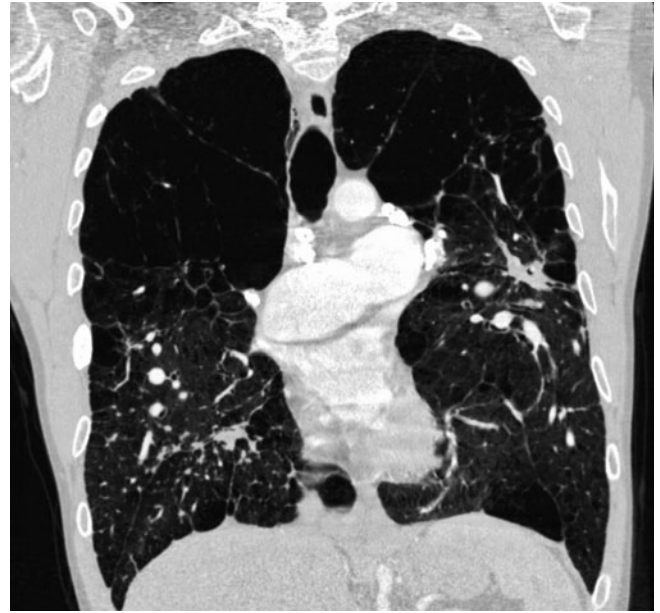
Up to 25% of patients develop irreversible pulmonary fibrosis with architectural distortion, septal displacement, traction bronchiectasis and honeycombing (stage IV). Conglomerate masses mostly in a perihilar location represent areas of fibrosis with characteristic traction bronchiectasis. Volume loss of the upper lobes is associated with hilar retraction. Airways abnormalities include airway compression caused by surrounding lymphadenopathy and traction bronchiectasis caused by surrounding fibrosis. Granulomas within the bronchial walls cause irregular bronchial-wall thickening with narrowing of the large and small airways. The latter results in a mosaic pattern on expiration CT, which may even precede other parenchymal abnormalities and is considered an early sign of extralymphatic spread of disease in sarcoidosis (expiration CT).

Table 1. Typical and atypical features of pulmonary sarcoidosis at high-resolution computed tomography (HRCT)

Characteristics	Description
Typical	
Lymphadenopathy	Hilar, mediastinal, bilateral symmetric, well defined
Nodules	Micronodules (2-4 mm), well defined, larger coalescing nodules
Perilymphatic distribution	Subpleural, interlobular, peribronchovascular
Fibrosis	Reticular densities, architectural distortion, traction bronchiectasis, volume loss
Distribution	Predominance of parenchymal abnormalities in upper lobes and perihilar areas
Atypical	
Lymphadenopathy	Unilateral, isolated, in atypical mediastinal locations
Airspace consolidations	Conglomerate masses, confluent alveolar opacities (alveolar sarcoidosis)
Linear opacities	Interlobular septal thickening
Fibrocystic changes	Cysts, bullae, honeycomb like opacities, upper lobe predominance
Airway involvement	Atelectasis, mosaic pattern
Pleural disease	Effusion, chylo/hemothorax, pneumothorax, pleural plaques

Modified from Criado et al (2010)

Sarcoidosis may present with very characteristic high-resolution CT (HRCT) features allowing for a secure diagnosis and obviating further invasive procedures. However, sarcoidosis is also known to present less typically features [e.g. lower-lobe predominance mimicking idiopathic pulmonary fibrosis (IPF), subpleural consolidations mimicking eosinophilic pneumonia, granulomas confluent to diffuse ground-glass opacities] (Table 1). Complications include the development of an aspergilloma in a cavitation, with potentially fatal hemoptysis (stage IV), pulmonary hypertension and pneumothorax (mostly in fibrobullous disease, Fig. 1).

**Fig. 1.** Fibrobullous disease in a patient with stage 4 sarcoidosis: note the volume increase of the upper lobes due to the bullous parenchymal destruction, calcifications of the mediastinal and hilar lymph nodes and enlarged pulmonary arteries due to pulmonary hypertension

Collagen Vascular Diseases

Involvement of the respiratory system is common in the collagen vascular diseases and results in significant morbidity and mortality. Many of these diseases are characterised by the presence of a specific type of autoantibody, which may greatly assist specific diagnosis. Lung injury from collagen vascular disease can affect each portion of the lung, pleura, alveoli, interstitium, vasculature, lymphatic tissue and airways both large and small (Table 2). Commonly, more than one compartment is involved. Most parenchymal manifestations of collagen vascular disease are similar to those found in idiopathic interstitial pneumonias and can be classified using the same system. Although there is some overlap, each collagen vascular

Table 2. Pulmonary complications of collagen vascular diseases

Pattern	RA	SLE	MCTD	Scleroderma	PM/DM	Sjögren syndrome
UIP	++	+	+	++	+	+
NSIP	+	+	++	++++	++	+
Organizing pneumonia	++	+	+	+	++	
Pulmonary hypertension	+	+	+	++		+
Bronchiectasis	++					++
Obliterative bronchiolitis	++	+				

+ Frequency (+ relatively uncommon, ++++ frequent clinical association). Empty cells indicate that the entity is not described or is rare. RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; MCTD, mixed connective tissue disease; PM/DM, polymyositis/dermatomyositis; UIP, usual interstitial pneumonia; NSIP, nonspecific interstitial pneumonia. Modified from Kim et al. (2002)

disease is associated with a characteristic pattern of pulmonary involvement (Table 2). The lung disease associated with collagen vascular disease may precede the clinical presentation of the collagen disease, sometimes by more than 5 years.

Rheumatoid Arthritis

Most patients with rheumatoid arthritis (RA) have abnormalities on chest HRCT. CT-detected abnormalities are often not associated with symptoms. Airways abnormalities such as bronchial-wall thickening (12-92%) or bronchial dilation (30-40%) are more common than parenchymal changes [reticular abnormality (10-20%), ground-glass opacity (15-25%), honeycombing (10%), consolidation (5%)]. They also may develop nodular changes and pleural disease, the latter preceding parenchymal changes.

Airways disease appears to be the earliest manifestation of RA in the lung. In a study of 34 patients with early RA (duration <1 year), CT showed expiratory air trapping in 69%, bronchiectasis in 58% and ground-glass opacity in 35%. An interesting recent study evaluated CT findings in 14 asymptomatic first-degree relatives of individuals with known RA. Six of seven individuals who had positive RA-related antibodies [anticyclic citrullinated peptide (anti-CCP)] had expiratory air trapping, compared with none of seven antibody-negative individuals. This intriguing finding suggests that the airways or the lung may be involved very early in the evolution of RA. The relatively high prevalence of air trapping in individuals with RA emphasises the importance of obtaining expiratory images in patients with RA, as inspiratory CT is often normal or near-normal in patients with obliterative bronchiolitis.

There is a recognised association between rheumatoid disease and obliterative bronchiolitis (constrictive bronchiolitis), in which bronchioles are destroyed and replaced by scar tissue. The characteristic CT finding is mosaic perfusion with expiratory air trapping, often associated with evidence of mild bronchial dilation. Follicular bronchiolitis is a second type of small airway disorder recognised in rheumatoid lung disease. It is characterised by lymphoid aggregates lying in the walls of bronchioles and possibly compressing their lumens. The major CT finding is centrilobular nodules, often associated with peribronchial nodules, and with areas of ground-glass abnormality.

Rheumatoid lung fibrosis is substantially more common in men than in women. The two commonest patterns of lung fibrosis in RA are usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP). Organising pneumonia (OP) may also be seen. Only a few cases of desquamative interstitial pneumonia (DIP) have been described. CT findings in interstitial pneumonia associated with RA are similar to those of the idiopathic variety. However, findings associated with nodules, mosaic attenuation, pulmonary arterial enlargement and pleural abnormality may provide a clue to the underlying diagnosis (multicompartment involvement, Fig. 2).

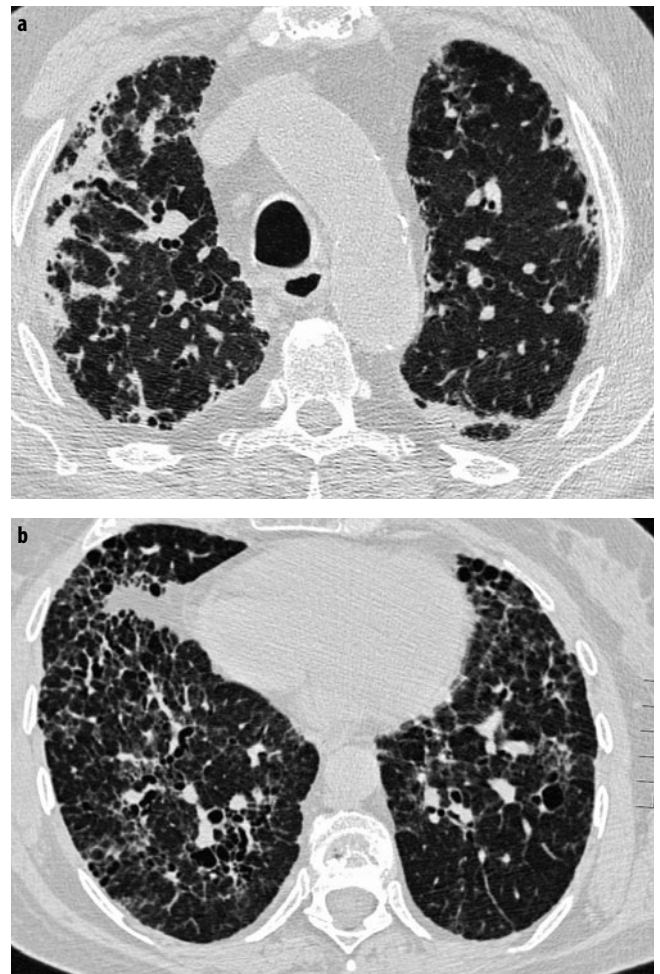


Fig. 2 a, b. A 56-year-old patient with rheumatoid arthritis: note the mix of patterns with subpleural consolidation due to organising pneumonia and areas of honeycombing, severe traction bronchiectasis and pleural thickening (multicompartment involvement)

Necrobiotic nodules, similar to subcutaneous rheumatoid nodules, may uncommonly occur in the lung. They are usually round and well-defined and may cavitate. The entity of Caplan syndrome (multiple, large, rounded nodules seen on the chest radiographs of coal miners with RA) now appears to be very rare, with only one published case report since 1965. Note that rheumatoid nodules are fluorodeoxyglucose (FDG)-avid in positron emission tomography (PET) examinations and must be differentiated from other (malignant) diseases. Pulmonary hypertension commonly occurs in patients with RA but is usually mild.

The new generation of biologic agents used to treat RA has resulted in a new array of potential pulmonary side effects. The most important of these is impaired immunity related to use of antitumor necrosis factor alpha (anti-TNF- α) antibodies (etanercept, infliximab, adalimumab), which results in a substantially increased incidence of tuberculosis (sometimes disseminated or extra-articular) and nontuberculous mycobacterial infection. Screening

chest radiographs are usually obtained when anti-TNF- α antibody treatment is planned. Mycobacterial or fungal infection should be strongly suspected when new parenchymal abnormalities are identified in these patients. Low-dose methotrexate may be associated with subacute hypersensitivity pneumonitis in 2-5% of cases. Pre-existing radiographic evidence of interstitial lung disease (ILD) probably predisposes to the development of methotrexate pneumonitis in patients with RA. There is a morphological overlap between acute pneumonitis under methotrexate therapy and pneumocystis infection. Whereas the association with reticular densities and a patchy distribution is favoured by the first, the latter is favoured by acute onset of ground-glass opacification with sparing of the subpleural space. Nevertheless, pneumocystis infection must be excluded before treatment of suspected drug-induced disease.

Scleroderma (Progressive Systemic Sclerosis)

Parenchymal lung involvement is very common in patients with scleroderma. At autopsy, the lungs are abnormal in at least 80% of cases. Lung fibrosis is the most common pattern of abnormality, with NSIP being much more common (>90%) than UIP. However, pulmonary hypertension is also common, either as an isolated finding or in association with lung fibrosis. Pulmonary hypertension is particularly common in patients with limited scleroderma (CREST syndrome: calcinosis, Raynaud's syndrome, esophageal dysmotility, sclerodactyly, telangiectasia). Oesophageal dilation is found in up to 80% of cases on CT. CT findings in scleroderma reflect the dominant NSIP histology and are characterised by confluent ground-glass opacification and fine reticular pattern, often posterior and subpleural, usually associated with traction bronchiectasis and bronchiolectasis (Fig. 3). Honey-



Fig. 3. Classic fine reticular pattern [nonspecific interstitial pneumonia (NSIP) pattern] with subpleural sparing in a patient with scleroderma

combing, when present, is usually mild. However, patients with honeycombing on initial CT are probably more likely to progress on serial evaluation. The lung fibrosis associated with scleroderma is associated with a much better prognosis than that found in idiopathic lung fibrosis, most likely due in part to the predominant NSIP histology. Fibrotic changes may stay stable for many years. In a large treatment study, the extent of lung fibrosis identified on baseline CT was an important independent predictor of physiologic progression and response to treatment. Pulmonary arterial hypertension usually causes enlargement of the main and proximal pulmonary arteries on chest radiograph or CT; however normal-sized pulmonary arteries do not exclude the diagnosis, and the presence of pericardial thickening or fluid in patients with scleroderma is also a strong predictor of echocardiographic pulmonary hypertension. There is an increased prevalence of lung cancer in scleroderma, with relative risk of malignancy ranging from 1.8% to 6.5%. Lung cancer in this condition often occurs in individuals with lung fibrosis.

Systemic Lupus Erythematosus

Pleuritis is the commonest pleuropulmonary manifestation of lupus, found in 40-60% of patients with systemic lupus erythematosus (SLE), and may or may not be associated with pleural effusion. Fibrotic ILD is less common in SLE than in the other collagen vascular diseases. UIP or NSIP may occur. CT abnormalities are often relatively mild and nonspecific, with linear thickened interlobular septa and parenchymal bands being most common. Whereas pulmonary infection is said to be the most common pulmonary complication of lupus, acute pulmonary haemorrhage is also an important complication, characterised radiologically by diffuse or patchy consolidation and ground-glass abnormality. Acute lupus pneumonitis is a poorly defined entity, characterised by a variable degree of respiratory impairment accompanied by focal or diffuse pulmonary consolidation. It is now believed that most cases previously identified as lupus pneumonitis probably represented acute interstitial pneumonia with or without pulmonary haemorrhage. It is mostly associated with renal infiltration and multiorgan failure.

Other complications of lupus may include diaphragmatic dysfunction, pulmonary hypertension and pulmonary thromboembolism, which may be related to antiphospholipid antibodies. Diaphragmatic dysfunction, thought to be due to a diaphragmatic myopathy, is manifested by reduced lung volumes ("shrinking lungs" with platelike atelectasis). Patients with drug-induced lupus erythematosus have a more mild course and better prognosis.

Polymyositis/Dermatomyositis

The presence of ILD in polymyositis/dermatomyositis (PM/DM) correlates strongly with the presence of anti-Jo-1. About 50-70% of patients who are anti-Jo-1 posi-

tive have ILD, whereas the frequency of ILD falls to about 10% if antibodies are absent. ILD may antedate myositis in patients with anti-Jo-1 antibodies. The most common pathologic findings are NSIP and OP, often occurring in combination. As with other collagen vascular disease, occurrence of interstitial pneumonia may precede the development of clinical myositis. Lung disease associated with PM/DM or with the antisynthetase syndrome, a closely related entity, is often associated with a characteristic CT appearance, characterised by confluent ground-glass opacity and consolidation in the lower lobes superimposed on a background of reticular abnormality with traction bronchiectasis. This pattern reflects the characteristic histologic combination of OP and fibrotic NSIP. On serial evaluation, consolidation changes, ground-glass abnormality, reticular abnormality and traction bronchiectasis may all be partially reversible with treatment. Consolidation may also progress to reticular abnormality. PM/DM can be associated with other collagen vascular diseases (SLE, scleroderma, RA, Sjögren syndrome). There is an increased risk for malignancy (especially for breast, lung, ovary and stomach malignancies), which is concurrently diagnosed within 1 year of follow-up in up to 20% of patients.

Sjögren Syndrome

CT provides substantial information regarding the pattern of pulmonary involvement by Sjögren syndrome. The patterns may be divided into airway abnormality, interstitial fibrosis, pulmonary hypertension and those suggestive of lymphoid interstitial pneumonia (LIP). In a study by Franquet et al. of 50 consecutive patients with primary Sjögren syndrome, 17 of 50 patients (34%) had CT abnormalities. Overall, changes were commonest in the lower zones. Airway-related abnormalities were common (11/17) and consisted of bronchial-wall thickening, bronchiectasis, bronchiolectasis, tree-in-bud pattern and air trapping. Septal or nonseptal lines occurred in a similar number of individuals (11/17). Other findings included patchy ground-glass opacity (7/17), nodules (5/17), honeycombing (4/17) and consolidation (1/17). Nodules >10 mm in diameter were caused by lymphoma. Although cysts were not described in this series, cystic abnormality is common in other series. Small-airway disease was manifest by a mosaic attenuation pattern and expiratory air trapping.

LIP occurring in Sjögren syndrome is characterised by ground-glass abnormality due to the homogenous lymphocytic infiltration (Fig. 4). Peribronchovascular, centrilobular and subpleural nodules may also be seen, and cysts measuring 5–30 mm are often present. These cysts frequently contain thin septa; they may be associated with soft-tissue nodules sitting close to them or in their walls. Similar cysts may be found in follicular bronchiolitis. These changes are ascribed to bronchiolar obstruction on the basis of lymphocytic wall infiltration. Cysts are helpful in distinguishing LIP from lymphoma.



Fig. 4. Lymphocytic interstitial pneumonia (LIP) in a patient with Sjögren syndrome: the combination of increased parenchymal density and thin-walled cysts in subpleural distribution is typical for LIP

Lymphoma should be suspected if consolidation, large nodules (>1 cm), mediastinal lymphadenopathy or effusions are present. However, similar large pseudo-alveolar, poorly defined nodules were found in four patients with combined amyloidosis and LIP. In contrast to other cystic lung diseases, such as lymphangioleiomyomatosis, LIP cysts show peribronchovascular and lower-lung predominance.

Mixed Connective Tissue Disease

Mixed connective tissue disease (MCTD) is an overlap syndrome that is a distinct clinicopathological entity. The principal characteristics are: (1) features of SLE, scleroderma and PM/DM, occurring together or evolving sequentially during observation; and (2) antibodies to an extractable nuclear antigen [ribonuclear protein (RNP)]. Pulmonary involvement is common in MCTD. A study of 144 unselected patients found CT evidence of infiltrative lung disease in 67%. Many affected patients are asymptomatic. The pulmonary abnormalities resemble those seen in SLE, scleroderma and PM/DM. Thus, pleural thickening and pleural and pericardial effusions are common. Ground glass attenuation is the commonest parenchymal abnormality. The CT pattern corresponds most closely to NSIP. Less common findings include honeycombing, consolidation, and poorly defined centrilobular nodules. Other important complications of MCTD include pulmonary arterial hypertension, and oesophageal dysmotility with sequelae of recurrent aspiration.

Ankylosing Spondylitis

Pleuropulmonary involvement is a rare complication of ankylosing spondylitis, found in only 1.3% of 2,080 patients in one series. It almost always involves males, with

long disease duration. Radiologic changes consist of nodular and linear opacity and/or pleural thickening that begin in the lung apices. The apical opacities progress slowly, with increasing apical nodularity and pleural thickening, elevation of the hila and development of multiple thin- or thick-walled cysts or cavities. These apical changes usually progress slowly, but they can remain stable for many years. Pleural calcification may occur. The cavities that develop within the fibrotic lung may be colonised by a variety of fungi and nontuberculous mycobacteria, most commonly mycetomas containing *Aspergillus fumigatus*. Hemoptysis is common in patients with mycetoma and may be life threatening.

Pulmonary Vasculitis/Diffuse Alveolar Haemorrhage

Clinical symptoms and radiologic signs suggestive of pulmonary vasculitis include diffuse alveolar haemorrhage (DAH), acute glomerulonephritis, upper airways disease, lung nodules or cavitary nodules, mononeuritis multiplex and palpable purpura. Pulmonary vasculitides encompass a clinically, radiologically and histopathologically heterogeneous group of diseases that are usually associated with a systemic vasculitis. Radiologic findings depend on the level of pulmonary vessel involvement. The Chapel Hill classification defined in 1992 is based on both the size of the vessels involved and the laboratory findings. According to this classification, large artery refers to the aorta and the largest branches, medium-sized artery to visceral arteries and small artery to distal intraparenchymal arteries (Table 3). Pulmonary involvement is seen in Wegener granulomatosis, Goodpasture syndrome, Churg-Strauss syndrome (CSS), microscopic polyangiitis, Behçet's disease and Takayasu

disease. The combined affection of lungs and kidneys by some of these diseases is also described as pulmonary-renal syndrome. Note that capillaritis also manifests as a complication of a disease course of various kinds of collagen vascular diseases.

Antineutrophil Cytoplasmic Autoantibody-associated Granulomatous Vasculitis (former Wegener Granulomatosis)

Wegener affects the sinuses, kidneys and lungs, resulting in the classic triad of symptoms comprising sinusitis and/or tracheobronchitis, pathological CXR (with or without hemoptysis) and microhaematuria. However, any part of the body may be affected. Females and males are affected equally and at any age (mostly age 40-55). Airway involvement is more frequent in men. The most common cause of death is renal failure. With treatment, the 24-month survival rate is 80%. Histologic findings include necrotising granulomatous vasculitis of small to medium vessels without associated infection. Serologically, up to 90% of patients are positive for circulating antineutrophil cytoplasmic antibodies (circulating-ANCA). The most frequently seen pulmonary abnormalities are multiple nodules with or without a CT halo sign (haemorrhage) (Fig. 5). Cavitations have thick walls. Peripheral wedge-shaped consolidations represent infarcts that may also cavitate. Diffuse consolidations or ground-glass opacities represent pulmonary haemorrhage. Fibrotic changes reflect pre-existing disease. In addition there may be a concentric thickening of tracheal or bronchial walls, with diameter reduction potentially causing atelectasis.

Table 3. CT-findings of pulmonary (Pulm) vasculitis syndromes

Vasculitis	Size of involved vessels	Pulm-renal syndrome	Pulm haemorrhage	Pulm hypertension
Wegener	Small	50-75%	In up to 8%, diffuse	-
Churg-Strauss	Small	Up to 25%	Rare, diffuse	-
Microscopic polyangiitis	Small	In 75-100%	Rare, diffuse	-
Polyarteritis nodosa	Medium	-	Very rare, diffuse (associated with hepatitis B)	-
Giant-cell arteritis	Large	-	Rare, focal	Rare
Takayasu	Large	-	Rare, focal	Rare
RA	CTD	-	Very rare, diffuse	Up to 60%
Systemic sclerosis	CTD	-	Rare, diffuse, with necrotising vasculitis	10-60%
MCTD	CTD	-	Rare, diffuse	Up to 45%
SLE	CTD	Up to 60%, late	In 4% (potentially more frequent), diffuse	5-45%
Obliterative bronchiolitis	++	+		

According to the Chapel Hill classification 2002. CTD, connective tissue disease
Modified from Marten K et al. (2005)

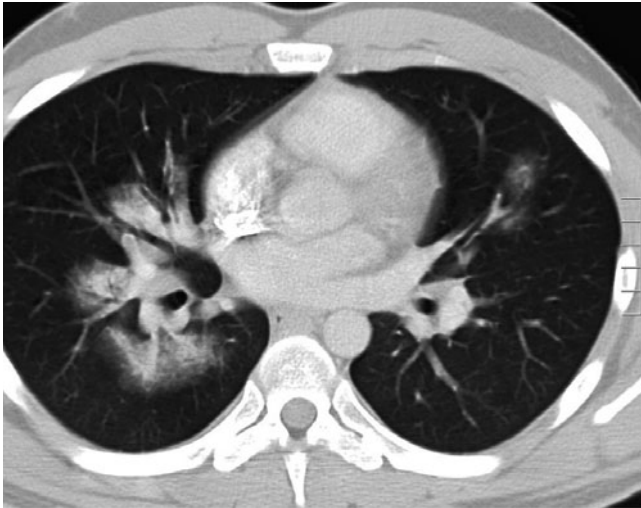


Fig. 5. A 45-year-old patient with acute onset of Wegener's disease: there is multifocal consolidation surrounded by a halo (haemorrhage) tracking along the central bronchovascular bundles

Churg-Strauss Syndrome

CSS is caused by a small-vessel systemic vasculitis that almost exclusively occurs in patients with asthma and is characterised by a marked serum eosinophilia. Clinically, radiologically and pathologically, it combines features of Wegener granulomatosis and eosinophilic pneumonia (allergic granulomatosis and angiitis). Many other organs may be involved, including the heart (up to 47%), the skin (up to 40%) and the musculoskeletal system (up to 50%). Involvement of the peripheral nerves is more frequent, whereas glomerulonephritis (GN) and pulmonary haemorrhage are less frequent compared to Wegener's disease. Histology demonstrates small-vessel (arteries and veins) vasculitis with eosinophilic infiltrates and vascular and extravascular granulomas. Serological findings include myeloperoxidase (MPO)-ANCA in up to 70% of cases, and serum eosinophilia. The 5-year survival is reported in up to 80% of patients; 50% of deaths are related to cardiac involvement. Upper airways disease and pulmonary abnormalities are seen in up to 70% of patients with CSS. The most common pulmonary findings include transient, multifocal and nonsegmental consolidations without zonal predilection. The presence of (noncavitating) small nodules or diffuse reticular densities has also been reported. If located subpleurally, the consolidations mimic eosinophilic pneumonia. Diffuse consolidations or ground-glass attenuation reflect haemorrhage. Airway abnormalities are also an important thoracic manifestation and include wall thickening, dilatation, small nodules and mosaic perfusion. Increased interlobular septa are due to oedema caused by cardiac and/or renal involvement, eosinophilic infiltrates or mild fibrosis. Eosinophilic pleural effusion is seen in up to 50% of patients.

Microscopic Polyangiitis/Diffuse Alveolar Haemorrhage

Microscopic polyangiitis is a systemic, necrotising, small-vessel vasculitis with granulomatous inflammation. Clinically it is characterised by a long prodromal phase with weight loss and fever, followed by a rapidly progressive GN. Microscopic polyangiitis is the most common cause of pulmonary-renal syndrome: renal involvement is seen in up to 90%, pulmonary involvement in up to 50%. Perinuclear antinuclear antibodies (ANA) is positive in 25-50%. Please note that microscopic polyangiitis is different from polyarteritis nodosa, which is a medium-sized vasculitis that affects the kidneys but only rarely the lung.

Microscopic Polyangiitis

Microscopic polyangiitis is characterised by the combination of GN and DAH. Imaging findings include patchy bilateral or diffuse air-space opacities. The opacity can show both features of consolidations and ground-glass opacities dependent on the amount of alveolar filling by blood. The opacifications may be diffuse or more pronounced in the dependent lower parts of the lungs. A halo surrounding a consolidation or nodule underlines the character of haemorrhage. During the resorption phase, there are increasingly seen interlobular lines (crazy paving). Repeated haemorrhage leads to fibrosis with honeycombing, reticulation and traction bronchiectasis.

Goodpasture Syndrome/Diffuse Alveolar Haemorrhage

Goodpasture syndrome describes the clinical triad of circulating antiglomerular basement membrane antibody, DAH and GN. Presenting symptoms comprise an acute onset of dyspnea and hemoptysis. Histologically, there is a linear deposition of immunoglobulin G (IgG) along the glomerular basement membranes. Thus, renal biopsy is used to establish diagnosis. Serology comprises c-ANCA or perinuclear ANCA (p-ANCA) positivity in 30% and anti-basement-membrane antibodies in >90%. Young men are more often affected than women (M:F = 9:1), though it may also be seen in elderly women. With treatment, the prognosis is good. Recurrent episodes cause pulmonary fibrosis. Imaging features consist of diffuse or patchy ground-glass opacities or consolidations based on alveolar haemorrhage that typically resolve within days. Typically, there is sparing of the subpleural space and the lung base; if not, another diagnosis should be considered. Pleural effusion is uncommon.

Inflammatory Bowel Disease

Ulcerative colitis and Crohn's disease are associated with a wide variety of pulmonary complications. Pulmonary complications may precede the diagnosis of inflammatory bowel disease or may occur years after the

initial diagnosis and even after complete colectomy for ulcerative colitis. Indeed, there is some suggestion that pulmonary complications may be more common after surgical treatment, perhaps because anti-inflammatory treatment is withdrawn. Both Crohn's disease and ulcerative colitis can be associated with an intense tracheo-bronchitis, sometimes associated with subglottic, tracheal or bronchial stenosis. Bronchiectasis and bronchial-wall thickening are also common. Small-airway involvement can have a pattern of panbronchiolitis. Parenchymal abnormalities associated with inflammatory bowel disease include OP, pulmonary haemorrhage, and granulomatous infiltration in Crohn's disease. Sulphasalazine treatment may cause OP or eosinophilic pneumonia. Infliximab and similar agents may also be associated with tuberculosis and nontuberculous mycobacterial infection.

Suggested Reading

Sarcoidosis

- Brauner MW, Lenoir S, Grenier P et al (1992) Pulmonary sarcoidosis: CT assessment of lesion reversibility. *Radiology* 182:349-354
- Criado E, Sanchez M, Ramirez J et al (2010) Pulmonary sarcoidosis: typical and atypical manifestations at high resolution CT with pathologic correlation. *Radiographics* 30:1567-1586
- Handa T, Nagai S, Fushimi Y et al (2006) Clinical and radiographic indices associated with airflow limitations in patients with sarcoidosis. *Chest* 130(6):1851-1856
- Nakatsu M, Hatabu H, Morikawa K et al (2002) Large coalescent nodules in pulmonary sarcoidosis: "sarcoid galaxy sign". *AJR Am J Roentgenol* 178 (6):1389-1393

Collagen Vascular Diseases

- American Thoracic Society (2002) American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. *Am J Respir Crit Care Med* 165:277-304
- Hwang JH, Misumi S, Sahin H et al (2009) Computed tomographic features of idiopathic fibrosing interstitial pneumonia: comparison with pulmonary fibrosis related to collagen vascular disease. *J Comput Assist Tomogr* 33:410-415.
- Kim EA, Lee KS, Johkoh T et al (2002) Interstitial lung diseases associated with collagen vascular diseases: radiologic and histopathologic findings. *RadioGraphics* 22:S151-S165
- Lynch DA (2009) Lung disease related to collagen vascular diseases. *J Thorac Imag* 24:299-309

Rheumatoid Arthritis

- Aquino SL, Webb WR, Golden J (1994) Bronchiolitis obliterans associated with rheumatoid arthritis: findings on HRCT and dynamic expiratory CT. *J Comput Assist Tomogr* 18:555-558
- Arakawa H, Honma K, Shida H et al (2003) Computed tomography findings of Caplan syndrome. *J Comput Assist Tomogr* 27:758-760
- Bouros D, Hatzakis K, Labrakis H, Zeibecoglou K (2002) Association of malignancy with diseases causing interstitial pulmonary changes. *Chest* 121:1278-1289
- Gabbay E, Tarala R, Will R et al (1997) Interstitial lung disease in recent onset rheumatoid arthritis. *Am J Respir Crit Care Med* 156:528-535

- Golden MR, Katz RS, Balk RA, Golden HE (1995) The relationship of preexisting lung disease to the development of methotrexate pneumonitis in patients with rheumatoid arthritis. *J Rheumatol* 22:1043-1047
- Hilliquin P, Renoux M, Perrot S et al (1996) Occurrence of pulmonary complications during methotrexate therapy in rheumatoid arthritis. *Br J Rheumatol* 35:441-445
- Metafratzi ZM, Georgiadis AN, Ioannidou CV et al (2007) Pulmonary involvement in patients with early rheumatoid arthritis. *Scand J Rheumatol* 36:338-344
- Mori S, Cho I, Koga Y, Sugimoto M (2008) Comparison of pulmonary abnormalities on high-resolution computed tomography in patients with early versus longstanding rheumatoid arthritis. *J Rheumatol* 35:1513-1521
- Mutlu GM, Mutlu EA, Bellmeyer A, Rubinstein I (2006) Pulmonary adverse events of anti-tumor necrosis factor-alpha antibody therapy. *Am J Med* 119:639-646
- Remy-Jardin M, Remy J, Cortet B et al (1994) Lung changes in rheumatoid arthritis: CT findings. *Radiology* 193:375-382
- Perez T, Remy-Jardin M, Cortet B (1998) Airways involvement in rheumatoid arthritis: clinical, functional, and HRCT findings. *Am J Respir Crit Care Med* 157:1658-1665
- Tanaka N, Kim JS, Newell JD et al (2004) Rheumatoid arthritis-related lung diseases: CT findings. *Radiology* 232:81-91

Systemic Sclerosis

- Bouros D, Wells AU, Nicholson AG et al (2002) Histopathologic subsets of fibrosing alveolitis in patients with systemic sclerosis and their relationship to outcome. *Am J Respir Crit Care Med* 165:1581-1586
- Fischer A, Misumi S, Curran-Everett D et al (2007) Pericardial abnormalities predict the presence of echocardiographically defined pulmonary arterial hypertension in systemic sclerosis-related interstitial lung disease. *Chest* 131:988-992
- Goldin JG, Lynch DA, Strollo DC et al (2008) High-resolution CT scan findings in patients with symptomatic scleroderma-related interstitial lung disease. *Chest* 134:358-367
- Kim DS, Yoo B, Lee JS et al (2002) The major histopathologic pattern of pulmonary fibrosis in scleroderma is nonspecific interstitial pneumonia. *Sarcoidosis Vasc Diffuse Lung Dis* 19:121-127
- Pearson JE, Silman AJ (2003) Risk of cancer in patients with scleroderma. *Ann Rheum Dis* 62:697-699
- Remy-Jardin M, Remy J, Wallaert B et al (1993) Pulmonary involvement in progressive systemic sclerosis: sequential evaluation with CT, pulmonary function tests, and bronchoalveolar lavage. *Radiology* 188:499-506
- Wells AU, Cullinan P, Hansell DM et al (1994) Fibrosing alveolitis associated with systemic sclerosis has a better prognosis than lone cryptogenic fibrosing alveolitis. *Am J Respir Crit Care Med* 149:1583-1590

Lupus Erythematosus

- Bankier AA, Kiener HP, Wiesmayr MN et al (1995) Discrete lung involvement in systemic lupus erythematosus: CT assessment. *Radiology* 196:835-840
- Fenlon HM, Doran M, Sant SM, Breatnach E (1996) High-resolution chest CT in systemic lupus erythematosus. *AJR Am J Roentgenol* 166:301-307
- Swigris JJ, Fischer A, Gillis J (2008) Pulmonary and thrombotic manifestations of systemic lupus erythematosus. *Chest* 133:271-280
- Wiedemann HP, Matthay RA (1992) Pulmonary manifestations of systemic lupus erythematosus. *J Thorac Imaging* 7:1-18

Dermatomyositis/Polymyositis

- Arakawa H, Yamada H, Kurihara Y et al (2003) Nonspecific interstitial pneumonia associated with polymyositis and dermato-

myositis: serial high-resolution CT findings and functional correlation. *Chest* 123:1096-1103

Fischer A, Swigris JJ, du Bois RM et al (2009) Anti-synthetase syndrome in ANA and anti-Jo-1 negative patients presenting with idiopathic interstitial pneumonia. *Respir Med* 103:1719-1724

Mino M, Noma S, Taguchi Y et al (1997) Pulmonary involvement in polymyositis and dermatomyositis: sequential evaluation with CT. *AJR Am J Roentgenol* 169:83-87

Sjögren Syndrome

Franquet T, Gimenez A, Monill JM et al (1997) Primary Sjogren's syndrome and associated lung disease: CT findings in 50 patients. *AJR Am J Roentgenol* 169:655-658

Honda O, Johkoh T, Ichikado K et al (1999) Differential diagnosis of lymphocytic interstitial pneumonia and malignant lymphoma on high-resolution CT. *AJR Am J Roentgenol* 173:71-74

Jeong YJ, Lee KS, Chung MP et al (2004) Amyloidosis and lymphoproliferative disease in Sjogren syndrome: thin-section computed tomography findings and histopathologic comparisons. *J Comput Assist Tomogr* 28:776-781

Johkoh T, Müller NL, Pickford HA et al (1999) Lymphocytic interstitial pneumonia: thin-section CT findings in 22 patients. *Radiology* 212:567-572

Taouli B, Brauner MW, Mourey I et al (2002) Thin-section chest CT findings of primary Sjogren's syndrome: correlation with pulmonary function. *Eur Radiol* 12:1504-1511

Mixed Connective Tissue Disease

Bodolay E, Szekanecz Z, Devenyi K et al (2005) Evaluation of interstitial lung disease in mixed connective tissue disease (MCTD). *Rheumatology (Oxford)* 44:656-661

Fagan KA, Badesch DB (2002) Pulmonary hypertension associated with connective tissue disease. *Prog Cardiovasc Dis* 45:225-234

Kozuka T, Johkoh T, Honda O et al (2001) Pulmonary involvement in mixed connective tissue disease: high-resolution CT findings in 41 patients. *J Thorac Imaging* 16:94-98

Ankylosing Spondylitis

Hillerdal G (1983) Ankylosing spondylitis lung disease – an underdiagnosed entity? *Eur J Respir Dis* 64:437-441

Pamuk ON, Harmandar O, Tosun B et al (2005) A patient with ankylosing spondylitis who presented with chronic necrotising aspergillosis: report on one case and review of the literature. *Clin Rheumatol* 24:415-419

Vasculitis

Attali P, Begum R, Romdhane HB et al (1998) Pulmonary Wegener's granulomatosis: changes at follow up CT. *Eur Radiol* 8:1009-1113

Chung MP, Yi CA, Lee HY et al (2010) Imaging of pulmonary vasculitis. *Radiology* 255:322-341

Cordier JF, Valeyre D, Guillevin L et al (1990) Pulmonary Wegener's granulomatosis. A clinical and imaging study of 77 cases. *Chest* 97:906-912

Haworth SJ, Savage COS, Carr D et al (1985) Pulmonary hemorrhage complicating Wegener's granulomatosis and microscopic polyarteritis. *BMJ* 290:1175-1178

Jennette JC, Falk RJ (2007) Nosology of primary vasculitis. *Curr Opin Rheumatol* 19:10-16

Marten K, Schnyder P, Schirg E et al (2005) Pattern-based differential diagnosis in pulmonary vasculitis using volumetric CT. *AJR Am J Roentgenol* 184:720-733

Specks U, Deremee RA (1990) Granulomatous vasculitis. Wegener's granulomatosis and Churg Strauss syndrome. *Rheum Dis Clin North Am* 16:377-397

Susanto I, Peters JI (1997) Acute lupus pneumonitis with normal chest radiograph. *Chest* 111:1781-1783

Worthy SA, Muller NL, Hansell DM, Flower CD (1998) Churg-Strauss syndrome: The spectrum of pulmonary CT findings in 17 Patients. *AJR Am J Roentgenol* 170:297-300

Inflammatory Bowel Disease

Camus P, Piard F, Ashcroft T et al (1993) The lung in inflammatory bowel disease. *Medicine (Baltimore)* 72:151-183

Garg K, Lynch DA, Newell JD (1993) Inflammatory airways disease in ulcerative colitis: CT and high-resolution CT features. *J Thorac Imaging* 8:159-163

Kelly MG, Frizelle FA, Thornley PT et al (2006) Inflammatory bowel disease and the lung: is there a link between surgery and bronchiectasis? *Int J Colorectal Dis* 21:754-757

Three- and Four-Dimensional Imaging in Acute Aortic Syndrome

Dominik Fleischmann¹, Anne S. Chin², D. Craig Miller³

¹ Department of Radiology, Stanford University, Stanford, CA, USA

² Department of Radiology, University of Montréal, Montréal, Québec, Canada

³ Department of Cardiothoracic Surgery, Stanford University, Stanford, CA, USA

Introduction

Computed tomography angiography (CTA) is an established imaging technique providing highly accurate clinical information of the thoracic aorta. The widespread availability and round-the-clock accessibility of modern-day multidetector-row CT (MDCT) technology in virtually all emergency rooms, a proven track record of CTA with sensitivity and specificity approaching 100% for the detection of acute thoracic aortic disease and the ability to detect other potentially clinically important pathology has led to the replacement of conventional diagnostic angiography by CTA [1]. The development of CTA with ECG gating provides additional advantages by eliminating cardiac pulsation and motion artefacts, further extending the clinical applicability of CTA to include aortic-root imaging. ECG gating, when performed retrospectively over the entire cardiac cycle, allows cardiac phase-resolved (time-resolved) cine imaging and visualisation, adding yet another dimension (4D) to this robust technique.

In this article, we provide an overview of the main disease entities encompassing acute aortic syndromes, describe the principles of 3D and 4D imaging of the thoracic aorta and review the clinical application and state of the art of computed tomography for imaging patients presenting with acute aortic syndrome.

Acute Aortic Syndrome

Acute aortic syndrome is a contemporary clinical term – analogous to acute coronary syndrome – referring to a spectrum of acute life-threatening abnormalities of the aorta associated with intense chest or back pain [2]. Acute aortic syndromes are much less common than acute cardiac events, with an estimated annual incidence of approximately 2.5–3.5 per 100,000 for acute aortic dissection (the most common acute aortic condition requiring emergency operative repair) versus more than 400 per 100,000 for acute myocardial infarction. Whereas the presumptive diagnosis of acute myocardial infarction is usually considered first, excluding acute thoracic aortic disease

is imperative to expedite appropriate treatment, avoid deleterious thrombolysis and circumvent unnecessary delays associated with emergency coronary angiography.

The clinical picture of acute aortic syndrome can be caused by a wide range of aortic lesions and predisposing underlying conditions but has traditionally been related to three main abnormalities [2]: (1) aortic dissection (AD), (2) intramural hematoma (IMH), and (3) penetrating atherosclerotic ulcer (PAU). This classification of acute aortic syndromes is almost universally used in the literature [3–5] but is, in fact, confusing and misleading. First, it does not reflect the extent of aortic pathology possible. The more important conceptual shortcoming of this classification is that the three categories do not represent comparable entities: two of them are disease manifestations (AD is a manifestation of media degeneration and PAU is a manifestation of severe atherosclerosis), whereas one “category” (IMH) is a nonspecific imaging finding referring to the presence of blood or haemorrhage within the aortic wall, which can be seen in association with either AD or PAU, in addition to other conditions, including acute trauma and rupturing aortic aneurysm. An analogy is that appendicitis and diverticulitis are manifestations of diseases that may cause an acute abdomen, but abdominal fat-stranding is a nonspecific imaging finding that can be seen in both, and other pathologic processes associated with the clinical picture of an acute abdomen. It is this inaccurate classification of acute aortic syndromes that, in the past, has led to several unconvincing attempts to explain the dynamic evolution of one entity into the other [3–5].

Conceptually, we classify acute aortic syndromes as shown in Table 1. We regard the acute aortic syndrome as a spectrum of disease manifestations caused by two main pathologic processes: (1) AD and its variants, resulting from a diseased media; (2) PAU, resulting from severely diseased intima in the form of advanced atherosclerosis. In addition, we also list (3) rupturing aortic aneurysm as a cause of acute aortic syndrome, even though this is more commonly a complication involving the abdominal aorta rather than the thoracic aorta. Furthermore, the numerous aetiologies that can cause aneurysm formation are well known and are not specifically discussed in this article.

Table 1. Acute aortic syndromes

1. Dissection complex: aortic dissection and dissection variants (diseased media)
 - 1a Classic aortic dissection^a
 - 1b Intramural hematoma (IMH)
 - 1c Limited intimal tear (limited dissection)^a
2. Penetrating atherosclerotic ulcer (PAU) (diseased intima)^a
3. Rupturing aortic aneurysm^a

^a Lesions can occur with or without associated IMH

Note that IMH is not part of our conceptual classification of acute aortic syndromes but, rather, is an imaging finding associated with several disorders. The justification for the traditional inclusion of IMH as one of the rank categories in the acute aortic syndrome stems from its significance as a reliable indicator of an acute process.

CT Imaging Strategy and Postprocessing

A complete CT evaluation of patients with suspected acute aortic abnormalities always includes an initial nonenhanced scan followed by a contrast-enhanced CTA of the chest, abdomen and pelvis. We use a section thickness of 3–5 mm for unenhanced scans to detect IMH and blood within the chest, abdomen or pelvis. For the contrast-enhanced CTA acquisition, we use 1.0- to 1.25-mm section thickness with 0.7- to 0.8-mm section spacing and scan the entire chest, abdomen and pelvis from the thoracic inlet to the groin. This is of critical importance in patients with a high index of suspicion for AD because the CT data set serves not only a diagnostic purpose but is also used for treatment planning by providing a roadmap for femoral access to the true versus false lumen and respective side-branches.

Since 2004, we have routinely used ECG gating for the thoracic portion of the CTA acquisition in all patients with acute aortic syndromes, using a 16-channel CT scanner. In contrast to coronary CTA, a gated CTA of the chest does not require a section thickness of less than <1.25 or 2 mm, and no premedication with beta-blockers or nitroglycerine is required. We do not use the fastest gantry rotation possible for the gated portion of the scan if the scanner does not permit the same gantry rotation speed for the abdominal portion of the CTA. This is because changing gantry rotation speeds between the thoracic (gated) and abdominal (nongated) portions of the scan would result in a long interscan pause to slow down the gantry. This additional pause would require administration of larger volumes of contrast medium to maintain adequate opacification for the entire scan time. For GE scanners, for example, the gantry rotation is set to 400 ms/rotation rather than 350 ms/rotation for both the gated thoracic and nongated abdominal and pelvic scans, which allows the entire scanning range to be acquired within approximately 25 s (16-channel CT) or 15 s (64-channel CT).

The first major clinical benefit of motion-free 3D imaging of the thoracic aorta is the elimination of the no-

torious pulsation artefacts in the ascending aortic, which may mimic dissection and can obscure subtle but important aortic abnormalities (Fig. 1). Motion-free 3D imaging in acute AD allows visualisation of a dissection flap extending into the aortic root and the coronary arteries. Furthermore, it is possible to precisely visualise, characterise and localise the site of the primary intimal tear (PIT), which is increasingly important in the stent-graft era [6, 7]. Motion-free images allow the detection of less common subtle, but equally clinically important intimal lesions, which have been notoriously difficult to detect in vivo with any current imaging modality [8].

Because suppression of motion artefacts is the most important advantage of ECG gating in patients with acute aortic syndromes, retrospective ECG gating should be used with tube current modulation in order to reduce radiation exposure. Prospective ECG triggering allows the use of even lower radiation dose and should be used if available and if the scan time is fast enough to cover the chest in a single breath-hold. In the clinical setting where acute aortic lesions are statistically very unlikely, an alternative strategy to routine ECG gating of the thoracic CTA would be to routinely perform a standard nongated CTA of the entire aorta, and only repeat the thoracic portion with gating if ambiguous findings are observed or the clinical suspicion is high.

3D and 4D Image Postprocessing

Transverse CT source images remain the most important images to scrutinize in the acute setting to make the diagnosis, characterise a lesion and assess for potential complications. The imaging findings that should be sought in patients with acute aortic syndromes are summarised in Table 2. After reviewing the transverse

Table 2. Diagnostic information sought in patients with acute aortic syndrome

1. Lesion identification and characterisation
 - Aortic dissection (AD) and its variants versus penetrating atherosclerotic ulcer (PAU)
 - Presence of associated intramural hematoma (IMH)
 - For dissections, identify location of primary intimal tear (PIT)
2. Lesion location and extent
 - Involvement of the ascending aorta (type A vs. type B)
 - Lesion location relative to important side branches
 - Distal extent and location of distal re-entry points and flap fenestrations
3. Presence of complications
 - Type A lesions
 - Presence of pericardial fluid
 - Sinus of Valsalva and aortic valve involvement
 - Coronary artery involvement
 - Distal complications
 - Side-branch involvement and organ perfusion status
4. Signs of leakage and rupture
 - Periaortic stranding, notably if haemorrhagic
 - Active extravasation/pseudoaneurysm formation

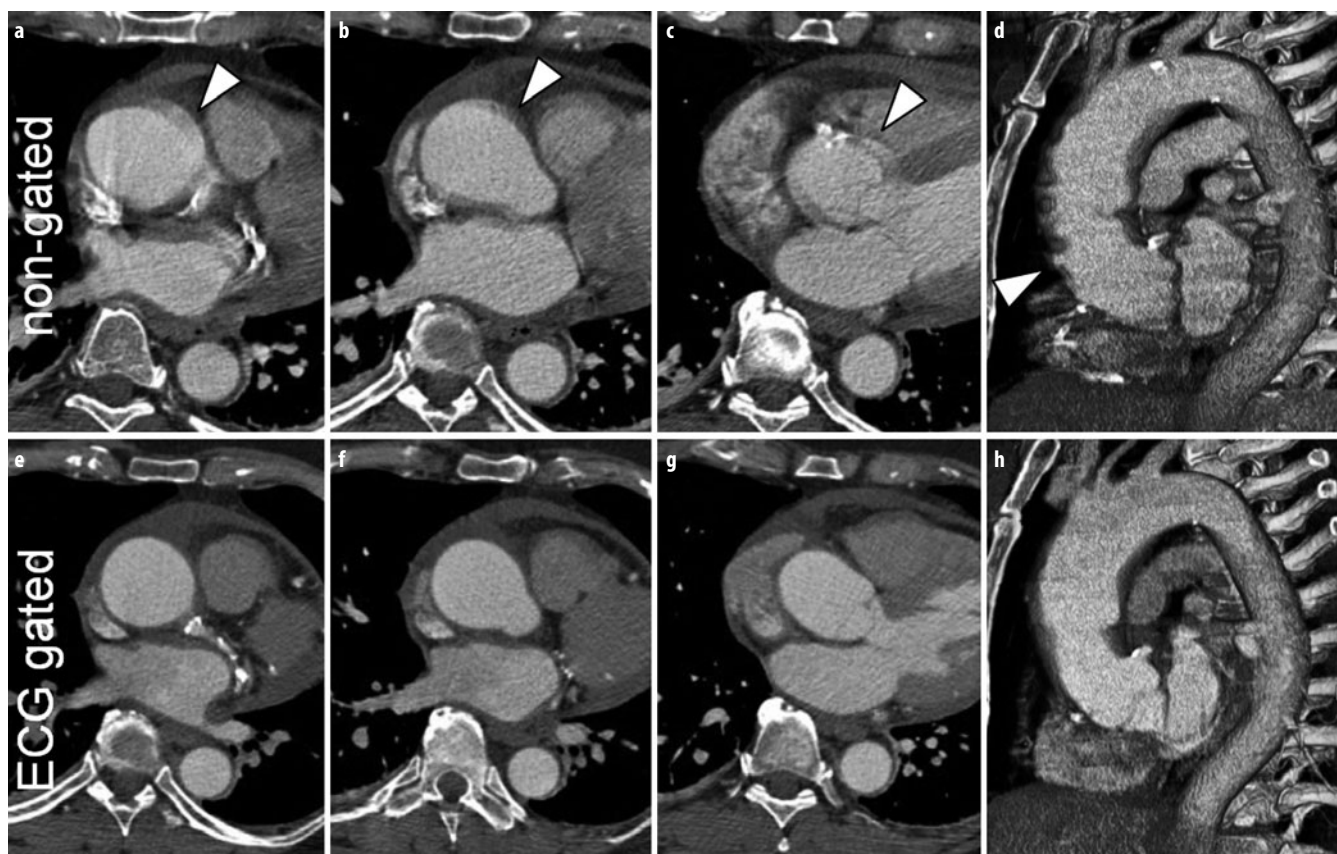


Fig. 1 a-h. Aortic motion-artefact suppression with electrocardiographic (ECG)-gated computed tomography angiography (CTA). Three transverse CT images obtained with a nongated 16-channel CT show typical motion artefacts with double contours (*arrowheads*) at the mid ascending aorta (**a**), proximal ascending aorta (**b**) and aortic root (**c**). Corresponding volume-rendered image (**d**) shows artifactual contour abnormalities (*arrowhead*) in the ascending aorta due to transmitted cardiac pulsation. This study was repeated 12 h later with ECG gating, which eliminates motion artefacts in the corresponding transverse (**e-g**) and volume-rendered (**h**) images. From [9], with permission (for color reproduction see p 273)

source images, postprocessing is often helpful to fully characterise a lesion and to communicate to the referring and treating physician the specific findings on representative images. The most important role for postprocessing is treatment planning, notably for endovascular repair of ADs or PAU, where accurate measurements of luminal diameters and distances to important side branches are critical. Three- and four-dimensional visualisation of the valve apparatus, coronary ostia and complex type A dissections (Fig. 2) are also helpful for surgical treatment planning.

Interactive 3D and 4D postprocessing requires powerful hardware and software that is easy to use and readily available, within reach of the interpreting physician, and – if possible – available to treating physicians as well. Most of these requisites are available on modern workstations and – in the opinion of the authors – best fulfilled by so-called thin-client systems, which are commercially available from a number of manufacturers.

Aortic Dissection and Dissection Variants

Acute AD is the most common acute aortic condition requiring emergency operative repair. Whereas the initiating event leading to AD is unknown, most patients have a structural abnormality of the aortic media. A diseased medial layer of the aortic wall is, therefore, the common denominator of AD. Modern imaging technology has taught us that the spectrum of ADs is much wider than just classic dissection, ranging from subtle, discrete intimomедial lesions to extensive and complex lesions with frequently observed overlapping features of intimomедial tears, intramural blood and frank dissection, often in the same individual [9].

Pathology of Aortic Dissection

AD is a manifestation of a diseased aortic media, the thickest layer of the aortic wall. The aortic media has a complex structure and organisation, consisting of layers

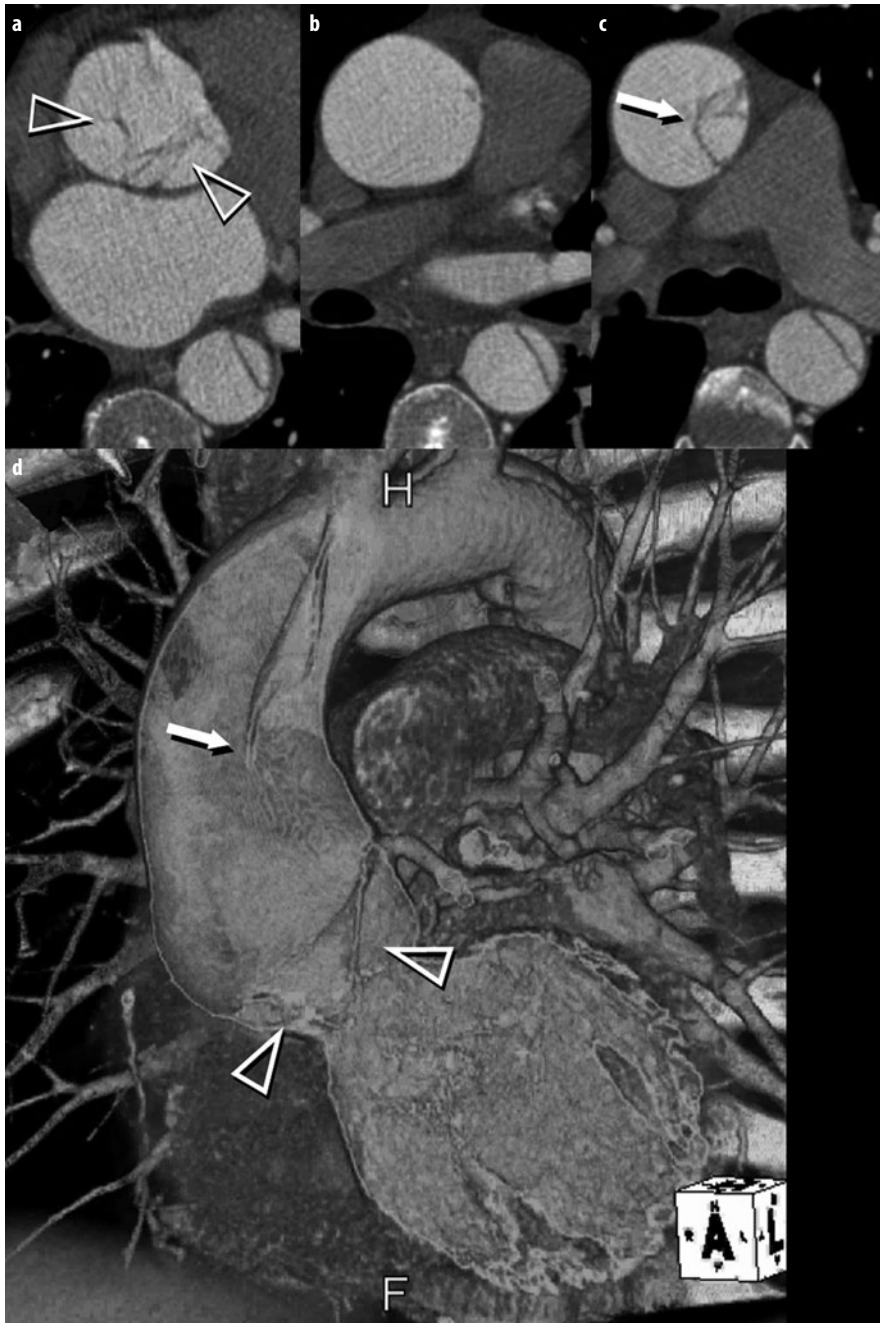


Fig. 2 a-d. Acute type A dissection in a 45-year-old man. Transverse computed tomography (CT) images (a-c) show irregular linear opacities (arrowheads) at the level of the aortic root (a), which are difficult to interpret on this transverse image, but no clear dissection flap in the mid ascending aorta (b). In the distal ascending aorta (c), a dissection flap (arrow) between a true and false lumen is identified. Volume-rendered image (d) clearly depicts an extensive dissection with the proximal portion of the dissection flap torn off and prolapsing onto and through the aortic valve (arrowheads). Arrow points to dissection flap in the distal ascending aorta. From [9], with permission (for color reproduction see p 273)

of collagen, elastin and smooth-muscle cells interconnected with microfibrils [10]. Degeneration of the aortic media results in separation of these layers. In 1929, the pathologic process responsible for this medial degeneration was coined “cystic medial necrosis” by Erdheim [11, 12], who defined the associated histological features: accumulation of basophilic substance in cyst-like spaces, fragmentation of elastic fibres and noninflammatory loss of vascular smooth-muscle cells. Although widely propagated, the term cystic medial necrosis is, in fact, a misnomer; noncystic structural faults are responsible for the cystic appearance of the media, and necrosis is rarely

present. The etiology of medial degeneration is diverse. Marfan syndrome, perhaps the most well-recognised condition associated with cystic medial necrosis, is characterised by degeneration of elastin, collagen and other extracellular matrix proteins, resulting in structural weakening of the aortic media due to abnormal fibrillin-1. Other heritable diseases with deficiencies in fibrillin-1, a glycoprotein responsible for structural integrity of the aortic wall, are also associated with accelerated degeneration of the aortic media. These include other connective tissue disorders such as Ehlers-Danlos and Loeys Dietz syndromes, familial thoracic aortic aneurysm, as well as

bicuspid aortic valve (BAV)-associated ascending aortic aneurysm. Accelerated degeneration of collagen, elastin and smooth-muscle cells (medial substrate problem) is seen in those with severe or long-standing hypertension; however, these changes are also an expected feature of the normal aging process in older individuals. From an epidemiologic perspective, long-standing hypertension is the most important cause of AD. Intimal disease – atherosclerosis – is not a prerequisite for AD, but can coexist.

Classic Aortic Dissection

Classic AD is characterised by the presence of a PIT and a clear separation between layers of the aortic media, resulting in two separate flow channels – the true lumen, and the false lumen separated by a so-called intimal flap – and at least one exit- or re-entry tear. Note that the false lumen is entirely within the media and that the dissection flap consists of a thin intima layer but mostly of aortic media (Fig. 3). Relative blood flow and true and false lu-

men shape are very variable and depend on the size of the entry tear; the degree of media degeneration; the presence, location, number and size of re-entry tears; and the number and resistance of side branches supplied by the true versus false lumen. The size of the two channels, orientation and degree of arterial enhancement, therefore, do not allow reliable identification of the true versus false lumen. This can usually be accomplished, however, by analysing the entire aorta and tracing the respective lumens to their origins. This is particularly important when ischemic complications occur (cerebral, renal, mesenteric, or lower limb) and percutaneous treatment options are contemplated.

Anatomic Classification of Aortic Dissection

We use the 1970 Stanford classification of AD, which is traditionally based exclusively on the location of the dissection flap [13]. In addition, we specifically describe the PIT site as advocated by Gripeps Mt. Sinai cardiovascular surgical group [14], which was not included in the original Stanford classification scheme.

Definition of a Stanford Type A Dissection

Type A dissection is exclusively based on the presence of a dissection flap in the ascending aorta (anything proximal to the origin of the brachiocephalic artery), irrespective of PIT location, which may be in the ascending aorta as well, as seen in approximately 60% of Stanford type A dissections, but can also be located more distally in the arch or descending aorta with retrograde extension into the ascending aorta. Involvement of the ascending aorta in acute dissection is a surgical emergency owing to its high mortality rate if untreated (1-3% per hour). Blood seeping through the diseased wall – even without frank rupture – can lead to pericardial tamponade. Ascending AD can extend into the sinuses of Valsalva and compromise the coronary artery ostia, causing aortic regurgitation or myocardial ischemia and also leading to frank intrapericardial rupture.

Definition of a Stanford Type B Dissection

Type B dissection is defined as absence of a dissection flap in the ascending aorta (Fig. 4). Whereas most type B dissections involve the descending aorta and have a dissection flap distal to the origin of the left subclavian artery, this is not strictly how type B dissections are defined – despite notorious propagation of misinterpretation in the literature. It is important to emphasise that type B dissections commonly have some retrograde involvement of the transverse aorta (aortic arch), and the false lumen in the arch may either be thrombosed or patent. Arch involvement without involvement of the ascending aorta (proximal to the brachiocephalic artery) is thus classified as Stanford type B. This is clinically meaningful because it predicts the biological behaviour of the process if left

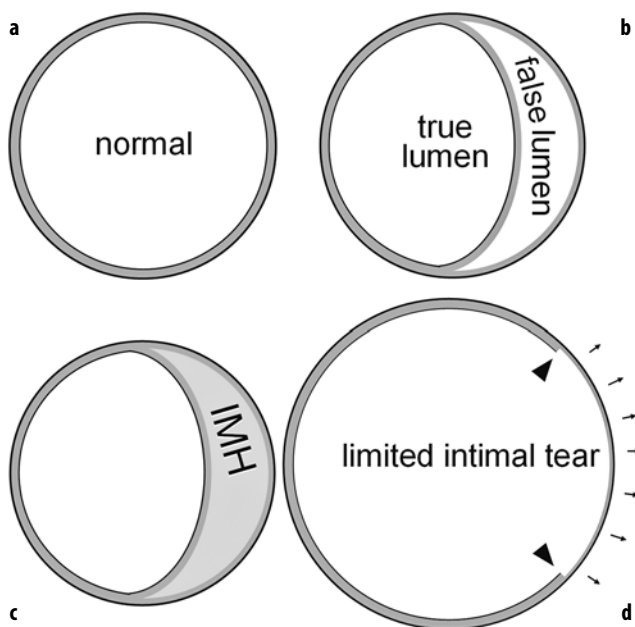


Fig. 3 a-d. Schematic of aortic dissection variants. Layers of the normal extrapericardial thoracic aortic wall consist of intima, media and adventitia (a). Most of the substance of the aortic wall is media (gray). Both intima and adventitia (drawn schematically as *black inner and outer contours* of the aortic wall) are not visible on CT. All dissection variants have an abnormal media in common, historically and erroneously referred to as cystic medial necrosis (see text for details). Classic aortic dissection (b) occurs within the outer third of the medial layer, resulting in two channels of blood flow. Note that the tissue separating the true and false lumen is mostly composed of media tissue and correctly should be termed the intimo-medial flap (in lieu of intima flap). When the separation plane within the media is filled with stationary instead of flowing blood, this is an intramural hematoma (IMH) (c). A limited intimal tear (d) is a partial-thickness tear (*arrowheads*) through the intima and inner portion of the media, exposing the residual media/adventitia, which tends to bulge out (*small arrows*) relative to the remainder of the aortic circumference. From [9], with permission

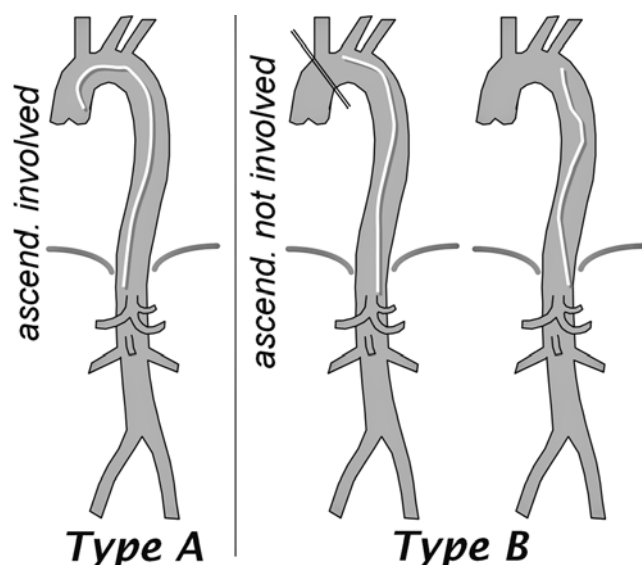


Fig. 4. Stanford classification of aortic dissection. Type A dissection (*left panel*) is defined by the presence of an intimal flap in the ascending aorta (meaning proximal to the origin of the brachiocephalic artery). Type B aortic dissection is defined by the absence of the dissection flap in the ascending aorta and therefore also includes dissections that begin in the transverse aortic arch. Importantly, it should be realised that most type B dissections have some degree of retrograde false lumen extension back into the transverse arch; this does NOT make it a type A dissection, which is a common clinical misconception. From [9], with permission

untreated, and therefore dictates appropriate management: ascending aortic involvement (acute type A dissection) mandates emergency surgical repair, whereas uncomplicated type B dissection – defined as no involvement of the ascending aorta, but regardless of arch involvement – is treated conservatively, unless there are complications. Possible complications include aortic rupture, leaking aneurysm, distal body malperfusion due to true lumen collapse, rapid false lumen expansion, refractory pain, malignant hypertension or branch-vessel ischemia, which require urgent surgical or stent-graft intervention. The terms type A (ascending involvement) and type B (no ascending involvement) are also used to describe the location of aortic IMH, if present. More detailed anatomic descriptions of IMH location have recently been proposed in the literature [4].

Intramural Hematoma as a Dissection Variant

IMH is defined as a hyperdense, often crescent-shaped, lesion within the aortic wall seen on nonenhanced CT images (Fig. 5). Whereas IMH is, strictly speaking, a nonspecific imaging finding seen in a variety of acute aortic conditions, it can be a prominent, and often the only, manifestation of a diseased aortic media. In this context, IMH is best considered a variant of AD where separation of layers within the aortic media still occurs but is filled with stationary blood or clot in what would otherwise be the false lumen, rather than with flowing

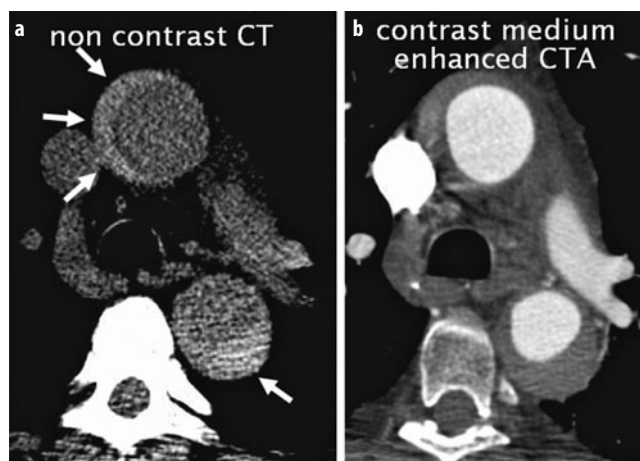


Fig. 5 a, b. Acute intramural hematoma (type A). Nonenhanced computed tomography (CT) image (**a**) in a 62-year-old hypertensive man with squeezing chest and back pain shows hyperdense crescent-shaped abnormality (*arrows*) in the ascending and descending thoracic aorta, consistent with intramural hematoma. Corresponding postcontrast medium CT angiography (**b**) image at the same anatomic level. From [9], with permission

blood (Fig. 3). IMH as a dissection variant affects patients in the same demographic group as those with classic AD, with similar risk factors, underlying media degeneration, presenting symptoms, risk of rupture and treatment implications. IMH can be very dynamic – particularly within the first hours or days of the acute event – and progression to classic dissection in this population is not uncommon.

The most commonly cited mechanism in the literature for IMH development is rupture of the vasa vasorum; however, the evidence for this conjecture is thin. Whereas absence of any communication between the true lumen and the wall hematoma was a defining condition of an IMH, this is no longer considered a strict criterion [5]. In fact, it is quite common to see small local PITs associated with IMH on contrast-enhanced CT images, which closely resemble PITs associated with classic dissection. In addition, we frequently observe cases of IMH with one or more small communications more distally between the aortic flow channel and the IMH, typically at the site of torn side-branch ostia of intercostal or bronchial arteries. These small puddles of transmural communication, also referred to as side-branch pseudoaneurysms [15], should not be confused with ulcers [16] or classic dissection with two parallel flow channels.

Dissection Variant: Limited Intimal Tear (Limited Dissection)

So called isolated or limited intimal tears are probably the least common and most unfamiliar intimomedial lesions of the aorta. This is not surprising, because these lesions are rare, difficult to detect on imaging studies and the few reported cases in the literature use inconsistent terminology, such as intimal tear without hematoma [8], subtle discrete dissection [17], incomplete dissecting aneurysm

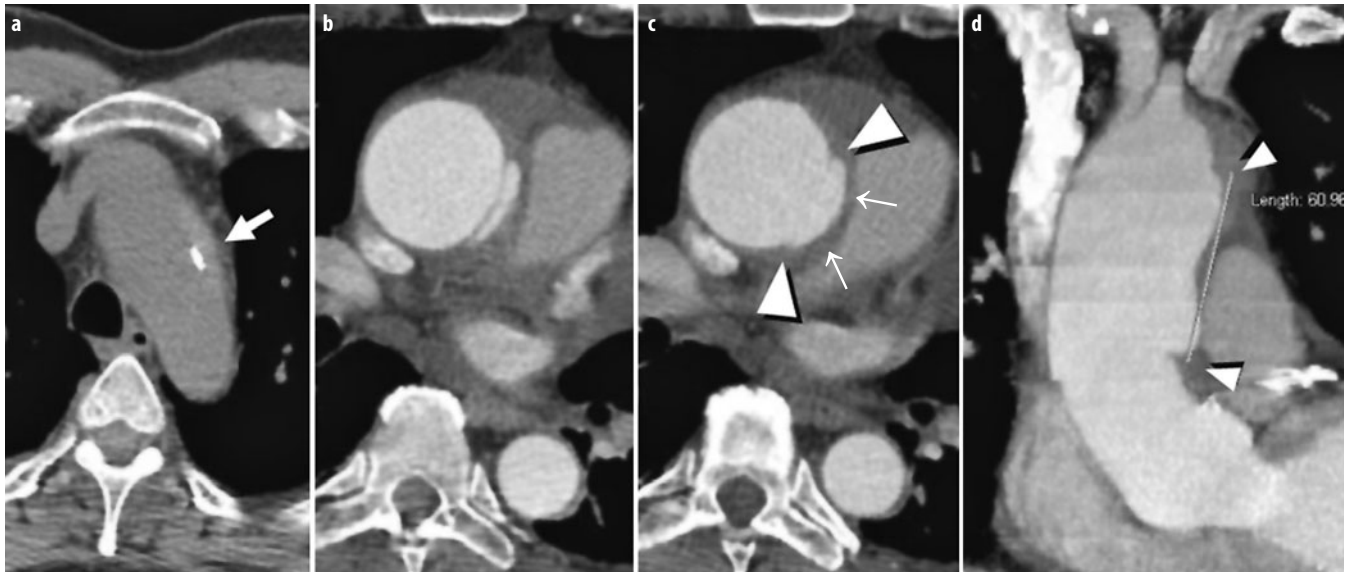


Fig. 6 a-d. Limited intimal tear of the ascending aorta. Nonenhanced computed tomography (CT) image (**a**) and electrocardiographic (ECG)-gated axial CT angiography images (**b**, **c**) show a small intramural hematoma at the level of the proximal aortic arch (*arrow* in **a**). Note the displaced small calcification, indicating the location of the intima. In the proximal ascending aorta, a single image (**b**) demonstrates a small flap, consistent with an undermined edge of a limited intimal tear. Image (**c**), immediately superior to (**b**), shows the edges of the limited intimal tear (*arrowheads*) and bulge of the exposed residual aortic wall (*small arrows*). The full longitudinal extent of the lesion is shown in a thin-slab maximum intensity projection image. **d** The tear extends from the proximal ascending aorta to the proximal arch, with a length of more than 6 cm (between *arrowheads*). From [9], with permission

[18] or spontaneous nontraumatic rupture [19]. The European Society of Cardiology recognises subtle/discrete dissection as one of the classes of AD [3]. The true prevalence of limited dissections is unknown but may be as high as 5% of patients undergoing acute ascending aortic repair, if specifically sought [8]. Limited intimal tears occur predominantly in the ascending aorta and are often associated with aortic dilatation. The pathologic findings of media degeneration and the association with Marfan syndrome suggest that these lesions are part of the dissection spectrum. Pathologically, these lesions represent partial-thickness linear or stellate tears through the intima and underlying superficial media, exposing the deeper media and adventitia, resulting in focal bulging of the thinned residual aortic wall (Fig. 3) [8].

The edges of a limited intimal tear can be undermined to a variable degree but do not result in a more extensive separation between the torn and intact layers of the aortic wall or frank dissection of medial layers. Owing to this morphology, these lesions are particularly difficult to detect on imaging studies. In fact, the nine patients described in Svensson's study were all diagnosed intraoperatively despite multiple preoperative noninvasive and invasive studies, including ultrasonography (US), CT, magnetic resonance imaging (MRI) and angiography [8].

Angiographically, these lesions resemble “mushroom-cap” lesions, or very localised dissections. On nongated contrast-enhanced CT, the focal outpouching of the aortic contour is difficult to distinguish from cardiac pulsation artefacts, but with thin section acquisitions on state-

of-the-art equipment, these lesions can be at least suspected. ECG gating certainly improves the confidence in detecting or ruling out these lesions. Limited intimal tears with focal bulging of the aortic contour are at one end of the spectrum of aortic intimomedial lesions, and transitional features can often be observed. CT sections at the level of an undermined edge typically show a linear filling defect that is indistinguishable from a dissection flap when viewed on a single slice. Limited intimal tears can also be associated with intramural blood in proximity of the lesion. Both of these findings – a small local flap of intimomedial tissue and a small IMH at both ends of a longitudinal tear – are shown in the same patient imaged with ECG-gated CTA (Fig. 6).

The main implication for the diagnostic imager is that with continuously improving temporal and spatial resolution of modern CT systems, ever more subtle, acute aortic lesions are becoming detectable and should not be ignored. In our opinion, the clinical implication is identical to other acute aortic syndromes, and surgical repair is indicated when the ascending aorta (type A) is involved.

Intramural Hematoma – A Clarification

Whereas we maintain the importance of considering IMH first and foremost as a nonspecific imaging finding that can be seen in a broad variety of acute aortic abnormalities, the term IMH is used inconsistently in the literature to either reflect an imaging finding; a specific variant of

AD; or the equivalent of a “disease”, where several underlying conditions and diseases are lumped into a pseudocategory among the causes of the acute aortic syndrome [2]. Unfortunately, this has been done consistently throughout the literature, despite the fact that patient demographics, prognosis and potential IMH progression can be quite different depending on the underlying cause.

In the context of IMH being semantically treated as a disease entity, its lump-sum reported incidence is approximately 5-20% of patients admitted for acute aortic syndromes [4]. Independent of the underlying cause, a type A IMH (involving the ascending aorta) has a four times greater mortality rate than type B IMH (39.1% vs 8.3%). Surgical treatment for type A IMH is considered the treatment of choice in the West [4], regardless of underlying pathology. In Asia, however, type A IMH is increasingly managed conservatively, with aggressive antihypertensive treatment and short-interval follow-up. Type B IMH is treated conservatively, unless complications or progression occur.

The key message for the imager in this context is that regardless of the semantics, and independent of the underlying aortic lesion – which can range from rupturing atherosclerotic or mycotic aneurysm, aortic trauma (iatrogenic or noniatrogenic), PAU and lesions within the dissection spectrum, the finding of intramural aortic blood in a symptomatic patient is always an aortic emergency.

Penetrating Atherosclerotic Ulcer

PAU are a distinct entity and represent approximately 5-15% of acute aortic syndromes [4]. Pathologically, these lesions are defined as ulcers of the inner lining of the aorta, typically a thickened intima with chronic atherosclerotic change, that penetrate through the internal elastic lamina into the aortic media. This can result in a local aortic wall hematoma, or it can penetrate through the entire aortic wall and result in a (contained) rupture (Fig. 7). As the internal elastic lamina cannot be resolved on any available imaging studies, this definition cannot be used as a diagnostic criterion on US, CT or MRI. As a result, the radiologic diagnosis of a PAU is based on the presence of an ulcer-like aortic-wall lesion, which typically protrudes beyond the aortic circumference, commonly associated with a local IMH or signs of rupture. Indeed, the term ulcer-like projection (ULP) has been used in the Japanese literature to describe these lesions. Clinical correlation is crucial, as ulcer-like lesions of variable depth can be a common incidental finding in asymptomatic patients. In the absence of symptoms and in the absence of IMH, ulcer-like lesions represent either a benign, ulcerated atherosclerotic plaque (which does not penetrate into the media) or a chronic, healed (re-endothelialised) ulcer. There may be a continuum between the latter chronic healed ulcers and atherosclerotic

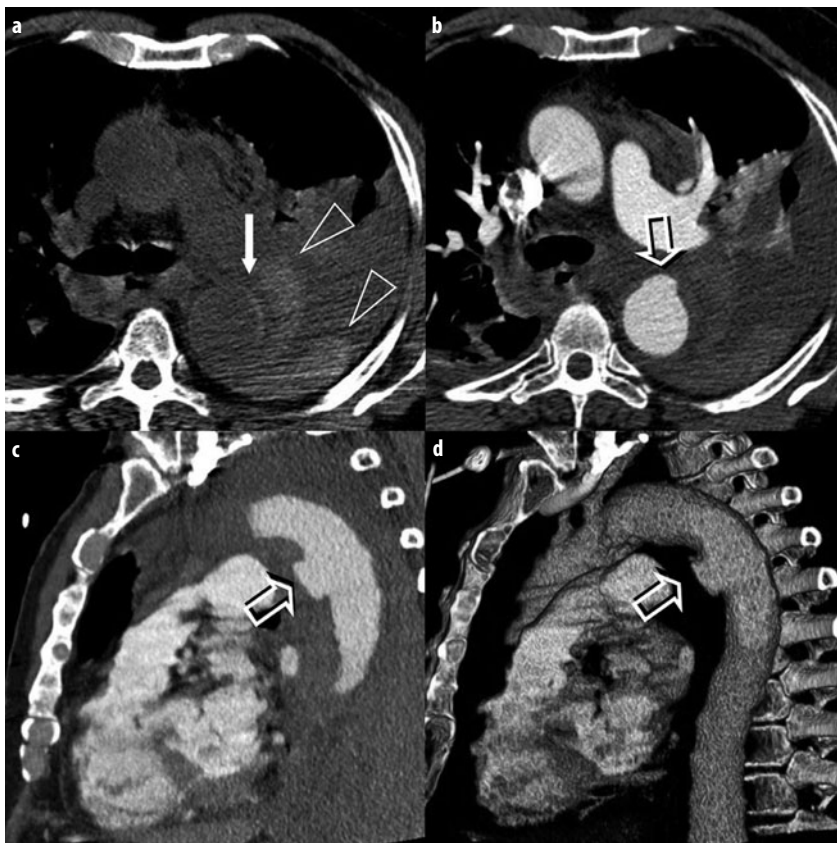


Fig. 7 a-d. Penetrating atherosclerotic ulcer (PAU). Nonenhanced computed tomography (CT) image (a) in an 83-year-old man with acute chest pain shows small hyperdense crescent-shaped abnormality (arrow) in the descending thoracic aorta, consistent with intramural hematoma. Note a large amount of hyperdense periaortic and pleural fluid (arrowheads), indicating mediastinal hematoma and hemothorax. Corresponding post-contrast medium CT angiogram (b) image at the same anatomic level shows large ulcer (open arrow) in the descending thoracic aorta, which is better characterised on a sagittal reformation (c) and on a volume-rendered image (d). From [9], with permission (for color reproduction see p 273)

aneurysms, as some believe most degenerative atherosclerotic aneurysms originate from PAUs.

PAUs can be considered a consequence of a severely diseased intima (i.e. advanced atherosclerosis). This is in contradistinction to AD and dissection variants where intimal disease is not a prerequisite but in which degenerative changes of the elastic fibres and smooth-muscle cells of the aortic media are paramount. This is also in keeping with the observation that PAUs tend to occur in older patients with significant atherosclerotic plaque burden, concomitant history of hypertension and predilection for involvement of the descending thoracic aorta. More than one PAU is not uncommon in a given patient. When IMH is seen in patients with PAU, it is usually more focal than IMH in patients within the dissection variant category. If a dissection flap-like filling defect is seen in patients with a PAU, it is usually due to deep overhanging edges of the ulcer rather than a true dissection (which would require entry- and exit-tears, and a double-barrel flow channel). Also, IMH associated with PAU usually does not evolve into classic dissection (which requires a diseased media). Some morphologic overlap and ambiguity on imaging studies, however, do occur.

The risk of rupture of thoracic PAUs is in the range of 20-50% [4] and associated with a high mortality rate. Given the typically older patient population with advanced atherosclerosis, the risk of perioperative neurologic deficit (28%) and mortality is high (7-25%). Endovascular repair with stent-grafting has emerged as a preferred therapeutic alternative for descending thoracic aortic penetrating ulcers owing to its lower perioperative morbidity and mortality rates of 9% and 12%, respectively [20].

Summary: CTA Image Evaluation in Acute Aortic Syndromes

CT evaluation in patients presenting with an acute aortic syndrome begins with acquiring the best study technically possible, owing to inherent obstacles in imaging the thoracic aorta and subtleties of certain aortic lesions. This should always include noncontrast images to exclude intramural aortic blood, followed by an ECG-gated CTA of the thoracic aorta (if possible), and nongated angiographic study of the abdominal aorta and pelvic vessels. A thorough review of the transverse CT source images for any vascular or extravascular abnormality within the chest, lung, airways, abdominal wall and visceral organs is required. 3D and 4D manipulation of the data set can help with visualisation of subtle or complex lesions and for treatment planning but is not generally essential for diagnosis. Knowledge of the pathologic entities and associated imaging findings related to acute aortic syndromes, discussed throughout this article, allows for detection and accurate interpretation of pertinent imaging findings. Identification and an attempt to characterise an aortic lesion as classic AD, dissection variant, PAU or rupturing aneurysm is typically the first step (Table 2). The second step – which is arguably more

important than the first step of lesion characterisation – is ascertaining whether the lesion involves the ascending aorta. Acute aortic lesions involving the ascending aorta are considered a surgical emergency. Signs of instability with periaortic stranding and haemorrhage or frank rupture are usually obvious and often correlate with refractory pain and deteriorating clinical symptoms. These findings are also a surgical emergency regardless of lesion morphology or location. Localising any focal lesion relative to aortic side branches that may be amenable to stent-grafting is key to directing management decisions and planning therapeutic intervention. Lastly, a detailed assessment of morphology of the true versus false lumen and respective blood supply of aortic branches is important in the setting of clinically or chemically suspected side-branch ischemia.

References

1. Hayter RG, Rhea JT, Small A et al (2006) Suspected aortic dissection and other aortic disorders: multi-detector row CT in 373 cases in the emergency setting. *Radiology* 238: 841-852
2. Vilacosta I, Roman JAS (2001) Acute aortic syndrome. *Heart* 85:365-368
3. Erbel R, Alfonso F, Boileau C et al (2001) Diagnosis and management of aortic dissection. *Eur Heart J* 22:1642-1681
4. Evangelista A, Mukherjee D, Mehta RH et al (2005) Acute intramural hematoma of the aorta: a mystery in evolution. *Circulation* 111:1063-1070
5. Hiratzka LF, Bakris GL, Beckman JA et al (2010) 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with Thoracic Aortic Disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. *Circulation* 121:e266-369
6. Dake MD, Kato N, Mitchell RS et al (1999) Endovascular stent-graft placement for the treatment of acute aortic dissection. *N Engl J Med* 340:1546-1552
7. Dake MD, Wang DS (2006) Will stent-graft repair emerge as treatment of choice for acute type B dissection? *Semin Vasc Surg* 19:40-47
8. Svensson LG, Labib SB, Eisenhauer AC, Butterly JR (1999) Intimal tear without hematoma: an important variant of aortic dissection that can elude current imaging techniques. *Circulation* 99:1331-1336
9. Fleischmann D, Mitchell RS, Miller DC (2008) Acute aortic syndromes: new insights from electrocardiographically gated computed tomography. *Semin Thorac Cardiovasc Surg* 20: 340-347
10. Fedak PW, Verma S, David TE et al (2002) Clinical and pathophysiological implications of a bicuspid aortic valve. *Circulation* 106:900-904
11. Erdheim J (1929) Medionecrosis aortae idiopathica. *Virch Arch Pathol Anat* 273:454-479
12. Erdheim J (1930) Medionecrosis aortae idiopathica cystica. *Virch Arch Pathol Anat* 276:187-229
13. Daily PO, Trueblood HW, Stinson EB et al (1970) Management of acute aortic dissections. *Ann Thorac Surg* 10:237-247

14. Ergin MA, O'Connor J, Guinto R, Griep RB (1982) Experience with profound hypothermia and circulatory arrest in the treatment of aneurysms of the aortic arch. Aortic arch replacement for acute arch dissections. *J Thorac Cardiovasc Surg* 84:649-655
15. Williams DM, Cronin P, Dasika N et al (2006) Aortic branch artery pseudoaneurysms accompanying aortic dissection. Part I. Pseudoaneurysm anatomy. *J Vasc Interv Radiol* 17:765-771
16. Williams DM, Cronin P, Dasika N et al (2006) Aortic branch artery pseudoaneurysms accompanying aortic dissection. Part II. Distinction from penetrating atherosclerotic ulcers. *J Vasc Interv Radiol* 17:773-781
17. Chirillo F, Salvador L, Bacchion F et al (2007) Clinical and anatomical characteristics of subtle-discrete dissection of the ascending aorta. *Am J Cardiol* 100:1314-1319
18. Murray CA, Edwards JE (1973) Spontaneous laceration of ascending aorta. *Circulation* 47:848-858
19. Widder DJ, Novelline RA, Derkac WM (1983) Spontaneous nontraumatic rupture of the thoracic aorta. *J Thorac Cardiovasc Surg* 86:626-628
20. Demers P, Miller DC, Mitchell RS et al (2004) Stent-graft repair of penetrating atherosclerotic ulcers in the descending thoracic aorta: mid-term results. *Ann Thorac Surg* 77:81-86

Clinical Applications of 3D Imaging in Thoracic Vascular Pathology: Pulmonary Vascular Applications

Mathias Prokop

Department of Radiology, Radboud University Nijmegen, The Netherlands

Introduction

The chest vasculature profits particularly from 3D imaging. In principle, with regard to 3D image quality, it is irrelevant whether the data set is acquired with magnetic resonance angiography (MRA) or computed tomography angiography (CTA), but near isotropic spatial resolution is an important prerequisite for optimal results. The challenges, however, encountered by MRA and CTA are different: MRA suffers mainly from limited coverage and inhomogeneous signal intensity within the vessels, whereas CTA has problems with image noise and superimposing bone. Both are influenced by the fact that, frequently, not only the systemic or pulmonary vascular system but multiple portions of both vascular systems are enhanced simultaneously and may have to be separated by processing. Separate display of systemic veins, pulmonary veins, pulmonary arteries, or systemic arteries is frequently challenging and requires major postprocessing.

Three-dimensional imaging comprises exploration of the 3D data set using various postprocessing tools: it ranges from simple multiplanar reformations (MPR) to curved planar reformations (CPR), maximum intensity projections (MIP), shaded-surface displays (SSD), and volume rendering techniques (VRT). Rendering can involve only a single layer of pixels (MPR or CPR), a parallel slab of varying thickness (thick MPR, thick CPR, slab MIP, slab VRT) or a whole volume (MIP, SSD, or VRT) that can comprise the entire data set or an edited volume in which certain regions are included or excluded.

Simple 3D imaging techniques, such as thick MPR, thick CPR, or slab MIP, are used on a routine basis for chest imaging. Advanced 3D imaging tools, such as VRT, are most valuable in cases in which the anatomy is complex or visualization of the spatial relationships with surrounding structures is important for diagnosis or therapy planning. Complex visualization tools are almost always used after editing out disturbing and superimposing structures or actively including the vascular structure of interest.

The following text describes appropriate data acquisition strategies for 3D imaging with CT and MR and discusses the various 3D imaging techniques. As examples for typical clinical applications for 3D vascular imaging of the chest, this chapter focuses on the pulmonary vasculature.

Data Acquisition for 3D Imaging

MR Angiography

MRA of the chest needs to be based on near isotropic data acquisition for 3D imaging. The most frequently used non-contrast-enhanced technique is steady-state free precession (SSFP) imaging, also known as balanced fast-field echo (FFE), true fast imaging with steady-state precession (true-FISP) or fast imaging employing steady state acquisition (FIESTA). This technique is based on segmented k-space acquisition and creates very high signal intensity within blood. When combined with parallel imaging, speed and/or spatial resolution can be increased.

The alternative is contrast-enhanced MRA. For chest imaging, gadolinium chelates are injected intravenously at a flow rate of 1.5-3 ml/s. The scan is initiated by a bolus tracking sequence. Data can be either acquired dynamically with lower spatial resolution but high temporal resolution or at specific phases of the contrast enhancement with high spatial resolution but low temporal resolution. For both variants, a heavily T1-weighted sequence with the shortest possible rotation time (TR) is chosen. To maximize spatial resolution, the width of the imaging slab is kept as narrow as possible.

For most thoracic vessels, no electrocardiographic (ECG) gating is required. As soon as heart or coronary imaging is required, ECG gating becomes mandatory. ECG gating increases acquisition time and makes preparation (e.g., electrode lead placement) more challenging. Typical acquisition parameters are given in Table 1.

CT Angiography

Scan Parameters

Isotropic data acquisition for CTA of the chest is already possible with a 4-slice scanner. In this case, scan duration remains in the order of 20-30 s. With 16-slice scanners, scan duration can be reduced to <10 s. With 64-slice scanners, retrospective ECG gating of the entire aorta is possible without having to sacrifice resolution. With the

Table 1. Magnetic resonance angiography (MRA) of the chest: example of ECG-synchronized scan sequences

	Contrast-enhanced MRA	Steady-state free procession MRA
Sequence	3D GE (FLASH)	T2-prepared segmented 3D SSFP
Breathing	Breath-hold	Free breathing
T2 preparation time	–	40 ms
K-space sampling	Asymmetric	Symmetric
Field of view (FOV)	400 × 400 mm	400 × 400 mm
Flip angle	25°	90°
TR/TE (ms)	2.5-3/1.0-1.5	2.3/1.0
Acceleration factor	2-4	2
Matrix size	320 × 512	256 × 256
Resolution (mm)	1.6 × 0.8 × 1.0-1.6	1.6 × 1.6 × 3 (1.5 interpolated)
ECG synchronization	Diastole	Diastole
Navigator	–	30-60% acceptance rate
Imaging time	20 s	5-10 min
Contrast dose	0.2 mmol/kg	–
Flow rate	1.5-2 ml/s	–
Timing	2 ml test bolus	–

Table 2. Computed tomography angiography (CTA) of the chest: suggested scan parameters

	4-slice	16-slice	64-slice
Scanner			
Collimation (mm)	1.0-1.25	0.5-1.25	0.5-0.625
Pitch	1.5	1.25	0.9
Slice thickness (mm)	1.25	0.75-1.25	0.75-0.9
Exposure settings			
Standard (no ECG)	100-200 mAs	90-180 mAs	75-150 mAs
ECG triggering	–	200-300 mAs	150-250 mAs
ECG gating (chest) ^a	–	–	200-300 mAs
ECG gating (coronaries) ^b	–	400-600 mAs	500-700 mAs
Body weight (kg)	<60 kg	60-80 kg	>80 kg
Tube voltage (kV)	80 kV	100 kV	120 kV

ECG, electrocardiography

^a Best results if tagged (ECG used) and untagged (ECG neglected) reconstructions are created from the same dataset

^b ECG dose modulation recommended

newest generation of scanners, prospective ECG triggering becomes feasible for scanning not only the heart but also the aorta. With all techniques, slice collimation is kept in the order of 0.5-1.25 mm (Table 2).

Exposure Parameters

Radiation exposure has to be adapted to patient size, ideally using automated exposure control algorithms and adaptive filtering. Wherever possible, iterative reconstruction techniques should be used. Image quality can be further optimized and radiation exposure reduced by lowering the tube voltage from 120 kV to 100 kV in standard-size patients (up to 80 kg) and 80 kV in slim patients and children (<60 kg). The result is very high vascular enhancement that requires wider window settings for MPR and MIP. VRT images are usually of excellent quality (Fig. 1).

ECG Synchronization

Retrospective ECG gating uses a spiral acquisition to continuously acquire data and retrospectively combine acquisition data from the desired cardiac phase to reconstruct an image. The technique is very dose inefficient: for reconstruction of images from a specific cardiac phase between 50% and 80% of the radiation dose given to the patient is not used for reconstruction. However, images can be reconstructed during multiple cardiac phases, which allows cardiac and valvular function to be assessed.

Some vendors allow for separate reconstruction of tagged and untagged images. Tagged images use the ECG information and “freeze” the cardiac motion (just like all retrospectively gated acquisitions) but suffer from a higher image noise because they use only part of the acquired data for image reconstruction (see above). Untagged images neglect the ECG information and use all raw data for

Fig. 1 a, b. Prospective echocardiographically triggered low-dose control computed tomography angiography of 10-year-old boy with scimitar syndrome and an extralobar sequester, performed with 116×0.625 -mm collimation at 80 kV and 135 mAs [computed tomography volume dose index = 3.2 mGy]. The scimitar veins were anastomosed to the right atrium and the sequester was embolized. **a** Volume rendering better demonstrates drainage of the middle and lower lobes via the scimitar vein and the systemic supply of the sequester arising from the abdomen (celiac trunk). **b** Maximum intensity projection (MIP) better demonstrates that embolisation was not successful: there is residual perfusion of the systemic supply of the lung (*arrow*). The density discrimination of MIP makes it possible to determine that the connection between the scimitar vein and right atrium is no longer patent (*arrow-head*) (for color reproduction see p 273)

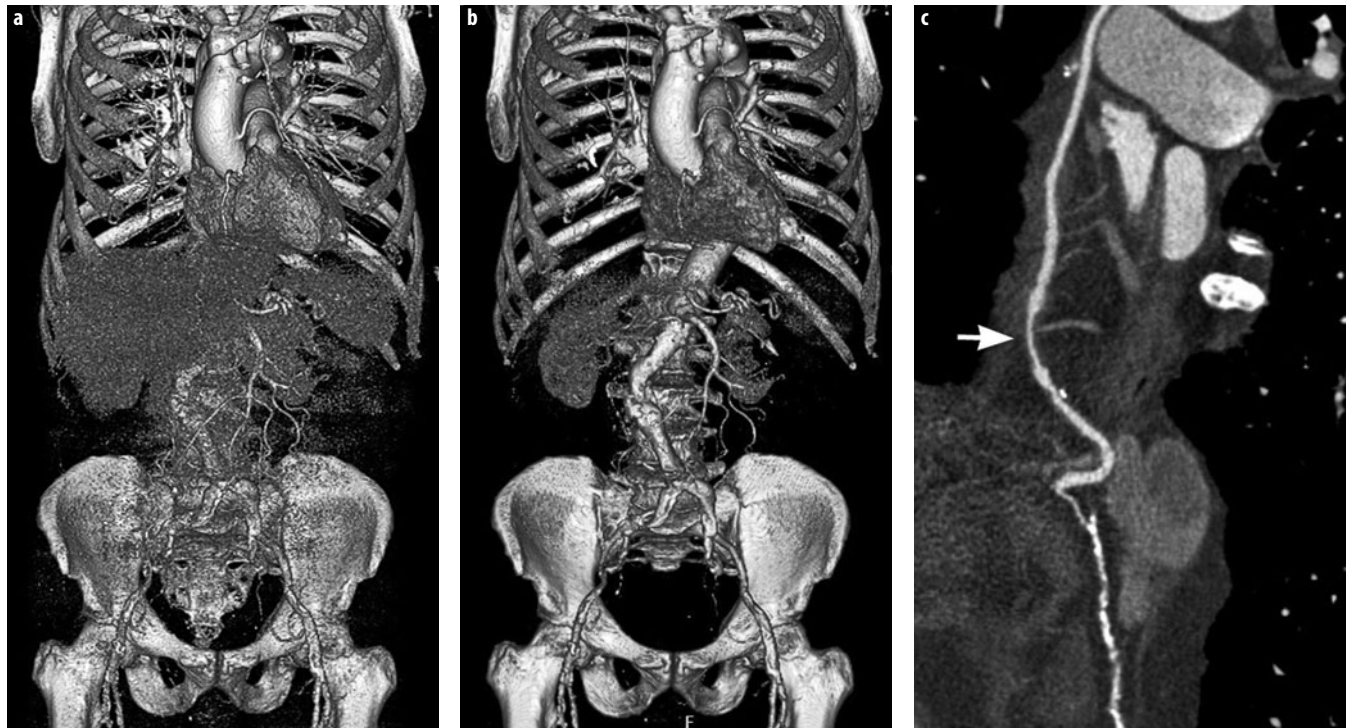
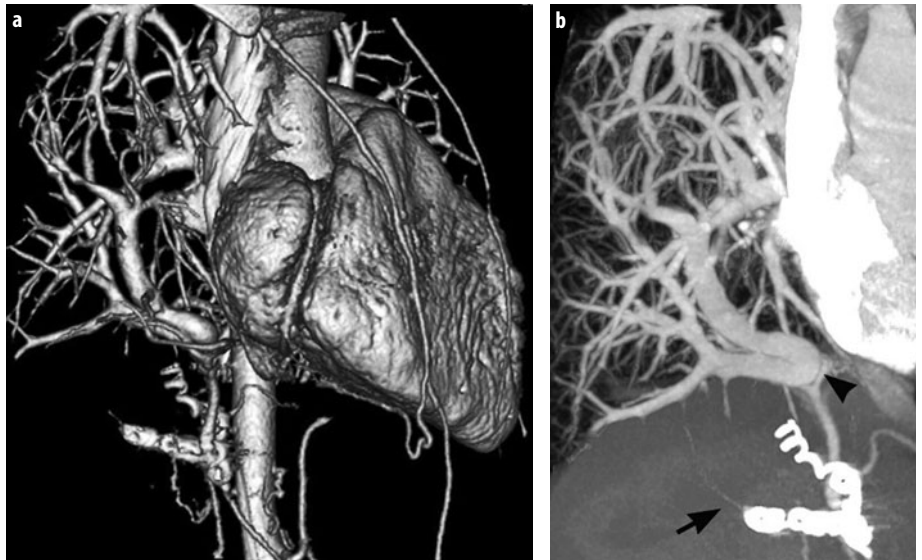


Fig. 2 a-c. Preoperative retrospective electrocardiographically (ECG)-gated computed tomography angiography of the entire thoracoabdominal aorta in a 73-year-old man at 120 kVp and 250 mAs. **a** Volume rendering (VRT) of the ECG-gated reconstruction suffers from artifacts due to noise and flying pixels. **b** Untaged reconstruction (neglecting the ECG information) leads to less noise and better VRT quality but blurring of the cardiac structures. **c** The curved planar reconstruction through the coronary artery bypass graft is good enough to detect a bypass stenosis on the ECG-gated data set (*arrow*) (for color reproduction see p 273)

image reconstruction, irrespective of the cardiac phase. This results in a maximized signal-to-noise ratio with superb image quality (especially for VRT) in areas that hardly pulsate, such as the pulmonary arteries, the aortic arch, or descending aorta. Regions that pulsate become blurred due to cardiac motion. By using both types of re-

constructions, a good compromise can be reached between cardiac and vascular imaging (Fig. 2).

Prospective ECG triggering is normally based on a sequential acquisition technique (step and shoot) and acquires images of the heart during a specific predefined phase, usually the diastole. Data is acquired only during

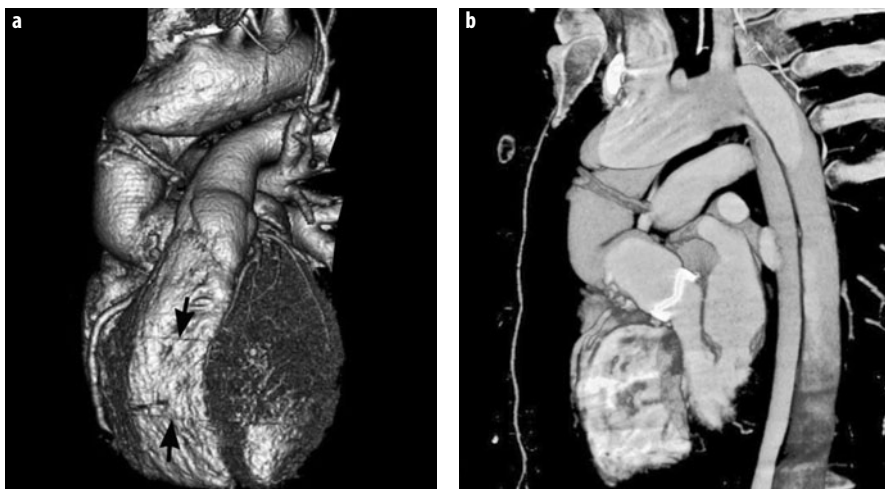


Fig. 3 a, b. Prospectively ECG-triggered scan of the thoracic aorta in a patient after composite graft of the aortic valve and ascending aorta in type A aortic dissection. Note slight step artifacts in the region of the heart (*arrows*). **a** Volume rendering technique (VRT) with surface shading. **b** VRT without shading after cutting away part of the left chest. Image **a** has been edited to (partially) remove the spine (for color reproduction see p 273)

this predefined phase, which makes this technique very radiation-dose efficient. However, changes in heart rate may cause the cardiac phase captured during the acquisition that is not fully consistent between each stepwise acquisition (Fig. 3). For this reason, the radiation dose is switched on a little earlier and switched off a little later than absolutely acquired. This so-called “padding” ensures more consistent image quality and less dependence on heart rate. Best results are seen in patients with low heart rate (<60 bpm), which is why administration of oral or IV beta-blockers is advisable.

Contrast Material Injection

CTA relies on the intravenous injection of iodinated contrast agents during the scan. Contrast enhancement depends on the iodine injection rate (IDR; flow rate $F \times$ concentration C) and total iodine dose (total volume V of injected contrast material $\times C$). After contrast injection, the intravascular enhancement builds up rapidly during the first pass and then continues to rise steadily in the recirculation phase. During the first pass, the IDR is the dominant factor, whereas during recirculation, the total iodine dose determines contrast enhancement. This means that a high IDR has to be chosen for short injection durations, whereas a sufficiently high iodine dose has to be chosen for longer injection durations. In clinical practice on modern scanners, this dilemma is solved by choosing high IDR (depending on patient size) and employing bolus triggering.

The start delay (D) for bolus triggering is increased to 8–10 s for very fast acquisition times to allow for sufficient contrast build-up during the first pass. The total iodine dose (TID) is adapted to the scan duration (T_{inj}) by the following formula: $TID = IDR \times (D + T_{inj})$. Contrast volume and flow rate can then be calculated as follows: $V = TID/C$ and $F = IDR/C$.

By placing the trigger region in the pulmonary trunk or in the proximal descending aorta, enhancement can be

optimized for the pulmonary vasculature or the aorta. Visualization of the superior vena cava requires a different approach: best results are obtained with the simultaneous injection of 1:5–1:10 diluted contrast agent into both cubital veins using a y-shaped adaptor piece that connects the injector to both venous cannulas.

3D Imaging Techniques

Primary Sections

The orientation of primary sections is axial (= transverse) for CTA and, in most cases, parasagittal (parallel to the aortic arch) or coronal (for the pulmonary vessels and systemic veins) for MRA. If the level of radiation dose has been chosen correctly for CTA, the thin axial sections acquired during scanning contain too much noise to be used for diagnostic purposes. Image analysis is therefore mainly based on thick MPR or other 3D techniques. The only exception is imaging of the coronary arteries, for which the radiation dose is chosen so that a diagnostic quality is gained also for the original set of thin sections. Immediate review of the primary sections for MRA is an option, but the use of MPR allows for better choice of the optimum imaging plane.

Multiplanar and Curved Planar Reformations

If abnormalities are suspected, evaluation in a problem-adapted plane is mandatory.

- Interactive MPRs are best suited for this task. Longitudinal sections help identify the length and shape of a structure of interest, whereas sections perpendicular to the vessel's course help define the vessel diameter precisely and thus the degree of stenosis or the size of an aneurysm. For CTA, 3- to 5-mm thick MPR are most appropriate. For MRA, increasing the MPR thickness can be useful if the noise is too high.

- CPRs along the course of a vessel substantially simplify its evaluation. To completely evaluate the vessel, CPR must be rotated around the centerline of the vessel. This centerline is determined semiautomatically by modern vessel-tracking software using two-click (mark beginning and end of vessel), one-click (mark vessel), or zero-click (completely automatic) techniques. Completely automatic techniques are only available for the coronaries. CPRs are mainly used for this purpose but are also helpful for assessing the supraaortic vessels.

Stretching the vessel out can simplify length measurements but causes the anatomic overview to deteriorate. Vessel cross-sections perpendicular to the centerline substantially improve the grading of stenosis or evaluation of other abnormalities. In addition, software tools are available that automatically calculate the local vascular diameter and display the location and degree of maximum vessel stenosis or dilatation. Such tools are most reliable for the aorta but may fail for smaller vessels, especially in cases with increased image noise (obese patients), crossing or branching vessels (errors in determining the vessel wall), or limited spatial resolution.

Maximum Intensity Projection

MIP is an excellent tool for providing angiography-like images. It optimizes contrast between vessel and background, and is therefore excellently suited for displaying peripheral pulmonary vessels or bronchial arteries that are otherwise hard to demonstrate by 3D techniques. Slab MIP with a section thickness of approximately 10 mm is most suitable for the chest. MIP has been used as a standard technique for MRA, usually without editing the acquired volume. The technique provides an angiography-like display of the aorta and pulmonary vessels but has the disadvantage that superprojections may hide important details (Fig. 4). As with CTA, interactive MPR, CPR, or volume rendering should be used as an alternative.



Fig. 4. Maximum intensity projection (MIP) of the pulmonary vasculature after removal of the chest wall, ribs, and spine. Due to superprojection of the various vessels, the focal stenosis in this patient with chronic thromboembolic pulmonary hypertension can be easily missed (*arrow*)

Shaded Surface Displays

Shaded surface displays can demonstrate complex 3D relationships but are no longer used. The technique of choice for this purpose is volume rendering.

Volume Rendering

Volume rendering has become the standard rendering technique for many CTA indications in the chest and is increasingly used for MRA data sets, as well. An appropriate color scale can be used to better differentiate between vessels of varying density (such as arteries and veins) or to differentially display lumen and calcified plaques, stents or coils (see Fig. 1). A color scale may also be used to code density range, which is particularly helpful for evaluating enhancement differences in the pulmonary parenchyma (Fig. 5). Editing with bone and

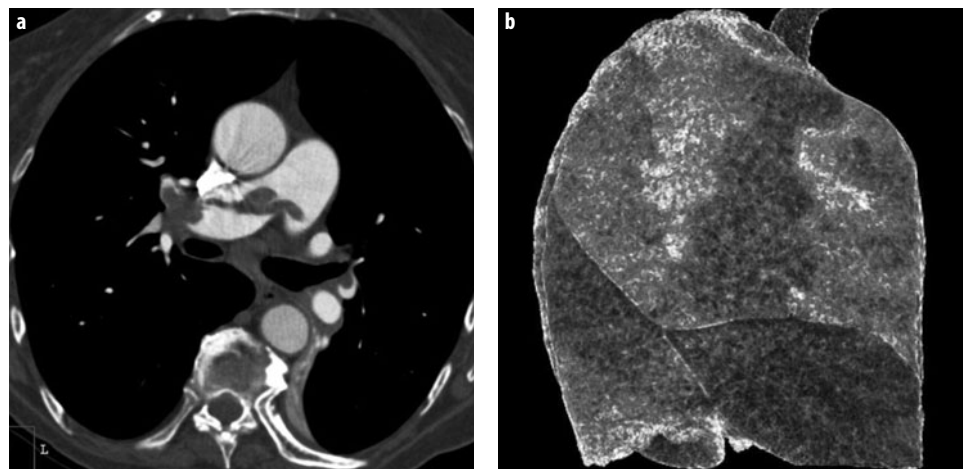


Fig. 5 a, b. **a** Recurrent pulmonary emboli and chronic as well as fresh components. **b** Color-coded volume rendered image of the lungs demonstrates differences in density due to focal hypoperfusion (for color reproduction see p 273)

overlying structure removal may further improve visualization of small detail (see Fig. 1 or 4) but is usually not essential. Thin-slab rendering is an easy tool to free the data set from overlying structures without much further editing.

Virtual Angioscopy

Virtual angioscopy relies on the same principle as other virtual endoscopic techniques with the exception that the high-density areas (contrast-enhanced vessel lumen) must be rendered transparent. Virtual angioscopy, however, frequently suffers from noise-related vascular irregularities and from difficulties in finding the correct opacity settings, especially in small vascular structures. Vessels that are in direct contact with the vessel of interest may blend and leave a connecting hole in the vascular wall. Virtual angioscopy rarely adds diagnostic information over other 2D- or 3D-rendering techniques. In a few cases, virtual angioscopy may improve the assessment of stent-graft localization relative to branching arteries or may be used to assess the abnormalities in the region of the cardiac valves (Fig. 6). Volume rendering with the opacity settings used for virtual angioscopy may often be superior for this purpose, especially when the vessel is cut open perpendicular or longitudinal to the course of the lumen.

Pulmonary Arteries

Three-dimensional imaging is best suited for vascular anomalies and for displaying aneurysms and stenosis, for example, in chronic thromboembolic pulmonary hypertension. Developmental pulmonary artery abnor-

malities in children should be evaluated with MRA whenever possible. If CTA is necessary, low-dose techniques with reduced kVp (effective dose approximately 1-2 mSv) can be employed in most patients. CTA may be preferred because of substantially faster scan times, which allow for less sedation in smaller or non-compliant children.

Congenital Aneurysms and Stenoses

- *Congenital aneurysms* of the pulmonary arteries usually present as fusiform dilatation of a central pulmonary artery and are best displayed by VRT. They are associated with other pulmonary or cardiovascular abnormalities and in particular often result from blowout by systolic jets just distal to a stenotic pulmonary valve.
- *Pulmonary artery coarctation* is characterized by pulmonary artery stenoses in variable number, severity, and anatomical distribution. This entity consists of short focal pulmonary artery strictures without wall thickening or perivascular abnormality of the mediastinal fatty tissue. It is often associated with pulmonary atresia and congenital cardiac defects. It can be related to intrauterine rubella infection or may be associated with Ehlers-Danlos or Williams-Beuren syndromes.
- *Proximal interruption of one main pulmonary artery* refers to the obliteration of a proximal segment of one pulmonary artery, which can reconstitute distally or remain occluded into the lung periphery. It should be differentiated from absence (agenesis) or *aplasia of a pulmonary artery*, in which no pulmonary artery can be found and which is accompanied by a mediastinal

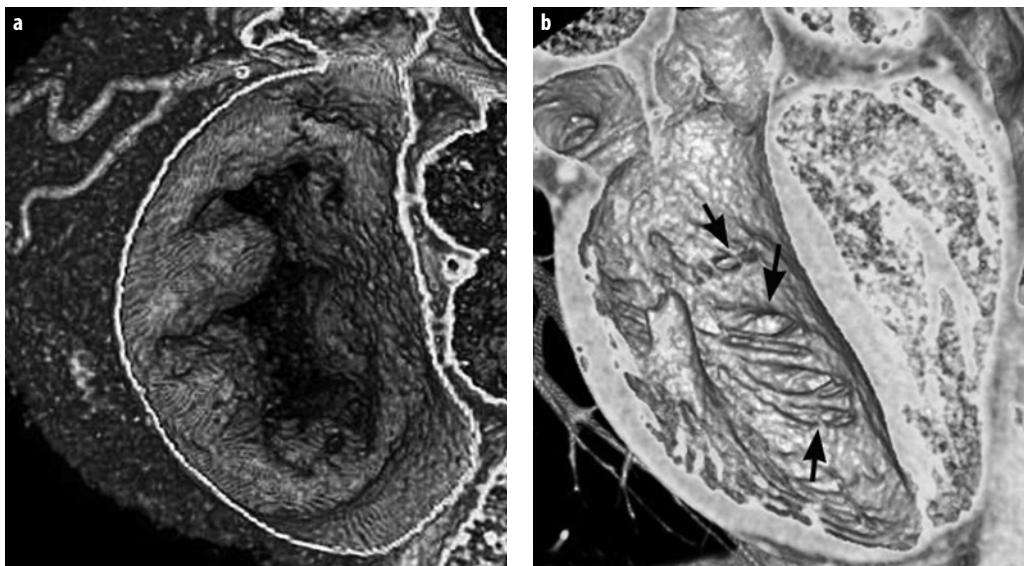


Fig. 6 a, b. Virtual angioscopy is most useful for displaying the inner surface of complex 3D structures, such as the heart. Usually, rendering without using perspective yields good results. **a** Display of the mitral valve in diastole as seen from left atrium. **b** Section parallel to the aortic outflow tract demonstrating multiple outpouchings of the left ventricular wall (cardiac diverticula, arrow) in a patient with arrhythmia (for color reproduction see p 273)



Fig. 7. Agenesis of the left lung: volume rendering image without color coding

shift to the side of the hypogenetic lung (Fig. 7). The pulmonary blood supply is maintained via bronchial or intercostal collaterals; anomalous arteries originating from the ascending aorta (right lung), descending aorta (left lung), subclavian or brachiocephalic artery; and, rarely, infradiaphragmatic collaterals. MIP is an excellent visualization tool. The affected lung is commonly hypoplastic and can display small peripheral bullae on CT.

Pulmonary Sling

Anomalous origin of the left pulmonary artery from the right pulmonary artery results in a pulmonary sling with compression of the trachea and right main bronchus (volume rendering). Characteristic is an atypical course of the left pulmonary artery posterior to the trachea.

Systemic Arterial Supply to the Lung

- *Congenital systemic arterial supply* to the lung is commonly found in *bronchopulmonary sequestration*. Information about the vascular supply (MIP) is important prior to embolization or surgery. The systemic vessel originates most often from the inferior thoracic or superior abdominal aorta and less frequently from the supra-aortic, chest wall, pericardiophrenic, or abdominal aortic side branches (see Fig. 1). The abnormal lung segment is ventilated in cases of intralobar sequestration, usually with venous drainage to the left atrium. It is collapsed in patients with extralobar sequestration, usually with drainage to a systemic vein.
- *Acquired systemic arterial pulmonary supply* can be found in various conditions, including aspergilloma, tuberculosis (TBC) or other inflammation, neoplasia,

after trauma or surgery, and in chronic pulmonary arterial or venous obstruction. It is commonly associated with hemoptysis and bronchiectasis. MIP displays can be valuable in these patients to exclude bronchial artery aneurysms or a Rasmussen aneurysm in TBC.

Chronic Thromboembolic Pulmonary Hypertension

Chronic thromboembolic pulmonary hypertension (CTEPH) is the consequence of incompletely resolved pulmonary embolism. CTEPH develops if a sufficiently large cross-sectional area of the pulmonary arteries is occluded or suffers from reduced perfusion due to vasoconstriction. Causative treatment is possible if central thrombotic material in the pulmonary arteries can be removed by pulmonary arterial thromboendarterectomy. CTA plays a crucial role in differentiating CTEPH from other causes of pulmonary hypertension and in defining the presence of wall-adherent thrombotic material in the proximal pulmonary arteries.

Peripheral stenoses may form during recanalization of vessels. They can be seen on MIP (see Fig. 4) but are better appreciated on volume-rendered views or thin-slab MIP. Chronically occluded vessels have a substantially reduced size and are associated with mosaic oligemia (mosaic perfusion) that can be excellently seen on color-coded volume-rendered displays of the lung parenchyma (see Fig. 5). Such displays enhance the differences in density in the lung parenchyma and make it easier to establish the extent of mosaic perfusion. Bronchial arteries frequently hypertrophy in chronic pulmonary embolism and can often be seen running alongside the occluded (central) artery.

Pulmonary Veins

Three-dimensional imaging is best suited for displaying variants but has become increasingly important prior to electroablation of arrhythmogenic foci in the left atrium.

Anomalous Pulmonary Veins

- *Anomalous unilateral single pulmonary veins* (AUSPV) with normal connection to the left atrium are rare and usually do not require treatment. VRT or MIP demonstrates a large single tortuous vessel draining the entire lung to the left atrium.
- *Partial anomalous pulmonary venous return* (PAPVR) and scimitar syndrome refer to anomalous connections of pulmonary veins to the systemic circulation that are associated with left-to-right shunting. CTA as well as MRA yields excellent morphologic results, whereas time-resolved or phase-contrast MRA techniques provide additional functional information. PAPVR may be easily missed on routine evaluation of axial sections but is readily evident if one searches for characteristic

patterns. On the right side, the anomalous vessels enter the superior vena cava or the right atrium directly. On the left, the anomalous vessels drain into an aberrant venous structure that is usually located lateral to the aortic arch in a position similar to a left superior vena cava. This vessel drains into a dilated left brachiocephalic vein. In rare cases, the draining vein may have other positions, such as medial to the aortic arch. The anomalies are best identified and classified on volume-rendered displays.

Congenital Pulmonary Vein Stenosis

Congenital pulmonary vein stenosis (PVS) can occasionally be occult if only one pulmonary vein ostium is involved. Similar to the pulmonary veins in lung transplants, it can be complicated by retrograde pulmonary vein thrombosis. Identification of a PVS requires thorough evaluation of the width of the veins in the vicinity of the pulmonary venous ostia into the left atrium. Rarely, substantial stenosis may lead to signs of venous congestion with increased size of intrapulmonary veins and interstitial fluid retention. Iatrogenic pulmonary vein stenosis or occlusion may occur as a consequence of electroablation treatment of atrial fibrillation.

Catheter Ablation of Arrhythmogenic Foci

Catheter ablation of arrhythmogenic foci in the left atrium may be performed in patients with severe atrial fibrillation. For this purpose, a loop-shaped electrocoagulation wire is placed in the orifices of the pulmonary veins to interrupt the electrophysiological connection between the pulmonary veins and the atria. The anatomy of the pulmonary venous orifices is highly variable, and cardiac angiography only provides projection images that provide little information about the sagittal diameter of the veins, thus making the procedure time consuming and risky because overcoagulation may lead to stenosis or even occlusion of a pulmonary vein.

CTA at low tube voltage (80-100 kV) is sufficient to provide the necessary anatomical information about the left atrium and the pulmonary veins. Gating is not mandatory because it requires an unnecessarily high dose for this purpose and often leads to only minor improvements in image quality.

Volume rendering after removal of the aorta is best suited to provide an overview of the venous anatomy, and multiplanar cross-sections through the orifices of the pulmonary veins can be used to provide the measurements necessary for the choice of loop size.

Summary

Three-dimensional imaging has become an indispensable tool for vascular imaging of the chest. CTA and MRA are

similarly suited for providing the input data given that data acquisition is nearly isotropic. VRT is commonly used to visualize the aorta and pulmonary vessels but is most helpful for displaying complex vascular structures. However, VRT is also suited for visualizing mosaic perfusion of the lung parenchyma. MIPs are excellent for displaying small vessels, such as peripheral pulmonary arteries or bronchial arteries. CPR is excellent for displaying stenosis and aneurysms of the coronary or supraaortic arteries. MPR remains the standard for any CTA or MRA application.

Suggested Reading

MRA: Technique

- Amano Y, Takahama K, Kumita S (2008) Non-contrast-enhanced MR angiography of the thoracic aorta using cardiac and navigator-gated magnetization-prepared three-dimensional steady-state free precession. *J Magn Reson Imaging* 27:504-509
- Gebker R, Gomaa O, Schnackenburg B et al (2007) Comparison of different MRI techniques for the assessment of thoracic aortic pathology: 3D contrast enhanced MR angiography, turbo spin echo and balanced steady state free precession. *Int J Cardiovasc Imaging* 23:747-756
- Kawel N, Jhooti P, Dashti D et al (2011) MR-imaging of the thoracic aorta: 3D-ECG- and respiratory-gated bSSFP imaging using the CLAWS algorithm versus contrast-enhanced 3D-MRA. *Eur J Radiol* 2011 doi:10.1016/j.ejrad.2010.12.040
- Krishnam MS, Tomasian A, Deshpande V et al (2008) Noncontrast 3D steady-state free-precession magnetic resonance angiography of the whole chest using nonselective radiofrequency excitation over a large field of view: comparison with single-phase 3D contrast-enhanced magnetic resonance angiography. *Invest Radiol* 43:411-420

MRA: Aorta

- Didier D, Saint-Martin C, Lapierre C et al (2006) Coarctation of the aorta: pre and postoperative evaluation with MRI and MR angiography; correlation with echocardiography and surgery. *Int J Cardiovasc Imaging* 22:457-475
- François CJ, Tuite D, Deshpande V et al (2008) Unenhanced MR angiography of the thoracic aorta: initial clinical evaluation. *AJR Am J Roentgenol* 190:902-906
- Krishnam MS, Tomasian A, Malik S et al (2010) Image quality and diagnostic accuracy of unenhanced SSFP MR angiography compared with conventional contrast-enhanced MR angiography for the assessment of thoracic aortic diseases. *Eur Radiol* 20:1311-1320

MRA: Congenital Abnormalities

- Naehle CP, Kaestner M, Müller A et al (2010) First-pass and steady-state MR angiography of thoracic vasculature in children and adolescents. *JACC Cardiovasc Imaging* 3:504-513
- Prakash A, Torres AJ, Printz BF et al (2007) Usefulness of magnetic resonance angiography in the evaluation of complex congenital heart disease in newborns and infants. *Am J Cardiol* 100:715-721
- Tomasian A, Lohan DG, Laub G et al (2008) Noncontrast 3D steady state free precession magnetic resonance angiography of the thoracic central veins using nonselective radiofrequency excitation over a large field of view: initial experience. *Invest Radiol* 43:306-313

CTA: Technique

- Bae KT (2010) Optimization of contrast enhancement in thoracic MDCT. *Radiol Clin North Am* 48:9-29
- Blanke P, Bulla S, Baumann T et al (2010) Thoracic aorta: prospective electrocardiographically triggered CT angiography with dual-source CT-feasibility, image quality, and dose reduction. *Radiology* 255:207-217
- Frush DP (2009) Thoracic cardiovascular CT: technique and applications. *Pediatr Radiol* 39(Suppl 3):464-470
- Lawler LP, Fishman EK (2001) Multi-detector row CT of thoracic disease with emphasis on 3D volume rendering and CT angiography. *Radiographics* 21:1257-1273
- Schindera ST, Graca P, Patak MA et al (2009) Thoracoabdominal-aortoiliac multidetector-row CT angiography at 80 and 100 kVp: assessment of image quality and radiation dose. *Invest Radiol* 44:650-655

CTA: Aorta

- Agarwal PP, Chughtai A, Matzinger FR, Kazerooni EA (2009) Multidetector CT of thoracic aortic aneurysms. *Radiographics* 29:537-552
- Aladham F, Sundaram B, Williams DM, Quint LE (2010) Traumatic aortic injury: computerized tomographic findings at presentation and after conservative therapy. *J Comput Assist Tomogr* 34:388-394

- Chung JH, Ghoshhajra BB, Rojas CA et al (2010) CT angiography of the thoracic aorta. *Radiol Clin North Am* 48:249-264
- Hoang JK, Martinez S, Hurwitz LM (2009) MDCT angiography after open thoracic aortic surgery: pearls and pitfalls. *AJR Am J Roentgenol* 192:W20-W27
- Johnson PT, Horton KM, Fishman EK (2010) Aortic valve and ascending thoracic aorta: Evaluation with isotropic MDCT. *AJR Am J Roentgenol* 195:1072-1081

CTA: Congenital Abnormalities

- Berko NS, Jain VR, Godelman A et al (2009) Variants and anomalies of thoracic vasculature on computed tomographic angiography in adults. *J Comput Assist Tomogr* 33:523-528
- Carette MF, Parrot A, Fartoukh M et al (2009) [Normal and abnormal systemic pulmonary circulation: CT imaging features]. *J Radiol* 90:1789-1800
- Jakanani GC, Adair W (2010) Frequency of variations in aortic arch anatomy depicted on multidetector CT. *Clin Radiol* 65:481-487
- Maldonado JA, Henry T, Gutiérrez FR (2010) Congenital thoracic vascular anomalies. *Radiol Clin North Am* 48:85-115
- Oguz B, Haliloglu M, Karcaaltincaba M (2007) Paediatric multidetector CT angiography: spectrum of congenital thoracic vascular anomalies. *Br J Radiol* 80:376-383

Morphologic Cardiac and Pericardiac Imaging with CT and MRI for the Chest Radiologist

Albert de Roos¹, Didier Revel²

¹ Department of Radiology, Leiden University Medical Center, Leiden, The Netherlands

² Department of Radiology, Hôpital Louis Pradel, University Claude Bernard Lyon1, Lyon-Montchat, France

Introduction

A number of imaging techniques is available for evaluating the thorax. Currently, conventional and digital chest radiography, multidetector-row computer tomography (MDCT), and magnetic resonance imaging (MRI) are the most widely used. The chest radiologist generally is especially focussed on imaging the lungs, mediastinum, chest wall, and large vessels. Less attention may be given to interpreting cardiac and pericardial disease. The purpose of this course is to draw attention to cardiac/pericardial diseases that may be detected on MDCT and MRI of the chest. A short description of technology is provided, then normal cardiovascular anatomy is discussed. Finally, case material is presented to illustrate the most common diseases that can be diagnosed.

Multidetector-row Computed Tomography

MDCT is undergoing rapid technological evolution. The technique has great potential for evaluating chest and heart disease. We are using 320-row and 64-row MDCT, preferably with prospective gating, for cardiovascular chest imaging. Other institutions may use dual-source CT technology for cardiac imaging with improved temporal resolution and high speed acquisitions. The rapid acquisition time allows breath-hold imaging during peak enhancement of a compact bolus of iodinated contrast material. Shorter acquisition times reduce the total amount of contrast material needed but require higher rates of iodine administration. Retrospective reconstruction algorithms allow anatomic and functional evaluation of the heart. Cardiac imaging requires estimation of the scan delay time by using a test bolus or automated detection of contrast material arrival in, for example, the ascending aorta. Nonionic contrast material with a 350- to 400-mgI/ml concentration is advocated. The reconstruction window has to be selected for individual coronary arteries in order to optimize image quality when using retrospective gating. The phase is predefined when using prospective gating, depending on heart rate.

Protocols may be used to evaluate specific clinical questions (e.g., coronaries or aortic dissection) or may comprehensively evaluate the entire chest to rule out a number of causes of acute chest pain (triple rule out). Cardiac and pericardiac evaluation is becoming a routine part of chest evaluation, especially when using gating. Effective strategies available to lower radiation dose are prospective gating, on-line tube-current modulation, and noise-reduction techniques.

Magnetic Resonance Imaging

MRI techniques for chest imaging are still evolving. Chest imaging can be performed with the standard body coil; a dedicated phased-array coil is helpful for improving image quality of cardiac images. Such coil allows parallel imaging [sensitivity encoding (SENSE)] by using various coil elements. For example, using three elements (SENSE-factor 3) speeds up the examination threefold. The improvement in speed can also be traded off for improved spatial resolution. Breath-holding during image acquisition minimizes respiratory motion artefacts. On the other hand, navigator technology traces the position of the diaphragm and allows chest imaging while the patient is free-breathing. Free-breathing-navigator whole-heart MR angiography (MRA) is commonly used to image coronary arteries. Motion from the heart itself is "frozen" by the use of electrocardiographic (ECG) triggering.

The setup of a chest MRI study starts with a series of scout views for general orientation and for planning additional acquisitions. Simple transverse image orientation is generally used to visualize chest morphology. Conventional spin-echo images have largely been replaced by new black-blood pulse sequences for evaluating the anatomy. A black-blood sequence consists of a nonselective 180° pulse to invert the signal, followed by a slice-selective 180° pulse (double-inversion technique). Blood with an inverted signal flows into the slice plane. After a delay time, the blood signal is zero, and actual data acquisition is performed with a fast-spin-echo pulse train

during a breath-hold. Flow artefacts are efficiently suppressed, thereby providing high-quality images with exquisite anatomical detail. Movie loops of the heart can be obtained with gradient-echo pulse sequences. It is important to note contrast behavior of lesions on both spin-echo and gradient-echo MR sequences.

Balanced fast-field echo (b-FFE) or true fast imaging with steady-state precession (true-FISP) pulse sequences yield movie loops of consistent and reliable image quality. A very good contrast is seen between the flowing blood (bright) and cardiac walls (dark). Acquisitions are performed during breath-holding. Contraction of the heart, blood flow, and valvular motion are well visualized, similar to echocardiography. Slice thickness may be chosen depending on the structures under investigation (mostly 8- to 10-mm slice thickness). Movie loops can be obtained in simple transverse orientation and sometimes in angulated orientations to image the heart (short axis; long axis; four-chamber; three-chamber). Flow mapping is an additional MRI pulse sequence for measuring flow in large- and medium-sized vessels. Flow can be expressed in milliliters per second (volume flow) or centimeters per second (velocity). The technique is very helpful and reliable for measuring flow parameters. Furthermore, gadolinium-enhanced MRA is a widely used and practical technique to study large-vessel disease. Delayed-enhancement MRI after gadolinium administration is widely used to detect myocardial scar and fibrosis in a number of diseases (e.g., myocardial infarction, different cardiomyopathies, myocarditis).

Description of Normal Anatomy

Transverse sections obtained with CT or MRI extent from the base of the heart to the cranial portion of the liver to depict the cardiovascular anatomy. In transverse sections, parts of the normal pericardium are visualized, most consistently, the anterior to the right ventricle (RV). The normal pericardial thickness is <2 mm, and the low signal intensity/density line of the pericardial layers is well contrasted by the surrounding epicardial and pericardial fat. The pericardium is composed of fibrous tissue and some fluid (10-50 cc) within the pericardial sac. The superior pericardial recess extends posterior to the ascending aorta and can be mistaken for a lymph node or dissecting flap. At the base of the heart, size and spatial relationship of the aorta and pulmonary artery are depicted. The aorta is normally located to the right and posterior to the pulmonary artery or the RV outflow tract. The tricuspid nature of the aortic and pulmonary valve is routinely visualized. The RV is normally located anteriorly and to the right, has a triangular shape, reveals the moderator band as an intracardiac muscular structure, and has a muscular outflow tract (infundibulum). The left ventricle (LV) is located posteriorly and to the left, has an elliptical shape, and lacks a moderator band and

infundibulum. Also, the atria have distinct anatomic features. The right atrium is located to the right and has a broad-based triangular appendage. The tricuspid valve between the right atrium and RV is located closer to the apex than the mitral valve, between the left-sided left atrium and LV. The left atrium has a narrow tubular appendage and characteristically receives four pulmonary veins. A number of normal variants should be recognized (e.g., Chiari network in the lateral wall of the right atrium; pericardial recess posterior to the ascending aorta; lipomatous change of atrial septum; thin fossa ovalis). CT is well suited to assess anatomic details in the atrial compartments (e.g., visualization of patent foramen ovale; thrombi in left-atrial appendage in patients with atrial fibrillation).

Newer MRI techniques in particular provide exquisite detail of ventricular function, flow, and valve function. The normal LV has a homogeneous wall thickening during contraction (note especially endocardial inward motion). The normal end-diastolic wall thickness is <1 cm (note local or diffuse hypertrophy). Regional or global functional abnormalities are easily recognized by visual inspection of the movie loop. Valve opening and closing is well visualized with current techniques, thereby allowing diagnosis of stenotic and thickened valve leaflets (e.g., bicuspid aortic valve; mitral valve regurgitation). Overall size, shape, and spatial relationship of cardiac compartments and large vessels are well depicted on transverse CT or MRI images. Recognition of the abnormal arrangement of spatial relationships between vascular structures and other anatomic landmarks (e.g., trachea) is the basis for diagnosing a number of entities (e.g., vascular ring; pulmonary sling). Finally, knowledge of the normal anatomy of the coronary vessels is required for recognition of anatomic variations and to localize coronary artery stenosis. CT and MRI are clinically used to diagnose variations in the normal course and origin of coronary arteries. The ostium of the right coronary artery (RCA) is located in the right sinus of Valsalva at the level of the aortic ring and courses to the right and anterior between the right atrium and pulmonary outflow tract. The left main coronary artery (LCA) directs to the left between the pulmonary artery and left atrial appendage and then divides into two major branches, namely, the left anterior descending (LAD) and the left circumflex (LCX) artery. The LAD runs anteriorly in the interventricular sulcus (along the septum) to the apex of the heart, whereas the LCX runs posteriorly in the atrioventricular groove. The spatial relationship between the origin of these coronary vessels, the aortic root, and pulmonary artery is easily appreciated, allowing the detection of an anomalous course of these vessels (Fig. 1). Vascular anomalies and variants may be seen as incidental findings on chest CT or MRI. The venous anatomy of the atria and heart is gaining more importance for guiding interventional therapy (e.g., pulmonary-vein anatomy for guiding ablation in atrial fibrillation).

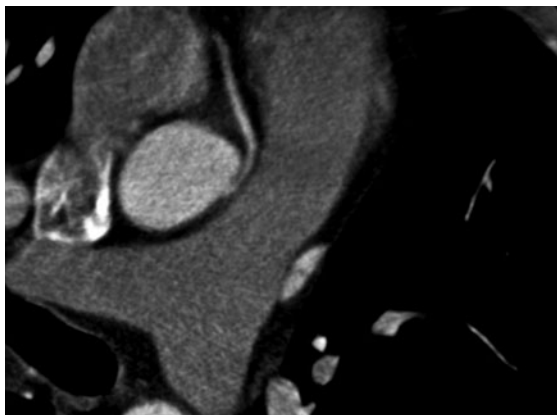


Fig. 1. Computed tomography (CT) gated to the cardiac cycle demonstrating the congenital abnormal right coronary artery arising from the left sinus of Valsalva. The inter-aortopulmonary course of the coronary artery should be considered a risk factor for cardiac angina and cardiac arrest

The Most Common Cardiac/Pericardial Diseases

Ischemic Heart Disease

Functional MRI and delayed gadolinium enhancement are routinely used to assess presence and extent of ischemic heart disease. The extent of myocardial scar is important for planning surgery and other interventions (e.g., viability imaging by assessing the transmural extent of scar; planning local resection of scar and LV aneurysms). In the setting of ischemic heart disease, it is important to characterize the presence and extent of mitral valve disease. MRI and CT are well suited to assess valve morphology (flailed leaflets; bulging). MR flow mapping is an excellent tool to assess valve regurgitation (absolute volume or regurgitant fraction) in conjunction with ventricular function. Accurate quantification of mitral-valve disease is important for therapy planning.

CT is widely used and clinically accepted for coronary artery stenosis detection in patients with an intermediate likelihood of disease. MRI and CT are also commonly used to define complications of ischemic heart disease (e.g., aneurysms; thrombi; mitral valvular disease). Delayed-enhancement imaging plays an important role in the differential diagnosis of various causes of myocardial disease (e.g., myocarditis; sarcoid; amyloid).

Pericardial Effusion

Cross-sectional imaging by CT or MRI is very sensitive in detecting generalized or loculated pericardial effusions. Some fluid in the pericardial sac contributes to the apparent thickness and should be considered normal. Commonly, free-flowing fluid accumulates first at the posterolateral aspect of the LV when imaging the patient in the supine position. Estimating the amount of fluid is possible to a limited extent based on the overall thick-

ness of the crescent of fluid. CT and MRI may be particularly helpful in detecting loculated effusions owing to the wide field of view compared with cardiac ultrasound. Hemorrhagic effusions can be differentiated from transudate or exudate based on signal characteristics (high signal on T1-weighted images) or density (high-density clot on CT). Pulsation artefacts may cause local areas of low signal in a hemorrhagic effusion. Effusions are often incidentally noted on CT scans that are obtained for other indications. Pericardial thickening (thickness >4 mm) is difficult to differentiate from a small generalized effusion. Both entities will reveal a low signal/density line that is thicker than the normal pericardial thickness. In acute pericarditis, the pericardial lining can show intermediate signal intensity and may enhance after gadolinium administration.

Constrictive Pericarditis

Pericardial thickening may result in constrictive pericarditis. In this entity, pericardial thickening will hamper cardiac function, resulting in hemodynamic consequences. Many causes may lead to constrictive pericarditis (infection; tumor; radiation; heart surgery). The diagnostic features include thickened pericardium in conjunction with signs of impaired RV function [dilatation of caval veins and hepatic veins; enlargement of right atrium; the RV itself may be normal or even reduced (tubular, sigmoid) in size due to compression]. Localized pericardial thickening may also cause functional impairment (localized constrictive pericarditis). Sometimes, constriction may occur despite a normal appearance of the pericardium. Pericardial calcifications are easily visualized by CT and may be difficult or impossible to appreciate on MRI.

Pericardial Tumor

A pericardial cyst is most commonly located at the right cardiophrenic angle (low signal on T1; sometimes intermediate signal due to high protein content; light-bulb appearance on T2). Unusual tumors may arise from the pericardium (mesothelioma; angiosarcoma). These malignant primary tumors have many overlapping imaging features and generally cannot be differentiated. The role of cross-sectional imaging is to establish a diagnosis and define the extent of the lesion (invasion of cardiac structures; veins; pericardium). Sometimes, lesions may have helpful signal characteristics to suggest a specific diagnosis (e.g., high-signal fat on T1; low-density fat on CT in lipoma/liposarcoma). Secondary tumors are much more common than primary tumors. Lung cancer may invade the mediastinal and cardiac structures directly or indirectly. The most common secondary tumors that may affect the heart are lung cancer, breast cancer, and lymphoma. Metastatic pericardial disease commonly presents as hemorrhagic effusion. Tumor nodules may enhance after intravenous administration of gadolinium.

Intracardiac Masses

Myxomas comprise up to 50% of all primary cardiac tumors and may be identified first by cardiac ultrasound in patients referred for suspected cardiac source for embolism or incidentally on cross-sectional imaging. Mostly, myxomas originate from the left atrium, although they may also arise from the right atrium (Fig. 2) or even from the ventricle. The variation of histological structure (myxoid matrix; areas of hemorrhage; cysts and calcifications; thrombotic material) may affect the appearance on CT or MRI. They are generally polypoid, often pedunculated, smooth-appearing lesions with variable size. Dynamic MRI reveals the mobility of the myxoma. Signal characteristics are variable (generally intermediate on T1 spin-echo MRI and low-signal on gradient-echo MRI due to hemorrhage or calcifications). Contrast uptake may be demonstrated after gadolinium administration due to lesion vascularity. A cardiac thrombus can have similar and overlapping imaging features, although the location is most commonly the left-atrial appendage or LV adjacent to an infarcted region. Other differentiating features are the high signal of fresh thrombus (met-hemoglobin) on T1-weighted spin-echo MRI, the very low signal intensity of a thrombus using gradient-echo MRI (susceptibility effect), and the usual lack of contrast enhancement after gadolinium administration.

Cardiac lipoma (Fig. 3) is a frequently occurring benign tumor of the heart. It may become quite large and thereby compromise cardiac function. The lesion may arise from the myocardium itself. A preferred location is the interatrial septum. Typical high signal on T1-weighted spin-echo MRI is helpful for making a diagnosis. There is a lack of contrast enhancement. Lipoma and liposarcoma are usually difficult to differentiate.



Fig. 2. Computed tomography (CT) of a polypoid myxoma arising from the right atrium and protruding through the tricuspid valve into the right ventricle. Note that there are myxomatous materials embolized in the pulmonary artery circulation

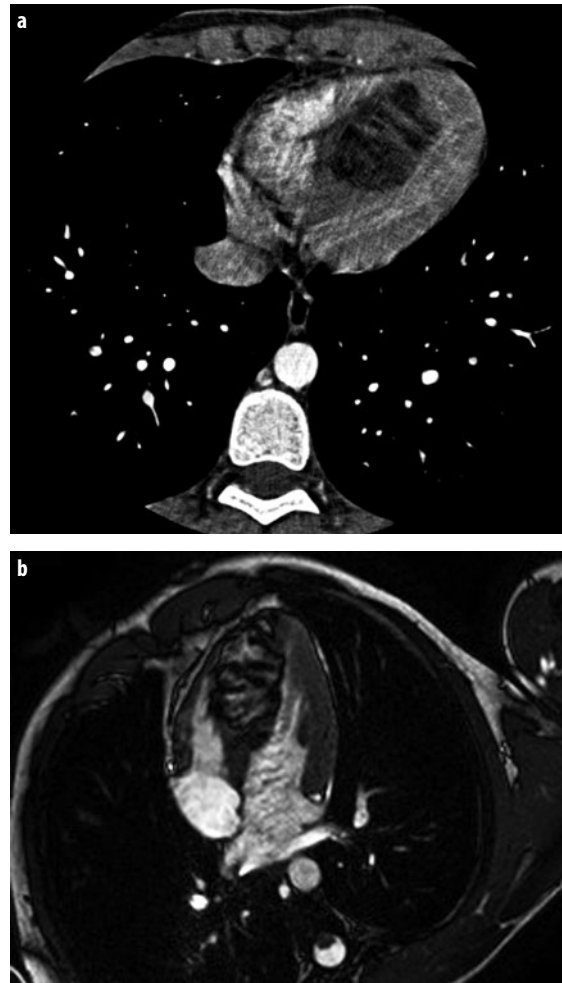


Fig. 3 a, b. Lipomatous infiltration of the interventricular septum. **a** Gated computed tomography (CT) demonstrating lobulated hypodense infiltration in the interventricular septum. The fatty nature of the lesion was confirmed by T1-weighted spin-echo acquisition with fat saturation (**b**)

Aortic Disease

Evaluation of the aorta is a common referral for CT or MRI after initial assessment with other techniques (chest radiography; ultrasound). Furthermore, aneurysms and other chronic diseases of the aorta are often incidentally noted on cross-sectional imaging. Thoracic aortic aneurysms are common (found in 10% of autopsies) and are frequently associated with atherosclerosis. Aortic atherosclerosis is considered to be the origin for thromboemboli in many patients presenting with stroke; therefore, recognizing aortic-wall disease may have important clinical implications. Treatment of thoracic aortic aneurysms depends on size, anatomy, growth rate, presence of complications, underlying cause, and involvement of adjacent structures, such as the aortic valve. MDCT and MRI are both well suited to image aortic disease and its complications. Method selection will depend on scanner availability, speed and ease of the examination, costs, and local expertise and preferences. Initial

diagnosis of aortic dissection is commonly performed by MDCT. First and foremost, the exam must confirm or refute the diagnosis of dissection. Second, the study must determine whether or not the dissection involves the ascending aorta (type A is indication for surgery). The speed and ease of image acquisition make MDCT an attractive first-line modality. In this regard, MDCT may also be preferred in patients with acute chest pain and trauma patients (diagnosis of aortic rupture). In acute chest pain, MDCT is a first-line modality for diagnosing pulmonary embolism. Commonly, other causes for acute chest pain may become evident on cross-sectional imaging (pneumonia; pericarditis; dissection; chest-wall disease). MRI may be reserved for follow-up of aortic disease in stable patients. Dynamic MRI permits detection and quantification of aortic valvular insufficiency by demonstrating flow across the aortic valve.

An important differential diagnosis of aortic dissection is intramural hematoma (IMH), which presents with a similar clinical picture and risk profile as classic dissection. IMH is probably a variant of aortic dissection and not a separate disease. Rupture of the aortic vasa vasorum may initiate the process of hemorrhage within the aortic wall (dissection without intimal flap). Cross-sectional imaging (ultrasound; MDCT; MRI) are all better suited to diagnose IMH than are angiographic approaches [X-ray, MRA, computed tomography angiography (CTA)] due to the lack of intraluminal abnormalities (Fig. 4). Aortic ulcers occur in the presence of aortic atherosclerosis and clinically may mimic subacute dissection or IMH. Penetrating aortic ulcers have a predilection for the descending and abdominal aorta. Cross-sectional imaging may reveal a localized ulcer within the aortic wall, sometimes with adjacent intramural hemorrhage.

Marfan syndrome is an inherited connective-tissue disease, which results from mutations in genes coding for fibrillin and commonly affects the aorta. Cardiovascular involvement decreases life expectancy, primarily from progressive aortic-root dilatation (typical pear shape of aortic root) and consequent aortic insufficiency, dissection, and

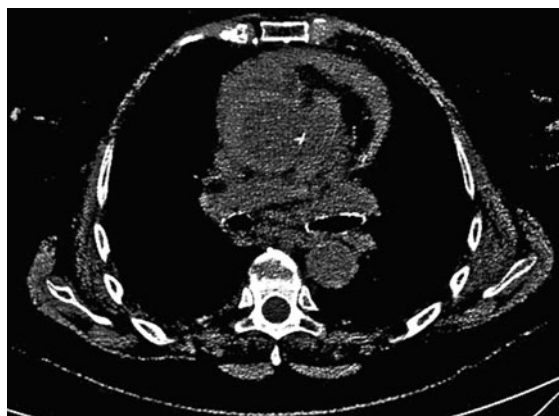


Fig. 4. Intramural hematoma. Computed tomography (CT) gated to the cardiac cycle before injection of contrast media demonstrating high density signal in half the circumference of the ascending aortic wall corresponding to the recent hematoma within the vessel wall. Note also the pericardial effusion

aortic rupture. MRI of the lumbar spine may add a major diagnostic criterion to establish the diagnosis of Marfan syndrome by demonstrating dural ectasia. Bicuspid aortic-valve disease may also be associated with intrinsic aortic-wall disease, leading to aneurysm formation and dissection. Therefore, it is important to recognize normal and abnormal valve anatomy and function as part of overall chest evaluation.

Recent Trends and Developments

After initial evaluation by echocardiography, further cross-sectional imaging by CT or MRI is regularly requested to solve problems that remain after initial evaluation. Unusual pathology may be diagnosed or excluded by CT or MRI. For example, Ebstein's disease of the tricuspid valve is well recognized on cine MRI, whereas the diagnosis may be difficult to establish with echocardiography. On the other hand, CT is becoming a first-line tool for evaluating patients presenting with acute chest pain, where CT – and to a lesser degree MRI – may have practical implications for organizing radiology practice. Expertise is required to read CT examinations, dedicated CT protocols are required with the use of cardiac gating techniques (e.g., protocol in acute coronary syndrome; pulmonary embolism; dissection; acute myocarditis) (Fig. 5), and rapid access and reporting is required. The differential diagnosis of acute chest pain is quite extensive (>30 differential diagnoses should be considered), and many of these diagnoses may

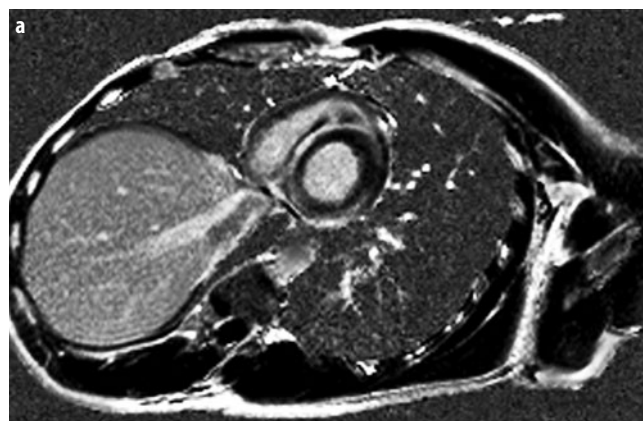
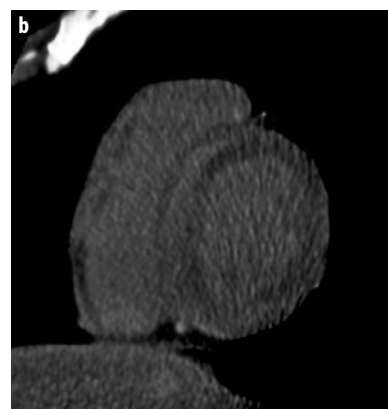


Fig. 5 a, b. Magnetic resonance imaging (MRI) (a) and gated computed tomography (CT) (b) of myocarditis in a young patient presenting acute chest pain with normal coronary arteries. Hyperdense signal intensity and high density with a subepicardial distribution are highly suggestive of acute myocarditis in this context. Note the absence of pericardial effusion



be manifest on CT that was not requested for that specific diagnosis. In conclusion, cross-sectional CT or MR imaging is increasingly requested as a first-line diagnostic tool in acute chest pain patients and for problem solving.

Suggested Reading

- Alkadhi H, Leschka S, Trindade PT et al (2010) Cardiac CT for the differentiation of bicuspid and tricuspid aortic valves: comparison with echocardiography and surgery. *AJR Am J Roentgenol* 195:900-908
- Elefteriades JA, Farkas EA (2010) Thoracic aortic aneurysm. Clinically pertinent controversies and uncertainties. *J Am Coll Cardiol* 55:841-857
- Halpern EJ (2009) Triple-rule-out CT angiography for evaluation of acute chest pain and possible acute coronary syndrome. *Radiology* 252:332-345
- Higgins CB, De Roos A (eds) (2006) MRI and CT of the cardiovascular system. Lippincott Williams & Wilkins, Philadelphia, PA
- Morris MF, Maleszewski JJ, Suri RM et al (2010) CT and MR imaging of the mitral valve: radiologic-pathologic correlation. *Radiographics* 30:1603-1620

Cardiac Function Imaging for the Chest Radiologist: Computed Tomography

Stephan Achenbach

Department of Cardiology, University of Erlangen, Erlangen, Germany

Cardiac Computed Tomography

The heart has small dimensions, an elaborate 3D structure and is subjected to rapid and constant motion. Whereas computed tomography (CT) imaging is perfectly suited to cope with the complex anatomy due to its tomographic nature and high spatial resolution, it has been a challenge to achieve sufficient temporal resolution for cardiac imaging. A number of developments in recent years have made it possible to use CT for cardiac imaging. Faster rotations times improve temporal resolution, and electrocardiographic (ECG)-gated partial-scan reconstruction algorithms allow imaging with exposure times per image that can be substantially shorter than the time of one rotation and permit synchronisation of image reconstruction with the cardiac cycle. Furthermore, multi-detector-row systems (MDCT) allow coverage of the cardiac volume with thin slices yet at the same time sufficiently short imaging time so that acquisition can comfortably be completed in one breath-hold. Sixty-four-slice CT systems are now considered the minimum prerequisite for high-quality cardiac imaging. Further developments include systems with even more detector rows (up

to 320 slices), which allow coverage of the cardiac volume in a shorter time, with 256- and 320-slice systems possibly in one single cardiac cycle. Systems with two tubes and detectors (dual-source CT) permit further increase in temporal resolution, which can be as low as 75 ms per image.

The main focus of cardiac CT is imaging the coronary arteries. On one hand, this is particularly complex, given the small dimensions of the coronary vessels, and on the other hand, it is particularly attractive, as no other noninvasive imaging modality allows a similarly robust visualisation of coronary vessels. Nonenhanced CT imaging can be used to detect and quantify coronary calcification (Fig. 1), a marker for the presence and extent of coronary atherosclerosis and thus a very good prognostic indicator concerning future cardiovascular events. Utilisation of CT coronary calcium imaging has therefore been suggested for risk stratification in asymptomatic individuals who, based on traditional risk-factor evaluation, seem to be at intermediate risk for future cardiovascular events. Also, the results of CT coronary calcium imaging can guide the intensity of risk modification therapy, such as the use of lipid-lowering

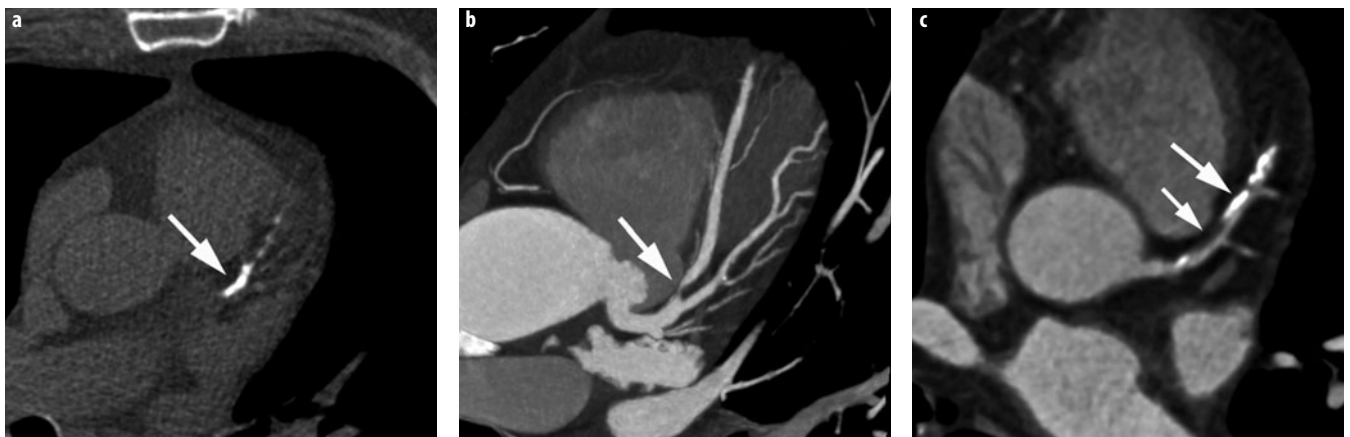


Fig. 1 a-c. Cardiac computed tomography for visualising the coronary arteries. **a** Coronary calcification of the left anterior descending coronary artery (arrow) in a nonenhanced scan. **b** Contrast-enhancement showing a high grade coronary artery stenosis in the proximal left anterior descending coronary artery (arrow). **c** Contrast-enhancement showing the presence of calcified (large arrow) and noncalcified (small arrow) plaque, but no relevant luminal stenosis, in the proximal left anterior descending coronary artery

agents [1, 2]. An even more prominent application is contrast-enhanced coronary CT angiography, which permits detection of coronary artery stenoses with high sensitivity and specificity [3, 4]. Furthermore, non-stenotic atherosclerotic plaque – both calcified and noncalcified – can be detected (Fig. 1). However, coronary CT angiography requires absolutely optimal image quality, so that patient preparation typically includes lowering the heart rate ≤ 60 beats/min to eliminate motion artefacts [5]. The clinical utilisation of coronary CT angiography focuses on patients who have an intermediate likelihood for coronary artery stenoses based on clinical presentation and other non-invasive testing and in whom the high negative predictive value of CT angiography is used to rule out coronary artery stenoses and thus avoid invasive coronary angiography [6].

Using CT, not only are static images of the heart available, so is functional information. This includes analysis of left and right ventricular function and cardiac valve assessment, mainly aortic and mitral valves. However, the ability to derive such information from the CT data sets depends heavily on the image acquisition protocol. For purposes of radiation dose reduction, protocols used for coronary CT angiography often limit radiation exposure to one short diastolic phase of the cardiac cycle, which makes functional imaging impossible. Protocols that collect data during the entire cardiac cycle are required in order to analyse cardiac function.

Data Acquisition Protocols for Cardiac Computed Tomography

Spiral or Helical Acquisition with Retrospective ECG Gating

The traditional image acquisition protocol for cardiac CT, including coronary artery visualisation, is spiral – or helical – imaging with retrospective ECG gating. While the patient table slowly moves through the scanner gantry, X-ray data and the ECG of the patient are recorded. Pitch values are typically low – around 0.2 – so that there is heavy oversampling. This allows retrospective use of only parts of the collected X-ray data for image reconstruction, and the ECG is used to specify which segments of the cardiac cycle are used for image reconstruction. A CT data set of the heart typically consists of 200-300 thin transaxial cross-sections (0.5-0.75 mm slice thickness with some overlap), and all of these images are reconstructed in the same cardiac phase. In most cases, diastolic images are reconstructed for anatomic visualisation of the heart and coronary arteries (because there is least cardiac motion in diastole, especially just before the onset of the p-wave). However, systolic images may be superior and have less motion artefact in patients with high heart rates (Fig. 2). If image reconstruction is repeated many times over, typically during ten time instants spaced equally throughout the cardiac cycle, then it is possible to obtain functional or 4D data sets, which can display the heart in motion and can be used to visualise cardiac function (Fig. 3).

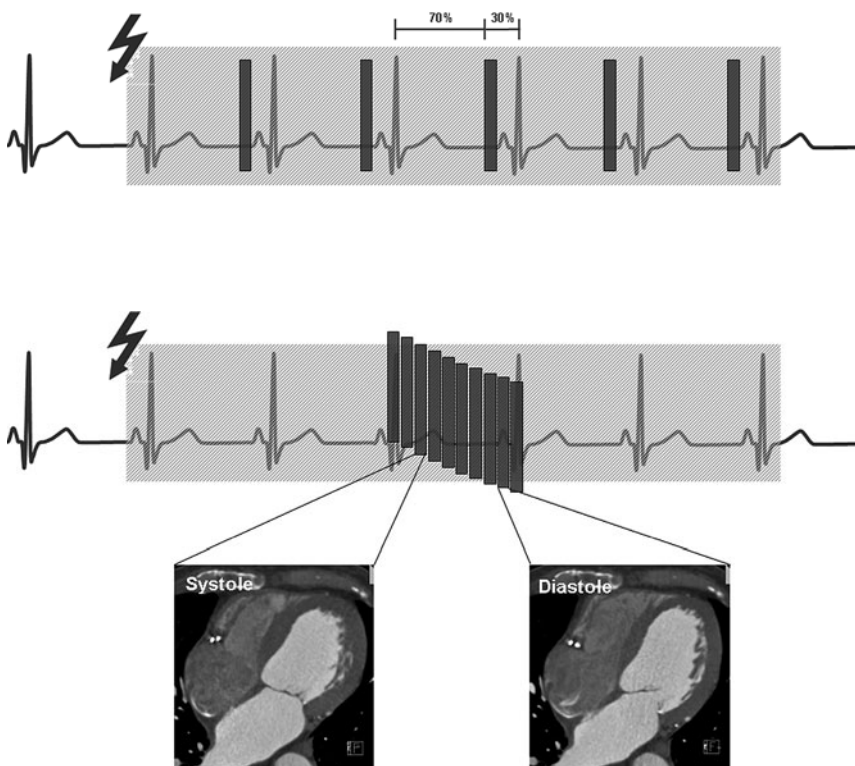


Fig. 2. Data acquisition in cardiac computed tomography using retrospectively electrocardiographic (ECG)-gated spiral (or helical) acquisition. X-ray data and the patient's ECG are simultaneously acquired, and retrospectively, data of prespecified time intervals, usually in diastole (*dark grey bars*, here positioned at 70% of the R-R interval), are used to reconstruct an image data set, all slices of which will display the heart in the same cardiac phase. Whereas this image acquisition mode provides maximum flexibility regarding post hoc image reconstruction, X-ray dose can be prohibitively high

Fig. 3. Reconstruction of a functional data set from retrospectively electrocardiographic (ECG)-gated spiral computed tomography. Image reconstruction is performed at various (here, ten, but for functional analysis, often 20) time instants spaced equidistantly throughout the cardiac cycle. The resultant images can be composed to show functional data (cine mode)

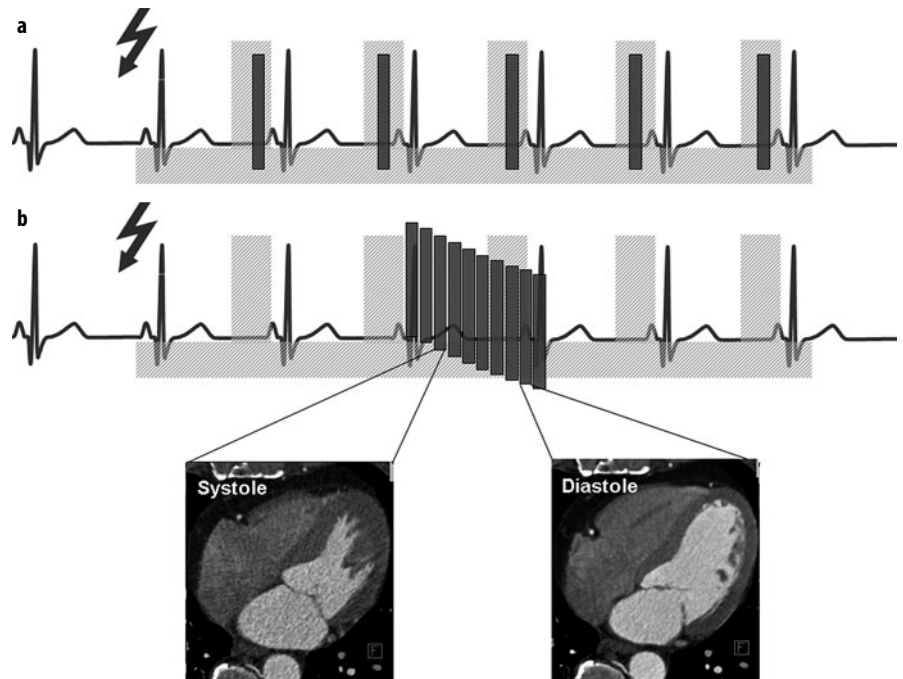


Fig. 4 a, b. Data acquisition in cardiac computed tomography using retrospectively electrocardiographic (ECG)-gated spiral (or helical) acquisition with ECG-based tube current modulation (ECG pulsing). X-ray data and the patient's ECG are simultaneously acquired. **a** At the same time, the patient's ECG data are used to reduce tube current during the systolic phase. Tube current is indicated by the *light grade shading*. Images can be reconstructed at any desired time instant in the cardiac cycle (*grey bars*), but image noise will be higher during the phases with low tube current. **b** For analysis of left ventricular function, the quality of low-current images is usually sufficient. The advantage of this image acquisition mode is substantially lower radiation dose than spiral acquisition without tube-current modulation

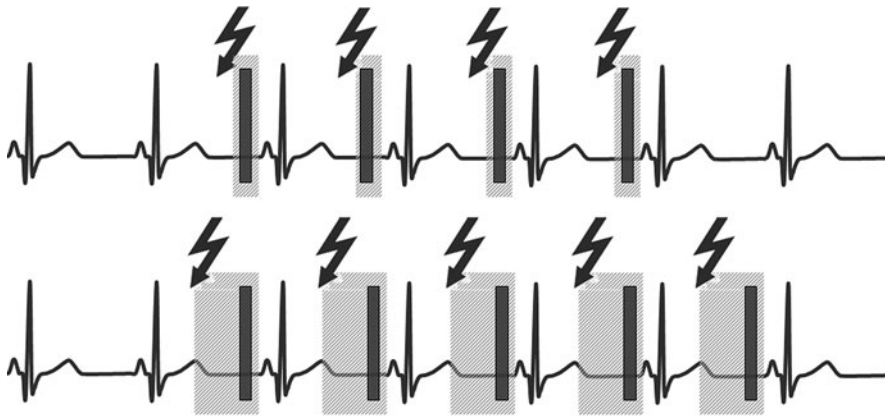
ECG-Related Tube-Current Modulation

The radiation exposure of retrospectively ECG gated spiral/helical image acquisition protocols can be high due to the low pitch values and substantial oversampling. Effective doses as high as 30 mSv have been reported [7]. For most purposes, systolic data are not required, and hence, a technique called ECG correlated tube-current modulation has been developed (often referred to as ECG pulsing). With ECG correlated tube-current modulation, full output of the X-ray tube during image acquisition is limited to a prespecified time interval, usually in diastole. A typical time interval with full tube output can be the time period from 60% to 80% of the cardiac cycle (with 0% and 100% representing the R-waves of the ECG) for low heart rates (<60 beats/min), because low heart rates practically always allow reconstruction of motion-free images in diastole. For higher heart rates, the time interval with full tube output is usually increased to encompass, e.g., the period from 35% to 80% of the cardiac cycle. This is necessary because higher heart rates often require systolic images in order to minimise motion artefacts. Outside the time window of full tube output, the tube current is typically reduced by about 80% (Fig. 4). This leads to increased image noise in data sets reconstructed during these low-current phases. For coronary artery visualisation, or to analyse finer details regarding anatomy, size and attenuation, this will not be sufficient. However, for analysis of left ventricular function in particular, which requires relatively low spatial resolution and uses the high-contrast interface between the myocardium and the left ventricular cavity filled with contrast agent, the lower image quality does not pose a problem, and analysis of

the left ventricular regional and global function remains possible, even if ECG-based tube current modulation is used (Fig. 4).

Prospectively ECG-Triggered Axial Acquisition

To further reduce radiation exposure, prospectively ECG-triggered axial acquisition protocols have become popular in the context of coronary CT angiography (and coronary calcium scoring). These protocols are also referred to as step and shoot or sequential acquisition. They use axial acquisition, without table movement, and the table is advanced to acquire subsequent images, at the subsequent position, between consecutive cardiac cycles (Fig. 5). If X-ray tube output is limited to the very time period that is necessary for image reconstruction (typically one half rotation of the gantry for single-source systems or one quarter rotation for dual-source systems), no functional analysis is possible. However, these protocols allow for varying amounts of padding, which means that X-ray exposure is started earlier and/or lasts longer than needed for the reconstruction of one data set, and depending on the duration of the padding window, some functional information can be derived (Fig. 5). It is theoretically possible to cover the entire cardiac cycle – and for 320-slice systems, this is, in fact, often done – to obtain a full functional data set of the heart (however, there will then be no major radiation dose savings over spiral acquisition with ECG-based tube-current modulation). It should be mentioned, however, that the major focus of prospectively ECG-triggered axial acquisition protocols is reduced radiation exposure in patients who undergo coronary CT angiography, and investigators are perfectly willing to sacrifice information



of image reconstruction and, hence, functional analysis. It is theoretically possible to cover the entire cardiac cycle. However, this scan mode is usually applied to minimise radiation exposure in coronary CT angiography, and preferentially, very little padding is used

on cardiac function because, in turn, these protocols allow reduced effective doses to values between approximately 1.5 and 5 mSv [7, 8]. A further, modern image acquisition protocol for maximum reduction of radiation exposure, prospectively ECG-gated high-pitch spiral acquisition – sometimes referred to as flash – acquisition does not allow functional analysis [8, 9].

Contrast Injection Protocols

Functional imaging of the heart requires intravenous injection of contrast agent. Either bolus tracking or a separate test injection is used to synchronise contrast injection and image acquisition. High contrast flow rates (4–7 ml/s) are recommended in order to achieve optimal contrast for coronary CT angiography, but lower flow rates (2 ml/s) are possible if analysis of left ventricular function only is attempted. Typically, to limit the overall contrast amount, injection timing and duration, especially for coronary CT angiography, are selected in a way that limits full contrast enhancement to the left ventricle and coronary arteries, with relatively short injection periods. Contrast injection is followed by saline in-

jection to keep the contrast bolus compact. In order to achieve better visualisation of the right ventricular cavity and contours of the interventricular septum, a mixture of contrast and saline (e.g. 20% contrast and 80% saline) is often used instead of pure saline injection (Fig. 6) [10]. Other investigators use triphasic protocols with high-flow injection of contrast agent initially, followed by lower-flow injection and then pure saline. An advantage of one injection protocol over another has not been demonstrated. Out of personal experience, this author recommends injecting contrast agent with a flow rate of 5 ml/s for the duration of the image acquisition but at least 10 s, followed by 50 ml of a mixture of 20% contrast and 80% saline, also at a flow rate of 5 ml/s. For patients of 100 kg or more, the injection rate is increased to 6 or 7 ml/s. If analysis of right ventricular structures is specifically required, it may be advantageous to increase the contrast content of the flush to 40%. Prolongation of the injection of pure contrast is not advantageous, because it can lead to substantial artefacts due to mixing of contrast and nonenhanced blood in the right atrium, and these artefacts can extend into the right ventricle.

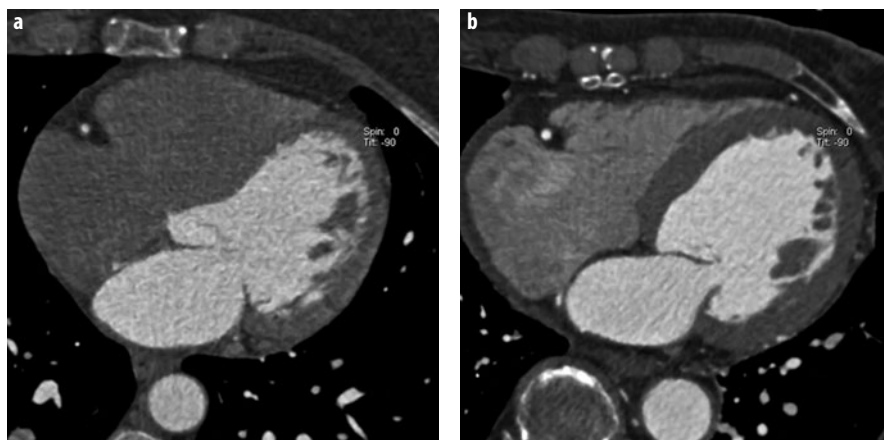


Fig. 6 a, b. Contrast injection. **a** Images acquired with 10 s of contrast injection (flow rate 5 ml/s), followed by saline injection. This results in very poor enhancement of the right ventricular cavity. **b** Images acquired with 10 s of contrast injection (flow rate 5 ml/s), followed by injection of a mixture containing 20% contrast and 80% saline (5 ml/s, total volume 50 ml). Visualisation of the right ventricular cavity and delineation of the septal contours is possible

Image Reconstruction for Functional Analysis

For functional analysis in a clinical setting, it is customary to reconstruct 10 data sets equally spaced throughout the cardiac cycle. Typically, the timing of the data sets is expressed as percent, such as 0%, 10%, 20%, and so on, with 0% and 100% referring to the time instant of the R-peak in the ECG. Many scientific studies are conducted with 20 data sets spaced in 5% increments. More data sets typically result in lower end-systolic volumes (because the state of most extreme contraction may be missed if too few reconstructions are available), and hence in a higher ejection fraction, too few data sets will lead to underestimation of ejection fraction [11]. Typical temporal resolu-

tions are approximately 160-200 ms per image for single-source systems and 75 ms per image for dual-source systems. Transaxial images are reconstructed with a slice increment slightly lower than the slice width in order to obtain slightly overlapping images. For coronary CT angiography and other anatomic imaging of the heart, a slice thickness between 0.5 and 0.75 mm is typically used; this is not necessary for functional imaging. In order to reduce the amount of data, most investigators use reconstructed slice thicknesses between 1 mm and 2 mm for reconstructing functional data sets (Fig. 7). Similarly, many investigators reconstruct images with a reduced matrix of 256×256 pixels (instead of the usual 512×512 pixels) for data sets used to analyse cardiac function (Fig. 8). This

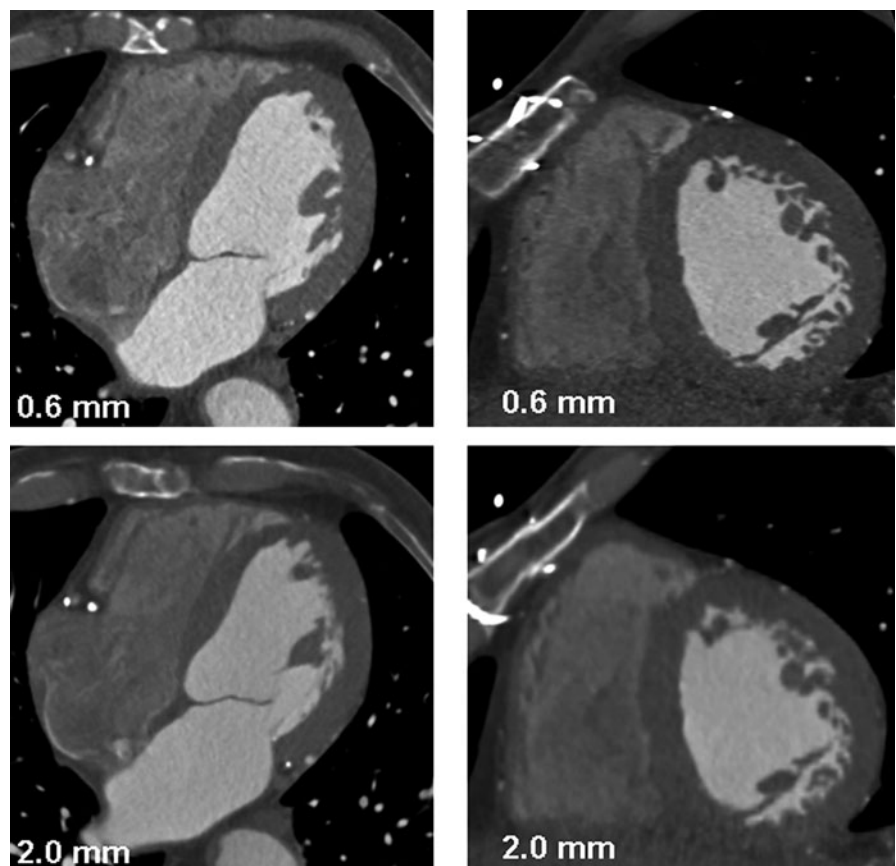


Fig. 7. Effect of slice width. For anatomic imaging, for example of the coronary arteries, the reconstructed slice width is typically 0.5-0.75 mm (*top row*: axial image and off-axis reconstruction to show a short-axis view of the left ventricle in diastole, reconstructed with 0.6-mm slices). For functional analysis, it is sufficient to use slice thickness between 1 and 2 mm (*bottom row*: 2-mm slice thickness)

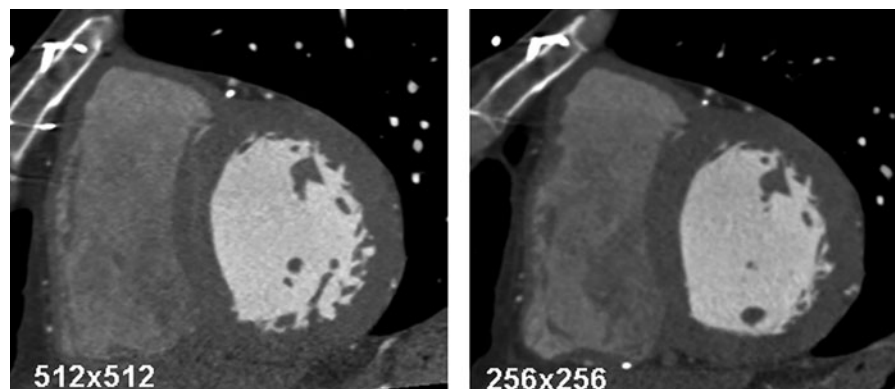


Fig. 8. Effect of reconstruction matrix. For high-resolution anatomic imaging, the reconstruction matrix is typically 512×512 pixels (*left*). For functional analysis, a matrix of 256×256 pixels is sufficient (*right*)

reduces the amount of data for reconstruction and storage by a factor of 4, yet is absolutely sufficient for analysis of global and regional ventricular function.

Image Analysis

Whereas CT data sets are typically reconstructed in axial orientation (some manufacturers allow off-axis reconstruction, but this feature is not often used), the axial orientation is not suitable for exact functional assessment – neither of the ventricles nor any other cardiac structures, such as the valves. Hence, multiplanar reconstruction is employed to obtain typical cardiac axes – such as

the two-chamber, four-chamber and short-axis views – parallel to the image planes typically used in ECG (Fig. 9). A stack of short-axis views, similar to that typically used in magnetic resonance for functional analyses, can also be obtained through multiplanar reconstruction. To analyse global and regional ventricular function, clinical investigators typically scrutinize images in the cardiac axes outlined above (Figs. 10 and 11). Automated software programmes are readily available that import the axially oriented CT image data sets [12], identify endocardial contours and provide “bull’s eye” views of regional-wall motion and wall thickening, as well as automated time-volume curves. However, in the author’s opinion, it is necessary to analyse the original image data sets visually in addition

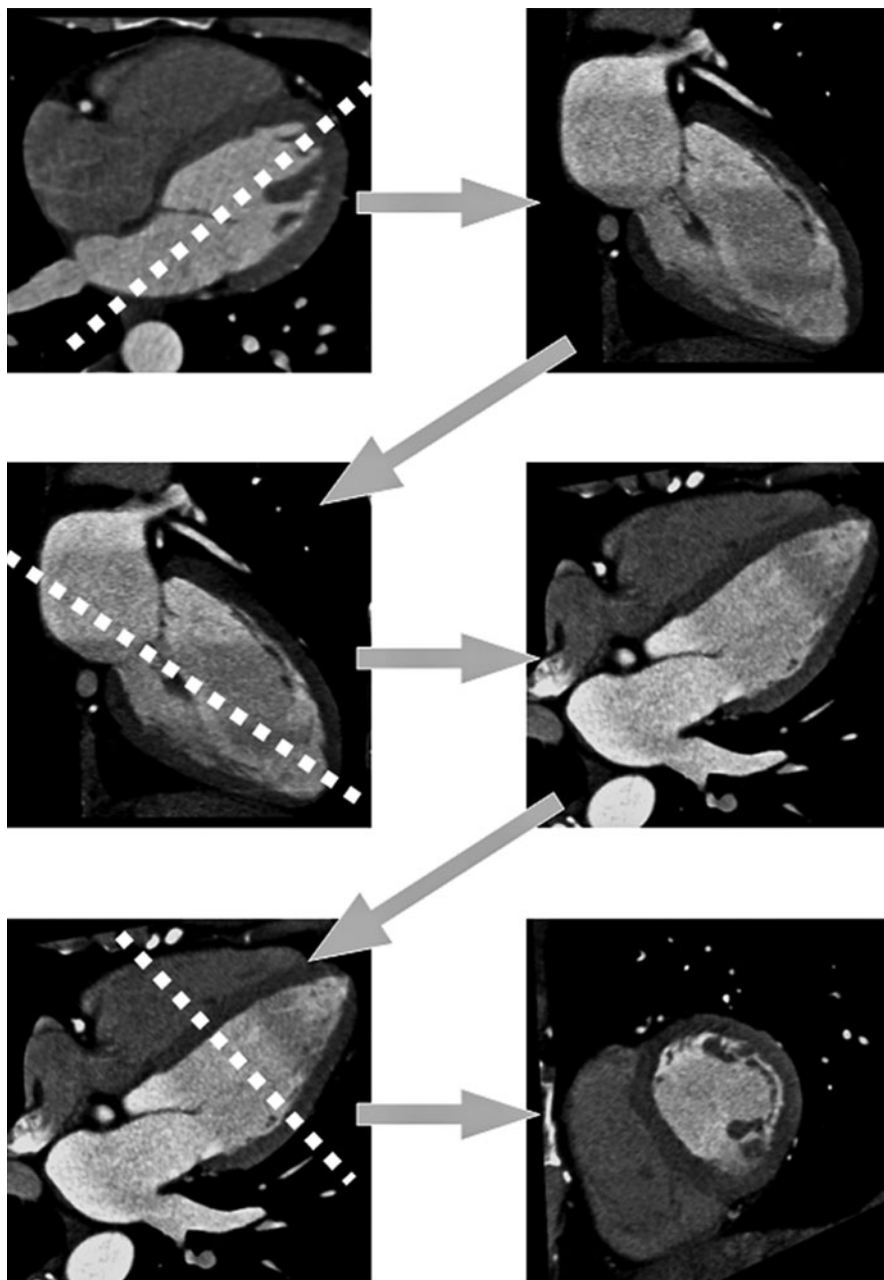


Fig. 9. Off-axis reconstruction to generate typical axial planes. Based on the axial images (*top left*), a two-chamber view can be generated (*top right*). This can be used to generate a four-chamber view (*middle right*), from which a short-axis view of the left ventricle can be obtained (*bottom right*)

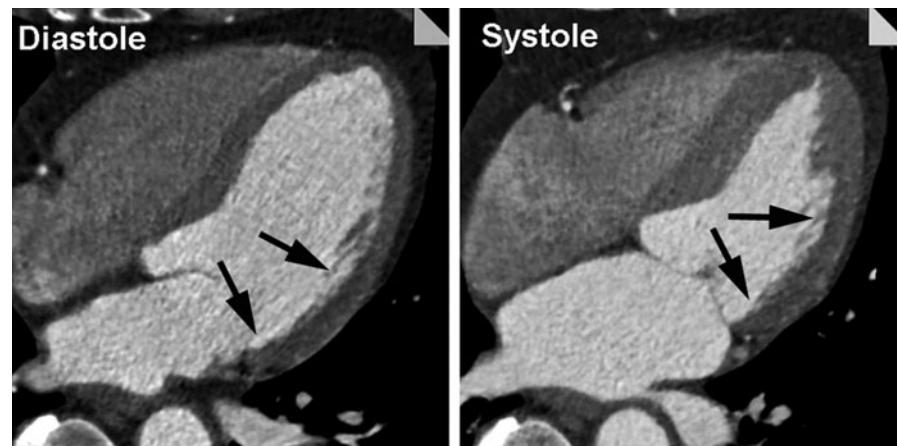


Fig. 10. Hypokinetic area in the posterolateral wall of the left ventricle (*arrows*). Inward motion and especially wall thickening are reduced in comparison with the other segments

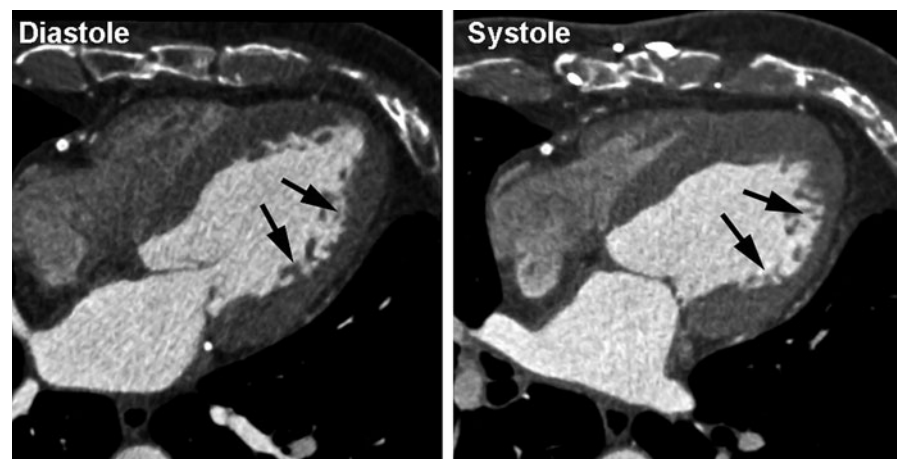


Fig. 11. Akinetic area in the anterolateral wall of the left ventricle (*arrows*). There is no inward motion or wall thickening in systole

to automated software analysis to verify findings and identify potential artefacts. Systematic analyses did not demonstrate significantly improved accuracy using automated analyses, and no significant differences between different software products [11-15]. For reporting left ventricular function, a consensus document exists as to the nomenclature of myocardial segments [16] (<http://circ.ahajournals.org/cgi/content/full/105/4/539>). It describes 17 segments. This may be too detailed for analysis of regional left ventricular function. In the author's opinion, reporting wall-motion abnormalities in the following regions may be sufficient for many clinical purposes unless very specific information is required: anterior, apical, inferior, lateral, septal.

Accuracy

In numerous studies, CT imaging has demonstrated high accuracy for analysing cardiac volumes and ventricular function. Close correspondence has been achieved both in comparison to echocardiography and cardiac magnetic resonance, the gold standard for

quantifying ventricular function [17-21]. *R* values were >0.95 for most of these studies, and no clinically relevant over- or underestimation was reported. Studies have also demonstrated high accuracy for assessing regional left ventricular wall motion, including detection of hypokinetic and akinetic segments [22, 23]. However, as in most modalities, there is relevant interobserver variability regarding visual analysis of regional left ventricular function [23]. Interestingly, a first analysis has demonstrated a relevant prognostic value of left ventricular function assessed by CT in patients with suspected coronary artery disease [24].

Right ventricular function is more difficult to assess than left ventricular function due to the more complex geometric shape of the right ventricular cavity. As in left ventricular function, CT has demonstrated extremely good correlation (with *r* values >0.98 and no relevant bias) to magnetic resonance imaging [25, 26]. Right ventricular dysfunction is a prognostic parameter in acute pulmonary embolism (and, when present in echocardiography, a possible indication for thrombolysis) [27]. One study in pulmonary embolism patients demonstrated that adding an ECG-gated cardiac study to the dedicated

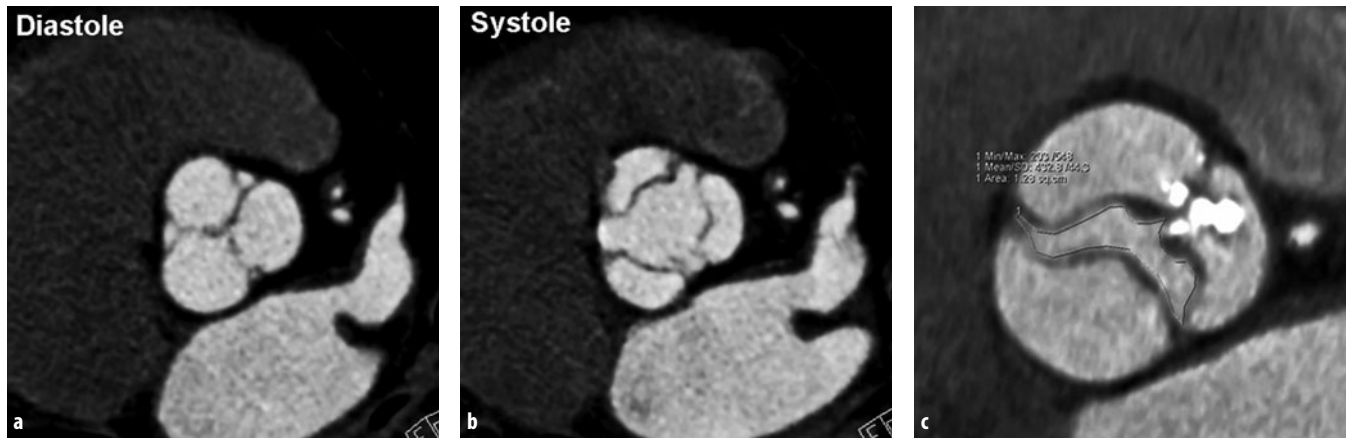


Fig. 12 a-c. Visualisation of aortic valve in an off-axis reconstruction to show the valve in an anatomically correct plane. Images in **a** diastole (closed valve) and **b** systole (open valve) demonstrate valvular function. **c** Mild aortic valve stenosis with an orifice area of 1.2 cm²

pulmonary embolism CT scan allowed right ventricular dysfunction to be identified, which was correlated to embolic load (however, it was also correlated to left ventricular function, so that left ventricular dysfunction needs to be taken into account in this situation) [28]. In fact, similar information may be drawn from static image data sets. In a recent study of 100 patients with pulmonary embolism, enlargement of the right ventricle in comparison with the left ventricle in nongated chest CT was a strong discriminator for identifying high-risk patients. The mean right ventricular to left ventricular volume ratio (RV/LV_{vol}) was 1.68 for high-risk patients who developed complications during the further course of disease compared with 0.93 for low-risk patients with an uneventful clinical course [$p < 0.001$; area under receiver operating characteristics (ROC) curve 0.82] [29].

Analysis of Cardiac Valves

Functional data sets that depict cardiac volume throughout the cardiac cycle allow not only assessment of left and right ventricular function but, within certain limitations, analysis of valvular function. Limitations pertain to contrast enhancement, which is usually sufficient only for the aortic and mitral valves, with restrictions for the pulmonary valve, and never for the tricuspid valve (because of inhomogeneous contrast enhancement of the mitral valve). Whereas quantification of the aortic orifice area in aortic valve stenosis is reliably possible by CT (Fig. 12), which has been demonstrated in numerous studies [30], there is no sufficient data regarding other valvular pathology. Quantification of the regurgitant orifice area in the aortic and mitral valves is possible but is only loosely correlated with regurgitation severity. Demonstration of vegetations in endocarditis is anecdotal. Case reports also demonstrate the ability of CT to visualise leaflet motion of prosthetic valves.

Summary

Cardiac CT is, in most cases, performed for visualising the coronary arteries. If data acquisition encompasses the entire cardiac cycle, it is possible to reconstruct 4D data sets that can be evaluated for regional and global left ventricular function. Data sets are typically reconstructed with reduced spatial resolution to reduce data volume and can be analysed either visually or with the help of dedicated software. Accuracy is high, as has been demonstrated in numerous comparisons with echocardiography and magnetic resonance imaging. CT imaging also allows analysis of right ventricular function and, with limitations, some aspects of valvular function. It must be recognised, however, that CT is typically not a first-line tool for evaluating cardiac function or valves (except in some very selected cases where other imaging modalities fail). Much rather, this is additional information that can be extracted from CT data sets acquired for different purposes.

References

1. Detrano R, Guerci AD, Carr JJ, et al (2008) Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med* 358:1336-1345
2. Greenland P, Bonow RO, Brundage BH et al (2007) ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography). *Circulation* 115:402-426
3. Schroeder S, Achenbach S, Bengel F et al (2008) Cardiac computed tomography: indications, applications, limitations, and training requirements: Report of a Writing Group deployed by the Working Group Nuclear Cardiology and Cardiac CT of the European Society of Cardiology and the European Council of Nuclear Cardiology. *Eur Heart J* 29:531-556
4. Meijboom WB, Meijjs MF, Schuijff JD et al (2008). Diagnostic accuracy of 64-slice computed tomography coronary angio-

- graphy: a prospective, multicenter, multivendor study. *J Am Coll Cardiol* 52:2135-2144
5. Abbara S, Arbab-Zadeh A, Callister TQ et al (2009) SCCT guidelines for performance of coronary computed tomographic angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. *J Cardiovasc Comput Tomogr* 3:190-204
 6. Taylor AJ, Cerqueira M, Hodgson JM et al (2010) ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 Appropriate Use Criteria for Cardiac Computed Tomography. A Report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance. *J Am Coll Cardiol* 56:1864-1894
 7. Hausleiter J, Meyer T, Hermann F et al (2009) Estimated radiation dose associated with cardiac CT angiography. *JAMA* 301:500-507
 8. Alkadhi H, Stolzmann P, Desbiolles L et al (2010) Low-dose, 128-slice, dual-source CT coronary angiography: accuracy and radiation dose of the high-pitch and the step-and-shoot mode. *Heart* 96:933-938
 9. Achenbach S, Marwan M, Ropers D et al (2010) Coronary computed tomography angiography with a consistent dose below 1 mSv using prospectively electrocardiogram-triggered high-pitch spiral acquisition. *Eur Heart J* 31:340-346
 10. Wuest W, Zunker C, Anders K et al (2008) Functional cardiac CT imaging: a new contrast application strategy for a better visualization of the cardiac chambers. *Eur J Radiol* 68:392-397
 11. Bardo DM, Kachenoura N, Newby B et al (2008) Multidetector computed tomography evaluation of left ventricular volumes: sources of error and guidelines for their minimization. *J Cardiovasc Comput Tomogr* 2:222-230
 12. Juergens KU, Seifarth H, Range F, Wienbeck S, Wenker M, Heindel W, Fischbach R (2008) Automated threshold-based 3D segmentation versus short-axis planimetry for assessment of global left ventricular function with dual-source MDCT. *AJR Am J Roentgenol* 190:308-314
 13. de Jonge GJ, van der Vleuten PA, Overbosch J et al (2010) Semi-automatic measurement of left ventricular function on dual source computed tomography using five different software tools in comparison with magnetic resonance imaging. *Eur J Radiol* 2010 Nov 25. [Epub ahead of print]
 14. Mahnken AH, Mühlenbruch G, Koos R et al (2006) Automated vs. manual assessment of left ventricular function in cardiac multidetector row computed tomography: comparison with magnetic resonance imaging. *Eur Radiol* 16:1416-1423
 15. Plumhans C, Keil S, Ocklenburg C et al (2009) Comparison of manual, semi- and fully automated heart segmentation for assessing global left ventricular function in multidetector computed tomography. *Invest Radiol* 44:476-482
 16. Cerqueira MD, Weissman NJ, Dilsizian V et al (2002) Standardized Myocardial Segmentation and Nomenclature for Tomographic Imaging of the Heart. A Statement for Healthcare Professionals From the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation* 105:539-342
 17. Belge B, Coche E, Pasquet A et al (2006) Accurate estimation of global and regional cardiac function by retrospectively gated multidetector row computed tomography: comparison with cine magnetic resonance imaging. *Eur Radiol* 16:1424-1433
 18. Sayyed SH, Cassidy MM, Hadi MA (2009) Use of multidetector computed tomography for evaluation of global and regional left ventricular function. *J Cardiovasc Comput Tomogr* 3(1 Suppl):S23-S34
 19. de Graaf FR, Schuijf JD, van Velzen JE et al (2010) Assessment of global left ventricular function and volumes with 320-row multidetector computed tomography: A comparison with 2D-echocardiography. *J Nucl Cardiol* 17:225-331
 20. Ko SM, Kim YJ, Park JH et al (2010) Assessment of left ventricular ejection fraction and regional wall motion with 64-slice multidetector CT: a comparison with two-dimensional transthoracic echocardiography. *Br J Radiol* 83:28-34
 21. van der Vleuten PA, Willems TP, Götte MJ et al (2006) Quantification of global left ventricular function: comparison of multidetector computed tomography and magnetic resonance imaging. A meta-analysis and review of the current literature. *Acta Radiol* 47:1049-1057
 22. Pflederer T, Ho KT, Anger T et al (2009) Assessment of regional left ventricular function by dual source computed tomography: interobserver variability and validation to laevocardiography. *Eur J Radiol* 72:85-91
 23. Lessick J, Ben-Haim T, Mutlak D et al (2009). Quantitative evaluation of regional left ventricular function by multidetector computed tomography. *J Comput Assist Tomogr* 33:204-210
 24. Min JK, Lin FY, Dunning AM et al (2010) Incremental prognostic significance of left ventricular dysfunction to coronary artery disease detection by 64-detector row coronary computed tomographic angiography for the prediction of all-cause mortality: results from a two-centre study of 5330 patients. *Eur Heart J* 31:1212-1219
 25. Müller M, Teige F, Schnapauff D et al (2009) Evaluation of right ventricular function with multidetector computed tomography: comparison with magnetic resonance imaging and analysis of inter- and intraobserver variability. *Eur Radiol* 19:278-289
 26. Plumhans C, Mühlenbruch G, Rapae A et al (2008) Assessment of global right ventricular function on 64-MDCT compared with MRI. *AJR Am J Roentgenol* 190:1358-1361
 27. Torbicki A, Perrier A, Konstantinides S et al (2008) Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). *Eur Heart J* 29:2276-2315
 28. Dogan H, Kroft LJ, Huisman MV et al (2010) Assessment of right ventricular function in acute pulmonary embolism using ECG-synchronized MDCT. *AJR Am J Roentgenol* 195:909-915
 29. Henzler T, Krissak R, Reichert M et al (2010) Volumetric analysis of pulmonary CTA for the assessment of right ventricular dysfunction in patients with acute pulmonary embolism. *Acad Radiol* 17:309-315
 30. Pflederer T, Achenbach S (2010) Aortic valve stenosis: CT contributions to diagnosis and therapy. *J Cardiovasc Comput Tomogr* doi:10.1016/j.jcct.2010.09.008

Cardiovascular Magnetic Resonance

Dudley J. Pennell

CMR Unit, Royal Brompton Hospital, London, UK

Introduction

Cardiovascular magnetic resonance (CMR) creates images from atomic nuclei with uneven spin using radio waves in the presence of a magnetic field. Full details of the physical principles can be found elsewhere [1]. For clinical purposes, MR is performed using hydrogen-1, which is abundant in water and fat. Radiofrequency waves excite the area of interest to create tissue magnetization, which decays (relaxation) and after a short period is induced to release energy as a radio signal. These echoes are converted using Fourier transformation into images of spatially resolved radio signals. Relaxation is quantified in spatially orthogonal directions as T1 and T2, which allows tissue characterization, thus creating a powerful clinical tool. A CMR scanner consists of a superconducting magnet, a radiofrequency transmitter and receiver connected to radio aerials, and gradient coils driven by powerful pulses of electricity to create transient magnetic fields. The imaging computer triggers to the electrocardiogram and runs scanning sequences that coordinate the complex processes. The spin-echo sequence yields static images with black blood, whereas the gradient-echo sequence usually acquires multiple images throughout the cardiac cycle, displaying cardiovascular function as cine loops. Preparation pulses can be used to display T1 or T2 contrast for tissue characterization. Fast and real-time sequences include fast low angle shot (FLASH), steady state with free precession (SSFP), spiral, and echo-planar imaging (EPI). Velocity and flow can be quantified using gradient-echo sequences with encoding of velocity in the signal phase.

CMR is extremely safe, which is unequivocally advantageous compared with X-rays, but special cautions apply. Ferromagnetic items become potentially dangerous projectiles in the scanner room. Whereas most metallic medical implants are MR compatible, including all prosthetic cardiac valves and coronary stents, care is required with cerebrovascular clips. Pacemakers and defibrillators present problems, in particular related to wire heating, and are a contraindication for CMR, although specialist centers have described dedicated approaches for patients with pressing clinical circumstances, and

approved MR-compatible pacemakers are now available. The MR contrast agent gadolinium has proved extremely safe in tens of millions of patients. Recently, however, nephrogenic sclerosing fibrosis (NSF) has been reported as a possible adverse event of the use of high doses in patients with severe renal impairment with glomerular filtration rate <30 ml/min. The risk appears extremely low, but many centers now use gadolinium tightly bound to a cyclic chelate, for which the incidence of NSF is near zero. MR with a cyclic gadolinium is still used in renal failure because of the significant dangers of iodinated contrast agents.

The Society of Cardiovascular Magnetic Resonance and major cardiology societies have published guidelines in a number of important areas of clinical practice of CMR, which are useful reference materials and include credentialing [2], appropriateness criteria [3], training [4, 5], imaging protocols [6], and reporting guidelines [7].

Volumes and Function

CMR measures ventricular volumes and mass using a simple acquisition of a 3D stack of contiguous short-axis cines with full biventricular coverage. Left (LV) and right (RV) ventricular volume and mass are determined by planimetry for each slice and summed for each entire ventricle. Commercially available software can correct for valve-plane movements during the cardiac cycle and measure the ventricular mass contribution from the papillary muscles and trabeculae. The high fidelity of the ventricular volumes allows normalization of the measurements to body surface area (BSA), gender, and age [8, 9]. These data demonstrate that normalization is important for confident diagnosis of conditions such as early dilated cardiomyopathy or LV hypertrophy. CMR is significantly more accurate and reproducible than other techniques [10, 11], which makes it the technique of choice for longitudinal study of patients over time and for lowering sample size for drug studies. Diastolic ventricular function can be routinely assessed by CMR, although echocardiography is often preferred for this purpose.

Great Vessels

CMR is widely used for imaging great-vessel disease. SSFP cines with planes optimized to the location and orientation of the pathology will often depict the lesion directly (stenosis) or will show signal loss due to phase incoherence (abnormal communication). Three-dimensional angiography with gadolinium enhancement may show the lesion more clearly in high resolution, as well as any associated pathology (collaterals). Velocity mapping provides reliable quantification in any direction of jet flow velocity and blood flow.

CMR angiography is often used to show the size, extent, and shape of aortic aneurysms and associated branch-vessel involvement. Spin-echo imaging may be used to show the vascular wall and the adjacent soft tissues. Inflammation in arteritis or infection may enhance with the use of gadolinium. A combination of spin-echo and cine imaging reliably identifies intra- or extraluminal thrombus. Spin-echo imaging is less prone than cines to dark artefacts from aortic stents. CMR is fast and accurate for diagnosing aortic dissection, although local issues regarding availability will determine whether CMR, computed tomography (CT) or echocardiography is used. Aortic dissection is characterized by an intraluminal intimal flap, and this is readily shown with cine CMR. The entire thoracoabdominal extent of the flap and branch-vessel involvement can readily be determined by CMR cines or 3D angiography. Therefore, CMR is valuable for follow-up in patients with chronic disease because longitudinal comparisons are straightforward and anatomical landmarks are obvious. Intramural hematoma is characterized by a false lumen without blood flow. Recent bleeding may show onion-ring enhancement with spin-echo imaging due to paramagnetic breakdown products of hemoglobin. Aortic ulcer is readily identified.

The pulmonary vessels are also well depicted by CMR. Pulmonary arterial angiography is useful in congenital heart disease, but CT is usually preferred for diagnosing pulmonary embolism, as it is faster and has higher resolution. Pulmonary venous anomalies are robustly imaged by CMR, which is helpful in patients with a dilated RV.

Valvular Heart Disease

CMR has a significant role in valve disease but is usually used as a second-line technique when echocardiography with Doppler proves problematic due to limited acoustic access, highly eccentric jets, or the need for quantification. Cine CMR is used to study valvular morphology and function. Valve leaflets are well seen, especially with SSFP cines, allowing thickening and motion visualization. Turbulent flow from stenosis or regurgitation causes signal loss within the jet, the size and extension of which is a semiquantitative measure for lesion

severity. Direct valve orifice planimetry has proven to be reliable by CMR, and imaging with thin, adjacent slices through the stenotic valve is performed. Valve stenosis can be quantified from blood flow velocity (m/s) in coherent jets using phase-contrast velocity mapping using optimized alignment guided by an iterative imaging approach with parallel and perpendicular cine acquisitions. Quantification of valve regurgitation is a strength of CMR because of its capability for measuring accurate ventricular stroke volumes from multislice ventricular planimetry and measuring great-vessel flow from velocity mapping in comparison with ventricular stroke volumes. In isolated valve regurgitation, regurgitant volume and fraction are simply calculated from the difference in LV and RV stroke volumes. Thus, isolated mitral and aortic regurgitation result in excess LV stroke volume whereas tricuspid and pulmonary regurgitation results in an excess RV stroke volume. For mixed regurgitant valve lesions, the integration of flow over time in a great vessel close to the ventriculoarterial valve provides the forward stroke volume, and further analysis allows the direct determination of antegrade and retrograde flow volumes for a direct assessment of the ventriculoarterial valve regurgitation. Comparison of flow measurements from both the pulmonary artery and aorta with RV and LV stroke volumes measured from the multislice ventricular planimetry technique enables a full quantitative solution for multivalve regurgitation, with discrimination of the regurgitant volume for all four individual valves.

Aortic regurgitation is quantified from the excess LV stroke volume measured by ventricular planimetry. An alternative is to measure the retrograde diastolic flow with the flow measurement taken immediately above the valve and below the coronary ostia to limit errors from coronary flow. Errors can occur in patients with dilated aortic roots because of through-plane motion, and a slice tracking technique has been developed to minimize this problem. The regurgitant fraction is obtained by dividing the retrograde flow volume by the antegrade flow. When echocardiography proves inadequate, aortic stenosis can be assessed by calculating the aortic valve jet gradient on phase-velocity mapping or by direct planimetry of the valve area [12]. Using similar techniques, CMR is valuable in pulmonary valve regurgitation and stenosis, especially in the setting of congenital heart disease, with additional information available on the valvular or outflow tract abnormalities, the RV, and the pulmonary circulation.

Multislice contiguous cines can be used for a full evaluation of mitral valve morphology and for identification of regurgitation at scallops for surgical repair. Quantification of mitral regurgitation is commonly assessed from the difference in ventricular stroke volumes, but other approaches have been used, including the difference between forward aortic flow and LV stroke volume or mitral inflow volume, and these methods may be more reliable. CMR has proved useful clinically when the regurgitant mitral jet or jets are highly eccentric, which can preclude adequate assessment by echocardiography.

For mitral stenosis assessment, both in- and through-plane velocity measurements can be used, but multiple parallel planes are again required to iterate to the correct jet alignment. For the tricuspid valve, CMR is usually second line to echocardiography, and Doppler is superior for measuring trace tricuspid regurgitation for estimating pulmonary artery pressure. CMR is used in Ebstein's anomaly, as valvular displacement and malformation are well depicted, and regurgitation RV function can be measured.

CMR can be performed safely in all prosthetic valves, although focal artefacts occur that can obscure small jets. Endocarditis lesions are best visualized by echocardiography because of erratic motion, but CMR is suitable for identifying paravalvular abscesses.

Congenital Heart Disease

CMR is widely used to assess congenital heart disease, and when used in concert with echocardiography, the need for invasive assessment is significantly reduced. CMR is particularly useful for safe, accurate, and reproducible quantification of left-to-right shunting of blood, which is frequent in congenital heart defects such as atrial or ventricular septal defects (ASD/VSD), patent ductus arteriosus, aortopulmonary window, and partial or total anomalous pulmonary venous return. Flow and velocity mapping is also used extensively to assess local flow in shunts after surgical repair when echocardiography may be problematic. Other valuable characteristics of CMR include the wide field of view, good reproducibility and absence of radiation for multiple serial scans, and availability of gadolinium angiography for 3D representation of the great vessels and complex anatomy. Echocardiography is usually the technique of choice in young children, but CMR becomes more valuable with older children and adults, in complex pathology, and after surgery when echocardiography may be difficult because of the presence of scar tissue, rib and chest deformity, and interposed lung tissue.

Arteries, Veins, and Conduits

CMR is considered the ideal imaging technique for visualizing native and repaired aortic coarctation, which usually occurs as a discrete stenosis of the proximal descending aorta, just opposite the ductus arteriosus insertion, and may be associated with poststenotic dilation. Peak jet velocity across the coarctation as measured by CMR provides a useful estimate of the pressure gradient. The collateral circulation can be quantified by comparing flow proximal and distal to the coarctation and is used to determine treatment success. CMR is also ideal for long-term follow-up of coarctation repair to identify complications such as recoarctation and aneurysm. Other rarer abnormalities of the aorta, such as double aortic arch, are easily identified and can be followed. Patent ductus arte-

riosus in newborns is assessed by echocardiography, but CMR is more reliable in older patients. CMR is valuable in abnormalities of the pulmonary circulation (both before and after repair), such as anomalies, reduced pulmonary artery flow, or systemic to pulmonary collaterals. Measurement of relative flow in the right and left pulmonary artery can be useful. Systemic venous abnormalities, such as left superior vena cava or interrupted inferior vena cava, can easily be visualized. CMR is valuable, and usually superior to echocardiography, for assessing pulmonary veins and any anomalies, with flow measurements allowing calculation of the shunt fraction [13]. It is often superior to echocardiography after surgical repair, especially for conduits and the RV, which is often overloaded due to its function as the systemic ventricle or to pulmonary insufficiency. In transposition of the great arteries, both ventriculoarterial and atrioventricular discordance can be readily identified from spin-echo and cine imaging to characterize complete or corrected forms. Most adult patients will have had early repair, either with an atrial level switch or more an arterial switch. CMR in atrial switch patients can identify systemic RV failure, systemic atrioventricular valve regurgitation, and baffle obstruction using multiple cines and flow maps. Persistent truncus arteriosus results from failure of the embryonic truncus to divide into a separate aorta and pulmonary artery, and all three types are well depicted by CMR, including origin, size, and location of the pulmonary arteries, as well as conduits used in repair.

Cardiac Chambers

CMR identifies the atria and ventricles using characteristic morphologic features, and in concert with anatomical features of the bronchus and spleen, CMR is accurate in assignment of situs and isomerism. ASD is well visualized with echocardiography, but CMR may be useful in older patients or those with limited acoustic windows and is preferable to quantify the shunt and the effects on RV function. ASD position relative to the atrioventricular valve and pulmonary veins can be established and associated pulmonary venous anomalies shown. The size and multiplicity of the defect(s) can be demonstrated using phase-contrast cine imaging with *en face* views in the right atrium, which is useful for planning percutaneous closure devices. Ventricular septal defects are seen by CMR cine signal loss in the jet, but CMR is only superior to echocardiography in complex lesions. Complex ventricular anomalies such as tetralogy of Fallot or univentricular hearts are well depicted with CMR, allowing quantification of morphologic and hemodynamic consequences. In tetralogy of Fallot, the presentation may vary from pulmonary atresia and multiple aortopulmonary collateral vessels to only mild pulmonary stenosis. In adults, surgical repair will usually have been undertaken, often with a palliative procedure to augment pulmonary blood flow, with later definitive repair. CMR can assess the degree of pulmonary regurgitation and any recurrent

pulmonary stenosis, RV dilatation or hypertrophy, tricuspid regurgitation, and any associated central pulmonary artery stenosis. The presence of myocardial fibrosis has been linked to impaired exercise capacity and adverse outcomes [14]. Double-outlet RV is an abnormal ventriculoarterial connection with more than half of both aorta and pulmonary artery arising from the morphologic RV. CMR is useful to characterize the relationship of VSD to the great vessels and to assess pulmonary arteries and any associated pulmonary stenosis or other anomaly, which assists in operative planning. CMR is also useful in the single ventricle to define atrioventricular and ventriculoarterial connections, characterize interventricular communication, and define connections of systemic and pulmonary veins and arteries.

Valves and Atrioventricular Concordance

Echocardiography is usually preferred for depicting valve morphology, but CMR is useful to assess valve morphology in some cases and quantify regurgitation and RV size and function. Valve abnormalities may be assessed by CMR along with the associated effects on cardiac chambers, including valve atresia, Ebstein's anomaly, bicuspid semilunar valve, single AV valve, and congenital mitral valve malformations. Assessing pulmonary regurgitation after tetralogy of Fallot repair is clinically useful to guide the timing of valve replacement [15].

Ischemic Heart Disease

Myocardial Ischemia

Myocardial ischemia can be assessed by CMR from stress myocardial perfusion imaging or stress ventriculography, and both are in use clinically as alternatives to myocardial perfusion single photon emission CT (SPECT) or stress echocardiography, respectively. Stress CMR ventriculography is a relatively mature technique, with reasonably sized single-center studies showing its diagnostic accuracy and prognostic capability. Stress perfusion CMR has been assessed for technical factors in relation to diagnostic accuracy in the multicenter setting, albeit with relatively modest sample sizes. Clinical results are highly encouraging, with the multivendor MR-IMPACT study of 241 patients showing perfusion CMR to be either equivalent or superior to perfusion SPECT. Prognostic studies are still limited, however, and the imaging technology will mature further. The relative strengths of the two techniques depend on many factors, including the clinical scenario and local expertise, but there is a general perception in the CMR community that perfusion imaging will develop into an important and versatile clinical tool [16].

Perfusion CMR is performed at rest and again during adenosine vasodilator stress using a first-pass technique with fast intravenous injection of a gadolinium contrast

agent. The myocardial signal increases in well-perfused myocardium, but this increase is impaired in regions of myocardial ischemia. Three short-axis slices are usually imaged per cardiac cycle, allowing 16 myocardial segments to be analyzed, excluding the apical cap. Ischemic myocardium in coronary disease affects the subendocardium, and the transmural extension defines ischemia severity. The resting study is only needed to identify endocardial artefacts and for perfusion quantification (absolute perfusion in ml/g/min, and perfusion reserve). Validation of perfusion CMR by microspheres shows a good linear relationship without roll-off at high perfusion that is typical of nuclear tracers, and this suggests perfusion CMR may be more sensitive for identifying moderate coronary stenosis. The optimal CMR perfusion sequence is not yet fully defined. Commercially available ultrafast sequences are being further enhanced with parallel imaging, which improves resolution and reduces artefacts. Potential developments include a new tracer that binds to myocardial collagen and allows perfusion CMR to be undertaken in the equilibrium phase, greatly simplifying imaging, providing improved image quality at 3Tesla, and allowing non-contrast-agent perfusion techniques such as T2* blood oxygen level-dependent (BOLD) [17]. As a diagnostic tool, perfusion CMR performs well against invasive coronary angiography or positron emission tomography (PET) as the gold standard, and the absence of perfusion abnormalities is a good prognostic indicator. Perfusion CMR is also used to investigate microvascular dysfunction in syndrome X and hypertrophic cardiomyopathy.

Stress CMR ventriculography uses incremental doses of dobutamine with additional atropine when needed to reach the target heart rate, is safe, and is operationally similar to stress echocardiography. Induction of new regional-wall motion abnormalities is assessed on short- and long-axis cines acquired at each stage of stress. Diagnostic accuracy is good compared with invasive angiography and superior to echocardiography if acoustic access is suboptimal [18]. Low cardiac event rates are associated with normal stress CMR, and increasing risk is seen with increasing extent of ischemia. Stress CMR can be combined with tagging to quantify myocardial strain, which improves diagnostic accuracy, reduces observer variability, and can be combined with perfusion imaging.

Myocardial Infarction

Myocardial infarction is detected with very high sensitivity by imaging some 10 min after injection of gadolinium contrast. Kinetic and volume of distribution effects result in high gadolinium concentration in abnormal myocardium, which appears bright on T1-weighted CMR. This technique of late gadolinium enhancement (LGE) yields high-resolution images of infarction (acute and chronic), fibrosis, and infiltration, which have excellent longitudinal reproducibility. LGE is also highly accurate for detecting infarction in both the acute and chronic

settings in a substantial multicenter trial of 566 patients [19]. LGE revolutionized the study of infarctions because CMR is considerably more sensitive than perfusion SPECT and wall-motion abnormality [20]. Thus, previously unrecognized infarctions have important prognostic importance over and above conventional risk measures in patients with clinical suspicion of coronary disease but no previous infarction; microinfarction after complex percutaneous coronary interventions can be demonstrated; and confident exclusion of infarction can be made in acute coronary syndromes. Quantification of infarct size also shows in vivo the shrinkage of acute infarcts over time, both in volume and transmural extent.

However, considerable additional information is available using supplementary techniques in acute infarction. Some acute infarcts have a central dark zone with gadolinium enhancement that represents microvascular obstruction where gadolinium penetration is very slow, being limited by diffusion. This is best imaged by early gadolinium enhancement (EGE) imaging at 1-2 min after injection. Infarcts with microvascular obstruction indicate a poorer prognosis, which is a predictor independent of ejection fraction. Microvascular obstruction slowly shrinks over weeks and is not seen in chronic infarctions. T2-weighted CMR is used in acute infarction to identify cellular edema – which allows clear differentiation of acute from chronic infarction – and reversible from irreversible ischemia. Edema imaging also allows identification of the area at risk in acute infarction, and by subtraction of the infarct size determined by LGE, the area of salvaged myocardium can be measured. CMR has been validated against SPECT to assess the area at risk. Because the high signal on T2 CMR caused by edema is persistent after the reversible ischemic insult, this can be measured hours or days after primary angioplasty, which makes research studies of adjuvant techniques for revascularization much easier than the previous gold standard technique of immediate radioactive technetium injection at presentation with SPECT needing to be performed within 6 h. T2* CMR identifies myocardial hemorrhage in acute infarction. EGE is also superior to echocardiography for identifying ventricular thrombi, which appear as dark filling defects on the endocardial surface of enhanced infarcts. Myocardial fiber microstructure remodelling postinfarction can also be studied using diffusion tensor tractography.

CMR has also been used in patients presenting with possible acute coronary syndrome to image resting wall motion, resting perfusion, and infarction enhancement to determine whether invasive investigation is required. Sensitivity and specificity for detecting acute coronary syndrome was 84% and 85% by CMR when performed within 12 h of presentation and was superior to electrocardiography (ECG), troponin, and thrombosis in myocardial infarction (TIMI) risk score. Additional T2-weighted imaging for edema associated with reversible injury only may be helpful in the acute setting to identify patients requiring invasive coronary angiography.

Low-risk patients may be assessed by stress testing, and CMR has good diagnostic accuracy for detecting >70% stenosis. Normal adenosine perfusion CMR in the emergency room identifies patients without subsequent CAD diagnosis and indicates a good prognosis. The majority of patients presenting with acute chest pain with elevated troponin but normal coronary arteries are alternatively diagnosed by CMR, with the most common cause being myocarditis.

Myocardial Viability

Using CMR to predict recovery of function following revascularization is possible with both LGE and low-dose dobutamine stress ventriculography. The transmural extent of LGE predicts the likelihood of regional function recovery, and when >20% of the myocardium is hibernating, ejection fraction improvement is likely [21]. However, low-dose dobutamine stress CMR may be more sensitive. LGE may show nontransmural scar that fails to recover function after adequate revascularization. This may relate to incomplete revascularization, structural hibernation requiring a longer than expected recovery period, or limited improvement in functional wall-motion recovery, which is only apparent at stress. Overall, LGE CMR has a negative predictive value of ~90% of no functional recovery in segments with >50% transmural infarction and a positive predictive value of ~80% of recovery in segments without infarction. Larger infarctions also predict a reduced likelihood of ejection fraction response to beta-blockers in patients with heart failure.

Cardiomyopathy

Dilated Cardiomyopathy

Structural functional abnormalities of both ventricles in established dilated cardiomyopathy (DCM) are well shown by CMR, and changes over time or with treatment can be monitored serially because of high longitudinal reproducibility. However, in patients newly presenting with an enlarged heart, the main question is differentiating the diagnosis of DCM from the sequelae of coronary artery disease. Many centers routinely perform coronary angiography as a gold standard, but this has significant limitations because of its inability to adequately characterize whether infarction has occurred (coronary stenosis often exists without downstream infarction, and infarction commonly occurs in relation to nonobstructive plaques). LGE CMR is a valuable technique as a noninvasive alternative. A study of patients labelled as DCM who all had normal coronary angiography showed no LGE in 59% and patchy or circumferential enhancement in the midwall in 28%, and this established that myocardial infarction was not the cause of ventricular dysfunction. The final 13% of patients had LGE showing often extensive infarction, which suggested that these patients were

incorrectly assigned as DCM following “normal” coronary angiography, probably due to coronary recanalization postinfarction and untreated ventricular remodelling. The midwall LGE seen in DCM patients matches the fibrosis found at post-mortem, is linked to diastolic dysfunction, and is an important predictor of major adverse cardiac events, including sustained ventricular tachycardia and sudden cardiac death [22]. This predictive value appears to be independent of more conventional markers of risk, such as ejection fraction. The amount of LGE also correlates with the likelihood of inducible ventricular tachycardia during electrophysiological testing. Also, CMR spectroscopy assesses a low phosphocreatine to adenosine triphosphate (ATP) ratio, which predicts an adverse outcome.

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is usually diagnosed by echocardiography, showing increased ventricular-wall thickness in the absence of pressure overload. CMR also has a role in diagnosis because the comprehensive myocardial coverage is superior in identifying regional hypertrophy, and this is particularly true for the basal regions. Apical variants of HCM are also better identified by CMR, which can show the other features of HCM such as small cavity, dynamic resting function, RV involvement, outflow-tract obstruction, and systolic anterior motion of the mitral valve and mitral regurgitation. The good discrimination of blood from myocardium allows accurate CMR measurements of not only wall thickness but also ventricular mass, which is normal in 20% of patients with HCM phenotype. It is also a more sensitive marker of outcomes in HCM than is maximal wall thickness. LGE CMR plays an important role in identifying myocardial replacement fibrosis in HCM. This may be limited to the superior and inferior insertion junctions of the RV (considered a benign finding) or can be extensive scarring. Scarring is typically, but is not always present, in the region of maximal wall thickness. There is an association between the extent of scarring and the development of the late dilated phase of HCM with heart failure. In patients >40 years, there is an increased prevalence of markers of sudden death. The fibrosis may therefore impact both systolic and diastolic function and act as a focus for re-entrant tachycardia. The link to arrhythmia has recently been confirmed and appears to be an independent predictor for new-onset atrial fibrillation. No data yet exist relating the use of LGE to guide defibrillator implantation. LGE is also used to assess the location and extent of therapeutic septal myocardial infarction. The accuracy of CMR in identifying HCM is helpful for screening relatives of probands.

Other CMR techniques are also used to assess HCM, although clinical utility remains to be determined. Stress perfusion CMR shows microvascular dysfunction related to wall thickness and fibrosis, which may be an early marker of disease, indicating an adverse prognosis. CMR

tagging shows abnormal strain, shear, and torsion in dysfunctional hypertrophy, which may be useful for differentiating HCM from athletic hypertrophy or hypertension. CMR spectroscopy of ATP shows a bioenergetic defect in HCM, suggesting that inefficient energy utilization may underlie the clinical manifestations of HCM. Fiber disarray may also be imaged directly by CMR using diffusion-weighted tractography, and this may find future diagnostic application in patients with borderline phenotype, particularly those with confounding pathology such as hypertension.

Fabry's Disease and Amyloidosis

About 4% of patients presenting with an HCM phenotype actually have Fabry's disease, in which α -galactosidase activity is reduced, which causes accumulation of glycosphingolipid GB3. In many cases, CMR shows midwall LGE of the basal lateral wall, which is unusual for HCM and not typical for myocarditis. The cause for this distribution may be increased wall stress. CMR can assess the efficacy of enzyme replacement treatment. Other patients with hypertrophic heart have restrictive cardiomyopathy amyloidosis, with diastolic dysfunction, ventricular hypertrophy, and interatrial septum thickening. Distinguishing from other forms of hypertrophy can be problematic in the early stages. Pericardial and pleural effusions are common in amyloidosis. However, LGE in amyloid infiltration is distinctive, with a global subendocardial enhancement pattern that results from interstitial amyloid deposition in the endocardial layer [23]. Patchy amyloid deposition is also seen. Another characteristic finding is a dark blood pool with LGE imaging, which is caused by abnormal gadolinium-handling kinetics. LGE has high diagnostic accuracy and predicts death, which seems to be superior to other conventional predictors.

Iron Overload (Siderotic) Cardiomyopathy

Siderotic cardiomyopathy mainly occurs in transfusion-dependent patients, such as those with thalassemia major. Heart failure from myocardial siderosis is the biggest cause of death in patients with thalassemia because free labile iron damages cell membranes and impairs mitochondrial function. When iron storage capacity is exceeded, micromagnetic particles of the ferrihydrite (hemosiderin) form disturb the magnetic field and lower CMR signal measured using the T2* relaxation parameters. Normal myocardial T2* is 40 ms, and the lower limit of normal is 20 ms. Myocardial T2* <10 ms indicates a high risk of toxic heart failure [24] that can rapidly spiral into death. This measurement is superior to liver iron and serum ferritin for determining prognosis. Studies show that the prevalence of myocardial siderosis is ~50%, which indicates that all thalassemia major patients require direct myocardial iron assessment to determine risk. Asymptomatic LV dysfunction is common in thalassemia but is underdiagnosed because of the higher than normal

ejection fraction and cardiac output caused by the chronic anemia. Decompensated heart failure is a medical emergency in myocardial siderosis, and immediate treatment with continuous intravenously administered deferoxamine is required, with later conversion to subcutaneous administration of deferoxamine combined with deferiprone. In less severe myocardial siderosis, deferiprone monotherapy or combination therapy is effective. Using T2* CMR with tailored cardiac treatment has been associated with a 71% reduction in UK cardiac deaths.

Arrhythmogenic Right Ventricular Cardiomyopathy

CMR has been widely used in arrhythmogenic RV cardiomyopathy (ARVC) because of good RV visualization, quantitative RV function analysis, and limitations of echocardiography due to proximity to the sternum. ARVC is now recognized as a disorder of intercellular connections known as desmosomes, and many gene defects are now known to affect desmosomal proteins such as desmoplakin and plakoglobin. ARVC is therefore recognized as a disease of injury and consequent repair with fibrofatty replacement, with dominant expression in the RV presumably only because of lower structural strength. However, LV involvement is also well recognized in up to 25% of cases. Imaging and plakoglobin protein expression from myocardial biopsy can be combined to augment diagnosis in ARVC.

CMR contributes to identification of diagnostic criteria for ARVC such as morphological abnormality, regional-wall-motion abnormality, increased volumes (including progression over time), and fibrofatty infiltration. Expert scan interpretation is needed, however, because of the wide range of normal RV findings, which can be specificity problematic in a population with a low incidence of disease. In particular, identifying fatty infiltration has high interobserver variability and can occur as a normal variant. LGE of the RV has been used, instead, to identify the fibrous replacement, but the thin RV wall makes this technique difficult. The best use of CMR is to ensure that evaluations are made in conjunction with recognized taskforce criteria. CMR is being evaluated to identify the risk of sudden cardiac death.

Myocarditis

CMR is now established as the first-line imaging technique for diagnosing myocarditis. Three CMR techniques are used: First, T1-weighted spin-echo myocardial signal may be increased in acute myocarditis 1–2 min after gadolinium injection, indicating hyperemia, and signal quantification of global myocardial enhancement relative to skeletal muscle may be increased. Second, T2-weighted spin-echo myocardial signal may be increased, indicating myocardial edema. Third, LGE may be present, especially in the epicardial portion of the lateral wall or septum, indicating myocardial necrosis [25]. LGE location predicts the viral pathogen and can be used to guide

myocardial biopsy for improved histological diagnosis. The extent of LGE and its presence in the septum are predictors of adverse long-term ventricular remodelling. Myocarditis is a common differential diagnosis in patients presenting with acute chest pain but normal coronary arteries. These CMR techniques used in myocarditis are also useful in diagnosing transplant rejection.

Other Cardiomyopathies

Cardiac sarcoidosis is reported in ~25% of autopsy hearts in sarcoid patients with extracardiac involvement. Endomyocardial biopsy has low accuracy due to sampling error, as cardiac involvement is usually patchy and mainly affects the LV. Changes in the ECG can be indicative. LGE CMR shows myocardial abnormalities in presumed areas of fibrosis in sarcoidosis, and these are typically distributed in a noncoronary manner and may appear punched out or bizarre. T2-weighted CMR may identify areas of active myocardial inflammation. CMR may also have value as an indication for steroid treatment. Non-compaction is a result of incomplete maturation in embryonic endomyocardial development, with persistence of spongy myocardium. Marked trabeculation typically affects the lateral wall and apex, with deep intertrabecular recesses and a thin epicardial layer. Progressive ventricular dysfunction, arrhythmias, and systemic embolism may occur. The diagnosis can be made by echocardiography, but CMR shows the abnormality well, with comprehensive ventricular coverage if there is limited involvement, and LGE can demonstrate underlying fibrosis. A noncompacted to compacted myocardial ratio of >2.3 in diastole is used as a quantitative criterion for diagnosis. CMR also shows LGE in Chagas disease, which is endemic in some parts of the world and a major cause of morbidity and mortality.

Coronary Arteries

CMR is widely used for visualizing the lumen of arteries and veins throughout the body, but the technical difficulties of imaging the small, tortuous coronary vessels on the curved surface of the moving heart make robust coronary imaging difficult [26]. Invasive coronary angiography has higher spatiotemporal resolution and is the only means by which to guide placement of coronary stents. A number of special CMR techniques are used to mitigate the problems: imaging performed during diastole limits cardiac motion; a 3D volume is acquired image tortuous vessels; respiratory gating with navigator echoes reduces breathing-induced blurring; parallel imaging accelerates acquisition time; contrast agent or prepulses improve coronary to background contrast. Whole-heart sequences are promising, but currently coronary CMR cannot replace invasive coronary angiography, and its overall diagnostic performance is inferior to CT. Coronary CMR has proven clinical utility in congenital coronary anomalies,

however, because the technique easily resolves the origin and proximal coronary course in relation to the aortic root and pulmonary trunk. CMR is the first-line choice in children and young adults in whom X-rays should be avoided when possible, and it may be used in the follow-up of coronary aneurysms in Kawasaki disease.

Other Conditions

Cardiac Tumors

Intracardiac masses are uncommon, and their diagnosis can be challenging. Whereas other imaging is usually performed first, CMR often yields significant additional value in characterizing the tissue and detailing the relation of the mass with surrounding tissue and organs. Visualization of a mass is first performed with simple spin echo and cine sequences. Tissue characterization can be approached with a number of additional sequences: for example, T1- and T2-weighted spin-echo imaging is used to identify melanoma metastasis (high T1 signal because melanin shortens T1), fibroelastoma (typically located on the aortic valve, with high T2 signal); fat suppression is used to identify atrial lipomatous hypertrophy and lipoma; first-pass perfusion imaging identifies increased vascularity in benign (hemangioma, myxoma) and malignant tumors, especially angiosarcoma in the anterior atrioventricular groove; early hypoenhancement 1-2 min after injection of gadolinium identifies thrombus; late enhancement at 10 min after gadolinium injection shows expanded interstitial space in fibroma. Other important diagnostic features include shape, location, and containment of the mass, in particular, whether tumor extension or invasion of tissue planes has occurred. Malignant tumors often have typical features, with associated findings such as pleural or pericardial effusion. Another important role of CMR is identifying normal variants – which can be mistaken for tumors – including false tendons, persistent venous valves, and the crista terminalis.

Pericardium

CMR shows the pericardium with good resolution, usually as a thin, dark line <4 mm over the heart, although the pericardium can show as the two visceral and parietal layers if pericardial fluid is present. CMR is useful in a wide range of pericardial abnormalities. Pericardial thickness can be visualized over the entire heart, which offers advantages over echocardiography and is useful therefore to show total or partial absence of the pericardium, which is diagnosed by the unusual position of the heart and absent pericardial layers. CT is superior for identifying pericardial calcification and may yield better image quality in sick patients with dyspnea and arrhythmias. Pericardial thickness is very often increased in constriction. Diagnosing constriction is difficult if this cannot be demonstrated, but constriction can rarely occur without thickening – or

localized thickening may be missed. In addition, pericardial thickening does not always indicate constriction. It is important, therefore, to demonstrate physiological sequelae of constriction, which is done using real-time short-axis cine CMR during respiration. During inspiration, intrathoracic pressure falls, which increases venous return to the RV, and in constriction causes the interventricular septum to bulge into the LV. This simple technique is effective and very useful clinically. Pericardial fluid is depicted as a high signal intensity space between the pericardial layers and is reliably detected. Clinical experience suggests that CMR is superior to echocardiography in this regard, especially over the inferior wall. Tamponade due to pericardial fluid is readily recognized with diastolic chamber collapse. Rare causation of tamponade with fat in egregious atrial lipomatous hypertrophy can be diagnosed with fat-suppression sequences. Gadolinium enhancement of acutely inflamed pericardium is useful diagnostically in pericarditis such as Dressler's syndrome, as the pericardium becomes bright. Late gadolinium enhancement imaging in pericarditis may show myocardial involvement of the underlying subepicardium with patchy necrosis. Pericardial cysts are identified from their typical location in the pericardiophrenic angle, encapsulation, and characteristically high T2 signal with intermediate T1 signal. Recently, CMR has been used for to quantify pericardial fat as a risk factor for coronary disease and its relation to other fat stores [27].

Future Clinical Developments in CMR

Atherosclerosis

CMR is used routinely to assess luminal consequences of atherosclerosis, but there is considerable interest in direct assessment of arterial wall structure and function. Most work has been performed in the carotid artery because of its superficial position, but coronary imaging has also been attempted at lower resolution. Arterial sclerosis can be assessed by measuring arterial-wall volume, and this acts as a useful measure of atheroma burden. Multiple contiguous slices of the carotid artery are acquired above and below the bifurcation using 2D or 3D techniques, and wall volume in a single slice is simply obtained from the difference in luminal and adventitial boundaries. This is summed over all slices to obtain the total vessel volume. However, this varies according to body size, and for comparisons between patients, the total wall volume is normalized to the outer-wall volume, yielding the wall to outer wall (W/OW) ratio. In normals, the wall volume and the W/OW ratio increase with age and are increased in atherosclerosis. CMR measurement of wall volume is reproducible, which makes it useful for demonstrating atherosclerosis regression with treatments such as statin. Multispectral CMR is also used to characterize arterial plaque using, in particular, proton density and T1- and T2-weighted sequences. The known plaque characteristics

associated with vulnerability and plaque rupture are presence of lipid pool, thickness of the fibrous cap, and plaque inflammation. These features can all be assessed by CMR. Lipid pools have low signal on T2-weighted images and can also be detected with novel fluorine-based contrast agents [28]. The fibrous cap is visualized as a continuous line over the plaque, and its thickness is reduced in patients with cerebrovascular events. Plaque inflammation can be assessed with iron oxide particles, which are ingested by activated macrophages in vulnerable plaques causing identifiable MR signal loss, and this macrophage activity can be reduced using statin treatment. Thrombus in the plaque or on the luminal surface shows high signal in T1 imaging because of paramagnetic enhancement effects from products of hemoglobin breakdown. T2* plaque imaging shows intraplaque iron content and has been linked to outcome. CMR can also image coronary plaque and arterial remodelling.

Arterial Function

CMR can measure endothelial function using flow-mediated dilation (endothelium dependent) and glyceryl trinitrate (endothelium independent). CMR assesses changes in the arterial area, which has advantages over ultrasound measurements of arterial diameter, especially in non-circular vessels. Validation studies in humans suggest that CMR has improved reproducibility, which reduces sample sizes for trials. Endothelial dysfunction has been demonstrated by CMR in smokers and patients with transfusional iron loading, which normalizes with iron-chelation treatment. Coronary endothelial function can be assessed by CMR using high-resolution, cross-sectional coronary imaging in response to glyceryl trinitrate vasodilation [29]. CMR can also assess arterial function by measuring aortic compliance and pulse-wave velocity, which become abnormal in early atherosclerosis and thus predict cardiac events.

Electrophysiology

The interface between CMR and electrophysiology has advanced significantly in recent years. The two main areas are in predicting arrhythmia related to LGE and assessing patients before and after atrial fibrillation (AF) ablation. In coronary disease, scar size assessed by LGE is related to the risk of future ventricular tachycardia (VT) and is a better predictor than ejection fraction [30]. The size of the grey zone of admixed viable and fibrotic tissue at the border zone of infarction is also a powerful predictor of VT, or defibrillator shocks. Myocyte-fiber tracking using diffusion tensor CMR can indicate fiber remodelling in the epicardial viable rim of infarctions with nodes of orthogonal myofiber intersection or contact (NOMIC), which are potential sources of arrhythmia in this region. In cardiomyopathy, the presence of LGE has also been linked to outcomes. In dilated cardiomyopathy, midwall LGE predicted sudden cardiac death and VT,

which was superior to ejection fraction [7] – findings that have been replicated. LGE in DCM may be useful in planning LV ablation. In hypertrophic cardiomyopathy, LGE is also associated with arrhythmias. CMR is also becoming established in AF management. Pulmonary vein and left atrial anatomy are well shown by CMR and can be merged into the mapping systems for improved ablation guidance. The extent of left-atrial scarring shown by LGE prior to ablation predicts AF recurrence after ablation. Recurrence is also predicted by incomplete isolation of pulmonary veins shown by left atrial LGE, suggesting that this technique may prove useful for periprocedural assessment of patients postablation.

Cardiac Resynchronization Therapy

Cardiac resynchronization therapy (CRT) improves LV function and outcomes in heart-failure patients with dyssynchrony. Accurate prediction of which patients will respond to pacing remains problematic, however, and new CMR methods show promise in this regard. The presence of inferolateral LV scar shown by LGE is an important predictor of failure of clinical response to CRT and adverse outcomes, as is the overall LV scar burden. Location of the LV pacing lead in the coronary sinus can be optimized by using CMR of the coronary venous system. Novel CMR-based measurements of dyssynchrony have been developed, and the Tissue Synchronization Index is an independent predictor of mortality and morbidity after CRT. The addition of LGE to dyssynchrony assessment improves the predictive value of CMR.

Interventional CMR

There has been substantial interest in the development of invasive CMR, in which specially developed MR-compatible devices are used to catheterize patients and perform interventions. The clinical advantages include visualization of soft tissues during interventions, on-line CMR assessment of procedural success, and reduced X-ray exposure. Clinical indications remain limited, but procedures in children are the most likely to emerge first. Other clinical applications may be in electrophysiology, valve replacement, stenting, and accurate placement of myocardial stem-cells injections for myocardial regeneration.

Novel Contrast Agents

The value of the conventional extracellular gadolinium contrast agents has been enormous for CMR over the past decade. However, contrast agents with high specificity for targeted epitopes are under development. Several approaches have been made, including highly flexible constructs linked to fragment antigen binding F(ab')-fragments carrying high gadolinium loads and labelled short peptides found *ex vivo* to bind to a target protein. Complex nanoparticles with tunable magnetic properties have been developed that might allow MR of multiple agents

with simultaneous color discrimination of different targets. Targeted molecules may also permit new solutions to established techniques, such as a recently described agent targeted to collagen that allows high-resolution MR of myocardial perfusion, which has potential to replace the currently used and more technically demanding first-pass method. There seems little doubt that important developments can be expected in this field.

Hardware Developments

High-field CMR (3 Tesla) has started entering clinical practice because of increased signal to noise ratio (SNR), which results in improved spatial or temporal resolution, which has useful application for perfusion imaging, angiography, and vascular-wall imaging. However, the ECG is harder to acquire, artefacts are more common, and some restrictions are necessary to limit heating effects from the radiofrequency energy. Accelerated imaging using multichannel coils and sophisticated postprocessing techniques allows substantial reduction in imaging time, and this combines well with high-field CMR. Fundamental design changes to MR scanners are possible, and a recent development attracting interest is the use of travelling wave systems in which the radiowave transmitter is based outside the magnet bore. This generates a greater field of view, especially for high-field systems, and increases the effective bore size, which can be used to alleviate claustrophobia and to reduce magnet price.

Conclusion

CMR continues to develop across a broad range of clinical applications, and much can be expected of this technology in the future. Assessing the role of CMR relative to other cardiac imaging techniques remains difficult in this fast-paced technological landscape where little remains constant over the period of any comparative study and that may leave the result obsolescent by the time of publication. The challenge is to identify as far as possible those unique capabilities of each technique and develop algorithms for their best integration into patient-care pathways. Unnecessary duplication of investigations must be avoided for cost-effective health-care delivery. Likewise, payors need to recognize that technological advance in imaging may result in more expensive but more effective investigations, with longer-term health-care benefits not seen at the time of imaging that are difficult to prove. Modern cardiology is becoming increasingly reliant on cardiac imaging, and this trend seems certain to continue.

References

- Manning WJ, Pennell DJ (2010) Cardiovascular magnetic resonance, 2nd edn. Saunders, Philadelphia, PA
- Kim RJ, de Roos A, Fleck E et al (2007) Society for Cardiovascular Magnetic Resonance (SCMR) Clinical Practice Committee. Guidelines for training in cardiovascular magnetic resonance (CMR). *J Cardiovasc Magn Reson* 9:3-4
- Hendel RC, Patel MR, Kramer CM et al (2006) ACCF/ACR/SCCT/SCMR/ASNC/NASCI/SCAI/SIR 2006 appropriateness criteria for cardiac computed tomography and cardiac magnetic resonance imaging: a report of the American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria Working Group, American College of Radiology, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, American Society of Nuclear Cardiology, North American Society for Cardiac Imaging, Society for Cardiovascular Angiography and Interventions, and Society of Interventional Radiology. *J Am Coll Cardiol* 48:1475-1497
- Pohost GM, Kim RJ, Kramer CM, Manning WJ for the Society for Cardiovascular Magnetic Resonance (2008) Task Force 12: training in advanced cardiovascular imaging (cardiovascular magnetic resonance [CMR]): endorsed by the Society for Cardiovascular Magnetic Resonance. *J Am Coll Cardiol* 51:404-408
- Kramer CM, Budoff MJ, Fayad ZA et al (2007) ACCF/AHA 2007 clinical competence statement on vascular imaging with computed tomography and magnetic resonance: a report of the American College of Cardiology Foundation/American Heart Association/American College of Physicians Task Force on Clinical Competence and Training: developed in collaboration with the Society of Atherosclerosis Imaging and Prevention, the Society for Cardiovascular Angiography and Interventions, the Society of Cardiovascular Computed Tomography, the Society for Cardiovascular Magnetic Resonance, and the Society for Vascular Medicine and Biology. *Circulation* 116:1318-1335
- Kramer CM, Barkhausen J, Flamm SD et al (2008) Standardized cardiovascular magnetic resonance imaging (CMR) protocols, society for cardiovascular magnetic resonance: board of trustees task force on standardized protocols. *J Cardiovasc Magn Reson* 10:35
- Hundley WG, Bluemke D, Bogaert JG et al (2009) Society for Cardiovascular Magnetic Resonance guidelines for reporting cardiovascular magnetic resonance examinations. *J Cardiovasc Magn Reson* 11:5
- Maceira AM, Prasad SK, Khan M, Pennell DJ (2006) Normalized left ventricular systolic and diastolic function by steady state free precession cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 8:417-426
- Maceira AM, Prasad SK, Khan M, Pennell DJ (2006) Reference right ventricular systolic and diastolic function normalized to age, gender and body surface area from steady-state free precession cardiovascular magnetic resonance. *Eur Heart J* 27:2879-2888
- Grothues F, Smith GC, Moon JC et al (2002) Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. *Am J Cardiol* 90:29-34
- Grothues F, Moon JCC, Bellenger NG et al (2004) Interstudy reproducibility of right ventricular volumes, function and mass with cardiovascular magnetic resonance. *Am Heart J* 147:218-223
- John AS, Dill T, Brandt RR et al (2003) Magnetic resonance to assess the aortic valve area in aortic stenosis: how does it compare to current diagnostic standards? *J Am Coll Cardiol* 42:519-526
- Prasad SK, Soukias N, Hornung T et al (2004) Role of magnetic resonance angiography in the diagnosis of major aortopulmonary collateral arteries and partial anomalous pulmonary venous drainage. *Circulation* 109:207-214
- Babu-Narayan SV, Kilner PJ, Li W et al (2006) Ventricular fibrosis suggested by cardiovascular magnetic resonance in adults with repaired tetralogy of Fallot and its relationship to adverse markers of clinical outcome. *Circulation* 113:405-413

15. Frigiola A, Tsang V, Bull C et al (2008) Biventricular response after pulmonary valve replacement for right ventricular outflow tract dysfunction: is age a predictor of outcome? *Circulation* 118 (14 Suppl):S182-S190
16. Gerber BL, Raman SV, Nayak K et al (2008) Myocardial first-pass perfusion cardiovascular magnetic resonance: history, theory, and current state of the art. *J Cardiovasc Magn Reson* 10:18
17. Fieno DS, Shea SM, Li Y et al (2004) Myocardial perfusion imaging based on the blood oxygen level-dependent effect using T2-prepared steady-state free-precession magnetic resonance imaging. *Circulation* 110:1284-1290
18. Nagel E, Lehmkuhl HB, Bocksch W et al (1999) Noninvasive diagnosis of ischemia-induced wall motion abnormalities with the use of high-dose dobutamine stress MRI: comparison with dobutamine stress echocardiography. *Circulation* 99:763-770
19. Kim RJ, Albert TS, Wible JH et al, for the Gadoversetamide Myocardial Infarction Imaging Investigators (2008). Performance of delayed-enhancement magnetic resonance imaging with gadoversetamide contrast for the detection and assessment of myocardial infarction: an international, multicenter, double-blinded, randomized trial. *Circulation* 117:629-637
20. Wagner A, Mahrholdt H, Holly TA et al (2003) Contrast-enhanced MRI and routine single photon emission computed tomography (SPECT) perfusion imaging for detection of subendocardial myocardial infarcts: an imaging study. *Lancet* 361:374-379
21. Kim RJ, Wu E, Rafael A et al (2000) The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. *N Engl J Med* 343:1445-1453
22. Assomull RG, Prasad SK, Lyne J et al (2006) Cardiovascular magnetic resonance, fibrosis, and prognosis in dilated cardiomyopathy. *J Am Coll Cardiol* 48:1977-1985
23. Maceira AM, Joshi J, Prasad SK et al (2005) Cardiovascular magnetic resonance in cardiac amyloidosis. *Circulation* 111:186-193
24. Kirk P, Roughton M, Porter JB et al (2009) Cardiac T2* magnetic resonance for prediction of cardiac complications in thalassemia major. *Circulation* 120:1961-1968.
25. Mahrholdt H, Goedecke C, Wagner A, Meinhardt G et al (2004) Cardiovascular magnetic resonance assessment of human myocarditis: a comparison to histology and molecular pathology. *Circulation* 109:1250-1258.
26. Johnson KR, Patel SJ, Whigham A et al (2004) Three-dimensional, time-resolved motion of the coronary arteries. *J Cardiovasc Magn Reson* 6:663-673
27. Rosito GA, Massaro JM, Hoffmann U et al (2008) Pericardial fat, visceral abdominal fat, cardiovascular disease risk factors, and vascular calcification in a community-based sample: the Framingham Heart Study. *Circulation* 117:605-613
28. Sirol M, Itskovich VV, Mani V et al (2004) Lipid-rich atherosclerotic plaques detected by gadofluorine-enhanced in vivo magnetic resonance imaging. *Circulation* 109:2890-2896
29. Nguyen PK, Meyer C, Engvall J et al (2008) Noninvasive assessment of coronary vasodilation using cardiovascular magnetic resonance in patients at high risk for coronary artery disease. *J Cardiovasc Magn Reson* 10:28
30. Bello D, Fieno DS, Kim RJ et al (2005) Infarct morphology identifies patients with substrate for sustained ventricular tachycardia. *J Am Coll Cardiol* 45:1104-1108

The Atherosclerotic Process and Its Relationship to Coronary Blood Flow

Dominique Delbeke¹, Philipp A. Kaufmann²

¹ Department of Radiology and Radiological Sciences, Vanderbilt University Medical Center, Nashville, TN, USA

² University Hospital of Zurich, Zurich, Switzerland

Introduction

Cardiovascular disease is the number one cause of mortality in the United States. Human atherosclerosis is a dynamic process that begins early and progresses throughout life. Cardiac risk factors – smoking tobacco, hypertension (HTN), hypercholesterolemia, diabetes mellitus (DM), or a positive family history of coronary artery disease (CAD) – are known to accelerate the atherosclerotic process that naturally affect all human beings [1]. Atherosclerosis will first cause narrowing of coronary arteries but without inducing ischemia. With progression, coronary stenoses will first affect coronary blood flow reserve (CBFR), which can be detected only with stress testing, before affecting myocardial blood flow (MBF) at rest. Periods of ischemia lasting >40 min cause irreversible injury. If the ischemic period is long enough to cause total necrosis (usually 6–12 h), the infarct is transmural. Chronically ischemic myocardium, in which the blood supply is adequate to preserve viability but not to maintain normal cell function, can result in regional dyssynergy (hibernating myocardium). Revascularization procedures with normal blood flow restoration to this tissue often leads to significant improvement in wall motion, ventricular function, symptomatology, and prognosis [2].

Nuclear Cardiology

Nuclear cardiology procedures allow evaluation of myocardial perfusion, viability, and function using gated single-photon emission computed tomography (SPECT) and positron emission tomography (PET). Indications for cardiac radionuclide imaging have been extensively reviewed and discussed in the American College of Cardiology/American Heart Association (ACC/AHA) Guidelines for the Clinical Use of Radionuclide Imaging [3] and the American College of Cardiology Foundation/American Society of Nuclear Cardiology (ACCF/ASNC) Appropriateness Criteria for SPECT MPI [4]. Updated imaging guidelines for nuclear cardiology procedures have been published [5], as have training guidelines for physicians in

training [6], clinical competence for physicians in practice [7], and technologist training in nuclear cardiology [8]. Myocardial perfusion scintigraphy (MPS) permits noninvasive CBFR evaluation, ischemia detection, and risk stratification, including the degree, location and extent to which CAD is affecting MBF. The prognostic and diagnostic value of MPS has been well established in the literature for more than two decades. The stress tests most commonly used to evaluate CBFR are exercise, dipyridamole [9], adenosine [10, 11], physical exercise combined with dipyridamole or adenosine [12–14], and dobutamine [15]. New, more specific, vasodilatory stress agents, called adenosine A_{2A} receptor agonists, have been developed. The results of a large first phase III trial evaluating regadenoson as a bolus demonstrated that it provides diagnostic information on the presence and severity of reversible defects, which is comparable with the information provided by a 6-min infusion of adenosine and may be more easily used in patients with bronchospasm [16, 17].

Choice of Diagnostic Tests Based on Disease Prevalence

The choice of one of the tests discussed above to evaluate a specific patient will depend on several factors, including: availability of technology, local experience with a given modality and the pretest probability of disease, as well as patient-specific factors such as body habitus and resting electrocardiogram (ECG) abnormalities. The appropriateness of noninvasive testing has to be considered in light of Bayes' theorem, which expresses the posttest likelihood of disease as a function of the test's sensitivity and specificity and the prevalence (or pretest probability) of disease in the population being tested. Algorithms used to evaluate patients for myocardial ischemia depend on the pretest probability for the presence of CAD.

The other important parameter is the presence or absence of symptoms. For asymptomatic patients, risk stratification is commonly evaluated using the Framingham Risk Score (FRS), which estimates 10-year risk for hard coronary events [myocardial infarction (MI) or coronary death]. The FRS is calculated based on age, gender, systolic blood pressure, total and high-density

lipoprotein (HDL) plasma cholesterol levels, and the presence of risk factors including diabetes and smoking [18]. Asymptomatic patients with an intermediate FRS (10-year risk of hard coronary events between 10 and 20%) should be considered for coronary calcium scoring (CCS) to further risk-stratify as recommended by the ACC/AHA and ASNC [19].

After a review of the literature covering 28,948 patients, Diamond and Forrester [20] reported the prevalence of CAD based on patient age, gender, and symptoms. With respect to symptoms, patients were classified as being asymptomatic or having nonanginal, atypical, or typical chest pain according to three characteristics of chest pain (substernal location, induction by exercise, relieved by nitroglycerin). When the three characteristics were present, patients were classified as having typical chest pain. Once the pretest probability of disease is estimated, an algorithm can be created to evaluate patients with chest pain. The posttest probability for CAD depends on the sensitivity and specificity of the test being performed [21].

Patients with Low-Pretest Probability of CAD

According to Diamond and Forrester [20], a positive result obtained with an MPS study or another method of evaluating myocardial ischemia is more likely to be false positive if the patient has a low pretest probability for CAD. Therefore, the evaluation approach to patients with a low pretest probability is to begin with a resting ECG and a treadmill stress test (TMT). If there are abnormalities on the resting ECG, making it noninterpretable during the TMT, imaging options should be considered such as MPS or coronary CT angiography (CTA). Coronary CTA may become the first test of choice in these low-probability patients because of its high negative predictive value (NPV) excluding CAD. However, when coronary CTA is abnormal, the functional impact on perfusion should be further evaluated with MPS [22].

Patients with Intermediate Probability for CAD

MPS has optimal discriminative value in the patient population with an intermediate pretest probability of CAD. This population includes:

1. patients with nonanginal chest pain and a positive or nondiagnostic exercise ECG;
2. asymptomatic patients with significant risk factors, abnormal resting ECG, or positive exercise ECG;
3. patients with atypical chest pain;
4. patients with typical chest pain and a negative exercise ECG.

Patients with a High Pretest Probability of CAD

Patients with a high pretest probability should almost always be investigated, at least once, more aggressively and invasively. According to the Bayes' theorem, a

negative MPS in a patient with a high pretest probability for CAD – for example, symptomatic patients – is more likely to be a false-negative than a true-negative result. Coronary angiography is often used as the initial evaluation in these patients. The advantage of performing nuclear imaging before proceeding to invasive angiography is to identify the lesion responsible for the patient's symptoms and document a baseline status, which is useful for therapy follow-up. Cost benefit has been demonstrated in patients with chest pain with a high pretest probability. Information obtained with MPS also allows accurate prognostic estimation. It is essential to remember that CAD is not synonymous with myocardial ischemia and that anatomic findings do not always provide information about the physiological significance of coronary lesions.

Accuracy for Detection of CAD and Prognosis

Sensitivity and specificity of exercise and vasodilator stress perfusion SPECT in detecting angiographically significant (>50% stenosis) CAD average 87% and 89% and 73% and 75%, respectively [3]. Sensitivity and specificity of PET perfusion scintigraphy is higher than with SPECT, in the 95% range, with a very high normalcy rate in patients without CAD [23, 24]. This results from the advantages of PET perfusion radiopharmaceuticals and technology compared with SPECT: (1) higher resolution (approximately 5 mm for PET versus 10 mm for SPECT) and therefore higher sensitivity of PET than SPECT for CAD detection; (2) more accurate attenuation correction algorithm for PET than SPECT, leading to better image quality and superior accuracy for CAD detection in both normal and obese patients; and (3) true stress left-ventricular ejection fraction (LVEF) because stress imaging is performed during dipyridamole-induced coronary hyperemia still has an effect rather than afterward with SPECT. A true stress LVEF increases the sensitivity for detecting ischemia, especially in patients with balanced multivessel disease. Failure of the LVEF to increase 5 points or a decrease in LVEF between rest and stress indicates ischemia [25]. In addition, rest/stress protocols are more efficient because of the shorter half-lives of PET perfusion radiopharmaceuticals.

Two factors identified as important for prognosis are increased pulmonary uptake of ^{201}Tl or $^{99\text{m}}\text{Tc}$ -sestamibi and stress-induced transient dilation of the LV cavity [26]. Hachamovitch et al. [27] previously demonstrated that stress MPS effectively risk-stratifies patients for cardiac events. In a study of >5,000 patients, the rates for both MI and cardiac death increased significantly with worsening perfusion abnormalities. The extent of ischemia is a predictor of adverse outcome but also identifies which patients will benefit from revascularization compared to which patients are better managed noninvasively [28]. Assessing the amount of stress-induced ischemia and the poststress EF can enhance the prediction

of cardiac death and nonfatal MI. In a study by Sharir et al. [29], 2,686 patients underwent dual isotope rest ^{201}Tl /stress $^{99\text{m}}\text{Tc}$ -mibi MPS. By Cox regression analysis, the most powerful predictor of cardiac death was post-stress EF, whereas the most powerful predictor of MI was the extent of ischemia as measured by the sum difference scores (SDS).

There is increasing evidence that $^{99\text{m}}\text{Tc}$ -sestamibi or tetrofosmin MPS may be effectively used to triage patients presenting to the emergency department (ED) with chest pain of unclear etiology. According to the results of the ERASE (Emergency Room Assessment of $^{99\text{m}}\text{Tc}$ -sestamibi in the Evaluation of Chest Pain) trial [30], MPS with $^{99\text{m}}\text{Tc}$ -sestamibi in the ED reduces the number of unnecessary admissions without increasing mistaken discharges. MPS is also recommended for risk assessment postrevascularization. For example, recommendation for MPS postpercutaneous intervention (PCI) include [3]: (1) symptomatic patients with suspicion of restenosis, and (2) asymptomatic patients at risk for silent ischemia (diabetics). For postcoronary bypass grafting (CABG) procedure patients, recommendations for MPS include: (1) symptomatic for diagnosis and prognosis, and (2) asymptomatic >5 years post-CABG or if exercise capacity is limited [<6 metabolic units above resting (METS)] regardless of CABG age or whether there is a possibility of silent ischemia. MPS is also helpful for follow-up of patients with CAD treated medically. Medical therapy (including anti-ischemic medications and risk-factor modification) is used to treat CAD even in the presence of anatomically significant lesions. The Clinical Outcome Using Revascularization and Aggressive Drug Evaluation (COURAGE) trial randomized 2,287 patients with objective evidence of myocardial ischemia to medical therapy versus PCI plus medical therapy. The 4- to 6-year follow-up revealed no significant difference between groups regarding death rate, myocardial infarct, stroke, or hospitalization for acute coronary syndromes. However, MPS played a significant role in the COURAGE trial not only as a modality to document ischemia but to monitor the efficacy of therapy and identify high-risk patients requiring coronary angiography and/or PCI [31].

Dysfunctional but viable myocardium invariably demonstrates abnormal wall motion (severe hypokinesis, akinesis, or dyskinesis). There is impaired myocardial perfusion, and cell membrane integrity and normal glucose metabolism characteristic of cellular viability are also impaired. [^{18}F]fluorodeoxyglucose ([^{18}F]-FDG) is still considered the reference standard for evaluating myocardial viability because of the large supportive literature [32]. However, [^{18}F]-FDG is not as available as SPECT radiopharmaceuticals (^{201}Tl or $^{99\text{m}}\text{Tc}$ -isonitriles). ^{201}Tl SPECT (typically with a 15-min rest/4-h redistribution protocol) demonstrates a sensitivity of 67% and a specificity of 77% compared with 89% and 81%, respectively, for [^{18}F]-FDG SPECT [33]. Excellent results have been obtained with nitrate-enhanced $^{99\text{m}}\text{Tc}$ -sestamibi SPECT imaging in detecting viable myocardium [32].

Hybrid Cardiovascular Imaging

Recent technological developments in nuclear imaging include improved software and hardware for better performance and interpretation of gated SPECT studies. For example, attenuation correction (AC) improves normalcy rate. In 2001, the ASNC and the Society of Nuclear Medicine (SNM) issued a joint position statement after reviewing the literature using at that time transmission maps acquired with radioisotopic sources [34]. The addition of AC improves specificity from an average of 64% to 81% and normalcy rates from an average of 80% to 89% without sensitivity loss. Attenuation correction can also be performed using CT attenuation maps from integrated imaging systems.

Multimodality imaging with integrated PET/CT and SPECT/CT systems offer the possibility for simultaneous evaluation of anatomy and function and is one of the most exciting new developments in imaging technology. Currently, most PET/CT imaging systems are equipped with a 16-slice CT scanner, but integrated PET/CT systems with 64-slice CT scanners are available for advanced cardiac applications and SPECT/64-slice MDCT are under development. Cardiac PET/CT and SPECT/CT technology allows evaluation in one imaging setting of rest/stress MPS with CT-AC, CCS, coronary artery anatomy with coronary CTA, and localization of the hypoperfused regions to specific coronary arteries with the help of fusion images of the coronary tree superimposed on a 3D perfusion map [35] (Fig. 1). The ACC/AHA recently



Fig. 1. This 3D representation of hybrid single-photon emission computed tomography/CT angiography image visualizes the ischemic area (blue) of the anterior wall caused by an in-stent restenosis (for color reproduction see p 273)

published guidelines for using CCS [36] and cardiovascular CT imaging [37], as well as appropriateness criteria for using cardiovascular CT [38]. The European Association for Nuclear Medicine (EANM) recently published a guideline on hybrid cardiac imaging [39], and the collaborative SNM/ACR/ASNC/SCCT Guideline for Cardiac SPECT/CT and PET/CT Imaging is in its final draft.

With the technical development of coronary CTA and hybrid nuclear/CTA procedures, radiation dose from cardiovascular imaging procedures is a concern to both patients and physicians. In 1998, the ACC published a consensus document discussing radiation safety in the practice of cardiology [40]. The issues regarding radiation dosage from various cardiac nuclear and radiographic procedures were recently summarized [41-43]. Radiation dose and acquisition time are linked with each other, as longer acquisition times could be used with lower injected doses and higher doses could be used to shorten acquisition times. The new technological developments combine approaches such as:

1. changing the detector geometry and optimizing tomographic sampling of the field of view for myocardial imaging;
2. improving detector material, such as cadmium zinc telluride (CZT), among others;
3. improving collimator design, such as multi-pinhole collimators, among others;
4. optimizing image reconstruction algorithms.

Recent hardware developments include a small, dedicated cardiac gamma camera with CZT solid-state crystals, allowing fast-acquisition protocols such as Digirad Cardiac 3XPO (Digirad, Poway, CA, USA), CardiaArc (CardiaArc, Lubbock, TX, USA), and D-SPECT (Spectrum Dynamics, Haifa, Israel) [44]. New software packages have been developed with advanced image reconstruction techniques allowing faster imaging. These developments focused on proprietary algorithms based on maximum likelihood expectation-maximization (MLEM) and accelerated methods of ordered subsets expectation maximization (OSEM) [43]. Protocols for performing stress-only myocardial perfusion imaging in selected patients are becoming validated in multicenter studies, allowing decreased radiation dose compared with rest/stress protocols, which require administration of two doses of the radiopharmaceutical [45]. Myocardial perfusion using PET radiopharmaceutical (Rb-82 and N-13-NH_3) give a radiation dose much lower than the SPECT radiopharmaceuticals [46]. Individualized algorithms with sequential low-dose prospective gating coronary CTA and low-dose stress-only cardiac SPECT also significantly reduce radiation exposure [47].

Not all stenoses detected on coronary CTA are flow limiting, and evaluation of the functional impact on myocardial perfusion using scintigraphic technique is critical. Coronary CTA has a relatively low positive predictive value to predict both a >50% stenosis on coronary angiography (56-87% with 64-slice MDCT) and perfusion defects on MPS (in the 30% range). Integrated

PET/SPECT and CT imaging are highly complementary because of the combination of anatomic and functional imaging data obtained. Combined information obtained by stress MPS along with CTA can be helpful in guiding patient management in multiple scenarios. For example, the vessel causing ischemia can be identified in patients with multivessel CAD so that management can be directed to that vessel. In addition, invasive coronary angiography may be avoided in patients with microvascular dysfunction without epicardial disease.

Discussion

In summary, anatomical and functional information obtained with combined MPS/coronary CTA is complementary. Debate continues regarding the cost-effectiveness of the combined approach and whether the sequential approach of MPS and coronary CTA, with one test guiding the other, would be more cost effective in specific clinical scenarios. With the ongoing development of new molecular imaging tracers for cardiovascular imaging, accurate co-registration of molecular and anatomical images may become critical and thus require hybrid nuclear/anatomical systems.

References

1. Stary HC (ed) (1999) Atlas of atherosclerosis: progression and regression. Parthenon, New York, NY
2. Dilsizian V, Bonow R (1993) Current diagnostic techniques of assessing myocardial viability in patients with hibernating and stunned myocardium. *Circulation* 87:1-20
3. Klocke FJ, Baird MG, Lorell BH et al for the American College of Cardiology; American Heart Association; American Society for Nuclear Cardiology (2003) ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging – executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). *J Am Coll Cardiol* 42:1318-1333
4. Brindis AG, Douglas P, Hendel, R et al for the ACCF Appropriateness Criteria Working Group (2005) ACCF/ASNC appropriateness criteria for single-photon emission computed tomography myocardial perfusion imaging (SPECT MPI). *J Am Coll Cardiol* 46:1587-1605
5. Holly TA, Abbott BG, Al-Mallah M et al (2010) ASNC imaging guidelines for nuclear cardiology procedures. *J Nucl Cardiol* 17:941-973
6. Cerqueira MD, Berman DS, Di Carli MF et al (2006) Task Force 5: training in nuclear cardiology. *J Am Coll Cardiol* 47:898-904
7. Budoff MJ, Cohen MC, Garcia MJ et al (2005) ACCF/AHA: Clinical competence on cardiac imaging with computed tomography and magnetic resonance: a report of the American College of Cardiology Foundation/American Heart Association/American College of Physicians Task Force on Clinical Competence and Training. *J Am Coll Cardiol* 46:383-402
8. Deman P, Eckdahl J, Folks R et al (1997) Guidelines for technologist training in nuclear cardiology. *J Nucl Cardiol* 4:422-425
9. Lette J, Tatum JL, Fraser S et al (1995) Safety of dipyridamole testing in 73,806 patients: the multicenter dipyridamole safety study. *J Nucl Cardiol* 2:3-17

10. Abreu A, Mahmarian JJ, Nishimura S et al (1991) Tolerance and safety of pharmacologic coronary vasodilation with adenosine in association with thallium-201 scintigraphy in patients with coronary artery disease. *J Am Coll Cardiol* 18:730-735
11. Cerqueira MD, Verani MS, Schwaiger M et al (1994) Safety profile of adenosine stress perfusion imaging: results from the Adenoscan multicenter trial registry. *J Am Coll Cardiol* 23:384-390
12. Vitola JV, Brambatti JC, Caligaris F et al (2001) Exercise supplementation to dipyridamole prevents hypotension, improves electrocardiogram sensitivity, and increases heart-to liver activity ratio on Tc-99m sestamibi imaging. *J Nucl Cardiol* 8:652-659
13. Elliot MD, Holly TA, Leonard SM, Hendel RC (2000) Impact of an abbreviated adenosine protocol incorporating adjunctive treadmill exercise on adverse effects and image quality in patients undergoing stress myocardial perfusion imaging. *J Nucl Cardiol* 7:584-589
14. Samady H, Wackers FJTh, Joska TM et al (2002) Pharmacologic stress perfusion imaging with adenosine: role of simultaneous low-level treadmill exercise. *J Nucl Cardiol* 9:188-196
15. Elhendy A, van Domburg RT, Vantrimpont P et al (2001) Impact of heart transplantation on the safety and feasibility of the dobutamine stress test. *J Heart Transplant* 20:399-406
16. Iskandrian AE, Bateman TM, Belardinelli L et al (2007) Adenosine versus regadenoson comparative evaluation in myocardial perfusion imaging: results of the advance phase III multi-center international trial. *J Nucl Cardiol* 14:645-658
17. Leaker BR, O'Connor B, Hansel TT et al (2008) Safety of regadenoson, an adenosine A2A receptor agonist for myocardial perfusion imaging, in mild asthma and moderate asthma patients: a randomized, double-blind, placebo-controlled trials. *J Nucl Cardiol* 15:329-336
18. Grundy SM, Becker D, Clark LT et al (2002) NCEP (National Cholesterol Education Program) Expert Panel on ATP III. *Circulation* 106:31-43
19. Shaw LJ, Berman DS, Bax JJ et al (2005) Complementary roles of nuclear cardiology and cardiac CT in the current healthcare environment. *J Nuc Cardiol* 12:131-142
20. Diamond GA, Forrester JS (1979) Analysis of probability as an aid in the clinical diagnosis of coronary artery disease. *N Engl J Med* 300:1350-1358
21. Hamilton GW, Trobaugh G, Richie JC et al (1978) Myocardial imaging with ²⁰¹Tl: an analysis of clinical usefulness based on Bayes' theorem. *Semin Nucl Med* 8:358
22. Goldstein JA, Gallagher MJ, O'Neill WW et al (2007) A randomized controlled trial of multi-slice coronary computed tomography for evaluation of acute chest pain. *J Am Coll Cardiol* 49:863-871
23. Bateman TM, Heller GV, McGhie AI et al (2006) Diagnostic accuracy of rest/stress ECG-gated Rb-82 myocardial perfusion PET: comparison with ECG-gated Tc-99m sestamibi SPECT. *J Nucl Cardiol* 13:24-33
24. Sampson UK, Dorbala S, Limaye A et al (2007) Diagnostic accuracy of rubidium-82 myocardial perfusion imaging with hybrid positron emission tomography/computed tomography in the detection of coronary artery disease. *J Am Coll Cardiol* 49:1052-1058
25. Dorbala S, Vangala D, Sampson U et al (2007) Value of vasodilator left ventricular ejection fraction reserve in evaluating the magnitude of myocardium at risk and the extent of angiographic coronary artery disease: a ⁸²Rb PET/CT study. *J Nucl Med* 48:349-358
26. Abidov A, Germano G, Berman DS (2007) Transient ischemic dilation ratio: a universal high-risk diagnostic marker in myocardial perfusion imaging. *J Nucl Cardiol* 14:497-500
27. Hachamovitch R, Berman DS, Shaw LJ et al (1998) Incremental prognostic value of myocardial perfusion single photon emission computed tomography for the prediction of cardiac death: differential stratification for risk of cardiac death and myocardial infarction. *Circulation* 97:535-543
28. Hachamovitch R, Hayes SW, Friedman JD et al (2003) Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation* 107:2900-2907
29. Sharir T, Germano G, Kang X et al (2001) Prediction of myocardial infarction versus cardiac death by gated myocardial perfusion SPECT: risk stratification by the amount of stress-induced ischemia and the poststress ejection fraction. *J Nucl Med* 42:831-837
30. Udelson JE, Beshansky JR, Ballin DS et al (2002) Myocardial perfusion imaging for evaluation and triage of patients with suspected acute cardiac ischemia. A randomized controlled trial. *JAMA* 288:2693-2700
31. Berman DS, Boden WE, O'Rourke RA et al (2007) Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 356:1-14
32. Slart RH, Bax JJ, van Veldhuisen DJ et al (2006) Imaging techniques in nuclear cardiology for the assessment of myocardial viability. *Int J Cardiovasc Imaging* 22:63-80
33. Bax JJ, Cornel JH, Visser FC et al (1998) Comparison of fluorine-18-FDG with rest-redistribution thallium-201 SPECT to delineate viable myocardium and predict functional recovery after revascularization. *J Nucl Med* 39:1481-1486
34. Hendel RC, Corbett JR, Cullom SJ et al (2002) The value and practice of attenuation correction for myocardial perfusion SPECT imaging: A joint position statement from the American Society of Nuclear Cardiology and the Society of Nuclear Medicine. *J Nucl Med* 43:273-280
35. Di Carli MF, Hachamovitch R (2007) New technology for non-invasive evaluation of coronary artery disease. *Circulation* 115:1464-1480
36. Greenland P, Bonow RO, Brundage BH et al (2007) Clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain. *Circulation* 23:403-426
37. Budoff MJ, Achenbach S, Blumenthal RS et al (2006) Assessment of coronary artery disease by cardiac computed tomography: a scientific statement from the AHA Committee on Cardiovascular Radiology and Intervention, and Committee on Cardiac Imaging. Council on Clinical Cardiology. *Circulation* 114:1761-1791
38. Hendel RC, Patel MR, Kramer CM et al (2006) ACCF/ACR/SCCT/SCMR/ASNC/NASCI/SCAI/SIR 2006 appropriateness criteria for cardiac computed tomography and cardiac magnetic resonance imaging: a report of the American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria Working Group, American College of Radiology, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, American Society of Nuclear Cardiology, North American Society for Cardiac Imaging, Society for Cardiovascular Angiography and Interventions, and Society of Interventional Radiology. *J Am Coll Cardiol* 48:1475-1497
39. Flotats A, Knuuti J, Gutberlet M et al on behalf of the Cardiovascular Committee of the EANM, the ESCR and the ECNC (2011) Hybrid cardiac imaging: SPECT/CT and PET/CT. A joint position statement by the European Association of Nuclear Medicine (EANM), the European Society of Cardiac Radiology (ESCR) and the European Council of Nuclear Cardiology (ECNC). *Eur J Nucl Med Mol Imaging* 38:201-212
40. Limacher MC, Douglas PS, Germano G et al (1998) ACC expert consensus document. Radiation safety in the practice of cardiology. *J Am Coll Cardiol* 31:892-913
41. Thompson RC, Cullom SJ (2006) Issues regarding dosage of cardiac nuclear and radiography procedures. *J Nucl Cardiol* 13:19-23

42. Stabin MG (2008) Radiopharmaceuticals for nuclear cardiology: radiation dosimetry, uncertainties, and risk. *J Nucl Med* 49:1555-1563
43. Mettler FA Jr, Bhargavan M, Thomadsen BR et al (2008) Nuclear medicine exposure in the United States, 2005-2007: preliminary results. *Semin Nucl Med* 38:384-391
44. Patton JA, Slomka PJ, Germano G, Berman DS (2007) Recent technologic advances in nuclear cardiology. *J Nucl Cardiol* 14:501-513
45. Bateman TM, Heller GV, McGhie AI et al (2009) Multicenter investigation comparing a highly efficient half-time stress-only attenuation correction approach against standard rest-stress Tc-99m SPECT imaging. *J Nucl Cardiol* 16:726-735
46. Senthamizhchelvan S, Bravo PE, Esaia C et al (2010) Human biodistribution and radiation dosimetry of ⁸²Rb. *J Nucl Med* 51:1592-1599
47. Pazhenkottil AP, Herzog BA, Husmann L et al (2010) Non-invasive assessment of coronary artery disease with CT coronary angiography and SPECT: a novel dose-saving fast-track algorithm. *Eur J Nucl Med Mol Imaging* 37:522-527

Imaging Congenital Cardiovascular Disease

Lawrence M. Box¹, Laureen M. Sena²

¹ Departments of Radiology and Medicine, Montefiore Medical Center, Albert Einstein College of Medicine of Yeshiva University, Bronx, NY, USA

² Department of Radiology, Children's Hospital Boston, Harvard Medical School, Boston, MA, USA

Introduction

The radiographic evaluation of congenital heart disease (CHD) is based upon identifying and characterizing structural changes reflecting abnormal blood flow or pathophysiologic homeostatic mechanisms resulting from structural or metabolic derangement. Evaluation of adult patients with CHD is complicated by the superimposition of acquired heart disease (with associated pathophysiologic changes) on the now chronic changes associated with palliated or untreated CHD. Progress in the diagnosing and managing pediatric and adult patients with CHD has been closely tied to progress and advancement in our ability to visualize cardiac structure. Correlation of clinical presentation with the demonstration of structural abnormalities is a cornerstone to early and accurate diagnosis and evaluation of medical and surgical management of CHD. Thus, the history of cardiac medicine can be told in terms of the history of cardiac imaging.

Early workers appreciated the embryologic basis for many malformations, correlated clinical presentation with the structural abnormality, and developed an organized approach to evaluating these patients. The radiographic (i.e., imaging) evaluation of these patients is therefore based on an organized search for abnormality and the analysis of these observations. Furthermore, organization of this search for evidence is logical and encourages a multimodality approach to diagnosis. In this chapter, we describe this organized approach to cardiac diagnosis. Rather than discuss the imaging modalities per se [i.e., plain film, magnetic resonance imaging (MRI), angiocardiology of CHD], we discuss the logic behind diagnosing CHD and illustrate the appearance of characteristic findings across the spectrum of radiologic imaging modalities.

Evaluating a child or adult with CHD should be performed in an organized manner. Echocardiography is the primary diagnostic modality for patients with CHD. The role of computed tomography (CT) and MRI is to complement echocardiography [1, 2]. That is, in individuals in whom echocardiography does not provide adequate structural or physiologic information, an alternative tomographic modality may be employed. An advantage of

MRI and CT is the similarity in the appearance of MR acquisitions and CT reconstructions with echocardiograms. Analysis of observed changes in cardiac structure is guided using the segmental analysis approach to the cardiac chambers and their connections. Examination of chest radiographs provides evidence of structural and functional cardiovascular changes and remains the most commonly performed cardiac imaging procedure. Changes in the contours of the heart border reflect changes in the size and myocardial mass of the cardiac chambers and the caliber, pressure, and flow within the great arteries and veins. Morphological data, which describes the character and degree of chamber structural abnormality, is obtained by interpreting cardiac imagery. The algorithm for integrating this data into accurate and clinically significant diagnosis is the segmental approach.

The segmental approach to CHD analysis is a methodology that has its roots in Maurice Lev's proposal [3] that the heart chambers should be called by what they are rather than where they are. In particular, each chamber has characteristics that identify it, no matter where it is in relation to the rest of the heart. Van Praagh [4] took this premise and, referring to the embryology of cardiac development, proposed that the two major determining features of cardiac structure are viscerotrial situs and ventricular looping. This approach was modified by Shinebourne et al. [5] to emphasize the sequence of connections between cardiac segments and great arteries, and by Freedom [6] to define the three embryologically independent building blocks of the heart. Cardiac atrial situs, ventricular looping, and the great artery relationship are all independent of each other. That is, each of these components of basic cardiac structure must be defined explicitly in order to characterize atrial situs and atrioventricular and ventriculoarterial connections.

An organized approach to evaluating cardiovascular disease can begin with evaluating the chest radiograph (Fig. 1). If the chest radiograph film is divided into arbitrary components, then a serial evaluation of these components will be the basis for evaluating pathologic change. Evaluating cardiovascular abnormality begins with assessing soft tissues and bony structure of the chest wall. Scoliosis, kyphosis, and pectus excavatum are

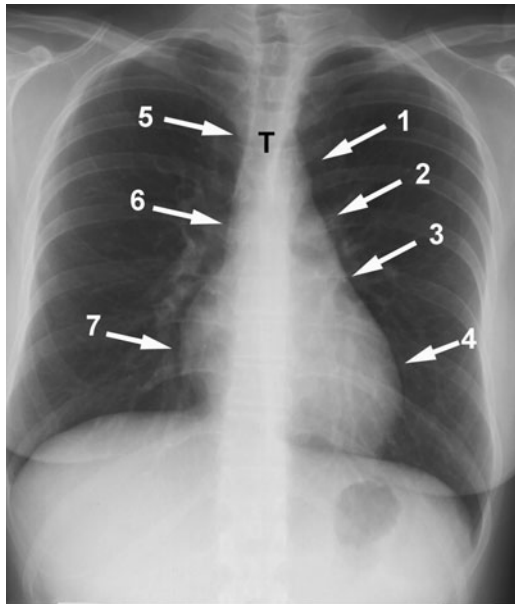


Fig. 1. Posteroanterior radiograph of a 40-year-old woman without cardiac disease. The left heart border is divided into the aortic arch segment (*arrow 1*), which displaces the trachea (*T*) toward the right; the main pulmonary artery segment (*arrow 2*), which lies superior to the lucency of the distal left bronchus; the concave toward the heart left atrial appendage segment (*arrow 3*); and the left ventricular contour (*arrow 4*). The superior-most portion of the right heart border is made up of the superior vena cava segment (*arrow 5*). The ascending aortic segment (*arrow 6*) barely crosses the right pulmonary hilum; the inferior-most right atrial contour (*arrow 7*)

commonly associated with congenital cardiovascular disease. Skeletal chest-wall abnormalities often result in changes in the shape of the thoracic cavity, causing displacement or rotation of the heart, giving the appearance of structural abnormality. Furthermore, chest-wall abnormality is frequently the result of chronic pulmonary changes resulting from cardiovascular disease.

Situs and Cardiac Chamber Morphology and Connections

In relation to CHD, numerous different problems can occur during embryologic development of the heart and great vessels, resulting in extreme variability in atrial, ventricle, and great-vessel morphology and connections. It is therefore useful to take a stepwise approach to describe the cardiac morphology by separating the heart into three major segments: (1) visceral-atrial situs, (2) position of the right and left ventricles as a result of ventricular looping, and (3) position of the great arteries (aorta and pulmonary artery). Next, the connecting segments or the atrioventricular and ventriculoarterial connecting segments are defined, followed by the systemic and pulmonary vein connections.

Visceral situs describes the distribution of the asymmetric organs of the body. Thoracic situs is determined by evaluating lung structure (Fig. 2). In the morphologic left

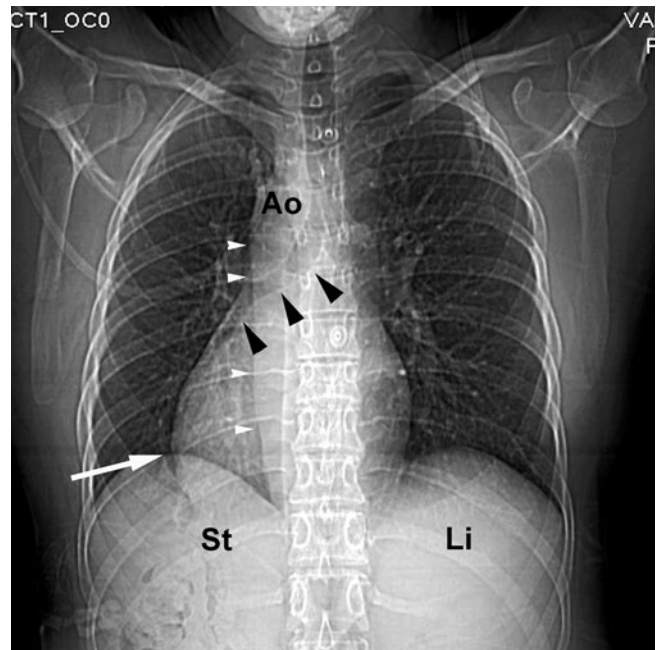


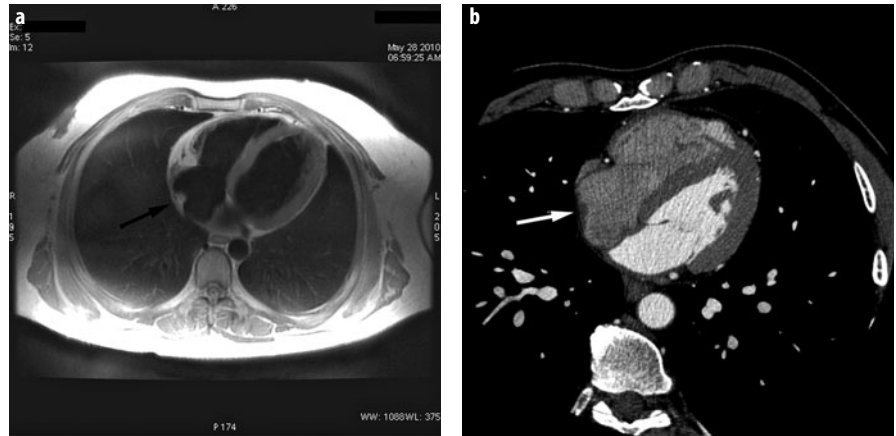
Fig. 2. Scout image from computed tomography examination of a 35-year-old man with complete situs inversus. The right-sided bronchus (*black arrowheads*) has a long course, indicating that it is the morphologic left bronchus. Notice the right-sided aortic arch (*Ao*) and right-sided descending aorta (*white arrowheads*). The cardiac apex (*arrow*) is toward the right. The right-sided stomach (*St*) and left-sided liver (*Li*) indicate abdominal situs inversus

lung, the bronchus has a relatively long course before giving rise to the upper-lobe branch, and the ipsilateral pulmonary artery passes over the top of the distal bronchus immediately proximal to the origin of the upper-lobe branch. The lingual segment is the remnant of a left-sided middle lobe; thus, the left lung has only two lobes and one fissure. The morphologic right lung has a main bronchus that gives rise to an upper-lobe branch after a short course; the ipsilateral pulmonary artery passes anterior to the bronchus. The morphologic right lung has three lobes and therefore two fissures. Thus, in situs solitus, the structurally appropriate lung is in the appropriate chest cavity. Situs inversus results in a mirror image (i.e., the left lung is on the right and the right lung is on the left).

Abdominal situs is characterized by the arrangement of the liver and stomach. In abdominal situs solitus, the liver, and thus the inferior vena cava (IVC), are on the right; and the stomach, and thus the upper abdominal aorta, are on the left. In situs inversus, the mirror image is found.

Cardiac situs is defined implicitly by evaluating thoracic and abdominal situs. That is, if both thoracic and abdominal situs are concordant, atrial situs follows. Thoracoabdominal situs concordance in situs solitus can predict atrial situs solitus; thoracoabdominal situs concordance in situs inversus can predict atrial situs inversus. If thoracoabdominal situs is discordant, then atrial situs cannot be predicted and must be characterized by

Fig. 3 a, b. Crista terminalis. **a** Axial double-inversion-recovery acquisition of a 43-year-old man without cardiac disease. Using this technique, the crista (*arrow*) appears as a high-signal mass along the lateral aspect of the right atrium. **b** Axial acquisition image from a contrast-enhanced computed tomography (CT) examination in a 60-year-old man with proximal coronary artery disease. The crista on CT examination appears as a filling defect along the lateral right atrial wall (*arrow*)



explicitly describing the morphology and connections of the atrial chambers.

All of cardiac chambers have distinctive structure. Starting with the atria, the morphologic right atrium (Fig. 3) is characterized by a broad-based and triangular-shaped appendage. Along the lateral wall of the morphologic right atrium the crista terminalis is found, which divides the morphologic right atrium into an anterior trabeculated portion and a smooth-walled posterior portion. The trabeculations of the anterior portion, the pectinate muscles (analogous to the trabecular myocardium of the morphologic right ventricle), extend into the right atrial appendage. The morphologic right atrium receives the systemic venous return [superior vena cava (SVC) and IVC], the hepatic veins, and coronary sinus. The morphologic left atrium is characterized by a bald, smooth, inner wall and a long and finger-like atrial appendage. The appendage contains pectinate muscles but fewer than those found in the right atrial appendage. On a practical level, morphologic features of the right and left atria and appendages can be difficult to characterize with imaging by CT or MRI in the setting of complex CHD. Therefore, when defining the atrial morphology by imaging, the most reliable identifying feature is to define the right atrium as the atrium that receives the IVC. This is because the SVC can be bilateral and may connect to an unroofed coronary sinus to the left atrium, and the pulmonary veins can have variable connections to either atria or to systemic veins.

The heterotaxy syndrome is a complex constellation of congenital malformations [7] in which solitus or inverted left-to-right distribution of paired organs (including the lungs and cardiac atria) is no longer found. Heterotaxy represents a spectrum of abnormality of sidedness, with bilateral left-sided or right-sided morphology at the extreme ends of this spectrum. For this reason, all patients with heterotaxy are considered individually when characterizing their malformations, as there is tremendous variability in the venous connections and atrial morphology, and relatively few patients fit perfectly into bilateral right or left sidedness. However, it is helpful to think in terms of complete bilateral right or left sidedness in order to understand

the possible malformations one may encounter in these patients. For example, bilateral left sidedness (left atrial isomerism), is associated with bilateral left-sided bronchial and lung morphology, polysplenia, and interruption of the IVC; bilateral right sidedness (right atrial isomerism) is associated with bilateral right-sided bronchial and lung morphology and asplenia (Fig. 4). In such individuals, thoracoabdominal situs is not concordant, and the liver is often transverse in orientation, with variable sidedness of the stomach or situs ambiguous. The atrial situs is also quite variable due to maldevelopment or complete absence of the atrial septum, which results in a common atrial chamber in situs ambiguous. Therefore, venous connections to the atria must be individually characterized.

Moving on to the ventricles: the right ventricle is defined as the ventricular chamber that tends to be more



Fig. 4. Right isomerism. Axial double-inversion-recovery acquisition of a 22-year-old man with complex congenital heart disease and heterotaxy syndrome. Note that the left-sided (*arrow 1*) and right-sided (*arrow 2*) pulmonary arteries both lie anterior to their respective left (*arrowhead 1*) and right (*arrowhead 2*) bronchi. The liver (not visualized) lies on the left

trabeculated, with an atrioventricular valve that has a distinct moderator band to the free wall and attachments to the septum. The right ventricle also has a conus, or infundibulum, which separates the ventricular chamber into distinct inflow and outflow regions so that the right-sided atrioventricular and semilunar valves are not in fibrous continuity. The left ventricle has no moderator band and a smooth septal surface, with its atrioventricular valve having attachments only to the free wall. The left ventricle usually does not have a conus so that there is fibrous continuity of the left-sided atrioventricular and semilunar valves. Ventricle looping refers to the looping of the heart in embryologic development as it transforms from a single tube with one inflow and one outflow to a four-chambered structure with separate inflow and outflow for pulmonary and systemic circulations. As a simplified approach to cardiac looping, one can consider the position of the ventricles relative to each other. (A more accurate method needed for complex malformations is the right-hand rule, which is not discussed here.)

The next level defines the positional relationship of the great arteries, with the pulmonary artery defined as the vessel that branches to the lungs and has no branches to the body. The aorta is the vessel with branches to the body and the coronary arteries (most of the time) and can give rise to branches to the lungs in the form of collaterals or bronchial arteries.

The next steps in this sequence involve describing how each segment of the heart is connected to the adjacent segment. The atrioventricular and ventriculoarterial relationships are defined as either concordant or discordant (such as in transposition of the great arteries). This is followed by a description of the associated anomalies, such as common atrioventricular canal, tricuspid atresia, double-inlet left ventricle, double-outlet right ventricle, and transposition of the great arteries, etc.

Connection

In atrial situs solitus, D-looping of the ventral cardiac tube brings the bulbus cordis portion to the right and the true ventricle to the left, creating atrioventricular concordance. That is, the right atrium is connected to the right ventricle and the left atrium is connected to the left ventricle. If the cardiac tube loops toward the left (L-looping), the ventricles are inverted. The inflow of the right ventricle lies to the left of the inflow of the left ventricle. That is, the right atrium becomes connected to the right-sided left ventricle and the left atrium to the left-sided right ventricle. This is referred to as atrioventricular discordance.

In the normal heart, the right-sided right ventricle supports the left-sided main pulmonary artery and the left-sided left ventricle supports the right-sided aorta. This is referred to as ventriculoarterial concordance. If a right-sided right ventricle supports the aorta and the left-sided left ventricle supports the pulmonary artery (atrioventricular concordance with ventriculoarterial discordance),

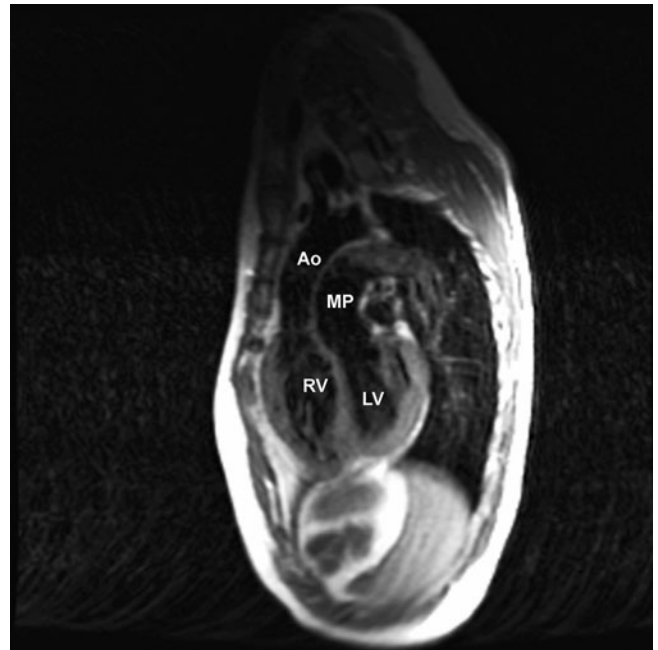


Fig. 5. Oblique sagittal double-inversion-recovery acquisition of a 6-year-old boy with D-transposition of the great arteries after a Senning atrial switch repair. The anterior aorta (*Ao*) is supported by the trabeculated right ventricle (*RV*) and lies parallel to the posterior main pulmonary artery (*MP*), supported by the posterior left ventricle (*LV*). Notice the flattened interventricular septum, reflecting the RV pressure load

this is referred to as D-transposition of the great arteries (D-TGA) (Fig. 5). This right-to-left relationship of the aorta and pulmonary artery is referred to as D-related great arteries. If the aorta lies to the left of the pulmonary artery, this is referred to as L-malposition of the great arteries. Although this may be found as an isolated lesion, it is more commonly found in atrioventricular discordance with ventriculoarterial discordance. This double discordance is called congenitally corrected transposition of the great arteries (L-TGA) (Fig. 6).

Great Artery and Chamber Analysis

The order in which anatomic information is obtained is often a result of the imaging modality employed for clinical evaluation. Echocardiographic evaluation is usually from caudad to cephalad, allowing characterization of the atria and then ventricles and their connection prior to analysis of the aorta and pulmonary artery. CT or MRI evaluation can be from caudad to cephalad or vice versa, depending on the clinical problem and manner in which slice acquisition is prescribed.

Chest radiograph analysis can be performed from cephalad to caudad, providing information about the great arteries prior to evaluating the atria and ventricles. As described earlier, chest radiograph evaluation begins with the

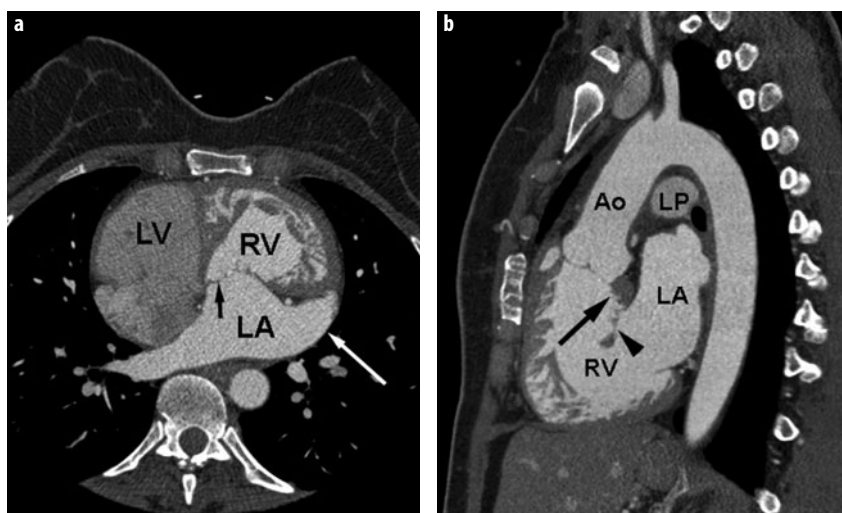


Fig. 6 a, b. Contrast-enhanced cardiac computed tomography of an asymptomatic 35-year-old woman. **a** Axial acquisition image obtained through the left-sided atrioventricular valve (*black arrow*). The left-sided ventricle is named the morphologic right ventricle (*RV*) because of the intense trabeculation along the left side of the interventricular septum. The right-sided ventricle is the morphologic left ventricle (*LV*). It is characterized by the smooth interventricular septum. The left-sided morphologic left atrium (*LA*) is characterized by a long, finger-like atrial appendage (*white arrow*). **b** Oblique sagittal reconstruction through the aorta (*Ao*), right ventricle (*RV*), and left atrium (*LA*). The anterior atrioventricular (tricuspid) valve leaflet (*arrowhead*) is separated from the semilunar (aortic) valve by the intermediate attenuation muscle of the RV infundibulum (*arrow*). The left pulmonary (*LP*) artery passes posterior to the left-sided ascending aorta

soft tissues and bony skeleton. Then the cardiomeastinal silhouette is divided into left and right heart borders. The left-heart border (Fig. 1) is formed (from cephalad to caudad) by the aortic arch segment, the pulmonary artery segment, the left atrial segment, and the left ventricular contour. We emphasize the importance of left heart border abnormalities, and briefly touch on the right heart border and the appearance of particular abnormalities.

The aortic arch segment is formed by the distal aortic arch and very proximal descending aorta. Congenital aortic malformations are more commonly characterized by inability to visualize a normal contour (Fig. 7) rather than

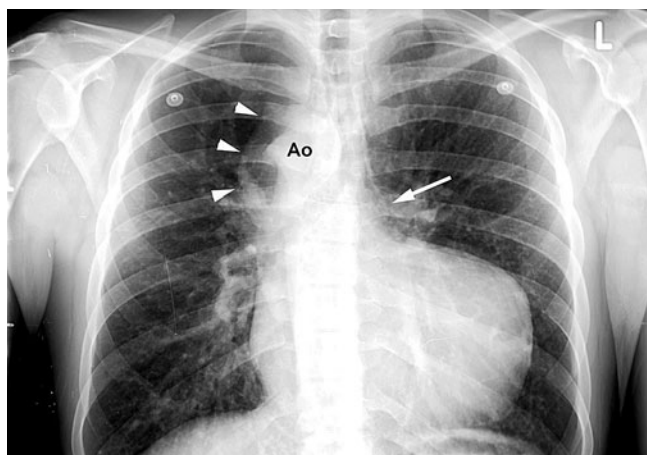


Fig. 7. Posteroanterior radiograph of a 24-year-old man with unoperated persistent truncus arteriosus with branch pulmonary artery stenosis. The right-sided aortic arch (*Ao*) displaces the trachea toward the left. The main pulmonary artery segment (*arrow*) is concave toward the heart, reflecting the absence of a main pulmonary artery. Pulmonary blood flow is derived from the ascending aorta. Notice the rightward displacement of the superior vena cava segment (*white arrowheads*) by the dilated ascending aorta. Despite the absence of a dilated pulmonary artery segment, the left-to-right shunt is seen in the increased pulmonary artery caliber in all lung segments

Table 1. Small or inapparent aortic arch segment

1. Right aortic arch
2. Coarctation of the aorta
3. Double aortic arch
4. Interruption of the aortic arch

a dilated appearance (Table 1). In the right aortic arch, this segment is absent (the aortic arch is on the right), and the tracheal air shadow is displaced toward the left. In double aortic arch, the dominant (larger) arch is usually on the right and higher, and the smaller, left-sided component is inferior. The trachea is often not displaced and remains midline. In interruption of the aortic arch, interruption proximal to the left subclavian artery typically presents without an apparent left-sided arch and without tracheal displacement.

The pulmonary artery segment is composed of the projection of the distal main pulmonary artery on the proximal left pulmonary artery. It lies inferior and to the left of the aortic arch segment (in individuals with left-sided aortic arch) and should be no greater in caliber than the aortic arch segment (left-sided cardiac output should equal right-sided cardiac output). The appearance of the pulmonary artery segment may be normal or increased or decreased in caliber.

An enlarged pulmonary artery segment (Fig. 8) is associated with increased pulmonary blood flow (shunts, including ventricular septal defects, atrial septal defects, endocardial cushion defects, and patent ductus arteriosus), increased pulmonary artery pressure (pulmonary hypertension and all of its associated etiologies), increased pulmonary artery pressure and flow, and valvular pulmonic stenosis (Table 2). Shunts are associated with shunt vascularity, enlarged main pulmonary artery segment, as well as the hilar (central) and the segmental pulmonary arteries. The vessels in the lower and upper lung

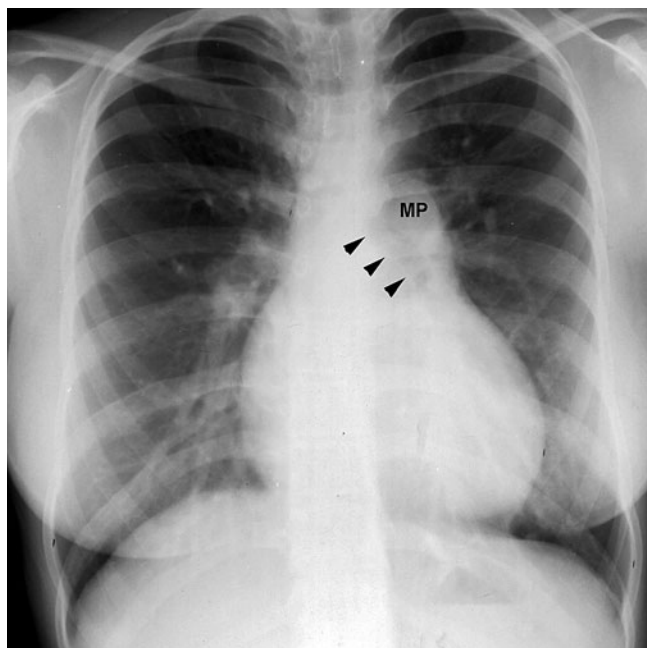


Fig. 8. Posteroanterior radiograph of a 23-year-old woman with a ventricular septal defect. The dilated main pulmonary artery (MP) segment resides over the left main bronchus (arrowheads). The aortic arch segment is not apparent, further narrowing the superior mediastinum. The upper left heart border appears to run parallel to the left bronchus, a sign of right heart enlargement, associated, in this instance, with the left-to-right shunt

Table 2. Dilated Pulmonary Artery Segment

- | |
|--|
| 1. Increased pulmonary blood flow |
| Shunts |
| Pulmonary insufficiency |
| 2. Increased pulmonary pressure |
| 3. Increased pulmonary flow and pressure |
| 4. Valvular pulmonic stenosis |

zones are enlarged, sharp, and extend further to the pleura than expected. When pulmonary blood flow is increased, vessels smaller in caliber than line-pair resolution of the chest radiograph are dilated to a caliber greater than this resolution, and thus, more vessels are seen. The anatomic level of the shunt can be characterized by the association of particular chamber enlargement with shunt vascularity. That is, in an atrial level shunt, shunt vascularity is associated with right heart (right ventricular and right atrial) enlargement and normal left heart (left atrium and ventricle) size. In ventricular level shunts, biventricular and left atrial enlargement is associated with shunt vascularity. In a patent ductus arteriosus, shunt vascularity is associated with left heart (left atrial and ventricular) enlargement and a normal-volume right ventricle.

The main pulmonary artery segment may be enlarged in valvular pulmonic stenosis (Fig. 9). In this condition, pulmonary blood flow and pressure may be normal, but turbulence resulting from acceleration of flow across the stenotic valve results in poststenotic dilatation (analogous to that seen in the ascending aorta in cases of valvular aortic stenosis). In pulmonic stenosis, the left pulmonary artery may be enlarged (probably caused by transmission of turbulence), but the hilar right pulmonary artery is of normal caliber. By the time the flow has passed through the transverse right pulmonary artery to reach the right hilum, Newtonian flow has been achieved and the stimulus for dilatation removed. Unless near critical in severity, valvular pulmonic stenosis is associated with the appearance of normal parenchymal blood flow.

The pulmonary artery segment may appear flat or concave (Fig. 10) when antegrade filling of the pulmonary arteries is impaired (Table 3). In such individuals, the abnormal pulmonary artery segment is associated with normal to decreased pulmonary blood flow. The latter circumstance may be difficult to appreciate on a chest radiograph (probably because fewer cases associated with

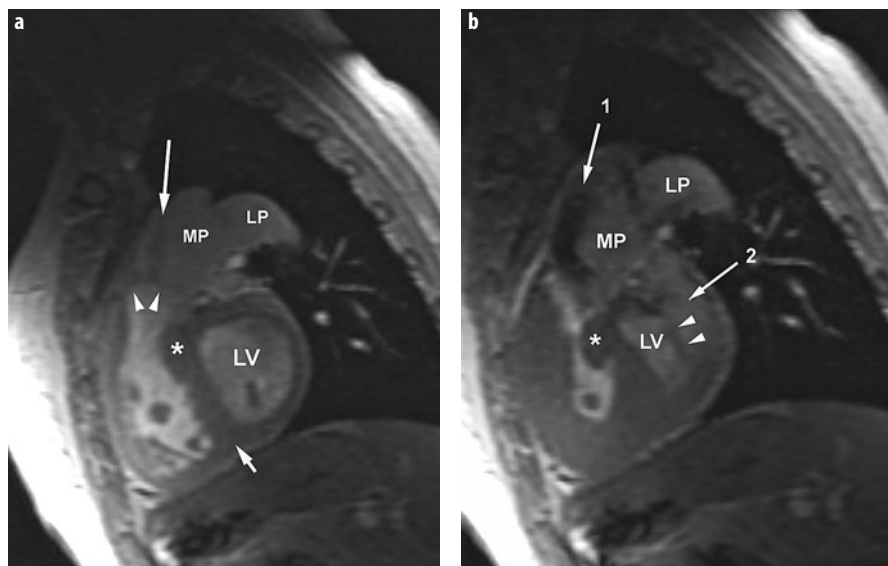


Fig. 9 a, b. Sagittal electrocardiographically-gated gradient-echo images obtained through the hypertrophied right ventricular sinus and outflow portions and dilated main (MP) and left (LP) pulmonary arteries. **a** Early in systole, the pulmonary-valve leaflets (arrowheads) have barely opened, and the faint signal void (long arrow) of a turbulent jet is seen in the dilated MP. At this anatomic section, the septomarginal trabeculation (*) is seen along the superior aspect of the flattened interventricular septum (short arrow). The left ventricle (LV) is labeled. **b** Late in systole, the signal-void jet of valvular pulmonic stenosis (arrow 1) is fully formed. There is marked thickening of the right ventricular myocardium. The interventricular septum beneath the septomarginal trabeculation (*) is bowed toward the left ventricle. This late in systole, the left atrium (arrow 2) and anterior mitral leaflet (arrowheads) are drawn into the imaging plane

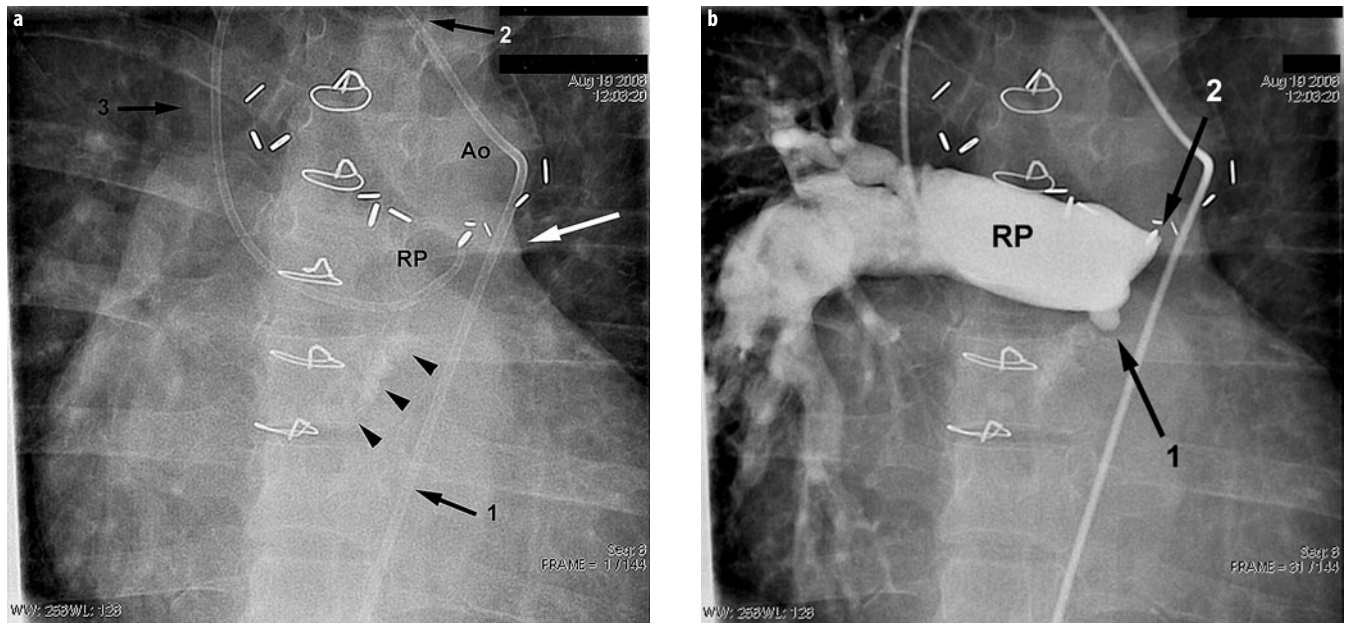


Fig. 10 a, b. Coronal cineangiogram of a 24-year-old woman many years after placement of a right-sided Blalock Thomas Taussig shunt (BTT) and ventricular septal defect (VSD) repair for severe tetralogy of Fallot, with pulmonary atresia and obstructed left pulmonary artery. **a** Cine frame obtained prior to contrast administration. A catheter is seen passing retrograde from the descending aorta (arrow 1), through the left-sided aortic arch (Ao), into the innominate artery (arrow 2), through the BTT (arrow 3), and into the right pulmonary (RP) artery. The concavity of the main pulmonary artery segment (white arrow) is marked. Notice the calcified ventricular septal defect patch (arrowheads). **b** After contrast injection, the right pulmonary (RP) artery and its branches are opacified and dilated. The atretic main pulmonary artery (arrow 1) and occluded left pulmonary artery (arrow 2) are seen. The main pulmonary artery segment is concave because there is no main or left pulmonary artery to occupy this space

Table 3. Small pulmonary artery segment

- | |
|--|
| 1. Right ventricular outflow obstruction |
| Tetralogy of Fallot |
| Tetralogy with pulmonary atresia |
| Pulmonary atresia with ventricular septal defect |
| Double outlet right ventricle |
| 2. Right atrial outflow obstruction |
| Ebstein malformation |
| Tricuspid atresia |
| 3. D-transposition of the great arteries |
| 4. Common truncus arteriosus |

decreased flow are seen compared with increased flow). However, careful attention will reveal that not only is the main pulmonary artery segment abnormal, and the hilar and segmental pulmonary arteries are all decreased in caliber, but the lungs appear darker, and fewer parenchymal vessels are apparent.

Sometimes, the pulmonary artery segment may not be visible, giving the impression that it is decreased in caliber. This may be seen in individuals in whom the pulmonary artery is present and, in fact, normal or even increased in caliber. However, in these cases, the pulmonary artery is not in its normal position (i.e., to the left of the aorta and supported by the right ventricle) (Figs. 6b and 11). This may be seen in individuals with

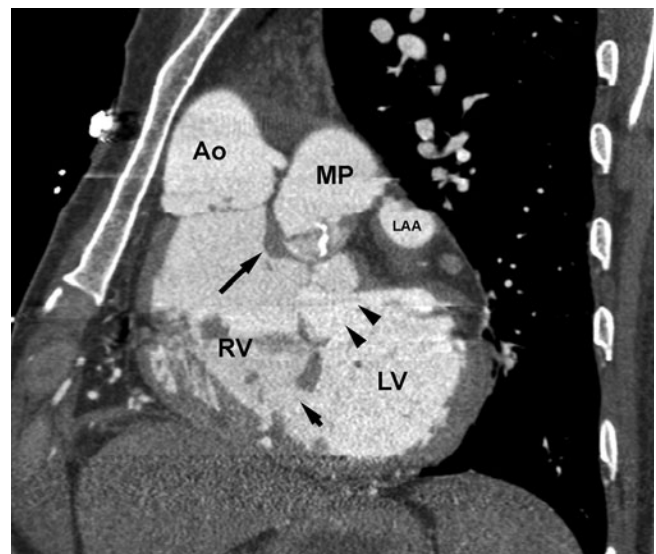


Fig. 11. Left anterior oblique reconstruction from a contrast-enhanced cardiac computed tomography of a 40-year-old man with double-outlet right ventricle, D-transposition of the great arteries, subpulmonic ventricular defect (Taussig Bing anomaly), and severe pulmonic stenosis. The aorta (Ao) and main pulmonary (MP) artery are separated by the infundibular myocardium (long arrow) and supported by the anterior right ventricle (RV). Note the calcification of the stenotic pulmonic valve. The left (LV) and right (RV) ventricles communicate via a large subpulmonic (arrowheads) and muscular (short arrow) ventricular septal defect. The left atrial appendage (LAA) is labeled

D-TGA (the pulmonary artery is to the left of the aorta but supported by the posterior left ventricle, and thus not heart-border forming). In congenitally corrected (L-) transposition, the main pulmonary artery may be normal in size or dilated, but the pulmonary artery arises to the right of the aorta, and the left heart border is formed by the left-sided ascending aorta. Hence, no pulmonary artery is visualized.

A third circumstance is associated with an inapparent pulmonary artery segment in individuals who do not have a main pulmonary artery, namely, in common truncus arteriosus (Fig. 5). In such individuals, there is no main pulmonary artery; pulmonary blood flow is derived from pulmonary arteries, but they arise from either the ascending or descending aorta. In all of these cases (D-TGA and L-TGA and truncus), the main pulmonary artery segment may appear flat or concave, but the hilar and parenchymal pulmonary arteries will be abnormal in the presence of a shunt.

The left atrial appendage segment of the left heart border extends from beneath the left bronchus crossing the left heart border to the top of the left ventricular segment. Left atrial enlargement causes the normally concave (toward the heart) segment to flatten and then become convex (Table 4). Left atrial hypertension is associated with appropriate changes in the parenchymal pulmonary vessels and parenchyma (i.e., interstitial edema).

The appearance of the left atrial portion of the heart border may be altered by right heart dilatation, and an associated leftward (looking from below, counterclockwise) rotation and displacement of the heart (Fig. 6). The right ventricular outflow, which normally does not form any part of either the left or right heart borders, will now occupy the portion of the left heart border formally occupied by the left atrial appendage. Clockwise cardiac rotation is associated with changes in the shape of the interventricular septum and leftward displacement of the right ventricular outflow tract and pulmonary artery. The left bronchus now appears to run parallel to the left heart border rather than crossing it. The left atrial appendage has been rotated off the left heart border and no longer radiographically contributes to it. There is no splaying of the bronchi, nor is there a double density to indicate other objective evidence of left atrial enlargement. Furthermore, right heart disease leading to rotation is strongly associated with chronic systemic venous hypertension and may contribute their radiographic signs of SVC, azygos vein, and right atrial enlargement. Chronic postoperative pulmonary insufficiency and Fontan physiology associated with repair of univentricular hearts are often presenting findings in such individuals.

Table 4. Apparent left atrial enlargement

Left-to-right shunt
Congenital mitral valve disease
Restrictive cardiomyopathy

The contour of the left ventricular portion of the left heart border in individuals with congenital heart disease (Fig. 12) appears to be more rounded, even if not conspicuously dilated (i.e., extends toward the left chest wall) (Table 5). This abnormal appearance may be associated with left ventricular dilatation (mitral regurgitation, shunt failure), hypertrophy (valvular, subvalvular aortic stenosis, coarctation of the aorta), and cardiomyopathy.

The SVC portion of the right heart border is normally visualized as a vertical line more or less parallel to the trachea and aortic arch. Widening of this stripe (Fig. 7) is associated with severe right atrial hypertension, chronic tricuspid regurgitation, SVC dilatation such as with distal caval obstruction, and displacement by a dilated aorta. Leftward rotation in right heart enlargement narrows the stripe, giving the appearance of a narrow mediastinum (Fig. 8).

The lateral aspect of the normal ascending aorta can be barely seen within the right hilum. Extension of the

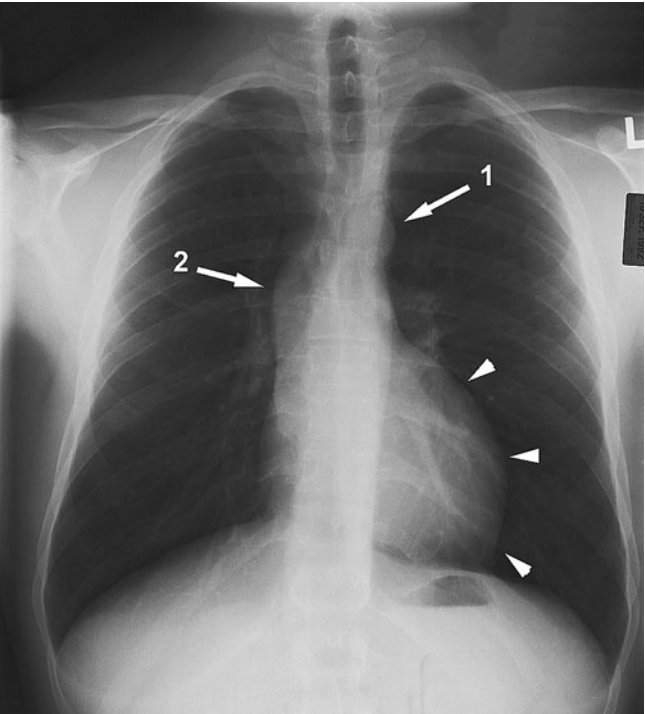


Fig. 12. Posteroanterior radiograph obtained from a 24-year-old man with coarctation of the aorta and bicuspid aortic valve stenosis. The aortic arch segment (arrow 1) displaces the trachea toward the right but barely extends past the spine. The lower left heart border (arrowheads) is rounded but does not approach the left chest wall. Poststenotic dilatation of the ascending aorta (arrow 2) extends to the right pulmonary artery

Table 5. Left ventricular contour abnormality

Left ventricular obstruction
Aortic insufficiency
Mitral insufficiency
Cardiomyopathy

aortic contour over the right hilar pulmonary artery reflects the increased aortic caliber, as may be found in a volume-loaded aorta (i.e., aortic regurgitation). It may also be the result of turbulent flow from poststenotic dilatation, as seen in valvular aortic stenosis.

The right atrial contour of the right heart border is abnormal in appearance when the right atrium is dilated but may not accurately reflect less severe changes in right-atrial and right-ventricular volume. Clockwise cardiac rotation in right heart dilatation may displace the right atrium toward the left, spuriously normalizing the appearance of the lower right heart border.

Putting it All Together

Although there are myriad radiologic observations that may be strongly associated, or diagnostic of a particular congenital malformation or sequela, the pressing need for accurate diagnosis necessitates a multimodal approach to data collection prior to synthesis of these findings. Limitations of one imaging modality necessitate the use of an alternative means of imaging. The choice of imaging modality should be dictated by the specific clinical or anatomic problem.

Assessing atrial situs and atrioventricular and ventriculoarterial connection provides the basis for analyzing specific structural abnormality. Furthermore, classifying complex hearts according to their situs and connections allows evaluation of classes of cardiac malformations, thus furthering our understanding of the effect of diagnosis and management on outcome.

There is no “one stop shop” for congenital cardiac diagnosis. Chest radiographic diagnosis, once the only imaging modality available, has now been supplanted with more accurate means of defining the particulars of intracardiac morphologic abnormality and quantitative

evaluation of cardiac function. Improved noninvasive tomographic technologies have changed the role of cardiac catheterization from the primary source of intracardiac anatomy and physiologic data to the platform for the growing area of percutaneous intra- and extracardiac intervention. The wide use of echocardiography reflects its safety, low cost, ready availability, and broad clinical utility. Already, cardiac MRI and CT have grown in utility and provide complementary imaging information to echocardiography, angiography, and radiographic evaluation. Whatever means of cardiac imaging employed, applying the techniques of observation, analysis, and correlation among imaging modalities will always be necessary to rapidly, accurately, and safely diagnose and manage patients.

References

1. Boxt LM (2004) Magnetic resonance and computed tomographic evaluation of congenital heart disease. *J Magn Reson Imag* 18:827-847
2. Sena L, Boxt LM, Miller SW (2009) Congenital Heart Disease. In: Miller S, Boxt LM, Abbara S (eds) *Cardiac Imaging: The Requisites*, 3rd ed. Elsevier Mosby, Philadelphia, PA, pp 297-376
3. Lev M (1954) Pathologic diagnosis of positional variations in cardiac structures in congenital heart disease. *Lab Invest* 3:71-82
4. Van Praagh R (1972) The segmental approach to diagnosis in congenital heart disease. *Birth Defects: Original Article Series* 8:4-23
5. Shinebourne EA, Macartney FJ, Anderson RH (1976) Sequential chamber localization-logical approach to diagnosis in congenital heart disease. *Br Heart J* 38:327-340
6. Freedom RM (1984) The “anthropology” of the segmental approach to the diagnosis of complex congenital heart disease. *Cardiovasc Intervent Radiol* 7:121-123
7. Calcaterra G, Anderson RH, Lau KC, Shinebourne EA (1979) Dextrocardia – value of segmental analysis in its categorization. *Br Heart J* 42:497-507

Interventional Techniques in the Thorax of Adults

Dierk Vorwerk

Department of Radiology, Klinikum Ingolstadt, Ingolstadt, Germany

Introduction

Interventional radiology in the thorax is somewhat ill-defined. Most people will reflect on nonvascular interventions such as lung biopsy. However, there is, in fact, a huge variety of different nonvascular and vascular interventions performed within thoracic structures, and more will be of growing importance, such as radiofrequency ablation (RFA) of lung tumors.

Nonvascular Interventions

Lung Biopsy

In the nonvascular field, computed tomography (CT)-guided lung biopsies are the best known and most frequently performed intervention in this part of the body. Both fine-needle aspiration biopsy (FNAB) for cytology and miniaturized cutting needles for histology not exceeding 18-20 gauge might be used for this purpose. Automated biopsy guns have several advantages, offering excellent sampling quality and the possibility of performing repeated biopsies using a single access. FNAB is more frequently recommended if an object for biopsy is located close to central and vascular structures in order to avoid major bleeding complications. Laurent et al. [1] compared accuracy and complication rate of FNAB and an automated biopsy device. Two consecutive series of 125 (group A) and 98 (group B) biopsies performed using 20- to 22-gauge coaxial FNAB (group A) and an automated 19.5-gauge coaxial biopsy device (group B) were studied. Groups A and B consisted of, respectively, 100 (80%) and 77 (79%) malignant lesions and 25 (20%) and 18 (21%) benign lesions. No significant difference was found between the two series regarding patients, lesions, and procedural variables. For a diagnosis of malignancy, a statistically significant difference in sensitivity was found (82.7% vs 97.4%) between results obtained with the automated biopsy device and FNAB, respectively. For a diagnosis of malignancy, the false negative rate of the biopsy result was significantly higher ($p < 0.005$) in group A (17%) than in group B (2.6%). For a specific diagnosis of benignity, no statistically significant difference

was found between the two groups (44% vs 26%), but the automated biopsy device provided fewer indeterminate cases. There was no difference between groups concerning pneumothorax rate, which was 20% in group A and 15% in group B, or hemoptysis rate, which was 2.4% in group A and 4% in group B. The authors concluded that for obtaining a diagnosis of malignancy, automated biopsy devices provide a lower rate of false negative results and a similar complication rate to FNAB.

Richardson et al. [2] undertook a survey in the UK of 5,444 lung biopsies. Complications included pneumothorax (20.5% of biopsies), pneumothorax requiring chest drain (3.1%), hemoptysis (5.3%), and death (0.15%). The timing of postprocedure chest radiography was variable. Centers that performed predominantly cutting-needle biopsies had similar pneumothorax rates to centers performing mainly FNAB (18.9% vs 18.3%). There is great variation in practice throughout the UK. Most procedures are performed on a day-case basis. Small pneumothoraces are common but infrequently require treatment. Chojniak et al. [3] reported retrospectively approximately 1,300 consecutive CT-guided biopsies performed within 6 years. Nodules or masses were suspected as primary malignancy in 845 cases (65%) or metastatic in 455 (35%). Six hundred and twenty-eight lesions were thoracic. For any site, sample adequacy and specific diagnosis rates were always better for cutting-needle biopsy. Among 530 lung biopsies, there were 84 pneumothorax (16%) and two hemothorax (0.3%) cases, with thoracic drainage in 24 (4.9%). Post-biopsy pneumothorax as a rather frequent complication can be treated relatively simply in most cases. In asymptomatic patients, we recommend not evaluating the pneumothorax earlier than 4 h after biopsy in order to achieve a durable success. In symptomatic patients or drainage failures with a single-needle approach, use of percutaneously introduced Heimlich valves is recommended.

Minimally invasive thoracoscopic procedures become more and more popular and offer a valid alternative if only a single pulmonary nodule exists that can be removed both for diagnostic and therapeutic purposes. In that case, interventional radiology offers a helpful service procedure by CT-guided hook marking of the nodule to allow its easy identification during thoracoscopy and to facilitate

removal. Poretti et al. [4] described their experience with percutaneous CT-guided placement of hook wires to localize such nodules before video-assisted thoracoscopy (VATS). Nineteen patients with newly diagnosed intrapulmonary nodules underwent CT-guided hook-wire localization by application of an X-Reidy set. After localization, the patients underwent a VATS resection of the lesion within a mean time of 30 (range 10-48) min. In all cases, nodule resection was successful. Eight patients developed an asymptomatic pneumothorax. In four patients, in whom the tumor was hit directly by the needle, local bleeding occurred. In one case, hemoptoe was present. In no patient did dislocation of the hook-wire system occur.

Abscess Drainage

Other nonvascular interventions include abscess drainage from the lung, pleura, and mediastinum. Percutaneous drainage of pleural, pulmonary, and mediastinal abscesses is a widespread technique that is more or less available in all radiological departments. Success depends on size of drainage catheters, composition of the drained material, organization of the pseudomembrane, and access routes, especially into mediastinal locations.

RFA of Lung Lesions

According to de Baère [5], RFA is used to treat primary and metastatic lung neoplasms with indications close to those of surgical resection. RFA is thus performed with curative intent in nonsurgical or borderline surgical candidates. Inoperability is most often due to poor respiratory function in relation to chronic obstructive pulmonary disease (COPD) in primary tumors and iterative surgery in metastatic patients. Because the intent is curative, a preablation imaging workup must be equivalent to a presurgical workup. In addition, the size and number of the tumors matter not only for the oncologic indication but also for the technical possibilities. It is usually thought that the number of tumors deposited per hemithorax should not be >5, and that the largest diameter should be <5 cm and ideally <3.5 cm.

Local Efficacy

A review of 17 of the most recent publication demonstrated a median reported rate of complete ablation of 90%, even though high variability exists between publications, with reports ranging from 38% to 97% [5]. Tumors <2 cm can be ablated in 78% to 96% of cases, according to several reports of CT-guided RFA performed with a lengthy imaging follow-up.

Survival

Survival data for RFA are scarce and not mature, with few series providing survival beyond 3 years [5]. There is thus no comparative study of RFA and surgery, either for

small-size (stage I) non-small-cell lung cancer (NSCLC) or lung metastases. Studies comparing RFA and other local ablative therapies or radiotherapy do not exist. Although early reports of survival rates after RFA seem close to rates after surgery, data are preliminary. Ideally, comparative randomized studies are needed in patients treated with curative intent.

Technical Considerations

The RF delivery must be adapted to tumor location because impedance before ablation is significantly different for the tumors, with >50% of the tumor abutting the pleura as well as tumors not abutting the pleura or tumors in which <50% abutted the pleura. Indeed, tumor surrounded by lung parenchyma is highly electrically and thermally insulated by the air-filled lung parenchyma compared with a tumor with pleura contact and thus requires less energy deposition.

Vascular Interventions

Vascular interventions can be divided between arterial and venous. In the arteries, balloon angioplasty of supraaortic arteries such as the subclavian artery, implantation of thoracic endografts, and embolization of bronchial arteries should be mentioned. Relatively rarely performed are transarterial techniques for tumor treatment such as chemoperfusion of the lateral thoracic, mammary and bronchial arteries in order to treat bronchial or breast cancer. Vascular interventions involving the pulmonary artery include occlusion of hepatic artery-portal vein fistulas, particularly in patients with Osler-Weber-Rendu disease. Local thrombolysis or thrombodestruction of pulmonary emboli is an intervention used relatively rarely but is a promising alternative in emergency cases with pulmonary embolism. In the venous area, central venous stents either to treat malignancies or to recanalize central venous stenoses to allow successful drainage in dialysis patients, placement, and maintenance of central venous catheters, fibrin-sheath stripping and foreign-body removal are frequently used vascular techniques in the thorax. Not all these interventions should be discussed in depth, but embolization of bronchial arteries and treatment of malignant venous stenoses should be more emphasized, as neither of them is completely well known in general, and understanding them might be helpful for physicians treating patients with acute symptoms.

Arterial Interventions

Stent-Graft Implantation

Routine commercial availability of stent grafts for the thoracic aorta has drastically changed the treatment of traumatic or iatrogenic pseudoaneurysms, true aneurysms,

intramural hematomas, and symptomatic type B dissections. There has been a change of strategy for some thoracoabdominal aneurysms, but they still represent a challenging, although small, group of patients. No good endoluminal alternative exists for type A dissections or other aneurysms of the ascending thoracic aorta.

Technically, stent-graft implantation into the thoracic aorta is straightforward, as it involves insertion of a simple tube graft or several tube grafts. Important landmarks are the left subclavian artery – which can be usually covered by a stent graft in the event the right vertebral artery is patent; sometimes the left common carotid artery – which should not be covered without performing a carotid-carotid bypass and the celiac trunk. Elongation of the aortic arch sometimes makes exact and easy stent-graft placement difficult. Paraplegia is a rare but serious side effect in case the descending aorta is treated but is less common compared with following open surgery.

Matsumura et al. [6] evaluated the safety and efficacy of thoracic endovascular aortic repair (TEVAR) using a contemporary endograft system compared with open surgical repair (open) of descending thoracic aortic aneurysms and large ulcers. They evaluated 230 patients: 160 TEVAR patients treated with one particular stent graft, and 70 patients undergoing open surgery. The 30-day survival rate for the TEVAR group compared with the open group was 98.1% vs 94.3% ($p < 0.01$). Cumulative major morbidity scores were significantly lower at 30 days for the TEVAR group compared with the open group (1.3 ± 3.0 vs 2.9 ± 3.6 , $p < 0.01$). TEVAR patients had fewer cardiovascular, pulmonary, and vascular adverse events. No ruptures or conversions occurred in the first year after TEVAR. Reintervention rates were similar in both groups. At 12 months, aneurysm growth was identified in 7.1% (8/112), endoleak in 3.9% (4/103), migration (>10 mm) in 2.8% (3/107), and other device-related problems were infrequent. The authors concluded that at 1 year of follow-up, TEVAR with the TX2 is a safer and more effective alternative to open surgical repair for treating anatomically suitable descending thoracic aortic aneurysms and ulcers.

In a prospective trial, Nienaber et al. [7] investigated 140 patients with stable type B dissection who were randomly assigned to elective stent-graft placement in addition to optimal medical therapy ($n = 72$) or to optimal medical therapy ($n = 68$) with surveillance. There was no difference in all-cause mortality: cumulative survival was $97.0\% \pm 3.4\%$ with optimal medical therapy vs $91.3\% \pm 2.1\%$ with TEVAR ($p = 0.16$). Aorta-related mortality was no different ($p = 0.42$), and the risk for the combined end point of aorta-related death (rupture) and progression (including conversion or additional endovascular or open surgical intervention) was similar ($p = 0.86$). Three neurologic adverse events occurred in the TEVAR group (one paraplegia, one stroke, and one transient paraparesis) vs one episode of paraparesis with medical treatment. The authors concluded that in survivors of uncomplicated type B aortic dissection, elective stent-graft placement

does not improve 1-year survival and adverse event rates. However, paraplegia after TEVAR is a significant risk. Matsuda et al. [8] investigated the vascular anatomy before TEVAR and found that one of eight patients in whom a stent graft had to be placed across the origin of the Adamkiewicz artery developed paraplegia after TEVAR. In case paraplegia occurs, immediate treatment with corticosteroid therapy and spinal drainage is recommended.

Percutaneous Transluminal Angioplasty of Supraaortic-Vessel Origins

Supraaortic percutaneous transluminal angioplasty (PTA) is mainly performed on the left subclavian artery and less frequently on the brachiocephalic trunk, the proximal carotid arteries, and the right subclavian artery. Stenosis or occlusions may be caused mainly by atherosclerosis and, less frequently, inflammatory processes such as Takayasu arteritis. Indications for interventions are embolic events, neurological symptoms due to vertebral steal syndrome or malperfusion or brachial claudication. In particular, dilatation of the left subclavian artery is relatively safe, with a low rate of vertebral embolization. However, stent placement is frequently necessary due to insufficient post-PTA result.

Sixt el al. [9] retrospectively analyzed 108 interventions of atherosclerotic lesions of subclavian arteries or the brachiocephalic representing 92% of patients treated with subclavian artery obstructive disease over a 10-year period. The primary success rate was 97% [100% for stenoses (78/78) and 87% for total occlusions (26/30)]. Treatment modalities included PTA alone (13%; $n = 14$) or stenting (87%; $n = 90$) with balloon-expandable ($n = 61$), self-expanding ($n = 17$), or both ($n = 12$) types of devices. The 1-year primary patency rate of the 97 patients eligible for follow-up was 88%, for the PTA subgroup 79%, and for the stenting subgroup 89% ($p = 0.2$).

Van Hattum et al. [10] evaluated the results of PTA and stent placement in isolated brachiocephalic trunk lesions in 30 patients with isolated clinically significant stenoses ($n = 25$) or occlusions ($n = 5$) of the brachiocephalic artery. The initial technical success rate was 83% (occlusions 60%, stenoses 88%), and the clinical success rate was 81%. Two patients had major and four minor complications. At a median follow-up of 24 months (4 weeks to 92 months), the primary clinical patency rate was 79% [95% confidence interval (CI) 57-104%], with 83% (95% CI 60-105%) for arteries with stents and 67% (95% CI 13-120%) for those without stents ($p = 0.11$). The primary technical patency rate was 50% (95% CI 24-76%).

AbuRahma et al. [11] compared the results of a large series of PTA/stenting procedures in the subclavian artery with the results of a series of carotid-subclavian bypass grafts (CSBG). One hundred and twenty-one patients underwent subclavian artery PTA/stenting and were compared with 51 patients with isolated subclavian artery occlusive disease treated with CSBG using polytetrafluoroethylene grafts. The mean follow-up for the PTA/stent

group was 3.4 years vs 7.7 years for the CSBG group. The technical success rate for the CSBG group was 100% vs 98% (119/121) for the PTA/stent group. The overall perioperative complication rate in the stent group was 15.1% (18/119: 11 minor and 7 major) vs 5.9% (3/51: 2 phrenic nerve palsy and 1 myocardial infarction) in the bypass group ($p = 0.093$). There was no perioperative stroke or mortality in the CSBG group. The major perioperative complications in the stent group included four thromboembolic events, one congestive heart failure, one reperfusion arm edema, and one pseudoaneurysm. The 30-day patency rate was 100% for the bypass group and 97% (118/121) for the PTA/stent group. The primary patency rates at 1, 3, and 5 years were 100%, 98%, and 96% for the CSBG group vs 93%, 78%, and 70% for the stent group, respectively ($p < 0.0001$). Freedom from symptom recurrence was also statistically superior in the bypass group vs the stent group ($p < 0.0001$). The authors concluded that PTA/stenting of the subclavian artery should be the procedure of choice for high-risk patients but that CSBG should be offered to good-risk surgical candidates who may be seeking a more durable procedure.

Bronchial Artery Embolization

Bronchial artery embolization (BAE) is not a simple intervention for many reasons. First, the bronchial artery anatomy is variant and the size of the arteries frequently very small, so cannulation can become difficult. Feeders to bronchial artery bleeding sources – which are mainly arteriopulmonary fistulae due to tumoral or inflammatory changes – can originate not only from the bronchial but from many other arteries in the thorax, such as the subclavian artery, the thyrocervical trunk, or the mammary or costal arteries. Moreover, there is a variation in collaterals in the region that includes the spinal arteries. As embolization material, particles, glue, and coils might be used, but the gold standard is sealing the artery as close as possible to the bleeding source, otherwise, recurrence via collateral feeders might occur. Benign reasons for bronchial bleeding include bronchiectasis, chronic bronchitis, aspergillosis, tuberculosis, pneumonia, and abscesses. Malignant sources are predominantly bronchial cancers.

Results of percutaneous intervention are fairly good. Kato et al. [12] treated 101 patients and achieved a technical success of 100%, a 1-year success of 77.7%, and a 5-year success of 62.5%. They described better outcome patients with tuberculosis and bronchitis and a less favorable outcome in pneumonia and abscesses. Lee et al. [13] described their experience with BAE in massive hemoptysis as a life threatening condition. In a 5-year period, 54 patients were treated for massive hemoptysis. The underlying pathology included bronchiectasis ($n = 31$), active tuberculosis ($n = 9$), pneumoconiosis ($n = 3$), lung cancer ($n = 2$), and pulmonary angiodysplasia ($n = 1$). Surgery was considered if the patient had acceptable pulmonary reserve and a bleeding source

was clearly identified. If the patient was not considered fit for surgery, BAE was attempted. Hemoptysis ceased with conservative management in seven patients (13%) only. Twenty-seven (50%) patients received surgical resection. The procedures included lobectomy ($n = 21$), bilobectomy ($n = 4$), and pneumonectomy ($n = 2$). The in-hospital mortality rate after surgery was 15%. Postoperative morbidity occurred in eight patients, including prolonged ventilatory support, bronchopleural fistulae, empyema, and myocardial infarction. Twenty-one patients not suitable for surgery were treated with BAE, which was successful in 17 patients without any complications.

In patients bleeding from bronchial carcinoma, Witt et al. [14] performed BAE using platinum coils with Dacron fibers in 30 consecutive patients. Their aim was to compare immediate results of bleeding cessation, recurrence, and survival rates with conservative management. Active bleeding stopped immediately in all patients. Comparing the BAE group and controls, the cessation of first-time hemoptysis (BAE 100% vs non-BAE 93%) and the rates of bleeding recurrence (BAE 50% vs non-BAE 47%) were similar. In case of recurrent bleeding, repeated BAE led to definite cessation of pulmonary hemorrhage in every case. In contrast, all patients with recurrent hemoptysis without a repeated BAE (eight patients, 27%) and all patients with bleeding recurrence in the non-BAE group died from pulmonary hemorrhage (eight patients, 53%). The mean survival time of the BAE group was significantly longer compared with the non-BAE group. The authors therefore concluded that consistent BAE proved beneficial in tumorous pulmonary bleeding.

Venous Interventions

Pulmonary Artery Embolectomy

Treatment of acute symptomatic pulmonary embolism by catheter-directed methods is an long-held dream of interventional radiologists. There are a couple of problems occurring with this approach, however. First, massive pulmonary embolism (PE) may lead to relatively mild symptoms not necessitating aggressive treatment. Second, i.v. thrombolysis is usually effective in most patients. On the other hand, patients who are candidates for the percutaneous approach die early or are in bad clinical shape, and most are hemodynamically unstable, requiring emergency treatment but are not transportable. The logistic shortcomings prevent widespread use of catheter-based interventions, and it is surprising that mainly, small cohorts of patients have been reported – with encouraging results, however. Kuo et al. [15] retrospectively studied 70 consecutive patients with suspected acute PE over a 10-year period and who had been referred for pulmonary angiography and/or intervention. The criteria for study inclusion were patients who received catheter-directed intervention (CDI) due to angiographically confirmed, massive PE and hemodynamic shock (shock index ≥ 0.9). CDI involved

suction embolectomy and fragmentation with or without catheter thrombolysis. Twelve patients were treated with CDI. Seven patients (58%) were referred for CDI after failing systemic infusion with 100 mg of tissue plasminogen activator, and five patients (42%) had contraindications to systemic thrombolysis. Catheter-directed fragmentation and embolectomy were performed in all patients (100%). Additionally, catheter-guided thrombolysis was performed in eight patients (67%). Technical success was achieved in 12 of 12 cases (100%). There were no major procedural complications (0%). Significant hemodynamic improvement (shock index <0.9) was observed in ten of 12 cases (83%). The remaining two patients (17%) died secondary to cardiac arrest within 24 h. Ten of 12 patients (83%) survived. The authors concluded that CDI is potentially a life-saving treatment for patients who have not responded to or cannot tolerate systemic thrombolysis.

Lin et al. [16] evaluated the treatment outcome in patients with massive PE who were treated with either ultrasound-accelerated thrombolysis using the EkoSonic Endovascular System (EKOS) or catheter-directed thrombolysis (CDT) intervention. Twenty-five patients underwent 33 CDIs for massive PE during the study period. Among them, the EKOS or CDT was performed in 15 (45%) and 18 (55%) procedures, respectively. In the EKOS group, complete thrombus removal was achieved in 100% cases. In the CDT cohort, complete or partial thrombus removal was accomplished in seven (50%) and two (14%) cases, respectively. Comparing treatment success based on thrombus removal, EKOS treatment resulted in an improved treatment outcome compared with the CDT group ($p < 0.02$). The mean time of thrombolysis in the EKOS and CDT groups was 17.4 ± 5.23 and 25.3 ± 7.35 h, respectively ($p = 0.03$). The mortality rate in the EKOS and CDT groups was 9.1% and 14.2%, respectively (not significant). Treatment-related hemorrhagic complication rates in the EKOS and CDT groups were 0% and 21.4%, respectively ($p = 0.02$). A significant reduction in Miller scores was noted in both groups following CDI.

Malignant Venous Obstruction Syndrome

Another percutaneous procedure that becomes more and more popular is placement of metallic stents to treat superior vena cava syndrome (SVCS). Other than emergency radiation, stenting gives rapid relief of symptoms – within a few hours or even immediately. The technique is relatively simple and can be achieved either from a brachial or transfemoral approach. If the obstruction is associated with thrombus, some authors prefer to combine stenting with thrombolysis.

Lanciego et al. [17] used stent placement as the first-choice treatment for symptom relief. Wallstent prostheses ($n = 73$ were inserted in 52 cancer patients who were diagnosed and confirmed by cavography or phlebography as having SVCS. A single stent was sufficient in 37 patients,

two were required in 11, three in two, and four in another two. Contraindications for the procedure were severe cardiopathy or coagulopathy. Symptom resolution of symptoms was achieved in all patients within 72 h. At follow-up, six obstructions, one partial migration to the right atrium, two incorrect placements, and four stent shortenings were noted. All were successfully resolved by repeated stenting. Symptom-free survival ranged from 2 days to 17 months (mean 6.4 months). The authors concluded that Wallstent vascular endoprosthesis is an effective initial treatment in SVCS of neoplastic origin.

Nagata et al. [18] retrospectively investigated the utility of metallic stent placement for treating malignant obstruction of the SVC in 71 patients with SVCS. Seventy-one patients underwent stent placement and were followed until death. The spiral Z-stent (S-Z-stent) was used primarily. Technical success rate was 100%, initial clinical success rate 87% (62/71), primary clinical patency rate 88% (57/65), and secondary clinical patency rate 95% (62/65). Stent obstruction rate was 12% (8/65) with secondary stenting. Survival of 57 patients in whom there was no recurrence of SVCS until death ranged from 1 week to 29 (mean 5.4) months, and the S-Z-stent appeared to be suitable for treating malignant obstruction of the SVC. Unilateral stent placement was effective for relief of SVCS with bilateral brachiocephalic vein (BCV) obstruction.

Benign Venous Stenoses and Occlusions

Partial venous obstruction usually does not become clinically evident as long as a collateral network is present. In patients with dialysis fistulae, however, high venous flow may result in severe venous congestion in case the ipsilateral venous outflow is obstructed. These obstructions are frequently sequelae of an earlier placement of venous dialysis catheters into the subclavian vein. Since the policy changed to a jugular access for those catheters, the rate of central venous outflow problems tends to be reduced. Treatment of benign venous stenoses is not simple, as balloon angioplasty usually fails to bear long-term improvement. Stent placement yielded excellent short-term results but was burdened by a high rate of recurrent stenoses due to massive neointimal tissue growth within the stents, which required frequent reinterventions. There is some hope that polymer-covered stent grafts are more promising in preventing recurrent stenoses, but larger studies are pending.

Haage et al. [19] analyzed the effectiveness of stent placement as the primary treatment for central venous obstruction in 50 patients undergoing hemodialysis with 57 Wallstents. Stent deployment was successful in all patients, and early rethrombosis (within 1 week) was noted in one patient (2%). Seventy-three episodes of reobstruction occurred and were treated percutaneously with angioplasty alone in 54 cases (74%). Nineteen cases (26%) necessitated additional stent placement. The 3-, 6-, 12-, and 24-month primary patency rates were 92%, 84%,

56%, and 28%, respectively. Cumulative overall stent patency was 97% after 6 and 12 months, 89% after 24 months, and 81% after 36 and 48 months.

Bakken et al. [20] compared the outcomes of primary angioplasty vs primary stenting in a dialysis access population. Stenting was used to treat 26 patients and angioplasty 47 patients, with 49 central venous stenoses. The stenting group underwent 71 percutaneous interventions per stenosis (average 2.7 ± 2.4 interventions), and the angioplasty group underwent 98 interventions per stenosis (average 2.0 ± 1.6 interventions). Primary patency was equivalent between groups by Kaplan-Meier analysis, with 30-day rates of 76% for both groups and 12-month rates of 29% for angioplasty and 21% for stenting ($p = 0.48$). Assisted primary patency was also equivalent ($p = 0.08$), with a 30-day patency rate of 81% and 12-month rate of 73% for the angioplasty group vs stenting-assisted patency rates of 84% at 30 days and 46% at 12 months. Ipsilateral hemodialysis access survival was equivalent between groups. The authors concluded that stenting does not improve on the patency rates more than angioplasty and does not add to the longevity of ipsilateral hemodialysis access sites.

Ferguson et al. [21] used stents in fibrosing mediastinitis with venous obstruction in six patients. Four were treated with intravascular stents placed percutaneously. One underwent surgical intravascular stent placement, and one declined surgical therapy. The right pulmonary artery was treated in three patients, the SVC was treated in one, and three pulmonary veins were treated in one. Each intervention resulted in hemodynamic improvement with subsequent clinical improvement. Reintervention was required within 12 months in two of four percutaneously treated patients. The authors concluded that stents are an effective option in improving short-term vascular patency. In-stent stenosis was a frequent complication rate in patients with fibrosing mediastinitis.

Riley et al. [22] investigated the treatment of SVCS as a complication of pacemaker implantation. They did a PubMed search to identify cases of symptomatic SVCS that developed following implantation of permanent pacemakers or implantable cardioverter defibrillators and were treated with one of five different modalities: anticoagulation, thrombolysis, venoplasty, stenting, and surgical reconstruction. One hundred and four eligible cases from 74 different publications were identified in which SVCS presented at a median of 48 months after device implantation. The authors found that over the last 40 years, conservative treatments have been replaced by surgical reconstruction, and most recently by stenting, as the most common therapeutic modality. Anticoagulation, thrombolysis, and venoplasty alone were all associated with high recurrence rates. Surgery and stenting were more successful: recurrence rates were 12% and 5% over a median follow-up of 16 (range 2-179) and 9.5 (range 2-60) months, respectively. There is some evidence now that expanded polytetrafluoroethylene (ePTFE)-coated stents are more effective in preventing restenosis com-

pared with angioplasty alone [23], but no evidence exists that compares bare stents vs stent grafts. Limitations in size and diameter and the problem of overriding collateral veins limit the widespread use of stent grafts in the thoracic venous circulation.

Conclusion

The great variation of vascular and nonvascular procedures in the thorax offers a huge opportunity for many more techniques – some rarely performed and relatively unimportant or related to only a few centers; some with a relevant and general importance for many patients.

References

1. Laurent F, Latrabe V, Vergier B, Michel P (2000) Percutaneous CT-guided biopsy of the lung: comparison between aspiration and automated cutting needles using a coaxial technique. *Cardiovasc Intervent Radiol* 23:266-272
2. Richardson CM, Pointon KS, Manhire AR, Macfarlane JT (2002) Percutaneous lung biopsies: a survey of UK practice based on 5444 biopsies. *Br J Radiol* 75:731-735
3. Chojniak R, Isberner RK, Viana LM et al (2006) Computed tomography guided needle biopsy: experience from 1,300 procedures. 124:10-14
4. Poretti FP, Brunner E, Vorwerk D (2002) Simple localization of peripheral pulmonary nodules – CT-guided percutaneous hook-wire localization. *Rofo Fortschr Geb Rontgenstr Neuen Bildgeb Verfahr* 174:202-207
5. de Baère T (2010) Lung tumor radiofrequency ablation: where do we stand? *Cardiovasc Intervent Radiol* [Epub ahead of print]
6. Matsumura JS, Cambria RP, Dake MD et al; TX2 Clinical Trial Investigators (2008) International controlled clinical trial of thoracic endovascular aneurysm repair with the Zenith TX2 endovascular graft: 1-year results. *J Vasc Surg* 47:247-257
7. Nienaber CA, Kische S, Akin I et al (2010) Strategies for subacute/chronic type B aortic dissection: the Investigation Of Stent Grafts in Patients with type B Aortic Dissection (INSTEAD) trial: 1-year outcome. *J Thorac Cardio Vasc Surg* 140(6 Suppl): S101-S108
8. Matsuda H, Fukuda T, Iritani O et al (2010) Spinal cord injury is not negligible after TEVAR for lower descending aorta. *Eur J Vasc Endovasc Surg* 39(2):179-186
9. Sixt S, Rastan A, Schwarzwälder U et al (2009) Results after balloon angioplasty or stenting of atherosclerotic subclavian artery obstruction. *Catheter Cardiovasc Interv* 73(3):395-403
10. van Hattum ES, de Vries JP, Lalezari F (2007) Angioplasty with or without stent placement in the brachiocephalic artery: feasible and durable? A retrospective cohort study. *J Vasc Interv Radiol* 18:1088-1093
11. AbuRahma AF, Bates MC, Stone PA et al (2007) Angioplasty and stenting versus carotid-subclavian bypass for the treatment of isolated subclavian artery disease. *J Endovasc Ther* 14:698-704
12. Kato A, Kudo S, Matsumoto K et al (2000) Bronchial artery embolization for hemoptysis due to benign diseases: immediate and long-term results. *Cardiovasc Intervent Radiol* 23:351-357
13. Lee TW, Wan S, Choy DK, et al (2000) Management of massive hemoptysis: a single institution experience. *Ann Thorac Cardiovasc Surg* 6:232-235
14. Witt Ch, Schmidt B, Geisler A et al (2000) Value of bronchial artery embolisation with platinum coils in tumorous pulmonary bleeding. *Eur J Cancer* 36:1949-1954

15. Kuo WT, van den Bosch MA, Hofmann LV et al (2008) Catheter-directed embolectomy, fragmentation, and thrombolysis for the treatment of massive pulmonary embolism after failure of systemic thrombolysis. *Chest* 134:250-254
16. Lin PH, Annambhotla S, Bechara CF et al (2009) Comparison of percutaneous ultrasound-accelerated thrombolysis versus catheter-directed thrombolysis in patients with acute massive pulmonary embolism. *Vascular* 17 (Suppl 3):S137-S147
17. Lanciego C, Chacon JL, Julian A et al (2001) Stenting as first option for endovascular treatment of malignant superior vena cava syndrome. *AJR Am J Roentgenol* 177:585-593
18. Nagata T, Makutani S, Uchida H et al (2007) Follow-up results of 71 patients undergoing metallic stent placement for the treatment of a malignant obstruction of the superior vena cava. *Cardiovasc Intervent Radiol* 30:959-967
19. Haage P, Vorwerk D, Piroth W (1999) Treatment of hemodialysis-related central venous stenosis or occlusion: results of primary Wallstent placement and follow-up in 50 patients. *Radiology* 212:175-180
20. Bakken AM, Protack CD, Saad WE et al (2007) Long-term outcomes of primary angioplasty and primary stenting of central venous stenosis in hemodialysis patients. *J Vasc Surg* 45:776-783
21. Ferguson ME, Cabalka AK, Cetta F, Hagler DJ (2010) Results of intravascular stent placement for fibrosing mediastinitis. *Congenit Heart Dis* 5:124-133
22. Riley RF, Petersen SE, Ferguson JD, Bashir Y (2010) Managing superior vena cava syndrome as a complication of pacemaker implantation: a pooled analysis of clinical practice. *Pacing Clin Electrophysiol* 33:420-425
23. Haskal ZJ, Trerotola S, Dolmatch B et al (2010) Stent graft vs balloon angioplasty for failing dialysis-access grafts. *N Engl J Med* 362:494-503

Imaging Breast Disease: Mammography and Breast Ultrasound

Edward A. Sickles¹, Rahel A. Kubik-Huch², Markus Müller-Schimpfle³

¹ Department of Radiology, University of California San Francisco (UCSF) School of Medicine, San Francisco, CA, USA

² Institute of Radiology, Department of Medical Services, Kantonsspital Baden, Baden, Switzerland

³ Institute of Radiology, Frankfurt/Main – Hoechst Hospital, Frankfurt/Main, Germany

Introduction

The most extensively used breast imaging technique is mammography, a plain-film X-ray examination. The routine use of mammographic screening for clinically occult breast cancer is widespread, primarily due to favorable results from multiple randomized controlled trials and the development of improved methods of preoperative needle biopsy and localization. A large percentage of radiologists interpret mammograms, with daily caseloads in many practices involving 50 or more examinations per day. Screening examinations comprise more than 75% of all mammography performed in most developed countries. As a result, the majority of detected lesions, both benign and malignant, are small and nonpalpable. In most general radiology practices, mammography accounts for at least 10% (sometimes as much as 20%) of all examinations performed.

In many countries, the widespread use of mammographic screening among asymptomatic women, coupled with a high level of general awareness of breast cancer as a public health problem, has prompted a series of governmental regulations affecting mammography. These regulations, although costly, also have resulted in an overall improvement in the quality of mammographic images, and due to the imposition of initial education, continuing education, and continuing experience requirements for radiologists, probably an improvement in the quality of mammographic interpretation as well.

Breast ultrasonography (US) also is widely used to aid in the diagnosis and management of either mammographically detected or palpable breast lesions. US reliably characterizes simple cysts, if rigorous interpretive criteria are utilized, thereby averting tissue diagnosis for these common, invariably benign, lesions (Fig. 1). In addition, several sonographic features are sufficiently suggestive of malignancy to prompt biopsy (often resulting in cancer diagnosis), even in the absence of suspicious findings at mammography or clinical breast examination (Fig. 2). These are major reasons why US has become an integral part of modern breast imaging practice, although it has not yet been proved to be effective for screening asymptomatic women (no randomized controlled trial data showing reduced breast cancer mortality).

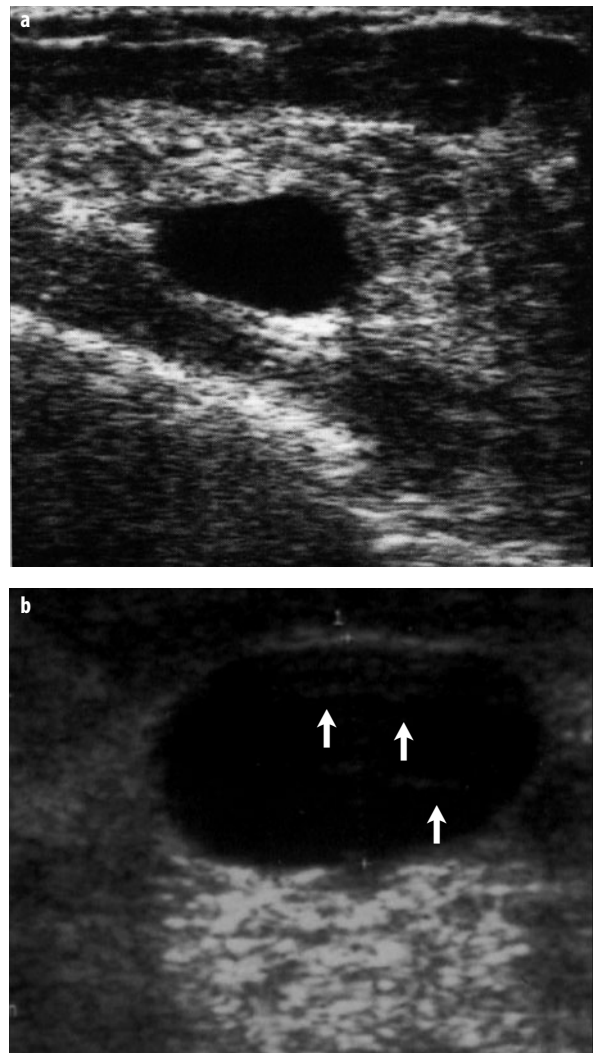


Fig. 1 a, b. Simple cysts [benign, Breast Imaging Reporting and Data System (BI-RADS) category 2 at ultrasound (US)] in two different patients. Breast US reliably characterizes simple cysts. Criteria for this diagnosis include circumscribed margins, oval (or round) shape with parallel (wider-than-tall) orientation, anechoic center, and posterior enhancement, as well as thin echogenic capsule and thin edge shadows. Note that reverberation echoes projecting within the cyst lumen (*arrows, b*) may create an appearance of complexity. Sonographic scanning from different angles and optimizing the focal zone may eliminate much of the artifact (from Hodler et al 2007)

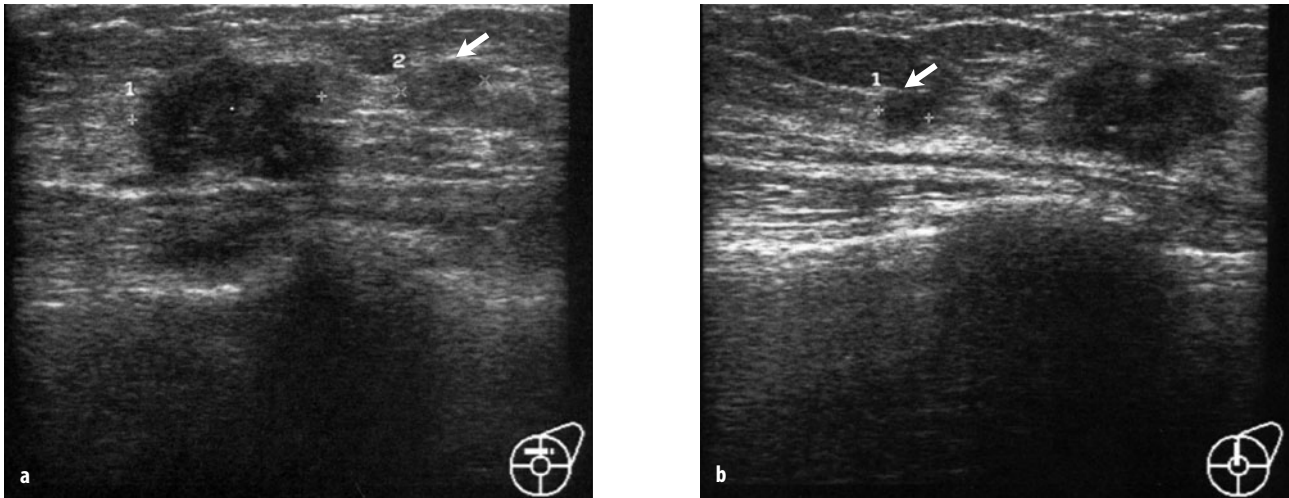


Fig. 2 a, b. Multifocal carcinoma of the left breast [highly suggestive of malignancy, BI-RADS category 4 at ultrasound (US)]. Breast US demonstrates an irregularly shaped hypoechoic mass with indistinct margins and some posterior shadowing, as well as focal hyperechoic spots probably representing calcifications. The normal tissue architecture is disrupted. A second, smaller, lesion (*arrows*) is seen superolateral to the larger mass (from Hodler et al 2007)

The radiologist utilizes an extensive range of interventional procedures to aid in the diagnosis and management of breast disease. As a first step, most screening-detected lesions (and even some palpable lesions) now undergo percutaneous tissue sampling, using either sonographic or stereotactic mammographic guidance. In some European countries, there are practice guidelines indicating that among suspicious lesions at least 70% of nonpalpable and 90% of palpable lesions should undergo percutaneous biopsy as a first-step approach to tissue diagnosis. US offers the advantages of greater patient comfort, real-time visualization of the biopsy needle entering the targeted lesion, and shorter procedure time – hence reduced operating cost. Stereotactic mammography is used for lesions not readily seen at US, including many clusters of microcalcifications and some small masses, especially masses that are surrounded by fatty tissue and located deep within large breasts. Tissue sampling usually is performed with core biopsy, with the exception that fine-needle aspiration may be an acceptable alternative (for selected cases) if there is available an on-site pathologist with considerable expertise in breast cytopathology interpretation. The potential advantage of fine-needle aspiration, given sufficient pathologist expertise, is the ability to provide on-site diagnosis with immediate reporting of results to the patient. Core biopsy, on the other hand, acquires a much larger volume of tissue, thereby reducing the frequency of obtaining insufficient material for diagnosis and incomplete sampling of the targeted lesion.

When percutaneous tissue diagnosis is both benign and concordant with pre-biopsy-imaging features, surgery is averted. The only lesions that require excision are those already found to be malignant or those for which pathologic results are inconclusive or discordant. This approach can substantially reduce the percentage of surgical biop-

sies performed for benign lesions, to 30% or even less, thereby considerably reducing morbidity and cost.

For those nonpalpable lesions that do require surgical excision, needle insertion usually is guided by mammography through a fenestrated breast-compression paddle, by stereotactic guidance, or by real-time US – all approaches permitting rapid and accurate needle placement inside or within a few millimeters of the targeted lesion. These techniques, coupled with the use of hooked wires that anchor in breast tissue at the site of needle placement, allow the surgeon to more precisely control the volume of excised tissue.

Circumscribed Noncalcified Mass

The major differential diagnostic possibilities for the circumscribed noncalcified mass seen at mammography are cyst, fibroadenoma, and circumscribed carcinoma (Fig. 3). Most circumscribed noncalcified masses are identified at screening, nonpalpable, and smaller than 1 cm. Such a mass is initially evaluated with US to reliably diagnose a simple cyst, thereby eliminating the need for any further workup. On the other hand, if the mass is solid but displays no sonographic features of malignancy, and if it continues to appear circumscribed at fine-detail mammography (using spot compression with or without magnification), then it may be assessed as being probably benign and managed with periodic mammographic surveillance. Tissue diagnosis is performed only for: (1) masses with suspicious imaging features at US or fine-detail mammography, (2) masses with suspicious features at palpation, or (3) masses seen to have enlarged when compared with a prior examination. Thus, the few circumscribed masses that prove to be malignant are diagnosed readily, but the

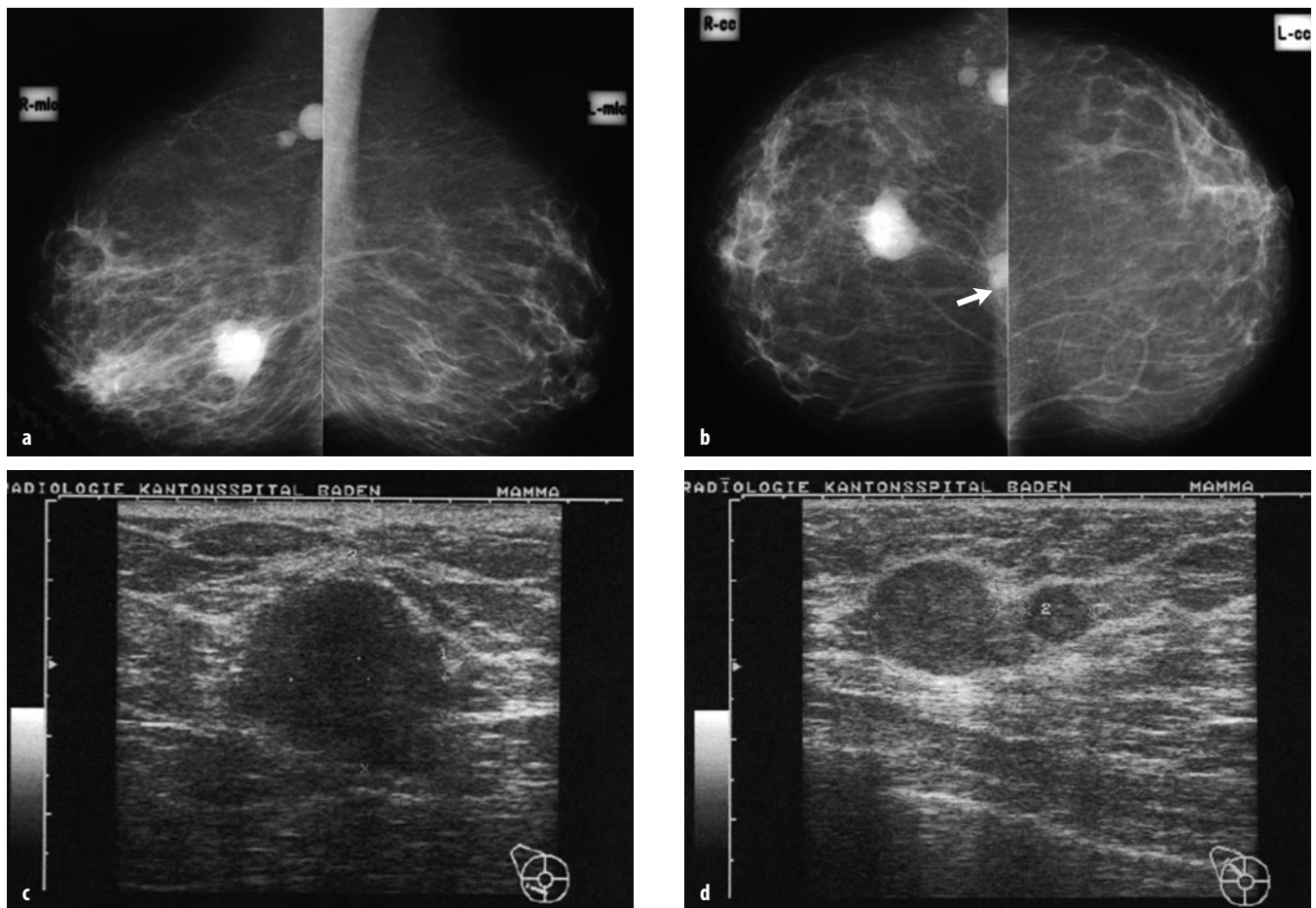


Fig. 3 a-d. A 40-year-old patient with multifocal invasive ductal carcinoma of the right breast, pT2N2M0. **a** Mammography, mediolateral oblique views; **b** mammography, craniocaudal views; **c** ultrasound (US) of the right breast; **d** US of the right axilla. Assessment: highly suggestive of malignancy (BI-RADS category 5). A large, partially circumscribed and partially irregular/indistinct mass is seen in the right breast at the 6 o'clock position. On the craniocaudal view, a second lesion is seen in the central aspect of the breast close to the chest wall (arrow). In addition, three smaller circumscribed lesions are present in the axilla, two of which represent enlarged lymph nodes. US confirms the presence of a partially circumscribed and partially irregular/indistinct hypoechoic mass, as well as axillary lesions that were subsequently confirmed to represent metastatic lymph nodes (from Hodler et al 2007)

great majority of benign masses are managed simply with mammography and US. A relatively small percentage of such masses now undergo percutaneous biopsy, and only very few benign lesions are actually excised.

Grouped Microcalcifications

Most cases of grouped microcalcifications are detected at mammographic screening, and most screening-detected cancers are treated with breast-preservation surgery. When grouped microcalcifications are detected (or even suspected) at screening, additional fine-detail imaging is usually obtained using spot-compression magnification mammography to portray with greater clarity the shapes, distribution, and extent of the calcifications (Figs. 4, 5). This permits classification of some otherwise “suspicious” cases into more benign categories, resulting in management by mammographic surveillance rather than

tissue diagnosis for truly benign lesions, thereby reducing morbidity and cost. This approach also provides additional information about the extent of disease prior to an appropriately indicated interventional procedure, which is very useful in planning exactly what type of intervention(s) to perform, especially if carcinoma is later found at biopsy. Standard practice is to sample suspicious calcifications using vacuum-assisted core biopsy.

Architectural Distortion

The mammographic feature of architectural distortion most often involves thin, radiopaque lines (spiculation) radiating from a central point, with no definite mass visible at the center of the lesion. Another less common manifestation of architectural distortion is focal retraction or distortion of the edge of the parenchyma at one of its interfaces with either the subcutaneous fat or

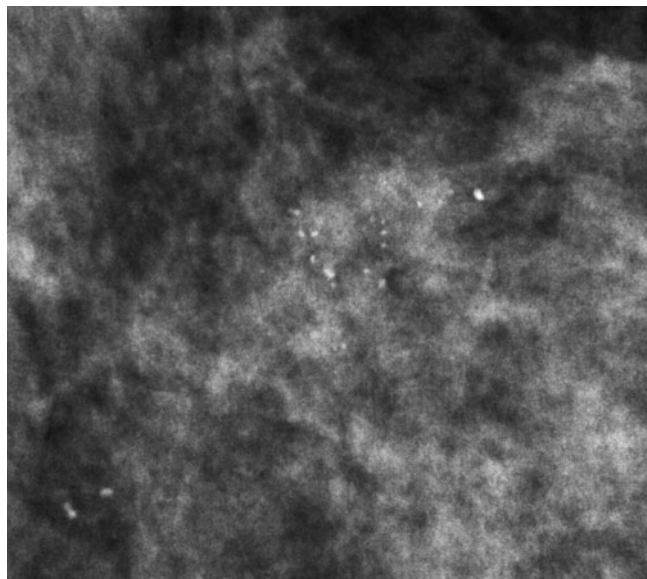


Fig. 4. Spot-compression magnification mammogram of the right breast. A group of microcalcifications is seen within dense breast tissue. Additional scattered calcifications are seen distributed throughout much of the right breast parenchyma. The calcifications are round and punctate, some larger and others smaller than 0.5 mm. Assessment: probably benign, BI-RADS category 3. The patient declined periodic mammographic surveillance, and stereotactic core biopsy was performed, with histology confirming the suspected diagnosis of sclerosing adenosis (from Hodler et al 2007)

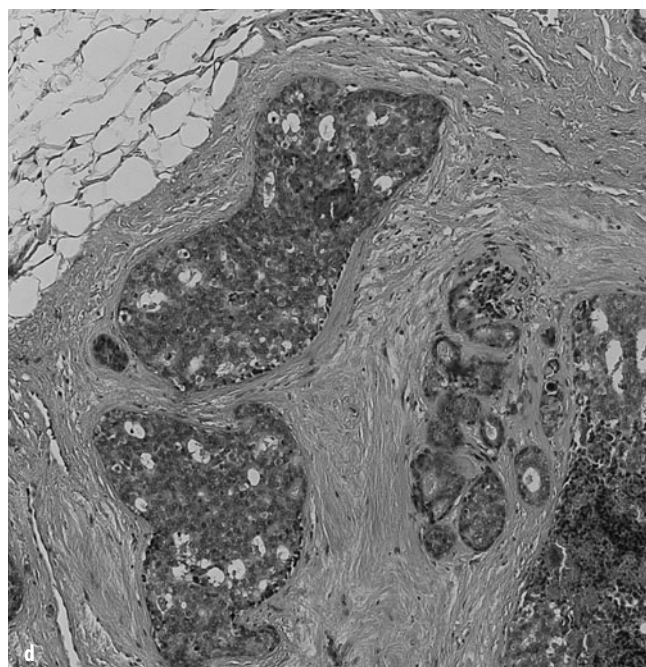
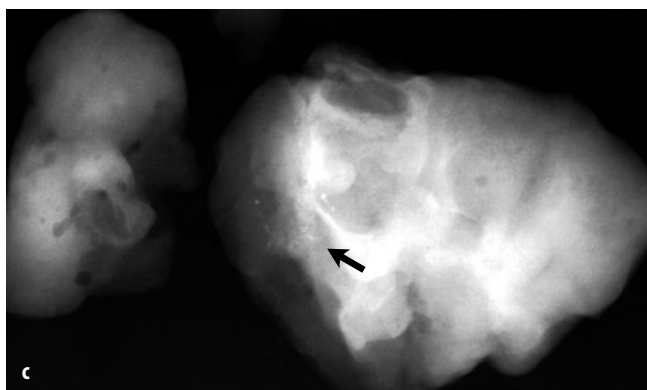
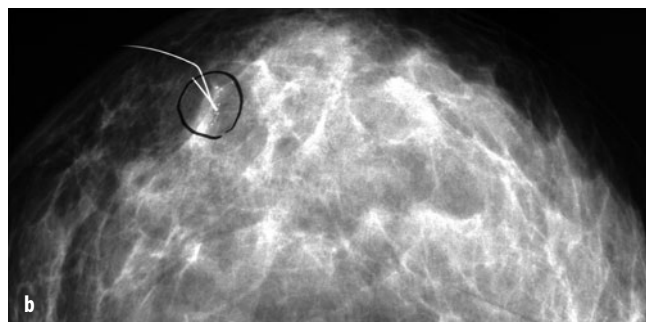


Fig. 5 a-d. First screening mammography study in a 52-year-old asymptomatic woman. **a** Spot-compression magnification view of the right breast. **b** Grouped fine-linear and branching (casting) microcalcifications are seen, highly suggestive of malignancy (BI-RADS category 5). Preoperatively, mammographically guided hook-wire localization was performed. **c** Complete excision of the lesion (arrow) was confirmed by a specimen radiograph. **d** Histology showed ductal carcinoma in situ (from Hodler et al 2007) (for color reproduction see p 273)

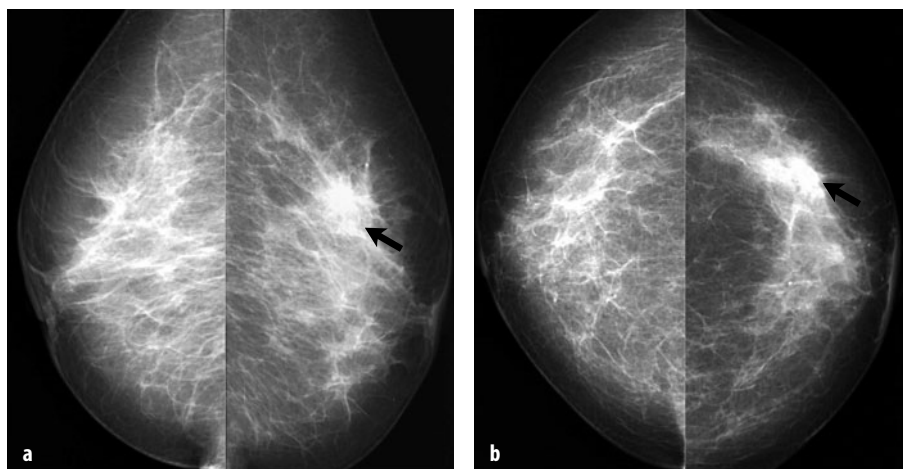
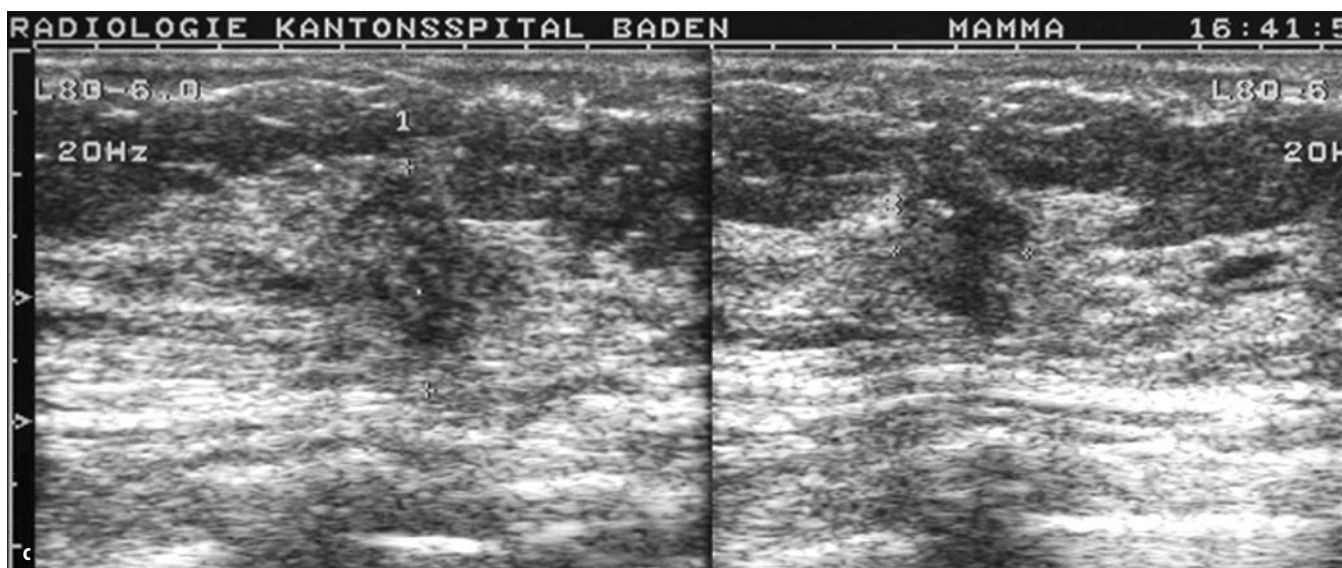


Fig. 6 a-c. A 65-year-old asymptomatic woman referred for screening mammography. Mammography, mediolateral oblique views (**a**), mammography, craniocaudal views (**b**), ultrasound (US) of the left breast (**c**). Mammography shows a focal asymmetry as well as architectural distortion in the upper outer quadrant of the left breast (*arrows*) (alternatively, some might describe the lesion as a spiculated mass because the lesion appears to be dense in its center). Superolateral and deep to the lesion a group of microcalcifications is seen. An irregular/indistinct hypoechoic lesion, nonparallel (taller-than-wide) in orientation, was confirmed at US (highly suggestive of malignancy, BI-RADS category 5). Histology showed invasive ductal carcinoma, pT2N0 (from Hodler et al 2007)



retromammary fat/fascia. In the absence of appropriate history of trauma or surgery, architectural distortion is suspicious for malignancy or radial scar, and biopsy is appropriate (Fig. 6). In a retrospective study of 300 consecutive nonpalpable breast cancers, 9% were identified as architectural distortion (Sickles 1986). The likelihood of malignancy among findings characterized as architectural distortion is estimated to range from 10% to 35%, depending on case selection, patient age, and other factors.

Asymmetry

There are four types of symmetry, all of which represent areas of fibroglandular-density tissue that is more extensive in one breast than the other. Asymmetry is usually distinguished from mass in that it demonstrates concave-outward rather than the convex-outward contours typical of a mass and is interspersed with fat rather than appearing denser in the center than at the periphery (typical of a mass).

Summation Artifact

Summation artifact is caused by superimposition of normal fibroglandular breast structures on a given mammographic projection. As such, this finding will be visible on only one of the two standard views and will not be seen on additional views taken in different projections. One must distinguish summation artifact from the other types of asymmetry described below because it never represents breast cancer and should not be subjected to biopsy.

Asymmetry

A one-view-only mammographic finding is called an asymmetry (*Verdichtung*) prior to diagnostic imaging evaluation. Most (>75%) asymmetries represent summation artifacts; the rest are found to be other types of asymmetry or masses.

Global Asymmetry

Global asymmetry (formerly called asymmetric breast tissue) represents a greater volume of fibroglandular tissue in one breast than in the corresponding location in the opposite breast, without an associated mass, microcalcifications, or architectural distortion. It is found in approximately 3% of screening mammography examinations. It almost always represents a normal variant, but occasionally it may indicate the presence of an underlying breast cancer if it corresponds to a palpable abnormality. In this latter clinical setting, the radiologist usually will recall the patient for additional imaging evaluation.

Focal Asymmetry

Focal asymmetry (formerly called focal asymmetric density) is an asymmetry of fibroglandular-density tissue seen on two different mammographic projections but lacking the convex-outward contours and conspicuity of a mass. It usually represents an island of normal dense breast tissue, but its lack of specific benign characteristics may warrant further evaluation, especially if it is not interspersed with fat. In a retrospective study of 300 consecutive nonpalpable breast cancers, 3% were identified as focal asymmetries (Sickles 1986). The likelihood of malignancy among findings characterized as focal asymmetry (without associated mass, calcifications, architectural distortion, sonographic abnormality, or palpable correlate) is less than 1%.

Developing Asymmetry

Developing asymmetry (formerly called developing density or neodensity) is a focal asymmetry that is either new or is larger or denser on current examination than previously. To identify such a lesion, one must have prior mammograms available for comparison. In a retrospective study of 300 consecutive nonpalpable breast cancers, 6% were identified as developing asymmetries (Sickles 1986). The likelihood of malignancy among findings characterized as developing asymmetry is approximately 15% (Leung 2007).

Typical Breast Cancer – Mass

The great majority of cancers presenting as masses are nonpalpable and detected at mammographic screening, often smaller than 1 cm in greatest dimension, and only rarely with signs of locally advanced disease. At the University of California – San Francisco (UCSF), 85% of the invasive cancers detected at screening have negative axillary lymph nodes, and 71% of invasive cancers are stage 1 lesions. Most malignant masses found at screening have indistinct rather than spiculated margins. Presumably this is due to earlier detection, before sufficient desmoplastic reaction has formed to be visible as spiculation on standard screening images.

Typical Breast Cancer – Calcifications

Due to the fairly widespread use of mammographic screening, a substantial percentage of cancer presents with calcifications alone. These lesions generally are nonpalpable, many are 1 cm or smaller, and the great majority are stage 0 lesions [ductal carcinoma in situ (DCIS)]. At UCSF, each year for the past 15 years, DCIS has accounted for between 25% and 30% of all cancers detected at mammographic screening. These highly curable malignancies now are treated with breast-preservation therapy as long as they do not occupy a large volume of the breast in relation to overall breast size to the extent that complete tumor excision would compromise cosmesis.

Breast Implants

Implant imaging with film-screen mammography does not include in the image field the most posterior portions of a breast implant, but the development of implant-displaced views has greatly improved visualization of the native breast tissues anterior to the implant. This occasionally permits detection of a nonpalpable breast cancer that otherwise would not have been visible. Breast magnetic resonance imaging (MRI) also adds to the capabilities of modern mammography by readily demonstrating extracapsular posterior-surface rupture and intracapsular rupture of a silicone-filled implant.

Reporting Breast Imaging Findings

Effective reporting of breast imaging findings requires the use of a logical structure, consistent terminology, and a straightforward assessment and associated management recommendations, all packaged in a clear and concise document. To achieve these goals, the American College of Radiology developed the Breast Imaging Reporting and Data System (BI-RADS) in the early 1990s. BI-RADS is now widely used throughout North and South America, and also is being used more extensively in European as well as other countries, having been translated into eight languages other than English. A major advantage of BI-RADS is that it utilizes standardized terminology for imaging features, associated with specific evidence-based clinical assessment categories and management recommendations (Table 1). The most recent update of BI-RADS (4th edition, 2003) includes not only mammography but also breast US and MRI. The next (5th) edition of BI-RADS is scheduled to be released in spring 2011. When a patient has more than one breast examination on the same day, a single report should be produced, describing the imaging findings of the component examinations and an integrated assessment that takes into account all findings and makes a single set of management recommendations.

Table 1. Breast Imaging Reporting and Data System (BI-RADS) assessment categories and management recommendations

Assessment	Category	Comments	Management recommendations
Incomplete	0	Use primarily for screening examinations	Additional imaging assessment (usually diagnostic mammography and ultrasound)
Negative	1	No findings described in report	Routine mammographic screening
Benign	2	Specific benign finding(s) described in report	Routine mammographic screening
Probably benign	3	Likelihood of malignancy <2%	Short-interval follow-up (usually 6 months)
Suspicious	4	Likelihood of malignancy 2-<95%	Tissue diagnosis (usually percutaneous biopsy)
Highly suggestive of malignancy	5	Likelihood of malignancy ≥95%	Appropriate action (usually biopsy)
Known biopsy-proven cancer	6	Already biopsied cancer, prior to surgical excision	Appropriate action (usually surgical excision)

Suggested Reading

- Azavedo E, Svane G, Auer G (1989) Stereotactic fine-needle biopsy in 2594 mammographically detected nonpalpable lesions. *Lancet* 1:1033-1036
- Bick U, Fischer U, Kuhl CK et al (2008) Interventionelle Techniken. In: Albert U-S (ed) *Stufe-3-Leitlinie Brustkrebs-Früherkennung in Deutschland. 1. Aktualisierung*. W. Zuckschwerdt Verlag München, Wien, New York, NY, pp 140-145
- D'Orsi CJ, Mendelson EB, Ikeda DM et al (2003) *Breast Imaging Reporting and Data System (BI-RADS)*. 4th ed. American College of Radiology, Reston, VA
- D'Orsi CJ, Sickles EA, Mendelson EB et al (2011) *Breast Imaging Reporting and Data System (BI-RADS)*. 5th ed. American College of Radiology (in press)
- Hodler J, von Schulthess GK, Zollikofer Ch.L (eds) (2007) *Diseases of the heart, chest & breast. Diagnostic imaging and interventional techniques*. 39th International Diagnostic Course in Davos (IDKD). Springer-Verlag Italia, Milan
- Jackson VP (1995) The current role of ultrasonography in breast imaging. *Radiol Clin North Am* 33:1161-1170
- Kopans DB (1989) Preoperative imaging-guided needle placement and localization of clinically occult breast lesions. *AJR Am J Roentgenol* 152:1-9
- Leung JWT, Sickles EA (2007) Developing asymmetry identified on mammography: correlation with imaging outcome and pathologic findings. *AJR Am J Roentgenol* 188:667-675
- Leung JWT, Sickles EA (2007) The probably benign assessment. *Radiol Clin North Am* 45:773-789
- Liberman L, Feng TL, Dershaw DD et al (1998) US-guided core breast biopsy: use and cost effectiveness. *Radiology* 208:717-723
- Müller-Schimpfle M (2008) Consensus meeting of course experts in breast diagnosis 5 May 2007 in Frankfurt am Main – Topic: microcalcinos. *Rofo/Fortschr Röntgenstr* 180:66-68
- Müller-Schimpfle MP, Heindel W, Kettritz U et al (2010) Consensus Meeting of Course Directors in Breast Imaging, 9 May 2009, in Frankfurt am Main – Topic: Masses. *Rofo/ Fortschr Röntgenstr* 182:671-675
- Parker SH, Burbank F, Jackman RJ et al (1994) Percutaneous large-core breast biopsy: a multi-institutional study. *Radiology* 193:359-364
- Sickles EA (1980) Further experience with microfocal spot magnification mammography in the assessment of clustered microcalcifications. *Radiology* 137:9-14
- Sickles EA (1986) Mammographic features of 300 consecutive nonpalpable breast cancers. *AJR Am J Roentgenol* 146:661-663
- Sickles EA (1998) Findings at mammographic screening on only one standard projection: outcomes analysis. *Radiology* 208:471-475
- Sickles EA (2007) The spectrum of breast asymmetries: imaging features, work-up, management. *Radiol Clin North Am* 45:765-771
- Stavros AT, Thickman D, Rapp CL et al (1995) Solid breast nodules: use of sonography to distinguish between benign and malignant lesions. *Radiology* 196:123-134
- Steinbach BG, Hardt NS, Abbitt PL et al (1993) Breast implants, common complications, and concurrent breast disease. *Radiographics* 13:93-97
- Suleiman OH, Spelic DC, McCrohan JL et al (1999) Mammography in the 1990s: the United States and Canada. *Radiology* 210:345-351

NUCLEAR MEDICINE SATELLITE COURSE
“DIAMOND”





Lymphoma: Differential Diagnosis of Mediastinal Masses and Response

Dominique Delbeke

Department of Radiology and Radiological Sciences, Vanderbilt University Medical Center, Nashville, TN, USA

Introduction

Recommendations for the clinical use of [^{18}F]-fluorodeoxyglucose positron emission tomography/computed tomography ([^{18}F]-FDG PET/CT) imaging have become available [1] and the imaging technique has been incorporated into the management algorithms recommended by the National Comprehensive Cancer Center Network (NCCN) [2]. Procedures and practice guidelines have been published by the Society of Nuclear Medicine (SNM) and the American College of Radiology (ACR) [3–5]. Recommendations in National Cancer Institute (NCI) clinical trials are also available [6]. For patients with lymphoma, consensus recommendations for assessing response have been published by the imaging subcommittee of the International Harmonization Project, including criteria for interpretation [7]. Response criteria for lymphoma have been revised based on PET/CT imaging, eliminating the “complete remission unconfirmed (CRu)” category [8].

Degree of [^{18}F]-FDG Avidity of Different Types of Lymphoma

Lymphomas are classified into two main groups: non-Hodgkin's (NHL) and Hodgkin's (HL). NHL is more common than HL and represents approximately 85% of lymphomas.

Hodgkin's Lymphoma

The World Health Organization (WHO) classifies HL as classical, with four subtypes (nodular sclerosis, mixed cellularity, lymphocyte-rich, lymphocyte-depleted). HL is virtually always intensively [^{18}F]-FDG avid [9].

Non-Hodgkin's Lymphoma

According to the WHO [10, 11], NHL is classified histologically into more than 30 subtypes of (1) B-cell neoplasms and (2) T-cell/natural killer (NK)-cell neoplasms. NHL can also be divided into two prognostic

groups: indolent and aggressive lymphomas [12]. Indolent types have a relatively good prognosis, with median survival as long as 10 years, but they usually are not curable in advanced clinical stages. Follicular lymphoma (FL) is the most common indolent type, representing 22%. Marginal-zone B-cell lymphoma and chronic lymphocytic lymphoma/small-lymphocytic lymphoma (CLL/SLL) are other types of indolent lymphoma, representing 6% and 8%, respectively. Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive lymphoma, representing 30%; other relatively common aggressive lymphomas include mantle cell lymphoma (MCL) and adult T-cell leukaemia/lymphoma, representing 6% and 8%, respectively.

Although there is a standard uptake value (SUV) overlap between aggressive and indolent NHL, on average, SUV in aggressive NHL and HL are higher than those obtained for indolent lymphomas [13]. Despite the overlap, all indolent lymphomas had an SUV <13 and all aggressive lymphomas had an SUV >13. An SUV >10 excluded indolent lymphoma with a specificity of 81%.

Two studies of 172 and 255 patients, respectively, evaluated [^{18}F]-FDG PET sensitivity for HL and NHL detection according to histology. Most aggressive NHL were intensively [^{18}F]-FDG avid [14, 15]. The sensitivity ranges were: HL, DLBCL and MCL 98–100%, FL 91–98%, marginal-zone lymphoma 67–82%, peripheral T-cell lymphoma 40% and CLL/SLL 50%. Other studies reported a more variable degree of avidity in MCL [16] and T-cell lymphoma [17]. [^{18}F]-FDG-PET is usually positive, with higher SUVs seen in NK T-cell lymphomas compared with peripheral T-cell lymphomas. CLL/SLL and extranodal marginal-zone B-cell lymphomas are low grade and often poorly [^{18}F]-FDG avid, unless they undergo transformation to a more aggressive subtype (Richter transformation) [18, 19]. In addition, [^{18}F]-FDG-PET can guide biopsy to the sites of high-grade transformation. FDG-PET sensitivity is reportedly higher in nodal marginal-zone lymphoma compared with extranodal marginal B-cell lymphoma, probably due to the differences in disease behaviour between these two entities [20, 21].

[¹⁸F]-FDG PET and PET/CT for Diagnosing Lymphoma

In patients presenting with lymphadenopathies or mediastinal masses, the differential diagnosis includes lymphoma or other malignancies, such as thymoma, pheochromocytoma and germ-cell tumors and inflammatory/infectious etiologies such as tuberculosis, sarcoidosis, histoplasmosis and coccidiomycoses. Both malignant and inflammatory etiologies (especially granulomatous) can be [¹⁸F]-FDG-positive, as [¹⁸F]-FDG is a marker of glucose metabolism.

However, in patients with suspected lymphoma, [¹⁸F]-FDG PET may be indicated in certain clinical settings and be helpful in finding the most appropriate biopsy site. Uptake can be heterogenous in the same patient, presumably representing different clones of lymphomatous cells with different glucose metabolism and different biologic behaviour. [¹⁸F]-FDG PET can guide biopsy to the site of maximum uptake, representing the most aggressive portion of the tumor.

[¹⁸F]-FDG PET and PET/CT for Staging of Lymphoma

Ann Arbor Staging

Ann Arbor staging is the universally accepted staging system for lymphomas [10]. This system is based on the distribution and number of involved sites, as well as the presence or absence of extranodal involvement and constitutional symptoms. Stages I, II, III and IV adult lymphomas can be subclassified into A and B categories: B for those with defined general symptoms, and A for those without B symptoms. Designation E is used when there is localised extranodal lymphoma near the major lymphatic aggregates. Lymphomas originate from extralymphatic organs in up to 30% of patients.

Stage I and II (lymph-node involvement only on one side of the diaphragm) have a high cure rate, whereas stages III (lymph node involvement on both sides of the diaphragm) and IV (systemic involvement) have a lower cure rate. For NHL and HL, the frequency of involvement of the spleen is ~22%, liver 15% and 3%, respectively, and bone marrow 25% and 10%, respectively.

Prognostic Factors

Prognostic factors for NHL include age, performance status, tumor size and stage, lactate dehydrogenase (LDH), B-symptoms and number of extranodal sites. To identify subgroups of patients most likely to relapse, the International Prognostic Index (IPI) has been developed for patients with aggressive NHL [22] and with follicular lymphoma (FLIPI) [23]. The International Prognostic Score (IPS) is used to predict prognosis in advanced HL, which includes albumin level, haemoglobin level, sex, age, stage, white-cell count and absolute lymphocytic count [24].

Prognostic Value of [¹⁸F]-FDG PET

A high degree of [¹⁸F]-FDG uptake pretherapy indicates a worse prognosis. In a study of 34 patients with untreated lymphoma and a follow-up of 15-50 months after starting therapy, patients with recurrence had higher SUV pretherapy than patients in remission. The SUV was 6.4 ± 3.0 [mean $\pm$ standard deviation (SD)] in patients in complete remission and no recurrence, the SUV was 7.0 ± 2.9 (mean $\pm$ SD) in patients who went in complete remission, then recurred, and the SUV was 14.4 ± 5.5 (mean $\pm$ SD) in patients with no remission. Survival was longer for patients with SUV <8.0 [25].

[¹⁸F]-FDG PET and PET/CT for Detecting Nodal and Extranodal Lymphoma

[¹⁸F]-FDG is the metabolic tracer of choice for lymphoma imaging. It is highly sensitive and superior to CT in detecting nodal and extranodal involvement in most histologic lymphoma subtypes [26, 27]. A study of 52 patients compared [¹⁸F]-FDG PET to CT using the receiver-operator curve (ROC) analysis [28]. PET was superior to CT for detecting both nodal and extranodal involvement on both sides of the diaphragm. For detecting bone marrow involvement, PET was equivalent to bone marrow biopsy, and both were superior to CT. PET changed stage and management in 8% of patients. In a meta-analysis of 14 of 20 selected studies with 854 patients with lymphoma, the median sensitivity for lymphoma detection was 90%, median specificity 90% and the pooled false-positive rate 10%. The maximum joint sensitivity and specificity was 88% [29]. Many studies have shown the superiority of PET compared with CT for detecting extranodal involvement because organomegaly is not always associated with disease involvement. [¹⁸F]-FDG-PET has been shown to be more sensitive than CT, identifying 23% more hepatic and splenic lesions [29-31].

[¹⁸F]-FDG PET and PET/CT for Detecting Bone Marrow Involvement by Lymphoma

For detecting bone marrow involvement, [¹⁸F]-FDG PET is more accurate than CT. Bone marrow biopsy suffers from sampling error, and [¹⁸F]-FDG PET can guide the biopsy to [¹⁸F]-FDG-avid lesions. A prospective evaluation of 78 untreated patients (39 HD, 39 NHL) compared PET and bilateral posterior iliac-crest biopsy. PET and biopsy were concordant in 64 patients, biopsy was positive and PET negative in four and biopsy was negative and PET positive in ten. A repeat PET-guided biopsy was positive in eight of these ten patients. The false-negative PET was in patients with low-grade lymphomas. PET changed staging in 10% (8/78) of these patients [32, 33]. A meta-analysis of 13 studies with 587 patients comparing

[¹⁸F]-FDG PET to bone marrow biopsy demonstrated an overall sensitivity of 51% and specificity of 91% [34]. In that study, six of 12 patients with positive [¹⁸F]-FDG PET and negative bone marrow biopsy had a positive repeat PET-guided biopsy. Analysis of patient subgroups demonstrated that [¹⁸F]-FDG PET was more sensitive for HL and aggressive lymphomas. [¹⁸F]-FDG PET is complementary to but cannot replace bone marrow biopsy because of its false-negative rate, especially in low-grade lymphoma.

[¹⁸F]-FDG PET criteria for diffuse spleen or bone marrow uptake is more intense than in normal liver parenchyma, which has an average SUV of ~2.0 [7]. The diffuse uptake pattern of reactive bone marrow hyperplasia after chemotherapy, and especially after concurrent administration of bone marrow stimulants, can mimic or mask diffuse bone marrow involvement. Therefore, appropriate history is critical. A delay of 3-4 weeks after completion of therapy permits the physiologic marrow activity to abate [7].

[¹⁸F]-FDG PET versus [¹⁸F]-PET/CT and CT Protocol for [¹⁸F]-FDG PET/CT

PET/CT is commonly performed without intravenously administered contrast material and a low-dose (40-80 mAs) CT component to reduce radiation dose. When the protocol for the CT component is not specified, the low-dose CT without intravenously administered contrast material is usually applied. However, the CT component can be performed using a diagnostic CT protocol with orally and intravenously administered contrast agent. Some studies concluded that PET/low-dose CT may be adequate for most patients and that contrast-enhanced CT may be recommended for selected cases [35-37]. The imaging subcommittee of the International Harmonization Project recommends the use of [¹⁸F]-FDG PET in addition to or integrated with contrast-enhanced CT for initial staging [7]. After therapy, PET should be complemented with CT using a low-dose CT protocol if there is no liver/spleen involvement at baseline and contrast-enhanced CT if there is liver/spleen involvement at baseline.

Impact of [¹⁸F]-FDG PET/CT on Managing Patients with Lymphoma

The change from stage I/II to III/IV has major therapeutic implications. A change of stage and management has been reported in various studies summarised in a review article [38]. Although a up-staging following [¹⁸F]-FDG PET imaging has been reported in 20-40% of patients, major management change occurs only in 10-35%. Besides staging, pretreatment PET is indicated to assess [¹⁸F]-FDG tumor avidity, especially in lymphoma subtypes with variable uptake patterns.

[¹⁸F]-FDG PET and PET/CT for Monitoring Lymphoma Therapy

An important indication of PET/CT is monitoring NHL and HL treatment response by following [¹⁸F]-FDG tumor uptake.

Differentiation of Viable Tumor from Residual Masses

Since the late 1990s, the value of [¹⁸F]-FDG-PET in differentiating viable tumor from residual masses on CT after first-line treatment is well known [39-41]. Subsequently, it could be shown that adding the results of [¹⁸F]-FDG-PET to currently used International Workshop Criteria (IWC) significantly improved response assessment [42, 43]. In particular, [¹⁸F]-FDG-PET was able to identify a significant number of patients considered as having achieved CRu or partial remission (PR) by IWC criteria who showed no [¹⁸F]-FDG uptake and whose progression-free survival (PFS) was comparable with patients considered in CR. Consequently, it was proposed to revise the response criteria for lymphoma by integrating IWC, mostly based on CT evaluation, using Response Evaluation Criteria in Solid Tumours (RECIST) assessment adapted to lymphoma and [¹⁸F]-FDG-PET, including immunohistochemistry (IHC) and flow cytometry [8]. According to these revised response criteria, CR is defined by negative PET of [¹⁸F]-FDG avid or pretreatment PET-positive lymphomas, the absence of palpable spleen and lymph nodes and a cleared bone marrow on repeat biopsy, confirmed by IHC if indeterminate by morphology. DLBCL, HL, FL and MCL are usually [¹⁸F]-FDG avid; other aggressive and indolent NHL have variable [¹⁸F]-FDG uptake and need to be scanned before treatment. In case of unknown or absent [¹⁸F]-FDG uptake on the pretreatment scan of such patients, all masses have to show complete regression on CT. This definition shows that [¹⁸F]-FDG-PET is the leading criterion for assessing CR in the great majority of malignant lymphomas. These response criteria were originally developed for clinical trials but are used more and more frequently for clinical patient management.

Prognostic Impact of [¹⁸F]-FDG PET

Early assessment of response to treatment has been found to have major prognostic impact [44, 45]. Most early studies had a retrospective design and were performed with PET and not PET/CT but concordantly demonstrated high accuracy in predicting outcome, both for HL and NHL. In an overview of studies evaluating response after one cycle, several cycles and midtreatment of lymphoma (mostly NHL), an overall sensitivity for predicting treatment failure of 79% with corresponding specificity of 92% (accuracy 85%) and positive and negative predictive values (PPV and NPV) of 90% and 81%, respectively, was reported [46]. Another systematic review [47] comes to somewhat less clear-cut

conclusions for response evaluated by [^{18}F]-FDG PET at completion of therapy. The authors found reported ranges for sensitivity of 50-100% and 33-77% for HL and NHL, respectively, with corresponding specificities of 67-100% and 82-100% for predicting outcome. Most chemotherapy regimen produce only a one log tumour mass reduction per cycle (90%), and effective treatment may require up to ten cycles. Two cycles, on average, reduce the cell number to 10^8 - 10^9 cells, corresponding to 0.3- to 1-cm-diameter nodes and therefore to the limit of detection of lymphoma containing nodes with PET. Accordingly, lesions with persistent [^{18}F]-FDG uptake after two cycles of chemotherapy are unlikely to be cured by six additional cycles, whereas lesions that no longer show uptake are likely to be cured during subsequent chemotherapy. This explains the superiority of early [^{18}F]-FDG PET versus end-treatment evaluation for assessment of outcome [48].

It must be recognised, however, that evidence of therapy changes based on the results of interim PET/CT, either in the sense of early introduction of intensification regimens or of reducing the prospected treatment, is still lacking.

Pitfalls in Interpreting [^{18}F]-FDG PET/CT in Patients with Lymphoma

False positive results may hamper the role of early PET. There are physiological and pathological as well as technical and methodological reasons for false positive studies. The presence of mass lesions by itself may contribute to some visible [^{18}F]-FDG uptake on PET. Besides the well-known reasons for [^{18}F]-FDG-uptake in nontumor tissue, such as brown adipose tissue, inflammatory lesions, granulomatous disease (particularly sarcoidosis), thymus, fractures, normal bowel and urinary tract, degenerative joints, normal bone marrow, muscles, contaminations, etc., which are most often easily recognised, especially with PET/CT [49], particular situations can occur in patients treated for lymphoma.

Physiological uptake in response to therapy can occasionally confuse interpretation. Reactive diffuse bone marrow hyperplasia and splenic uptake occur typically for 2-4 weeks after chemotherapy and can be intense after administration of marrow-stimulating factors, such as filgrastim [50, 51].

Thymic hyperplasia is common in children and young adults, with an incidence of 16% [52]. It typically occurs 2-6 months after completion of therapy and may persist for 12-24 months. The pattern of moderate [^{18}F]-FDG uptake and the inverted V shape are typical for thymic hyperplasia.

Under chemotherapy treatment, patients may quite frequently develop pulmonary infiltrates of an inflammatory, toxic or infectious nature that is usually not suspicious of lymphoma except in case of pulmonary involvement at diagnosis. In patients treated with radioimmunotherapy, due

to the prolonged action of this type of therapy, response evaluation is usually performed not earlier than 3 months after administration of the radiolabeled antibody [53-55].

[^{18}F]-FDG PET in Evaluating Stem Cell Transplantation

Several studies have addressed the question of the role of [^{18}F]-FDG PET in association with autologous stem cell transplant (ASCT) in lymphoma [56, 57]. Sixty consecutive lymphoma patients who underwent consolidation by ASCT after having achieved remission (31 CR, 23 PR) were studied [58]. In patients with negative [^{18}F]-FDG PET before ASCT, the estimated 1-year event-free survival (EFS) was 80% compared with 43% in patients who did not achieve [^{18}F]-FDG negativity before ASCT. In patients who remained [^{18}F]-FDG positive on post-ASCT PET, 1-year EFS was 25% only. Multivariate analysis indicated that, independent of the histological lymphoma subtype and ASCT timing, the most important adverse prognostic factor was persistence of [^{18}F]-FDG uptake on post-ASCT PET.

Guidelines and Recommendations for Using [^{18}F]-FDG PET and PET/CT in Lymphoma

The NCCN has incorporated [^{18}F]-FDG PET in the evaluation and management algorithm of most HL and NHL [11]. The use of [^{18}F]-FDG PET (PET/CT where available) is recommended in the following clinical scenarios: (1) baseline for lymphoma that is potentially curative (HD, DLBCL); (2) baseline to exclude systemic disease in clinically localised lymphoma (HD, DLBCL, FL, MCL, AIDS-related B-cell, nodal and splenic marginal zone, peripheral T-cell, marginal B-cell lymphoma); (3) to evaluate residual masses; (4) to monitor therapy of aggressive lymphoma (HD, DLBCL). [^{18}F]-FDG PET is not indicated for: (1) monitoring therapy if CT is normal; (2) surveillance.

Consensus recommendations regarding the use of [^{18}F]-FDG PET for response assessment has been published by the imaging subcommittee of the International Harmonization Project [7]:

1. Pretherapy [^{18}F]-FDG PET imaging is strongly encouraged but not mandatory for aggressive lymphoma (HL, DLBCL, MCL, FL) because they are routinely [^{18}F]-FDG avid. However, pretherapy [^{18}F]-FDG PET imaging is mandatory for lymphomas that are not typically [^{18}F]-FDG avid if response to treatment will also be evaluated with [^{18}F]-FDG PET.
2. [^{18}F]-FDG PET timing is critical to avoid equivocal interpretations and should be performed at least 3 weeks and preferably 6-8 weeks after chemotherapy completion and 8-12 weeks after radiation therapy. For evaluation during therapy, [^{18}F]-FDG PET imaging should be performed as close as possible before the subsequent cycle of therapy.

3. Visual assessment alone is adequate for interpreting PET findings as positive or negative. Mediastinal blood pool activity is used as a reference for assessment of residual masses greater than 2 cm.
4. Specific criteria for defining PET positivity in liver, spleen, lung and bone marrow are described in the consensus recommendations.

Treatment monitoring during the course of therapy should only be done in the setting of clinical trials, in which Cheson et al. [8] recommend using [^{18}F]-FDG-PET for potentially curable reliably FDG-avid lymphomas (HL and DLBCL), including a pretherapy and response-assessment PET. However, for routinely [^{18}F]-FDG-avid aggressive and indolent lymphomas that are incurable and for variably [^{18}F]-FDG-avid lymphomas, a pretherapy [^{18}F]-FDG PET is recommended only if overall response rate (ORR) and CR are end points. If the pretherapy PET is positive, PET is recommended to assess treatment response. At midtreatment, [^{18}F]-FDG PET is recommended only in clinical trials.

The SNM procedure guidelines [4] and ACR practice guidelines [5] for tumor imaging using [^{18}F]-FDG PET/CT address evaluation of malignancies in general. These procedure/practice guidelines include recommendations regarding patient preparation, PET and CT protocols, PET/CT reporting, and training of personnel who perform and interpret PET/CT. Regarding monitoring therapy response, the procedure guidelines recommend comparing uptake extent and intensity between pre- and posttherapy images. A change of uptake intensity with semiquantitative measurements, expressed in absolute values and percent change, may be appropriate in some clinical scenarios. However, the technical protocol and image analysis need to be consistent in the two sets of images.

References

1. Podaloff DA, Advani RH, Allred C et al (2007) NCCN Task Force Report: positron emission tomography (PET)/computed tomography (CT) scanning in cancer. *J Natl Compr Canc Netw* 5(Suppl 1):S1-S22
2. Fletcher JW, Djulbegovic B, Soares HP et al (2008) Recommendations for the Use of FDG (fluorine-18, (2-[^{18}F]fluoro-2-deoxy-D-glucose) positron emission tomography in Oncology. *J Nucl Med* 49:480-508
3. Coleman RE, Delbeke D, Guiberteau MJ et al (2005) Intersociety dialogue on concurrent PET-CT with an integrated imaging system: From the Joint ACR/SNM/SCBT-MR PET-CT Working Group. *J Nucl Med* 46:1225-1239
4. Delbeke, Coleman RE, Guiberteau MJ et al (2006) Society of Nuclear Medicine procedure guidelines for tumor imaging using FDG PET/CT. *J Nucl Med* 47:885-895
5. American College of Radiology (2007) ACR practice guidelines for performing FDG PET/CT in oncology. www.ACR.org
6. Shankar LK, Hoffman JM, Bacharach S et al (2006) National Cancer Institute. Consensus recommendations for the use of 18F-FDG PET as an indicator of therapeutic response in patients in National Cancer Institute Trials. *J Nucl Med* 47:1059-1066
7. Juweid ME, Stroobants S, Hoekstra OS et al (2007) Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. *J Clin Oncol* 25:571-578
8. Cheson BD, Pfistner B, Juweid ME et al (2007) Revised response criteria for malignant lymphoma. *J Clin Oncol* 25:579-586
9. Hutchings M, Loft A, Hansen M et al (2006) Different histopathological subtypes of Hodgkin lymphoma show significantly different levels of FDG uptake. *Hematol Oncol* 24:146-150
10. National Cancer Institute: [http://www.cancer.gov/cancer-topics/ Topic "Staging"](http://www.cancer.gov/cancer-topics/Topic%20Staging)
11. Harris NL, Jaffe ES, Diebold J et al (1999) World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting, Airlie House, Virginia, November 1997. *J Clin Oncol* 17:3835-3849
12. Ping Lu (2005) Staging and classification of lymphoma. *Semin Nucl Med* 35:160-164
13. Schoder H, Noy A, Gonen M et al (2005) Intensity of 18-fluorodeoxyglucose uptake in positron emission tomography distinguishes between indolent and aggressive non-Hodgkin's lymphoma. *J Clin Oncol* 23:4643-4651
14. Elstrom R, Guan L, Baker G et al (2003) Utility of FDG-PET scanning in lymphoma by WHO classification. *Blood* 101:3875-3876
15. Tsukamoto N, Kojima M, Hasegawa M et al (2007) The usefulness of (18)F-fluorodeoxyglucose positron emission tomography ((18)F-FDG-PET) and a comparison of (18)F-FDG-PET with (67)gallium scintigraphy in the evaluation of lymphoma: relation to histologic subtypes based on the World Health Organization classification. *Cancer* 110:652-659
16. Brepoels L, Stroobants S, De Wever W et al (2008) Positron emission tomography in mantle cell lymphoma. *Leuk Lymphoma* 49:1693-1701
17. Kako S, Izutsu K, Ota Y et al (2007) T-cell FDG-PET in T-cell and NK-cell neoplasms. *Ann Oncol* 18:1685-1690
18. Jerusalem G, Beguin Y, Najjar F et al (2001) Positron emission tomography (PET) with 18F-fluorodeoxyglucose (18F-FDG) for the staging of low-grade non-Hodgkin's lymphoma (NHL). *Ann Oncol* 12:825-830
19. Bruzzi JF, Macapinlac H, Tsimberidou AM et al (2006) Detection of Richter's transformation of chronic lymphocytic leukemia by PET/CT. *J Nucl Med* 47:1267-1273
20. Najjar F, Hustinx R, Jerusalem G et al (2001) Positron emission tomography (PET) for staging low-grade non-Hodgkin's lymphomas (NHL). *Cancer Biother Radiopharm* 16:297-304
21. Hoffmann M, Kletter K, Becherer A et al (2003) 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) for staging and follow-up of marginal zone B-cell lymphoma. *Oncology* 64:336-340
22. The International Non-Hodgkin's Lymphoma Prognostic Factors Project (1993) A predictive model for aggressive non-Hodgkin's lymphoma. *N Engl J Med* 329:987-994
23. Solal-Célgny P, Roy P, Colombat P et al (2004) Follicular lymphoma international prognostic index. *Blood* 104:1258-1265
24. Hasenclever D, Diehl V (1998) A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease. *N Engl J Med* 339:1506-1514
25. Okada J, Oonishi H, Yoshikawa K et al (1994) FDG-PET for predicting the prognosis of malignant lymphoma. *Ann Nucl Med* 8:187-191
26. Israel O, Keidar Z, Bar-Shalom R (2004) Positron emission tomography in the evaluation of lymphoma. *Semin Nucl Med* 34:166-179
27. Seam P, Juweid ME, Cheson BD (2007) The role of FDG-PET scans in patients with lymphoma. *Blood* 110:3507-3516
28. Buchmann I, Reinhardt M, Elsner K et al (2001) 2-(fluorine-18)fluoro-2-deoxy-D-glucose positron emission tomography

- in the detection and staging of malignant lymphoma. A bicenter trial. *Cancer* 91:889-899
29. Isasi CR, Lu P, Blaufox MD (2005) A metaanalysis of 18F-2-deoxy-2-fluoro-D-glucose positron emission tomography in the staging and restaging of patients with lymphoma. *Cancer* 104:1066-1074
 30. Thill R, Neuerburg J, Fabry U et al (1997) Comparison of findings with 18-FDG PET and CT in pretherapeutic staging of malignant lymphoma. *Nuklearmedizin* 36:234-239
 31. Moog F, Bangerter M, Diederichs CG et al (1998) Extranodal malignant lymphoma: detection with FDG PET versus CT. *Radiology* 206:475-481
 32. Moog F, Bangerter M, Kotzerke J et al (1998) 18-F-fluorodeoxyglucose-positron emission tomography as a new approach to detect lymphomatous bone marrow. *J Clin Oncol* 16:603-609
 33. Carr R, Barrington SF, Madan B et al (1998) Detection of lymphoma in bone marrow by whole-body positron emission tomography. *Blood* 91:3340-3346
 34. Pakos EE, Fotopoulos AD, Ioannidis JP (2005) 18F-FDG PET for evaluation of bone marrow infiltration in staging of lymphoma: a meta-analysis. *J Nucl Med* 46:958-963
 35. Schaefer NG, Hany TF, Taverna C et al (2004) Non-Hodgkin lymphoma and Hodgkin disease: coregistered FDG PET and CT at staging and restaging – do we need contrast-enhanced CT? *Radiology* 232:823-829
 36. Raanani P, Shasha Y, Perry C et al (2006) Is CT scan still necessary for staging in Hodgkin and non-Hodgkin lymphoma patients in the PET/CT era? *Ann Oncol* 17:117-122
 37. Rodríguez-Vigil B, Gómez-León N, Pinilla I et al (2006) PET/CT in lymphoma: prospective study of enhanced full-dose PET/CT versus unenhanced low-dose PET/CT. *J Nucl Med* 47:1643-1648
 38. Hicks RJ, MacManus MP, Seymour JF (2005) Initial staging of lymphoma with positron emission tomography and computed tomography. *Semin Nucl Med* 35:165-175
 39. Bangerter M, Kotzerke J, Griesshammer M et al (1999) Positron emission tomography with 18-fluorodeoxyglucose in the staging and follow-up of lymphoma in the chest. *Acta Oncol* 38:799-804
 40. Cremerius U, Fabry U, Neuerburg J et al (1998) Positron emission tomography with 18F-FDG to detect residual disease after therapy for malignant lymphoma. *Nucl Med Commun* 19:1055-1063
 41. Spaepen K, Mortelmans L (2001) Evaluation of treatment response in patients with lymphoma using [18F]FDG-PET: differences between non-Hodgkin's lymphoma and Hodgkin's disease. *Q J Nucl Med* 45:269-273
 42. Cheson BD, Horning SJ, Coiffier B (1999) Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. *J Clin Oncol* 17:1244
 43. Juweid ME, Wiseman GA, Vose JM et al (2005) Response assessment of aggressive non-Hodgkin's lymphoma by integrated International Workshop criteria and fluorine-18-fluorodeoxyglucose positron emission tomography. *J Clin Oncol* 23:4652-4661
 44. Jerusalem G, Beguin Y, Fassotte MF et al (1999) Whole-body positron emission tomography using 18F-fluorodeoxyglucose for posttreatment evaluation in Hodgkin's disease and non-Hodgkin's lymphoma has higher diagnostic and prognostic value than classical computed tomography scan imaging. *Blood* 94:429-433
 45. Mikhaeel NG, Timothy AR, O'Doherty MJ et al (2000) 18-FDG-PET as a prognostic indicator in the treatment of aggressive Non-Hodgkin's Lymphoma-comparison with CT. *Leuk Lymphoma* 39:543-553
 46. Jerusalem G, Hustinx R, Beguin Y, Fillet G (2005) Evaluation of therapy for lymphoma. *Semin Nucl Med* 35:186-196
 47. Terasawa T, Nihashi T, Hotta T, Nagai H (2008) 18F-FDG PET for posttherapy assessment of Hodgkin's disease and aggressive Non-Hodgkin's lymphoma: a systematic review. *J Nucl Med* 49:13-21
 48. Kelloff GJ, Sullivan DM, Wilson W et al (2007) FDG-PET lymphoma demonstration project invitational workshop. *Acad Radiol* 14:330-339
 49. Kazama T, Faria SC, Varavithya V et al (2005) FDG PET in the evaluation of treatment for lymphoma: clinical usefulness and pitfalls. *Radiographics* 25:191-207
 50. Abdel-Dayem HM, Rosen G, El-Zeftawy H et al (1999) Fluorine-18 fluorodeoxyglucose splenic uptake from extramedullary hematopoiesis after granulocyte colony-stimulating factor stimulation. *Clin Nucl Med* 24:319-322
 51. Gundlapalli S, Ojha B, Mountz JM (2002) Granulocyte colony-stimulating factor: confounding F-18 FDG uptake in outpatient positron emission tomographic facilities for patients receiving ongoing treatment of lymphoma. *Clin Nucl Med* 27:140-141.
 52. Ferdinand B, Gupta P, Kramer EL (2004) Spectrum of thymic uptake at 18F-FDG PET. *Radiographics* 24:1611-1616
 53. Joyce JM, Degirmenci B, Jacobs S et al (2005) FDG PET CT assessment of treatment response after yttrium-90 ibritumomab tiuxetan radioimmunotherapy. *Clin Nucl Med* 30:564-568
 54. Ulaner GA, Colletti PM, Conti PS (2008) B-cell non-Hodgkin lymphoma: PET/CT evaluation after 90Y-ibritumomab tiuxetan radioimmunotherapy--initial experience. *Radiology* 246:895-902
 55. Zinzani PL, Tani M, Fanti S et al (2008) A phase II trial of CHOP chemotherapy followed by yttrium 90 ibritumomab tiuxetan (Zevalin) for previously untreated elderly diffuse large B-cell lymphoma patients. *Ann Oncol* 19:769-773
 56. Johnston PB, Wiseman GA, Micallef IN (2008) Positron emission tomography using F-18 fluorodeoxyglucose pre- and post-autologous stem cell transplant in non-Hodgkin's lymphoma. *Bone Marrow Transplant* 41:919-925
 57. Schot BW, Zijlstra JM, Sluiter WJ et al (2007) Early FDG-PET assessment in combination with clinical risk scores determines prognosis in recurring lymphoma. *Blood* 109:486-491
 58. Filmont JE, Gisselbrecht C, Cuenca X (2007) The impact of pre- and post-transplantation positron emission tomography using 18-fluorodeoxyglucose on poor-prognosis lymphoma patients undergoing autologous stem cell transplantation. *Cancer* 110:1361-1369



Myocardial Perfusion Imaging with SPECT-CT

Philipp A. Kaufmann

Department of Radiology, Cardiac Imaging, University Hospital Zurich, Zurich, Switzerland

Introduction

Noninvasive cardiac imaging has experienced substantial advances, including the introduction of coronary computed tomography angiography (CCTA). Invasive coronary angiography has remained the anatomic standard of reference but is associated with a nonnegligible periprocedural morbidity and mortality rate that suggests confining its use to patients who will benefit from a subsequent revascularization procedure. Many parameters beyond the simple quantification of luminal narrowing and which therefore cannot be fully assessed with luminology will determine whether a given lesion is hemodynamically relevant and causes stress-induced ischemia. Myocardial perfusion scintigraphy by single photon emission CT (SPECT) is the most widely used and best established noninvasive tool for diagnosing ischemic heart disease. Although positron emission tomography (PET) offers a higher accuracy than SPECT, its use is often limited to large centers. Latest results suggest a great potential of cardiac hybrid imaging, allowing a comprehensive evaluation of coronary artery disease (CAD) by combining both morphological and functional information after fusing SPECT with CCTA. Hybrid imaging with SPECT-CT can provide entirely noninvasively unique information that helps improve diagnostic assessment and risk stratification and also impacts decision making with regard to revascularization in patients with CAD.

Coronary Stenoses versus Ischemic Heart Disease

Although invasive coronary angiography is affected by considerable morbidity (1.5%) [1] and mortality (0.3%) [2] rates, this has remained the most established method for visualizing the coronary arteries and, thus, the standard of reference for diagnosing coronary stenoses. It is, however, far from being a perfect diagnostic tool as, in fact, its accuracy is severely hampered by a large intraobserver and interobserver variability in defining the anatomic relevance of stenoses (up to 50%) [3, 4]. This is further supported by the fact that invasive coronary angiography is very poorly correlated with postmortem

coronary anatomy [5]. For daily clinical routine, the most important notion is that anatomic features of angiographically documented coronary stenoses are poor predictors of a lesion's physiologic relevance [4]. The fact that the majority (>60%) of all elective diagnostic invasive coronary angiograms reveal clinically insignificant disease or no disease at all [6] has stimulated the search for strategies of noninvasive coronary imaging, including dichromatic synchrotron radiation, electron beam tomography, magnetic resonance imaging, and CCTA. Only the latter has recently emerged as a clinically valuable alternative to the invasive coronary angiography for visualizing the coronary anatomy [7].

However, coronary anatomy rarely allows estimation with certainty of the pathophysiologic relevance of a coronary lesion. In intermediate lesions in particular, many factors influence the interrelation between anatomic finding and hemodynamic consequences that cannot be fully elucidated by anatomic evaluation alone, not even with the use of quantitative coronary angiography [8]. Therefore, according to the actual European and American guidelines, a test for ischemia before any elective coronary angiography is mandatory [9-11], and SPECT is recommended as a first-line test. The large gap between these evidence-based guidelines and the above-mentioned reality in daily clinical routine emphasizes the need to increase both awareness of the importance and availability of noninvasive testing by SPECT for CAD.

Clinical Role of Myocardial Perfusion Imaging with SPECT

Nuclear myocardial perfusion imaging (MPI) with SPECT represents the most widely available, robust, and by far best established noninvasive method for evaluating ischemic heart disease [12]. A perfect agreement of MPI SPECT and coronary angiography cannot – and should not – be expected as prerequisite for its clinical value. In the noninvasive diagnostic algorithm, the main role of SPECT is not to correctly predict or exclude epicardial coronary lesions but, rather, to evaluate the physiological relevance of known or suspected coronary stenoses. Nevertheless, functional tests, including SPECT, have often

been compared with those of coronary angiography, as this is the generally accepted standard of reference for coronary lesions. The results may depend at least in part from the size and selection of the study population. One of the largest recent reports, the British Royal Brompton and UCL Study of Thallium and Technetium (ROBUST) study, assessed 2,560 patients who were randomized to one of the commonly used tracers (thallium, sestamibi, or tetrofosmin) applying mainly adenosine stress. This study documented a sensitivity of 91% and a specificity of 87% without differences between tracers [13].

Time-consuming acquisition and cumbersome MPI protocols with the associated costs, impaired patient comfort, and radiation exposure have been perceived as limitations of SPECT MPI despite its success. Several attempts to improve the MPI method by using iterative reconstruction algorithms, early-imaging protocols, or different tracers have provided valuable improvements. However, the novel cadmium zinc telluride (CZT) detector systems have the potential to represent the much awaited milestone in technical improvement of MPI. The CZT technique has enabled a substantial miniaturization of the detectors, and the development of new cameras took advantage of this by allowing a stationary positioning of numerous CZT detectors to be chosen, with pinhole geometry around the heart. As a result, the scan on the CZT camera covers the entire heart, allowing very fast acquisition comparable with cardiac PET imaging. First clinical studies reported very encouraging results [14-16].

Role of Hybrid Imaging: Implications and Limitations

The continuing rapid evolution of CCTA suggests that, when combined with perfusion imaging, it has the potential to be implemented into clinical practice. As mentioned above, the advancements in fast-processing software for 3D reconstructions permitted promising initial attempts of purely noninvasive CAD assessment directly relating individual myocardial-wall territories with impaired myocardial perfusion to the subtending coronary artery with the use of PET and CT [17]. Recent data using SPECT and CT suggest that hybrid imaging provides added diagnostic clinical value beyond that of either technique alone or that of side-by-side analysis [18-20]. The added value seems to be found on both sides of the diagnostic spectrum, i.e., in low-risk populations [21] as well as in those with multivessel disease [20]. In low-risk populations, hybrid imaging may increase the confidence to rule out CAD – for example, in the stepwise evaluation of CAD when the first study has yielded equivocal results and a second modality is needed to finally rule out with certainty any disease. Many of those patients would end up having invasive coronary angiography, whereas hybrid imaging increases diagnostic confidence by avoiding equivocal findings, which helps to reduce the number of patients unnecessarily exposed to the risks associated with invasive coronary procedures. At the other end of the spectrum, i.e., in patients

older than those mentioned above and who often suffer from multivessel disease with more jeopardized myocardium, hybrid imaging provides important comprehensive information to allow for timely and appropriate treatment. In such settings, the value of hybrid imaging lies far beyond the simple addition of a further diagnostic test, as it allows accurate spatial association of perfusion defects to their subtending coronary stenosis (Fig. 1).

Hybrid imaging is a completely noninvasive approach to CAD and provides important information prior to any invasive procedure, as well as detailed information for evidence-driven intervention targeting the relevant lesion only. Although the CT part of hybrid imaging has an excellent ability to help rule out hemodynamically relevant CAD, an abnormal CCTA – as with an abnormal conventional angiography study – is a poor predictor of ischemia, and further perfusion imaging testing is warranted to identify patients who might benefit from a revascularization procedure [22, 23] and those in whom conservative management and risk modification may be justified [24]. Conversely, a normal MPI result does not exclude the presence of subclinical CAD as assessable with CCTA and conventional coronary angiography, for which aggressive cardiovascular risk modification may be warranted. The incongruence of CCTA and MPI is inherent to the duality of morphologic versus functional testing. The technologic refinements implemented in the latest generation of CT scanners have reduced the number of nonevaluable coronary segments, and further improvements may be expected. However, no matter how accurate CCTA may possibly get with future advances in technology, the two pieces of information obtained with perfusion imaging versus morphology are difficult to

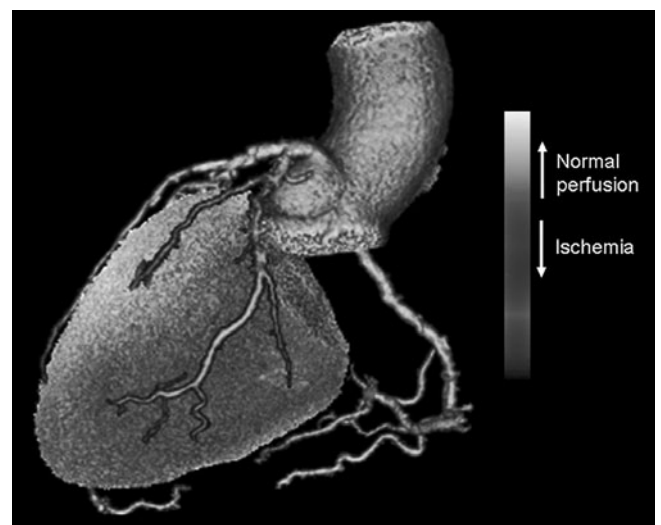


Fig. 1. Posterior view allows recognizing that in this patient, the ischemic basal inferior territory is subtended by the circumflex artery (CX), causing ischemia due to sequential lesions in the CX vessel. By contrast, the right coronary artery does not contribute to this ischemia despite anatomically similar atherosclerotic lesions (for color reproduction see p 273)

compare. This has been recently documented by Gaemperli et al., who found that the receiver operator characteristic analysis for detecting perfusion defects (by SPECT) showed similar area under the curve for the reference standard (conventional angiography) as for CCTA, documenting comparable performance and limitations of both anatomic and morphologic techniques [25].

Hybrid images offer superior diagnostic information with regard to identifying the culprit vessel, with the hemodynamically relevant lesion providing added diagnostic information not obtained on side-by-side analysis [20]. The incremental value seems most pronounced for functionally relevant lesions in distal segments and diagonal branches and in vessels with extensive coronary lesions or heavy calcifications on CCTA. Pioneering results from our group have been confirmed by others and formed the foundation for the recently published European guidelines for cardiac hybrid imaging [26]. Results from a first multicenter study emphasize the value of a combined functional and anatomical approach even without hybrid imaging, showing that this combination allows improved risk stratification [27]. The clinical usefulness in terms of impact on treatment strategy and subsequently on outcome by hybrid imaging remains, however, to be determined in prospective and long-term studies. Similarly, it remains uncertain at this point whether hybrid scanners offer advantages over software fusion of data sets obtained from different scanners, as by either method, hybrid images can be obtained [18].

The scan time discrepancy between emission from nuclear and CT transmission determines that high-end CT facilities constituting the CT component of hybrid cardiac scanners will be blocked by long emission scan time and is therefore forced to operate at low capacity. However, a combined device may fit into one room, require only one operating team, and not require patient positioning into two different scanners. The development of ultrafast SPECT scanners allowing substantially shorter acquisition time may shift the balance toward hybrid scanners in the future.

References

1. Achenbach S, Daniel WG (2001) Noninvasive coronary angiography – an acceptable alternative? *N Engl J Med* 345:1909-1910
2. Shaw LJ, Shaw RE, Merz CN et al (2008) Impact of ethnicity and gender differences on angiographic coronary artery disease prevalence and in-hospital mortality in the American College of Cardiology-National Cardiovascular Data Registry. *Circulation* 117:1787-1801
3. Galbraith JE, Murphy ML, Desoyza N (1981) Coronary angiogram interpretation: interobserver variability. *JAMA* 240:2053-2059
4. White CW, Wright CB, Doty DB et al (1984) Does visual interpretation of the coronary arteriogram predict the physiologic importance of a coronary stenosis? *N Engl J Med* 310:819-824
5. Vlodaver Z, Frech R, Van Tassel RA, Edwards JE (1973) Correlation of the antemortem coronary arteriogram and the post-mortem specimen. *Circulation* 47:162-169
6. Patel MR, Peterson ED, Dai D et al (2010) Low diagnostic yield of elective coronary angiography. *N Engl J Med* 362:886-895
7. Schroeder S, Achenbach S, Bengel F et al (2008) Cardiac computed tomography: indications, applications, limitations, and training requirements: report of a Writing Group deployed by the Working Group Nuclear Cardiology and Cardiac CT of the European Society of Cardiology and the European Council of Nuclear Cardiology. *Eur Heart J* 29:531-556
8. Bartunek J, Sys SU, Heyndrickx GR et al (1995) Quantitative coronary angiography in predicting functional significance of stenoses in an unselected patient cohort. *J Am Coll Cardiol* 26:328-334
9. Klocke FJ, Baird MG, Lorell BH et al (2003) ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging – executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). *Circulation* 108:1404-1418
10. Smith SC, Dove JT, Jacobs AK et al (2001) ACC/AHA guidelines of percutaneous coronary interventions (revision of the 1993 PTCA guidelines)--executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (committee to revise the 1993 guidelines for percutaneous transluminal coronary angioplasty). *J Am Coll Cardiol* 37:2215-2239
11. Wijns W, Kolh P, Danchin N et al (2010) Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 31:2501-2555
12. Underwood SR, Anagnostopoulos C, Cerqueira M et al (2004) Myocardial perfusion scintigraphy: the evidence. *Eur J Nucl Med Mol Imaging* 31:261-291
13. Kapur A, Latus KA, Davies G et al (2002) A comparison of three radionuclide myocardial perfusion tracers in clinical practice: the ROBUST study. *Eur J Nucl Med Mol Imaging* 29:1608-1616
14. Herzog BA, Buechel RR, Husmann L et al (2010) Validation of CT attenuation correction for high-speed myocardial perfusion imaging using a novel cadmium-zinc-telluride detector technique. *J Nucl Med* 51:1539-1544
15. Buechel RR, Pazhenkottil AP, Herzog BA et al (2010) Real-time breath-hold triggering of myocardial perfusion imaging with a novel cadmium-zinc-telluride detector gamma camera. *Eur J Nucl Med Mol Imaging* 37:1903-1908
16. Herzog BA, Buechel RR, Katz R et al (2010) Nuclear myocardial perfusion imaging with a cadmium-zinc-telluride detector technique: optimized protocol for scan time reduction. *J Nucl Med* 51:46-51
17. Namdar M, Hany TF, Koepfli P et al (2005) Integrated PET/CT for the assessment of coronary artery disease: a feasibility study. *J Nucl Med* 46:930-935
18. Gaemperli O, Kaufmann PA (2008) Hybrid cardiac imaging: more than the sum of its parts? *J Nucl Cardiol* 15:123-126
19. Gaemperli O, Schepis T, Kaufmann PA (2007) SPECT-CT fusion imaging integrating anatomy and perfusion. *Eur Heart J* 28:145
20. Gaemperli O, Schepis T, Valenta I et al (2007) Cardiac image fusion from stand-alone SPECT and CT: clinical experience. *J Nucl Med* 48:696-703
21. Husmann L, Herzog BA, Gaemperli O et al (2009) Diagnostic accuracy of computed tomography coronary angiography and evaluation of stress-only single-photon emission computed tomography/computed tomography hybrid imaging: comparison of prospective electrocardiogram-triggering vs. retrospective gating. *Eur Heart J* 30:600-607
22. Hachamovitch R, Hayes SW, Friedman JD et al (2003) Comparison of the short-term survival benefit associated with

- revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation* 107:2900-2907
23. Shaw LJ, Berman DS, Maron DJ et al (2008) Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. *Circulation* 117:1283-1291
 24. Boden WE, O'Rourke RA, Teo KK et al (2007) Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 356:1503-1516
 25. Gaemperli O, Schepis T, Valenta I et al (2008) Functionally relevant coronary artery disease: comparison of 64-section CT angiography with myocardial perfusion SPECT. *Radiology* 248:414-423
 26. Marcassa C, Delaloye AB, Cuocolo A et al (2006) The regulatory background of nuclear cardiology in Europe: a survey by the European Council of Nuclear Cardiology. *Eur J Nucl Med Mol Imaging* 33:1508-1512
 27. van Werkhoven JM, Schuijf JD, Gaemperli O et al (2009) Prognostic value of multislice computed tomography and gated single-photon emission computed tomography in patients with suspected coronary artery disease. *J Am Coll Cardiol* 53:623-632



Staging, Restaging and Response Evaluation of Non-Small-Cell Lung Cancer

Jeremy J. Erasmus

Division of Diagnostic Imaging, MD Anderson Cancer Center, Houston, TX, USA

Introduction

Imaging is important in the clinical staging of patients with non-small-cell lung cancer (NSCLC) and is typically performed with computed tomography (CT). Positron emission tomography (PET) using [^{18}F]fluro-2-deoxy-D-glucose (FDG) compliments conventional radiologic assessment when evaluating patients with NSCLC and is being routinely used to improve the detection of nodal and extrathoracic metastases. FDG-PET is also being evaluated for assessing prognosis and therapeutic response. This chapter discusses staging, restaging and assessing treatment response with an emphasis on the appropriate clinical use of FDG-PET in managing patients with NSCLC.

Staging

Patients with NSCLC are typically staged prior to initiation of therapy using tumor-node-metastasis (TNM) descriptors and stage grouping of the recently instituted 7th edition of the American Joint Committee on Cancer (AJCC) TNM staging system [1-3].

Primary Tumor (T Descriptor)

The T descriptor defines size, location and extent of the primary tumor (Fig. 1) [4]. There are numerous changes to the T descriptor in the 7th edition of the TNM classification of lung cancer that are based on differences in survival [1]:

1. T1 is now subclassified as T1a (≤ 2 cm) or T1b (>2 to ≤ 3 cm);
2. T2 is now subclassified as T2a (>3 to ≤ 5 cm or T2 by other factor and ≤ 5 cm) or T2b (>5 to ≤ 7 cm);
3. T2 tumors >7 cm are reclassified as T3;
4. T4 tumors by additional nodule(s) in the lung (primary lobe) are reclassified as T3;
5. M1 by additional nodule(s) in the ipsilateral lung (different lobe) is reclassified as T4;
6. T4 pleural dissemination (malignant pleural effusions, pleural nodules) is reclassified as M1a.

 International Association for the Study of Lung Cancer TNM Descriptors	
T – Primary Tumour	
TX	Primary tumour cannot be assessed, or tumour proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)
T1a	Tumour 2 cm or less in greatest dimension ¹
T1b	Tumour more than 2 cm but not more than 3 cm in greatest dimension
T2	Tumour more than 3 cm but not more than 7 cm; or tumour with any of the following features ² :
•	Involves main bronchus, 2 cm or more distal to the carina
•	Invades visceral pleura
•	Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a	Tumour more than 3 cm but not more than 5 cm in greatest dimension
T2b	Tumour more than 5 cm but not more than 7 cm in greatest dimension
T3	Tumour more than 7 cm or one that directly invades any of the following: chest wall (including superior sulcus tumours), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumour in the main bronchus less than 2 cm distal to the carina ¹ but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumour nodule(s) in the same lobe as the primary.
T4	Tumour of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina; separate tumour nodule(s) in a different ipsilateral lobe to that of the primary.
N – Regional Lymph Nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
M – Distant Metastasis	
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumour nodule(s) in a contralateral lobe; tumour with pleural nodules or malignant pleural or pericardial effusion ³
M1b	Distant metastasis

Notes:

¹ The uncommon superficial spreading tumour of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1a.

² T2 tumours with these features are classified T2a if 5 cm or less or if size cannot be determined, and T2b if greater than 5 cm but not larger than 7 cm.

³ Most pleural (pericardial) effusions with lung cancer are due to tumour. In a few patients, however, multiple microscopical examinations of pleural (pericardial) fluid are negative for tumour, and the fluid is non-bloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumour, the effusion should be excluded as a staging element and the patient should be classified as M0.

Fig. 1. Tumor-node-metastasis descriptors [4]. Reprinted with permission courtesy of the International Association for the Study of Lung Cancer. Copyright 2009 IASLC (for color reproduction see p 273)

Because PET has limited utility in evaluating the primary tumor at initial staging, CT is typically performed to assess the T descriptor. Evaluating the primary tumor (size; location; proximity to critical structures; degree of pleural, chest wall and mediastinal invasion; involvement of the central airways and pulmonary arteries) is important because it can determine whether the patient receives curative surgical resection, induction therapy prior to re-

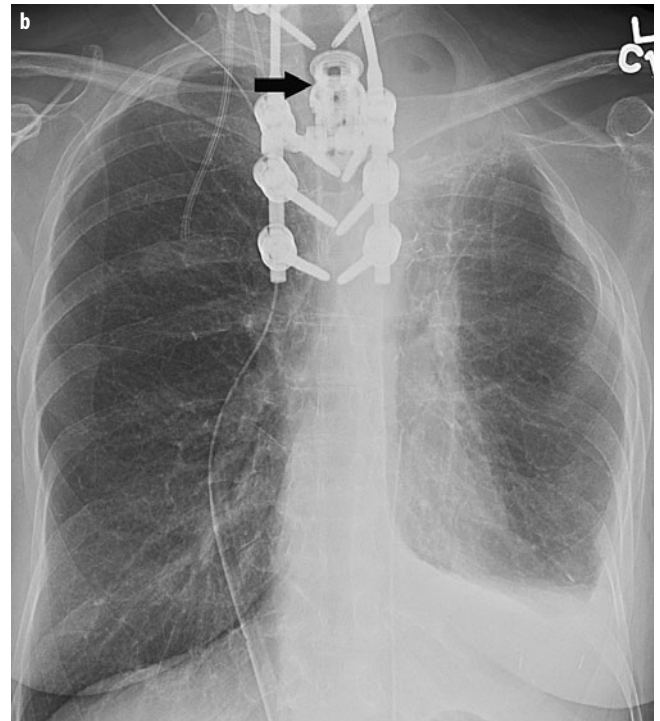


Fig. 2 a, b. Non-small-cell lung cancer in a 65-year-old woman with vertebral body invasion. **a** Axial computed tomography (CT) shows a left upper lobe mass (*M*) with focal destruction of the adjacent rib and T3 vertebral body (*arrowheads*). Note that because invasion of the vertebral body is <50%, the patient was able to have the mass and vertebral body resected. **b** Chest radiograph shows findings of left upper lobectomy and en bloc resection of the second, third and fourth ribs and resection of T2 and T3 vertebral bodies. There is air and fluid in the apex of the left hemithorax. Note expandable titanium cage (*arrow*) used for vertebral body reconstruction, and fixation rod and screw stabilisation hardware

section or palliative radiotherapy or chemotherapy. It is important to realize that although a T4 descriptor generally precludes resection, patients with additional nodule(s) in the ipsilateral lung (different lobe) and cardiac, tracheal and vertebral-body invasion are designated in the 7th TNM edition staging system as being potentially resectable in the absence of N2 and or N3 disease (Fig. 2).

Although CT is useful in defining the T parameters of the primary tumor in many patients, this assessment has limitations. For instance, CT is accurate in confirming gross chest-wall or mediastinal invasion but is inaccurate in differentiating between anatomic contiguity and subtle invasion. Although magnetic resonance imaging (MRI) offers superior soft-tissue contrast resolution compared with CT, sensitivity and specificity in identifying chest-wall and mediastinal invasion is not optimal. However, MRI is useful in evaluating cardiac invasion and assessing superior sulcus tumors [5-7].

Regional Lymph Nodes (N Descriptor)

Determining presence and location of nodal metastasis is important in management planning and prognosis in patients with NSCLC. Because survival differences in analysis by station are similar, the N descriptors in the 7th edition of the TNM classification have been maintained [2]. However, for further evaluation, lymph node stations are grouped together in six zones within the N1 and N2 patient subsets. Zones are defined as peripheral (stations 12, 13, 14) or hila (stations 10, 11) for N1 and upper mediastinal (stations 1, 2, 3, 4), lower mediastinal (stations

8, 9), aortopulmonary (stations 5, 6) and subcarinal (station 7) for N2 nodes (Fig. 3) [2].

Surgical resection and potential use of adjuvant therapy are dependent on the presence and location of nodal metastasis. CT is used to detect these metastases, and a short-axis nodal diameter of 1 cm is the upper limit for distinguishing normal from abnormal nodes. However, size is not a reliable parameter for evaluating nodal metastatic disease in patients with NSCLC [8, 9]. A meta-analysis of 20 studies (3,438 patients) evaluating CT accuracy for staging the mediastinum yielded a pooled sensitivity of 57% and specificity of 82% [9].

FDG-PET improves detection accuracy of nodal metastases (Fig. 4). In a meta-analysis (17 studies, 833 patients) in patients with NSCLC, sensitivity and specificity for detecting mediastinal lymph node metastases ranged from 66% to 100% (overall 83%) and from 81% to 100% (overall 92%), respectively, compared with sensitivity and specificity of CT of 20-81% (overall 59%) and 44-100% (overall 78%), respectively [10]. Additionally, significant improvements in the accuracy of nodal and overall tumor staging have been reported when using integrated PET-CT compared with CT and PET interpreted separately [11].

FDG-PET reduces the likelihood that a patient with nodal metastases that would preclude surgery (N3) will undergo attempted resection. However, invasive sampling of nodes with increased FDG uptake should be performed to confirm nodal metastatic disease when this will have an impact on management, as false positive results due to infectious or inflammatory etiologies are common. A meta-analysis evaluating the association between the size

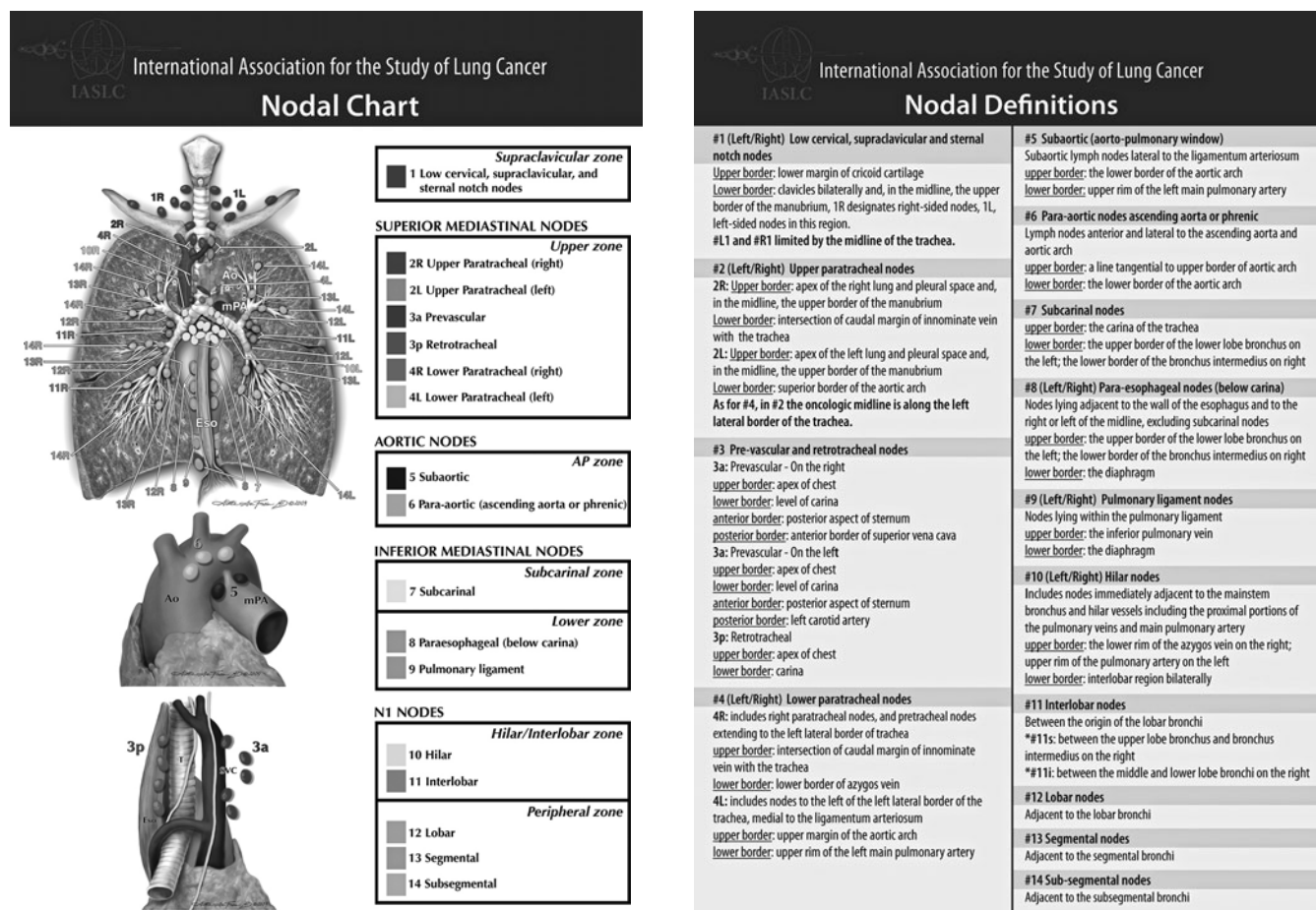
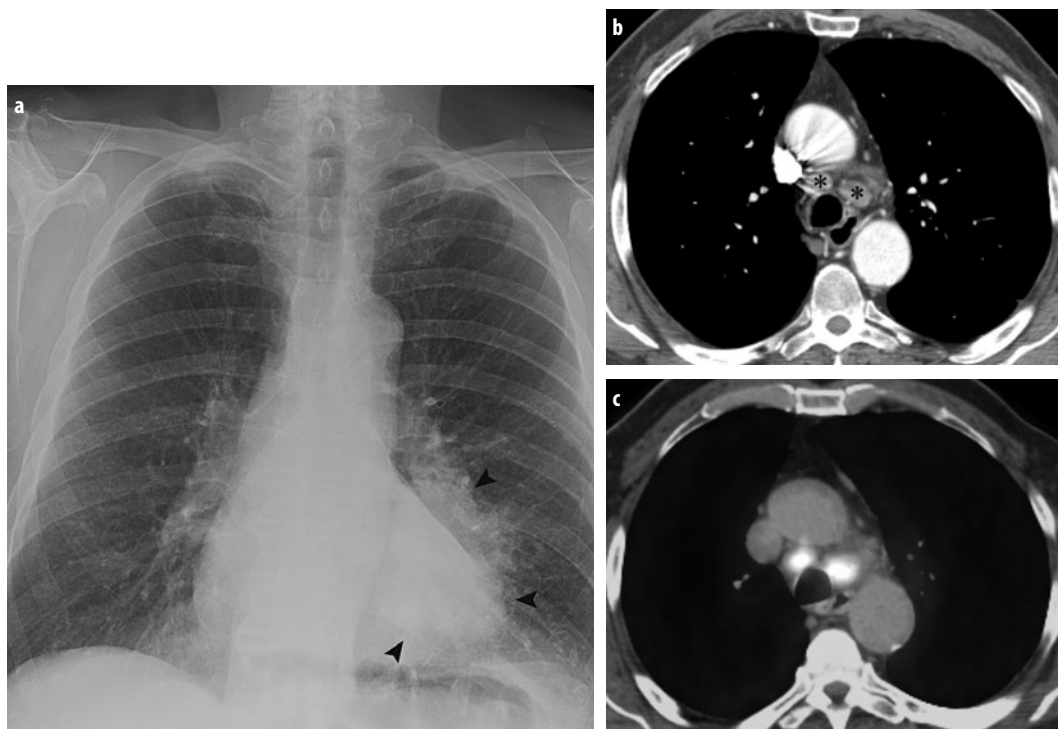


Fig. 3. Nodal chart [4]. Reprinted with permission courtesy of the International Association for the Study of Lung Cancer. Copyright 2009 IASLC and © 2008 Aletta Ann Frazier (for color reproduction see p 273)

Fig. 4 a-c. Nodal metastasis in a 78-year-old man with non-small-cell lung cancer. **a** Chest radiograph shows a poorly marginated large left lower lobe mass (arrowheads). **b** Chest computed tomography (CT) shows a normal-sized (short-axis diameter 1 cm) right lower paratracheal lymph node and slightly enlarged left lower paratracheal node (asterisks). **c** Fused positron emission tomography CT (PET-CT) reveals increased [^{18}F]fluoro-2-deoxy-D-glucose (FDG) uptake in the paratracheal nodes. Mediastinoscopy confirmed nodal metastasis. Note that because N3 (contralateral mediastinal) nodal metastasis is nonresectable, the patient was treated palliatively (for color reproduction see p 273)



of mediastinal lymph nodes and the probability of malignancy provides an indication of how FDG-PET should be used in the clinical evaluation on nodal metastasis [12]. The authors report a 5% posttest probability for N2 disease in patients with a negative FDG-PET if the mediastinal nodes are 10–15 mm on CT, suggesting that these patients should proceed directly to thoracotomy. In patients with a negative FDG-PET and lymph nodes >16 mm on CT, the posttest probability for N2 disease is 21%, suggesting that these patients should have mediastinoscopy prior to thoracotomy.

Metastatic Disease (M descriptor)

There are numerous changes to the M descriptor in the 7th edition of the TNM classification that are based on differences in survival (Fig. 1). The M1 descriptor is now subclassified into M1a (additional nodules in the contralateral lung) and M1b (distant metastases outside the lung and pleura) [3]. Additionally, the current M descriptor is modified to reclassify pleural metastases (malignant pleural effusions, pleural nodules) from T4 to M1a [3].

Distant metastases (M1a, M1b) are common in patients with NSCLC, and CT is usually used to detect these metastases. However, because FDG-PET has a higher sensitivity and specificity than CT in detecting metastases to the adrenals, bones and extrathoracic lymph nodes in patients with NSCLC, FDG-PET is increasingly being used in staging (Fig. 5). Whole-body PET imaging stages intra- and extrathoracic disease in a single study, detects occult extrathoracic metastases in up to 24% of patients selected for curative resection and has been shown to be cost effective [13–16]. The incidence of occult metastases detection has been reported to increase as the T and N staging descriptors increase, i.e. 7.5% in early-stage disease to 24% in advanced disease [16]. In a randomised controlled trial of the role of PET in early-stage lung cancer, distant metastases were rarely detected (<5%) [17]. However, detection of ipsilateral nodal metastases (N2 disease) occurred in 20% of patients [17]. In addition, two studies with a higher proportion of more advanced lung cancers considered resectable by standard clinical staging showed that FDG-PET prevented non-therapeutic surgery in one in patients [13, 15].

Although whole-body FDG-PET imaging improves staging accuracy and choice of the optimal therapeutic strategy, focal increased uptake of FDG in extrathoracic lesions unrelated to the primary NSCLC can accumulate FDG and mimic distant metastases. Accordingly, all extrathoracic FDG-avid lesions that potentially would alter patient management should be biopsied. The rationale for this management approach is supported by the results of a prospective study performed to assess the incidence and diagnosis of a single site of extrapulmonary accumulation of FDG in patients with a newly diagnosed NSCLC [18]. In the 350 patients in the study group, 72 (21%) had solitary FDG-avid lesions. Thirty-seven (54%) of those patients had a solitary metastasis, whereas 32 (46%) had lesions unrelated to the NSCLC.

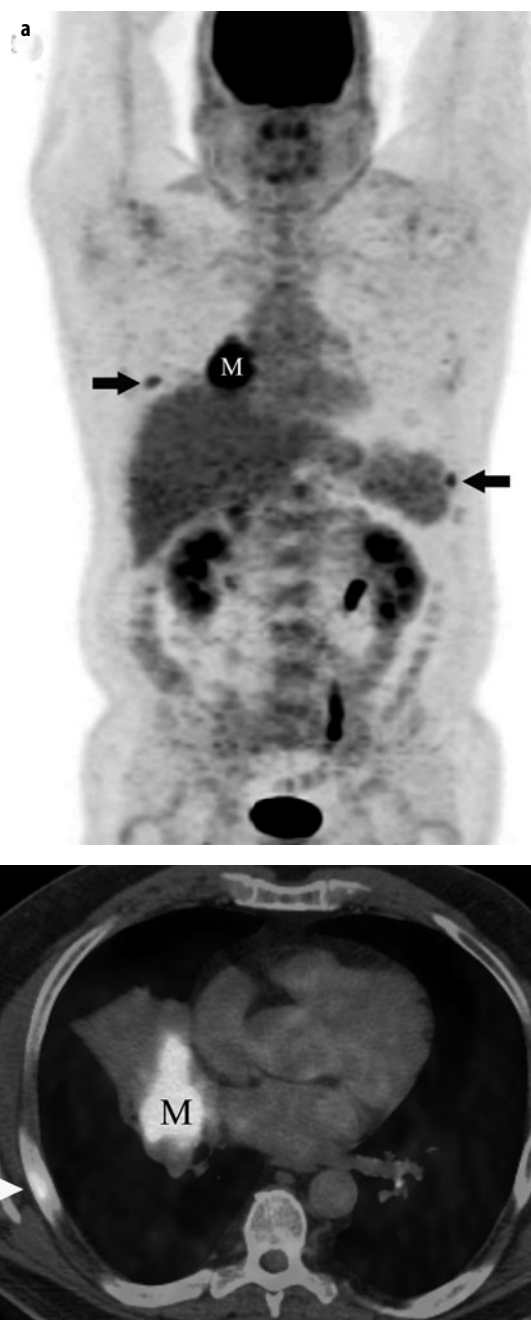


Fig. 5 a, b. Asymptomatic bone metastases in a 56-year-old man with non-small-cell lung cancer. **a** Whole-body positron emission tomography (PET) maximum intensity image shows increased [^{18}F]fluoro-2-deoxy-D-glucose (FDG) uptake in the right lung mass (*M*) and focal increased FDG uptake in bilateral rib metastases (*arrows*). **b** Fused PET-CT shows middle lobe malignancy (*M*) and distal obstructive atelectasis and right rib metastasis (*arrow*) (for color reproduction see p 273)

Restaging

Imaging has an important role in detecting local NSCLC recurrence. However, there is considerable variability in the imaging performed to evaluate for recurrent NSCLC due to a lack of evidence in the published literature

regarding optimal follow-up after treatment. In fact, there is no established standardised clinical algorithm to monitor patients with NSCLC for disease recurrence. It has been reported that an imaging study (either a chest radiograph or CT scan) every 6 months for 2 years and then annually is a clinically reasonable surveillance approach [19]. However, little is known about the effectiveness of follow-up regimens, and whereas it has been reported that intensive surveillance is not cost effective, a prospective study concluded that intensive may improve survival [20, 21].

A further limitation in evaluating recurrent disease is that CT or MRI is unreliable in distinguishing persistent or recurrent tumor from necrosis, posttreatment inflammation or fibrosis. FDG-PET can be useful in detecting local recurrence after definitive treatment with surgery, chemotherapy or radiotherapy before conventional imaging (Fig. 6) [22, 23]. In a prospective study of 62 patients who had undergone surgical resection of NSCLC, FDG-PET was able to detect tumor recurrence (sensitivity 93%, specificity 89%, accuracy 92%) and predict which patients would benefit most from surgical retreatment [24]. Diagnostic difficulties over the presence or absence of persistent or recurrent cancer most frequently arise after

radiotherapy, as associated radiation-induced inflammatory changes can result in false positive FDG uptake (Fig. 7). However, Hicks et al., in a study of 73 patients with NSCLC treated with radical radiotherapy, reported that the ability of FDG-PET performed a median of 70 (range 39–123) days in 90% of patients after completion of radical radiotherapy to assess therapeutic response was not confounded by radiation-induced inflammatory change [22].

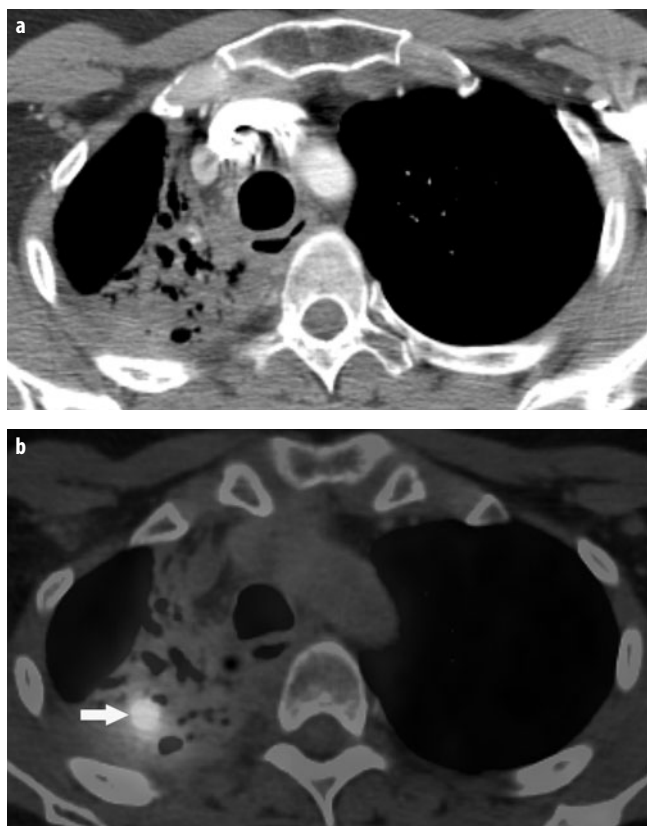


Fig. 6 a, b. Recurrence of non-small-cell lung cancer in a 50-year-old woman 11 months after chemoradiation therapy. **a** Chest computed tomography (CT) shows atelectatic and consolidative opacities due to radiation-induced lung injury. **b** Fused positron emission tomography CT (PET-CT) shows increased [^{18}F]fluoro-2-deoxy-D-glucose (FDG) focal increased FDG uptake (arrow) in radiation fibrosis consistent with recurrent malignancy (for color reproduction see p 273)

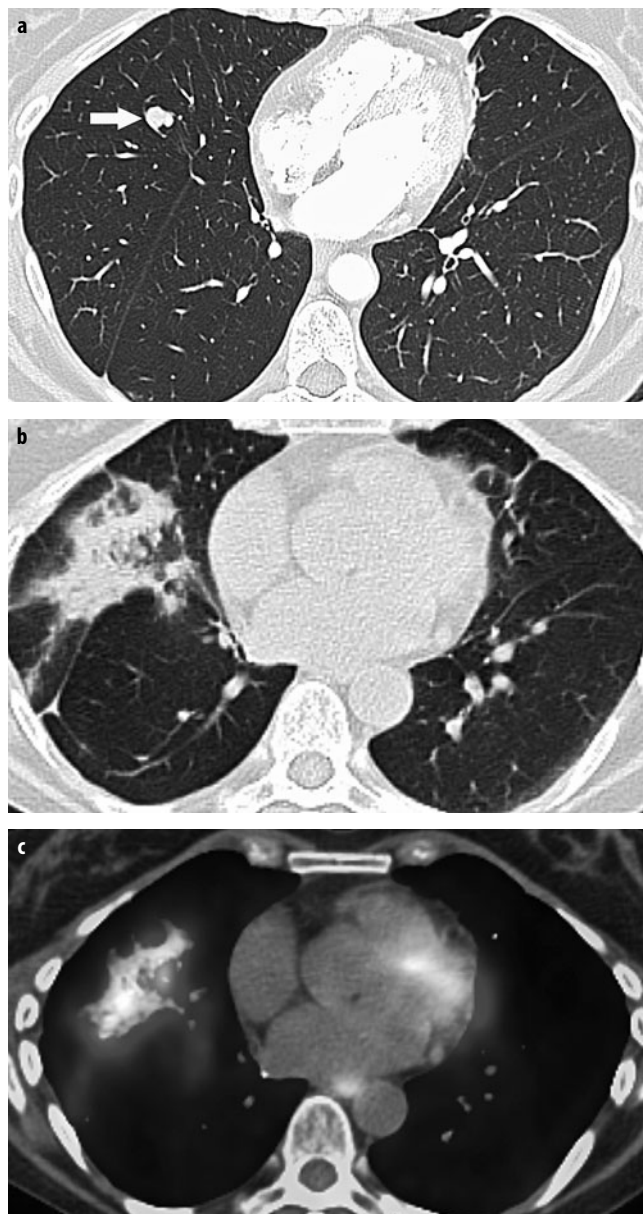


Fig. 7 a-c. False-positive uptake of [^{18}F]fluoro-2-deoxy-D-glucose (FDG) in a 56-year-old woman with non-small-cell lung cancer treated with stereotactic body radiation. **a** Chest computed tomography (CT) shows a small right lung nodule (arrow). **b** Chest CT component of positron emission tomography (PET-CT) 12 weeks after radiation shows focal consolidation in the right lung due to radiation-induced lung injury. **c** Fused PET-CT reveals diffuse increased FDG uptake in the right lung consolidation. Note radiation-induced inflammatory changes can result in false positive FDG uptake (for color reproduction see p 273)

Therapeutic Response Evaluation

Response to therapy is often determined clinically by image-based serial measurements of tumor size before and after treatment based on Response Evaluation Criteria In Solid Tumours (RECIST) [25]. However, morphological alterations detected by CT may not correlate with pathological response. FDG-PET may allow an early and sensitive assessment of the effectiveness of anticancer chemotherapy, as FDG uptake is not only a function of proliferative activity but is also related to viable tumor

cell number. Importantly, because metabolic response to therapy can occur earlier and may be more accurate than anatomical response, FDG-PET imaging could potentially improve the selection of patients for resection after neoadjuvant therapy (Fig. 8) [26-30]. In a prospective trial of 93 patients with NSCLC and biopsy-proven stage IIIA N2 disease, PET-CT was better than CT alone in evaluating these patients after neoadjuvant chemoradiation therapy [28]. A decrease of 75% or more in standard uptake value (SUV) of the primary tumor indicated a high likelihood of a complete response, and a decrease

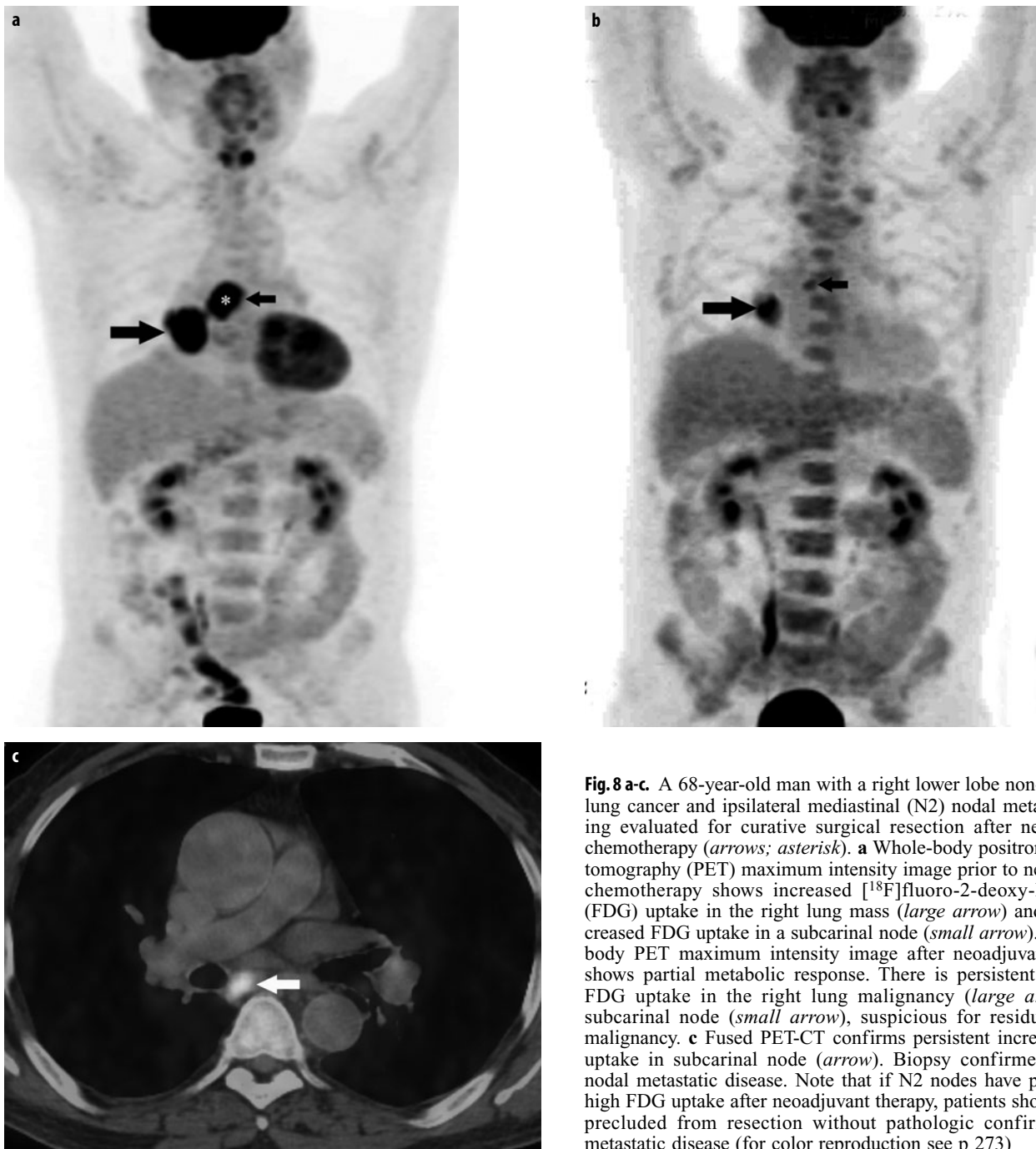


Fig. 8 a-c. A 68-year-old man with a right lower lobe non-small-cell lung cancer and ipsilateral mediastinal (N2) nodal metastases being evaluated for curative surgical resection after neoadjuvant chemotherapy (arrows; asterisk). **a** Whole-body positron emission tomography (PET) maximum intensity image prior to neoadjuvant chemotherapy shows increased [^{18}F]fluoro-2-deoxy-D-glucose (FDG) uptake in the right lung mass (large arrow) and focal increased FDG uptake in a subcarinal node (small arrow). **b** Whole-body PET maximum intensity image after neoadjuvant therapy shows partial metabolic response. There is persistent increased FDG uptake in the right lung malignancy (large arrow) and subcarinal node (small arrow), suspicious for residual, viable malignancy. **c** Fused PET-CT confirms persistent increased FDG uptake in subcarinal node (arrow). Biopsy confirmed residual nodal metastatic disease. Note that if N2 nodes have persistently high FDG uptake after neoadjuvant therapy, patients should not be precluded from resection without pathologic confirmation of metastatic disease (for color reproduction see p 273)

by >50% in the N2 node SUV indicated a high likelihood that there was no residual metastatic disease in the node.

Interpreting SUV measurements after neoadjuvant therapy can be confounded by different factors, including tumor-cell differentiation and macrophage infiltration. In fact, some tumors and nodes retain high SUV measurements at the end of therapy, even with histopathological complete remission at the time of resection [29, 31]. In this regard, Pöttgen et al. reported that in 19 patients with NSCLC with a complete pathologic response of the primary tumor after neoadjuvant therapy, the mean SUV was 3.0 (range, 0.4-9.8) [29]. Accordingly, FDG-PET imaging should not be used in isolation in therapeutic decisions concerning eligibility for surgical resection or dose-escalated radiotherapy after neoadjuvant treatment.

In patients with advanced-stage NSCLC, tumor progression can occur following chemotherapy initiation. Early determination of this therapeutic failure would assist clinical decisions concerning discontinuation of ineffective treatment and institution of alternative therapy. However, there have been comparatively few studies assessing the value of early FDG-PET in assessing tumor response while patients are still receiving therapy [32, 33]. A decrease in FDG uptake before and after one cycle of chemotherapy may predict outcome, with improved survival directly related to the magnitude of decreased uptake. In a prospective study of 57 patients with stage IIIB or IV unresectable NSCLC who underwent restaging FDG-PET after only one cycle of platinum-based chemotherapy, a fall in SUV of $\geq 20\%$ in the primary tumor was an independent predictor of long-term survival (median survival of responders: 252 days versus 151 days for nonresponders) [32].

A limitation in using FDG-PET when assessing therapeutic response in patients with NSCLC is the poor SUV reproducibility from institution to institution. This is partly due to the lack of standardisation when performing FDG-PET imaging. For instance, there is no consensus on performance timing of FDG-PET imaging or scanning and image reconstruction methods or the most appropriate criteria for assessing tumor response. To address this issue, the European Organization for Research and Treatment of Cancer (EORTC) PET Study Group and the Cancer Imaging Program of the National Cancer Institute proposed guidelines for FDG-PET imaging to determine prognosis and response to therapy [34, 35]. More recently, a draft framework for PET Response Criteria in Solid Tumours (PERCIST 1.0) was proposed. The criteria are intended to represent a framework for use in clinical studies and clinical care and as a foundation to refine and validate quantitative approaches to monitoring PET tumor response [36].

Conclusion

PET compliments conventional radiologic assessment of NSCLC and is being routinely used to improve the detection of nodal and extrathoracic metastases. FDG-PET is also being evaluated for assessing therapeutic response,

and by potentially allowing an earlier assessment of response may prove invaluable in the oncologic management of patients.

References

1. Rami-Porta R, Ball D, Crowley J et al (2007) The IASLC Lung Cancer Staging Project: proposals for the revision of the T descriptors in the forthcoming (seventh) edition of the TNM classification for lung cancer. *J Thorac Oncol* 2:593-602
2. Rusch VW, Crowley J, Giroux DJ et al (2007) The IASLC Lung Cancer Staging Project: proposals for the revision of the N descriptors in the forthcoming seventh edition of the TNM classification for lung cancer. *J Thorac Oncol* 2:603-612
3. Postmus PE, Brambilla E, Chansky K et al (2007) The IASLC Lung Cancer Staging Project: proposals for revision of the M descriptors in the forthcoming (seventh) edition of the TNM classification of lung cancer. *J Thorac Oncol* 2:686-693
4. Goldstraw P, ed (2009) IASLC Staging Reference Card in Thoracic Oncology, Editorial Rx Press, New Milford, PA
5. Bruzzi JF, Komaki R, Walsh GL et al (2008) Imaging of non-small cell lung cancer of the superior sulcus: part 2: initial staging and assessment of resectability and therapeutic response. *RadioGraphics* 28:561-572
6. Bruzzi JF, Komaki R, Walsh GL et al (2008) Imaging of non-small cell lung cancer of the superior sulcus: part 1: anatomy, clinical manifestations, and management. *RadioGraphics* 28:551-60; quiz 620
7. Bilsky MH, Vitaz TW, Boland PJ (2002) Surgical treatment of superior sulcus tumors with spinal and brachial plexus involvement. *J Neurosurg* 97(3 Suppl):301-309
8. Prenzel KL, Monig SP, Sinning JM et al (2003) Lymph node size and metastatic infiltration in non-small cell lung cancer. *Chest* 123:463-467
9. Toloza EM, Harpole L, Detterbeck F, McCrory DC (2003) Invasive staging of non-small cell lung cancer: a review of the current evidence. *Chest* 123(1 Suppl):S157-S166
10. Birim O, Kappetein AP, Stijnen T, Bogers AJ (2005) Meta-analysis of positron emission tomographic and computed tomographic imaging in detecting mediastinal lymph node metastases in nonsmall cell lung cancer. *Ann Thorac Surg* 79:375-382
11. Antoch G, Stattauss J, Nemat AT et al (2003) Non-small cell lung cancer: dual-modality PET/CT in preoperative staging. *Radiology* 229(2):526-533
12. de Langen AJ, Raijmakers P, Riphagen I et al (2006) The size of mediastinal lymph nodes and its relation with metastatic involvement: a meta-analysis. *Eur J Cardiothorac Surg* 29:26-29
13. Reed CE, Harpole DH, Posther KE et al (2003) Results of the American College of Surgeons Oncology Group Z0050 trial: the utility of positron emission tomography in staging potentially operable non-small cell lung cancer. *J Thorac Cardiovasc Surg* 126:1943-1951
14. Verboom P, Van Tinteren H, Hoekstra OS et al (2003) Cost-effectiveness of FDG-PET in staging non-small cell lung cancer: the PLUS study. *Eur J Nucl Med Mol Imaging* 30:1444-1449
15. van Tinteren H, Hoekstra OS, Smit EF et al (2002) Effectiveness of positron emission tomography in the preoperative assessment of patients with suspected non-small-cell lung cancer: the PLUS multicentre randomised trial. *Lancet* 359:1388-1393
16. MacManus MP, Hicks RJ, Matthews JP et al (2001) High rate of detection of unsuspected distant metastases by PET in apparent stage III non-small-cell lung cancer: implications for radical radiation therapy. *Int J Radiat Oncol Biol Phys* 50:287-293
17. Vinay RC, Boyer MJ, King MT et al (2004) Randomized controlled trial of the role of positron emission tomography in the management of stage I and II non-small-cell lung cancer. *J Clin Oncol* 22:2357-2362

18. Lardinois D, Weder W, Roudas M et al (2005) Etiology of solitary extrapulmonary positron emission tomography and computed tomography findings in patients with lung cancer. *J Clin Oncol* 23:6846-6853
19. Colice GL, Rubins J, Unger M (2003) Follow-up and surveillance of the lung cancer patient following curative-intent therapy. *Chest* 123(1 Suppl):S272-S283
20. Walsh GL, O'Connor M, Willis KM et al (1995) Is follow-up of lung cancer patients after resection medically indicated and cost-effective? *Ann Thorac Surg* 60:1563-1672
21. Westeel V, Choma D, Clement F et al (2000) Relevance of an intensive postoperative follow-up after surgery for non-small cell lung cancer. *Ann Thorac Surg* 70:1185-1190
22. Hicks RJ, Kalff V, MacManus MP et al (2001) The utility of (18)F-FDG PET for suspected recurrent non-small cell lung cancer after potentially curative therapy: impact on management and prognostic stratification. *J Nucl Med* 42:1605-1613
23. Hellwig D, Groschel A, Graeter TP et al (2006) Diagnostic performance and prognostic impact of FDG-PET in suspected recurrence of surgically treated non-small cell lung cancer. *Eur J Nucl Med Mol Imaging* 33:13-21
24. Curran WJ Jr, Herbert SH, Stafford PM et al (1992) Should patients with post-resection locoregional recurrence of lung cancer receive aggressive therapy? *Int J Radiat Oncol Biol Phys* 24:25-30
25. Therasse P, Eisenhauer EA, Verweij J (2006) RECIST revisited: a review of validation studies on tumour assessment. *Eur J Cancer* 42:1031-1039
26. De Leyn P, Stroobants S, De Wever W et al (2006) Prospective comparative study of integrated positron emission tomography-computed tomography scan compared with mediastinoscopy in the assessment of residual mediastinal lymph node disease after induction chemotherapy for mediastinoscopy-proven stage IIIA-N2 Non-small-cell lung cancer: a Leuven Lung Cancer Group Study. *J Clin Oncol* 24:3333-3339
27. Eschmann SM, Friedel G, Paulsen F et al (2007) Repeat 18F-FDG PET for monitoring neoadjuvant chemotherapy in patients with stage III non-small cell lung cancer. *Lung Cancer* 55:165-171
28. Cerfolio RJ, Bryant AS, Ojha B (2006) Restaging patients with N2 (stage IIIa) non-small cell lung cancer after neoadjuvant chemoradiotherapy: a prospective study. *J Thorac Cardiovasc Surg* 131:1229-1235
29. Pöttgen C, Levegrun S, Theegarten D et al (2006) Value of 18F-fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography in non-small-cell lung cancer for prediction of pathologic response and times to relapse after neoadjuvant chemoradiotherapy. *Clin Cancer Res* 12:97-106
30. Eschmann SM, Friedel G, Paulsen F et al (2007) 18F-FDG PET for assessment of therapy response and preoperative re-evaluation after neoadjuvant radio-chemotherapy in stage III non-small cell lung cancer. *Eur J Nucl Med Mol Imaging* 34:463-471
31. Ohtsuka T, Nomori H, Ebihara A et al (2006) FDG-PET imaging for lymph node staging and pathologic tumor response after neoadjuvant treatment of non-small cell lung cancer. *Ann Thorac Cardiovasc Surg* 12:89-94
32. Weber WA, Petersen V, Schmidt B et al (2003) Positron emission tomography in non-small-cell lung cancer: prediction of response to chemotherapy by quantitative assessment of glucose use. *J Clin Oncol* 21:2651-2657
33. Hoekstra CJ, Stroobants SG, Smit EF et al (2005) Prognostic relevance of response evaluation using [18]F-2-fluoro-2-deoxy-D-glucose positron emission tomography in patients with locally advanced non-small-cell lung cancer. *J Clin Oncol* 23:8362-8370
34. Young H, Baum R, Cremerius U et al (1999) Measurement of clinical and subclinical tumour response using [18F]-fluorodeoxyglucose and positron emission tomography: review and 1999 EORTC recommendations. European Organization for Research and Treatment of Cancer (EORTC) PET Study Group. *Eur J Cancer* 35:1773-1782
35. Shankar LK, Hoffman JM, Bacharach S et al (2006) Consensus recommendations for the use of 18F-FDG PET as an indicator of therapeutic response in patients in National Cancer Institute Trials. *J Nucl Med* 47:1059-1066
36. Wahl RL, Jacene H, Kasamon Y, Lodge MA (2009) From RECIST to PERCIST: evolving considerations for PET response criteria in solid tumors. *J Nucl Med* 50(Suppl 1):S122-S150



Lung Scintigraphy in Pulmonary Embolism

Giuliano Mariani¹, Laura Bruselli²

¹ Regional Center of Nuclear Medicine, University of Pisa Medical School, Pisa, Italy

² Nuclear Medicine Division, Department of Oncology, Transplantation and Advanced Technologies in Medicine, University of Pisa, Pisa, Italy

Introduction

As recently reviewed [1-4], lung scintigraphy has long been the mainstay for diagnosing acute pulmonary embolism (PE), whether based on the ventilation/perfusion study, as in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) approach [5, 6], or on perfusion only as in the Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis (PISA-PED) approach [7]. Nevertheless, advanced imaging technologies, most notably, multidetector-row CT pulmonary angiography (MDCT-PA), are now challenging the concept of lung scintigraphy as the first-line approach when diagnosing acute PE (APE) [8-11]. On the other hand, the issue is especially relevant considering the fact that APE is a relatively common cardiovascular emergency that, if not timely diagnosed and adequately treated, may cause sudden death or acute life-threatening right-ventricular failure [12, 13]. In the long term, untreated PE can also be a common cause of chronic pulmonary hypertension, a complication that can be avoided with efficient therapies readily and widely available, such as heparin or thrombolytic agents in the acute phase and oral anticoagulants for long-term secondary prevention [14-17]. The clinical problem is even more complicated because of the stringent requirement of employing an adequate diagnostic approach when APE is suspected on clinical ground [18] and because this condition often occurs with nonspecific or atypical presentations and thus remains a serious underlying challenge in the diagnostic pathway of any cardiovascular emergency.

When assessing the relative merits of the two imaging methods, which are often considered as competitive for diagnosing APE (i.e. MDCT-PA and lung scintigraphy) [19, 20], it should also be considered that in the last few years, the latter has considerably evolved from the original planar imaging technique by becoming tomographic first [as with single photon emission CT (SPECT)] then by incorporating (as with SPECT-CT) the diagnostic advantages, especially in terms of specificity, which hybrid imaging can offer in the approach to patients with suspected acute pulmonary embolism [21-24].

Clinical Background and Pretest Probability of Pulmonary Embolism

The clinical presentation of APE includes a wide spectrum of symptoms that can occur either suddenly or gradually over days and even weeks: unexplained breathlessness, chest pain, cough, syncope, haemoptysis, palpitations, tachypnoea, tachycardia, cyanosis, fever, hypotension, right atrial dysfunction, pulmonary hypertension, shock. Besides these symptoms of a cardiopulmonary condition, there can be other associated signs and symptoms of deep-vein thrombosis (e.g. leg swelling), the most common underlying condition causing pulmonary embolism; on the other hand, deep-vein thrombosis itself can be totally asymptomatic [25].

Decades of clinical experience have stimulated experts to elaborate diagnostic algorithms based on a preliminary evaluation of easy-to-obtain clinical data and designed to stratify patients with suspected APE according to their probability of actually having the disease. As reviewed in detail elsewhere [20], at least three widely employed systems have been developed for estimating semiquantitative scores defining the probability of a patient to have or not to have APE; these systems rely on varying combinations of relatively simple data, such as medical history, clinical examination, arterial blood gas analysis, electrocardiogram (ECG) and chest X-ray [26]. They are usually denominated as the the Hamilton score, the Pisa score and the Geneva score, respectively; the performance of all three systems is generally good for what concerns, in particular, their negative predictive value, i.e. between 90% and 97% of patients classified as having a low probability for APE are eventually diagnosed (after further imaging evaluation) as not being affected by the disease. There are, instead, some differences concerning their positive predictive value, i.e. when patients are classified as having high probability for APE; in fact, this parameter ranges between 78% and 97%. Finally, the proportion of patients eventually diagnosed as being affected by APE ranges between 30% and 40% across the three systems when the pretest probability for the disease is intermediate. Nevertheless, the Pisa score (at variance with the other two scores performs equally well for outpatients as for

inpatients) classifies the smallest fraction of cases as having intermediate probability for APE (22.1% vs. 32.5% for the Hamilton score and 44.3% for the Geneva score), and thus reduces to a minimum the uncertainties of pretest stratification. Models with increasing complexity have also been developed to assist in the diagnostic algorithm for APE [27, 28].

First-Line Imaging Investigations for APE

The simplest and most frequently employed imaging investigation in the diagnostic approach to patients with suspected APE is standard chest X-ray (preferably in the two orthogonal projections). Besides being sometimes included in the pretest probability score (as in the Hamilton and in the Pisa score systems), the results of chest X-ray are also taken into account in the interpretation of lung scintigraphy, both according to the PIOPED and PISA-PED criteria. Whereas definite diagnosis of APE is very seldom achieved on the basis of chest X-ray findings alone, such findings most frequently provide ancillary information on pre-existing and/or concomitant conditions that might explain abnormalities in the lung scintigraphy pattern and that might otherwise be erroneously interpreted as due to PE. Such conditions may include any of the following changes in chest X-ray: enlargement of the heart, hilum or mediastinum; elevated hemidiaphragm; effusion in the costophrenic angle or more extensive effusion of one third or more of the pleural cavity; intrafissural effusion; pleural thickening; isolated linear atelectasis.

Another simple imaging modality that provides useful information about the presence of deep-vein thrombosis as the possible origin of thromboemboli causing APE is represented by Doppler ultrasound examination of the lower limbs. More complex investigations aiming at detecting deep-vein thrombosis include gadolinium-enhanced magnetic resonance and, above all, the venous phase of contrast-enhanced CT angiography [29].

Diagnosing APE with Lung Scintigraphy

Since more than four decades, scintigraphic evaluation of lung perfusion is based on i.v. injection of radiolabeled macroaggregates of human serum albumin (MAA). As these particles are large enough to impact in the terminal arterioles and other precapillary vessels, their distribution within the lungs mirrors distribution of blood flow when such particles are evenly distributed with blood. This radiopharmaceutical is therefore a negative indicator of disease, as areas of the lungs where blood flow is reduced/absent due to embolisation show up as “cold” areas in the scan (perfusion defects) [20].

Lung perfusion scintigraphy has an extremely high negative predictive value for PE, as a truly normal perfusion scan virtually excludes the diagnosis of clinically

relevant PE; few exceptions to this rule include central, nonobstructing pulmonary embolism causing an evenly distributed reduction in whole lung perfusion or minimal perfusion defects below the resolution power of scintigraphy (therefore nonsignificant from the haemodynamic point of view). Whereas sensitivity of this imaging technique is likewise extremely high, its specificity is unfortunately rather low. In fact, several pathophysiologic conditions can cause focal defects in a lung perfusion scan, such as compression or invasion of pulmonary vessels by tumors or granulomata, emphysema (especially of the bullous type), interstitial fibrosis, bronchiectasis, pneumonic consolidation and atelectasis, localised bronchial obstruction, vasculitis, arteriovenous fistulae and other less frequent conditions. It is also worth mentioning that perfusion defects revealed by a lung scintigraphy can also be due to prior, unresolved pulmonary embolism, a condition that can affect as many as 35% of the patients with APE [20].

The mechanism by which in non-PE conditions blood flow is diverted from poorly ventilated to better-ventilated lung areas (to optimise ventilation/perfusion ratio) is represented by intrapulmonary events that tend to maximise respiratory gas exchanges in the presence of diseases that primarily affect air flow in the alveolar space. On the other hand, the reciprocal mechanism occurs in the case of primary reductions in blood flow to certain lung areas due, for instance, to PE. In fact, within a few hours after blood-flow obstruction, air flow is diverted from nonperfused to perfused lung zones to avoid ventilation of areas where respiratory gas exchanges cannot occur. Possible events underlying such mechanism include, among others, local bronchoconstriction caused by hypocapnia (early after embolisation, within about 30 min) and shrinkage of the alveolar space caused by reduced local production of surfactant distal to embolisation (a relatively late event, within about 18–24 h). These concepts are to be taken into account when interpreting the patterns possibly observed in a ventilation/perfusion scan, as is frequently performed in patients with suspected APE.

To increase specificity of lung perfusion scintigraphy for the diagnosis of APE, combined ventilation/perfusion scintigraphy was felt to represent the solution for better characterising perfusion deficits; the underlying assumption of this approach was that areas with reduced perfusion and ventilation (matching defects) would indicate some pre-existing parenchymal condition, making the diagnosis of APE unlikely, whereas underperfused but normally ventilated areas (mismatch pattern) would represent embolism [20, 21]. However, this approach did not represent a univocal solution to the diagnostic dilemma, as a retrospective study based on correlation of clinical data with autopsy findings indicated successful *in vitro* diagnosis of APE in only 30% of the cases.

The already mentioned PIOPED and PISA-PED studies have considerably improved upon the initial diagnostic performances of the ventilation/perfusion scan or the

perfusion scan alone, respectively. The PIOPED protocol correlates results of the ventilation/perfusion scan with the chest X-ray findings to classify patients as having high, intermediate or low probability of APE, respectively. Whereas the PISA-PED protocol correlates the results of perfusion lung scintigraphy alone with chest X-ray findings to classify patients as either having or not having APE; in PIOPED, shape and distribution (segmental or nonsegmental) of the perfusion defects are considered. The PIOPED actually increased specificity of ventilation/perfusion scintigraphy for diagnosing APE up to 97% when underperfused areas were normally ventilated; however, sensitivity was only 41% in patients with documented APE. In particular, underperfused but normally ventilated areas did not invariably represent APE, whereas the presence of matching ventilation/perfusion defects did not invariably exclude APE. Furthermore, in the original PIOPED protocol, as many as 44% of patients were classified as intermediate probability of having pulmonary embolism; this category neither confirmed nor

excluded APE, thus making the examination nondiagnostic. Moreover, there was a relatively wide interobserver variability in the estimation of perfusion defects percent size, a fundamental parameter for PIOPED criteria. Part of these limitations were reduced by a revision of the original interpretation criteria (Table 1) for easier application and also for better integration with the clinical pretest probability of APE; this resulted in increased sensitivity (83% vs. 41%), yet without reducing specificity (96% vs. 97%).

As to the PISA-PED protocol, which is based on perfusion lung scintigraphy alone (i.e. without ventilation scan), the diagnostic algorithm starts with clinical probability of disease assessed according to the pretest Pisa scoring system. The scintigraphic findings are interpreted by paying special attention mostly to the shape and type of segmental or nonsegmental distribution of perfusion defects, also considering possible abnormalities in the chest X-ray (Table 2). Furthermore, according to the PISA-PED approach, lung scintigraphy either confirms

Table 1. Modified Prospective Investigation of Pulmonary Embolism Diagnosis II (PIOPED) scintigraphic criteria for diagnosis of pulmonary embolism

Category	Findings
PE present (high probability)	Two or more segments of V/Q mismatch
PE absent (normal perfusion or very low probability)	Nonsegmental perfusion abnormalities: enlargement of the heart or hilum, elevated hemidiaphragm, costophrenic angle effusion, and linear atelectasis with no other perfusion defect in either lung Perfusion defect smaller than corresponding X-ray lesion Two or more matched V/Q defects with regionally normal chest X-ray and some areas of normal perfusion elsewhere in the lungs 1-3 small segmental perfusion defects (<25% of segment) Solitary triple-matched defect (defined as a matched V/Q defect with associated matching chest X-ray opacity) in the mid or upper lung zone confined to a single segment Stripe sign (a stripe of perfused lung tissue between a perfusion defect and the adjacent pleural surface; best seen on a tangential view) Pleural effusion of 1/3 or more of the pleural cavity with no other perfusion defect in either lung
Nondiagnostic (low or intermediate probability)	All other findings

PE, pulmonary embolism; V/Q, ventilation/perfusion scan (reproduced from [6], with permission)

Table 2. Reading of perfusion lung scintigraphy according to the Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis (PISA-PED) protocol

Category	Findings
Normal	No perfusion defects of any kind
Near normal	Perfusion defects smaller or equal in size and shape than extra-pulmonary chest X-ray abnormalities such as: cardiomegaly, enlarged aorta, enlarged hila and mediastinum, elevated diaphragm, blunting of the costophrenic angle, pleural thickening, intrafissural effusion collection
Abnormal scan with PE	Single or multiple wedge-shaped defects with or without matching pulmonary chest X-ray abnormalities; wedge-shaped areas of overperfusion usually coexist
Abnormal scan without PE	Single or multiple defects other than wedge-shaped, with or without matching pulmonary chest X-ray abnormalities; wedge shaped areas of overperfusion are usually not seen

PE, pulmonary embolism (reprinted from [7] with permission of the American Thoracic Society © American Thoracic Society)

or excludes the clinical suspicion of APE; nondiagnostic examinations are therefore virtually eliminated. Moreover, sensitivity of lung perfusion scintigraphy interpreted according to the PISA-PED criteria is much higher than that of the combined ventilation/perfusion scan interpreted according to the PIOPED criteria (86% vs. 41%), whereas specificity is only marginally reduced (from 97% to 93%). This superior diagnostic performance of the PISA-PED criteria is also maintained with respect to the revised PIOPED criteria, although to a lesser extent [20].

Growing application of the PISA-PED protocol (especially in Europe and elsewhere outside the United States, where the PIOPED protocol is almost universally adopted) is explained both by practical considerations (such as reduced radiation exposure to personnel, faster and easier handling of acutely ill patients) and by further analysis of the PIOPED data, indicating that the ventilation scan was not essential. On the other hand, the pathophysiologic adaptation mechanism mentioned above explains that air flow is diverted from underperfused to normally perfused lung areas in order to optimise respiratory gas exchanges, therefore undermining the assumption that matching defects would solely indicate pre-existing conditions as an alternative diagnosis to APE. As a matter of fact, when the perfusion scans and chest X-rays films from the PIOPED I study were reread according to the PISA-PED criteria, a higher sensitivity was found than when including also the ventilation scan in the analysis [7]. This pattern has been more recently confirmed by analysis of the PIOPED II according to the PISA-PED criteria [2, 3]. In particular, although diagnostic sensitivities and specificities were similar for the two reading methods (84.9% sensitivity of modified PIOPED vs. 80.4% for PISA-PED; 92.7% specificity of modified PIOPED vs. 96.6% for PISA-PED), there were still 20.6% nondiagnostic scans according to PIOPED criteria (that had therefore to be excluded from analysis of sensitivity and specificity), vs. 0% with PISA-PED criteria.

Direct Visualization of Emboli in the Pulmonary Arteries: MDCT-PA

The high spatial and temporal resolution of modern technology spiral MDCT has virtually replaced conventional PA (performed during right cardiac catheterisation), with MDCT-PA as the gold standard for directly visualising emboli, which appear as filling defects in the pulmonary arteries [8-11]. This trend has also resulted in a definite shift of diagnostic imaging procedures for patients with suspected APE from lung scintigraphy directly to MDCT-PA. In this regard, it should also be considered that most emergency rooms have immediate access to such equipment, even out of hours, whereas the same is not true for most nuclear medicine centres. It is also claimed that MDCT-PA with

the most recent equipment visualises the pulmonary arterial tree down to the subsegmental level (even to vessels <1 mm in diameter) and reduces interobserver variability in image interpretation. Another advantage of the procedure is that it also identifies alternative causes of signs/symptoms possibly suggesting APE, and therefore minimises the risks of inappropriately treating with heparin/thrombolytic agents patients who are not affected by APE while at the same time reduces delays in treating patients affected by other cardiovascular emergencies (e.g. acute myocardial infarction).

On the other hand, this imaging technique implies a considerable radiation burden to patients. Although dosimetric estimates vary greatly according to the different computation models employed, it is commonly acknowledged that the radiation dose absorbed by the critical organ for MDCT-PA (the breast) can be up to 100-fold higher than that caused by a ventilation/perfusion scintigraphy. This issue is of particular concern when young adult women with suspected APE must be evaluated, as the risk of developing breast cancer as a consequence of such exposure can be as high as 1 out of approximately 150-200, with variations depending on patient age, equipment type and imaging protocol employed [30]. In this regard, some caution should be issued about the possible overuse of MDCT-PA, for instance, when suspicion of APE is not preliminarily tested with the simple scoring systems mentioned above; as a matter of fact, it is estimated that the proportion of cases in which MDCT-PA confirms the presence of APE is only <10%, a value that should raise concerns about actual overuse of MDCT-PA.

Strengths and weaknesses of both MDCT-PA and lung scintigraphy for diagnosing APE are summarized in Table 3. Clearly, strict guidelines cannot be given as to which imaging procedure is to be employed as first-line diagnostic approach in suspected APE; local expertise and logistics dictates the practical implementation of internal protocols and procedures aiming to achieving maximum benefit and minimum risks to the patient from the procedures themselves. Obviously, clinical conditions such as, among others, reduced renal function and allergy to iodinated contrast media mandate lung scintigraphy [4, 18-20, 25, 30]. Finally, even when MDCT-PA performed as first-line imaging procedure confirms the presence of APE, a perfusion lung scan should always be obtained shortly afterwards (when the patient is clinically and hemodynamically stable) as a baseline evaluation of the underperfused lung areas for subsequent reference in follow-up during therapy. In fact, MDCT-PA for routine follow-up imaging in patients with PE is not recommended [31] and should actually be discouraged.

Evolution of Lung Scintigraphy: SPECT and SPECT/CT

Most experience cumulated on lung scintigraphy over approximately four decades has been based on planar imaging

Table 3. Relative strengths and weaknesses of multidetector-row computed tomography pulmonary angiography (MDCT-PA) and lung scintigraphy in the evaluation of pulmonary thromboembolism

	Strengths	Weaknesses
MDCT-PA	High overall accuracy High interobserver agreement Provision of alternative diagnoses High out-of-hours availability Rapidity of acquisition Assessment of haemodynamic surrogates for prognosis	High relative radiation burden Patient safety issues: contrast reactions renal impairment injection site trauma Dilemma of “incidental” PE Higher relative cost Variable worldwide availability Not suitable for follow-up
Lung scintigraphy	High NPV in low pretest probability High PPV in high pretest probability Relative safety in certain patient groups Lower radiation dose Lower relative cost Suitable for follow-up Higher worldwide availability	Lower overall specificity Lower interobserver agreement of intermediate probability scans (PIOPED) Poorer out-of-hours availability in some areas Longer acquisition time Does not provide alternative diagnoses

NPV, negative predictive value; PPV, positive predictive value



Fig. 1. Coronal, transaxial and sagittal fused single photon emission computed tomography slices from a lung perfusion scan (*left, middle and right panels*, respectively). The images demonstrate that reduced perfusion in the lingula corresponds to a lung area with extensive parenchymal consolidation, thus excluding acute pulmonary embolism as the cause of the perfusion defect (reproduced from [24], with permission by Elsevier, © Elsevier 2010) (for color reproduction see p 273)

for either the perfusion scan or the ventilation/perfusion scan, simply acquiring multiple views in a standardised fashion for better visualising specific segments of the lungs. As mentioned above, the more recent introduction of SPECT and especially of hybrid SPECT/CT has brought about novel potential to the interpretation of the scintigraphic patterns according to three-dimensional volumetric imaging; this potential is being increasingly recognised, and specific guidelines have recently been issued by the European Association of Nuclear Medicine for performing and interpreting lung scintigraphy acquired with SPECT modality, to be included in integrated diagnostic algorithms in patients with suspected APE [21, 22]. Furthermore, implementation of full diagnostic CT components in modern SPECT/CT cameras now allows full advantage of the possibilities offered by such hybrid equipment, not on-

ly for topographic localisation of perfusion deficits but also for better identifying conditions that lead to pathologic changes visualised in the CT component of the examination (Fig. 1). The ability of SPECT/CT to analyse data objectively or to incorporate both functional and anatomical information using image fusion also includes the possibility of co-registering MDCT-PA and lung scintigraphy postacquisition via dedicated software (Fig. 2) [24]. Even stand-alone SPECT confers higher diagnostic accuracy to lung scintigraphy in patients with suspected APE, thus possibly reducing the number of nondiagnostic ventilation/perfusion scans. At the same time, by performing adequate correction for tissue attenuation (based on the transmission X-ray scan), the new technique may be useful for more accurately quantifying ventilation/perfusion mismatch in PE as well as in other pulmonary disorders [24].



Fig. 2. Postacquisition coregistered multidetector-row computed tomography pulmonary angiography (MDCT-PA) and lung perfusion single photon emission computed tomography (SPECT, transaxial slice). The extensive perfusion defects in the SPECT component correspond to the presence of proximal bilateral filling defects (emboli, some of which are indicated by *red arrows*) in the MDCT-PA component (reproduced from [24], with permission by Elsevier, © Elsevier 2010) (for color reproduction see p 273)

References

- Freeman LM, Stein EG, Sprayregen S et al (2008) The current and continuing important role of ventilation-perfusion scintigraphy in evaluating patients with suspected pulmonary embolism. *Semin Nucl Med* 38:432-440
- Miniati M, Sostman HD, Gottschalk A et al (2008) Perfusion lung scintigraphy for the diagnosis of pulmonary embolism: A reappraisal and review of the prospective investigative study of pulmonary embolism diagnosis methods. *Semin Nucl Med* 38:450-461
- Sostman HD, Miniati M, Gottschalk A et al (2008) Sensitivity and specificity of perfusion scintigraphy combined with chest radiography for acute pulmonary embolism in PIOPED II. *J Nucl Med* 49:1741-1748
- Stein PD, Sostman HD, Bounameaux H et al (2008) Challenges in the diagnosis of acute pulmonary embolism. *Am J Med* 121:565-571
- PIOPED Investigators (1990) Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED). *JAMA* 263:2753-2759
- Sostman HD, Stein PD, Gottschalk A et al (2008) Acute pulmonary embolism: sensitivity and specificity of ventilation-perfusion scintigraphy in PIOPED II study. *Radiology* 246:941-946
- Miniati M, Pistolesi M, Marini C et al (1996) Value of perfusion lung scan in the diagnosis of pulmonary embolism: Results of the Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis (PISA-PED). *Am J Respir Crit Care Med* 154:1387-1393
- British Thoracic Society Standards of Care Committee Pulmonary Embolism Guideline Development Group (2003) British Thoracic Society guidelines for the management of suspected acute pulmonary embolism. *Thorax* 58:470-483
- Coche E, Vlassenbroek A, Roelants V et al (2005) Evaluation of biventricular ejection fraction with ECG-gated 16-slice CT: preliminary findings in acute pulmonary embolism in comparison with radionuclide ventriculography. *Eur Radiol* 15:1432-1440
- Broder J, Warshauer DM (2006) Increasing utilization of computed tomography in the adult emergency department. *Emerg Radiol* 13:25-30
- Kluge A, Luboldt W, Bachmann G (2006) Acute pulmonary embolism to the subsegmental level: Diagnostic accuracy of three MRI techniques compared with 16-MDCT. *AJR Am J Roentgenol* 187:7-14
- Douketis JD, Kearon C, Bates S, Duku EK, Ginsberg JS (1998) Risk of fatal pulmonary embolism in patients with treated venous thromboembolism. *JAMA* 279:458-462
- Goldhaber SZ, Visani L, De Rosa M (1999) Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet* 353(9162): 1386-1389
- Konstantinides S, Geibel A, Heusel G et al (2002) Management Strategies and Prognosis of Pulmonary Embolism-3 Trial Investigators. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. *N Engl J Med* 347:1143-1150
- Lang IM (2004) Chronic thromboembolic pulmonary hypertension: not so rare after all. *N Engl J Med* 350:2236-2238
- Pengo V, Lensing AW, Prins MH et al (2004) Thromboembolic Pulmonary Hypertension Study Group. Incidence of chronic pulmonary hypertension after pulmonary embolism. *N Engl J Med* 350:2257-2264
- Becattini C, Agnelli G, Pesavento L et al (2006) Incidence of chronic thromboembolic pulmonary hypertension after a first episode of pulmonary embolism. *Chest* 130:172-175
- Remy-Jardin M, Pistolesi M, Goodman LR et al (2007) Management of suspected acute pulmonary embolism in the era of CT angiography: a statement from the Fleischner Society. *Radiology* 245:315-329
- Miniati M, Monti S (2009) Should lung scan be abandoned for pulmonary embolism diagnosis in the age of multislice spiral CT? No. *Intern Emerg Med* 4:193-194
- Reid JH, Coche EE, Inoue T et al (2009) Is the lung scan alive and well? Facts and controversies in defining the role of lung scintigraphy for the diagnosis of pulmonary thromboembolism in the era of multidetector CT. *Eur J Nucl Med Mol Imaging* 36:505-521
- Bajc M, Neilly JB, Miniati M et al (2009) EANM guidelines for ventilation/perfusion scintigraphy. Part 1. Pulmonary imaging with ventilation/perfusion single photon emission tomography. *Eur J Nucl Med Mol Imaging* 36:1356-1370
- Bajc M, Neilly JB, Miniati M et al (2009) EANM guidelines for ventilation/perfusion scintigraphy. Part 2. Algorithms and clinical considerations for diagnosis of pulmonary emboli with V/PSPECT and MDCT. *Eur J Nucl Med Mol Imaging* 36:1528-1538
- Bajc M, Neilly B, Miniati M et al (2010) Methodology for ventilation/perfusion SPECT. *Semin Nucl Med* 40:415-425
- Roach PJ, Gradinscak DJ, Schembri CP et al (2010) SPECT/CT in V/Q scanning. *Semin Nucl Med* 40:455-466
- Torbicki A, Perrier A, Konstantinides S et al (2008) Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). *Eur Heart J* 29:2276-2315
- Kelly J, Hunt BJ (2003) The utility of pretest probability assessment in patients with clinically suspected venous thromboembolism. *J Thromb Haemost* 1:1888-1896
- Miniati M, Monti S, Bottai M (2003) A structured clinical model for predicting the probability of pulmonary embolism. *Am J Med* 114:173-179
- McLean RG, Carolan M, Bui C et al (2004) Comparison of new clinical and scintigraphic algorithms for the diagnosis of pulmonary embolism. *Brit J Radiol* 77:372-376
- Stein PD, Woodard PK, Weg JG et al (2007) Diagnostic pathways in acute pulmonary embolism: recommendations of the PIOPED II investigators. *Radiology* 242:15-21
- Pistolesi M (2008) Challenges in the diagnosis of acute pulmonary embolism. *Am J Med* 121:565-571
- Tunari N, Gibbs SJR, Win Z et al (2007) Ventilation-perfusion scintigraphy is more sensitive than multidetector CTPA in detecting chronic thromboembolic pulmonary disease as a treatable cause of pulmonary hypertension. *J Nucl Med* 48:680-684



PET Imaging in Cardiovascular Disease

Markus Schwaiger, Sibylle I. Ziegler, Stephan G. Nekolla

Klinikum rechts der Isar, Technische Universität München, Nuklearmedizinische Klinik und Poliklinik, München, Germany

Introduction

Cardiovascular imaging has rapidly grown during the last 20 years. The established gold standard invasive cardiac catheterization for documenting coronary artery disease (CAD) is increasingly challenged by noninvasive imaging technologies. In the late 1970s, Gould et al. introduced the concept of coronary flow reserve as a functional measurement for defining the hemodynamic significance of coronary artery stenosis [1]. Functional measurements such as perfusion imaging using scintigraphic, ultrasound, and magnetic resonance (MR) techniques have enjoyed increasing clinical acceptance. Fractional pressure measurements are recognized as an important adjunct of the therapeutic decision-making process in the catheterization laboratory, reinforcing the concept of functional characterization of CAD [2]. There is now widespread consensus that noninvasive tests provide important diagnostic and prognostic information that complements the anatomic delineation of CAD obtainable by cardiac catheterization. Most international guidelines based on evidence criteria demand the combination of anatomic and functional information for indicating coronary interventions [3]. Among the non-invasive cardiac imaging modalities, positron emission tomography (PET) represents the most advanced scintigraphic technology. It allows not only the quantitative assessment of myocardial perfusion but also application of numerous tracers for the molecular characterization of vascular and myocardial tissues. Molecular imaging as a translational tool transferring new biological knowledge to the in vivo characterization of human disease is most aptly supported by PET. The higher sensitivity of tracer approaches compared with MR and computed tomography (CT) imaging is matched by the quantitative nature of PET imaging. Several clinical investigations have demonstrated that the acquisition of metabolic, functional, and molecular information may be of clinical interest. Clinically accepted applications of PET include assessing regional myocardial perfusion and defining tissue viability, whereas visualizing cardiac innervation may contribute to the management of patients with heart failure.

With the increasing appreciation of molecular imaging, the need for correlation with structural information has

been widely recognized, which resulted in the integration of PET and CT in one instrument. The rapid clinical acceptance of PET-CT has been primarily driven by its application in clinical oncology. With the wider availability of such instrumentation, PET-CT imaging of patients with cardiovascular disease has to be re-evaluated. The rapid advances of multislice CT angiography (CTA) challenge diagnostic cardiac catheterization by providing noninvasive coronary angiography with acceptable diagnostic accuracy. In addition, CT imaging offers the possibility of assessing coronary artery calcification (CAC) as a biomarker for atherosclerosis, as well as the generation of attenuation maps that can be used to correct PET images. The first generation of PET-CT instrumentation was characterized by low-performance CT designed for whole-body imaging in oncology. However, 64- and even 128-slice CT scans have been combined with state-of-the-art PET instrumentation for cardiac applications.

PET Instrumentation

Cardiac imaging is most challenging for PET because of the complex physiologic motion of the heart during the cardiac cycle and the relatively small myocardial (8-10 mm) and vascular (1-2 mm) structures. Despite the limitations in temporal and spatial resolution, PET technology excels because of its high sensitivity and potential for quantitation of tissue tracer concentration. PET technologies have advanced over the years with regard to detector material, data acquisition mode, and data processing.

Cardiac PET imaging requires dynamic data acquisition in order to define tracer kinetics for quantitation of blood flow and other molecular signals, as well as to control for cardiac and respiratory motion. Most PET scanners allow electrocardiographic (ECG) gating of data acquisition, but for imaging vascular structures, additional respiratory gating may be required to correctly localize vascular activity and improve the coregistration of PET and CT information. To fully exploit the possible dynamic information provided by PET and CT imaging, list-mode acquisition is the method of choice to retrospectively sort and correlate PET and CT data.

The most important aspect of PET-CT is the use of CT information for attenuation correction (AC) in PET. Due to coincidence detection of radioactive decay, the effect of attenuation is greater for PET than for single photon emission CT (SPECT) imaging. As both photons associated with annihilation reaction must leave the body, the likelihood of attenuation is increased. Attenuation correction for PET is easier to apply, however, as the total attenuation of the pair of detected photons is independent of the origin of the radioactive event within the body. CT images of the chest require only a few seconds using multislice CT (MSCT) instrumentation, and low-dose CT images can be generated with good spatial resolution while minimizing radiation exposure to <1 mSv [4].

Cardiac PET-CT Radiation Exposure

Radiation exposure from a PET-CT study is the sum of the effective dose from the incorporated radiotracer and the dose from external X-ray irradiation during the selected CT acquisition protocol. For a 370-MBq fluorodeoxyglucose (FDG) injection, the effective dose is 7 mSv. For rest-stress, the effective doses for (13)N-ammonia (2×550 MBq) and rubidium-82 (Rb-82) (2×740 MBq) are 2.2 mSv and 3.6 mSv, respectively [5] (Fig. 1).

The effective dose per CT exam depends on the acquisition parameters chosen (kV, mAs) and the body region being scanned. Reducing radiation exposure by limiting the axial field of view or changing the CT tube current according to anatomy has been proposed in order to reduce radiation exposure by up to 30-40%. The protocol for ECG-related tube-current modulation introduced for coronary artery calcium scoring leads to a very low dose of 0.72 mSv [6, 7].

Coronary Artery Disease Diagnosis

Conventionally, the presence of 50-75% stenosis of a coronary artery is considered indicative for obstructive CAD. It has been shown that a large subset of patients with acute myocardial infarction have coronary-culprit lesions of <50% narrowing, limiting the use of the degree of stenosis as a predictor for acute ischemic syndromes [8]. In symptomatic and asymptomatic patients with CAD, a large body of data exists indicating that the prognosis is dependent upon the extent and severity of perfusion abnormalities during stress interventions. Therefore, the therapeutic management of patients with known CAD is based on functional characterization of the disease process.

Blood Flow Assessment

The advantage of using PET in combination with CT to assess myocardial blood flow is the availability of tracers with a very short physical half life, reducing the radiation dose and the time required to perform the test. Oxygen-15 water (O-15 water) has a physical half live of only 120 s and suitable tracer kinetics for evaluating myocardial blood flow. Rb-82 has physiologic characteristics very similar to those of ^{99m} technetium-labeled blood-flow markers. In addition, its short half life of 76 s allows the determination of rest and stress perfusion studies within 30 min [9]. Several PET studies using Rb-82 as a blood-flow marker have shown high diagnostic accuracy compared with invasive procedures and SPECT perfusion imaging. Rb-82 is a generator-derived radiopharmaceutical and thus does not require an on-site cyclotron for radioisotope production. Because of the

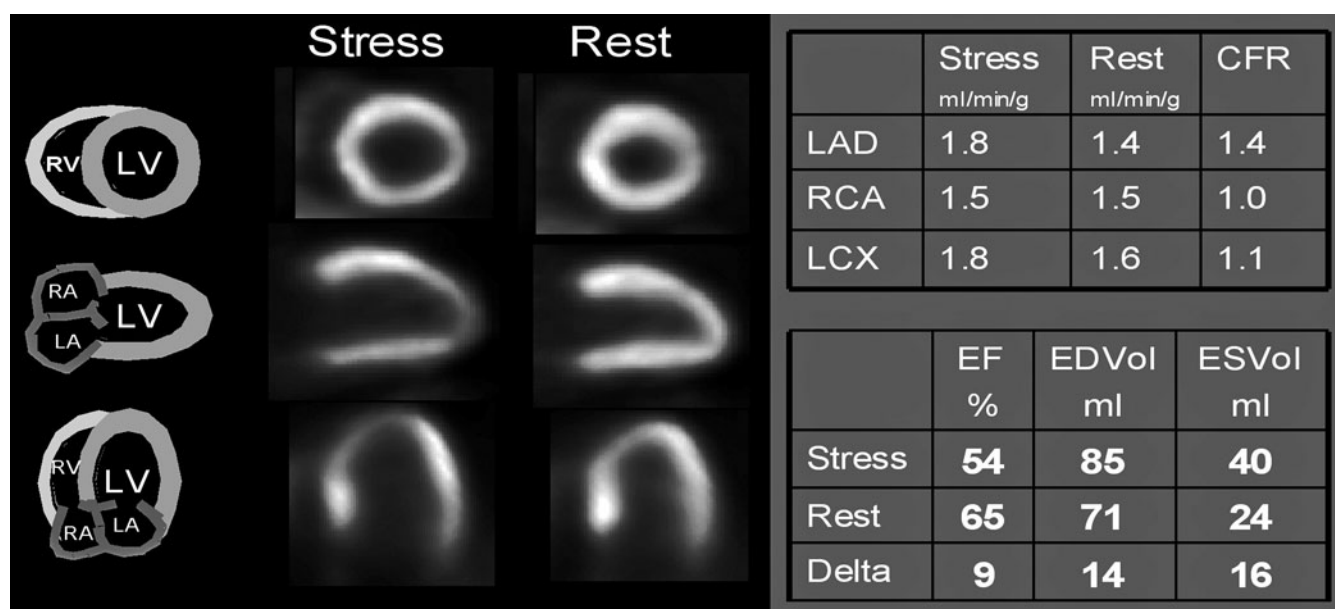


Fig. 1. Comprehensive summary of quantitative positron emission tomography results from a (13)N-ammonia rest-stress study in a female patient with three-vessel disease resulting in significantly reduced flow reserve values and transient ischemic dilation (for color reproduction see p 273)

practical advantages of Rb-82, several groups have evaluated the diagnostic performance of this tracer in combination with PET-CT. Sampson et al. evaluated 64 patients with rest-stress Rb-82 PET-CT imaging and invasive coronary angiography within 7 days [10]. In addition, 38 patients with low likelihood for CAD were studied. The overall diagnostic accuracy was 87% in the patients with coronary angiography, representing a sensitivity of 93% and a specificity of 83%. The normalcy rate in low-likelihood patients was 100%. Similar results were obtained by investigators at Emory University, USA. Seventy-five patients with intermediate likelihood of CAD underwent Rb-82 PET-CT with a stress-rest protocol. Sensitivity for detecting CAD was 90%, specificity was 83%, and normalcy rate was 100%. Therefore, this radiopharmaceutical appears to be very practical and useful for evaluating rest and stress perfusion using PET-CT instrumentation [11, 12]. Similar to SPECT perfusion imaging, Rb-82 PET imaging carries prognostic value, as indicated by Yoshinaga et al. [13]. These investigators used Rb-82 PET to followed 367 patients over a 3-year period. Cardiac death and myocardial infarction were related to extent of Rb-82 perfusion abnormalities. The annual hard event rates were 0.4%, 2.3%, and 7% in normal, mid, and moderate-severe groups, respectively.

An alternative flow tracer is $(13)\text{N}$ -ammonia, which has a 10-min physical half life but requires an on-site cyclotron for production. This tracer provides excellent image quality and has been extensively validated, demonstrating high diagnostic and prognostic accuracy for detecting CAD [14]. Siegrist et al demonstrated high impact of $(13)\text{N}$ -ammonia PET-CT on clinical decision making, which appeared to be cost effective [15]. An $[^{18}\text{F}]$ -FDG-labeled flow marker BMS 7857342 introduced as a myocardial blood-flow tracer targets mitochondrial proteins with high affinity. In isolated perfused rat-heart preparation, a high myocardial extraction was demonstrated, which was largely independent of flow rates. A direct comparison of PET flow estimates with this tracer and microsphere flow measurements in a pig model demonstrated a linear relationship over a wide flow range [16]. There are distinct advantages compared with SPECT perfusion imaging. Balanced CAD can only be detected by measuring regional flow reserve [11] (Fig. 1). PET appears to be more sensitive than SPECT for characterizing local stenosis and defining the extent of vascular impairment. Yoshinaga et al. demonstrated that PET flow reserve measurements identified abnormalities associated with coronary artery stenosis ($>50\%$) more frequently than SPECT [17]. Husmann et al. compared $^{99\text{m}}\text{Tc}$ flow-tracer SPECT with $(13)\text{N}$ -ammonia PET in 150 patients. PET proved to be more sensitive (97% vs 77%) and more specific (91% vs 74%) [18].

Early Detection of CAD in Asymptomatic Patients

Risk-factor analysis and epidemiological models based on the Framingham or Prospective Cardiovascular Mun-

ster (PROCAM) studies may allow an individual risk profile to be established for each patient defining the likelihood for developing CAD. First results evaluating the presence of CAC as incremental information in individual risk assessment are emerging. Pletcher et al. published a meta-analysis that demonstrated an adjusted relative risk of 2.1 [95% confidence interval (CI) 1.6-2.9] for a coronary calcium score of 1-100. Relative risk estimates for higher scores ranged from 3.0 to 17.0. The authors concluded that CAC is an independent predictor of a CAD event [19]. Greenland et al. showed in a prospective observational study of 1,461 asymptomatic adults comparing Framingham risk score (FRS) with CAC score (CACS) that high CACS can modify predicted risk based on FRS alone, especially among patients in the intermediate risk category, for whom clinical decision making is most important [20].

Several studies compare CACS and stress-induced perfusion abnormalities in asymptomatic adults [21, 22]. Anand et al. observed a high prevalence of silent ischemia (18%) based on myocardial perfusion imaging (MPI) in 18% of individuals with CACS 100-400. Patients with CACS >400 showed abnormal MPI in 45% of cases. In contrast to these results, other studies suggest a much lower incidence of MPI abnormalities associated with CAC. Brown et al. compared Rb-82 PET with CAC scores in 70 patients. There was a significant relationship between calcification and extent of perfusion abnormalities, although 26% of patients without evidence of calcification had perfusion abnormalities [23].

Therefore, it is likely that the combination of CAC and myocardial flow reserve measurements by PET may further enhance the management of individuals at risk to develop premature CAD. There have been relatively few data published defining the prognostic value of absolute flow reserve measurements as a marker of endothelial dysfunction. However, reports by Schächinger and Zeiher, Schindler et al., and Halcox et al. indicate that patients with impaired coronary vascular reactivity (determined invasively and noninvasively) have a worse prognosis than patients with a normal coronary response pattern [24-27].

Identifying Plaques by Molecular Markers

CT compared with intravascular ultrasound revealed a 19% incidence of noncalcified lesions. There are no data indicating whether calcified or noncalcified lesions are more likely to rupture during acute ischemic syndrome. However, a retrospective study in a larger cohort of symptomatic CAD patients [28] suggests that noncalcified plaques have prognostic value. The first clinical evidence for increased FDG uptake in atherosclerotic plaques was provided by Rudd et al. [29], who observed increased FDG uptake in patients with symptomatic carotid lesions compared with asymptomatic patients. There was a colocalization of FDG in cells surrounding the lipid core in close proximity to the fibrous cup of the

plaque, suggesting that it may be possible to identify the inflammatory component of atherosclerotic plaques in vivo, thereby allowing the biological activity within plaques to be studied. First reports addressing the incidence of FDG uptake in coronary arteries of patients with CAD have been published. In 15 of 32 patients, Wykrzykowska et al. [30] identified regional FDG uptake, which was not significantly associated with angiographically defined obstructive CAD. FDG is taken up not by plaques only but by myocardial tissue, limiting the contrast between different tissue types and requiring dietary preparation. New radiopharmaceuticals that target the extracellular matrix metalloproteinases (MMPs) or proteins that are upregulated during the inflammatory process may also be of interest [31]. First data using MMP inhibitors, as shown by Schäfers et al. indicate specific uptake of this tracer in a transgenic mouse model with atherosclerotic plaques [31].

Assessing Heart Failure

Results of multicenter trials in patients with heart failure indicate that up to 50% of patients with impaired left ventricular function suffer from CAD. As the treatment strategies are different for patients with CAD and for those with primary myocardial disease, such as dilative cardiomyopathy, the accurate differentiation of ischemic and nonischemic heart disease is important. Again, with the advent of noninvasive CTA, the combination of PET

and CT may help not only to separate patients with and without CAD but also to define the extent of reversible and irreversible ventricular dysfunction based on metabolic evaluation of the left ventricular myocardium (Fig. 2). PET has been extensively validated in assessing tissue viability using the combination of metabolic imaging with [^{18}F]-FDG and evaluating myocardial blood flow. The extent of tissue viability is predictive for the recovery of left ventricular function after revascularization. The comprehensive cardiac evaluation with PET-CT includes not only CTA and myocardial tissue characterization, but also assessment of regional function in left ventricular ejection fraction [32]. Therefore, with one noninvasive imaging procedure, the extent and severity of left ventricular dysfunction, the extent of tissue viability, and the overall extent of CAD can be characterized and used to risk-stratify each patient prior to clinical decision making.

Remodeling of the left ventricle after ischemic injury still represents a poorly understood phenomenon. Molecular imaging may help identify biological processes defining the repair process of myocardial tissue. First results employing radiolabeled ligands to adhesion molecules integrins indicate tracer uptake from 2 weeks to 6 months after injury [33]. Correlation of this new imaging signal with the incidence of remodeling will define the predictive value of molecular imaging. It is hoped that such signal may help monitor therapy targeting the remodeling process.

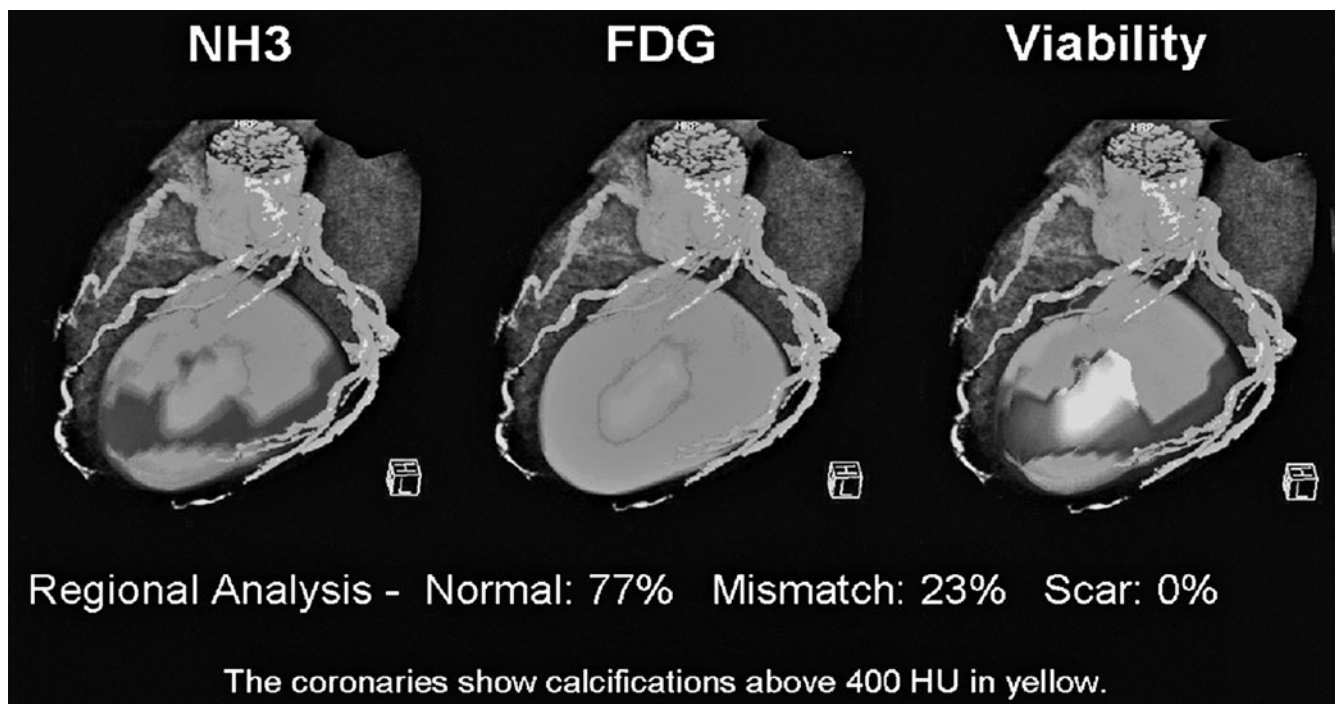


Fig. 2. Viability assessment with positron emission tomography perfusion and metabolism data mapped onto the endocardial surface of a computed tomography angiography study and displayed simultaneously with the segmented coronary tree. In addition to relative or absolute perfusion data, more complex information from protocols such as viability studies can be visualized as well in the junction with the coronary tree (for color reproduction see p 273)

Conclusion

The clinical success of PET-CT as an imaging modality in cardiology will depend on the prospective validation of this comprehensive imaging approach in larger patient populations. MDCT technology is rapidly approaching the long-awaited goal of noninvasive coronary angiography. With the ability to characterize coronary lesion severity with a diagnostic accuracy similar to that provided by invasive coronary angiography, the close correlation of plaque morphology with functional measurements such as myocardial perfusion will be increasingly appreciated. Furthermore, early CAD detection will be improved by the use of detailed structural and molecular information provided by PET-CT. For example, coronary calcification measurements combined with specific tracer techniques for characterizing inflammatory processes within coronary plaques may help identify patients at high risk for developing acute ischemic syndromes. Tracer techniques will continue to be of use for characterizing myocardial tissue viability in patients with advanced CAD and heart failure and may also be used to monitor new metabolic therapy strategies.

References

- Gould KL (2009) Coronary flow reserve and pharmacologic stress perfusion imaging: beginnings and evolution. *JACC Cardiovasc Imaging* 2:664-669
- Tonino PA, De Bruyne B, Pijls NH et al (2009) Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 360(3):213-224
- Silber S, Albertsson P, Aviles FF et al (2005) Guidelines for percutaneous coronary interventions. The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. *Eur Heart J* 26:804-847
- Kinahan PE, Townsend DW, Beyer T, Sashin D (1998) Attenuation correction for a combined 3D PET-CT scanner. *Med Phys* 25:2046-2053
- Schwaiger M, Ziegler SI, Nekolla SG (2005) PET/CT: Challenge for Nuclear Cardiology. *J Nucl Med* 46:1664-1667
- Kajander S, Ukkonen H, Sipilä H et al (2009) Low radiation dose imaging of myocardial perfusion and coronary angiography with a hybrid PET/CT scanner. *Clin Physiol Funct Imaging* 29:81-88
- Rixe J, Conradi G, Rolf A et al (2009) Radiation dose exposure of computed tomography coronary angiography – comparison of dual source –, 16-slice and 64-slice-CT. *Heart (British Cardiac Society)* 95:1337-1342
- Libby P (2001) Current concepts of the pathogenesis of the acute coronary syndromes. *Circulation* 104:365-372
- Bateman TM (2004) Cardiac positron emission tomography and the role of adenosine pharmacologic stress. *Am J Cardiol* 94:19D-24D; discussion 24D-25D
- Sampson UK, Dorbala S, Limaye A et al (2007) Diagnostic accuracy of rubidium-82 myocardial perfusion imaging with hybrid positron emission tomography/computed tomography in the detection of coronary artery disease. *J Am Coll Cardiol* 49:1052-1058
- Parkash R, deKemp RA, Ruddy TD et al (2004) Potential utility of rubidium 82 PET quantification in patients with 3-vessel coronary artery disease. *J Nucl Cardiol* 11:440-449
- Esteves FP, Sanyal R, Nye JA et al (2008) Adenosine stress rubidium-82 PET/computed tomography in patients with known and suspected coronary artery disease. *Nucl Med Commun* 29:674-678
- Yoshinaga K, Chow BJ, Williams K et al (2006) What is the prognostic value of myocardial perfusion imaging using rubidium-82 positron emission tomography? *J Am Coll Cardiol* 48:1029-1039
- Beanlands RS, Muzik O, Melon P et al (1995) Noninvasive quantification of regional myocardial flow reserve in patients with coronary atherosclerosis using nitrogen-13 ammonia positron emission tomography. Determination of extent of altered vascular reactivity. *J Am Coll Cardiol* 26:1465-1475
- Siegrist PT, Husmann L, Knabenhans M et al (2008) (13)N-ammonia myocardial perfusion imaging with a PET/CT scanner: impact on clinical decision making and cost-effectiveness. *Eur J Nucl Med Mol Imaging* 35:889-895
- Nekolla SG, Reder S, Saraste A et al (2009) Evaluation of the novel myocardial perfusion positron-emission tomography tracer 18F-BMS-747158-02: comparison to 13N-ammonia and validation with microspheres in a pig model. *Circulation* 119:2333-2342
- Yoshinaga K, Katoh C, Noriyasu K et al (2003) Reduction of coronary flow reserve in areas with and without ischemia on stress perfusion imaging in patients with coronary artery disease: a study using oxygen 15-labeled water PET. *J Nucl Cardiol* 10:275-283
- Husmann L, Wiegand M, Valenta I et al (2008) Diagnostic accuracy of myocardial perfusion imaging with single photon emission computed tomography and positron emission tomography: a comparison with coronary angiography. *Int J Cardiovasc Imaging* 24:511-518
- Pletcher MJ, Tice JA, Pignone M, Browner WS (2004) Using the coronary artery calcium score to predict coronary heart disease events: a systematic review and meta-analysis. *Arch Intern Med* 164:1285-1292
- Greenland P, LaBree L, Azen SP et al (2004) Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. *JAMA* 291:1831-1832
- Anand DV, Lim E, Raval U et al (2004) Prevalence of silent myocardial ischemia in asymptomatic individuals with subclinical atherosclerosis detected by electron beam tomography. *J Nucl Cardiol* 11:450-457
- Berman DS, Wong ND, Gransar H et al (2004) Relationship between stress-induced myocardial ischemia and atherosclerosis measured by coronary calcium tomography. *J Am Coll Cardiol* 44:923-930
- Brown TL, Merrill J, Hill P, Bengel FM (2008) Relationship of coronary calcium and myocardial perfusion in individuals with chest pain. Assessed by integrated rubidium-82 PET-CT. *Nuklearmedizin* 47:255-260
- Schächinger V, Zeiher AM (2001) Prognostic implications of endothelial dysfunction: does it mean anything? *Coron Artery Dis* 12:435-443
- Schindler TH, Hornig B, Buser PT et al (2003) Prognostic value of abnormal vasoreactivity of epicardial coronary arteries to sympathetic stimulation in patients with normal coronary angiograms. *Arterioscler Thromb Vasc Biol* 23:495-501
- Halcox JP, Schenke WH, Zalos G et al (2002) Prognostic value of coronary vascular endothelial dysfunction. *Circulation* 106(6):653-658
- Herzog BA, Husmann L, Valenta I et al (2009) Long-term prognostic value of 13N-ammonia myocardial perfusion positron emission tomography added value of coronary flow reserve. myocardial infarction. *J Am Coll Cardiol* 54:150-156
- van Werkhoven JM, Schuijff JD, Gaemperli O et al (2009) Prognostic value of multislice computed tomography and gated single-photon emission computed tomography in patients

- with suspected coronary artery disease. *J Am Coll Cardiol* 53:623-632
29. Rudd JH, Warburton EA, Fryer TD et al (2002) Imaging atherosclerotic plaque inflammation with [18F]-fluorodeoxyglucose positron emission tomography. *Circulation* 105:2708-2711
30. Wykrzykowska J, Lehman S, Williams G et al (2009) Imaging of inflamed and vulnerable plaque in coronary arteries with 18F-FDG PET/CT in patients with suppression of myocardial uptake using a low-carbohydrate, high-fat preparation. *J Nucl Med* 50:563-568
31. Schäfers M, Dutka D, Rhodes CG et al (1998) Myocardial presynaptic and postsynaptic autonomic dysfunction in hypertrophic cardiomyopathy. *Circ Res* 82:57-62
32. Hundt W, Siebert K, Wintersperger BJ et al (2005) Assessment of global left ventricular function: comparison of cardiac multidetector-row computed tomography with angiocardiology. *J Comput Assist Tomogr* 29:373-381
33. Makowski MR, Ebersberger U, Nekolla S, Schwaiger M (2008) In vivo molecular imaging of angiogenesis, targeting alphabeta3 integrin expression, in a patient after acute myocardial infarction. *Eur Heart J* 29:2201



PET-CT Evaluation of the Pleura and Chest Wall

Hans C. Steinert

Department of Medical Radiology, Division of Nuclear Medicine, Zurich, Switzerland

Introduction

Malignant pleural mesothelioma (MPM) is the most common primary neoplasm of the pleura. It is 1,000 times more common in the population exposed to asbestos. Its incidence has been increasing and is expected to do so until 2020. In Western Europe, 250,000 men are expected to die from MPM by 2030.

Diagnostic imaging in MPM is required on presentation of suspicious clinical features, both for differential diagnosis of pleural disease and clinical management. Computed tomography (CT) often cannot establish the nature of disease, as diffuse pleural thickening may be due to a benign or malignant process. There are some limitations in assessing diaphragm invasion due to partial volume effect on curved surfaces, and lymph node staging is of suboptimal accuracy, so that biopsy is required for definitive diagnosis.

Similarly to lung cancer, excellent fluorodeoxyglucose (FDG) uptake in MPM has been described [1]. There is higher uptake in MPM compared with benign pleural disease (sensitivity 91%, specificity 100%). Pleural fluid cytology and histology have low diagnostic yield. Moreover, should these tests be negative, the diagnosis of MPM cannot be excluded so that further investigations are required. It is important to reduce the number of invasive procedures, as the average risk of malignant seeding is about 20%. In this setting, the role of positron emission tomography computed tomography (PET-CT) is to identify an optimal biopsy site, thereby increasing diagnostic accuracy.

The goals of staging are to assess operability and, in patients deemed inoperable, offer prognostic information, evaluate those entering clinical trials, and compare different studies. Tumor-node-metastasis (TNM) stratifies patients into prognostic categories based on surgical and pathological criteria (resectability, invasiveness), thus describing postoperative findings. MPM shows a loco-regional growth pattern with direct extension and recurrences within the ipsilateral hemithorax. The most frequently affected nodal site is mediastinal lymph nodes. As MPM is primarily a parietal pleural disease, the lymphatic spread pattern seems different from lung cancer, as N2 rather than N1 may be the first draining station.

The natural history of MPM is of ipsilateral hemithorax local recurrence with increased risk in patients with infiltrated surgical edges or after invasive diagnostic or therapeutic procedures. Lymphatic and hematogenous metastases occur commonly and are found at autopsy in more than half of the MPM cases, although they are usually late and seldom cause problems. There is increasing evidence that disease extent, extrapleural nodal status, cell type, and surgical resection margins affect prognosis in resected tumors [2].

Staging

Bénard et al. [3] assessed 28 patients with suspected MPM who underwent PET and quantitative analysis. Results were compared with surgical biopsy. FDG uptake was significantly higher in malignant [standard uptake value (SUV) = 4.9 ± 2.9] than in benign lesions (SUV = 1.4 ± 0.6). For an SUV cutoff value of 2, sensitivity was 91% and specificity 100%. PET-CT imaging is useful in localizing the areas involved with MPM. However, it is unable to differentiate MPM from pleural adenocarcinoma, so that tissue confirmation is required. Thoracoscopy remains the primary diagnostic modality for MPM, with sensitivity >90%. In this setting, the role of PET-CT is to identify an optimal biopsy site, diagnose recurrence, and monitor therapy response by quantifying disease activity.

Schneider et al. [4] evaluated eighteen cases of MPM with PET and concluded that it is a useful noninvasive staging modality for patients being considered for aggressive combined modality therapy. PET-CT is particularly valuable for distinguishing between benign and malignant pleural processes and may also allow noninvasive extrathoracic metastases, as it correctly identified the presence or absence of metastatic disease in 89% of patients. This study suggests that PET scan findings must be correlated with CT findings. On the basis of their findings, the authors routinely obtain both PET and CT scans on all patients referred for MPM evaluation.

Carretta et al. [5] studied 14 patients presenting with pleural thickening or fluid on CT to evaluate the accuracy of [^{18}F]-FDG-PET in diagnosing pleural diseases. In the

differential diagnosis, PET had a sensitivity of 100%, a specificity of 78%, and accuracy of 92%. However, PET cannot distinguish pleural tumors from metastatic involvement caused by other tumors, such as adenocarcinoma. Therefore, histological thoracoscopic diagnosis remains mandatory before treatment planning. PET-CT may have great potential in the differential diagnosis of pleural disease and evaluating treatment response.

Prognosis

Sugarbaker et al. [1] assessed 52 patients who underwent multimodality treatment, establishing that prolonged survival occurred in cases with epithelial histologic variant and mediastinal lymph nodes. The same group [2] studied 183 patients managed with multimodality treatment, concluding that patients with epithelial, margin-negative, extrapleural (N2), node-negative resection had extended survival. Bénard et al. [6] studied 28 patients with suspected MPM assessing the SUV of lesions on PET scans as a predictor of survival. They concluded that cases with highly active MPMs on FDG-PET imaging have a poor prognosis. Increased tumour metabolic activity measured by SUV is associated with a poor prognosis in malignant pleural MPM. The prognostic information provided by FDG-PET could be of value in considering an aggressive approach. There is a trend toward lower FDG uptake in MPMs of the epithelial subtype, thought to be a less aggressive form of the disease.

A prospective study by Rusch et al. [7] of 405 patients staged with the International Mesothelioma Interest Group (IMIG) who underwent surgical treatment showed that stages I and II have better survival rates. Locally advanced T and N status and nonepithelial histology identified patients with poor prognosis. Regarding lymph node metastases, N1 involvement is uncommon, whereas involvement of mediastinal lymph nodes in unusual locations often occurs. This report suggests that the combina-

tion of CT imaging, thoracoscopy, mediastinoscopy, and occasionally laparoscopy may be the best approach to pretreatment staging. However, 10-20% of patients will have more advanced disease than anticipated despite these procedures. PET-CT may be able to preoperatively and noninvasively stage these patients.

Conclusion

In summary, PET-CT is an emerging modality for evaluating MPM that may be useful in the preoperative setting to document and quantify the extent of pleural disease, evaluate chest-wall and transdiaphragmatic invasion, and estimate tumor aggressiveness.

References

1. Sugarbaker DJ, Strauss GM, Lynch TJ et al (1992) Node status has prognostic significance in the multimodality therapy of diffuse, malignant MPM. *J Clin Oncol* 11:1172-1178
2. Sugarbaker DJ, Flores RM, Jaklitsch MT et al (1999) Resection margins, extrapleural nodal status and cell type determine postoperative long-term survival in trimodality therapy of malignant pleural MPM: results in 183 patients. *J Thorac Cardiovasc Surg* 117:54-63
3. Bénard F, Sterman D, Smith RJ et al (1998) Metabolic imaging of malignant pleural MPM with fluorodeoxyglucose positron emission tomography. *Chest* 114:713-722
4. Schneider DB, Clary-Macy C, Challa S et al (2000) Positron emission tomography with F18-fluorodeoxyglucose in the staging and preoperative evaluation of malignant pleural MPM. *J Thorac Cardiovasc Surg* 120:128-133
5. Carretta A, Landoni C, Melloni G et al. (2000) 18-FDG PET in the evaluation of malignant pleural diseases – a pilot study. *Eur J Cardiothorac Surg* 17:377-383
6. Bénard F, Sterman D, Smith RJ et al (1999) Prognostic value of FDG PET imaging in malignant pleural MPM. *J Nucl Med* 40:1241-1245
7. Rusch VW, Venkatraman ES (1999) Important prognostic factors in patients with malignant pleural MPM, managed surgically. *Ann Thorac Surg* 68:1799-1804

PEDIATRIC SATELLITE COURSE
“KANGAROO”





Abnormal Chest in Children: Other than Pneumonia and Heart Disease

Veronica Donoghue

Department of Radiology, Children's University Hospital, Dublin, Ireland

Introduction

This chapter addresses the commonest disorders of the paediatric chest, excluding infections and heart disease. It also excludes the various medical conditions in the newborn chest. The main issues discussed include congenital lung lesions, pleural effusions, mediastinal and diaphragmatic abnormalities and pulmonary hypoplasia. A discussion of the commonest systemic disorders that give rise to lung abnormalities in the older child is also included.

Congenital Lung Lesions

Prior to the routine use of foetal ultrasonography, congenital lung lesions were considered rare. There has been a significant increase in the numbers diagnosed in recent decades with the increased use of foetal imaging [1]. Recent reports of pathology in these lesions suggest that the initial insult to the lung bud is airway obstruction [2, 3].

The recognition of a common pathogenesis and the more frequent recognition of hybrid lesions have resulted in the term congenital cystic adenomatoid malformation (CCAM) being replaced with congenital pulmonary airway malformations (CPAM) [4]. No organisational structure or nomenclature system exists to describe all lung abnormalities [5].

Nowadays, however, congenital lung lesions are classified as follows [6]:

1. bronchopulmonary malformations (CPAM, pulmonary sequestration, bronchogenic cyst, bronchial atresia);
2. pulmonary hyperplasia and related conditions [congenital high airway obstruction syndrome (CHAOS), polyalveolar lobe];
3. congenital lobar overinflation and related conditions (congenital lobar emphysema, bronchial obstruction/compression);
4. systemic arterial connections to normal lung;
5. other cystic lesions.

Bronchopulmonary Malformations

CPAM, representing a hamartomatous development of the terminal respiratory structures, is the commonest congenital pulmonary lesion, accounting for up to 85% of all foetal lung masses and involves only one lobe or part of a lobe in 95% of cases [6]. Five histological types apply only to pathological specimens [4]:

1. involvement of all lobes (incompatible with life);
2. large cysts (>2 cm) – pseudostratified columnar epithelium;
3. medium-sized cyst(s) – cuboidal or columnar epithelium;
4. small cyst(s) (<0.5 cm) – cuboidal epithelium;
5. large air-filled cysts, lined by flattened epithelial cysts.

Sonographic monitoring in utero will document regression of lesion size during the third trimester in up to 75% of cases. Most survivors are asymptomatic at birth (60-90%) [6]. If the residual mass is large at birth, it is dense on the plain radiograph but after some hours shows air-filled cysts. If the mass involves the lower lobes, it may obscure the hemidiaphragm and mimic a congenital diaphragmatic hernia. Computed tomography (CT) is helpful in defining lesion extent and involved lobes. In many infants in whom there has been a reduction in size in utero, the postnatal chest radiograph will be normal. It is important to perform a CT scan of the lungs shortly after birth in these infants to assess the presence of any residual lesion [7].

Pulmonary sequestration is a mass of lung tissue supplied by systemic arteries. The supply is usually from the thoracic aorta but may also be from the abdominal aorta by a vessel that passes through the diaphragm or other systemic arteries. Intralobar sequestration usually drains to the pulmonary venous system and usually does not have a separate pleural covering. As many as 50% remain asymptomatic throughout childhood. Extralobar sequestrations usually drain to the systemic circulation, are most commonly located in the left lower lobe and have a separate pleural covering. Approximately 50% have other associated congenital abnormalities, particularly diaphragmatic

hernias and congenital cardiac lesions. Approximately 15% of lesions are intra-abdominal, usually in the region of the adrenal gland. Sequestrations usually cause dense masses on chest radiography. The identification of the systemic arterial blood supply may be by ultrasonography, CT or magnetic resonance (MR) angiography [8].

Hybrid lesions are common, with areas of CPAM associated with up to 50% of pulmonary sequestrations. Pulmonary sequestration may also be associated with bronchogenic cysts and scimitar syndrome [9]. Managing the symptomatic infant with CPAM or sequestration is by resection. Successful treatment by endovascular embolisation has been described. Treating the asymptomatic infant is controversial. The risk of infection, malignant transformation, pneumothorax, haemorrhage and the fact the pulmonary compensatory growth is optimal when the resection is early, have been put forward as arguments for removing asymptomatic lesions. The incidence of infection has been reported as 10% [10]. These authors state that there is no increase in the postoperative complication rate if surgery is deferred until infection onset. At present, it is not possible to quantify the long-term malignant potential of nonresected CPAM. Some cases of previously described malignant transformation may have been cystic pleuropulmonary blastoma (PPB) from the outset, which can be indistinguishable from CPAM radiologically. There are some case reports in the adult literature of carcinomas occurring with CPAM.

Pulmonary Hyperplasia: Congenital High Airway Obstruction Syndrome

These abnormalities are extremely rare with a very poor prognosis. It is due either to tracheal or laryngeal obstruction. There is marked enlargement of both lungs, and the diaphragms are flattened. Associated anomalies are frequent.

Congenital Lobar Hyperinflation

The aetiology of congenital lobar emphysema is unclear but probably results from an abnormality of the lobar bronchus, which may have a cartilage abnormality that causes obstruction. It most commonly involves the left upper lobe (50%). The next commonest sites are the right middle lobe (30%) and right upper lobe (20%). There is an associated ventricular septal defect or patent ductus arteriosus in 15% of patients. The radiograph immediately after birth may show opacification of the involved lobe, but with time the affected lobe is hyperexpanded and hyperlucent. This may cause compression of the adjacent lobes(s) and mediastinal shift. CT is useful to confirm the lobe involved, and treatment of symptomatic cases is by resection [11]. Secondary lobar emphysema may be caused by a persistent patent ductus arteriosus, an aberrant left pulmonary artery or very dilated pulmonary arteries. Bronchial atresia may be considered a variant of lobar emphysema. Though congenital, it seldom presents in the newborn period.

Systemic Arterial Connections to Normal Lung

An area of normal lung may very rarely have a systemic blood supply, and the condition is probably in the sequestration spectrum. It may present incidentally on a chest radiograph or as a left to right shunt. The affected area may have an increased blood supply but is otherwise normal.

Congenital Pleural Effusions

Congenital pleural effusions, unless associated with cardiac disease or hydrops, are most likely due to chylothorax. The aetiology of chylothorax is not known. Late maturation of the thoracic duct has been proposed and may explain the resolution of the abnormality following repeated episodes of aspiration. Trauma has also been proposed as a cause, but this does not explain the fact that the effusion may be seen antenatally. The chest radiograph demonstrates an effusion that maybe unilateral or bilateral and when large may opacify the entire hemithorax. The diagnosis is confirmed by aspiration of the fluid, which is initially clear and will show a high lymphocyte count. The fluid will have a milky appearance once the infant has a feed containing fat. The condition resolves following aspiration, and frequently, repeated aspiration is necessary.

Mediastinal Lesions

Mediastinal abnormalities are rare in children. Teratomas involving the pericardium and thymus have been reported. Mediastinal cysts include bronchogenic, neurenteric and oesophageal duplication cysts. Bronchogenic cysts are thought to be due to abnormal bronchial budding during lung development. They are located in the mediastinum if they occur early in lung development and may be intraparenchymal if they occur late. Chest radiography demonstrates a discrete dense mass, and CT or MR imaging will demonstrate the cystic features [12]. Bronchogenic cysts may be associated with sequestration, bronchial atresia or lobar emphysema. Neurenteric cysts result from failure of the lung bud to separate from the notochord. The cyst is usually located in the posterior mediastinum and is associated with vertebral abnormalities. It may communicate with the spinal canal or the oesophagus.

Diaphragmatic Abnormalities

Congenital diaphragmatic hernia (Bochdalek type) results from a defect in the diaphragm as a result of failure of the pleuroperitoneal canal to close, which should occur by the tenth week of gestation. The foetal bowel, which has migrated outside the abdominal cavity, returns by the week 10-12 and moves into the chest if the diaphragm has not completely formed. The presence of bowel loops in the thorax results in hypoplasia of one or both lungs, which depends on the number of bowel loops

present and the length of time the abnormality is present. However, Tenbrink et al. [13] suggest that the mass effect adjacent to the lung does not adequately explain all the pulmonary findings in congenital diaphragmatic hernia, as other mass lesions do not affect the lungs to the same degree. They suggest that a primary teratogenic abnormality in the lung leads to failure of the lung to induce diaphragmatic closure. The condition may be diagnosed antenatally and is left-sided in 90% of cases. It is associated with other congenital cardiac, genitourinary, central nervous system and chromosomal abnormalities in 10–50% of infants.

Direct intrauterine repair of the hernia was pioneered in the early 1990s [14]. Foetal tracheal ligation, known as PLUG (plug the lung until it grows), has been shown to increase alveolar and vascular growth [15]. However neither technique has found worldwide favour to date. The prognosis ultimately depends on the degree of pulmonary hypoplasia, which depends largely but not entirely on the size of the herniated contents [16]. The presence of the stomach in the thorax is related to a poorer prognosis, as it indicates that the diaphragmatic defect is large.

The chest radiograph initially shows opacification with significant mediastinal shift to the contralateral side. Over the subsequent hours, air outlines the bowel loops. An abdominal radiograph should also be performed, which will show a scaphoid appearance due to absence of bowel loops from their normal location in the abdomen. This helps to differentiate the condition from congenital cystic adenomatoid malformation or a large pleural effusion. Right-sided diaphragmatic hernias may involve herniation of the liver or kidney in addition to bowel loops. Ultrasonography may also be helpful diagnostically, as it is useful in outlining the presence of the diaphragm and in detecting the presence of fluid-filled bowel loops prior to their filling with air. It is also useful to detect the liver or kidney in a right-sided lesion. It is seldom necessary to use a contrast bowel examination to confirm the presence of bowel loops in the chest.

Initial therapy includes continuous deflation of the bowel loops, mechanical ventilation and the use of nitric oxide to produce pulmonary vasodilatation. If this treatment is unsuccessful, the infant may be treated with extracorporeal membrane oxygenation (ECMO). Repair is undertaken after the infant is stabilised. Following repair of the diaphragmatic defect, the chest radiograph shows the true volume of the underlying lungs.

Eventration of the diaphragm is usually asymptomatic but is very rarely large enough to cause neonatal respiratory distress as a result of reduced overall diaphragmatic function and the mass effect of the upwardly displaced structures beneath it.

Pulmonary Hypoplasia

Pulmonary hypoplasia may be secondary to oligohydramnios – for example, in Potter sequence – or a large

intrathoracic mass such as a diaphragmatic hernia. Unilateral pulmonary hypoplasia, usually the right, is associated with a small or absent pulmonary artery with mediastinal shift to the affected side. This latter abnormality does not usually present in the neonatal period.

Common Systemic Disorders Involving the Lungs

Cystic Fibrosis

Cystic fibrosis (CF) is a complex, multiorgan disorder primarily affecting the respiratory tract, gastrointestinal tract, pancreas and hepatobiliary system. It has an incidence of ~1 in 2,500 births. This autosomal recessive disorder is caused by mutations in a single gene on the long arm of chromosome 7 that encodes the cystic fibrosis transmembrane regulator protein. Presentation varies with age. Chronic villus biopsy or amniocentesis identifies CF antenatally. Newborn CF screening in countries where this is available identifies children at a presymptomatic stage. Children <2 years of age commonly present with recurrent respiratory tract infections, respiratory symptoms and failure to thrive secondary to pancreatic exocrine insufficiency. In the older child, the common presentations include recurrent respiratory tract infection, finger clubbing, bronchiectasis, nasal polyps ± sinusitis, chronic intestinal obstruction and intussusception. Less commonly, children in this age group present with acute pancreatitis, liver disease, malabsorption or pulmonary infection with atypical mycobacteria.

Imaging findings are variable and depend on the age at diagnosis and disease severity. In younger infants, the chest radiograph may be normal. There is typically some degree of hyperinflation. There may be areas of atelectasis, mimicking bronchiolitis or asthma. As the disease progresses, bronchial-wall thickening develops together with bronchiectasis. The latter can be suggested on radiography when the bronchus is larger than the adjacent pulmonary vessel. Areas of ill-defined opacification suggest mucous impaction or allergic bronchopulmonary aspergillosis. Hilar lymphadenopathy is common and can occur during an episode of acute infection. Lobar pneumonia and pleural effusions are uncommon. In very severe disease, there may be evidence of right-sided cardiac failure. Although severity and extent of the various radiographic features have been scored by other methods, the Brasfield system is in widest use, as it correlates closely with pulmonary function. It uses scores of 0–5 to assess air trapping, linear shadows, nodular cystic lesions, large pulmonary shadows and general severity [17].

CT studies are the most accurate method of evaluating the changes in lung disease. It is more sensitive than radiography in detecting the extent of bronchiectasis, bronchial-wall thickening, mucous plugging, infiltration and hilar adenopathy. At present, however, there is no

consensus on when to use CT in the various paediatric age groups with cystic fibrosis. There is also the issue of cumulative radiation dose in patients with any life-long condition. This has become even more important since the introduction of multislice CT, which has a much higher dose burden than high-resolution thin slices at intervals. At present, there is still no consensus on when a volume sequence is required instead of high-resolution images.

In 1991, Bhalla et al. [18] introduced a system in which they scored the severity and extent of bronchiectasis, severity of bronchial-wall thickening, mucous plugging, bullous disease, emphysema, collapse and consolidation together with the involvement of the number of bronchial divisions. Since then, other scoring systems have been published and adopted by several clinicians.

Constrictive Bronchiolitis (Bronchiolitis Obliterans)

This condition can be idiopathic or secondary to various insults, such as infections, bone marrow or lung transplantation, collagen vascular disease or toxic fume inhalation. Chest radiographs are usually normal, but there may be hyperinflation. High-resolution CT demonstrates a mosaic perfusion pattern due to oligemia and air trapping, which is better seen on the expiratory scan. Central or peripheral bronchiectasis, bronchial-wall thickening and mucous plugging of the centrilobular bronchioles may also be seen [18].

Allergic Bronchopulmonary Aspergillosis

Allergic bronchopulmonary aspergillosis (ABPA) is an immunological disorder characterised by immediate hypersensitivity due to endobronchial growth of *Aspergillus fumigatus*. In patients with immunoglobulin E (IgE)-mediated asthma, *A. fumigatus* may trigger an asthmatic reaction. The diagnosis is based on a clinical history of asthma, skin-test reaction, elevated IgE and measurement of serum precipitins. The presence of predominantly central, moderate to severe bronchiectasis affecting three or more lobes, bronchial-wall thickening and centrilobular nodules in an asthmatic patient is highly suggestive of ABPA [19-21].

Primary Ciliary Dyskinesia

Primary ciliary dyskinesia (PCD) is a rare disease with a prevalence of 1 in 20,000. The cilia themselves are highly complicated organelles that perform important functions, particularly in the respiratory and reproductive tracts [22], and PCD is the result of a congenital defect in the airway cilia action. The features include sinus and chest infections and decreased fertility. Approximately 50% of patients have associated situs inversus and are classified as having Kartagener's syndrome. Radiologically, the features are similar to those of cystic fibrosis.

References

1. Marshall KW, Blaine CE, Teitelbaum DH et al (2000) Congenital cystic adenomatoid malformation: impact of prenatal diagnosis and changing strategies in the treatment of the asymptomatic patient. *AJR Am J Roentgenol* 175:1551-1554
2. Langston C (2003) New concepts in the pathology of congenital lung malformations. *Semin Pediatr Surg* 12:17-37
3. Riedlinger WF, Vargas SO, Jennings RW et al (2006) Bronchial atresia is common to extralobar sequestration, intralobar sequestration, congenital cystic adenomatoid malformation, and lobar emphysema. *Pediatr Dev Pathol* 9:361-373
4. Stocker JT (2002) Congenital pulmonary airway malformation (CPAM): a new name and an added classification of CCAM of the lung. *Histopathology* 41:424-431
5. Biyyam DR, Chapman T, Ferguson MR et al (2010) Congenital lung abnormalities: embryologic features, prenatal diagnosis, and postnatal radiologic-pathologic correlation. *Radiographics* 30:1721-1738
6. Garel L (2008) Antenatal imaging of chest malformations. In: Donoghue V (ed) *Radiological imaging of the neonatal chest*, 2nd edn. Springer-Verlag, Berlin, Heidelberg New York
7. Ryan S (2008) Postnatal imaging of chest malformations. In: Donoghue V (ed) *Radiological imaging of the neonatal chest*, 2nd edn. Springer-Verlag, Berlin, Heidelberg New York
8. Kouchi K, Yoshida H, Ohtsuka Y et al (2000) Intralobar bronchopulmonary sequestration evaluated by contrast enhanced three-dimensional MR angiography. *Pediatr Radiol* 30:774-775
9. Bratu I, Flageole H, Chen M et al (2001) The multiple facets of pulmonary sequestration. *J Pediatr Surg* 35:784-790
10. Aziz D, Langer JC, Tuuha SE et al (2004) Prenatally diagnosed asymptomatic congenital cystic adenomatoid malformation: To resect or not? *J Pediatr Surg* 39:329-334
11. Karnak I, Senocak ME, Ciftci AO et al (1999) Congenital lobar emphysema: diagnostic and therapeutic considerations. *J Pediatr Surg* 34:1347-1351
12. McAdams HP, Kiejczyk WM, Rasado-de-Christenson ML et al (2000) Bronchogenic cyst: imaging features with clinical and histopathological correlation. *Radiology* 217:441-446
13. Tenbrink R, Tibboel D, Gaillard JJJ et al (1990) Experimentally induced congenital diaphragmatic hernia in rats. *J Pediatr Surg* 25:426-429
14. Harrison MR, Adzick NS, Flake AA et al (1993) Correction of congenital diaphragmatic hernia in utero VI Hard earned lessons. *J Pediatr Surg* 28:1411-1418
15. Hendrick MH, Estes JM, Sullivan KM et al (1994) Plug the lung until it grows (PLUG): a new method to treat congenital diaphragmatic hernia in utero. *J Pediatr Surg* 29:612-617
16. Donnelly LF, Sakurai M, Klosterman LA et al (1999) Correlation between findings on chest radiography and survival in neonates with congenital diaphragmatic hernia. *AJR Am J Roentgenol* 173:1589-1593
17. Brasfield D, Hicks G, Soong SJ et al (1980) Evaluation of scoring system of the chest radiograph in cystic fibrosis: a collaborative study. *AJR Am J Roentgenol* 134:1195-1198
18. Bhalla M, Turcios N, Aponte V et al (1991) Cystic fibrosis: scoring system with thin-section CT. *Radiology* 179:783-788
19. Lucaya J, Ducou Le Pointe H (2008) High resolution CT of the lung in children – Part II. Clinical applications. In: Lucaya J, Strife JL (eds) *Pediatric chest imaging – chest imaging in infants and children*, 2nd edn. Springer-Verlag, Berlin Heidelberg New York
20. Ward S, Heyneman L, Lee MJ et al (1999) Accuracy of CT in the diagnosis of allergic bronchopulmonary aspergillosis in asthmatic patients. *AJR Am J Roentgenol* 173:937-942
21. Mitchell TA, Hamilos DL, Lynch DA et al (2000) Distribution and severity of bronchiectasis in allergic bronchopulmonary aspergillosis (ABPA). *J Asthma* 37:65-72
22. Meeks M, Bush A (2000) Primary ciliary dyskinesia (PCD). *Pediatr Pulmonol* 29(4):307-316



Pulmonary Infections in Children

Silvia Cacaci¹, Catherine Owens²

¹ Department of Radiology, Policlinico Universitario "A. Gemelli", Rome, Italy

² Cardiothoracic Radiology Department, Great Ormond Street Hospital for Children, London, UK

Introduction

Respiratory tract infection is the most common cause of illness in children, carrying significant morbidity and mortality. Host immunity is important in helping the clinician to understand and classify the different end-organ responses to a particular organism and, indeed, whether various pathogens are virulent and their degree of virulence. It is therefore prudent to consider separately the immunocompetent from the immunocompromised child when considering the radiological profiles of acute chest infection.

The Immunocompetent Child

Empyema

The incidence of pleural empyema in children is increasing. This is a very different condition from that in adults: most strikingly, empyema, whilst causing significant morbidity, is almost never fatal in children [1]. A parapneumonic pleural collection may be suggested by a clinical assessment and may be readily demonstrable on a frontal chest radiograph. Early signs include obliteration of the costophrenic angle and a rim of fluid tracking in a meniscus

up the lateral chest wall. Radiographic diagnosis becomes more challenging in the presence of extensive underlying consolidation and particularly in the case of a white-out of the hemithorax. A supine film may also fail to clearly demonstrate a pleural collection. Ultrasound (US) can be used to confirm the presence of pleural fluid collection when this is suspected on clinical and radiological grounds. US is able to detect even very small effusions, and it is readily capable of distinguishing between pleural fluid and underlying lung consolidation. US can also help characterise its nature, showing the eventual presence of cellularity, haemorrhage, fibrin deposits within a pleural collection, loculation and septation.

The British Thoracic Society (BTS) Guidelines for Management of Pleural Infection in Children [2, 3] acknowledges that chest radiography and US scans are sufficient in the majority of paediatric patients, whereas, it states: "CT is NOT necessary in most cases of paediatric empyema but has a role in complicated cases, i.e. initial failure to aspirate fluid, failed medical treatment and especially immunocompromised children" (Fig. 1).

Mycobacterium Tuberculosis

In children, pulmonary tuberculosis (TB) usually occurs as a result of primary infection acquired from an infected

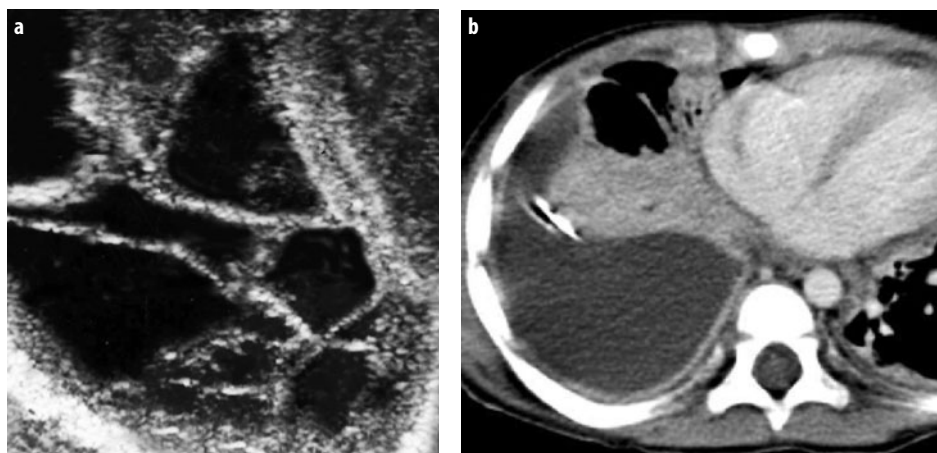


Fig. 1 a, b. Ultrasound (US) and computed tomography (CT) findings of empyema. **a** US shows heavily septated fluid collection in a child with a right-sided empyema. **b** Contrast-enhanced axial CT image of the thorax shows pleural fluid collection with a drainage tube tip in the collection area. The underlying lung is collapsed

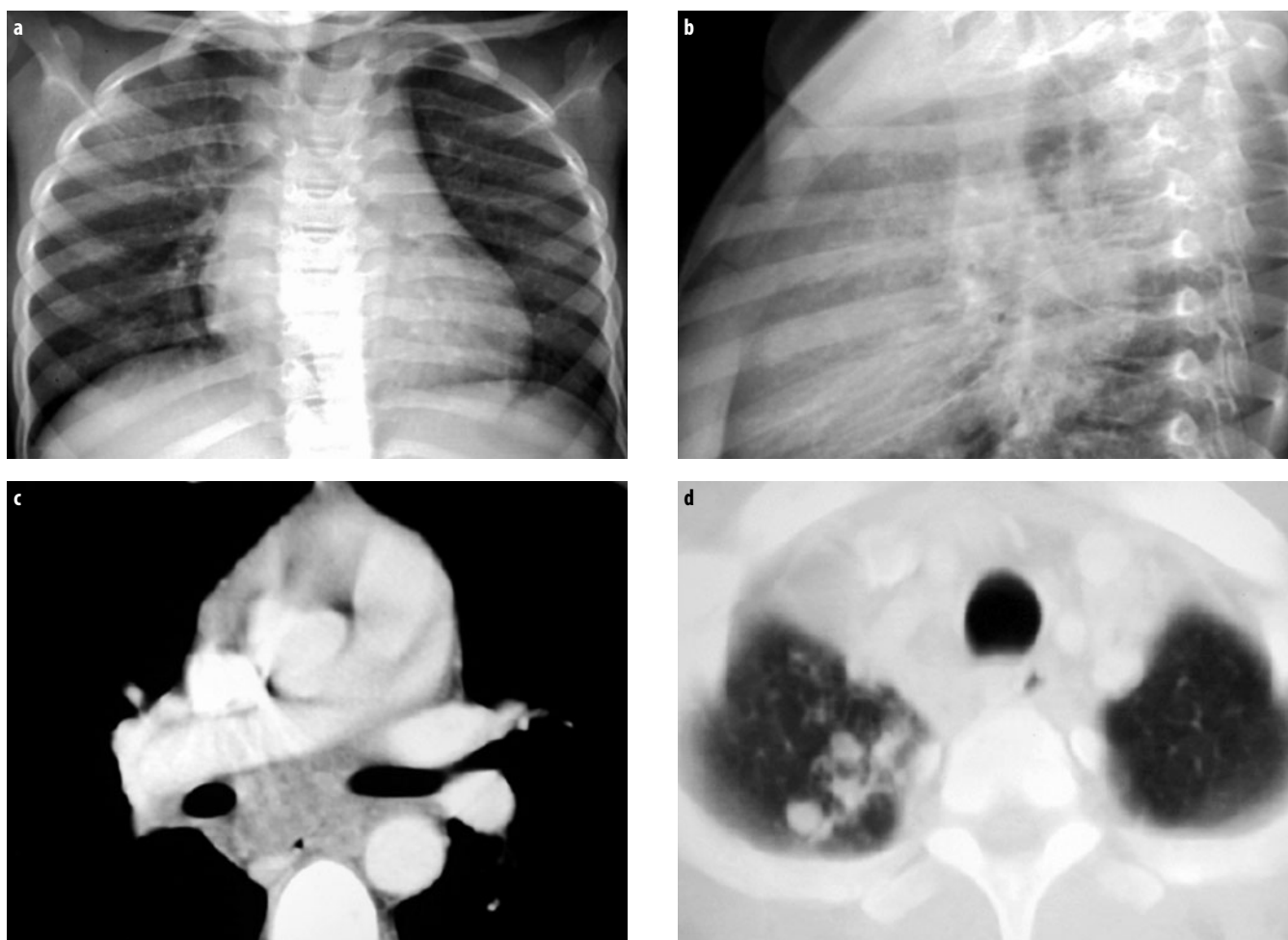


Fig. 2 a-d. Pulmonary tuberculosis (TB) in children: mediastinal and associated lung disease. **a, b** Frontal and lateral chest radiographs show a subcarinal lymphadenopathy. **c** Contrast-enhanced axial computed tomography (CT) image of the thorax shows mediastinal disease; there is subtle peripheral enhancement of the mass. **d** Associated lung disease may help in the diagnosis, shown here with small right apical pulmonary nodules

adult. Disseminated or extrapulmonary TB is relatively rare in children and raises the possibility of underlying immunodeficiency (and is classified as a potential AIDS indicator in children). Radiological features are usually similar to those in immunocompetent controls and include lobar consolidation, segmental or lobar atelectasis, pleural effusions and lymphadenopathy. Pulmonary cavitation is uncommon. Large-volume lymphadenopathy is a frequent finding, the paratracheal and hilar regions being the most common sites. Occasionally, the chest radiograph appears normal. Miliary disease is uncommon, although when it occurs, it may be indistinguishable from lymphocytic interstitial pneumonitis (LIP).

Contrast-enhanced computed tomography (CECT) and high-resolution CT (HRCT) are of particular value for confirming mediastinal and miliary disease. Mediastinal lymphadenopathy is often large in volume and typically demonstrates prominent peripheral enhancement following intravenously administered contrast (Fig. 2). Classic HRCT features of miliary TB are of a reticulonodular in-

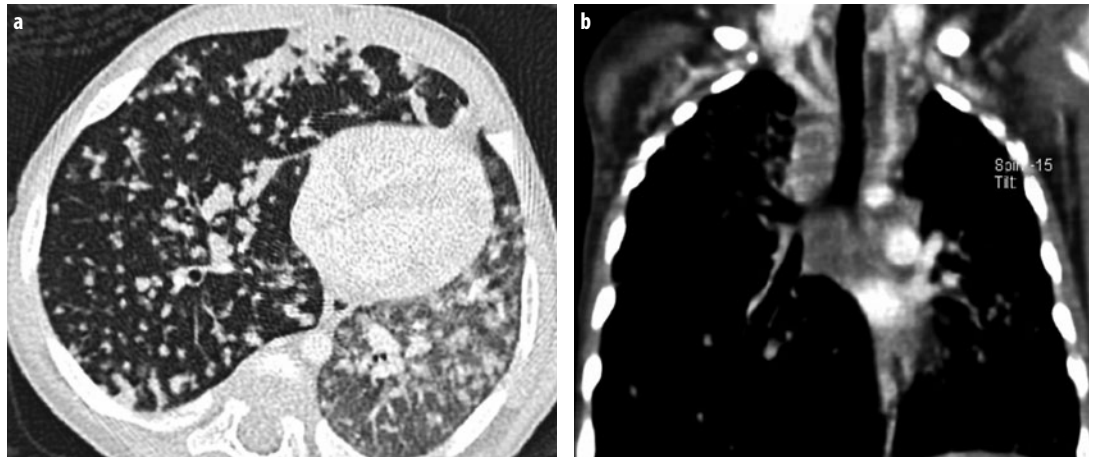
filtrate. In adults, the nodules are typically uniform in size, measuring 1-3 mm. However, in children nodules are more varied in size, and their definition is that of the classic Fleischner description based on adult criteria (Fig. 3).

The Immunocompromised Child

Primary Immunodeficiency Disorders

The congenital or primary immunodeficiency disorders (PID) represent a rare heterogeneous group of genetically determined disorders characterised by defects of cell-mediated immunity, antibody production and/or the complement and phagocyte systems. Perhaps the most important and frequent clinical manifestation of PID is recurrent sinopulmonary infections, which, if inadequately treated, may result in the development of obstructive lung disease, chronic respiratory failure and ultimately premature death. After infection, malignancy is the second leading cause of death.

Fig. 3 a, b. Acute disseminated (miliary) disease in a child. **a** Contrast-enhanced axial computed tomography (CT) image of the thorax (lung window) demonstrates reticulonodular infiltrate with nodules varying in size. **b** Coronal image of the same CT scan (soft-tissues window) shows the associated mediastinal lymphadenopathy causing extrinsic right main bronchial partial obstruction and right lung over-inflation



Important Pulmonary Complications

Diffuse Lung Disease

Typical radiographic features include hyperinflation and bronchial-wall thickening with or without dilation. The chest radiograph is, nevertheless, insensitive and commonly appears normal or shows only subtle change. HRCT detects abnormalities not visible on the chest radiograph and improves diagnostic accuracy compared with the chest radiograph and allows earlier diagnosis.

Pneumocystis Jiroveci Pneumonia

Pneumonia caused by *Pneumocystis jiroveci* usually occurs in children whose primary immunodeficiency is undiagnosed and, indeed, is frequently the first indicator of an underlying immunodeficiency state. Classic radiographic appearances include hyperinflation with diffuse bilateral interstitial or nodular infiltrates that may be subtle initially, progressing rapidly to widespread alveolar shadowing.

Angioinvasive Aspergillosis

Invasive pulmonary aspergillosis (IPA) typically manifests as multifocal areas of parenchymal inflammation caused by haematogenous dissemination of the organisms. It is associated with angioinvasive infarction and necrosis secondary to vascular obstruction. Classic radiographic features include either solitary or multiple nodules or masses, with or without cavitation (Fig. 4). In some cases, however, the chest radiograph appears normal or may demonstrate a focal infiltrate indistinguishable from a pyogenic pneumonia. Specific HRCT features have been described, probably the most characteristic being a halo of ground-glass attenuation representing perilesional necrosis and haemorrhage surrounding a central fungal nodule or infarct. A second commonly described characteristic feature of IPA

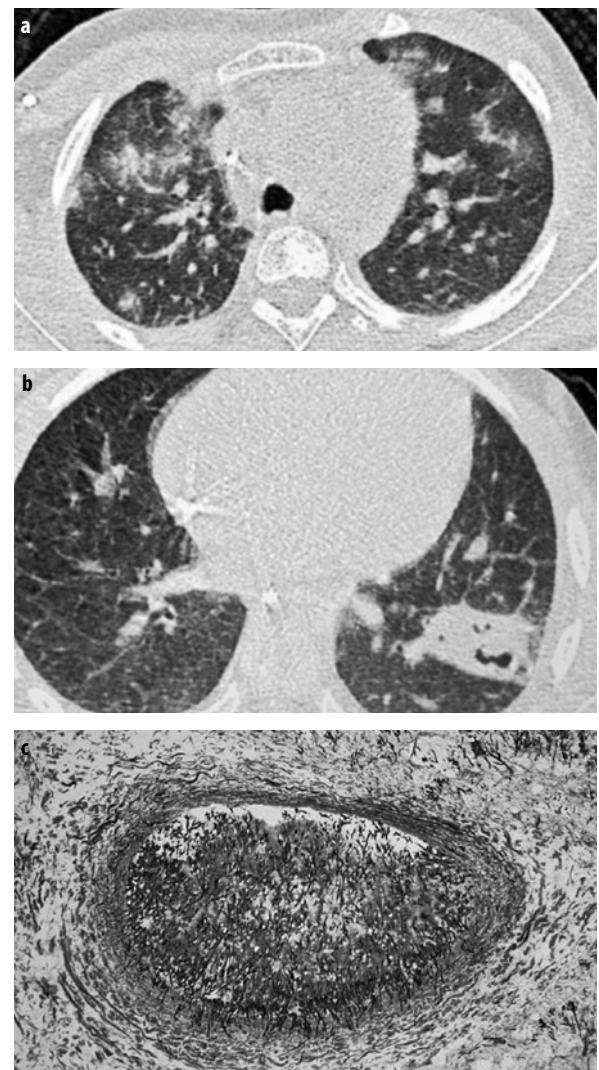


Fig. 4 a-c. Angioinvasive pulmonary aspergillosis post bone marrow transplant. **a** Contrast-enhanced axial computed tomography (CT) image of the thorax (lung window) demonstrates multiple perilesional nodular ground-glass haloes. **b** Another slice of the same scan shows a lesional cavitation in the lung with the air-crescent sign. **c** Macroscopic histological excision specimen confirms aspergillus cavity (for color reproduction see p 273)

is lesional cavitation with the formation of an air crescent [4]. Although these classic features have been described, in many cases, imaging appearances are non-specific [5].

Secondary (Acquired) Immunodeficiencies

Immunodeficiency Secondary to Immunosuppressive or Myeloablative Chemoradiotherapy

Respiratory complications may be subdivided into two broad categories: infectious and noninfectious. The frequency, range and severity of pulmonary complications are influenced by the intensity and length of immunosuppression and are also dependant on whether the treatment goal is immunosuppression or myeloablation.

Stem Cell Transplantation/Bone Marrow Transplantation

Pulmonary complications occur in 40-60% of patients following stem cell transplantation (SCT)/bone marrow transplantation (BMT) and are responsible for 10-40% of transplant-related deaths [5]. The type of pulmonary complication will be influenced by the type of underlying immune defect and may be subdivided into early (up to 100 days) and late (after 100 days) complications.

Pulmonary Complications: Early

Infectious Complications

Bacterial pneumonias: Bacterial pneumonias occur in approximately 10% of patients during the preengraftment period and are associated with a high mortality rate.

Viral pneumonias: Viral infections with, for example, respiratory syncytial virus, herpes simplex, adenovirus and varicella typically occur within the early posttransplant period.

Respiratory syncytial virus (RSV): Following SCT/BMT (particularly in the very early posttransplant period), RSV infection commonly leads to a devastating viral pneumonia, with a mortality rate approaching 50% [6].

Fungal pneumonias: Angioinvasive pulmonary aspergillosis (IPA) is reported to occur in approximately 4% of children undergoing SCT/BMT [7]. Children are at particular risk during episodes of prolonged neutropenia or with the use of high-dose corticosteroids for treating graft-versus-host disease (GVHD). The most common infecting organisms are *Aspergillus fumigatus* or *A. flavus*. As a consequence of a profound neutropenia, radiographic appearances may be atypical and, as a result, the diagnosis of IPA is often delayed. A definitive diagnosis can be established only with certainty after histological confirmation of hyphae within lung tissue. Using the European Organization for Research and Treatment of Cancer (EORTC) criteria, probability rates can be

high, and empirical therapy is begun following the presence of CT findings of multifocal nodules, perifissural consolidation, the halo sign and cavitation.

Acute, Noninfectious Pulmonary Complications

These types of complications occurring within the early posttransplant period include idiopathic pneumonia syndrome (IPS), pulmonary oedema, pulmonary haemorrhage, pulmonary venoocclusive disease (VOD) and relapse of the underlying malignancy.

Pulmonary Complications: Late

Infectious Pulmonary Complications

Patients continue to be at risk from bacterial infections even after engraftment due to continuing defective humoral (B-cell) immunity. The most common infecting organisms are encapsulated bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae*. Others include *P. jiroveci* (particularly in those where prophylactic antibiotic compliance is poor), cytomegalovirus and adenovirus.

Noninfectious Pulmonary Complications

These include obliterative bronchiolitis (OB), diffuse alveolar damage (DAD), LIP and relapse of the underlying disease.

Solid-Organ Transplantation

As a consequence of long-term immunosuppressive therapy, recipients of solid-organ transplants are at risk from recurrent infections as well as an increased incidence of neoplasia, the lymphoproliferative disorders being the most frequent [3]. The type of organ transplantation in addition to the type and intensity of immunosuppression regimen used will influence the pulmonary complications encountered.

Posttransplant Lymphoproliferative Disorders

The posttransplant lymphoproliferative disorders (PT-LPD) represent a spectrum of disease ranging from polyclonal lymphoid hyperplasia to monoclonal malignant lymphoma [2, 3, 8]. The majority of PT-LPD is of B-cell origin and is almost invariably associated with Epstein-Barr virus (EBV) infection. The incidence varies from 1% in renal transplant recipient to 10% in heart and heart/lung transplant recipients [3]. The time between transplant and onset varies from 1 month to several years [2, 8].

Radiographic appearances of intrathoracic LPD are variable and range from discrete parenchymal nodules, which may be solitary or multiple, to diffuse or focal reticulonodular infiltrates or consolidation. These findings may or may not be associated with mediastinal lymphadenopathy. Imaging appearances may mimic

pyogenic or fungal infection and, as a consequence, biopsy is usually required.

Human Immunodeficiency Virus: Associated Acquired Immunodeficiency Syndrome

Pulmonary Complications

Pulmonary disease is the most common initial manifestation of human immunodeficiency virus (HIV) in children and is the primary cause of death in 50% of children with AIDS [9]. The most common respiratory manifestations of HIV are bacterial pneumonias, *P. jiroveci* pneumonia and LIP.

Pneumocystis Jiroveci Pneumonia

This is frequently the initial manifestation of HIV, often presenting in early infancy. It is the most common opportunistic pulmonary infection in children with AIDS, occurring in up to 50%, and is the leading pulmonary cause of death [9, 10]. Radiographic appearances are variable and include hyperinflation with diffuse bilateral interstitial or nodular infiltrates and widespread alveolar shadowing. Asymmetric, focal or patchy infiltrates are also frequent. In contrast to the disease in children with primary immunodeficiency disorders, cavitary nodules and cysts are common, occurring in up to one third of cases. Lymphadenopathy and pleural effusions are uncommon and, if present, an alternative diagnosis such as LIP or *M. tuberculosis* should be considered. Pneumothoraces and/or pneumomediastinum are frequent complications; HRCT findings include patchy or diffuse ground-glass opacity, consolidation, cysts or cavities, centrilobular opacities, nodules and interlobular septal thickening.

Lymphocytic Interstitial Pneumonitis

LIP occurs in approximately one third of infected children. It occurs as part of the diffuse infiltrate lymphocytosis syndrome (DILS) and is thought to represent a direct hyperimmune lung response to the presence of either HIV or EBV. It appears to be restricted to children expressing the HLA DR 5 alleles and is associated with a slower rate of disease progression [11]. Radiographic appearances include interstitial reticulonodular infiltrates, which may progress to patchy air-space consolidation in contrast to *P. jiroveci* pneumonia; lymphadenopathy is common and often becomes more prominent during episodes of superadded infection [9, 11].

Viral Infections

Infection may occur as a result of a primary infection or reactivation of a latent virus. Viruses include RSV, influenza and parainfluenza virus, CMV and occasionally measles and varicella zoster virus (VZV).

Varicella Zoster Virus

Immunodeficient children often present with a more protracted illness than in immunocompetent controls, with approximately 50% suffering from chronic or recurrent VZV infection. The risk of complications increases with increasing immunological impairment. The chest radiograph typically shows bilateral diffuse reticulonodular infiltrates. The nodules are variable in size, ranging from 3 to 10 mm; they often coalesce, resulting in focal areas of consolidation. Superimposed bacterial infection is common.

Mycobacterium Tuberculosis

This may occur at any stage of HIV infection. In children, it usually occurs as a result of primary infection acquired from an infected adult. Disseminated or extrapulmonary TB is classified as an AIDS indicator in children.

Conclusion

Pulmonary complications are common in immunocompetent and immunodeficient children, and the chest radiograph is the first-line imaging technique. TB, sadly, has returned to challenge us, and the radiologist must keep this in mind when analysing radiographs with abundant lymphadenopathy or consolidation that is not resolving on conventional antimicrobial agents. A respiratory presentation is the most common first manifestation of immunodeficiency states in children, with infectious complications being the most common. There is overlap in the radiological findings, and correlation with the cause and severity of the underlying immunodeficiency state is important when interpreting imaging findings.

All immunodeficiency states are associated with an increased incidence of neoplasia, particularly LPD, the chest being a frequent site of disease. Radiological manifestations in addition to clinical presentations are often atypical and may be misinterpreted as infection. It is therefore vital that both clinicians and radiologists be aware of the protean manifestations of these potentially treatable conditions.

References

1. Calder A, Owens CM (2009) Imaging of parapneumonic pleural effusions and empyema in children. *Pediatr Radiol* 39:527-537
2. Balfour-Linn IM, Abrahamson E, Cohen G et al (2005) BTS guidelines for the management of pleural infection in children. *Thorax* 60:94-96
3. Sonnappa S, Cohen G, Owens CN et al (2006) Comparison of urokinase and video-assisted thoracoscopic surgery for treatment of childhood empyema. *Am J Respir Crit Care Med* 174:221-227
4. Thomas KE, Owens CM (2003) The radiological spectrum of invasive aspergillosis in children: a 10-year review. *Pediatr Radiol* 33:453-460

5. Palmas A, Tefferi A, Myers JL et al (1998) Late-onset non infectious pulmonary complications after allogenic bone marrow transplantation. *Br J Haematol* 100:680-687
6. Englund JA, Sullivan JC, Jordan MC et al (1988) Respiratory syncytial infection in immunocompromised patients. *Ann Intern Med* 109:203
7. McWhinney PH, Kibbler CC, Hamon MD et al (1993) Progress in the diagnosis and management of aspergillosis in bone marrow transplantation: 13 years' experience. *Clin Infect Dis* 17:397-404
8. Bragg DG, Chor PJ, Murray KA et al (1994) Lymphoproliferative disorders of the lung: histopathology, clinical manifestations and imaging features. *AJR Am J Roentgenol* 163: 73-281
9. Haller JO, Cohen HL (1994) Paediatric HIV infection: an imaging update. *Pediatr Radiol* 24:224-230
10. Sivit CJ, Miller CR, Rakusan TA et al (1995) Spectrum of chest radiographic abnormalities in children with AIDS and pneumocystis carinii pneumonia. *Pediatr Radiol* 25:389-392
11. Owens CM, Allan R, Thomas K et al (1996) Pictorial review: the radiological spectrum of vertically-acquired HIV infection. *Br J Radiol* 69:777-782



Imaging Vascular Anomalies of the Pediatric Chest: Rings, Slings, and Other Things

Alan S. Brody

Department of Radiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Introduction

This chapter begins with a discussion of the techniques used in computed tomography (CT) and magnetic resonance imaging (MRI) to evaluate suspected vascular anomalies of the chest in children. Selected examples of vascular anomalies of the great vessels and more peripheral lung vessels are then described. Examples of lesions that are less commonly described have been chosen. Technique is emphasized in order to address some of the challenges in obtaining diagnostic-quality imaging of the pediatric thoracic vasculature. In most cases, contrast material can only be administered a single time, so there is only one chance to get the images. Young children cannot cooperate with breathing instructions or even lie still. Respiratory motion is greater in children than in adults, and a respiratory rate of 60 is normal for an infant. Good quality images can easily be compared with numerous examples available in textbooks and through the World Wide Web, or the images can be shared with other imagers to arrive at the correct diagnosis. Poor image quality due to motion, poor contrast bolus, artifacts, or limitations of technique will limit all attempts at interpretation.

Vascular anomalies of the chest in children are rare in the general population, but the suspicion of a vascular anomaly is a relatively common indication for imaging the pediatric chest. In great-vessel anomalies, airway or esophageal compression is the most frequent concern. Children with swallowing difficulty will usually present initially for an esophagram, with further imaging depending on the findings. Children with noisy breathing or other symptoms suggesting airway narrowing may present directly for cross-sectional imaging or may initially be studied by endoscopy. Vascular pulsation of the airway wall at a site of airway narrowing is a common reason to pursue imaging for a vascular anomaly.

Plain Radiographs, Fluoroscopy, and Echocardiography

Plain radiographs are the initial study in most children with vascular anomalies of the chest. If the child presents with symptoms of dysphagia or noisy breathing, an aortic

arch anomaly will be suspected. Close attention should be paid to the position of the airway and any impressions on the airway [1]. This has been discussed in the section on the pediatric airway and will not be discussed here in detail. The position of the aortic arch, either seen directly or by midline or left-sided position of the trachea, must be assessed.

Other vascular anomalies involve more peripheral thoracic vessels. Abnormal vessels in the lung parenchyma can have appearances ranging from well-defined nodular lesions to ill-defined opacities similar to those seen with atelectasis and infiltrate. A history of recurrent pneumonia may lead to further imaging due to the presence of a persistent parenchymal opacity. The relative volumes of the two lungs may be an important clue to the presence of pulmonary vascular abnormalities. There may be shift of the mediastinum or heart. It is often difficult to assess pulmonary vascularity in children and to differentiate large vessels from diffuse pulmonary parenchymal abnormalities. The possibility of a vascular abnormality may not be considered until cross-sectional imaging is performed.

Standard radiographic technique suffices for these radiographs. If a suboptimal chest radiograph is obtained, it requires far fewer resources and often much less radiation exposure to repeat the chest radiograph than to proceed to cross-sectional imaging. Suspected basilar opacities are often better evaluated using decubitus positioning and imaging the "up" lung. High kilovolt technique with added filtration can be used to improve airway visualization, but if there is suspicion of a vascular anomaly on clinical grounds, initial imaging will often be followed by cross-sectional imaging without regard to the results of other imaging studies. In this case, further airway images will not affect the child's care.

If fluoroscopy has been performed, great-vessel anomalies have specific patterns of impression on the airway and esophagus. Impressions on the anterior trachea and posterior esophagus suggest a double aortic arch or variant. An isolated anterior impression closer to the carina than the thoracic inlet suggests innominate artery compression. An isolated posterior impression on the esophagus suggests a left aortic arch with aberrant right subclavian

artery. Impression on the posterior trachea and the anterior esophagus is seen with pulmonary artery sling.

Echocardiography is frequently used to evaluate for the presence of intracardiac abnormalities. Echocardiography is somewhat limited in evaluating the great vessels and is very rarely of value in evaluating suspected parenchymal vascular lesions. One situation in which echocardiography may be very useful is when arteriovenous malformations (AVMs) are suspected. In this case, echocardiography using microbubbles to detect left to right shunting can be very useful.

When an abnormality involving the pulmonary parenchyma is suspected, CT scanning will usually be the modality of choice. For suspected great-vessel anomalies or other vascular lesions of the mediastinum, both CT and MRI can be used to good effect.

Patient Preparation for Cross-Sectional Imaging

Young children cannot provide the necessary cooperation with instructions to obtain the highest quality images. Patient motion and respiratory motion may limit image quality, even with very rapid imaging. Sedation and general anesthesia can both be used safely and efficiently [2]. The use of either requires an institutional commitment to a program that safeguards the patient and does not disrupt the workflow of the imaging department. Effective methods using sedation and mask ventilation to provide motion-free images at specified lung volumes have been described [3]. Older children will cooperate far better if expectations are communicated prior to imaging and if questions are encouraged. Often, a parent in the room is very helpful. As a guideline, children <6 years old cannot usually be expected to follow breathing instructions. At 8 years old, most children will be able to follow instructions. A person in the scan room often improves cooperation up to the age of 10 years old.

Choosing between CT and MRI

Cross-sectional imaging provides definitive evaluation of vascular anomalies of the pediatric chest. CT and MR scanning are the modalities of choice. CT scanning requires the use of ionizing radiation, which carries with it a risk of later cancer. This is only one of the factors that should be considered when choosing between these two modalities. Current CT scanners with 64 or more channels can image the entire chest in <10 s. A single-volume scan provides the entire data set, which can be used to form images in any plane, curved reconstructions, and three-dimensional reconstructions. CT scanning is the imaging modality of choice for the lungs, and so a single examination provides complete evaluation of the thoracic vasculature and the lungs. The child only needs to be still for a period of seconds and remains accessible for monitoring and support, if needed.

MRI scanning requires a much longer time to complete. Monitoring can be challenging with the child completely enclosed by the magnet with the strong magnetic field environment. MRI also has several important advantages. No ionizing radiation is required, and it can be performed effectively without the use of intravenously administered contrast material if the patient has impaired renal function. Functional information including detecting stenosis or regurgitation, and blood flow direction and velocity can be determined.

Radiation risk is an important consideration when deciding on the imaging modality. Whereas no studies have shown an increase in cancer related to CT scanning, there is a great deal of concern about this possible risk. The ongoing discussion of radiation risk from CT scanning has increased the perception that the decision to perform a CT scan should be viewed as a risk/benefit decision. There is, however, wide agreement that any reasonable clinical benefit is greater than the small possible risk of later developing cancer [4]. Risk and benefit should also be considered when deciding on CT technique. Risk should be minimized by using the appropriate technique, and benefit should be maximized by obtaining high-quality images that fully address the clinical question.

CT Technique

CT technique should be chosen to provide the necessary information at the lowest radiation dose. CT angiography (CTA) is often recommended for these studies, but with current high-channel CT scanners, in most cases, a standard pediatric chest imaging protocol using intravenously administered contrast material is sufficient for an accurate diagnosis. CTA can provide greater resolution and decreased motion artefacts, but using slower table motion and narrower collimation increases radiation dose [5]. An additional refinement of CTA is to obtain images at a specific time in the cardiac cycle, usually during diastole when cardiac motion is least. This technique, called gating, further decreases motion artefact and improves resolution. If gating is used, it is important to recognize that two different techniques can be used to obtain gated images. The first, prospective gating, uses the patient's electrocardiographic tracing to identify diastole and signals the CT scanner to obtain images only during diastole. This technique increases overall imaging time but does not necessarily increase radiation dose. Prospective gating requires a regular heart rate, as the CT scanner cannot trigger quickly enough to complete the image in real time. Instead, the system uses the prior several cardiac cycles to predict when diastole will occur and initiates scanning so that imaging is obtained at the expected time of diastole. The second technique, retrospective gating, obtains a series of images throughout the cardiac cycle and uses only those obtained during diastole. Because this requires some of the image data to be discarded, the radiation dose is increased, often markedly [6]. Whereas gating markedly improves imaging of the heart, this degree of resolution is

rarely needed when evaluating for extracardiac vascular anomalies. Contrast injection technique is also simplified by using a standard 1- to 2-cc/kg dose injected at 2 cc/s for most children.

Technique should be determined based on the CT scanner used and the child's size or weight. Low-dose technique should be used for all children. Image quality should be continually reviewed both to ensure adequate image quality and to identify opportunities to decrease dose. Either 80 or 100 kVp should be used to take advantage of increased contrast between vessels and surrounding soft tissue when using iodinated contrast material: 80 kVp produces greater contrast but may result in unacceptable streak artifact. A sample technique for a 10-kg child could be 100 kVp, 50 mA, 0.5-s rotation speed, pitch 0.828 (helical pitch 53), 64×0.5 detectors. When adjusting technical parameters, changing kVp has a greater effect on dose and noise than does changing mA. Increasing from 80 to 100 mA increases dose by approximately 50%. Increasing from 100 to 120 kVp increases dose >40%.

MRI Technique

MRI technique is much more variable due to the wide range of imaging options as well as the ability to provide functional information. As with CT scanning, in most cases, vascular anomalies can be well characterized with basic imaging protocols. Vascular imaging can be divided into black-blood and white-blood sequences. Black-blood sequences are optimized to image static protons, so that the rapidly moving protons in flowing blood produce no signal and appear black. Black-blood sequences provide the highest contrast and are very useful for overall assessment of vascular anatomy. The black-blood sequences overestimate the size of vessels and should not be used to provide measurements of vessel size. Double inversion recovery fast spin echo is an example of a black-blood imaging sequence. White-blood sequences can be obtained in a number of ways, including time of flight, phase contrast, and with contrast enhancement [7]. Time of flight sequences take advantage of the fact that protons lose signal when they are exposed to excitation pulses. Blood outside of the imaged volume has not experienced excitation pulses and so has high signal. If stationary protons are exposed to multiple excitation pulses and flowing blood only few excitation pulses, the protons in flowing blood will have higher signal than those in the rest of the image. Gradient recalled echo sequences are used for time of flight imaging. With special techniques, it is possible to obtain time of flight images with both two- and three-dimensional acquisition techniques. Phase contrast angiography uses the difference in phase of flowing vs. stationary spins to produce image contrast. Phase is a measure of the change in angle of precessing protons between the time that the proton is tipped with the excitation pulse to the time that that signal is detected with the readout pulse. Phase contrast images can be obtained

with or without the direction and speed of blood flow affecting the signal of the flowing blood. When the signal reflects the characteristics of blood flow, functional information can be obtained. Contrast-enhanced techniques use the T1 shortening effect of intravenously administered MR contrast material to increase the signal of blood relative to the surrounding tissues [8]. Contrast is greatest when a bolus of blood containing contrast material enters the imaged volume. With contrast-enhanced imaging, careful timing is necessary to coordinate the contrast material injection and the imaging sequence.

Representative Thoracic Lesions Characterized by Vascular Abnormalities

Aortic Arch Anomalies

When evaluating an abnormal aortic arch, the hypothetical double aortic arch of Edwards provides a useful guide (Fig. 1) [9]. This image of a complete double aortic arch can help explain the various anomalies of the aortic arch resulting from atypical persistence or involution of portions

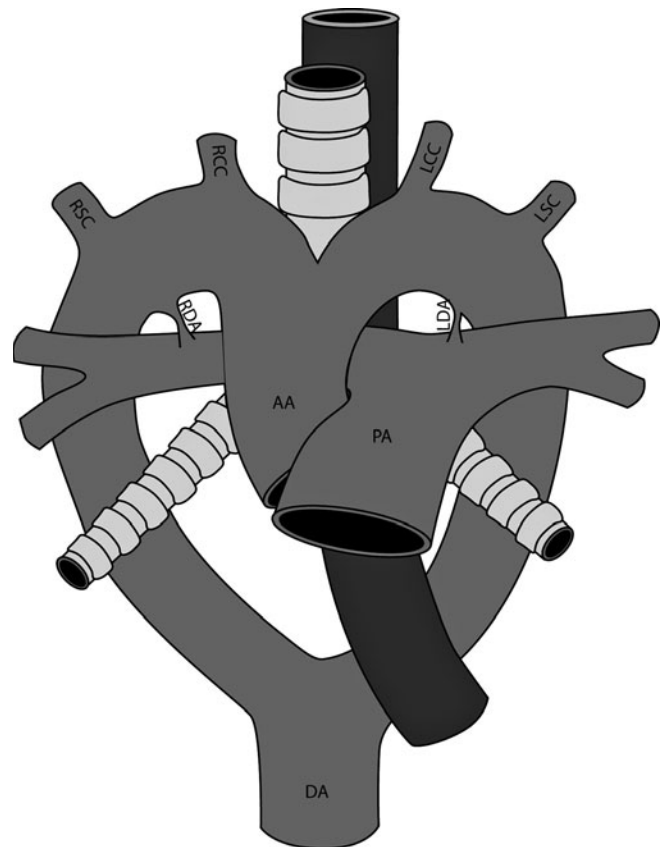


Fig. 1. Hypothetical double aortic arch of Edwards can be a useful aid when evaluating aortic arch anomalies. *RCC* right subclavian artery, *RDA* right ductus arteriosus, *AA* ascending aorta, *PA* pulmonary artery, *DA* descending aorta, *LCC* left common carotid artery, *LSC* left subclavian artery, *LDA* left ductus arteriosus

of the developing aorta. There are very few data on the incidence of aortic arch anomalies. These are rare anomalies, estimated to be responsible for approximately 1% of congenital heart disease. In all vascular anomalies of the mediastinum, the airway must be examined carefully in order to differentiate between airway narrowing due to vascular compression and intrinsic airway narrowing. Tracheal stenosis due to complete tracheal rings can be associated with many vascular anomalies and will require complex airway surgery in order to relieve the narrowing [10].

Right Aortic Arch

Right aortic arches occur in the range of 0.1-0.2% of the population. There are multiple types, but two are by far the most common, accounting for at least 80% of cases [11]. The most common is the right aortic arch with an aberrant left subclavian artery (RAALS). RAALS occurs in two types. In the first, the left subclavian artery originates directly from the descending aorta and a left ligamentum arteriosum completes a vascular ring. In the second, a large aortic diverticulum passes posterior to the esophagus (diverticulum of Kommerell) and gives rise to both the left subclavian artery and the ligamentum arteriosum.

The second most common right aortic arch is a mirror image of the normal left aortic arch. The mirror image right arch has been estimated to occur with congenital heart disease (CHD) in 95% of people, whereas right arch with aberrant subclavian is associated with CHD in <20% of cases. This further increases the chances that a child outside the newborn period with a right aortic arch will have RAALS. Due to the presence of the left ductus ligament, RAALS forms a vascular ring. This ring has been described as "loose", so that respiratory and gastrointestinal symptoms are rare. In children presenting with symptoms such as stridor or feeding difficulty, however, due to the greater frequency of RAALS in the population, this is not an uncommon cause of a vascular ring in a symptomatic older child.

Double Aortic Arch

Double aortic arch is an anomaly with two vessels arising from the ascending aorta, one on each side of the trachea and esophagus. Most double aortic arches descend on the left. As with right aortic arches, double aortic arches also occur in multiple types, with a few occurring far more commonly. The most common type has a right arch that is larger, higher, and anterior to the left arch. In some cases, one of the arches, usually the left, is atretic. In this case, the appearance is similar to a right aortic arch with either mirror image branching or with an aberrant left subclavian artery.

Pulmonary Venolobar Syndrome

Although the term scimitar syndrome is often applied to this form of anomalous pulmonary venous drainage, the scimitar appearance of the draining vein is often not ap-

preciated on chest radiographs. Frequently, once the diagnosis is made, a bit of imagination allows one to point out the scimitar. On plain radiographs, dextroposition of the heart may be the most striking finding, with increased attenuation of the right lung. This characteristic large pulmonary vein drains into the systemic system, usually into the inferior vena cava, although other vessels including the portal vein may be involved. Anomalous drainage can be partial or complete, with the vein draining the entire lung in two thirds and the lower portion of the lung in one third [12]. The right lung is usually affected, although very rare left sided cases have been reported.

The term scimitar syndrome emphasizes the large draining vein that is often the finding that leads to the correct diagnosis. Other terms, such as pulmonary venolobar syndrome and hypogenetic lung syndrome, better characterize this anomaly. This syndrome is not limited to the abnormal pulmonary venous drainage but involves all components of the affected lung. The lung is always small, and the lung parenchyma is abnormal, with parenchymal abnormality often seen on CT scanning. Anomalous bronchial branching is common. The pulmonary artery may be hypoplastic, and additional blood supply through an artery arising from the descending aorta may be present.

An infantile and an adult form have been described. The infantile form is more severe, usually presenting in the first 2 months with tachypnea, heart failure, and failure to thrive. Recurrent pneumonia is also a commonly reported symptom, although this may be due in part if the abnormal appearance of the right lung is incorrectly attributed to pneumonia. Because the hemodynamic effect of the abnormal venous drainage is a left to right shunt, cyanosis is not usually seen, except when additional cardiac defects are present. These occur in approximately one third of children with venolobar syndrome [13]. Symptomatic patients must be carefully evaluated for the presence of other cardiac and extracardiac anomalies, as consideration should be given to treating these at the same time that correction of the abnormal pulmonary venous drainage is performed. The adult form is less severe, with some patients remaining asymptomatic. Children may present for persistent right-sided infiltrate or with wheezing [14]. Patients may remain asymptomatic through adulthood.

Unilateral Pulmonary Vein Atresia

This anomaly is included because of its often confusing, but characteristic, appearance. Unilateral absence of the pulmonary veins usually presents in infancy but also outside the neonatal period. Adults with this anomaly have been reported [15]. Children usually present with a history of recurrent infections or, less commonly, with hemoptysis. Either lung can be affected, with the affected lung usually being small. Chest radiographs usually show unilateral diffuse increased pulmonary attenuation with a variable pattern that can range from reticulonodular to

coarse opacity. On CT scanning, the striking feature of unilateral absence of the pulmonary veins is the pattern of marked interlobular septal thickening on the affected side, which is due to increased pulmonary venous pressure. In addition, the central lung at the level of the atria may contain abnormal soft tissue, but no enhancing vessels are seen entering the left atrium. The wall of the contrast-enhanced left atrium on the affected side is smoothly contoured at the expected site of the junction of the pulmonary veins and the atrium, with no remnant of the pulmonary veins seen.

Pulmonary Arteriovenous Malformations

There are multiple etiologies for pulmonary arteriovenous malformations (PAVMs), including infection, trauma, chronic inflammation, and hepatic cirrhosis. In children, congenital PAVMs are most common. PAVMs are frequently symptomatic in adults, but in children seem to be more often identified as an incidental finding. There is a broad range of presentations, however, from asymptomatic, to severe cyanosis and congestive heart failure.

It has been estimated that more than half of PAVMs occur in patients with hereditary hemorrhagic telangiectasia (HHT), also called Osler-Weber-Rendu syndrome [16]. HHT is inherited as an autosomal dominant trait, and up to 20% of these patients will develop PAVMs [17]. Family members may be screened with CT for PAVMs. Whereas patients with ataxia telangiectasia are at increased risk from ionizing radiation, this has not been seen with HHT.

PAVMs are more common in boys during infancy, but in older patients, they are more common in women. PAVMs occur in both focal and diffuse forms. Focal PAVMs occur more commonly in the lower lobes. Disease is unilateral in 75% and multiple in 36% [18]. When present, focal PAVMs are often seen on chest radiographs as nodular opacities, sometimes with visible feeding and draining vessels. Diffuse PAVMs are rarely seen on chest radiographs, and in cases of very small PAVMs, these may not be identified on CT scanning. In some cases, distinct PAVMs may not be well seen, but large peripheral vessels may suggest the diagnosis. Focal PAVMs can be classified into simple and complex based on the arterial supply, with simple lesions supplied by a single segmental artery and complex lesions by two or more.

Most PAVMs remain stable in size, with approximately 25% increasing slowly. Regression is rare but has also been reported [17]. Studies of symptoms and complications of PAVMs are difficult due to the number of patients with HHT and symptoms and complications that may be due to HHT rather than to PAVMs. The most common pulmonary symptom is dyspnea, followed by hemoptysis. The classic triad of dyspnea, cyanosis, and clubbing is present in only a small number of patients [16].

Arterial supply is usually from a pulmonary artery, but systemic supply can be seen. PAVMs are best character-

ized on contrast-enhanced CT. Thin sections and coronal or sagittal reformatted images are recommended if the goal is to detect any tiny PAVMs that may be present or if treatment of a PAVM is planned. Because of the high incidence of multiple lesions, the entire lung should be scanned if chest radiographs or clinical signs and symptoms strongly suggest PAVM.

In addition to hemoptysis, complications of PAVMs include stroke and central nervous system (CNS) infection due to the arteriovenous shunt. One criterion for treatment has been a feeding vessel measuring 3 mm or more. Transcatheter embolization is the treatment of choice, and pediatric series have shown this to be safe and effective [19]. Identifying all lesions and their feeding and draining vessels using CT scanning is performed prior to catheterization to provide a roadmap for intervention.

Bronchopulmonary Sequestration

In both prenatal and postnatal imaging, identifying an abnormal artery or confidently excluding such a vessel is one of the essential goals of imaging in a child with a suspected focal congenital lung lesion. Bronchopulmonary sequestration (BPS) is formally defined as a bronchopulmonary foregut malformation in which the abnormal lung does not have a connection to the normal airway. In practice, the presence of an abnormal arterial supply is used as the major criterion for the identification of BPS, and the presence or absence of this vessel differentiates sequestrations from other focal congenital lesions of the lung. Identifying this artery is important to properly categorize the lung lesion, and it is essential information for the surgeon planning resection. This abnormal artery originates from the descending aorta and is usually intrathoracic, but can originate from the upper abdominal aorta as well. Drainage of these lesions is through the pulmonary veins in BPS within the visceral pleura (intralobar BPS), although systemic drainage can be seen. BPS outside the visceral pleura (extralobar BPS) more commonly have systemic drainage.

Imaging suspected BPS is one of the few indications for which it is appropriate to include the upper abdomen on a CT scan of the chest. Imaging of this malformation may benefit from the use of CT or MR angiographic technique, as the abnormal vessels may be small and tortuous. Imaging optimized for maximum contrast enhancement of the descending aorta has the greatest chance of clearly identifying this vessel.

It is increasingly recognized that the classic descriptions of the bronchopulmonary foregut malformations are both poorly supported by pathological findings and of limited value when most lesions are identified and evaluated prenatally. The use of terms such as hybrid lesion to describe malformations that have features of both BPS and congenital pulmonary airway malformation (CPAM) supports the understanding that many of these lesions are part of a spectrum rather than distinct

entities [20]. Careful pathologic examination of BPS and CPAM have shown atretic airways within these lesions, suggesting that intralobar BPS, CPAM, and bronchial atresia all stem from airway obstruction during development [21]. Areas of controversy in our understanding of congenital lung lesions include etiology, nomenclature, natural history, and complications, including the risk of malignancy. Patients are probably best served by a careful description of the lesion, including lesion number and location, the size of cysts if present, and the presence or absence of feeding and draining vessels.

There are no evidence-based and widely accepted recommendations for imaging follow-up of these lesions. It is important to recognize that it is common for lesions identified prenatally to decrease in size during gestation and that postnatal chest radiographs may be normal despite the continued presence of a congenital lung lesion [22]. One guideline that can be suggested is to defer postnatal cross-sectional imaging in infants who are asymptomatic and in whom a chest radiograph is normal.

References

- Pickhardt PJ, Siegel MJ, Gutierrez FR (1997) Vascular rings in symptomatic children: frequency of chest radiographic findings. *Radiology* 203:423-426
- Schulte-Uentrop L, Goepfert MS (2010) Anaesthesia or sedation for MRI in children. *Curr Opin Anaesthesiol* 23:513-517
- Long FR, Castile RG, Brody AS et al (1999) Lungs in infants and young children: improved thin-section CT with a noninvasive controlled-ventilation technique-initial experience. *Radiology* 212:588-593
- Brody AS, Frush DP, Huda W, Brent RL (2007) Radiation risk to children from computed tomography. *Pediatrics* 120:677-682
- Frush DP (2005) Technique of pediatric thoracic CT angiography. *Radiol Clin North Am* 43:419-433
- Huang B, Li J, Law MW et al (2010) Radiation dose and cancer risk in retrospectively and prospectively ECG-gated coronary angiography using 64-slice multidetector CT. *Br J Radiol* 83:152-158
- Korosec FR (2009) Principles of magnetic resonance angiography. In: Rubin GD, Rofsky NM (eds) *CT and MR angiography: comprehensive vascular assessment*. Lippincott, Williams, and Wilkins, Philadelphia, PA, p 52
- Swan JS, Carroll TJ, Kennell TW et al (2002) Time-resolved three-dimensional contrast-enhanced MR angiography of the peripheral vessels. *Radiology* 225:43-52
- Edwards JE (1953) Pathology of anomalies of thoracic aorta. *Am J Clin Pathol* 23:1240-1258
- Fraga JC, Gabra OH, Calkoen EE et al (2009) Long segment congenital tracheal stenosis in twins successfully treated by slide tracheoplasty. *J Pediatr Surg* 44:640-643
- Kellenberger CJ (2010) Aortic arch malformations. *Pediatr Radiol* 40:876-884
- Gao YA, Burrows PE, Benson LN et al (1993) Scimitar syndrome in infancy. *J Am Coll Cardiol* 22:873-882
- Wang CC, Wu ET, Chen SJ et al (2008) Scimitar syndrome: incidence, treatment, and prognosis. *Eur J Pediatr* 167:155-160
- Midyat L, Demir E, Aşkin M et al (2010) Eponym. Scimitar syndrome. *Eur J Pediatr* 169:1171-1177
- Heyneman LE, Nolan RL, Harrison JK, McAdams HP (2001) Congenital unilateral pulmonary vein atresia: radiologic findings in three adult patients. *AJR Am J Roentgenol* 177:681-685
- Puskas JD, Allen MS, Moncure AC et al (1993) Pulmonary arteriovenous malformations: therapeutic options. *Ann Thorac Surg* 56:253-257; discussion 257-258
- Vase P, Holm M, Arendrup H (1985) Pulmonary arteriovenous fistulas in hereditary hemorrhagic telangiectasia. *Acta Med Scand* 218:105-109
- Gossage JR, Kanj G (1998) Pulmonary arteriovenous malformations. A state of the art review. *Am J Respir Crit Care Med* 158:643-661
- Faughnan ME, Thabet A, Mei-Zahav M et al (2004) Pulmonary arteriovenous malformations in children: outcomes of transcatheter embolotherapy. *J Pediatr* 145:826-831
- Langston C (2003) Intralobar sequestration, revisited. *Pediatr Dev Pathol* 6:283
- Kunisaki SM, Fauzo DO, Nemes LP et al (2006) Bronchial atresia: the hidden pathology within a spectrum of prenatally diagnosed lung masses. *J Pediatr Surg* 41:61-65
- Winters WD, Effmann EL (2001) Congenital masses of the lung: prenatal and postnatal imaging evaluation. *J Thorac Imaging* 16:196-206



Airway Obstruction in Children

Janet L. Strife

Department of Radiology, Cincinnati Children's Hospital, University of Cincinnati, Cincinnati, OH, USA

Introduction

The radiologist plays a key role in the diagnosis of airway obstruction in children. In some instances, foetal imaging has significantly contributed to our understanding of congenital lesions, their natural history, and the effects of airway obstruction. In infants and young children, diagnosis, and obstruction site and severity are frequently determined by chest radiographs or airway images. Advanced imaging techniques with computed tomography (CT) and magnetic resonance (MR) play a role in children with chronic upper airway compromise or who are suspected of having extrinsic airway compression by a mass or vascular arch anomaly. Technical advances with faster scanners with gating utilising CT and MR with sophisticated postprocessing graphic workstations has made it much easier for both the radiologists and clinical services to understand the anatomy.

Common causes of paediatric airway abnormalities at the obstruction site are presented in Table 1 [1]. This chapter presents illustrative cases with discussion and differential diagnoses. For practical purposes, the cases are divided into common acute upper airway problems, such as retropharyngeal abscess, croup and epiglottitis; and lower intrathoracic causes of airway obstruction.

Normal Anatomy

Problems with the airway occur much more commonly in children than in adults. This is partially due to airway anatomy, which in young children is small. The head appears to rest on the shoulders, and the larynx is relatively high. In normal infants, the cartilage can be flaccid, causing noisy respiration, a condition called laryngomalacia. On chest radiographs, one should always look at the trachea first. The intrathoracic trachea usually demonstrates parallel walls, except for the indentation of the aortic arch. The position of the trachea is usually towards the right, near the pedicles, rather than midline.

Table 1. Causes of airway obstruction

Cause and effect	
Congenital	Trauma
– Choanal atresia	– Foreign body
– CHAOS	– Airway
– Nasal encephalocele	– Oesophagus
– Micrognathia or macroglossia	– Prior intubation, granuloma
– Thyroglossal duct cyst	– Prior tracheostomy
– Laryngeal atresia, stenosis	Laceration
– Subglottic tracheal stenosis	– Secondary tracheal stenosis
– Syndromes associated with abnormal cartilage	– Caustic ingestion
	– Radiation
Inflammatory	Miscellaneous
– Enlarged tonsils and adenoids	– Laryngomalacia
– Retropharyngeal abscess	
– Infectious mononucleosis	Vocal cord paralysis
– Croup	
– Epiglottitis	Tracheomalacia
– Oesophageal inflammatory disease	– Extrinsic compression
– Stevens-Johnson syndrome	– Angioneurotic oedema
– Lymphadenopathy	– Radiation
	– Caustic ingestion
Mass (noninflammatory)	– Stevens-Johnson syndrome
– Laryngeal cyst	Vascular lesions compressing trachea
– Aryepiglottic cyst	– Double aortic arch
– Epiglottic cyst	– Right arch, aberrant left subclavian artery
– Lymphatic malformation	– Pulmonary sling
– Papilloma	– Midline descending aorta
– Subglottic hemangioma	– Pre and post-operative congenital heart lesions
– Rhabdomyosarcoma	
– Dermoid-teratoma	
– Bronchogenic cysts	
– Lymphoma	
– Other masses	

Modified from [1]

In Utero Obstruction: Congenital High Airway Obstruction Lesions

With the increase in foetal imaging, congenital high airway obstruction lesions (CHAOS) is a syndrome increasingly recognised by sonography and/or MR. The condition occurs when there is tracheolaryngeal obstruction, which can be caused by intrinsic or extrinsic causes.

Intrinsic causes can be tracheal atresia or web. External causes are more common and include lymphatic malformations and high midline mass in the neck, throat, tongue or face. Obstruction of the trachea results in retention of bronchial secretion, which actually helps locate obstruction site. The obstruction site is recognised by the fluid-filled trachea distal to the obstruction, with overexpanded lungs and eversion or flattening of the diaphragm. Infants may also have foetal hydrops or ascites, which may relate to impaired venous return to the heart [2, 3]. On ultrasound, the heart is central, the lungs are echogenic and ascites and anasarca may be present. Whereas CHAOS lesions were considered to always be fatal, there has been occasional survival with ex utero intrapartum therapy (EXIT). At caesarean section, tracheal cannulation is done distal to the obstruction, which provides access to the airway prior to delivery. Even after the tracheal obstruction is removed, the lung does not function normally, and prolonged ventilation may be necessary. In utero obstruction in the trachea prevents the lung from receiving normal growth factors from the amniotic fluid, and thus normal lung growth does not occur. Pathology of such fetuses demonstrates abnormal lung development with a decrease in number of lung segments, which are poorly subdivided compared with normal foetal lung. It is postulated that in utero, the normal growth factors that are present in the amniotic fluid are not able to connect with the lungs and thus, even when the obstruction is relieved, the infant lung is underdeveloped.

Common Acute Upper Airway Obstruction

Acute Croup, or Laryngotracheobronchitis

This is a self-limiting disease of infants and young children seen from 6 months to 3 years. It presents with barking cough and inspiratory stridor. Croup is viral and usually involves the proximal 1 cm of the tracheal mucosa, which becomes inflamed with narrowing of the airway. The anterior-posterior (AP) airway radiograph demonstrates symmetric subglottic oedema (steeple effect) and a long and thin appearance to the initial part of the trachea. On lateral imaging, there is ballooning of the hypopharynx, with normal-appearing epiglottis and aryepiglottic folds. Airway imaging is not usually done unless there are persistent symptoms or a need to exclude other entities. The severity of subglottic narrowing seen on radiographs does not always correlate with clinical findings. Treatment is supportive, although occasionally inhaled steroids are given.

Subglottic Hemangioma

Hemangioma is the most common benign tumour of the head and neck in infants [4]. Typically, these children present with stridor and are <3 months of age. Approximately 30% will have cutaneous lesions. In isolated he-

mangioma, the AP radiograph appears to have asymmetric subglottic narrowing. However, some of these lesions have extensive airway compromise and are circumferential lesions with concentric airway narrowing. With sudden growth, the narrowing progresses. On CT, there is intense enhancement, which is the result of rapid filling of the vessels that make up the hemangioma, indicating a high-flow lesion. The infantile subglottic hemangioma may be associated with superficial hemangiomas of the head and neck that have a facial or beard distribution. This subgroup of children may exhibit additional associated structural anomalies of the brain, cerebral vasculature, cardiovascular, eyes and chest wall in the neurocutaneous syndrome called PHACE association.

Epiglottitis

This can be a life-threatening event, but the incidence has significantly reduced with the advent of the *Haemophilus influenzae* vaccine. There are other causes of acute epiglottitis that should be considered, including trauma, inhalation burn injury, abscess, bleeding in a haemophilic patient, postradiation, foreign body, etc. There is also a normal variant of an omega epiglottis that is congenitally large and may be noted in radiographs of the neck for other reasons. Clinical correlation is always appropriate. In children with severe symptomatic obstruction, imaging should be performed in an upright lateral position, as placing them in a recumbent position may further compromise the airway. Imaging findings include markedly enlarged epiglottis (thumb sign) and thickening of the aryepiglottic folds, which causes subglottic narrowing.

Bacterial Croup, or Tracheitis

This entity is also known as membranous croup and is characterised by inflammatory response in the mucosa of the trachea, which affects the airway. The children are usually from 6-12 years of age. It is often seen in children who initially have a viral infection and then get a superimposed bacterial infection. Small exudates or linear densities are seen within the trachea, which relate to semiadherent pus that causes subtle irregularity of the tracheal wall. Occasionally, during coughing, the membranes can be sloughed and move distally, partially obstructing the airway. Tracheal-wall abnormalities and/or membranes within the lumen can be seen on either AP or lateral images.

Retropharyngeal Cellulitis and Abscess

Retropharyngeal abscesses and cellulitis occur more frequently in young children and are related to infections of the ears, nose and throat that occur between the ages of 8 months and 3 years. Children present with fever, occasional stridor, stiff neck and dysphasia. Lateral view of the neck will demonstrate increased prevertebral soft tissues. It is often stated that the soft tissues between the posterior aspect of the aerated pharynx and the anterior

aspect of the vertebral bodies should not exceed the AP dimension of the vertebral body. However, this rule should cautiously be applied in young children, as there is normal motion of the airway and changes in its position related to positioning of the chin. When the chin is flexed in expiration, there may be remarkable increase in prevertebral soft tissue size and the child can be normal. Repeating the lateral radiographs is sometimes helpful. Currently, if an abscess is suspected, the patient is admitted to the hospital and begun on antibiotics. If the patient has increasing symptoms or persistent high fever following 24–48 h of antibiotic therapy, an ultrasound or CT may be performed to distinguish an abscess that may need drainage from diffuse cellulitis. CT may demonstrate a low-attenuating, well-defined mass with an enhancing rim, indicative of peritonsillar abscess. Additional findings on CT should be evaluation of the vessels. The carotid artery may appear small related to spasm on the affected side. The jugular vein may be thrombosed, and potentially, if the venous clot embolises to the lung, the child could have Lemierre's syndrome. Lemierre's disease consists of septic thrombophlebitis of neck veins, usually involving the jugular vein secondary to oropharyngeal infection with *Fusobacterium necrophorum*. Septic embolism may go to the lung, causing multiple lung abscesses.

Infectious Mononucleosis

In adolescent patients, infectious mononucleosis enlarges the tonsils, adenoids and prevertebral space. This is caused by Epstein-Barr virus and may be seen in children who are immunocompromised or in adolescence. Other symptoms in the adolescent group consist of malaise, splenomegaly and low-grade fever. The diagnosis should be suggested in older children with the typical radiographic findings of prevertebral soft tissue swelling and enlarged lymph node.

Papillomatosis

Juvenile-onset respiratory papillomatosis are benign tumours of the airway due to infections with human papilloma virus. In 95% of cases, children have laryngeal involvement. They usually present within the first 5 years of life. These warty lesions of the larynx and tracheobronchial tree spread to the lung where they are initially slow-growing nodules and subsequently can cavitate. CT is useful to determine disease extent and identify complications. Usually, there is disease progression and increased incidence of malignant degeneration.

Enlarged Tonsils and Lymph Nodes

Most young children have prominent adenoids and tonsils. The question arises as to whether they are abnormally enlarged and the cause of upper air sounds, sleep apnoea and/or other symptoms. Adenoids are absent at

birth, rapidly grow during infancy and reaching maximum size between 2 and 10 years. They usually decrease in size during the second year of life. Interestingly, it has been demonstrated that in children with obstructive sleep apnoea, the adenoids can be removed and then regrow and cause recurrent symptoms. How large is too large? If adenoids measure >12 mm from anterior to posterior diameter and are associated with hypopharyngeal collapse, they can cause snoring and obstruction. The associated collapse of the hypopharynx occurs because the relatively superior obstruction generates negative pressure in the hypopharynx during inspiration.

Palatine tonsillar enlargement with symptoms is frequently a cause of tonsillectomy. In some complex patients, cine MR studies of the airway are performed and the enlarged tonsillar tissues moves centrally and inferiorly, causing intermittent obstruction. The palatine tonsillar tissue does not grow back following removal.

Obstructive Sleep Apnoea

It is estimated that approximately 2 million children in the USA have obstructive sleep apnoea syndrome [5]. Many go unrecognised, as they appear normal during the day, but they may exhibit mild attention deficit disorder. Some have hyperactive behaviours, irritability, poor attention span, daytime fatigue and lack of concentration, leading them to perform poorly in school. There are a variety of tests for evaluating these patients. In children, the most common cause of obstructive sleep apnoea is enlarged adenoids and tonsils, which is confirmed by history, physical exam and single lateral view of the neck. Other causes are craniofacial anomalies, such as Pierre Robin sequence, congenital syndromes such as Down syndrome, achondroplasia and mucopolysaccharidosis [6].

When a child has an intrinsic or dynamic problem of the airway, an MR sleep study can be obtained. Sequences performed include T1-weighted (for anatomy) and T2-weighted images with fat saturation (depicts tonsillar tissue as bright on a dark background), as well as fast gradient-echo images that are displayed in a cine mode. The cine MR studies are useful in complex cases to help determine the appropriate surgical therapy [7].

Glossoptosis is a term that defines the posterior motion of the tongue during sleep. The tongue can abut the anterior portion of the pharyngeal wall causing intermittent obstruction. It is most commonly seen when children have craniofacial anomalies, macroglossia, micrognathia and decreased muscular tone. The soft palate may become oedematous, which is thought to be a sign of significant obstruction.

Foreign Bodies

Young children frequently put things in their mouth and occasionally swallow them. Foreign bodies can be the cause of high and lower airway obstruction. They can be radiopaque or nonradiopaque, the latter being most com-

mon. A coin is the most common foreign body swallowed, and although it usually never enters the trachea, when it is lodged in the oesophagus, it may secondarily affect the airway. On lateral radiographs, if there is narrowing of the trachea and increased soft tissue density separating the trachea and oesophagus, it suggests that the foreign body has been there for some time and it may be more difficult to remove. Whereas coins are the most common foreign body swallowed, there has been increasing attention related to the danger of button batteries ingested and lodged in the oesophagus. In the presence of alkaline environment, these batteries may leak and cause caustic burn and perforation of the oesophagus. Many of the batteries can be recognised on imaging, as they have a double rim that may distinguish them from typical coins. The importance of early recognition of button-battery ingestions is emphasised, as there are serious complications of oesophageal perforation and tracheal-oesophageal fistulas. Button batteries lodged in the oesophagus require urgent intervention to prevent complications. However, not all batteries will leak and cause necrosis of the oesophagus.

Laryngeal foreign bodies or tracheal foreign bodies are far less common. The hotdog or a piece of meat is the most nonradiopaque foreign body to become lodged in either the pharynx, proximal oesophagus or, occasionally, proximal airway. The peanut or popcorn are common lodged foreign bodies and can be recognised on chest radiographs if they are within the right or left bronchus, which may cause asymmetric aeration of the lungs. Inspiratory or expiratory chest radiographs can be obtained but with difficulty, as the child does not cooperate. Bilateral decubitus chest imaging is often preferred. The side that is dependent should always be less expanded when there is a lodged foreign body, and the upper side should be distended. Occasionally, diagnosis is delayed and children present with cough, fever and asymmetric wheezing related to the foreign body in more distal lung segment. Atelectasis may occur. Most foreign bodies are non-radiopaque, which makes the diagnosis difficult, especially when the child is young and nonverbal.

Tracheal Stenosis; Complete Tracheal Rings

This lesion rarely occurs as an isolated abnormality but usually is associated with congenital heart disease, syndromes or other anomalies. Complete tracheal rings are seen on axial CT imaging by a circular appearance rather than slightly elliptical at the site of the membranosa. In a recent review of 41 cases, there were many associated lesions, including cardiovascular anomalies, tetralogy of Fallot, atrial septal defect (ASD), ventricular septal defect (VSD), anomalous origin of the left pulmonary artery and/or congenital syndromes such as Down syndrome, Pfeiffer, VATER (vertebrae, anus, trachea, esophagus, and renal) syndrome and chondrodysplasia punctata [8, 9]. It is important to make the diagnosis and examine the length of the tracheal involvement. Associated

abnormalities include abnormal tracheal bifurcation and tracheal bronchus. Proper classification of these lesions will contribute to the understanding of the morbidity and mortality associated with the tracheal anomaly.

Masses Causing Airway Obstruction

There is an extensive list of masses that compress or displace the airway, causing symptoms. Many of them have characteristics that are fairly specific by compression location and site. Increasingly, the lesions are apparent on foetal imaging [10-14]. Few are malignant and many represent congenital lesions. Displacement of the trachea is frequently used as a guide to masses in the chest and anterior, middle and posterior mediastinum. A list of lesions is included in Table 1.

Bronchogenic Cyst

Bronchogenic cysts are usually located in the middle mediastinum and can compress the trachea or right or left mainstem bronchus but can also occur in the posterior mediastinum, lung parenchyma, pleura or diaphragm. Bronchogenic cysts are part of the spectrum of foregut duplication cysts and are developmental lesions resulting from abnormal ventral budding of the tracheobronchial tree, occurring between the 26th and 40th days of foetal life. They can be seen on prenatal imaging and are usually unilocular and fluid-filled. Postnatal imaging demonstrates a well-circumscribed, smooth-walled lesion, water density that has no enhancement or an enhancing rim.

Vascular Anomalies

Vascular anomalies are a group of congenital malformations of the developing aortic arch that cause tracheal compression [15]. Multiplanar imaging and postprocessing has simplified evaluating the extent of airway compression, relative size of the arch and identifying any associated abnormalities, such as coarctation of one of the segments.

Double Aortic Arch

Double aortic arch is the most common symptomatic abnormality that occurs in young children. The ascending aorta rises anterior to the trachea and divides into an anterior left arch and a posterior right arch. These then join posteriorly to form the descending aorta, which may be on the right or left side. There are many variables, including relative size of each arch, patency, position of the upper descending aorta and site of the ductus arteriosus. This entity is usually recognised on chest radiographs, with subsequent MR and/or CT imaging done for further definition. Imaging aids surgical planning, and in some cases, there may be a coarctation in one of the segments.

Right Aortic Arch with Anomalous Left Subclavian Artery

This entity usually presents in childhood with history of persistent wheeze or cough. In symptomatic patients, the aortic arch is right-sided, and there is frequently a diverticulum of Kommerell; a fibrous ductus band completes the ring. The left subclavian artery has its origin from the diverticulum [16, 17].

Innominate Artery Compression Syndrome

Although not a true vascular ring, the innominate artery may produce an isolated anterior tracheal compression. In children, the normal innominate artery has an origin to the left of the trachea and must cross obliquely to the right as it ascends into the neck. As it crosses the trachea in young children, it sometimes indents or appears to compress the trachea but usually does not cause symptoms [18]. In a small percent of children, the innominate artery can cause significant persistent compression of the trachea, and the child may have signs and symptoms of airway obstruction. The term reflex apnoea is used to describe episodes of reflex respiratory arrest that occurs during feeding in patients with significant innominate artery compression.

Diagnosis is made on lateral radiographs on which localised anterior compression of the trachea is visible near the thoracic inlet. This is seen as a normal finding without clinical symptoms in approximately one third of children. However, in children who have oesophageal atresia, the dilated oesophagus compresses the trachea posteriorly and pushes it anteriorly, allowing compression by the innominate artery. Any cause of persistent tracheal narrowing may result in tracheomalacia.

Pulmonary Sling

Children with pulmonary sling present with respiratory issues during the first few months of life; however, it is also recognised in foetal imaging. There is an anomalous origin of the left pulmonary artery, which is usually part of a more complex anomaly. The left pulmonary artery has its origin from the right pulmonary artery and crosses over the proximal portion of the right mainstem bronchus or trachea and then runs posterior towards the left. Increasingly, the associated abnormalities are being recognised [19-21]. In recent study, one third of all children had short- or long-segment tracheal narrowing, complete tracheal rings, abnormal bifurcation of the trachea and anomalies of accessory bronchi to the right upper lobe [9].

Malposition of the Descending Aorta

When the descending aorta is abnormally located immediately anterior to the spine instead of the normal left paraspinal location, mediastinal structures are compressed in a confined space between the anterior chest wall and the spine. This leads to compression of the dis-

tal airway between the pulmonary artery and the malpositioned descending aorta. Causes include descending aortic-carinal compression syndrome, right aortic arch with left descending aorta, left aortic arch with right-sided aorta and unilateral hypoplastic right lungs [22].

Cardiac Anomalies or Postoperative Cardiac Patients

Other less common vascular causes of compression of the trachea include enlarged pulmonary arteries, as seen in tetralogy of Fallot, with absent pulmonary valve. The pulmonary arteries are aneurysmal and compress the mainstem bronchi bilaterally, causing retained foetal fluid initially, and then partial obstruction. Occasionally, postoperative cardiac grafts can compress the trachea or right or left mainstem bronchus in children.

Inflammatory Diseases

Lymph nodes may cause tracheal narrowing and can be seen in a variety of diseases, the most common being tuberculosis. Usually, there are multiple nodes and some evidence of lung disease.

References

1. Kirks DR (ed) (1991) Practical pediatric imaging: diagnostic radiology of infants and children. Little Brown, Boston, MA
2. Courtier J, Poder L, Wang ZJ et al (2010) Fetal tracheolaryngeal airway obstruction: prenatal evaluation by sonography and MRI. *Pediatr Radiol* 40:1800-1805
3. Guimaraes CV, Linam LE, Kline-Fath BM et al (2009) Prenatal MRI findings of fetuses with congenital high airway obstruction sequence. *Korean J Radiol* 10:129-134
4. Koplewitz BZ, Springer C, Slasky BS et al (2005) CT of hemangiomas of the upper airways in children. *AJR Am J Roentgenol* 184:663-670
5. Owens J, Opiari L, Nobile C et al (1998) Sleep and daytime behavior in children with obstructive sleep apnea and behavioral sleep disorders. *Pediatrics* 102:1178-1184
6. Donnelly LF, Strife JL (2001) Advanced techniques for imaging the pediatric airway. In: Strife JL (ed) *Pediatric chest imaging*. Springer, Berlin, pp 155-169
7. Donnelly LF (2005) Obstructive sleep apnea in pediatric patients: evaluation with cine MR sleep studies. *Radiology* 236:768-778
8. Berdon WE, Baker DH, Wung JT et al (1984) Complete cartilage-ring tracheal stenosis associated with anomalous left pulmonary artery: the ring-sling complex. *Radiology* 152:57-64
9. Radhakrishnan R, Fleck RJ, Donnelly LF et al (2010) Complete tracheal rings: CT imaging features in 40 cases. *Society for Pediatric Radiology*, Boston, MA
10. Azizkhan RG, Crombleholme TM (2008) Congenital cystic lung disease: contemporary antenatal and postnatal management. *Pediatr Surg Int* 24:643-657
11. Berrocal T, Madrid C, Novo S et al (2004) Congenital anomalies of the tracheobronchial tree, lung, and mediastinum: embryology, radiology, and pathology. *Radiographics* 24:e17
12. McAdams HP, Kirejczyk WM, Rosado-de-Christenson ML et al (2000) Bronchogenic cyst: imaging features with clinical and histopathologic correlation. *Radiology* 217:441-446
13. Newman B (2006) Congenital bronchopulmonary foregut malformations: concepts and controversies. *Pediatric radiology* 36:773-791

14. Daltro P, Werner H, Gasparetto TD et al (2010) Congenital chest malformations: a multimodality approach with emphasis on fetal MR imaging. *Radiographics* 30:385-395
15. Berdon WE, Baker DH (1972) Vascular anomalies and the infant lung: rings, slings, and other things. *Semin Roentgenol* 7:39-64
16. Cina CS, Althani H, Pasenau J et al (2004) Kommerell's diverticulum and right-sided aortic arch: a cohort study and review of the literature. *J Vasc Surg* 39:131-139
17. Donnelly LF, Fleck RJ, Pacharn P et al (2002) Aberrant subclavian arteries: cross-sectional imaging findings in infants and children referred for evaluation of extrinsic airway compression. *AJR Am J Roentgenol* 178:1269-1274
18. Strife JL, Baumel AS, Dunbar JS (1981) Tracheal compression by the innominate artery in infancy and childhood. *Radiology* 139:73-75
19. Biyyam DR, Chapman T, Ferguson MR et al (2010) Congenital lung abnormalities: embryologic features, prenatal diagnosis, and postnatal radiologic-pathologic correlation. *Radiographics* 30:1721-1738
20. Lee KH, Yoon CS, Choe KO et al (2001) Use of imaging for assessing anatomical relationships of tracheobronchial anomalies associated with left pulmonary artery sling. *Pediatr Radiol* 31:269-278
21. Zhong YM, Jaffe RB, Zhu M et al (2010) CT assessment of tracheobronchial anomaly in left pulmonary artery sling. *Pediatr Radiol* 40:1755-1762
22. Donnelly LF, Bisset GS, 3rd, McDermott B (1995) Anomalous midline location of the descending aorta: a cause of compression of the carina and left mainstem bronchus in infants. *AJR Am J Roentgenol* 164:705-707

BREAST IMAGING SATELLITE COURSE

Microcalcifications of the Breast: An Approach to Radiologic Classification

Markus Müller-Schimpfle

Institute of Radiology, Frankfurt/Main-Hoechst Hospital, Frankfurt/Main, Germany

Introduction

Since the first description of black spots in the centre of a carcinoma in 1913 by Salomon, much work has been done to detect, characterise and classify microcalcifications systematically [1]. Particularly during the second half of the twentieth century, studies by Lanyi, Leborgne, and Le Gal et al. had a major influence on the diagnosis of microcalcifications of the breast [2-4]. However, diagnostic determination remains difficult [5].

The Breast Imaging Reporting and Data System (BI-RADS) now defines parameters that help to sort masses and microcalcifications into standardised diagnostic categories [6, 7]. However, data on the prospective classification of microcalcifications according to the BI-RADS lexicon are rare [8-10]. Furthermore, there are no recommendations for the clinician on how to link descriptive findings listed in the BI-RADS lexicon to the BI-RADS assessment categories. With respect to the level of suspicion, classification of masses seems more reliable than classification of microcalcifications [11].

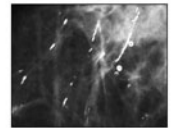
In order to accurately characterise breast microcalcifications, apart from the two-view standard mammograms (mediolateral oblique and craniocaudal view), additional mediolateral and craniocaudal compression magnification views are useful and are recommended.

The classification is applicable to a group of more than four microcalcifications (<2 mm single calcification) within a volume of 1-2 cc [6, 7, 11, 12]. A pragmatic approach is suggested, as follows [13, 14]:

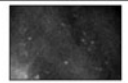
A. Classification of the type of microcalcifications into three groups (Fig. 1):

1. Typically benign (green in Fig. 1): vascular, popcorn-like, lucent-centred, round, rim, rod-like, curvilinear, suture calcifications; “typically benign” according to [6, 7].
2. Indeterminate (orange): amorphous or coarse heterogeneous; “intermediate concern, suspicious calcifications” according to [6, 7].
3. Typically malignant (red): fine pleomorphic according to [7], fine linear or fine-linear branching ([7], casting according to [6]), combinations of granular

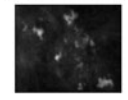
I. Typically benign (incl. punctated)



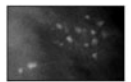
II. Amorphous



II. Coarse heterogeneous (>0.5 mm)



III. Fine pleomorphic (<0.5 mm)



III. Fine linear, branching

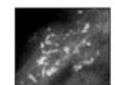


Fig. 1. Microcalcifications: from benign to malignant morphology. *Green frame:* microcalcifications with typically benign morphology (I); *orange frame:* microcalcifications with indeterminate morphology (II); *red frame:* microcalcifications with typically malignant morphology (III) (for color reproduction see p 273)

types with casting types (earlier a.c. polymorphous: fine linear plus granular, or fine linear plus branching, or branching and granular); “higher probability of malignancy” according to [6, 7].

B. Classification of microcalcification distribution into five groups (Fig. 2):

1. Diffuse: equal distribution over the entire breast parenchyma;
2. Round or oval (as in blunt duct adenosis): “clustered”, if not otherwise specified (NOS), typically within a volume of 1 cc;
3. Regional: not conceivably related to the ductal system (typically with a volume of >1 cc);
4. Segmental: related to the segment of the ductal system;
5. Linear: ductal distribution, typically oriented towards the nipple); branching: linear distribution with additional side branches.

These distribution modifiers are evaluated as suggested by the BI-RADS lexicon, which itself neither de-

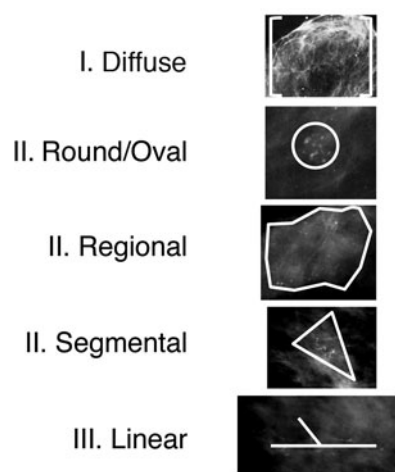


Fig. 2. Microcalcifications: from benign to malignant distribution. *Green frame:* microcalcifications with benign distribution (I); *orange frame:* microcalcifications with indeterminant distribution (II); *red frame:* microcalcifications with typically malignant distribution (III) (for color reproduction see p 273)

finer nor quantifies the varying influence of distribution modifiers on assessment categories. Some distribution modifiers (regional vs. segmental) were not proven to be of different statistical significance in the literature [15, 16]. Using data found in current literature, distribution modifiers are attributed to varying probability levels for malignancy [2-4, 15-18]. Thereby, we developed the standardised scheme we use to classify microcalcifications according to the BI-RADS morphology and distribution parameters [14]. The matrix system is demonstrated in Fig. 3.

Distribution	Morphology		
	Typically benign	Indifferent	Typically malignant
Disseminated	2	3	4B
Round/oval	3	4A	4C
Regional	4A	4B	4C
Segmental	4A	4C	4C
Linear/branching	4B	4C	5
MODIFIATORS			
- Number - Additional findings - Location - Follow up - Risk			

Fig. 3. The Microcalcification matrix serves as a guide for classifying grouped microcalcifications according to morphology and distribution, additionally considering modification aspects (modifiers) [13, 14] (for color reproduction see p 273)

BI-RADS and Indications for Biopsy

The routine indications in our centre for vacuum core biopsy (VCB) depending on the BI-RADS categories are explained in the following paragraphs.

1. BI-RADS 2 (typically benign): Biopsy is not indicated. Nevertheless, if a patient who was sent for VCB insists on histologic proof despite comprehensive information provided by the breast unit, we tend to perform the VCB.
2. BI-RADS 3 (probably benign): Typically, a short-interval follow-up is suggested (e.g. 6-month intervals for the first two examinations, 12 months for the subsequent two examinations, total follow-up time 3 years). If the patient still insists on histologic evaluation after comprehensive information about the risk of malignancy, or if additional risk factors are present, we perform a VCB. The additional risk factors are:
 - history of at least two female family members with breast or ovarian cancer, one of whom was diagnosed <50 years of age;
 - one first-degree family member with a single-sided breast cancer <35 years of age;
 - one first-degree family member with a double-sided breast cancer <40 years of age;
 - one first-degree family member with ovarian cancer <40 years of age;
 - one male family member with breast cancer;
 - personal history of invasive breast cancer, ductal carcinoma in situ (DCIS), lobular carcinoma in situ (LCIS) or atypical ductal/lobular hyperplasia (ADH/ALH).
3. BI-RADS 4 (suspicious abnormality; Figs 4-6): A VCB is performed if a representative specimen can be obtained with reasonable likelihood.

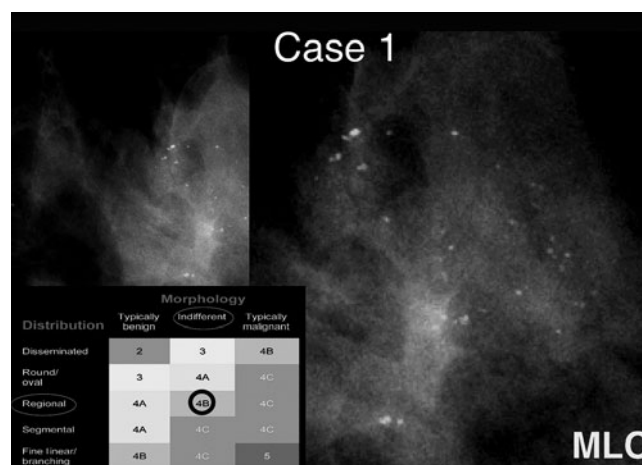


Fig. 4. Case 1: Indifferent type of microcalcifications with regional distribution (BI-RADS, 4B). Histology: fibrocystic changes, sclerosing adenosis, usual ductal hyperplasia. *MLO*, mediolateral oblique view (for color reproduction see p 273)

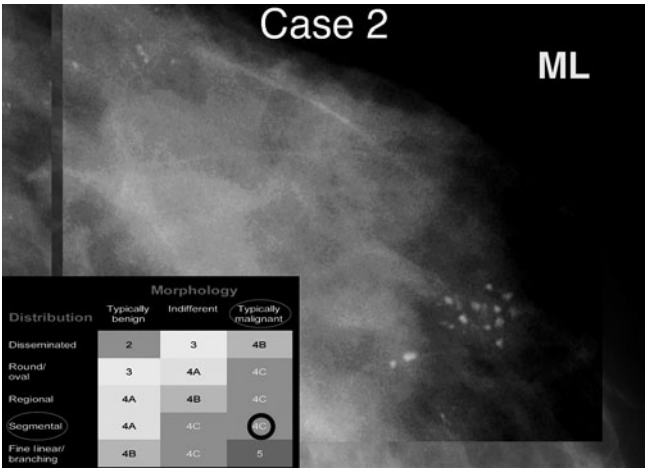


Fig. 5. Case 2: Typically malignant type of microcalcifications with segmental distribution (BI-RADS, 4C). Histology: invasive ductal cancer. *ML*, mediolateral view (for color reproduction see p 273)

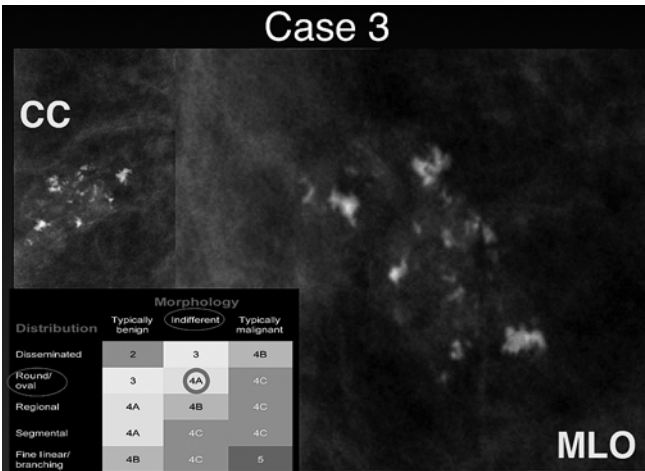


Fig. 6. Case 3: Indifferent (including coarse heterogeneous) type of microcalcifications with round/oval distribution (BI-RADS, 4A). Histology: fibroadenoma, fibrocystic changes. *CC*, craniocaudal view; *MLO*, mediolateral oblique view (for color reproduction see p 273)

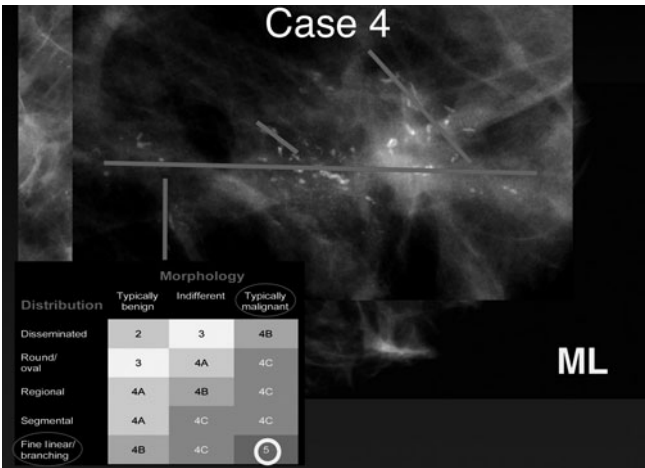


Fig. 7. Case 4: Typically malignant type of microcalcifications with linear and branching distribution (BI-RADS, 5). Histology: ductal carcinoma in situ (high grade). *ML*, mediolateral view (for color reproduction see p 273)

4. BI-RADS 5 (highly suggestive of malignancy; Fig. 7). A VCB is performed to confirm the diagnosis of cancer, to reduce the rate of underdiagnosis (biopsy: DCIS; operation: invasive cancer; this has potential implications for lymph node biopsy) and to define the extent of breast cancer/DCIS in order to clarify the surgical options (breast conservation therapy, mastectomy) with biopsy at the two most distant regions of the lesion, if applicable.

Several instruments are on the market to perform the VCB procedure (Mammotome, Breast Care/Ethicon; Vacora, BARD; Atec, Suros/Medicor; Encor, SenoRX/BARD). For needle guidance, a dedicated imaging system with the patient in prone position can be used (e.g. Lorad table, Horlogic) as well as an add-on device using a routine mammography unit (e.g. Senovision, GE). Core biopsies are gained after obtaining a digital scout image and stereotactic images (e.g. $\pm 15^\circ$; target, postfire, post-biopsy). In our institution, a local anaesthesia is given in combination with adrenaline (Xylocaine 2%, Adrenaline 1/200,000; Astra Chemicals, Wedel, Germany). Further details have already been reported [10].

Summary

Particularly with the advent of these minimally invasive procedures, which sample more tissue than standard core-cut biopsy, it has become even more important to know the diagnostic indices of imaging: a higher number of false positive imaging calls due to a lower barrier for tissue sampling is unacceptable by reimbursing insurances; and the number of false negatives, which we would probably accept if an operation was exclusively able to gain tissue, will presumably not be accepted in the future by the patient nor by the judge.

Therefore, standardisation in description and classification of lesions as achieved by the BI-RADS lexicon is helpful and a great step forward. However, we still face problems, as we lack a clear and logical pathway from the description to the diagnosis, causing a marked inter- and intraobserver variability in scientific studies and posing problems in the routine use of these characterisation systems [16-18]. Even the systematic approach of the BI-RADS lexicon in its current fourth edition, which describes different types of microcalcifications, lacks a translation of these microcalcification types into the BI-RADS assessment categories. Beyond this, not all types are clearly defined or necessarily lead to a particular diagnostic category. In a work addressing this topic, Berg et al. indicated that they continued to see variability in the use of the term punctate (according to the third edition of the BI-RADS lexicon) and suggested, that “a cluster of round punctate calcifications may be probably benign, but similar calcifications in a segmental or linear distribution would be at least suspicious” [18].

The combined assessment of morphology and microcalcification distribution is suggested in the BI-RADS lexicon, but no rules for such an assessment are defined. The systematic workup of calcifications suggested in this paper tries to narrow the gap between the microcalcification description on the one hand and the BI-RADS categorisation on the other hand (Table 1). It uses types of calcification morphology and microcalcification distribution patterns.

In conclusion, the BI-RADS lexicon describes microcalcifications of the breast and provides diagnostic categories that lead to standardised biopsy recommendations. Nevertheless, how to link the descriptive findings to the assessment categories still seems to be a difficult diagnostic task in evaluating microcalcifications, presumably more difficult than for masses. Microcalcification classification as proposed in this chapter helps set standards in the clinical routine as well as for comparability of scientific data.

References

- Salomon A (1913) Beiträge zu Pathologie der Mammacarcinome. Arch Klin Chir 101:573-668
- Lanyi M (1986) Diagnostik und Differentialdiagnostik der Mamma-Verkalkungen. Springer, Berlin, Heidelberg, New York
- Leborgne R (1951) Diagnosis of tumors of the breast by simple roentgenography: calcifications in carcinomas. AJR Am J Roentgenol 65:1-11
- Le Gal M, Durand JC, Laurent M, Pellier D (1976) Management following mammography revealing grouped microcalcifications without palpable tumor. Nouv Presse Med 5:1623-1627
- de Lafontan B, Daures JP, Salicru B et al (1994) Isolated clustered microcalcifications: diagnostic value of mammography – Series of 400 cases with surgical verification. Radiology 190:479-483
- American College of Radiology (ACR) (1998) Illustrated Breast Imaging Reporting And Data System (BI-RADS™), 3rd edn. American College of Radiology, Reston, VA, pp 53-181
- American College of Radiology (ACR) (2003). ACR BI-RADS® – Mammography, 4th edn. In: ACR Breast Imaging Reporting and Data System, Breast Imaging Atlas. American College of Radiology, Reston, VA, pp 61-259
- Sickles EA (1991) Periodic mammographic follow-up of probably benign lesions: results in 3,184 consecutive cases. Radiology 179:463-468
- Orel SG, Kay N, Reynolds C, Sullivan DC (1999) BI-RADS categorization as a predictor of malignancy. Radiology 211:845-850
- Siegmann KC, Wersebe A, Fischmann A et al (2003) Stereotactic vacuum-assisted breast biopsy-success, histologic accuracy, patient acceptance and optimizing the BI-RADS™-correlated indication. Rofo 175:99-104
- Hall FM, Storella JM, Silverstone DZ, Wyshak G (1998) Non palpable breast lesions: Recommendations for biopsy based on suspicion of carcinoma at mammography. Radiology 167:353-358
- Kopans DB (1989) Breast imaging. JB Lippincott, Philadelphia, PA, pp 118-122
- Müller-Schimpfle M, Wersebe A, Xydeas T et al (2005) Microcalcifications of the breast: how does radiologic classification correlate with histology? Acta Radiol 46:774-781
- Müller-Schimpfle M (2008) Consensus meeting of course experts in breast diagnosis 5 May 2007 in Frankfurt am Main-topic: microcalcinoses. Rofo 180:66-68
- Fondrinier E, Lorimier G, Guerin-Boblet V et al (2002) Breast microcalcifications: Multivariate analysis of radiologic and clinical factors for carcinoma. World J Surg 26:290-296
- Liberman L, Abramson AF, Squires FB et al (1998) The Breast Imaging Reporting and Data System: Positive predictive value of mammographic features and final assessment categories. AJR Am J Roentgenol 171:35-40
- de Lafontan B, Daures JP, Salicru B et al (1994) Isolated clustered microcalcifications: Diagnostic value of mammography-series of 400 cases with surgical verification. Radiology 190:479-483
- Berg WA, Campassi C, Langenberg P, Sexton M (2000) Breast Imaging Reporting and Data System: inter- and intraobserver variability in feature analysis and final assessment. AJR Am J Roentgenol 174:1769-1777

Mammography: Asymmetries, Masses, and Architectural Distortion

Edward A. Sickles

Department of Radiology, University of California San Francisco (UCSF) School of Medicine, San Francisco, CA, USA

Asymmetries

Right- and left-breast mammograms are traditionally displayed back-to-back, projection for projection, to facilitate the perception of areas of asymmetry, which may on occasion be the only manifestation of breast cancer on standard mammographic views. Asymmetry is usually distinguished from mass in that it demonstrates concave-outward rather than the convex-outward contours typical of a mass, and that it is interspersed with fat rather than appearing denser in the center than at the periphery (typical of a mass). There are four types of asymmetry, all of which represent areas of fibroglandular-density tissue that is more extensive in one breast than the other:

1. **Summation artifact:** This is caused by superimposition of normal fibroglandular breast structures on a given mammographic projection. As such, this finding will be visible on only one of the two standard views and will not be seen on additional views taken in different projections. One must distinguish summation artifact from the other types of asymmetry described below, because it never represents breast cancer and should not be subjected to biopsy. A one-view-only mammographic finding is called an asymmetry prior to diagnostic imaging evaluation. Most (>75%) asymmetries represent summation artifacts; the rest are found to be other types of asymmetry or masses.
2. **Global asymmetry:** formerly called asymmetric breast tissue, represents a greater volume of fibroglandular tissue in one breast than in the corresponding location in the opposite breast, without associated mass, microcalcification, or architectural distortion. It is found in approximately 3% of screening mammography examinations. It almost always represents a normal variant, but occasionally it may indicate the presence of an underlying breast cancer if it corresponds to a palpable abnormality. In this latter clinical setting, the radiologist usually will recall the patient for additional imaging evaluation.
3. **Focal asymmetry:** formerly called focal asymmetric density, is an asymmetry of fibroglandular-tissue density seen on two different mammographic projections but lacking the convex-outward contours and con-

spicuity of a mass. It usually represents an island of normal dense breast tissue, but its lack of specific benign characteristics may warrant further evaluation, especially if it is not interspersed with fat. In a retrospective study of 300 consecutive nonpalpable breast cancers, 3% were identified as focal asymmetries. The likelihood of malignancy among findings characterized as focal asymmetry (without associated mass, calcifications, architectural distortion, sonographic abnormality, or palpable correlate) is <1%.

4. **Developing asymmetry:** formerly called developing density or neodensity, is a focal asymmetry that is new, larger, or denser on current examination than previously. To identify such a lesion, one must have prior mammograms available for comparison. In a retrospective study of 300 consecutive nonpalpable breast cancers, 6% were identified as developing asymmetries. The likelihood of malignancy among findings characterized as developing asymmetry is approximately 15%.

Medical History

The presence of a palpable correlate to a global asymmetry, focal asymmetry, or developing asymmetry raises some concern that breast cancer may account for some (perhaps all) of the asymmetric dense tissue seen at mammography. Therefore, the radiologist should check the medical history form completed by the patient or technologist, and the request for service provided by the referring clinician, to search for the report of a palpable lesion in the same or similar location as the mammographic finding. If there is such a report, or if the technologist places a radiopaque marker over a palpable finding that corresponds to the asymmetry, the radiologist usually will recall the patient for additional imaging evaluation.

Assessment at Screening Mammography

In addition to the presence of a palpable correlate, several associated mammographic findings also raise some concern that breast cancer may underlie a global asymmetry, focal asymmetry, or developing asymmetry. These findings include microcalcifications, architectural distortion,

tion, and mass. Therefore, if even one of these associated mammographic findings is visible at screening mammography within or adjacent to the asymmetry, the radiologist usually will recall the patient for additional imaging evaluation. In some cases, it will be possible to confidently assess an area of asymmetric dense fibroglandular tissue as representing summation artifacts. This usually takes place when: (1) the finding is visible on only one of the two standard mammographic views; (2) the area of asymmetric dense tissue is sufficiently anterior to the chest wall (as seen on the view on which it is visible) that it must be included in the image field on the other standard view; and (3) the breast is sufficiently fatty in content that, on the standard view not showing an asymmetry, there is no concern about substantial additional dense tissue obscuring the asymmetry. If the radiologist can confidently characterize an asymmetry as representing summation artifact at screening mammography, the examination should be assessed as negative [Breast Imaging Reporting and Data System (BI-RADS) category 1], with a recommendation for routine mammographic screening in 1 year.

Additional Imaging Evaluation

If additional imaging evaluation is performed to further assess an asymmetry, the first step should be to differentiate between summation artifact and true lesion. If the asymmetry is no longer seen on repeat images taken in the same or similar mammographic projections (including shallow oblique views or roll views, with or without spot compression and/or magnification) to those on which it was initially visible, then the radiologist will make a confident diagnosis of summation artifact, render a negative (BI-RADS category 1) assessment, and recommend routine mammographic screening in 1 year. Ultrasound examination plays no role in establishing or excluding the diagnosis of summation artifact. For findings that prove to be real, the next step should be to precisely triangulate the three-dimensional location on orthogonal (usually craniocaudal and 90° lateral) mammographic views. This permits accurate placement of a spot-compression paddle for additional standard or magnification views to more clearly define the morphology of the underlying lesion and specifically to search for the associated findings of microcalcifications, architectural distortion, or an underlying mass. Precise triangulation also permits targeted breast ultrasound examination in the search for a sonographic or palpable correlate to the mammographic finding. Except under the special circumstance that either mammography or ultrasound examination permits a definitive benign diagnosis, the final assessment for a given lesion will reflect the mammographic or sonographic assessment that is more abnormal.

Managing Asymmetries after Full Imaging Evaluation

Unless a definitive benign diagnosis (e.g., simple cyst as seen at ultrasound) can be given for a palpable asymmetry, the standard recommendation is tissue diagnosis because

of the approximately 10-15% frequency of underlying breast cancer. For lesions <2 cm, if percutaneous biopsy is performed instead of surgical excision, imaging guidance may be helpful in maximizing the likelihood that the target lesion is actually sampled. Unless a definitive benign diagnosis (e.g., simple cyst as seen at ultrasound) can be given for a (nonpalpable) developing asymmetry, the standard recommendation is also tissue diagnosis because of the approximately 10-15% frequency of underlying breast cancer. If the presence of associated microcalcifications, architectural distortion, or underlying solid mass raises some suspicion of malignancy at either diagnostic mammography or ultrasound of a nonpalpable lesion, the standard recommendation is also tissue diagnosis, in this case with an even greater likelihood of underlying breast cancer. Imaging-guided biopsy usually targets the most suspicious imaging feature of the lesion. The remaining cases involve nonpalpable focal asymmetries with no associated mammographic or sonographic abnormalities. If no previous mammograms are available for comparison, these lesions often are assessed as probably benign (BI-RADS category 3), with a recommendation for periodic mammographic surveillance, including one short-interval (6 month) follow-up examination. When previous mammograms are indeed available for comparison, demonstration of short-term (1-year) stability eliminates the need for short-interval follow-up, but usually requires annual follow-up until 2-year or 3-year stability is shown. Demonstration of lesion regression permits a definitively benign diagnosis, whereas lesion progression effectively establishes the diagnosis of developing asymmetry, which (as stated above) is managed by tissue diagnosis.

Masses

Some breast masses present with characteristically benign radiographic features, and even fewer masses demonstrate typically malignant features. As a result, most masses have at least some intermediate features, often requiring additional images to supplement the standard two-view mammography examination. Following is a systematic approach to the mammographic analysis of masses.

1. Step 1: Determine whether an asymmetry seen on only one mammographic projection represents a real lesion or a summation artifact produced by fortuitous superimposition of normal fibroglandular tissues. This step may be skipped if the mammographic finding is already seen on both standard mammographic projections and is confidently triangulated on those views to represent the same finding.
2. Step 2. Differentiate true masses from global and focal asymmetries. All of these findings are visible on at least two different mammographic projections, hence are real lesions. True masses have rounded (convex-outward) contours and are denser in the center than at the periphery; asymmetries have scalloped (concave-outward) contours and usually are interspersed with

fat. For lesions that are determined to be masses, it is helpful to obtain a 90° lateral (ML or LM) mammographic view to permit precise triangulation. This will facilitate targeted ultrasound examination and planning for imaging-guided biopsy (if biopsy is determined to be appropriate).

3. Step 3: Evaluate size. This cannot predict benign versus malignant etiology but it may well govern whether a mass will be aspirated or biopsied on clinical grounds (larger masses are more likely to be palpable, therefore more likely to undergo tissue diagnosis).
4. Step 4: Evaluate location. Quadrant location also cannot predict benign versus malignant etiology. However, get tangential views to determine whether superficial masses are within the skin (and therefore definitely benign), and consider additional images for deep-seated lesions that may not have been fully or even partially included on standard projections.
5. Step 5: Evaluate density. Classify masses into fatty or mixed- or fibroglandular-density groups. Fatty masses are invariably benign [fatty lobule (pseudomass), lipoma, fat necrosis, galactocele]. Mixed-density masses also are benign (hamartoma, intramammary lymph node). Fibroglandular-density masses usually are cysts, fibroadenomas, or carcinomas. With effective breast compression, especially spot compression, some invasive carcinomas appear to be higher in density than areas of benign fibroglandular-density tissue of equal volume.
6. Step 6: Evaluate shape and clarity of margins. This is the most important evaluation. Benign masses tend to be round or oval, circumscribed, and with smooth or macrolobular contours. Malignant masses classically have irregular contours and indistinct margins, often also showing a spiculated appearance. Alternatively, some malignancies demonstrate multiple small lobulations (microlobulated margins). However, most small breast cancers identified at screening simply have indistinct margins and/or are somewhat irregular in contour. Spot-compression or spot-compression magnification mammograms are particularly helpful in better defining the shapes and clarity of margins of indeterminate breast masses, often permitting more definitive mammographic interpretation. Circumscribed masses often undergo aspiration if ultrasound examination does not establish the diagnosis of benign cyst. All other masses usually undergo biopsy.
7. Step 7: Assess for interval change. If there has been prior mammography, make all reasonable efforts to obtain the films for comparison. Interval increase in size or increase in indistinctness/irregularity of margins should suggest the need for prompt further evaluation. Stability makes a given lesion more likely to be benign than thought simply on the basis of its mammographic features, especially if the interval between examinations is lengthy. Most stable lesions are managed by periodic mammographic follow-up as an alternative to biopsy. Interval decrease in size is almost always a reliable indicator of benignity.

Summary

Overall mammographic interpretation of breast masses involves a synthesis of all these separate step-by-step analyses, into which one also must factor the findings of physical examination, the woman's cancer risk profile (age, personal history of breast cancer, strong family history of breast cancer, etc.), and the findings at ultrasound examination (which usually is performed as an adjunct to mammography in the evaluation of breast masses).

Architectural Distortion

Invasive carcinoma may distort the interfaces between fat and normal breast parenchyma due to the desmoplastic response of host tissues to the malignancy. In the fatty breast, there is no diagnostic dilemma, as images will appear as the typical spiculated mass seen at mammography. However, in the very dense breast, the tumor mass can be so obscured by adjacent benign tissues as to be invisible, leaving as the only indication of underlying malignancy an area of focal architectural distortion. Depending on the location of the cancer, the retractive phenomena producing architectural distortion will result in different mammographic appearances. Invasive cancers completely surrounded by a substantial mantle of dense parenchyma will be detected only if there is sufficient adjacent fat to permit visualization of some coarse retractive strands radiating from a central area. On the other hand, cancers in locations close to the interfaces between parenchyma and subcutaneous or retromammary fat will be identified, even if no coarse strands are visible, by the infolding of the interfaces themselves, caused by retractions from the tumors. Focal architectural distortion is the most commonly encountered "indirect" sign of malignancy, accounting for the detection of 9% of nonpalpable cancers. However, it should be noted that the presence of focal fibrosis, scarring, or other benign retractive phenomena also produces coarse stranding and distortion of normal fat-parenchyma interfaces, in patterns that easily can be confused with the appearance of malignancy. The result is that for cases of unexplained focal architectural distortion, several benign lesions must undergo tissue diagnosis to ensure detection of each cancer.

Suggested Reading

- Bassett LW (2000) Imaging of breast masses. *Radiol Clin North Am* 38:669-691
- D'Orsi CJ, Mendelson EB, Ikeda DM et al (2003) Breast Imaging Reporting and Data System (BI-RADS), 4th edn. American College of Radiology, Reston, VA
- D'Orsi CJ, Sickles EA, Mendelson EB et al (2011) Breast Imaging Reporting and Data System (BI-RADS), 5th edn. American College of Radiology, Reston, VA (in press)
- Kopans DB, Swann CA, White Get al (1989) Asymmetric breast tissue. *Radiology* 171:639-643

- Leung JWT, Sickles EA (2000) Multiple bilateral masses detected on screening mammography: assessment of need for recall imaging. *AJR Am J Roentgenol* 175:23-29
- Leung JWT, Sickles EA (2007) Developing asymmetry identified on mammography: correlation with imaging outcome and pathologic findings. *AJR Am J Roentgenol* 188:667-675
- Moskowitz M (1983) The predictive value of certain mammographic signs in screening for breast cancer. *Cancer* 51:1007-1010
- Piccoli CW, Feig SA, Palazzo JP (1999) Developing asymmetric breast tissue. *Radiology* 211:111-117
- Samardar P, de Paredes ES, Grimes MM, Wilson JD (2002) Focal asymmetric densities seen at mammography: US and pathologic correlation. *RadioGraphics* 22:19-33
- Sickles EA (1984) Mammographic features of "early" breast cancer. *AJR Am J Roentgenol* 143:461-464
- Sickles EA (1986) Mammographic features of 300 consecutive nonpalpable breast cancers. *AJR Am J Roentgenol* 146:661-663
- Sickles EA (1989) Breast masses: mammographic evaluation. *Radiology* 173:297-303
- Sickles EA (1994) Nonpalpable, circumscribed, noncalcified solid breast masses: likelihood of malignancy based on lesion size and age of patient. *Radiology* 192:439-442
- Sickles EA (1995) Management of probably benign breast lesions. *Radiol Clin North Am* 33:1123-1130
- Sickles EA (1998) Findings at mammographic screening on only one standard projection: outcomes analysis. *Radiology* 208:471-475
- Sickles EA (2007) The spectrum of breast asymmetries: imaging features, work-up, management. *Radiol Clin North Am* 45:765-771

Ultrasound of the Breast, Including Interventions: An Update

Alexander Mundinger

Radiological Department and Breast Centre, Niels-Stensen-Clinics, Osnabrueck, Germany

Introduction

The quality of breast ultrasound (US) has constantly improved over recent decades. New transducer technology using high frequencies between 7 and 18 MHz are the physical base for a high spatial resolution. Advances in imaging techniques eliminate speckles and artefacts and improve contrast resolution. International standards are in place for examination technique, description of findings and assessment categories. Future automated volume scanning promises to reduce the problems of operator dependence. US is the breast imaging method of choice for most patients with clinical signs and symptoms. The sensitivity of standard US for breast cancer ranges from 55% to 95%. It transfers an additional diagnostic yield of 30-40% in comparison with mammography to patients with radiodense breasts. US improves detection and characterisation of lesions in preoperative staging and in patients under surveillance after breast cancer. US is inferior to mammography and magnetic resonance imaging (MRI) in the primary detection of ductal carcinoma in situ (DCIS) and does not add information compared with MRI in familiar breast cancer. To date, US has no role in population-based screening due to a lack of prospective and randomised data. US-guided core needle biopsy is the minimally invasive biopsy method of choice for all breast lesions that correlate with findings of other imaging modalities. Sensitivity of US-guided large-core needle biopsy is 93-98%; specificity ranges from 95% to 100%.

Basics of Ultrasound Anatomy

Breast anatomy is the basis for understanding breast US. The breast is a modified skin gland enveloped in fibrous fascia. The undersurface of the breast lies on the deep pectoralis fascia. The superficial pectoralis fascia is located beneath the skin and nipple. The breast is composed of three major structures: skin, subcutaneous tissue and breast tissue, which encompasses parenchyma and stroma. The parenchyma is divided in 15-20 lobes or segments that converge at the nipple in a radial arrangement. Each lobe contains 20-40 lobules. Each lobule contains

10-100 ductules or acini. The terminal duct lobular unit (TDLU) is the functional unit composed of a lobule and its terminal duct. Major ducts join below the nipple in a netlike pattern and widen in a portion named lactiferous sinus before opening into the orifices of the nipple. The converging larger ducts drain the segmental ducts arising from subsegmental ducts and terminal ducts. Various proliferative breast diseases including DCIS arise from the TDLUs. Only DCIS cells expand throughout all ducts. Distended TDLUs can be detected by high-resolution US (HRUS) in many benign but only a few malignant lesions (Fig. 1). Therefore, additional information is necessary, such as a suspicious segmental distribution or the correlation to suspect imaging findings with mammography or MRI. Tiny changes as small as 2-5 mm in diameter can be dismissed in analogy with MRI-detected foci. On the contrary, such small pseudocystic changes must be assessed in the presence of concern about multifocality or duct extension of DCIS.

The echogenicity of fat is the reference comparing other anatomical structures with in breast US [1, 2]:

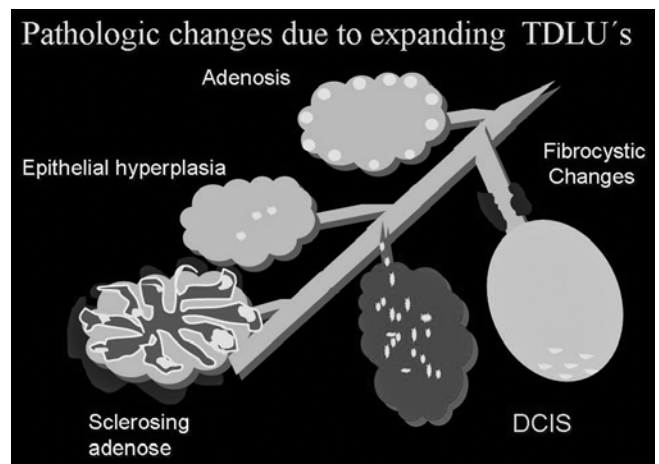


Fig. 1. Pathologic changes within dilated terminal duct lobular units (TDLUs). Benign and malignant proliferative or fibrocystic changes can result in a distension of the TDLU. Calcifications can occur within the TDLU and will form a cluster (for color reproduction see p 273)

- Isoechoic echogenicity is found in fat, epithelium, loose periductal and intralobular fibrous tissue and some TDLUs.
- Hyperechoic echogenicity is found in skin, Cooper's ligaments, stromal fibrous tissue (interlobular) and some TDLUs.
- Hypoechoic echogenicity is found in nipple and blood in vessels.
- Anechoic echogenicity is found in dilated TDLUs (cysts), ducts and lymphatics.

Physics and Equipment

US of the breast provides physical information about the impedance of tissue interfaces that influence US transmission and reflection across the breast. The different physical base of US, X-ray mammography and MRI of the breast explains the independent and complementary diagnostic information given by each modality. The most relevant advances made in recent years are due to high-frequency US transducer equipment using frequencies between 7 and 18 MHz. Scanning with 15 MHz in comparison with 7.5 MHz results in a lateral (0.4 mm) and axial (0.2 mm) spatial resolution that is twice as high as the spatial resolution at 7.5 MHz. On the other hand, penetration depth is reduced to half. Compounding and harmonic imaging improves contrast resolution and reduces speckle artefacts. The high spatial and contrast resolution of modern breast US equipment has expanded the detection and conspicuity of subtle lesions at the size of expanded terminal duct lobular units such as DCIS and microinvasive lesions. Color Doppler techniques detect and characterise blood flow within lesions, permitting valuable discrimination information between solid nodules and complicated cysts. Three-dimensional (3D) diagnostic imaging of the breast includes multidimensional reformations, reconstructions and tomographic US. The additional diagnostic information of 3D US focuses on demonstrating suspicious radial retractions around a tumor in the coronal plane, which is unique to this technique. Elastography reflects strain properties of lesions. Malignant nodules are generally less compressible than benign tissue. The potential benefit of elastography lies in the assessment of, on the one hand, probably benign lesions that can better be discriminated on follow-up, and on the other hand, suspicious lesions, compared with morphological description. The future role of elastography continues to be evaluated. New horizons in high-end US technology encompass miniaturised and portable US systems, automated whole-breast US and imaging fusion of US information with digital mammography, tomosynthesis or MRI [3, 4].

Indications for Breast Ultrasound

A list of updated recommendations pertaining to indications is given in Table 1 (modified according to [3]). US

Table 1. Updated indications for high-resolution ultrasound

Differentiation of cysts and solid tumours
Differentiation between solid, benign and malignant lesions
Characterisation of palpable abnormalities
Assessment of mammographic screening abnormalities
Dense breasts showing with reduced mammographic sensitivity
Diagnosis and follow-up of women with benign breast disease or risk lesions
Women, during pregnancy or lactation
Significant nipple discharge
Under hormonal replacement therapy
Inflamed breast and abscesses formation
Extended screening for high-risk patients
Second look after magnetic resonance mammography
Guidance of interventional procedures, such as fine needle aspiration, core biopsy, diagnostic and therapeutic vacuum biopsy and preoperative tumor localisation, axillary lymph node biopsy
Preoperative staging of lesion size, skin and nipple distance for planning breast conservative surgery, mastectomy or oncoplastic reconstruction with implants, assessment of multifocality, multicentricity, intraductal extension, lymph node changes and contralateral lesions
Preoperative staging and follow-up under neoadjuvant chemotherapy
Surveillance after breast-conservation therapy
Silicone implants

is the first-line imaging technique for women <40 years presenting with symptoms or clinical signs. In the presence of a suspicious lesion, US is the method of choice to guide core biopsy in order to harvest tissue. US-guided vacuum-assisted biopsy (VAB) is used increasingly to diagnose intraductal lesions, small architectural distortions and borderline lesions; to complete preoperative staging in patients with extensive ductal component; and for therapeutic excision. Stereotactic-guided VAB is the method of choice to sample screen-detected microcalcifications and architectural distortions not seen on US. In the dense breast, the combination of US and screening mammography improves cancer detection considerably compared with mammography alone but with an increase in biopsy rate. The additional diagnostic yield of US after negative mammography is 3.2:1,000 women with dense breasts. Intraoperative surgeon-performed US focuses on accurately defining the resection segment or sector and the margin analysis of the resection specimen. MRI is useful preoperatively to assess the extent of ipsilateral disease and exclude contralateral breast cancer, particularly for women at increased risk of mammographically occult disease. Second-look US can detect up to 50% of MR-enhancing cancers with negative mammography [5-8].

Examination Technique

The International Breast Ultrasound School (IBUS) and American College of Radiology (ACR) guidelines for

breast US examination advise a systematic, comprehensive and reproducible examination technique, followed by documentation, description, reporting, classification and recommendation. The examination starts with proper positioning of the patient in a supine or anterior oblique position depending on the breast volume, with elevation of the ipsilateral arm. Positioning should result in a maximum flattening of the breast portion being examined. Automated tissue optimisation and focal zone and field of view settings should be optimised before scanning with the transducer perpendicular to skin. A minimum of two scan planes is recommended in whole-breast US. Image analysis of a detected lesion or pseudolesion requires rotation of the transducer over the entire lesion using changing compression intensities and angulations. Radial imaging of adjacent ducts is mandatory to assess ductal extensions. Breast Imaging Reporting and Data System (BI-RADS) descriptors; and further criteria of additional elastography, 3D tissue criteria, vascularisation and associated lymph node morphology, characterise state-of-the art lesion assessment by US. The o'clock position and distances to skin and nipple describe the exact localisation of a lesion within the volume of the breast. Indication of palpability and imaging correlation to other modalities complete the documentation [9-12].

Concepts of Interpretation Based on Ultrasound BI-RADS Descriptors

The categorisation of a mass finding in all modalities relates to a 3D macropathological tissue lesion. The pathology defines lesion shape, margin and texture. These features have already been described individually for the varying modalities. A uniform wording of the major diagnostic criteria for all modalities would be logical. The BI-RADS concept stepped first in this direction and was designed primarily as a mammographic language with a clear, defined terminology. In 2003, the ACR published the *Breast Imaging Atlas*, which is a BI-RADS lexicon for mammography, US and MRI. The US chapters were originally arranged under the chair of Ellen B. Mendelson [11], and the descriptors or diagnostic criteria are presented with increasing probability of malignancy. Descriptors of a mass include shape, orientation, margin, boundary, echo pattern, posterior acoustic feature and characteristics of surrounding tissue as well as associated distinguishing findings. The combination of several descriptors predicts malignancy better than one single descriptor. However, the reader should use further explanatory elements in the guidance chapters of the atlas, such as clinical context conditions, tumor biology and epidemiological prevalence, to cover the complex field of breast lesions. Assumptions regarding the expected prevalence and individual risk for cancer in a patient drive the intuitive recommendation for or against a biopsy and influence the choice of a final BI-RADS assessment

category. In other words, the threshold for performing a biopsy is lower for a probably benign-looking lesion compared with a screening setting if advanced age, large lesion, palpability or individual high-risk situation concern the reader. BI-RADS categories 3-5 imply a defined probability of malignancy for each category. For BI-RADS 3, these probabilities are <2%, for BI-RADS 4 between 3% and 94%, for BI-RADS 5 $\geq 95\%$. Most European US societies have adopted or modified the ACR-BI-RADS-US guidelines. In addition to the 2003 US descriptors, various features have been suggested, such as elastic compressibility, movability, 3D criteria, detailed lymph node morphology and others. Further prospective multicentre studies still have to validate the complementary diagnostic importance of such associated features as an adjunct to the basic characteristics of a lesion [12, 13]. Recently, several authors disclosed that interobserver agreement with the new BI-RADS terminology is good, and validated the lexicon in retrospect following landmark studies in the 1990s. Only fair agreement exists in most studies for margin evaluation. Further, a trend towards lower concordance was noted for evaluating small masses. Classification into subdivisions 4a, 4b and 4c was more or less reproducible. Despite its limitations, most authors agree that stratification predicting the likelihood of malignancy could be useful for decision making and communication with patients and between researchers, physicians and physicians of different specialties [14-17]. The updated second edition of BI-RADS-US (2011) will reemphasise the importance of basic features, such as mass shape, margin and orientation on one hand and associated findings as an adjunct on the other. The amended chapters cover expanded general issues, detailed lexicon images and US descriptors, reporting system and guidance. Figure 2 presents a training schema for beginners in the field of breast diagnostics that can be used to learn standardised BI-RADS-US reading of larger masses. This schema has no scientific proof for use in daily workup. Table 2 highlights some underlying intrinsic and extrinsic concepts of BI-RADS-US assessment categories that must be considered in daily work.

Concepts of Interpretation and Clinical Decision Making

The US characterisation of a lesion in the daily routine follows a reproducible diagnostic algorithm and should involve fundamental US and all advanced applications of the used US system, preferably on a one-click basis.

First, the reader must define whether or not the lesion resembles a typical benign finding, such as cyst, lipoma, lymph node or previously known scar or fibroadenoma (Fig. 3). Complicated cysts with internal debris are challenging. When the debris is mobile or a fluid-debris level is seen, complicated cysts can be dismissed as benign findings, i.e. BI-RADS-US category 2 [11, 18].

Second, a typical oval-shaped, hypoechoic lesion with circumscribed margins and horizontal orientation in

Adopted BI-RADS-US training schema			
Shape Margin	round, oval	lobulated	irregular
	circumscribed	2 (multiple) 3 (singular)	3 (moderate) 4 (marked)
	indistinct	4	4
	angular		5
	microlobulated		
	spiculated	5	5

-Indicator of benignity
typical cyst,
lymph node,
lipoma

-Indicator of malignancy
echogenic halo,
taller than wide,
strongly hypoechoic,
shadowing,
ductal extension,
retraction pattern,
hypervascularity,
reduced compressibility,

**Change of
BI-RADS
category**

Fig. 2. Adopted Breast Imaging Reporting and Data System Ultrasound (BI-RADS-US) training schema. BI-RADS characterisation of a mass can be taught using basic descriptors and associated findings that upgrade or downgrade the overall assessment category. The teaching schema aims to support beginners in the field of breast diagnosis. This schema provides no scientific proof to be used in daily workup, as it can miss cancers (for color reproduction see p 273)

Table 2. Underlying concepts of Breast Imaging and Reporting Data System ultrasound (US) assessment categories

Categorisation and management depend on the most suspicious diagnostic criterion
 Benign lesions must look typically benign; no suspicious image descriptor
 Malignant lesions frequently show one or more suspicious criteria
 Predefined thresholds for positive predictive value or cancer risk influence the classification in categories 2-5
 Overall BI-RADS category must consider further clinical context conditions, expected prevalence and other risk factors besides morphological criteria of each imaging modality assessment category
 Typical indicators of benignancy such as cysts, fat in a lesion (hamartoma) or benign macrocalcification (popcorn calcification with fibroadenoma) diagnosed by multimodality evaluation can downgrade overall assessment category compared with US category
 Indicators of potential malignancy in other modalities can upgrade overall assessment category compared with US category
 Overall assessment category should also be based on the most urgently needed procedure. This point of view ensures critical re-evaluation of final assessment category

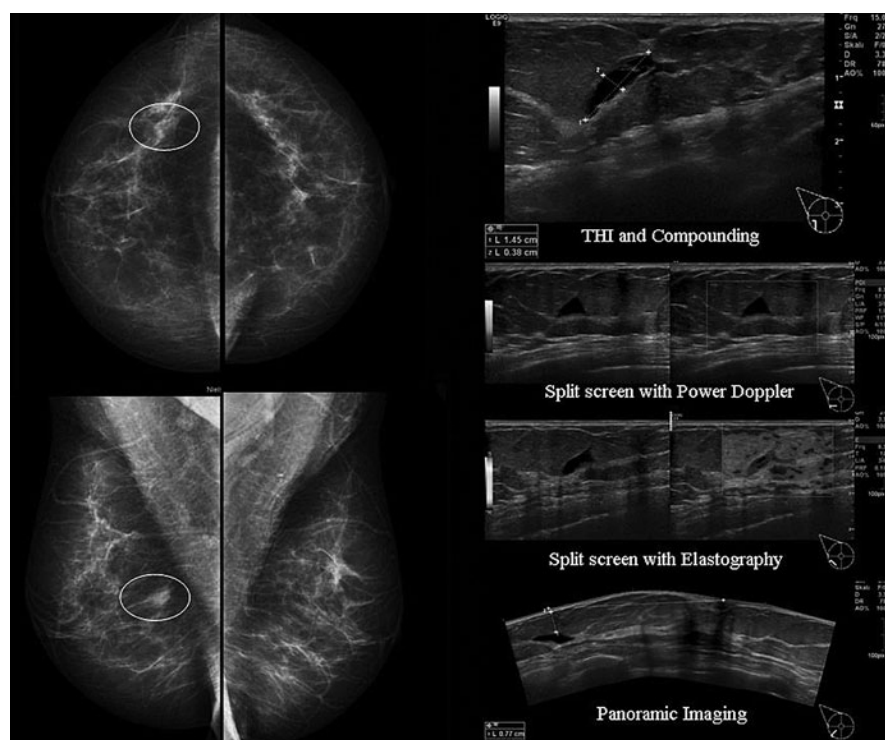


Fig. 3. Cyst. Mammography and advanced ultrasound applications in a nonpalpable, oval anechoic lesion that is deformed and clings to straight septa under pressure. Histology: cyst. *THI*, tissue harmonic imaging; *circles* correspond to the deformed cyst in mammography (for color reproduction see p 273)

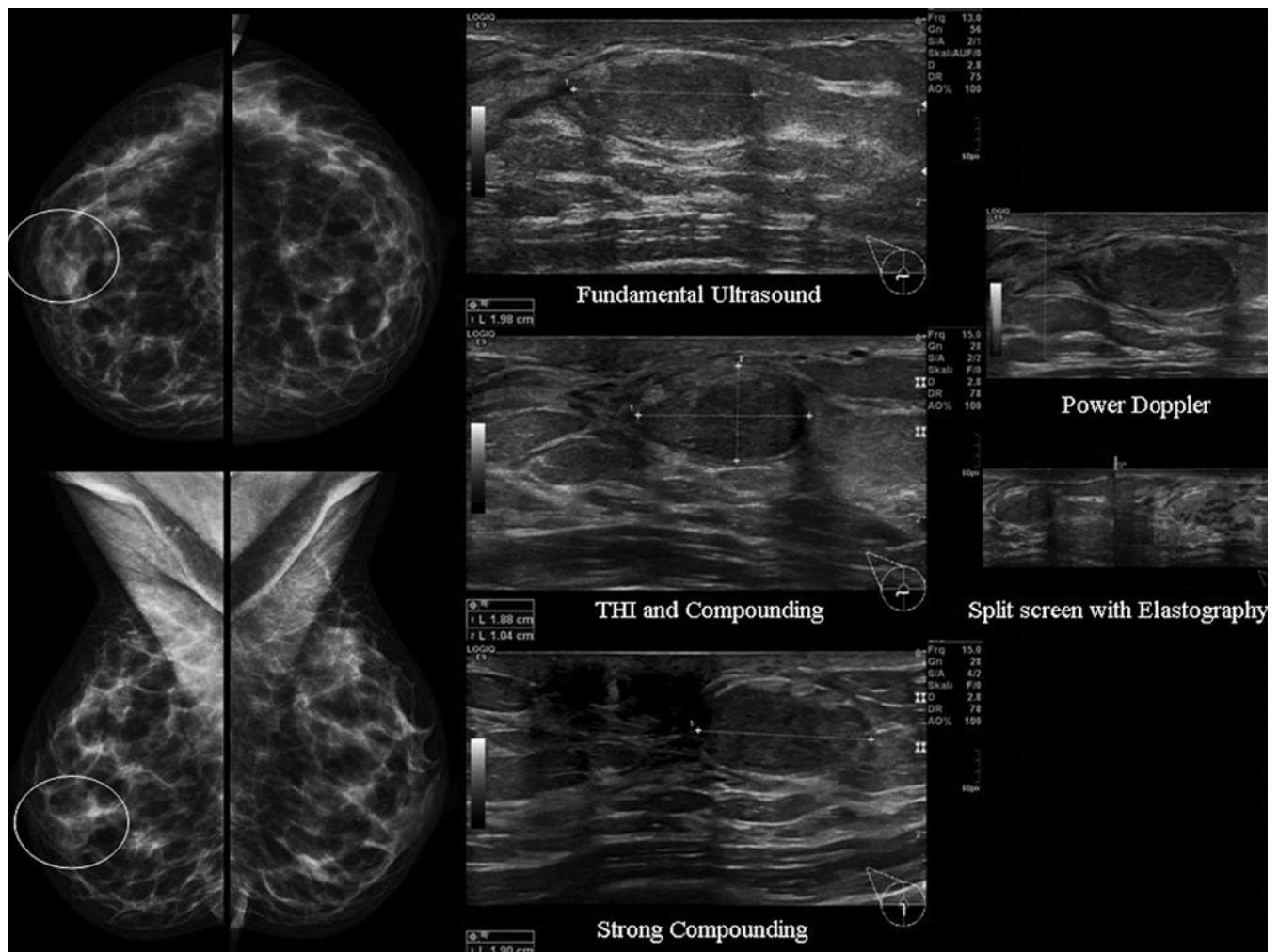


Fig. 4. Fibroadenoma. Mammography, fundamental and advanced ultrasound applications in a palpable oval isoechogenic lesions that has increased in size. Histology: fibroadenoma. *THI*, tissue harmonic imaging; *circles* correspond to the deformed cyst in mammography (for color reproduction see p 273)

young women is most likely a fibroadenoma (Fig. 4). Short-term follow-up can be used. Several studies concluded that short-term follow-up of such BI-RADS-US category 3 lesions is associated with a cancer rate <2% [19-21]. Being older than 45 years, palpability or any pre-selection that enriched cancer cases in the collective is associated with cancer rates >2%. In a recent study, 0.8% of 4,000 women with lesions that were initially classified as probably benign proved to be malignant at follow-up. The most frequent reason for a false negative assessment on US was failure to recognise suspicious margin characteristics (28 of 32 malignancies, 87.5%). Malignancy was more frequent in palpable (2.4%, 21 of 859) than nonpalpable lesions (0.4%, 11 of 3141) [22]. As an isolated finding, homogeneous complicated cysts and clustered microcysts can be classified as probably benign, particularly if the lesion is new or rather small or deep, i.e. diagnostic uncertainty exists [18].

Third, detailed analysis of US morphology, vascularity and elasticity of a lesion should disclose any suspicious ba-

sic descriptor or suspicious associated finding. The presence of suspicious descriptors results in a BI-RADS-US category 4 or 5 depending on the total number and character of these descriptors. A biopsy is recommended in these cases and also in benign-looking lesions that are significantly increasing in size during follow-up (Fig. 5) [11].

Updated Role of Ultrasound, Including Interventions

US studies in up to 12,000 asymptomatic patients yielded tumor detection rates of only 0.3-0.4%; however, a similar size and stage was reported compared with mammographically detected clinically occult cancers. The advantage of US as an adjunct to mammography is greatest in women with palpable lesions and those at high risk, including women with dense breasts, which is a risk factor. The US signs of malignancy develop with increasing tumor size. No single diagnostic sign can pick up all cancers due to their heterogeneous appearance (Fig. 6).

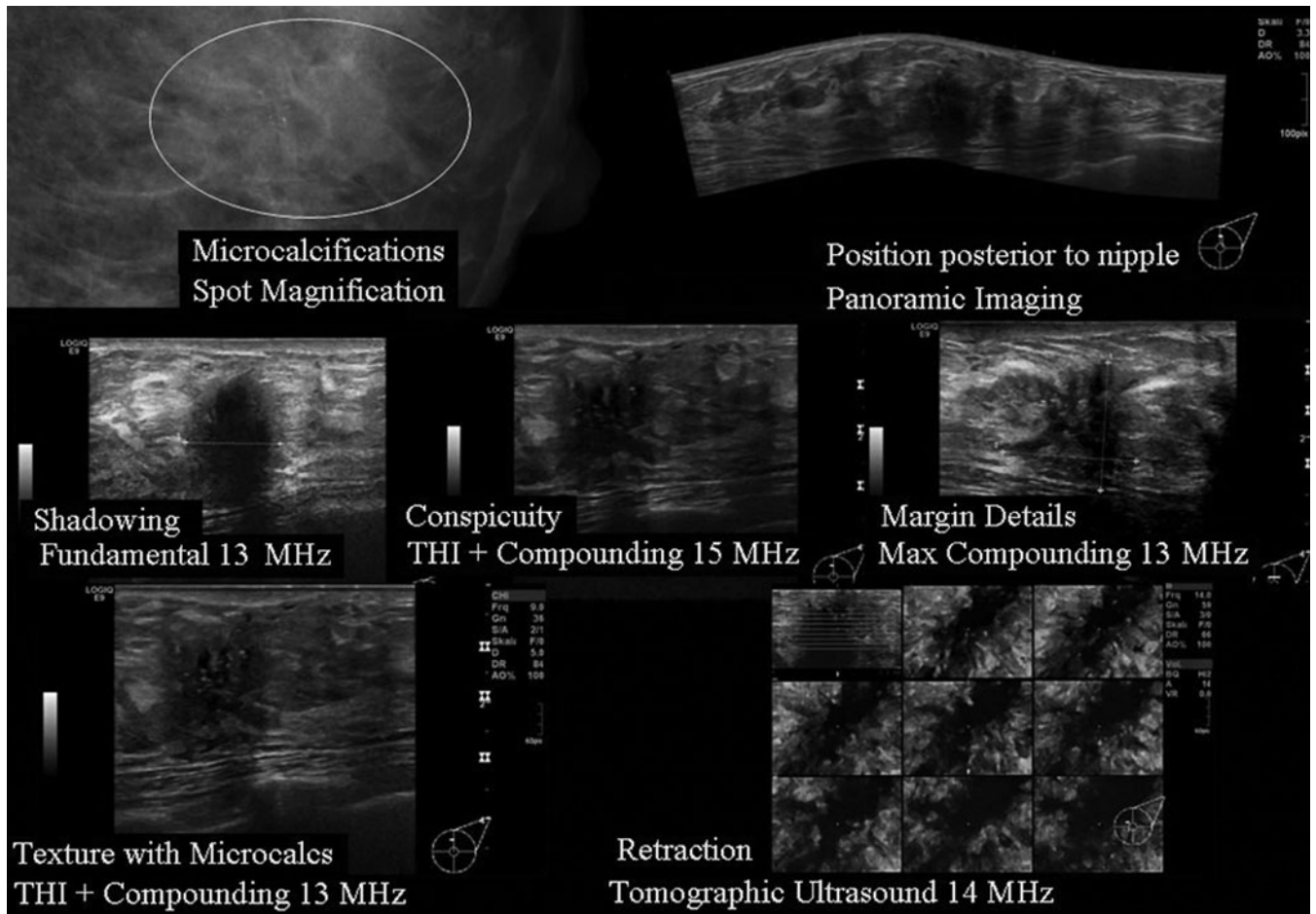


Fig. 5. Cancer. Suspicious microcalcifications in spot mammography and heterogeneous appearance of corresponding invasive cancer dependent on the various ultrasound (US) applications used. The advantage of fundamental US is the depiction of shadowing. Advanced applications enhance the presentation of conspicuity, margin details, tumour matrix with microcalcifications, or retraction of the surrounding tissue around an irregular mass. Histology: invasive ductal cancer. *THI*, tissue harmonic imaging; *circles* correspond to the deformed cyst in mammography

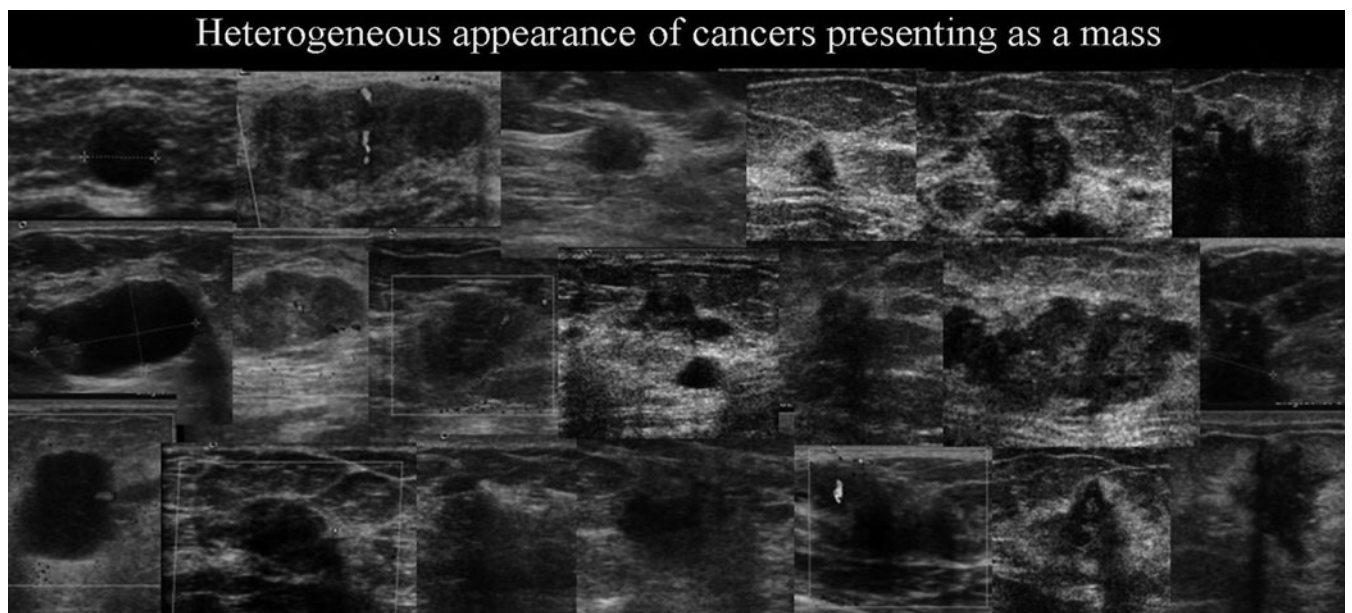


Fig. 6. Heterogeneous ultrasound appearance of invasive cancers. Stage T1c and T2 cancers show more typical signs of malignancy compared to smaller cancers. No single diagnostic descriptor can pick up all cancers (for color reproduction see p 273)

Patients with a high mammographic density (>75%) have a four- to six-fold increased risk compared with women with low radiodense breasts [7]. The sensitivity of standard US for breast cancer ranges from 55% to 95%. US transfers an additional diagnostic yield of 30-40% in comparison with mammography to patients with radiodense breasts (Fig. 5). In national screening programmes, mammography is still the method of choice of early breast cancer detection. To date, mammography still provides the best compromise between advantages, disadvantages and costs [23]. Breast US is indicated for further assessment of mammographic abnormalities and guiding minimally invasive biopsy. Masses in mammography and on MRI can be correlated with US confidently with increasing size, starting at a diameter of 0.5 cm [24-26]. Although HRUS is suitable for detecting subtle changes of DCIS, the detection rate of DCIS by US is low without prior knowledge of focal DCIS at mammography. Targeted US of suspected DCIS finds frequently hypoechoic lesions that represent dilated TDLUs and look similar to them, such as fibroadenoma, papilloma, ductectasia or microcystic changes. US is the method of choice when assessing and puncturing such solid-looking small masses, dilated ducts, pseudomicrocystic lesions or dense accumulations of microcalcifications that corresponded with mammographic changes. A radiogram of large-core cylinders is mandatory to correlate the US finding with index calcifications [3].

HRUS shows a comparable diagnostic performance in preoperative staging with MRI in invasive ductal cancer. MRI performs better in preoperative staging of lobular invasive cancer, DCIS, multifocality, multicentricity and posterior breast-wall involvement, as well as diagnosing recurrence, failing silicon prosthesis and monitoring during neoadjuvant therapy. The median additional detection yield for MRI is estimated as 16% in meta-analyses. To date, there is no evidence that preoperative MRI improves surgical care or prognosis [27]. The analogue statement is probably true for the role of US in preoperative staging.

Sentinel lymph node (SLN) biopsy is associated with a low local recurrence and similar survival rates to axillary lymph node dissection and is now the standard of care. All patients with invasive breast cancer should have US of the axilla to exclude obvious nodal local spread. The presence of asymmetric focal hypoechogenic cortical lobulations >2 mm, or a completely hypoechogenic node with US, should direct further examination to fine-needle aspiration of the index lymph node [28]. US-guided biopsy of axillary lymph nodes has a sensitivity that varies between 30.6% (22.5-39.6%) and 62.9% (49.7-74.8%) and a specificity of 100% (94.8-100%) [29]. When the cytological or histological finding is positive, SLN biopsy can be omitted and primary axillary lymph node dissection performed. Intraoperative breast US can guide segmental surgery with wide distances to the malignant lesions. HRUS presents an additional diagnostic yield compared with mammography in postoperative surveillance after breast-conserving and oncoplastic surgery. MRI would be

the method of choice for surveillance with respect to its better diagnostic performance in comparison with mammography and US [30]. However, costs and availability restrict the use of MRI to high-risk patients and differentiation between scar and recurrence with a problematic diagnostic background presented by the other modalities.

Summary

Modern breast care requires definitive nonoperative diagnosis of all potential breast abnormalities in a timely and cost-effective way. US-guided core needle biopsy (USCNB) has developed as the minimal invasive biopsy method of choice for all breast lesions (sensitivity 93-98%; specificity 95-100%). US-guided VAB is increasingly being used for diagnosing borderline lesions, for complete preoperative staging in patients with extensive ductal component and for therapeutic excision of biopsy-proven benign lesions such as fibroadenoma and some papillary lesions and radial scars. The diagnostic accuracy of US-guided VAB is close to 100% [3, 24, 26].

References

1. Stavros AT (2003) Breast ultrasound. Lippincott Williams & Wilkins, Philadelphia, PA, pp 56-108
2. Madjar H, Mendelson E (2008) The practice of breast ultrasound, 2nd edn. Thieme, Stuttgart, New York, pp 23-69
3. Munding A, Wilson ARM, Weismann C et al (2010) Breast ultrasound – update. EJC Supplements 8:11-14
4. Weismann C, Hergan K (2007) Current status of 3D/4D volume ultrasound of the breast. *Ultraschall Med* 28:273-282
5. American College of Radiology (ACR) (2009) Practice guideline for the performance of ultrasound-guided percutaneous breast interventional procedures. Revised 2009. http://www.acr.org/SecondaryMainMenuCategories/quality_safety/guidelines/breast/us_guided_breast.aspx
6. American College of Radiology (ACR) (2009) Practice guideline for the performance of stereotactically guided breast interventional procedures. Revised 2009. Res. 28. http://www.acr.org/SecondaryMainMenuCategories/quality_safety/guidelines/breast/stereotactically_guided_breast.aspx
7. Nothacker M, Duda V, Hahn M et al (2009) Early detection of breast cancer: benefits and risks of supplemental breast ultrasound in asymptomatic women with mammographically dense breast tissue. A systematic review. *BMC Cancer* 9:335
8. Heywang-Köbrunner SH, Schreier I, Heindel et al (2008) Imaging studies for the early detection of breast cancer. *Dtsch Arztebl Int* 105:541-547
9. Madjar H, Rickard M, Jellins J et al (1999) IBUS guidelines for the ultrasonic examination of the breast. *Eur J Ultrasound* 9:99-102
10. Khouri NF (2009) Breast ultrasound. In: Harris JR et al (eds) *Diseases of the breast*, 4th edn. Wolter Kluwer, Lippincott Williams & Wilkins, Philadelphia, PA, pp 131-151
11. American College of Radiology (ACR) (2003) ACR BI-RADS® – Ultrasound. In: ACR Breast Imaging Reporting and Data System. Breast imaging atlas. American College of Radiology, Reston VA
12. Madjar H, Ohlinger R, Munding A et al (2006) BI-RADS-analogue DEGUM criteria for findings in breast ultrasound – Consensus of the DEGUM Committee on Breast Ultrasound. *Ultraschall Med* 27(4):374-379

13. Wojcinski S, Farrokh A, Weber S et al (2010) Multicenter study of ultrasound real-time tissue elastography in 779 cases for the assessment of breast lesions: improved diagnostic performance by combining the BI-RADS®-US classification system with sonoelastography. *Ultraschall Med* 31:484-91
14. Lazarus E, Mainiero MB, Schepps et al (2006) BI-RADS lexicon for US and mammography: interobserver variability and positive predictive value. *Radiology* 239:385-91
15. Lee HJ, Kim EK, Kim MJ et al (2008) Observer variability of Breast Imaging Reporting and Data System (BI-RADS) for breast ultrasound. *Eur J Radiol* 65:293-298
16. Santana Montesdeoca JM, Gómez Arnáiz A, Fuentes Pavón R et al (2009) Diagnostic accuracy and interobserver variability in the BI-RADS ultrasound system. *Radiologia* 51:477-486
17. Abdullah N, Mesurolle B, El-Khoury M et al (2009) Breast imaging reporting and data system lexicon for US: interobserver agreement for assessment of breast masses. *Radiology* 25:2665-2672
18. Berg WA, Sechtn AG, Marques H et al (2010) Cystic breast masses and the ACRIN 6666 experience. *Radiol Clin North Am* 48:931-987
19. Graf O, Helbich TH, Hopf G et al (2007) Probably benign breast masses at US: is follow-up an acceptable alternative to biopsy? *Radiology* 244:87-93
20. Fu CY, Hsu HH, Yu JC et al (2010) Influence of age on PPV of sonographic BI-RADS categories 3, 4, and 5. *Ultraschall Med* 32:8-13
21. Moon HJ, Kim MJ, Kwak JY et al (2010). Probably benign breast lesions on ultrasonography: a retrospective review of ultrasonographic features and clinical factors affecting the BI-RADS categorization. *Acta Radiol* 51:375-382
22. Moon HJ, Kim MJ, Kwak JY et al (2010) Malignant lesions initially categorized as probably benign breast lesions: retrospective review of ultrasonographic, clinical and pathologic characteristics. *Ultrasound Med Biol* 36:551-559
23. Berg WA, Blume JD, Cormack JB et al (2008) Combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer. *JAMA* 299:2151-2163
24. Munding A (2006) Staging the breast and axilla. *EJC Supplements* 4:35-37
25. Lehman CD, DeMartini W, Anderson BO et al (2009) Indications for breast MRI in the patient with newly diagnosed breast cancer. *J Natl Compr Canc Netw* 7:193-201
26. Cho N, Moon WK, Cha JH et al (2009) Ultrasound-guided vacuum-assisted biopsy of microcalcifications detected at screening mammography. *Acta Radiol* 50:602-609
27. Houssami N, Hayes DF (2009) Review of preoperative magnetic resonance imaging (MRI) in breast cancer: should MRI be performed on all women with newly diagnosed, early stage breast cancer? *CA Cancer J Clin* 59:290-302
28. Choi YJ, Ko EY, Han BK et al (2009) High-resolution ultrasonographic features of axillary lymph node metastasis in patients with breast cancer. *Breast* 18:119-122
29. Alvarez S, Añorbe E, Alcorta P et al (2006) Role of sonography in the diagnosis of axillary lymph node metastases in breast cancer: a systematic review. *AJR Am J Roentgenol* 186:1342-1348
30. Pan L, Han Y, Sun X et al (2010) FDG-PET and other imaging modalities for the evaluation of breast cancer recurrence and metastases: a meta-analysis. *J Cancer Res Clin Oncol* 136:1007-1022

MRI of the Breast: Technique, Indications and BI-RADS Classification

Rahel A. Kubik-Huch

Institute of Radiology, Department of Medical Services, Kantonsspital Baden, Baden, Switzerland

Introduction

Breast cancer comprises about 10% of all cancer incidences among women worldwide, making it the most common type of non-skin cancer in females. In recent decades, great strides have been made toward early detection of breast cancer, with X-ray mammography being the mainstay of breast imaging. However, there are some limitations inherent to this technique. Therefore, efforts have been made to develop adjunctive diagnostic techniques, including high-resolution breast ultrasound (US) and magnetic resonance imaging (MRI).

Dynamic contrast-enhanced MRI of the breast is an imaging technique that not only offers cross-sectional information on lesion morphology but, in particular, provides functional information, i.e. tissue perfusion and enhancement kinetics. Whereas MRI is highly sensitive in detecting invasive breast cancer, with reported rates of 89-100%, specificity is variable, reported at 37-97% [1-4].

Since the introduction of breast MRI in the early 1990s, substantial progress has been made, including in hardware (e.g. breast coil technology) and software, definition of technical standards for image quality and development of MR-guided minimally invasive biopsy procedures. These prerequisites, together with continuing scientific investigations and guidelines for standardisation of interpretations and reporting by radiologists, e.g. the American College of Radiology Breast Imaging and Reporting Data System (ACR BI-RADS), have led to a wide acceptance of this technique, well-accepted indications and transfer into clinical practice as an adjunct to mammography [1-10].

Imaging Protocol and Postprocessing Techniques

When scheduling the patient, it is important to note that in premenopausal women, the MR examination should be performed during the second week (days 7-14) of the menstrual cycle, because contrast medium uptake is dependent on the phase of the menstrual cycle, and hormonal stimulation might result in false

positive findings. Background enhancement is also expected to be increased by other hormonal influences, such as hormone replacement therapy and lactation, whereas enhancement is expected to decrease under tamoxifen therapy. Radiation treatment has been shown to cause parenchymal oedema and increased enhancement for several months following completion of therapy [5].

A state-of-the-art breast MR exam requires a high-field magnet and the use of a dedicated multichannel breast coil, with the patient in the prone position. To date, breast MRI is still performed mostly on 1.5-T magnets because of their widespread availability; however, with the installation of larger numbers of 3-T magnet systems, the impact of field strength on breast MRI performance may become more apparent [11].

For breast MRI, a high spatial resolution (slice thickness ≤ 3 mm, in-plane pixel resolution ≤ 1 mm) is important to resolve morphologic details of even small tumors. At the same time, a high acquisition speed is required to allow semiquantitative enhancement kinetic lesion analysis. Breast-imaging protocols are therefore optimised for simultaneous acquisition of high spatial and temporal resolution [3, 5, 11].

In our institution, a precontrast T2-weighted sequence is obtained at the beginning of the protocol. In patients with silicone implants, additional sagittal T2-weighted and axial silicon-selective sequences are acquired (Fig. 1). Next, a precontrast T1-weighted 3D gradient-echo sequence with a fat suppression pulse is performed to serve as the mask for postcontrast images. In our experience, additional image subtraction is useful, even though we use an active fat-saturated approach (Fig. 2). Following injection of gadolinium (0.1 mmol/kg body weight), sequential postcontrast 3D gradient-echo sequences are obtained in dynamic fashion over 6-7 min to assess the enhancement kinetic of a suspicious lesion. As the peak enhancement for most invasive carcinomas will be seen within the first 2 min after injection, short dynamic imaging acquisition times (60-120 s) are necessary [11]. Dynamic contrast-enhanced MRI protocols (samples) at 1.5 T and 3 T from our institution are presented. The parameters are only guidelines and are, of

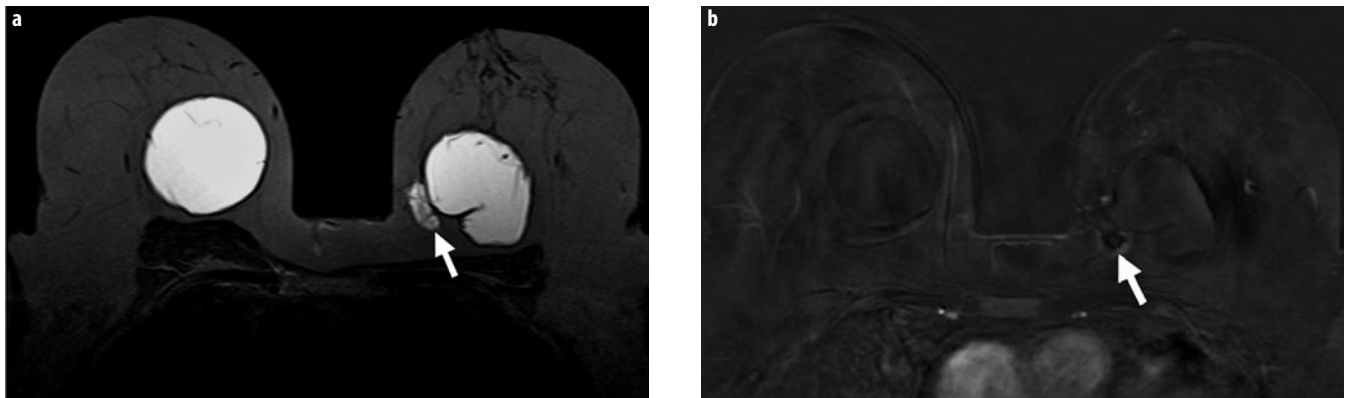


Fig. 1 a, b. A 60-year-old patient with a history of breast augmentation with newly detected lump in the upper inner left quadrant, suspicious for breast cancer. Magnetic resonance imaging was performed. **a** Axial silicone-sensitive sequence; **b** dynamic contrast-enhanced study, early subtraction image. Bilateral silicone implants in prepectoral localisation with signs of capsular fibrosis. A hyperintense structure (*arrow* in **a**) without enhancement (*arrow* in **b**) is seen adjacent to the left implant. Extracapsular rupture with siliconoma was diagnosed; no signs of malignancy

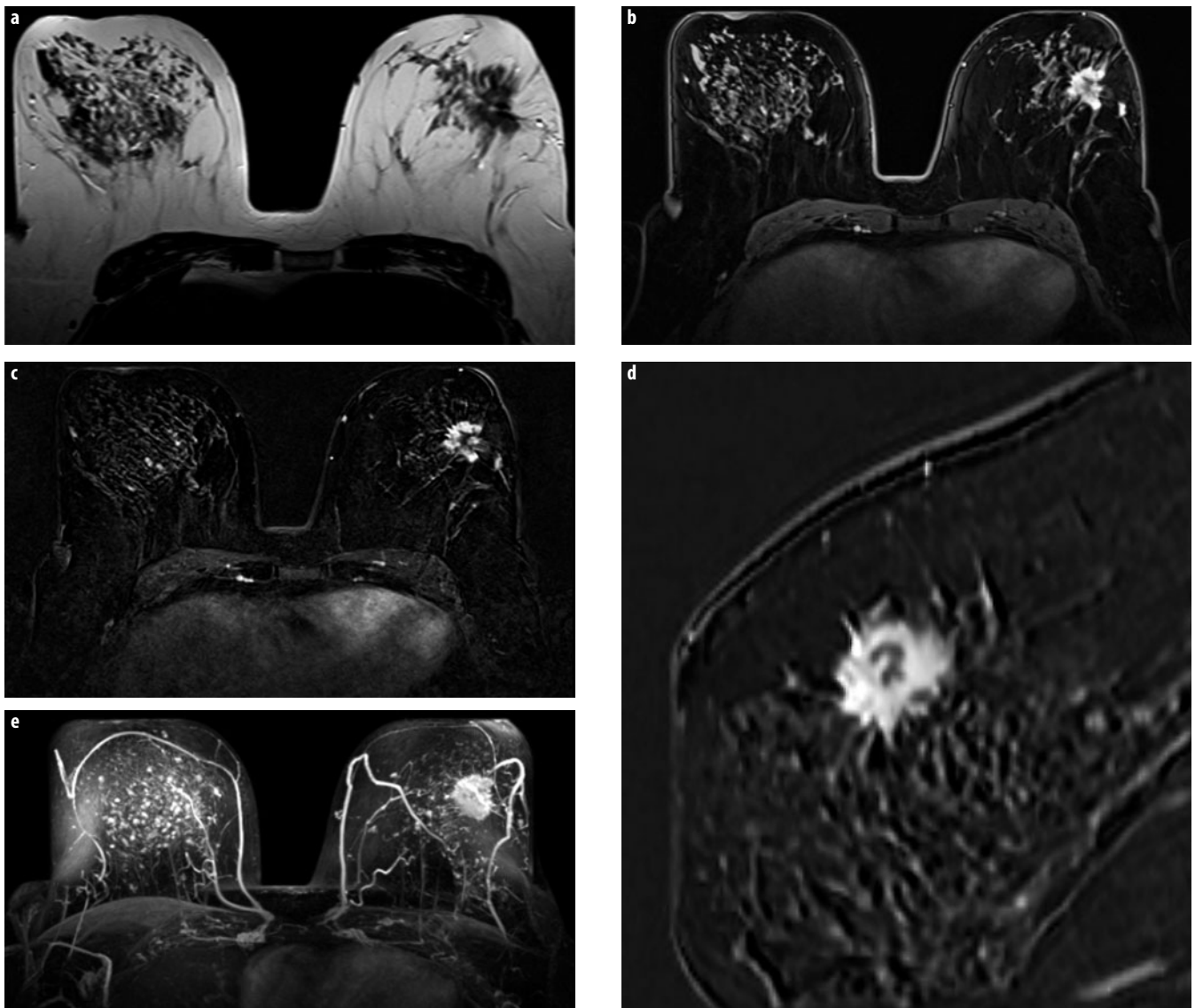


Fig. 2 a-e. A 45-year-old patient with histologically proven invasive ductal carcinoma in the upper left quadrant, fibrocystic changes. **a** Axial T2-weighted sequence; **b** contrast-enhanced T1-weighted 3D gradient-echo sequence with fat suppression; **c** early subtraction image; **d** sagittal reformation; **e** 3D maximum intensity projection image

course, dependent on the manufacturer and type of magnet (Tables 1 and 2).

If an enhancing focal lesion is present, a semiquantitative analysis of the percent change in signal intensity from the precontrast value will be plotted over time. Based on the type of the time-signal intensity curve, different types of enhancement patterns are defined as shown in Fig. 3 and described below [5, 6, 11].

Three-dimensional rendering methods using post-processing techniques such as maximum intensity projections (MIP) are useful for visualizing the shape and location of a suspicious lesion relative to nipple, skin and chest wall (Fig. 2e).

Diffusion-weighted imaging (DWI), well established for intracranial imaging in patients with stroke, is a func-

tional imaging technique in which contrast derives from the random motion of water molecules within the extracellular tissue.

Due to recent technical advances allowing for much faster data acquisition, DWI can now be successfully implemented for other body applications and has a potential for breast imaging, e.g. to differentiate benign from malignant lesions or for pretreatment prediction of response to neoadjuvant chemotherapy in patients with histologically proven breast cancer [12]. Invasive breast cancer demonstrates more restricted diffusion, i.e. lower apparent diffusion coefficient (ADC) than normal breast tissue and benign lesions. The actual clinical value of this technique, however, still needs to be established [1].

Table 1. Sample breast magnetic resonance imaging protocol at 1.5 T (Avanto, Siemens Medical Systems) as currently used at our institution

Parameter	Imaging Sequence	
	Axial T2-weighted	Sagittal T1-weighted 3D gradient recalled echo (GRE) (precontrast, 5 times post contrast)
TR (ms)	8250	5.23
TE (ms)	118	2.38
Fat-saturation	yes	no
Flip angle	150	12
FOV (mm)	360	340
Matrix	512	448
Slice thickness (mm)	3.0	2.0
No. of sections	40	144
Voxel size (mm)	1.4×0.7×3	1.0×0.8×1
Bandwidth (Hz/pixel)	130	380
Imaging time (min:sec)	4.17	1.30 (per acquisition)

Table 2. Sample breast magnetic resonance imaging protocol at 3 T (Verio, Siemens Medical Systems) as currently used at our institution

Parameter	Imaging Sequence	
	Axial T2-weighted	Sagittal T1-weighted 3D gradient recalled echo (GRE) (precontrast, 5 times post contrast)
TR (ms)	5000	4.51
TE (ms)	86	1.58
Fat-saturation	yes	no
Flip angle	135	10
FOV (mm)	360	360
Matrix	512	448
Slice thickness (mm)	4.0	1.0
No. of sections	34	144
Voxel size (mm)	0.9×0.7×4	11.2×0.8×1
Bandwidth (Hz/pixel)	208	400
Imaging time (min:sec)	3.57	1.30 (per acquisition)

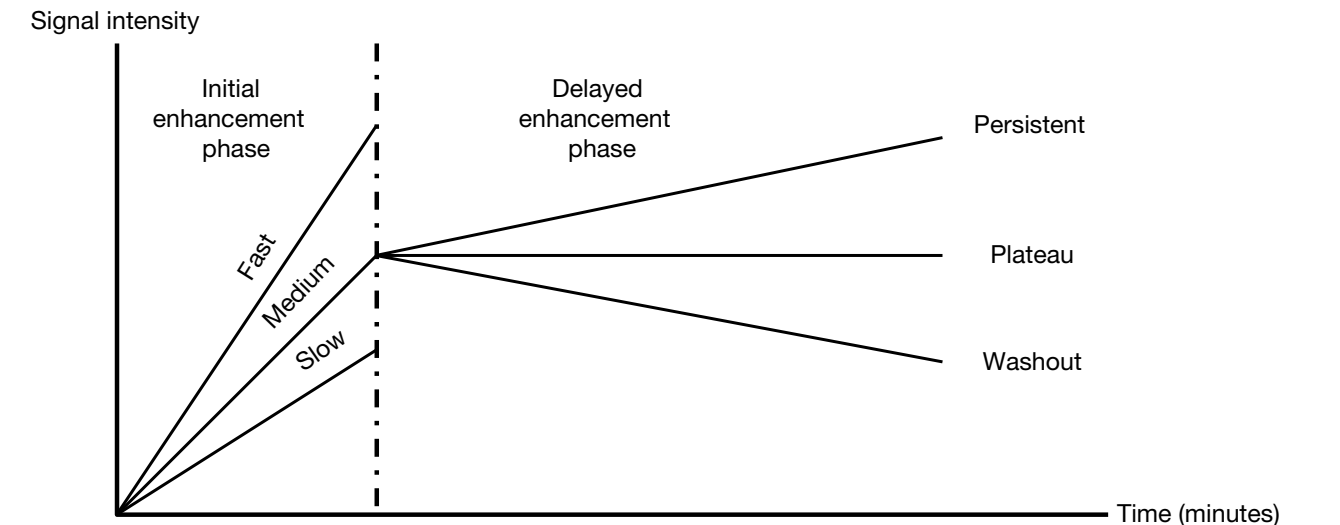


Fig. 3. Signal intensity/time curve describes enhancement characteristics of a breast lesion during contrast-medium injection [adapted from Breast Imaging and Reporting Data System (BI-RADS) lexicon]

Images Analysis and BI-RADS Classification

In 2003, ACR added MRI and US to its publication of BI-RADS. The use of this lexicon provides guidelines for performing and interpreting breast MRI and allows radiologists to communicate findings to referring physicians in a uniform and concise fashion [3, 5, 6, 13]. It is important to point out that MRI findings must always be correlated with clinical history, physical examination and mammography and sonography results.

As most invasive tumors show rapid, intense contrast uptake, kinetic evaluation is important. The kinetic curve assessment describes enhancement characteristics during contrast medium injection. The early phase constitutes the first 2 min after contrast. In the lexicon, the curve during this period demonstrates the rate of contrast uptake by the lesion being described as slow, medium or rapid, with specific threshold values varying with imaging protocols [5]. The remainder of the curve is considered the delayed phase. Based on the type of the time-

signal intensity curve, three different types of enhancement patterns (persistent enhancement, plateau and washout) are defined (Fig. 3).

Besides kinetic assessment, a morphologic evaluation is performed assigning a lesion to the categories focus, “mass or non-mass-like enhancement”.

- A focus is a tiny spot of enhancement (usually <5 mm) and does not clearly represent a space-occupying lesion. Multiple tiny foci are typically seen in fibrocystic breast changes.
- A mass, in contrast, is a space-occupying lesion that can be further characterised by size, shape, margin and enhancement characteristics.
- A non-mass-like enhancement is characterised as enhancement of an area that is not a mass. This type of enhancement displays areas or spots of normal glandular tissue or fat interspersed between the abnormally enhancing components. It is seen in benign disease, e.g. fibrocystic changes, but also in ductal carcinoma in situ (Fig. 4).

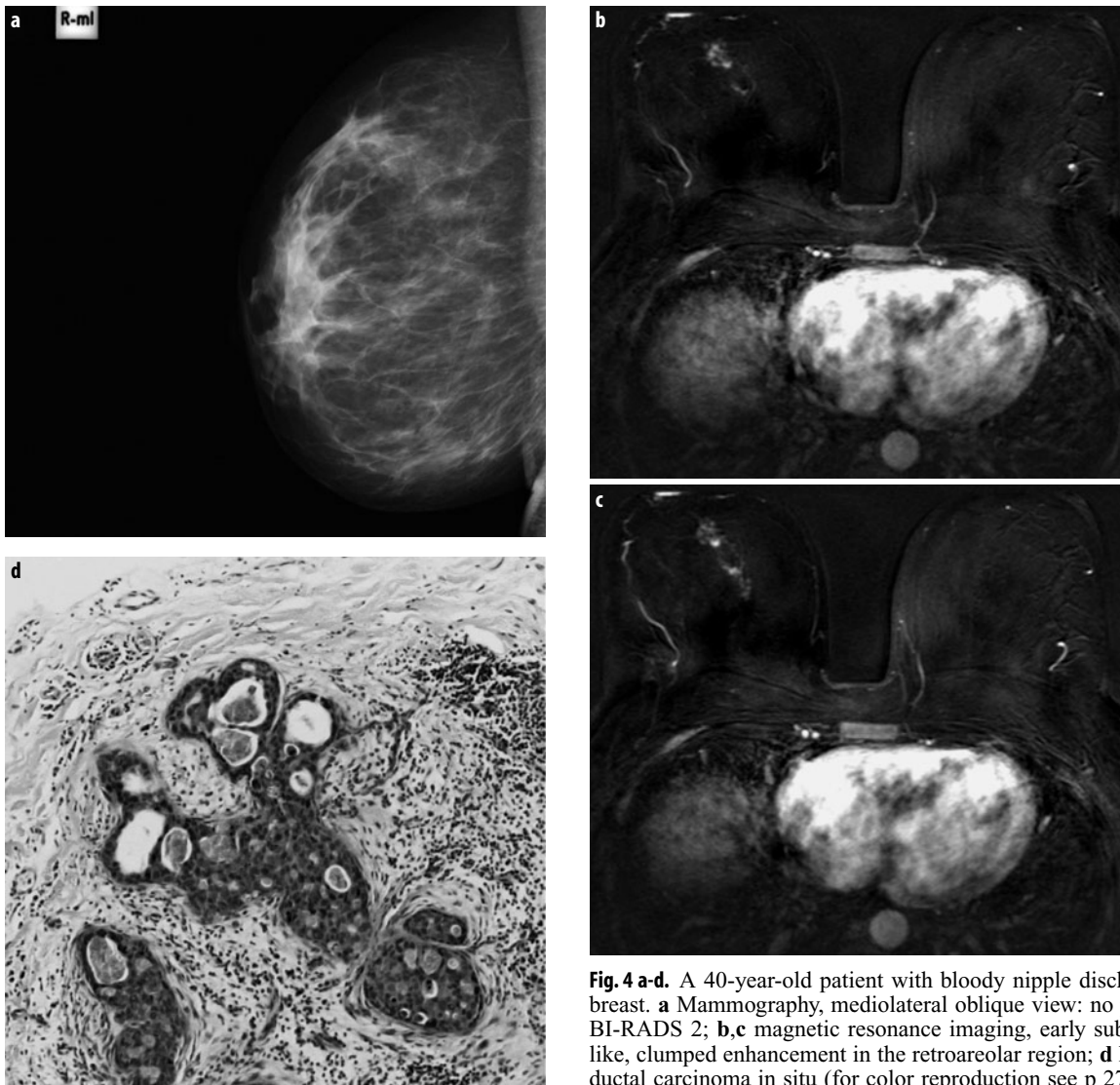


Fig. 4 a-d. A 40-year-old patient with bloody nipple discharge from the right breast. **a** Mammography, mediolateral oblique view: no pathologic findings, BI-RADS 2; **b,c** magnetic resonance imaging, early subtraction: non-mass-like, clumped enhancement in the retroareolar region; **d** histology confirmed ductal carcinoma in situ (for color reproduction see p 273)

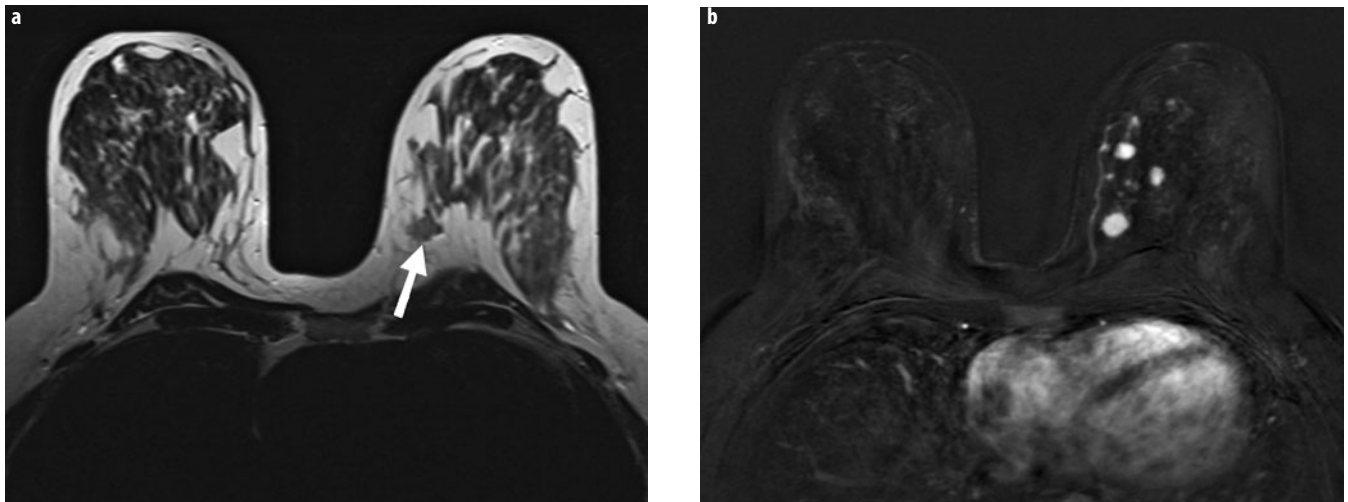


Fig. 5 a, b. A 44-year-old patient with histologically proven invasive ductal carcinoma in the left inner lower quadrant (*arrow*). **a** Axial T2-weighted magnetic resonance imaging sequence; **b** early subtraction image showed multifocal tumor manifestations

Associated findings such as nipple retraction, skin thickening, chest-wall invasion, oedema or lymphadenopathy can increase the suspicion of a lesion and should therefore always be reported [5, 6].

The final assessment categories are based on BI-RADS categories developed for mammography. In categories 1 (negative) and 2 (benign), there is no evidence of malignancy. Category 3 suggests a probably benign finding, and a short-interval follow-up is suggested. Categories 4 (suspicious abnormality) and 5 (highly suggestive of malignancy) will need further diagnostic workup, usually biopsy, whereas category 6 means that the cancer diagnosis has already been established by histology [5, 6].

Indications for Breast MRI

According to the ACR practice guidelines for performing contrast-enhanced breast MRI, last revised 2008 (www.acr.org) indications for breast MRI include [1, 2, 5, 6]:

- high-risk patients, i.e. in women with >20% lifetime risk of breast cancer;
- contralateral breast in patients with a new breast malignancy, as MRI was shown to detect occult malignancy in 3-5% of breast cancer patients;
- patients with breast augmentation, postoperative reconstruction and free injections of filling materials in whom mammography is difficult; additional silicone-sensitive and T2-weighted sequences furthermore allow to assess the integrity of silicone implants (Fig. 1);
- disease extent assessment; in patients with newly diagnosed breast cancer, breast MRI may be useful to determine disease extent presence of multifocality, centricity and tumour relationship to the pectoral fascia (Fig. 5);

- residual disease evaluation in patients with positive margins following lumpectomy;
- treatment response evaluation following neoadjuvant chemotherapy;
- suspicion of recurrence in women with prior history of breast cancer when clinical, mammographic and sonographic findings are inconclusive;
- metastatic cancer with unknown primary and axillary adenopathy;
- problem solving for lesion characterisation when mammography and US are inconclusive, e.g. asymmetry is seen on one view only and cannot be localised for biopsy;
- interventions for breast lesions demonstrable only with MRI guidance.

References

1. Weinstein S, Rosen M (2010) Breast MRI imaging: current indications and advanced imaging techniques. *Radiol Clin North Am* 48:1013-1042
2. Yeh ED (2010) Breast magnetic resonance imaging: current clinical indications. *Reson Imaging Clin N Am* 18:155-169
3. Kuhl CK (2007) The current status of breast MR imaging part I. Choice of technique, image interpretation, diagnostic accuracy, and transfer to clinical practice. *Radiology* 244:356-378
4. Kuhl CK (2007) Current Status of Breast MR imaging part 2. Clinical applications. *Radiology* 244:672-691
5. Molleran V, Mahoney MC (2010) The BI-RADS breast magnetic resonance imaging lexicon. *Reson Imaging Clin N Am* 18:171-185
6. ACR BI-RADS – MRI (2003) Breast Imaging Reporting and Data System. In: ACR BI-RADS Breast Imaging Reporting and Data System, Breast Imaging Atlas, 4th edn. Reston, VA
7. Morrow M (2010) Magnetic resonance imaging for screening, diagnosis, and eligibility for breast-conserving surgery: promises and pitfalls. *Surg Oncol Clin N Am* 19:475-292
8. Brennan S, Liberman L, Dershaw David D, Morris E (2010) Breast MRI screening of women with a personal history of breast cancer. *AJR Am J Roentgenol* 195:510-516

9. Gavenonis SC, Roth SO (2010) Role of magnetic resonance imaging in evaluating the extent of disease. *Reson Imaging Clin N Am* 18:199-206
10. Shimauchi A, Jansen SA, Abe H et al (2010) Breast cancers not detected at MRI: review of false-negative lesions. *AJR Am J Roentgenol* 194:1674-1679
11. Chatterji M, Mercado CL, Moy L (2010) Optimizing 1.5-Tesla and 3-Tesla dynamic contrast-enhanced magnetic resonance imaging of the breasts. *Reson Imaging Clin N Am* 18:207-224
12. Park SH, Moon WH, Cho N et al (2010) Diffusion-weighted MR imaging: pretreatment prediction of response to neoadjuvant chemotherapy in patients with breast cancer. *Radiology* 257:56-63
13. ACR (2008) ACR practice guidelines for the performance of contrast-enhanced magnetic resonance imaging (MRI) of the breast, revised 2008. www.acr.org

APPENDIX: FULL COLOR FIGURES

This section reproduces in colors those figures that for technical reasons are found in a black and white version in the various chapters.

Current Concepts in Diagnosis and Staging of Lung Cancer

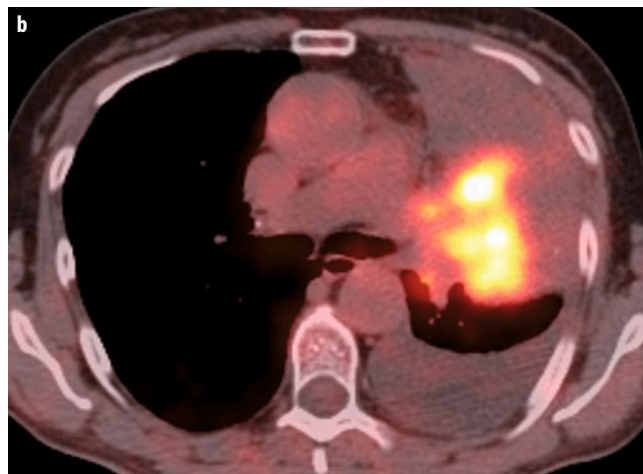
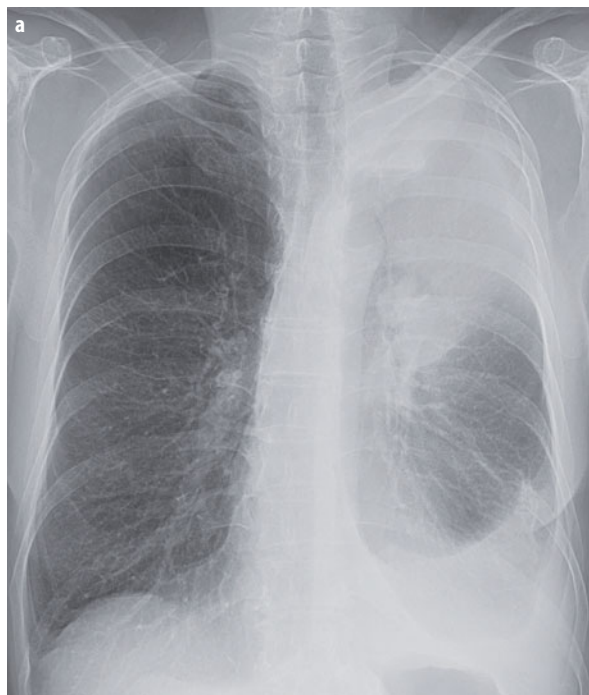


Fig. 7 a, b. Non-small-cell lung cancer with complete atelectasis of the left upper lobe. **a** Chest radiograph shows a left perihilar mass and complete atelectasis of the left upper lobe. Note left pleural effusion. **b** Fused positron emission tomography computed tomography (PET-CT) shows the [^{18}F]-2-deoxy-D-glucose-avid left upper lobe tumor and the distal atelectatic lung. Note PET-CT can assist the radiation oncologist in radiation treatment planning by delineating the primary tumor



International Association for the Study of Lung Cancer

TNM Descriptors

T – Primary Tumour

- TX Primary tumour cannot be assessed, or tumour proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
- T0 No evidence of primary tumour
- Tis Carcinoma in situ
- T1 Tumour 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)
 - T1a Tumour 2 cm or less in greatest dimension¹
 - T1b Tumour more than 2 cm but not more than 3 cm in greatest dimension
- T2 Tumour more than 3 cm but not more than 7 cm; or tumour with any of the following features²:
 - Involves main bronchus, 2 cm or more distal to the carina
 - Invades visceral pleura
 - Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
 - T2a Tumour more than 3 cm but not more than 5 cm in greatest dimension
 - T2b Tumour more than 5 cm but not more than 7 cm in greatest dimension
- T3 Tumour more than 7 cm or one that directly invades any of the following: chest wall (including superior sulcus tumours), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumour in the main bronchus less than 2 cm distal to the carina¹ but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumour nodule(s) in the same lobe as the primary.
- T4 Tumour of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina; separate tumour nodule(s) in a different ipsilateral lobe to that of the primary.

N – Regional Lymph Nodes

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
- N2 Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
- N3 Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

M – Distant Metastasis

- M0 No distant metastasis
- M1 Distant metastasis
 - M1a Separate tumour nodule(s) in a contralateral lobe; tumour with pleural nodules or malignant pleural or pericardial effusion³
 - M1b Distant metastasis

Notes:

¹The uncommon superficial spreading tumour of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1a.

²T2 tumours with these features are classified T2a if 5 cm or less or if size cannot be determined, and T2b if greater than 5 cm but not larger than 7 cms.

³Most pleural (pericardial) effusions with lung cancer are due to tumour. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumour, and the fluid is non-bloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumour, the effusion should be excluded as a staging element and the patient should be classified as M0.

Fig. 9. Descriptions of malignant lung tumors, nodes, and metastases for classification purposes. Reprinted with permission courtesy of the International Association for the Study of Lung Cancer. Copyright 2009 IASLC

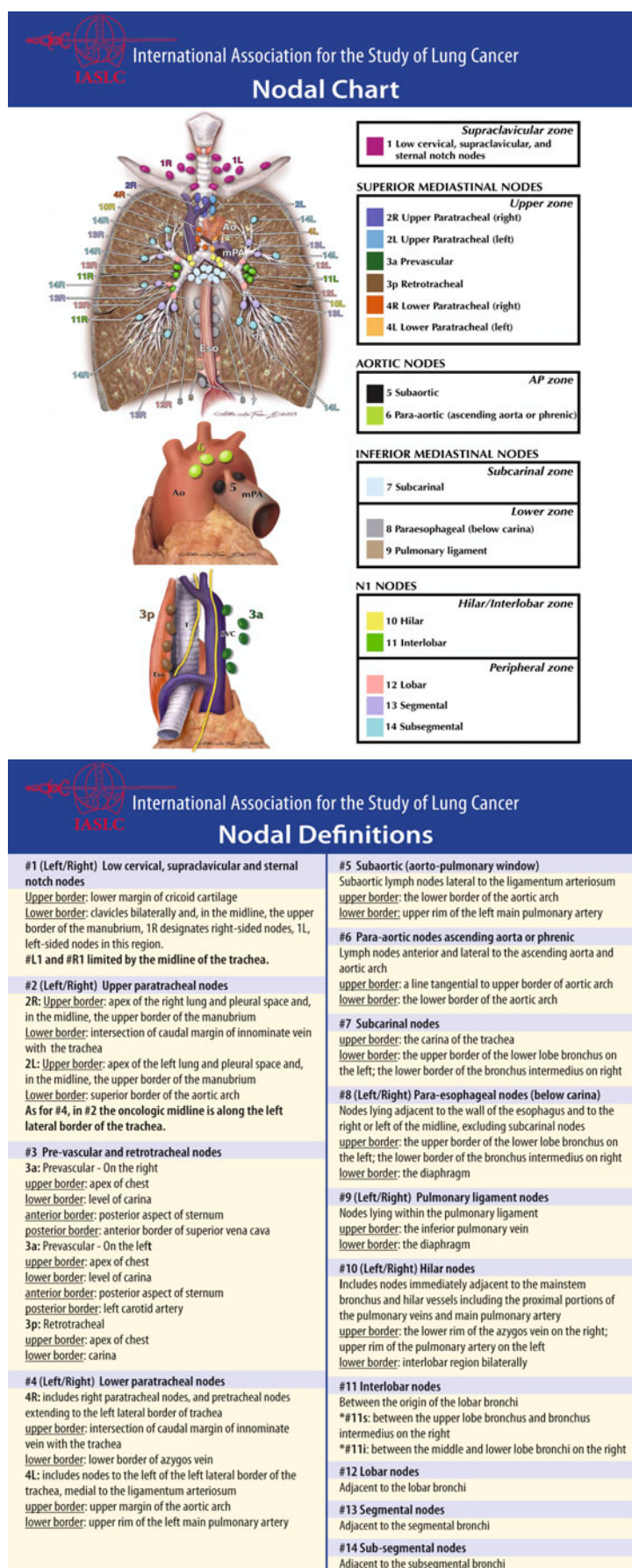


Fig. 10. Positions and descriptions of malignant lung nodes. Reprinted with permission courtesy of the International Association for the Study of Lung Cancer. Copyright 2009 IASLC and © 2008 Aletta Ann Frazier



Fig. 11 a-c. Nodal metastasis in a 78-year-old man with non-small-cell lung cancer. **a, b** Chest computed tomography (CT) shows a large left lower lobe mass and a normal-sized (short axis diameter <1 cm) right lower paratracheal lymph node (*arrow in b*). **c** Fused positron emission tomography CT (PET-CT) reveals increased [^{18}F]-2-deoxy-D-glucose uptake in the right paratracheal node. Mediastinoscopy confirmed nodal metastasis. Note that because N3 (contralateral mediastinal) nodal metastasis is nonresectable, the patient was treated palliatively

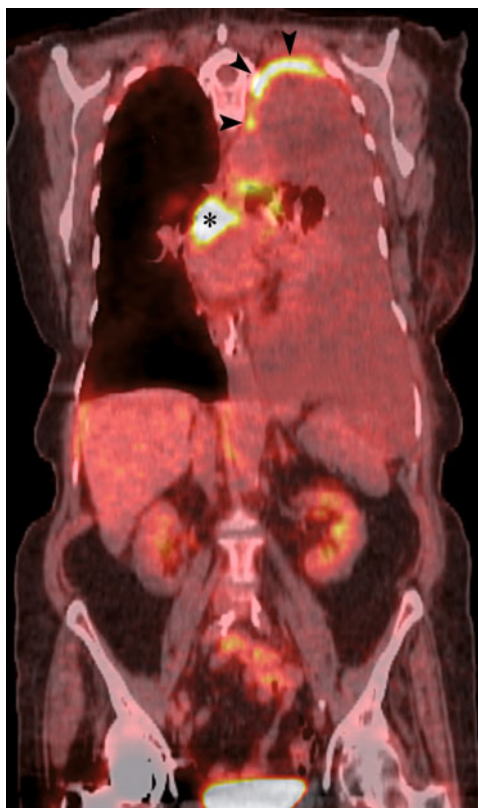


Fig. 12. Malignant pleural effusion in an 86-year-old woman with non-small-cell lung cancer. Coronal positron emission tomography computed tomography (PET-CT) shows a large left pleural effusion and diffuse [^{18}F]-2-deoxy-D-glucose (FDG)-avid pleural metastasis (*arrowheads*). Note enlarged and FDG-avid mediastinal nodal metastasis (*asterisk*)



Fig. 14 a-c. Adrenal and intramuscular metastases in a 49-year-old woman with non-small-cell lung cancer presenting with right leg mass and pain. **a** Chest radiograph shows a large right upper lobe mass. **b** Computed tomography (CT) shows a right adrenal nodule and large heterogeneous left adrenal mass (*arrows*). **c** Coronal whole-body fused positron emission tomography CT (PET-CT) shows increased [^{18}F]-2-deoxy-D-glucose uptake in primary right upper lobe malignancy (*M*), bilateral adrenal metastases (*asterisks*), and intramuscular metastasis in the right thigh (*arrow*)

CT Diagnosis and Management of Focal Lung Disease

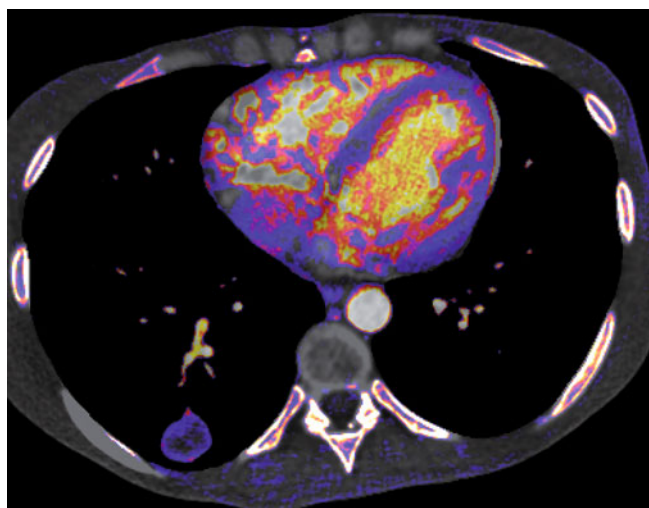


Fig. 4. Dual-energy computed tomography demonstrating peripheral enhancement of a pulmonary metastasis

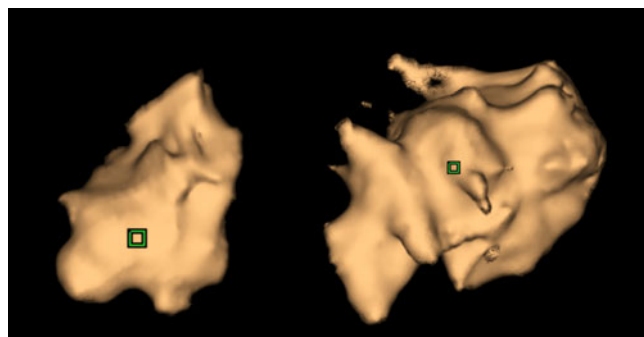


Fig. 5. Lung adenocarcinoma. Computer-aided 3D volumetric evaluation demonstrating asymmetric growth over an 11-month period

Plain-Film and CT Evaluation of the Adult Mediastinum and Hilum: Pitfalls vs. Disease

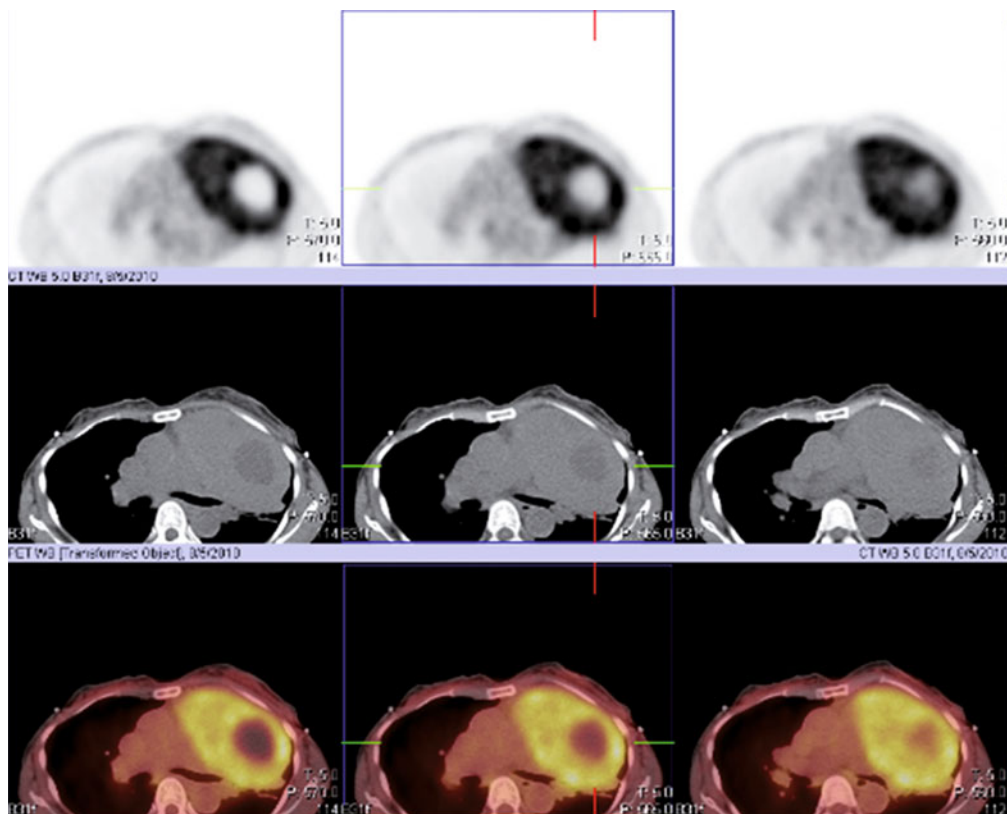


Fig. 7. Thymic carcinoma. FDG-PET-CT shows the marked increased uptake in an anterior mediastinal mass which was confirmed to be thymic carcinoma at surgery

CT Evaluation of Pediatric Chest in Routine Practice

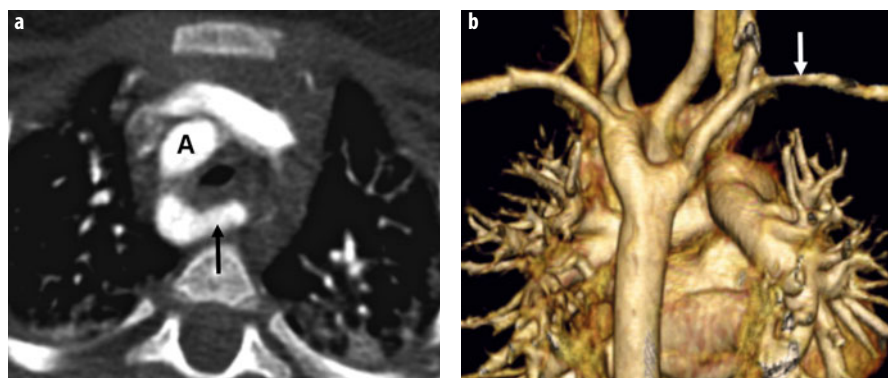


Fig. 11 a, b. Right aortic arch with aberrant left subclavian artery. **a** Axial computed tomography scan demonstrates a right aortic arch (*A*) with the aberrant left subclavian artery (*arrow*) crossing the mediastinum posteriorly. **b** Coronal 3D reconstruction: the left subclavian artery (*arrow*) is the last vessel arising from the aorta

Modern Diagnosis in the Evaluation of Pulmonary Vascular Disease



Fig. 1. Lateral view of the left hemithorax in a 51-year-old patient evaluated with a high pitch (3.2), high temporal resolution (75 ms) scanning mode (volume-rendered image). Note the sharpness of all pulmonary and systemic vessels in the volume scanned (data acquisition 0.79 s)

Imaging the Chest Trauma Patient

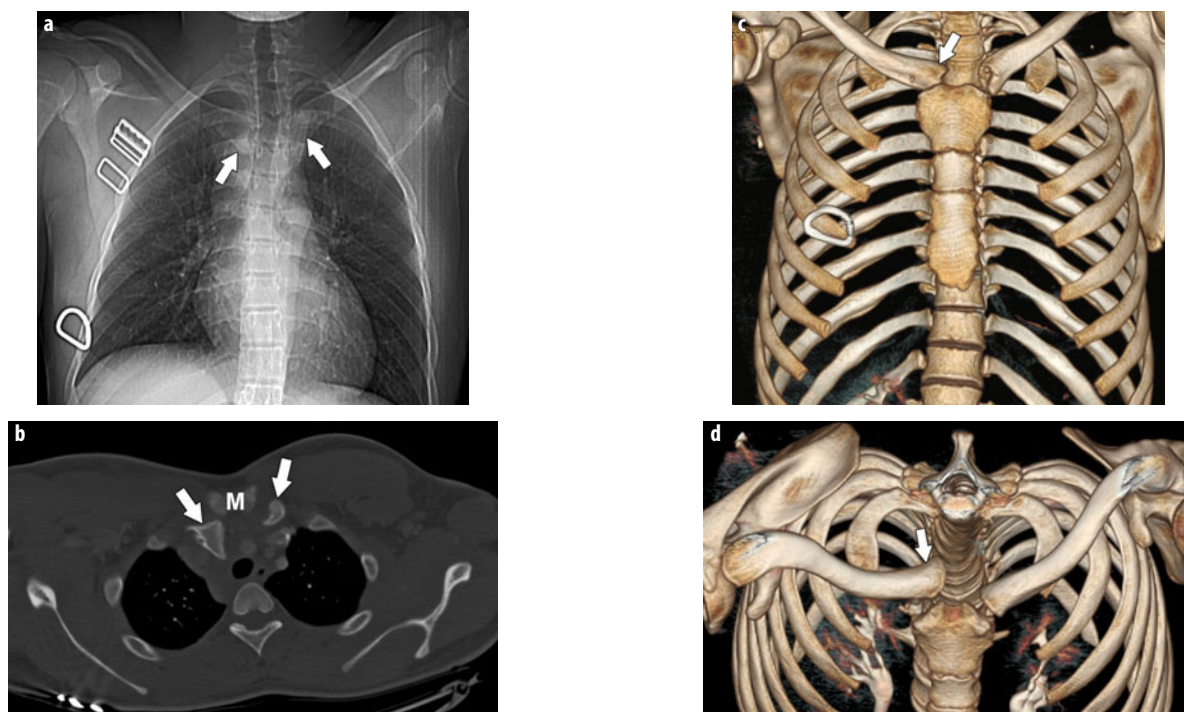


Fig. 1 a-d. Right posterior sternoclavicular dislocation: **a** Chest radiograph shows asymmetry of the clavicular heads (*arrows*). The right head of the clavicle is displaced inferiorly and medially. **b** Axial computed tomography (CT) scan at the level of the manubrium (*M*). The right head of the clavicle is dislocated posteriorly compared with the normally positioned left head. **c,d** Frontal and superior views of a volumetric (3D) CT reformation display the posteriorly displaced right clavicle (*arrows*)

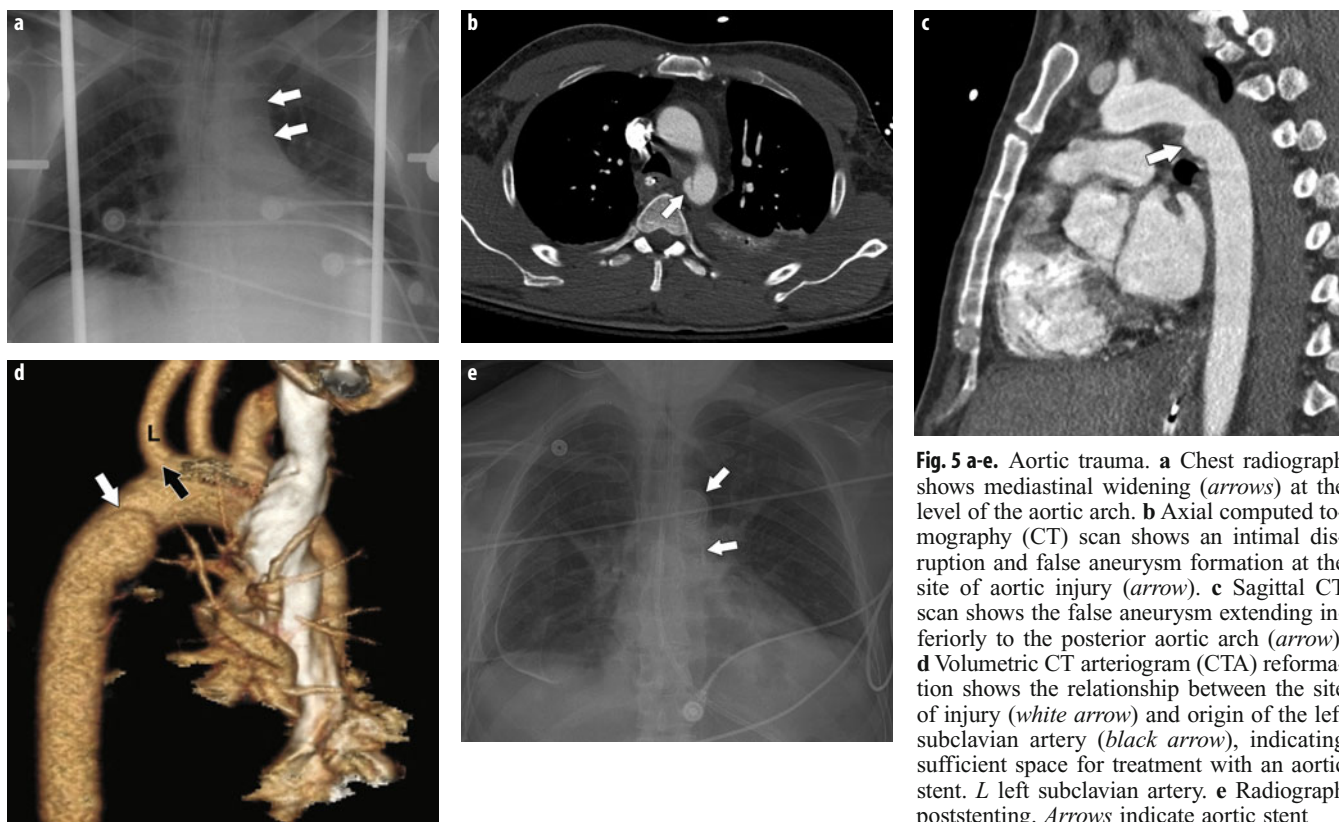


Fig. 5 a-e. Aortic trauma. **a** Chest radiograph shows mediastinal widening (*arrows*) at the level of the aortic arch. **b** Axial computed tomography (CT) scan shows an intimal disruption and false aneurysm formation at the site of aortic injury (*arrow*). **c** Sagittal CT scan shows the false aneurysm extending inferiorly to the posterior aortic arch (*arrow*). **d** Volumetric CT arteriogram (CTA) reformation shows the relationship between the site of injury (*white arrow*) and origin of the left subclavian artery (*black arrow*), indicating sufficient space for treatment with an aortic stent. *L* left subclavian artery. **e** Radiograph poststenting. *Arrows* indicate aortic stent

Diseases of the Chest Wall, Pleura, and Diaphragm

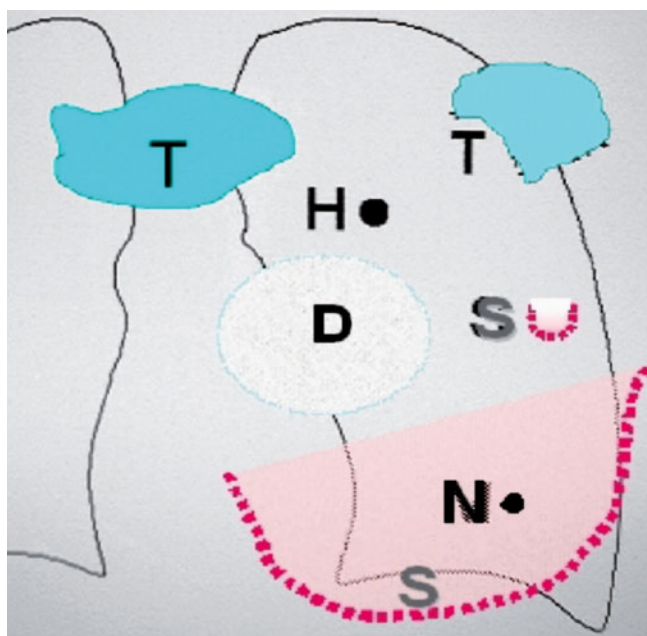


Fig. 1. Extrathoracic soft-tissue lesions. *T* opacities going beyond the parietal pleural border (inner rib contour), often mobile (e.g., skin fold, hematoma, tumor), *D* poorly margined density, *N/H* rounded opacities (often projecting on the lung in one plane) (e.g., nipple/skin tumor), *S* inferiorly rounded, superiorly not margined, opacity (e.g., female breast, pedunculated skin tumor)

Three- and Four-Dimensional Imaging in Acute Aortic Syndrome

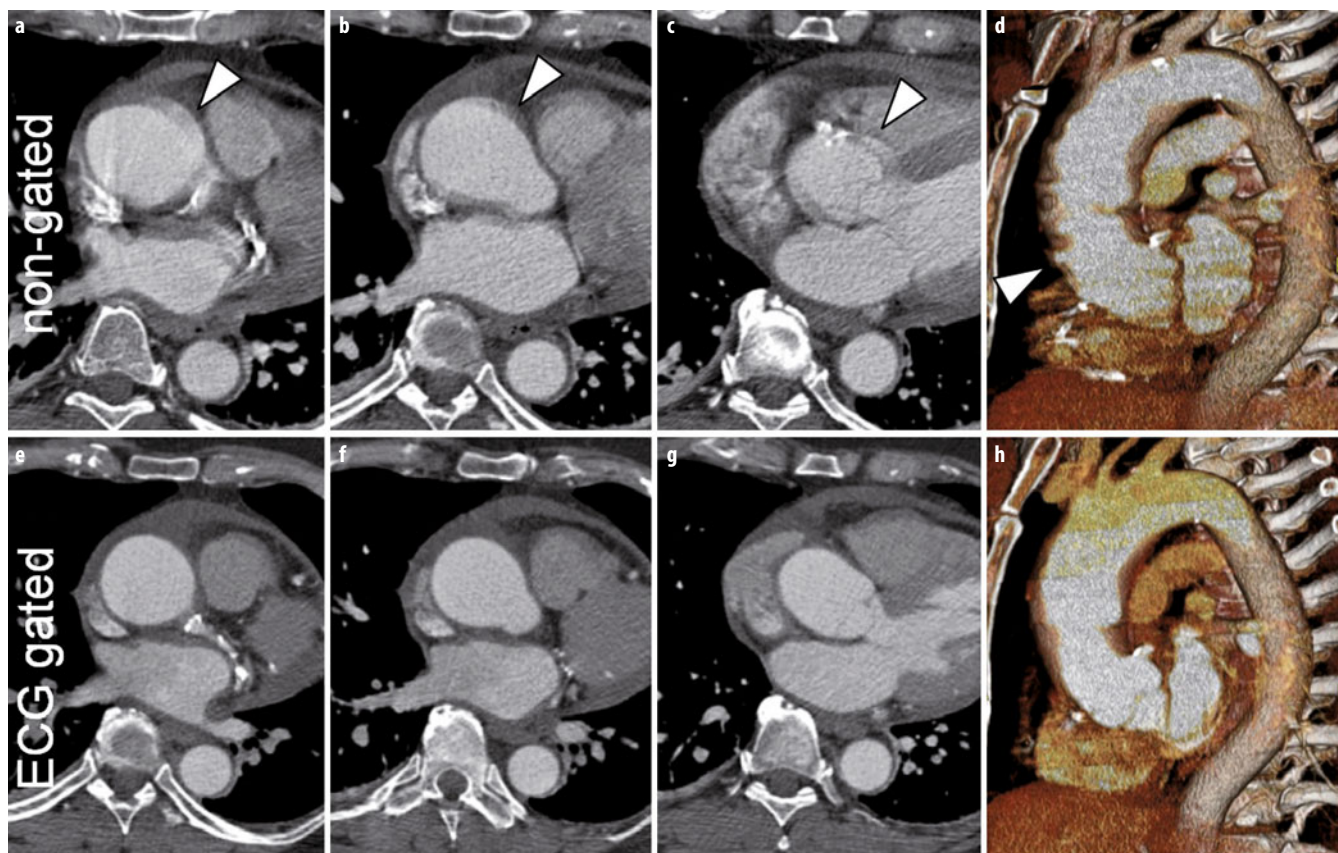


Fig. 1 a-h. Aortic motion-artefact suppression with electrocardiographic (ECG)-gated computed tomography angiography (CTA). Three transverse CT images obtained with a nongated 16-channel CT show typical motion artefacts with double contours (*arrowheads*) at the mid ascending aorta (**a**), proximal ascending aorta (**b**) and aortic root (**c**). Corresponding volume-rendered image (**d**) shows artifactual contour abnormalities (*arrowhead*) in the ascending aorta due to transmitted cardiac pulsation. This study was repeated 12 h later with ECG gating, which eliminates motion artefacts in the corresponding transverse (**e-g**) and volume-rendered (**h**) images. From [9], with permission

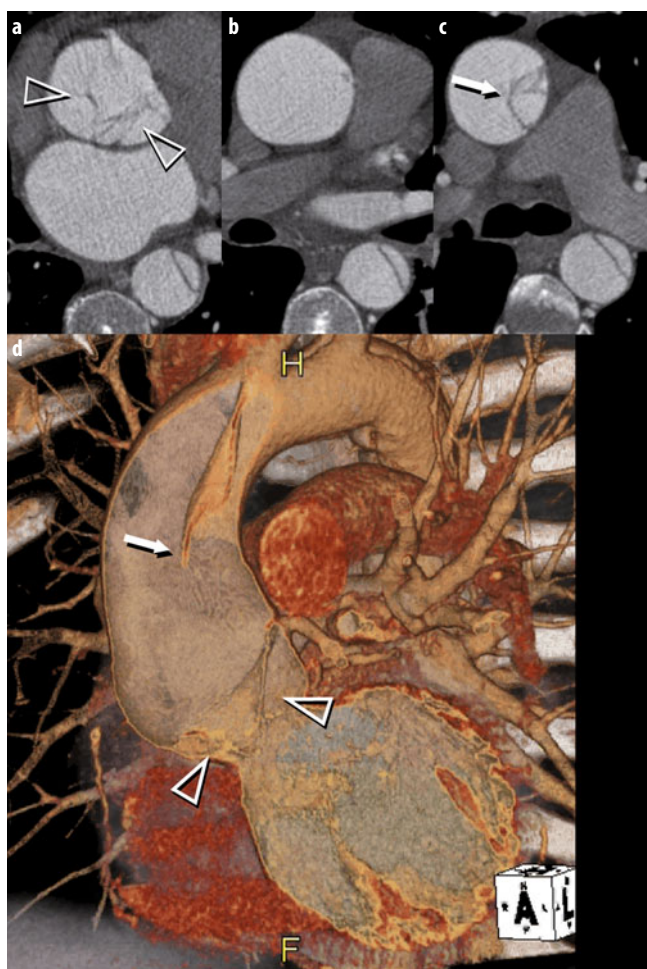


Fig. 2 a-d. Acute type A dissection in a 45-year-old man. Transverse computed tomography (CT) images (a-c) show irregular linear opacities (arrowheads) at the level of the aortic root (a), which are difficult to interpret on this transverse image, but no clear dissection flap in the mid ascending aorta (b). In the distal ascending aorta (c), a dissection flap (arrow) between a true and false lumen is identified. Volume-rendered image (d) clearly depicts an extensive dissection with the proximal portion of the dissection flap torn off and prolapsing onto and through the aortic valve (arrowheads). Arrow points to dissection flap in the distal ascending aorta. From [9], with permission

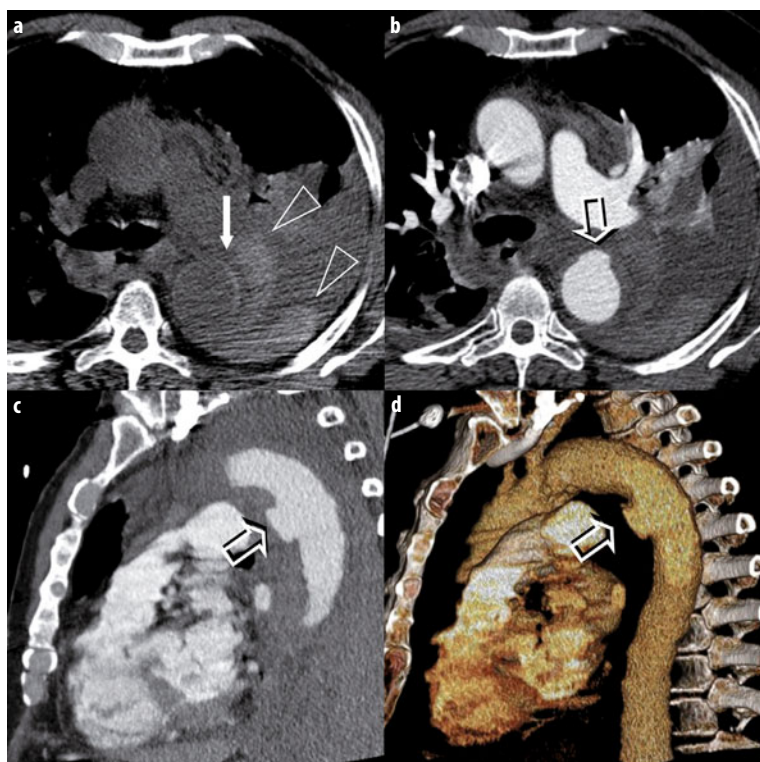


Fig. 7 a-d. Penetrating atherosclerotic ulcer (PAU). Non-enhanced computed tomography (CT) image (a) in an 83-year-old man with acute chest pain shows small hyperdense crescent-shaped abnormality (arrow) in the descending thoracic aorta, consistent with intramural hematoma. Note a large amount of hyperdense periaortic and pleural fluid (arrowheads), indicating mediastinal hematoma and hemothorax. Corresponding postcontrast medium CT angiogram (b) image at the same anatomic level shows large ulcer (open arrow) in the descending thoracic aorta, which is better characterised on a sagittal reformation (c) and on a volume-rendered image (d). From [9], with permission

Clinical Applications of 3D Imaging in Thoracic Vascular Pathology: Pulmonary Vascular Applications

Fig. 1 a, b. Prospective echocardiographically triggered low-dose control computed tomography angiography of 10-year-old boy with scimitar syndrome and an extralobar sequester, performed with 116×0.625 -mm collimation at 80 kV and 135 mAs [computed tomography volume dose index = 3.2 mGy]. The scimitar veins were anastomosed to the right atrium and the sequester was embolized. **a** Volume rendering better demonstrates drainage of the middle and lower lobes via the scimitar vein and the systemic supply of the sequester arising from the abdomen (celiac trunk). **b** Maximum intensity projection (MIP) better demonstrates that embolisation was not successful: there is residual perfusion of the systemic supply of the lung (*arrow*). The density discrimination of MIP makes it possible to determine that the connection between the scimitar vein and right atrium is no longer patent (*arrowhead*)

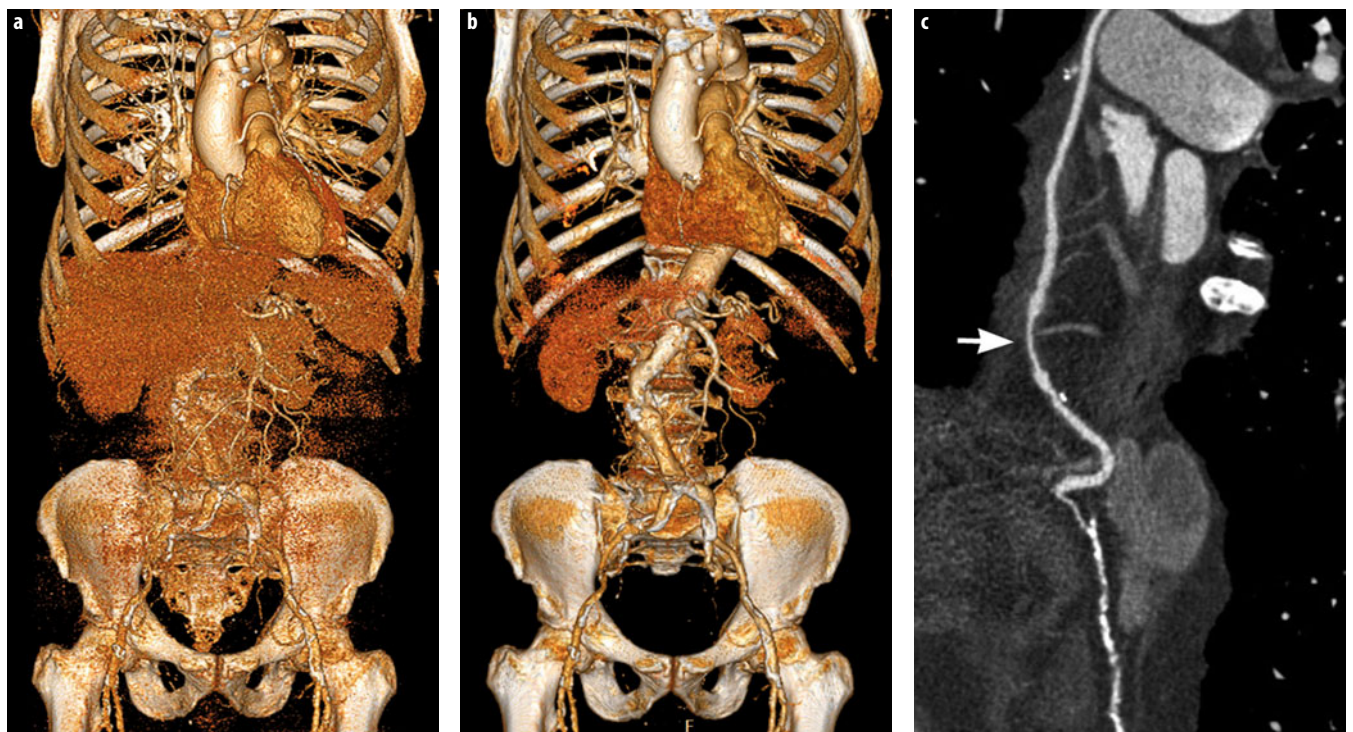
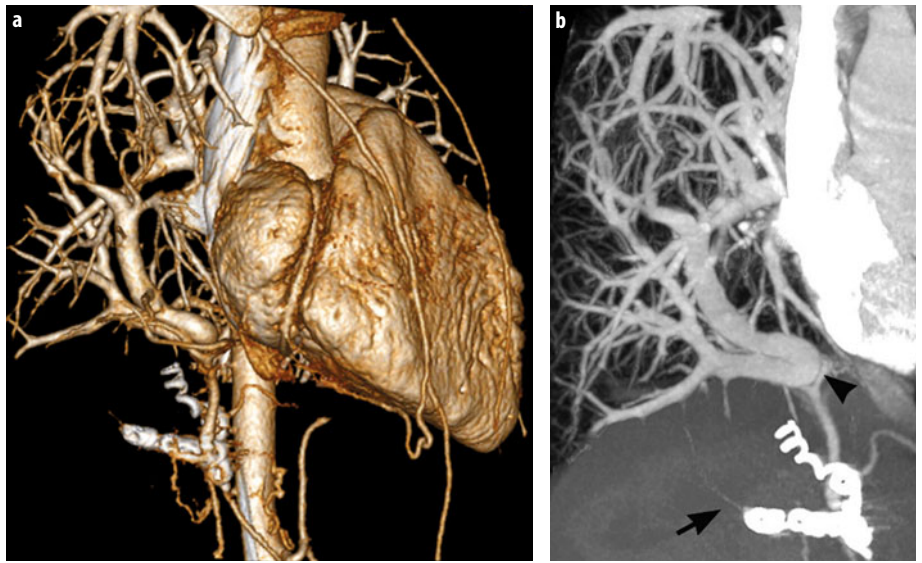


Fig. 2 a-c. Preoperative retrospective electrocardiographically (ECG)-gated computed tomography angiography of the entire thoracoabdominal aorta in a 73-year-old man at 120 kVp and 250 mAs. **a** Volume rendering (VRT) of the ECG-gated reconstruction suffers from artifacts due to noise and flying pixels. **b** Untagged reconstruction (neglecting the ECG information) leads to less noise and better VRT quality but blurring of the cardiac structures. **c** The curved planar reconstruction through the coronary artery bypass graft is good enough to detect a bypass stenosis on the ECG-gated data set (*arrow*)

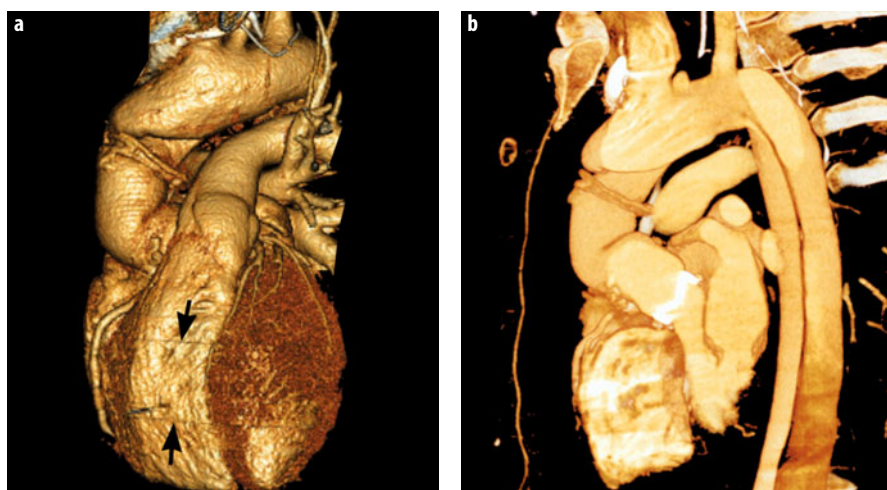


Fig. 3 a, b. Prospectively ECG-triggered scan of the thoracic aorta in a patient after composite graft of the aortic valve and ascending aorta in type A aortic dissection. Note slight step artifacts in the region of the heart (*arrows*). **a** Volume rendering technique (VRT) with surface shading. **b** VRT without shading after cutting away part of the left chest. Image **a** has been edited to (partially) remove the spine

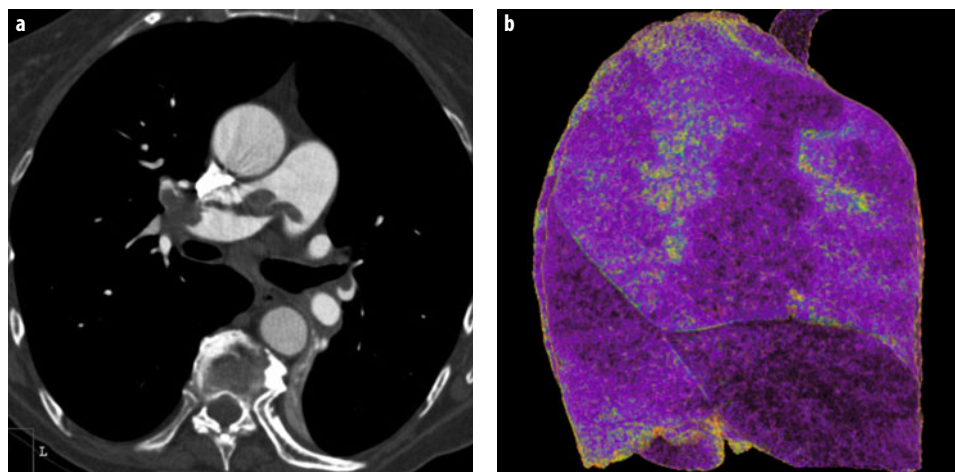


Fig. 5 a, b. **a** Recurrent pulmonary emboli and chronic as well as fresh components. **b** Color-coded volume rendered image of the lungs demonstrates differences in density due to focal hypoperfusion

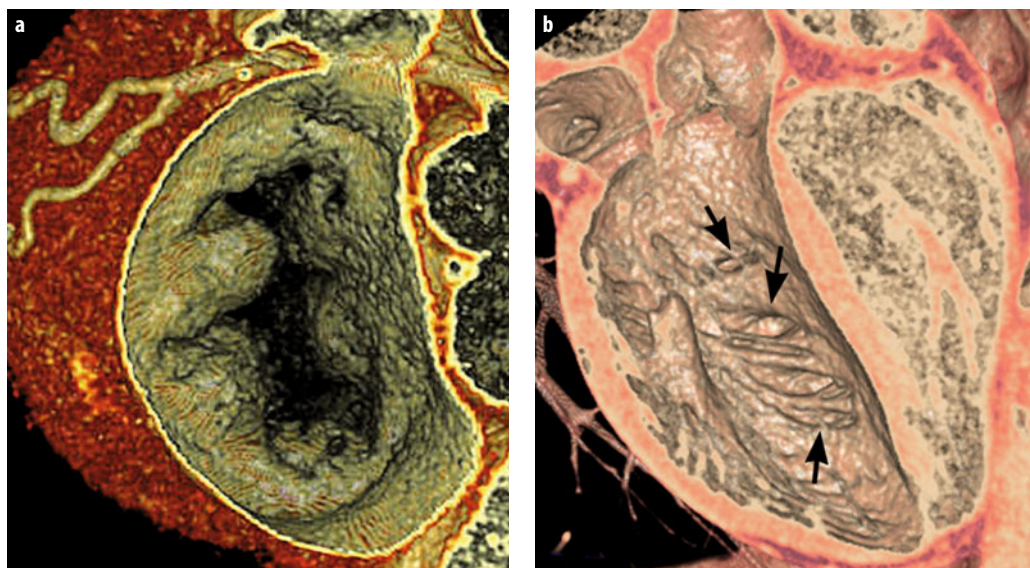


Fig. 6 a, b. Virtual angiography is most useful for displaying the inner surface of complex 3D structures, such as the heart. Usually, rendering without using perspective yields good results. **a** Display of the mitral valve in diastole as seen from left atrium. **b** Section parallel to the aortic outflow tract demonstrating multiple outpouchings of the left ventricular wall (cardiac diverticula, *arrow*) in a patient with arrhythmia

The Atherosclerotic Process and Its Relationship to Coronary Blood Flow

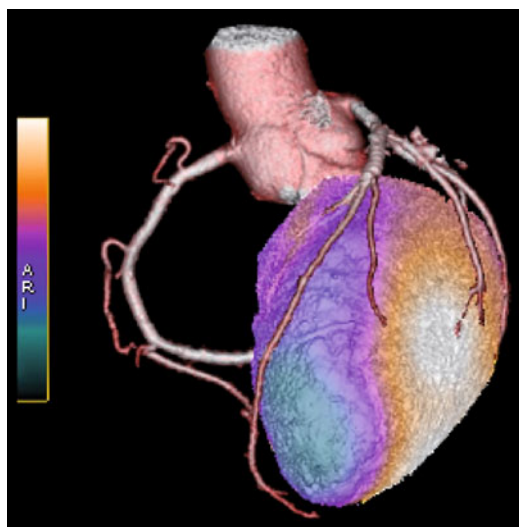


Fig. 1. This 3D representation of hybrid single-photon emission computed tomography/CT angiography image visualizes the ischemic area (*blue*) of the anterior wall caused by an in-stent restenosis

Imaging Breast Disease: Mammography and Breast Ultrasound

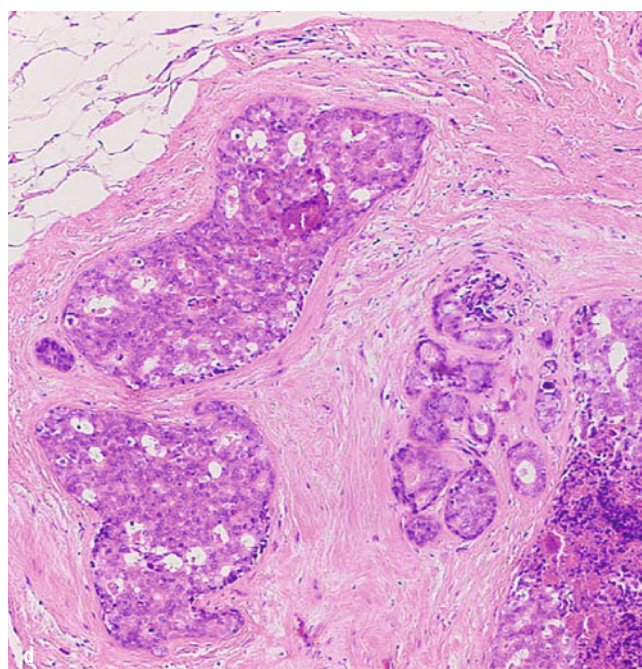
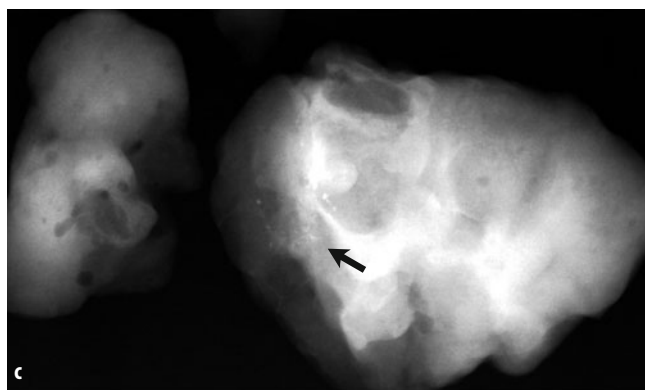
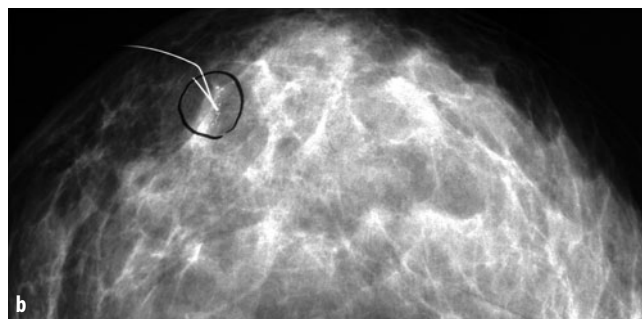
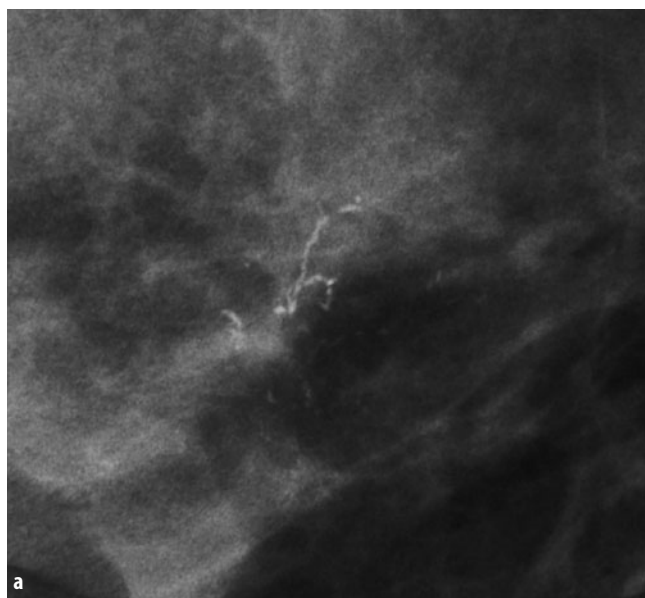


Fig. 5 a-d. First screening mammography study in a 52-year-old asymptomatic woman. **a** Spot-compression magnification view of the right breast. **b** Grouped fine-linear and branching (casting) microcalcifications are seen, highly suggestive of malignancy (BI-RADS category 5). Preoperatively, mammographically guided hook-wire localization was performed. **c** Complete excision of the lesion (*arrow*) was confirmed by a specimen radiograph. **d** Histology showed ductal carcinoma in situ (from Hodler et al 2007)

Myocardial Perfusion Imaging with SPECT-CT

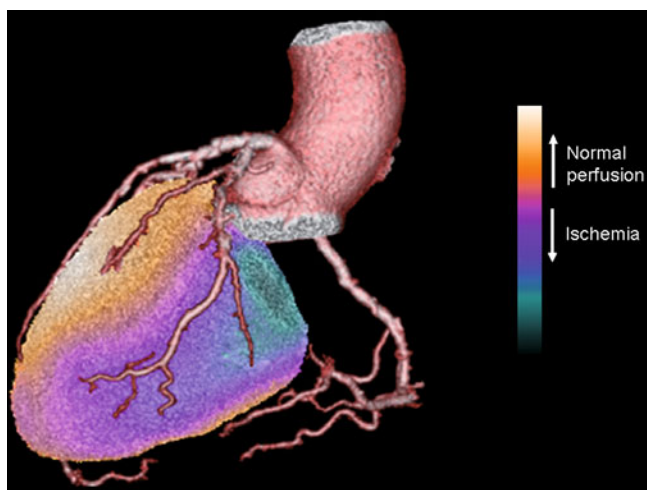


Fig. 1. Posterior view allows recognizing that in this patient, the ischemic basal inferior territory is subtended by the circumflex artery (CX), causing ischemia due to sequential lesions in the CX vessel. By contrast, the right coronary artery does not contribute to this ischemia despite anatomically similar atherosclerotic lesions

Staging, Restaging and Response Evaluation of Non-Small-Cell Lung Cancer

International Association for the Study of Lung Cancer
TNM Descriptors

T – Primary Tumour

TX Primary tumour cannot be assessed, or tumour proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy

T0 No evidence of primary tumour

Tis Carcinoma in situ

T1 Tumour 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)

T1a Tumour 2 cm or less in greatest dimension¹

T1b Tumour more than 2 cm but not more than 3 cm in greatest dimension

T2 Tumour more than 3 cm but not more than 7 cm; or tumour with any of the following features²:

- Involves main bronchus, 2 cm or more distal to the carina
- Invades visceral pleura
- Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung

T2a Tumour more than 3 cm but not more than 5 cm in greatest dimension

T2b Tumour more than 5 cm but not more than 7 cm in greatest dimension

T3 Tumour more than 7 cm or one that directly invades any of the following: chest wall (including superior sulcus tumours), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumour in the main bronchus less than 2 cm distal to the carina¹ but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumour nodule(s) in the same lobe as the primary.

T4 Tumour of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina; separate tumour nodule(s) in a different ipsilateral lobe to that of the primary.

N – Regional Lymph Nodes

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension

N2 Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)

N3 Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

M – Distant Metastasis

M0 No distant metastasis

M1 Distant metastasis

M1a Separate tumour nodule(s) in a contralateral lobe; tumour with pleural nodules or malignant pleural or pericardial effusion³

M1b Distant metastasis

Notes:

¹The uncommon superficial spreading tumour of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1a.

²T2 tumours with these features are classified T2a if 5 cm or less or if size cannot be determined, and T2b if greater than 5 cm but not larger than 7 cms.

³Most pleural (pericardial) effusions with lung cancer are due to tumour. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumour, and the fluid is non-bloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumour, the effusion should be excluded as a staging element and the patient should be classified as M0.

Fig. 1. Tumor-node-metastasis descriptors [4]. Reprinted with permission courtesy of the International Association for the Study of Lung Cancer. Copyright 2009 IASLC

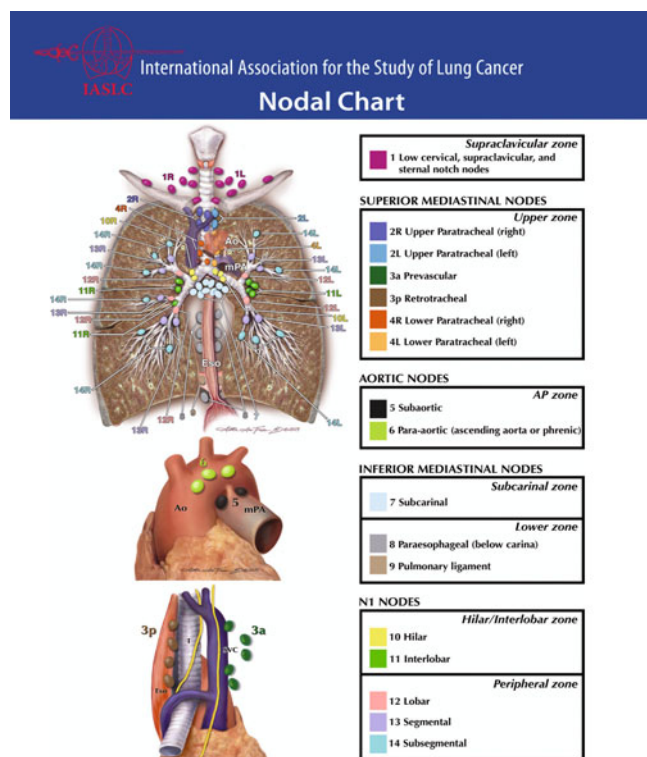


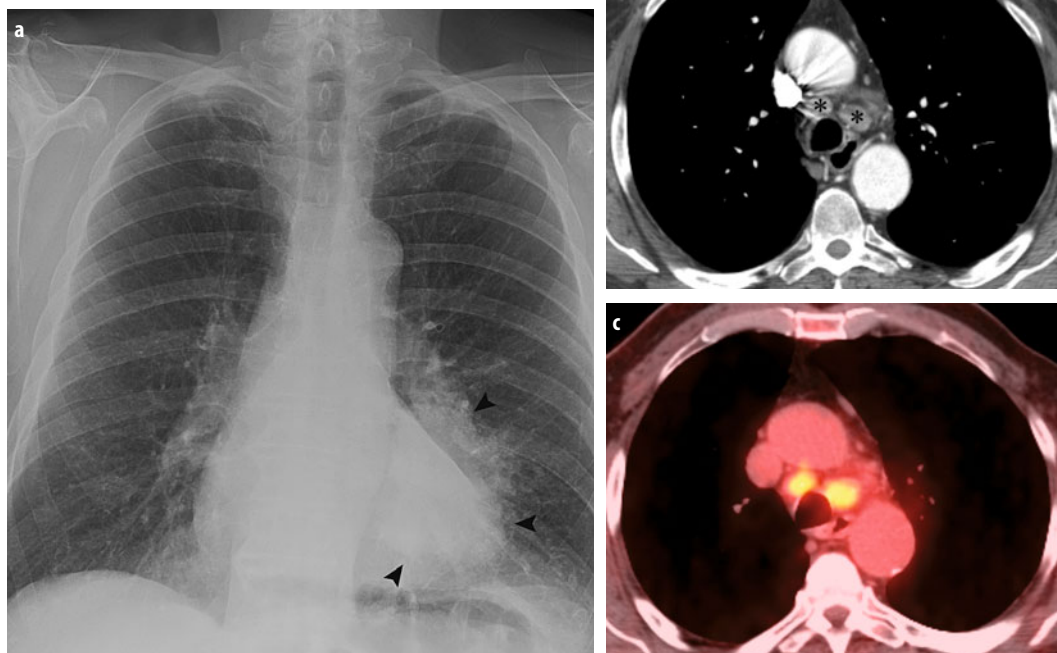
Fig. 3. Nodal chart [4]. Reprinted with permission courtesy of the International Association for the Study of Lung Cancer. Copyright 2009 IASLC and © 2008 Aletta Ann Frazier

International Association for the Study of Lung Cancer
IASLC

Nodal Definitions

#1 (Left/Right) Low cervical, supraclavicular and sternal notch nodes Upper border: lower margin of cricoid cartilage Lower border: clavicles bilaterally and, in the midline, the upper border of the manubrium, 1R designates right-sided nodes, 1L, left-sided nodes in this region. #1L and #1R1 limited by the midline of the trachea.	#5 Subaortic (aorto-pulmonary window) Subaortic lymph nodes lateral to the ligamentum arteriosum upper border: the lower border of the aortic arch lower border: upper rim of the left main pulmonary artery
#2 (Left/Right) Upper paratracheal nodes 2R: Upper border: apex of the right lung and pleural space and, in the midline, the upper border of the manubrium Lower border: intersection of caudal margin of innominate vein with the trachea 2L: Upper border: apex of the left lung and pleural space and, in the midline, the upper border of the manubrium Lower border: superior border of the aortic arch As for #4, in #2 the oncologic midline is along the left lateral border of the trachea.	#6 Para-aortic nodes ascending aorta or phrenic Lymph nodes anterior and lateral to the ascending aorta and aortic arch upper border: a line tangential to upper border of aortic arch lower border: the lower border of the aortic arch
#3 Pre-vascular and retrotracheal nodes 3a: Prevascular - On the right upper border: apex of chest lower border: level of carina anterior border: posterior aspect of sternum posterior border: anterior border of superior vena cava 3a: Prevascular - On the left upper border: apex of chest lower border: level of carina anterior border: posterior aspect of sternum posterior border: left carotid artery 3p: Retrotracheal upper border: apex of chest lower border: carina	#7 Subcarinal nodes upper border: the carina of the trachea lower border: the upper border of the lower lobe bronchus on the left; the lower border of the bronchus intermedius on right
#4 (Left/Right) Lower paratracheal nodes 4R: includes right paratracheal nodes, and pretracheal nodes extending to the left lateral border of trachea upper border: intersection of caudal margin of innominate vein with the trachea lower border: lower border of azygos vein 4L: includes nodes to the left of the left lateral border of the trachea, medial to the ligamentum arteriosum upper border: upper margin of the aortic arch lower border: upper rim of the left main pulmonary artery	#8 (Left/Right) Para-esophageal nodes (below carina) Nodes lying adjacent to the wall of the esophagus and to the right or left of the midline, excluding subcarinal nodes upper border: the upper border of the lower lobe bronchus on the left; the lower border of the bronchus intermedius on right lower border: the diaphragm
#9 (Left/Right) Pulmonary ligament nodes Nodes lying within the pulmonary ligament upper border: the inferior pulmonary vein lower border: the diaphragm	#10 (Left/Right) Hilar nodes Includes nodes immediately adjacent to the mainstem bronchus and hilar vessels including the proximal portions of the pulmonary veins and main pulmonary artery upper border: the lower rim of the azygos vein on the right; upper rim of the pulmonary artery on the left lower border: interlobar region bilaterally
#11 Interlobar nodes Between the origin of the lobar bronchi *#11s: between the upper lobe bronchus and bronchus intermedius on the right *#11i: between the middle and lower lobe bronchi on the right	#12 Lobar nodes Adjacent to the lobar bronchi
#13 Segmental nodes Adjacent to the segmental bronchi	#14 Sub-segmental nodes Adjacent to the subsegmental bronchi

Fig. 4 a-c. Nodal metastasis in a 78-year-old man with non-small-cell lung cancer. **a** Chest radiograph shows a poorly margined large left lower lobe mass (arrowheads). **b** Chest computed tomography (CT) shows a normal-sized (short-axis diameter 1 cm) right lower paratracheal lymph node and slightly enlarged left lower paratracheal node (asterisks). **c** Fused positron emission tomography CT (PET-CT) reveals increased [^{18}F]fluoro-2-deoxy-D-glucose (FDG) uptake in the paratracheal nodes. Mediastinoscopy confirmed nodal metastasis. Note that because N3 (contralateral mediastinal) nodal metastasis is nonresectable, the patient was treated palliatively



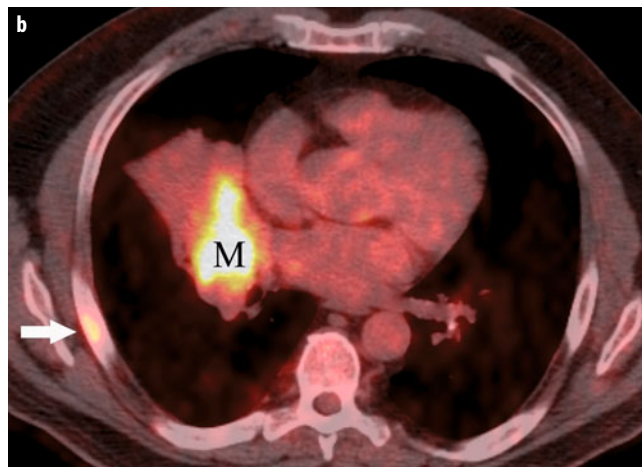


Fig. 5 a, b. Asymptomatic bone metastases in a 56-year-old man with non-small-cell lung cancer. **a** Whole-body positron emission tomography (PET) maximum intensity image shows increased [^{18}F]fluoro-2-deoxy-D-glucose (FDG) uptake in the right lung mass (M) and focal increased FDG uptake in bilateral rib metastases (arrows). **b** Fused PET-CT shows middle lobe malignancy (M) and distal obstructive atelectasis and right rib metastasis (arrow)

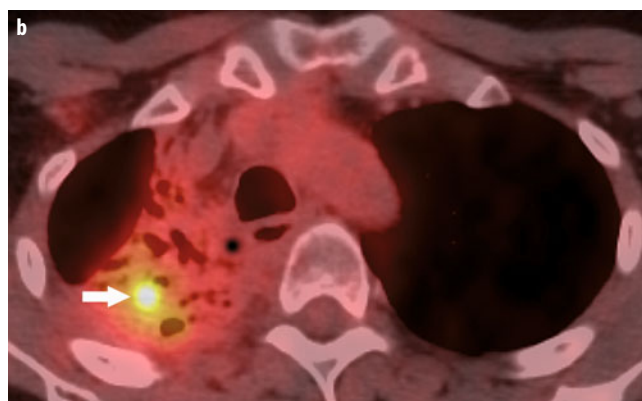
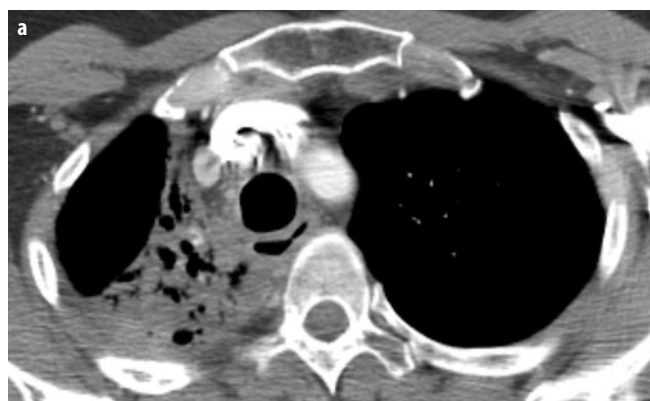


Fig. 6 a, b. Recurrence of non-small-cell lung cancer in a 50-year-old woman 11 months after chemoradiation therapy. **a** Chest computed tomography (CT) shows atelectatic and consolidative opacities due to radiation-induced lung injury. **b** Fused positron emission tomography CT (PET-CT) shows increased [^{18}F]fluoro-2-deoxy-D-glucose (FDG) focal increased FDG uptake (arrow) in radiation fibrosis consistent with recurrent malignancy

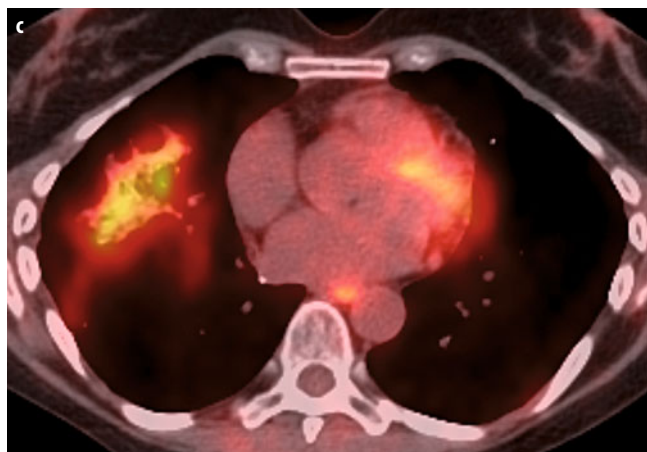


Fig. 7 a-c. False-positive uptake of [^{18}F]fluoro-2-deoxy-D-glucose (FDG) in a 56-year-old woman with non-small-cell lung cancer treated with stereotactic body radiation. **a** Chest computed tomography (CT) shows a small right lung nodule (*arrow*). **b** Chest CT component of positron emission tomography (PET-CT) 12 weeks after radiation shows focal consolidation in the right lung due to radiation-induced lung injury. **c** Fused PET-CT reveals diffuse increased FDG uptake in the right lung consolidation. Note radiation-induced inflammatory changes can result in false positive FDG uptake

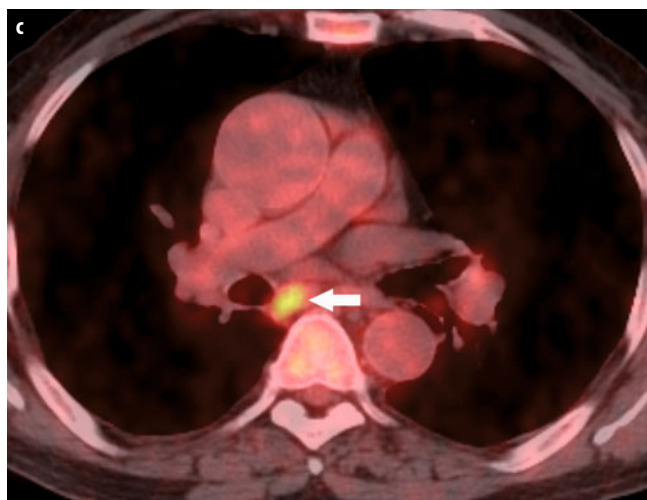


Fig. 8 a-c. A 68-year-old man with a right lower lobe non-small-cell lung cancer and ipsilateral mediastinal (N2) nodal metastases being evaluated for curative surgical resection after neoadjuvant chemotherapy (*arrows; asterisk*). **a** Whole-body positron emission tomography (PET) maximum intensity image prior to neoadjuvant chemotherapy shows increased [^{18}F]fluoro-2-deoxy-D-glucose (FDG) uptake in the right lung mass (*large arrow*) and focal increased FDG uptake in a subcarinal node (*small arrow*). **b** Whole-body PET maximum intensity image after neoadjuvant therapy shows partial metabolic response. There is persistent increased FDG uptake in the right lung malignancy (*large arrow*) and subcarinal node (*small arrow*), suspicious for residual, viable malignancy. **c** Fused PET-CT confirms persistent increased FDG uptake in subcarinal node (*arrow*). Biopsy confirmed residual nodal metastatic disease. Note that if N2 nodes have persistently high FDG uptake after neoadjuvant therapy, patients should not be precluded from resection without pathologic confirmation of metastatic disease

Lung Scintigraphy in Pulmonary Embolism

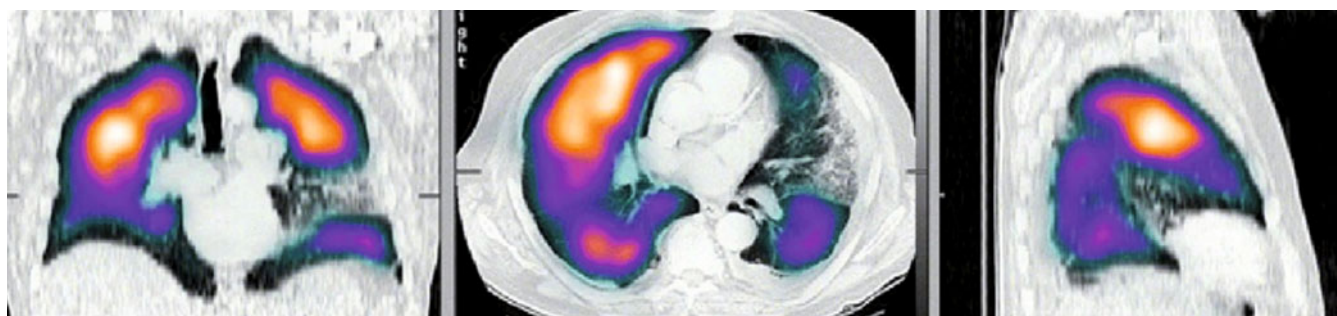


Fig. 1. Coronal, transaxial and sagittal fused single photon emission computed tomography slices from a lung perfusion scan (*left, middle and right panels, respectively*). The images demonstrate that reduced perfusion in the lingula corresponds to a lung area with extensive parenchymal consolidation, thus excluding acute pulmonary embolism as the cause of the perfusion defect (reproduced from [24])

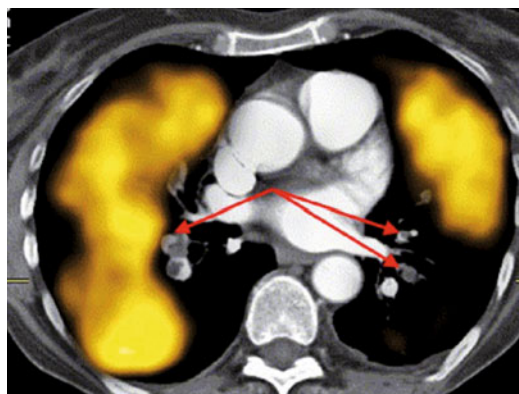


Fig. 2. Postacquisition coregistered multidetector-row computed tomography pulmonary angiography (MDCT-PA) and lung perfusion single photon emission computed tomography (SPECT, transaxial slice). The extensive perfusion defects in the SPECT component correspond to the presence of proximal bilateral filling defects (emboli, some of which are indicated by *red arrows*) in the MDCT-PA component (reproduced from [24])

PET Imaging in Cardiovascular Disease



Fig. 1. Comprehensive summary of quantitative positron emission tomography results from a (^{13}N) -ammonia rest-stress study in a female patient with three-vessel disease resulting in significantly reduced flow reserve values and transient ischemic dilation

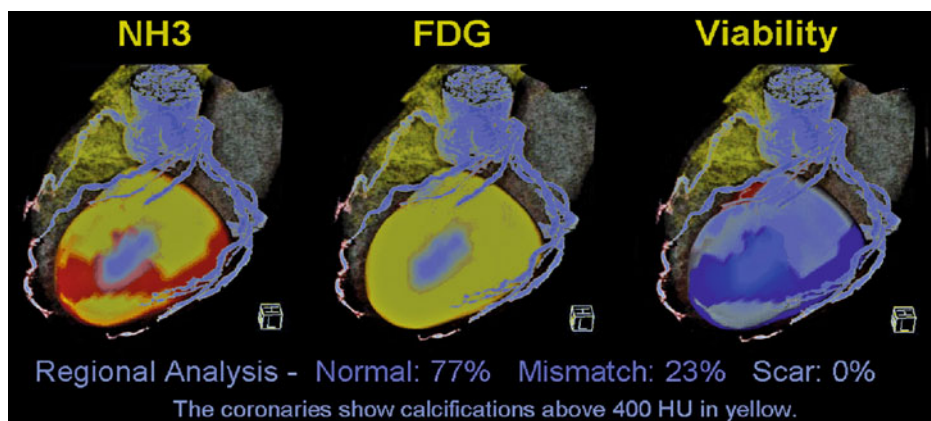


Fig. 2. Viability assessment with positron emission tomography perfusion and metabolism data mapped onto the endocardial surface of a computed tomography angiography study and displayed simultaneously with the segmented coronary tree. In addition to relative or absolute perfusion data, more complex information from protocols such as viability studies can be visualized as well in the junction with the coronary tree

Pulmonary Infections in Children

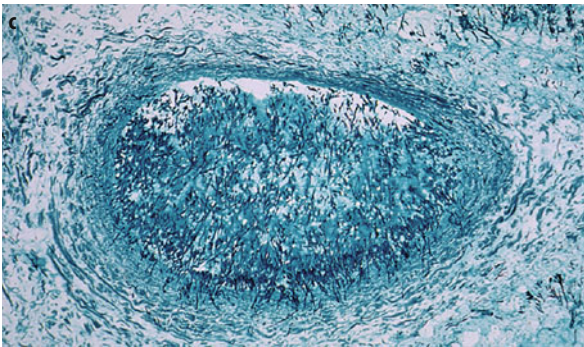


Fig. 4 a-c. Angioinvasive pulmonary aspergillosis post bone marrow transplant. **a** Contrast-enhanced axial computed tomography (CT) image of the thorax (lung window) demonstrates multiple perilesional nodular ground-glass haloes. **b** Another slice of the same scan shows a lesional cavitation in the lung with the air-crescent sign. **c** Macroscopic histological excision specimen confirms aspergillus cavity

Microcalcifications of the Breast: An Approach to Radiologic Classification

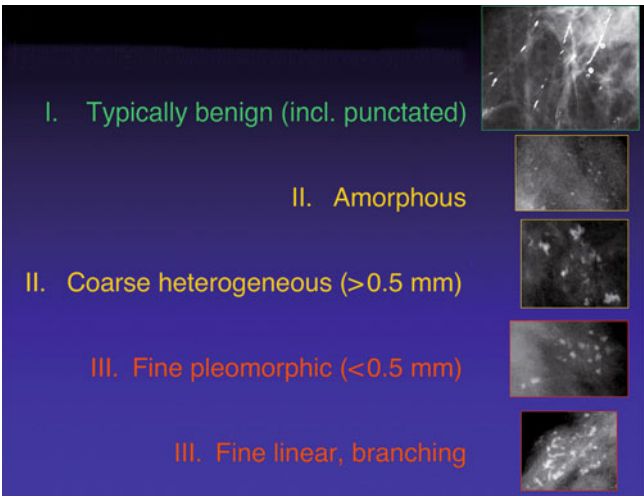


Fig. 1. Microcalcifications: from benign to malignant morphology. *Green frame:* microcalcifications with typically benign morphology (I); *orange frame:* microcalcifications with indeterminant morphology (II); *red frame:* microcalcifications with typically malignant morphology (III)

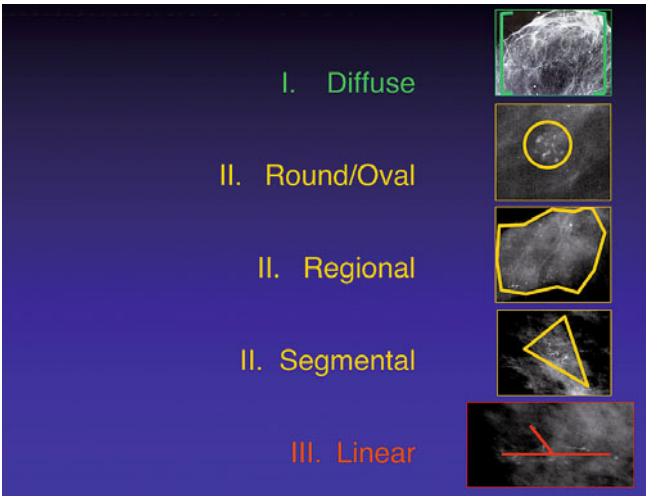


Fig. 2. Microcalcifications: from benign to malignant distribution. *Green frame:* microcalcifications with benign distribution (I); *orange frame:* microcalcifications with indeterminant distribution (II); *red frame:* microcalcifications with typically malignant distribution (III)

Distribution	Morphology		
	Typically benign	Indifferent	Typically malignant
Disseminated	2	3	4B
Round/oval	3	4A	4C
Regional	4A	4B	4C
Segmental	4A	4C	4C
Linear/branching	4B	4C	5
MODIFIATORS			
- Number - Additional findings - Location - Follow up - Risk			

Fig. 3. The Microcalcification matrix serves as a guide for classifying grouped microcalcifications according to morphology and distribution, additionally considering modification aspects (modifiers) [13, 14]

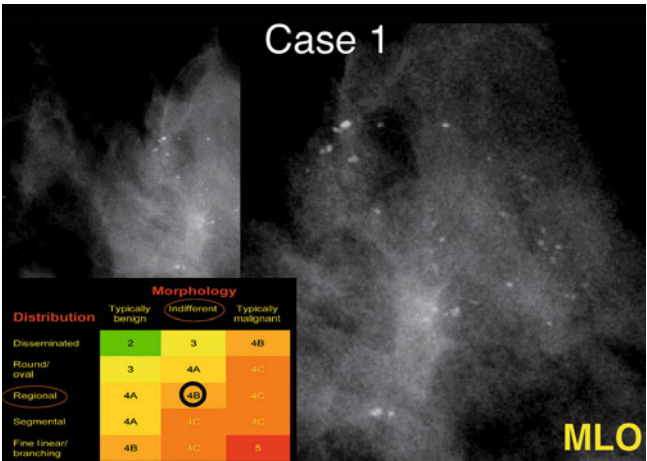


Fig. 4. Case 1: Indifferent type of microcalcifications with regional distribution (BI-RADS, 4B). Histology: fibrocystic changes, sclerosing adenosis, usual ductal hyperplasia. *MLO*, mediolateral oblique view

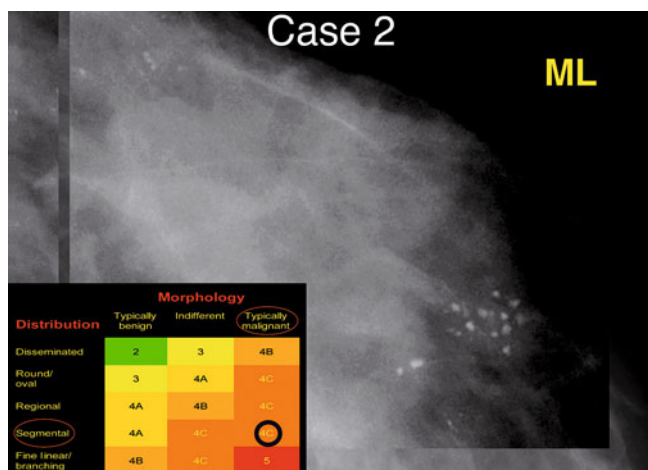


Fig. 5. Case 2: Typically malignant type of microcalcifications with segmental distribution (BI-RADS, 4C). Histology: invasive ductal cancer. *ML*, mediolateral view

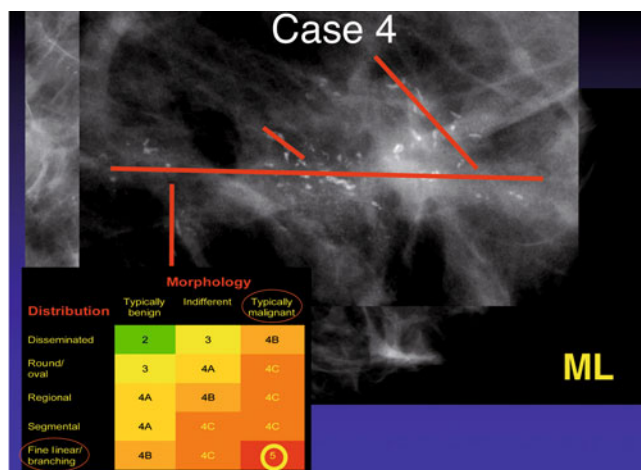


Fig. 7. Case 4: Typically malignant type of microcalcifications with linear and branching distribution (BI-RADS, 5). Histology: ductal carcinoma in situ (high grade). *ML*, mediolateral view

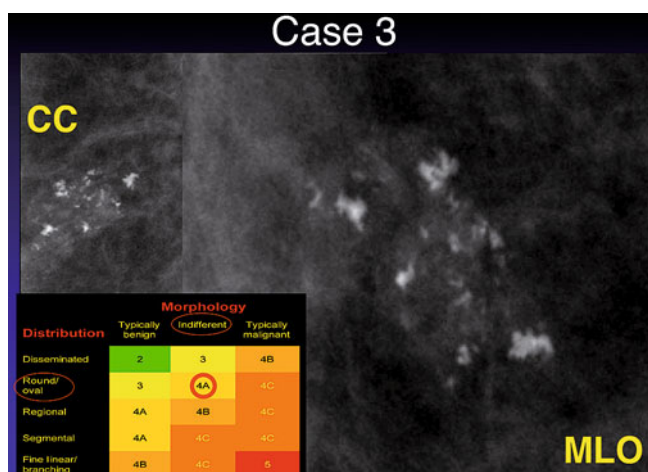


Fig. 6. Case 3: Indifferent (including coarse heterogeneous) type of microcalcifications with round/oval distribution (BI-RADS, 4A). Histology: fibroadenoma, fibrocystic changes. *CC*, craniocaudal view; *MLO*, mediolateral oblique view

Ultrasound of the Breast, Including Interventions: An Update

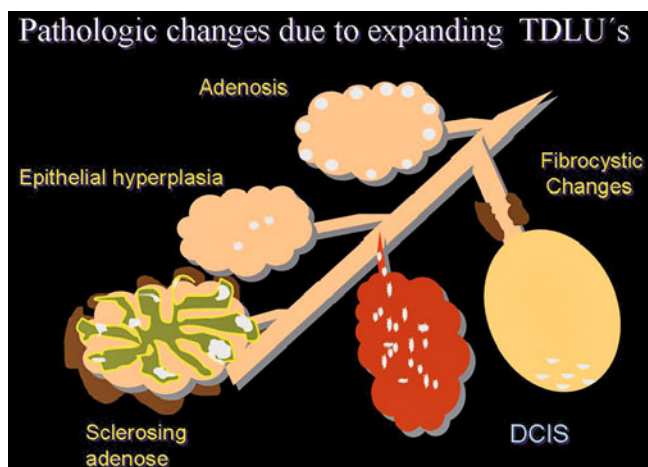


Fig. 1. Pathologic changes within dilated terminal duct lobular units (TDLUs). Benign and malignant proliferative or fibrocystic changes can result in a distension of the TDLU. Calcifications can occur within the TDLU and will form a cluster

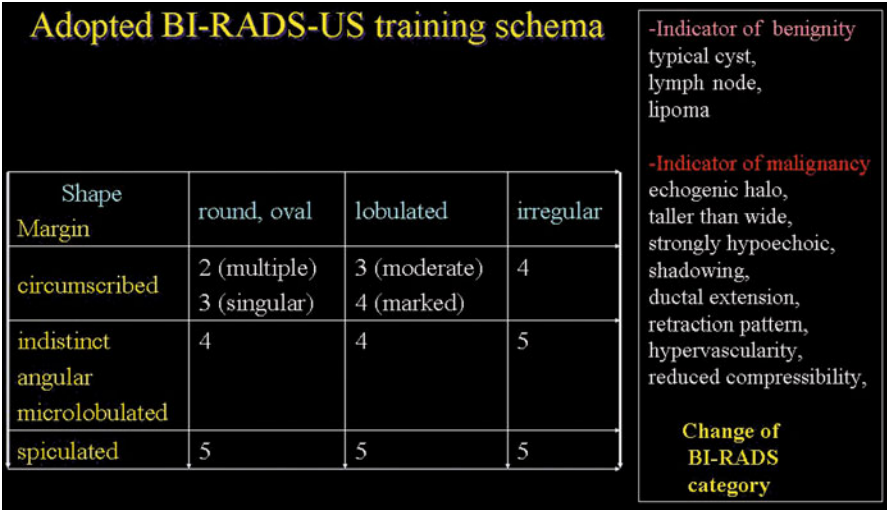


Fig. 2. Adopted Breast Imaging Reporting and Data System Ultrasound (BI-RADS-US) training schema. BI-RADS characterisation of a mass can be taught using basic descriptors and associated findings that upgrade or downgrade the overall assessment category. The teaching schema aims to support beginners in the field of breast diagnosis. This schema provides no scientific proof to be used in daily workup, as it can miss cancers

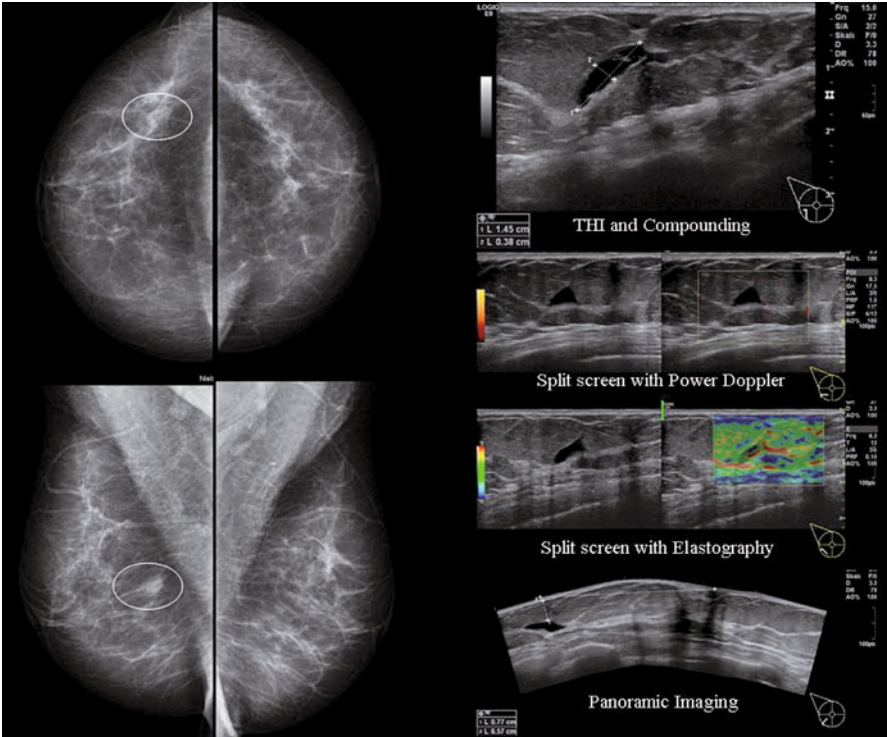


Fig. 3. Cyst. Mammography and advanced ultrasound applications in a nonpalpable, oval anechogenic lesion that is deformed and clings to straight septa under pressure. Histology: cyst. *THI*, tissue harmonic imaging; *circles* correspond to the deformed cyst in mammography

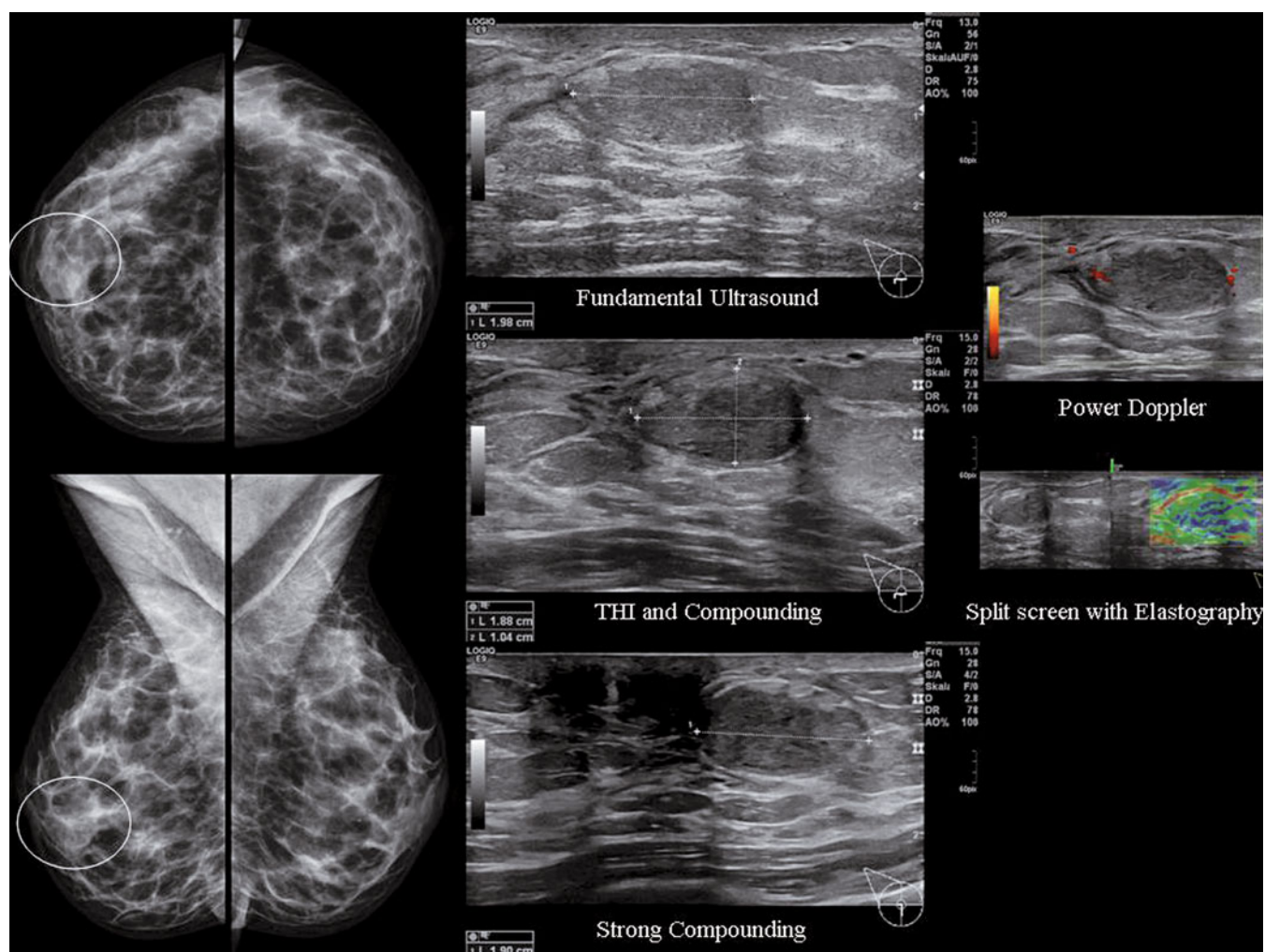


Fig. 4. Fibroadenoma. Mammography, fundamental and advanced ultrasound applications in a palpable oval isoechogenic lesions that has increased in size. Histology: fibroadenoma. *THI*, tissue harmonic imaging; *circles* correspond to the deformed cyst in mammography

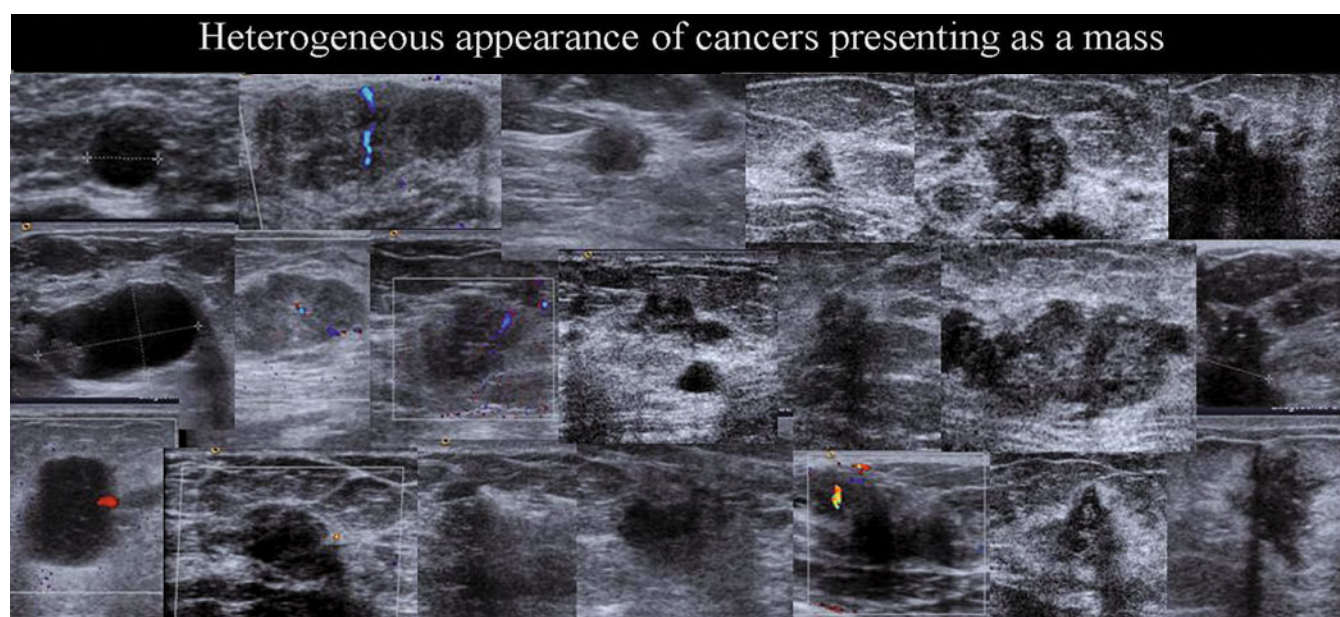


Fig. 6. Heterogeneous ultrasound appearance of invasive cancers. Stage T1c and T2 cancers show more typical signs of malignancy compared to smaller cancers. No single diagnostic descriptor can pick up all cancers

MRI of the Breast: Technique, Indications and BI-RADS Classification

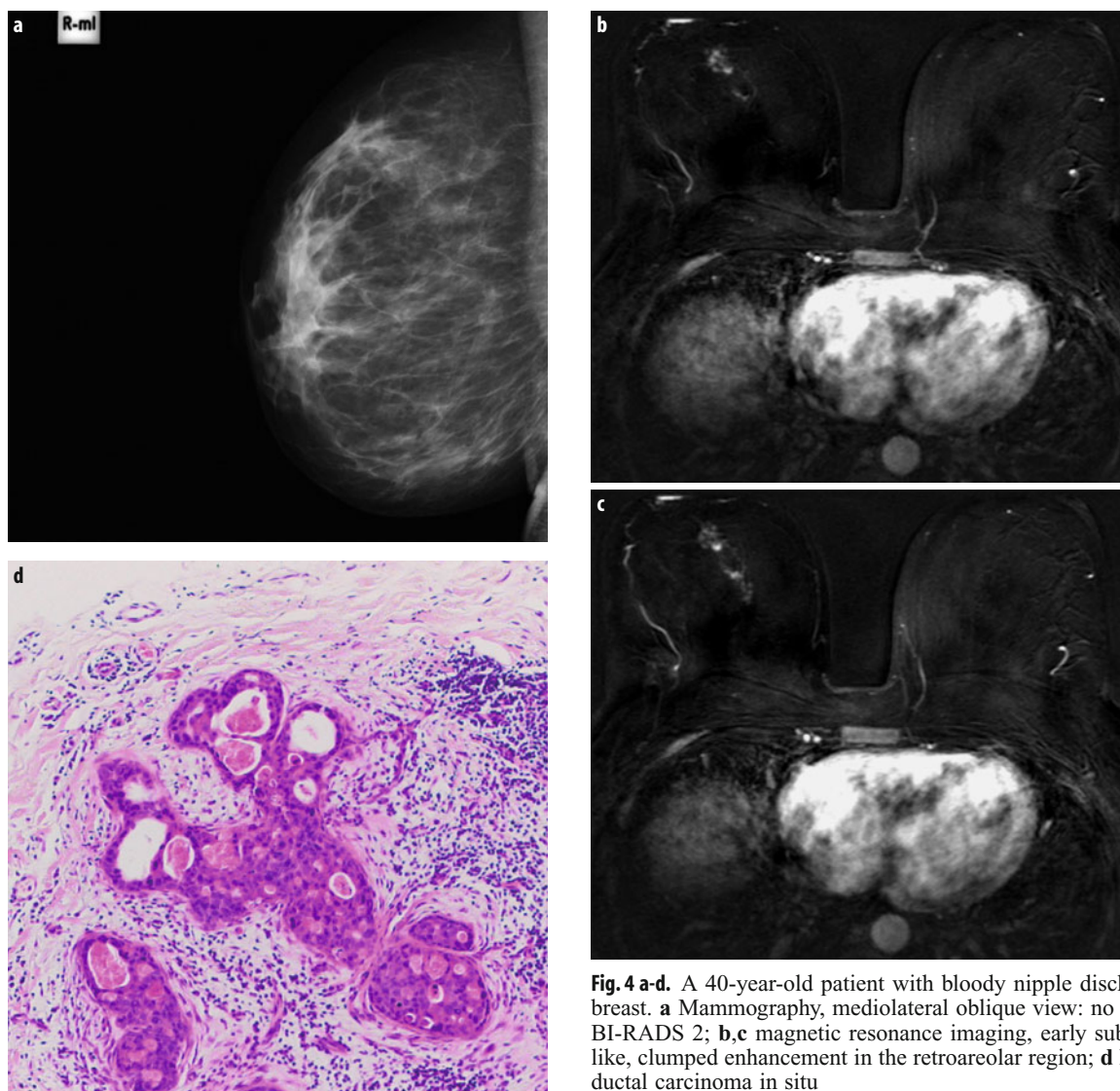


Fig. 4 a-d. A 40-year-old patient with bloody nipple discharge from the right breast. **a** Mammography, mediolateral oblique view: no pathologic findings, BI-RADS 2; **b,c** magnetic resonance imaging, early subtraction: non-mass-like, clumped enhancement in the retroareolar region; **d** histology confirmed ductal carcinoma in situ