MEDICAL RADIOLOGY

Radiation Oncology

L. W. Brady
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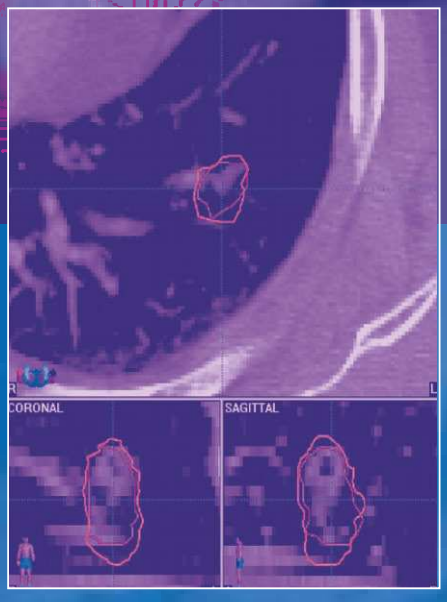
M. Molls

Advances in Radiation Oncology in Lung Cancer

B. Jeremić
Editor



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Branislav Jeremić (Ed.)

Advances in Radiation Oncology in Lung Cancer

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Foreword by

L. W. Brady, H.-P. Heilmann, and M. Molls

With 89 Figures in 133 Separate Illustrations, 50 in Color and 85 Tables

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Medical Radiology · Diagnostic Imaging and Radiation Oncology
Series Editors: A. L. Baert · L. W. Brady · H.-P. Heilmann · M. Molls · K. Sartor

Continuation of Handbuch der medizinischen Radiologie
Encyclopedia of Medical Radiology

Library of Congress Control Number: 2004106356

ISBN 3-540-00522-6 Springer Berlin Heidelberg New York

Springer is a part of Springer Science+Business Media

http//www.springeronline.com

Printed in Germany

Medical Editor: Dr. Ute Heilmann, Heidelberg
Desk Editor: Ursula N. Davis, Heidelberg
Production Editor: Kurt Teichmann, Mauer
Cover-Design and Typesetting: Verlagsservice Teichmann, Mauer

Printed on acid-free paper 21/3150xq – 5 4 3 2 1 0

This book is dedicated

To the memory of my late mother, Olga,
for initiating the spirit

To my father, Budimir,
for following a path of expression

To my wife, Aleksandra,
for endless love and sacrifice

To my daughter, Marta,
for making everything worthwhile

Foreword

The volume prepared by Dr. B. Jeremic represents a composite and detailed review of the advances in the management of patients with cancer of the lung. Cancer of the lung is one of the most common primary invasive malignancies seen in oncology practice. In the United States in 2004, 173,770 new cases are anticipated, which represents about 12% of all invasive cancers diagnosed during this time period. The advances in diagnostic technology have more truly identified local versus regional versus distant presentations with more cases being identified and diagnosed as having metastatic disease.

The advances in treatment regimens have had an important impact on survival, but there has been no major or dramatic improvement in long-term survival in cancer of the lung over the last 20 years in spite of more innovative treatment programs in radiation oncology, more innovative treatment programs in medical oncology, the development of new drugs, as well as the refinement of surgical techniques in terms of management.

This volume clearly emphasizes the molecular biology and genetics of lung cancer, the impact of angiogenesis in lung cancer, as well as contemporary issues in staging of lung cancer. Basic treatment considerations are developed with regards to lung cancer surgery, radiation therapy, chemotherapy, as well as combinations of surgery, radiation therapy, and chemotherapy. Strategies in non-small cell cancer are discussed in great length including radiation therapy alone, postoperative radiation therapy, as well as the potential for photodynamic therapy. In locally advanced non-small cell cancers of the lung, the impact of multimodal management is explored in detail and the case made for intraoperative electron beam radiotherapy. The indications for intraluminal brachytherapy programs are also discussed. The treatment of small cell lung cancer is dealt with emphasis on limited disease as well as on the role of prophylactic cranial irradiation.

The volume covers the management of recurrent lung cancer, management in elderly patients, and the advances in supportive and palliative care for lung cancer patients while also considering the toxicities of the various treatment regimens being employed. Future strategies in the management of lung cancer are dealt with in detail, pointing the way toward new and innovative programs in practical management. The volume represents a hallmark statement of the present status of the management of lung cancer.

Philadelphia — Luther W. Brady
Hamburg — Hans-Peter Heilmann
Munich — Michael Molls

Preface

If you look at the map of the world and check the incidence rates of cancer, you will find lung cancer as one of the major health problems worldwide. This is irrespective of sex and age, health care systems and current media reports. It is simply a fact that we sometimes forget, but it always comes again as a reminder with every new patient worldwide. This burden is present for decades and although there seems to be stagnation in males, plateau is not reached in females yet. Even then, we would still have to deal with thousands of patients suffering from the deadly disease.

And we deal with it with radiation therapy, a treatment modality being now older than one-hundred years. During that period we have learnt how to fractionate the dose and observe the effects both on tumors and normal tissues. We have also learnt how to combine radiation therapy with other treatment modalities. With the time, we became increasingly capable of documenting dose distribution and to build on computerised-driven technologies to image, verify and record. We also became capable of concentrating on progressively smaller and smaller constituents; from the whole body to organs and tissues and from them to cells and molecules. We use radiation biology and molecular oncology to provide necessary framework for the science of radiation oncology in lung cancer.

And this book is about it; what had been done and what is going on. But much more than that, it is a book of what we have learnt from the past and how successfully we should incorporate it in our future endeavours, all having the same aim, better radiation oncology of lung cancer patients.

I feel privileged of having a distinguished faculty joining me on this task. My dear colleagues who have devoted their professional lives to the fight of lung cancer have made substantial contribution to this field in recent decades. Jointly we have built and steamed towards the same: better understanding of biology and technology in radiation oncology of lung cancer, ultimately ending up in a combination of these two which would lead us towards better treatment for our patients.

I also feel I should thank all of my former and current colleagues with whom I have collaborated during last two decades in sometimes distant, but beautiful places. Their dedication to the cause and timeless efforts made my professional life interesting and rewarding, always opening up new doors of cancer research.

I would also like to express my thanks to the Alexander von Humboldt Foundation, Bonn for support since 1998 as well as to Bund deer Freunde of the Technical University Munich, Klinikum rechts der Isar, Munich for support in the year 2002-2003. Special thanks to Ms. Ursula Davis, Mr. Kurt Teichmann and Ms. Chrstine Schaeffer for their kind and patient, yet effective management of the whole process of preparing the book, without whom this book would not have such fate, I am sure.

Munich

Branislav Jeremić

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1.1 Molecular Biology and Genetics of Lung Cancer

Neil E. Martin, Stephen M. Hahn, and W. Gillies McKenna

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1.1.1 Introduction

Lung cancer has come to be known as a genetic disease characterized by numerous molecular abnormalities occurring in a stepwise fashion. While a full understanding of these molecular changes and their interactions remains a formidable challenge, extensive research has produced a useful foundation upon which to build knowledge of both the disease and potential therapies. A framework has been proposed by Hanahan and Weinberg (2000) that functionally categorizes the molecular defects into the following "hallmarks of cancer": (a) self-sufficiency in growth signals, (b) insensitivity to growth-inhibitory signals, (c) evasion of programmed cell death, (d) limitless replicative potential, (e) sustained angiogenesis, and (f) tissue invasion and metastasis. This framework will be used to organize the material presented in this chapter.

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1.1.2 Basics of Genetics and Molecular Biology

Understanding oncology requires an integrated knowledge of the basics of molecular biology and genetics. While a general overview is provided here, more detailed descriptions should be sought in genetics textbooks. The central dogma of molecular biology holds that cellular genetic information flows from DNA which undergoes replication, to RNA by the process of transcription and finally to proteins by the process of translation (Crick 1958). All of these steps are highly coordinated into a sequence of events known as the cell cycle. Of importance in lung cancer are alterations in the structure and transcription of DNA and subsequent disruption of critical processes associated with the cell cycle.

DNA is a linear polymer of the four bases adenine (A), guanine (G), cytosine (C), and thymine (T) which define the genetic code. These bases, which differ in their ring structure, are attached to an invariant backbone of deoxyribose sugars connected by phosphodiester bonds. Two strands of DNA hybridize to form a double helix through hydrogen bonding between bases, A to T and G to C (Watson and Crick 1953). The double stranded DNA associates with accessory proteins such as histones which package the long polymer into a stable form called chromatin (Laskey and Earnshaw 1980). For the processes of replication and transcription to take place, the DNA must first be uncoiled from the histones to allow the appropriate molecular machinery to bind.

Genes, the most basic unit of inheritance, are coded by DNA. The linear sequence of the bases, in sets of

three, define each amino acid to be translated and hence, the structure of proteins. While there are over three billion base pairs in the human genome, only approximately 1%–2% are coding, resulting in an estimated 30,000–40,000 genes (Lander et al. 2001). The structure of genes can be simplified conceptually into two components, a coding region and a promoter region. The promoter is a section of DNA upstream of the coding region which, in concert with other "enhancer" and "silencing" regions of DNA and numerous associated proteins, controls gene transcription. This regulation depends on a number of factors including cell type, extracellular signals, and stresses.

A particularly important method by which gene transcription is regulated in cancer is methylation of the promoter region leading to gene silencing (Herman and Baylin 2003). In this process, termed "epigenetics", a cytosine that precedes a guanosine (CpG dinucleotide) in the DNA sequence is methylated. While this can be a normal process utilized by the cell to inhibit transcription, abnormal levels of methyl cytosines have been observed in lung cancer cells. This aberrant transcriptional inhibition appears to play a significant role in disruption of tumor suppressor genes and can act as one or both hits in Knudson's (1971) two-hit hypothesis. The actual inhibition of transcription occurs as a result of the complex interplay of histones and proteins binding the methyl cytosines.

Another mechanism of gene alteration is inherited or de novo mutations in the DNA code. DNA is damaged from a variety of sources including inherent instability, exposure to environmental and toxic stresses, and a natural limit to its replicative accuracy, necessitating repair mechanisms to maintain genetic integrity. The responsible DNA repair genes can be altered early in carcinogenesis leading to a greater propensity for mutations (Ronen and Glickman 2001). Chromosomal rearrangements also alter genes and are frequently seen in lung cancers. This process involves the exchange of DNA from one chromosome to another and can lead to abnormal gene activation or aberrant coding regions.

A target of many of the genetic changes noted in lung cancer is the cell cycle. The cell cycle is the discrete states through which cells must pass for replication and is normally tightly regulated from external and internal signaling. Lung cancer cells frequently acquire genetic changes which disrupt the normal balance of positive and negative signals resulting in a variety of growth abnormalities. This deregulation represents a fundamental change from normal cells.

The Hanahan and Weinberg framework is helpful in understanding how the current body of knowledge regarding the molecular biology and genetics of lung cancer fit into the observed disease process. Many of the abnormalities described below are outlined in Fig. 1.1.1 and a summary of the different expression levels between lung cancer types is provided in Table 1.1.1.

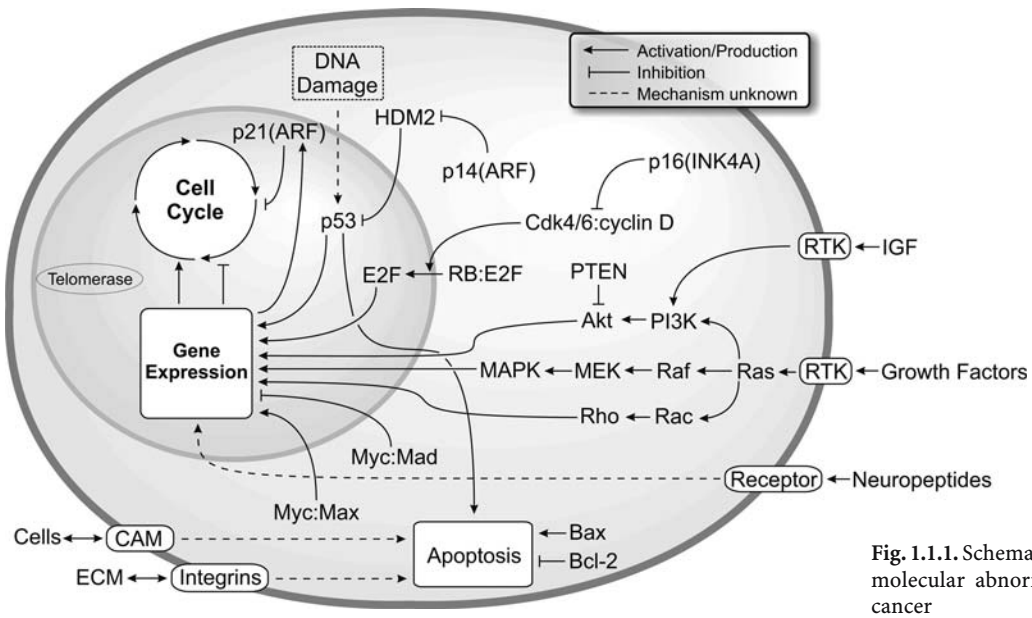

Fig. 1.1.1. Schematic model of the molecular abnormalities in lung cancer

Table 1.1.1. Molecular Abnormalities in Lung Cancer

	Frequency of Abnormality (%)[a]	
	NSCLC	SCLC
Growth Signals		
Ras	25	<1
Akt	70–90	65
Myc	20–60	20–30
EGFR	50	0–50
HER2/neu	30	30
c-Kit	30–40	50
Neuropeptides	~50	~50
IGF	~90	~90
Tumor Suppressor Genes		
RB	15–30	>90
p16(INK4A) inactivation	50–70	0–20
3p deletions	70	90
FHIT inactivation	40–70	70
RASSF1A silencing	50	90
Apoptosis		
p53	40–50	60–75
Bcl-2	20–35	71
Replicative Potential		
Telomerase	80–100	80–100
Angiogenesis		
VEGF	75	75
COX-2	>70	not reported
Metastasis		
N-CAM, non-adhesive	not reported	90
Laminin-5 inactivation	20–60	65–85

[a] See text for selected references

1.1.3 Self-Sufficient Growth Signaling

In cancer, the tight growth control of normal cells is lost, allowing for continuous proliferation. The regular homeostasis is disrupted as cells acquire the ability to both produce their own growth factors and increase their sensitivity to exogenous ones. Key factors in these paracrine and autocrine loops are encoded by proto-oncogenes, many of which are activated in lung cancer. Proto-oncogenes encode proteins important for normal cell growth and are called oncogenes only after becoming abnormally activated. This activation, usually a result of point mutations or chromosomal translocations, leads to gain-of-function effects for the cell. Several well studied families of oncogenes have been identified in lung cancer including *RAS, MYC,* and *ERB-B.*

Ras: The *RAS* family of oncogenes, including H-, K-, and N-*RAS*, encode a 21-kDa protein acting at the cytoplasmic cell membrane as a guanosine-associated switch. The protein is associated with receptor tyrosine kinases (RTKs) and plays a pivotal role in transducing extracellular signals to numerous growth signaling pathways. Ras is activated by binding guanosine triphosphate (GTP), a process accomplished by associated proteins; hydrolysis of this GTP to guanosine diphosphate inactivates Ras. Once active, Ras activates multiple effector molecules including components of the following pathways: Raf-MAPK, PI3K-Akt, and Rac-Rho (Shields et al. 2000).

K-*RAS* is mutated in 25% of non-small cell lung cancer (NSCLC), with rates highest in adenocarcinoma at 30%–50%, and lowest in squamous cell at 0%–5% (Graziano et al. 1999). The mutations in K-*RAS* are usually in codons 12, 13, and 61 and have been associated with frequent G-T transformations linked to polycyclic hydrocarbons found in cigarette smoke (Rodenhuis and Slebos 1992). While a common occurrence in NSCLC, mutations in *RAS* are not seen in small cell lung cancer (SCLC) (Wistuba et al. 2001). Although results have been mixed, K-*RAS* mutational status appears to be related to prognosis in NSCLC. Early studies found shortened disease-free- and overall survival for patients with K-*RAS* point mutations (Slebos et al. 1990). Subsequent studies did not consistently find this relationship but on meta-analysis an increased risk of worsened 2-year survival was noted (Huncharek et al. 1999). A possible explanation for this relationship is that mutated *RAS* appears to confer treatment resistance to cancer cells. Its role in chemotherapeutic resistance is unclear but there is a growing body of evidence showing the importance of the Ras pathway in radiation resistance. In vitro studies have demonstrated increased radiation resistance in cell lines expressing mutant *RAS* (Sklar 1988). Therapeutics have been developed which inhibit the activation of Ras and lead to reversal of radiation resistance in studies in vivo (Cohen-Jonathan et al. 2000). The mechanism for the radiation resistance is still unclear but may relate to activation of signals downstream of Ras such as phosphoinositide 3-kinase (PI3K) or Rho (Lebowitz and Prendergast 1998).

Akt: Akt is a protein kinase downstream of PI3K in a growth signaling pathway. It is activated by many growth signals including insulin-like growth factor (IGF) and Ras activation. Once activated, Akt plays a role in progression through the cell cycle and cell survival. Akt is inactivated by PTEN, a protein frequently mutated or epigenetically inhibited in lung cancer (Soria et al. 2002). Akt is constitutively activated at high rates in both NSCLC (70%–90%) and

SCLC (65%) and is associated with chemotherapeutic and radiation resistance in SCLC cell lines (Kraus et al. 2002).

Myc: The *MYC* oncogenes, c-, N-, and L-, encode DNA-binding proteins associated with transcriptional regulation. The activity of the Myc protein is regulated through homo- and heterodimerization (Henriksson and Luscher 1996). When Myc is bound to the protein Max for example, it activates transcription of cell cycle checkpoint proteins such as Cdc25A which promote cell replication (Santoni-Rugiu et al. 2000). Similarly, inhibition of Myc occurs through heterodimerization with proteins such as Mad.

MYC activation occurs through dysregulated expression of the normal gene (Krystal et al. 1988). Overexpression is seen in approximately 20%–60% of NSCLC and 30% of SCLC (Gazzeri et al. 1994). In SCLC, Myc overexpression has been linked to cell lines treated with chemotherapeutics suggesting a response mechanism. Additionally, overexpression of *MYC* is associated with worsened prognosis in SCLC but not NSCLC. In vitro studies indicate that while v-Myc expression alone does not affect radiation resistance, when coexpressed with H-Ras, there is synergistically increased radioresistance compared to Ras expression alone (McKenna et al. 1990).

Receptor tyrosine kinases: The *ERB-B* family of transmembrane RTKs include epidermal growth factor receptor (*EGFR* or *ERB-B1*) and *HER2/neu* (*ERB-B2*). When bound to ligands, these proteins homo- or heterodimerize, becoming activated. The downstream effectors of the receptors include Ras and mitogen-activated protein kinase (MAPK) leading to various processes including cell growth and proliferation. Ligands are produced exogenously as well as from the cancer cells themselves, creating self-activating loops.

Overexpression of EGFR is seen in 50% of NSCLC, with the highest rate (80%) noted in squamous cell. Higher expression appears to predict a slightly worsened survival for those with NSCLC (Meert et al. 2002). Increased expression of HER2/neu is seen in 30% of both NSCLC and SCLC and appears in both cases to predict worsened survival (Meert et al. 2003; Potti et al. 2002). The worsened prognosis may be a result of chemotherapeutic resistance but this is still unclear. EGFR is known to be an upstream regulator of the PI3K-Akt pathway, possibly through Ras, and thus may play a role in radioresistance (Gupta et al. 2002). Similarly, cells overexpressing HER2/neu have been shown to be radioresistant (Pietras et al. 1999).

Another RTK highly expressed (50%) in SCLC is c-Kit. This receptor is frequently coexpressed with its ligand, stem cell factor, leading to stimulated growth. As with EGFR and HER2/neu, c-Kit represents a potential target for therapy.

Other factors: Neuropeptides act as both neurotransmitters in the central nervous system and as endocrine factors in non-neurologic tissue. The family of bombesin-like peptides includes gastrin-releasing peptide (GRP) and neuromedin B (NMB). SCLC cells have been shown to synthesize and secrete these factors which function in a complex system of neuropeptide induced cell growth (Heasley 2001). Other growth factors such as IGF, found to be elevated in ~90% of NSCLC and SCLC, have been shown to play a role in carcinogenesis and are associated with an increased risk of acquiring lung cancer (Yu et al. 1999). Interestingly, overexpression of the IGF receptor has been shown to induce radiation resistance in vitro (Macaulay et al. 2001).

1.1.4 Insensitivity to Antigrowth Signals

The growth of normal cells is kept in check by antigrowth signals, many of which are encoded by tumor suppressor genes (TSGs). The loss of one allele either through inheritance or damage and the second through damage from mutation or epigenetics, leads to complete loss of function of these factors. When intact, many of the proteins encoded by these genes exert their control through regulation of the cell cycle. The ability to evade the inherent checkpoints of this system gives the cell the capacity to grow without inhibition. While important antigrowth pathways such as p16(INK4A)-RB have been studied in lung cancer, other TSGs and their roles are just beginning to be evaluated.

RB: The *RB1* gene located on chromosome 13q14.11 was identified initially in retinoblastoma but has been subsequently identified in many human cancers including lung. The RB protein plays a pivotal role in inhibiting G1/S transition via the E2F family of transcription factors. RB inhibits transcriptional activation by binding E2F. As the cell progresses from G1 to the S phase, RB becomes increasingly hyperphosphorylated in which state it disassociates from the E2F. Once unbound, the E2F can induce transcription of genes necessary for normal DNA synthesis. Cyclin D-dependent kinases (Cdks) control

phosphorylation of RB and are regulated by multiple factors including Myc and E2F (Beier et al. 2000).

RB1 was one of the first TSGs recognized in lung cancer and loss of RB function allows dysregulated advancement through the G1/S checkpoint. *RB1* is expressed abnormally in 15%–30% of NSCLC and >90% of SCLC but has not been associated with prognosis (Shimizu et al. 1994). The loss of function of this important factor can occur through chromosomal abnormalities, mutations, or inhibition of the required disassociation from E2F.

p16(INK4A): The protein p16(INK4A), encoded by the *CDKN2A* gene at 9p21, inhibits the Cdk4/6:cyclin D complex essential in RB phosphorylation. When inactivated, p16(INK4A) fails to inhibit E2F-induced transcription in cells with wild-type RB function. Its role in other cell cycle pathways, important when RB is absent, shows similar inhibitory functions (Kaye 2002). Absent p16(INK4A) expression has been found in 50%–70% of NSCLC but less frequently in SCLC (20%). The mechanisms for inactivation include mutations and hypermethylation of the promoter. When the data from *RB1* and p16(INK4A) are taken together, they suggests that RB inactivation occurs in both types of lung cancer, through genetic loss in SCLC and through p16(INK4A) loss in NSCLC. While studies have not found that RB plays a significant role in radiation resistance, expression of p16(INK4A) in vitro increased radiosensitivity in lung cancer cells (Gao et al. 2001).

3p deletions: For TSGs to play a role in carcinogenesis, both alleles must be disrupted. Identification of areas where one allele is already abnormal, termed loss of heterozygosity (LOH), is a technique used to identify potential TSGs. Detailed studies have identified the short arm of chromosome 3 (3p) as a frequent site of LOH in both SCLC (90%) and NSCLC (70%) (Wistuba et al. 2000).

The fragile histidine triad (*FHIT*) gene is located at 3p14.2 and may be a TSG important in lung cancer. While its exact role is still unclear, the FHIT protein appears to bind diadenosine nucleotides and dimerize to form an active complex. In a large study, 73% of NSCLC tumors were FHIT negative with highest rates in squamous cell. Similarly high rates of SCLC have FHIT mRNA abnormalities (Sozzi et al. 1996). Lack of FHIT expression is twice as likely in smokers compared to non-smokers and independently predicts worsened survival in NSCLC.

Another gene showing LOH on 3p is *RASSF1A* which encodes a Ras binding protein. It is epigenetically silenced in 90% of SCLS and 50% of NSCLC. In vitro studies have demonstrated that RASSF1A suppresses lung tumor growth and mutations in the gene reverse this suppression (Protopopov et al. 2002). Hypermethylation of CpG islands in the *RASSF1A* gene has been associated with decreased survival in the presence of mutated *RAS*. In addition to its possible role in Ras signaling pathways, RASSF1A has been shown to cause cell cycle arrest through the RB pathway.

Other genes suggested to be TSGs through LOH studies on 3p include: *BLU*, *FOXP1*, *DDR1*, and the *HYAL* family (Zabarovsky et al. 2002). The specific roles of many of these genes are still unclear but they may represent potential future targets of therapy.

1.1.5 Evasion of Programmed Cell Death

The process of programmed cell death, apoptosis, occurs in cells throughout the body in response to various signals. This stereotyped process involves a cascade of signals from cell surface receptors and internal monitoring processes to effector proteins which act on the mitochondria and nucleus to kill the cell. Signals that induce apoptosis include activation of oncogenes, DNA damage, absence of stroma–cell and cell–cell interactions, and hypoxia. Apoptosis is important in cancer because the tumor's rate of growth is determined not only by the constituent cells' ability to replicate but also the attrition rate of those same cells. In addition, the end result of many cancer therapies is apoptosis and treatment resistant cells have frequently developed mechanisms to evade this fate.

p53: p53 is a central factor in the cellular response to internal and external stresses in lung cancer (Robles et al. 2002). It exerts its effects through several mechanisms including transcriptional activation, interaction with other signaling pathways and DNA repair. The protein HDM2, which is under p53 transcriptional control, regulates p53 activity through degradation, creating an autoregulatory loop. Inhibition of HDM2 occurs via the phosphorylation of p53 by stress kinases or the binding of HDM2 by p14(ARF), a protein upregulated by oncogenes such as *MYC*, *RAS*, and E2F. The stress kinases respond to DNA damage from ionizing radiation and other carcinogens. Once activated, p53 homotetramerizes, allowing transcriptional activation of genes involved in apoptosis, cell cycle arrest, and DNA repair. In addition to inducing apoptosis through activation of genes such as *BAX*, p53 can interact directly with DNA binding proteins

which themselves induce cell death. DNA repair is similarly controlled by expression of several genes, *GADD45* and *p48(DDB2)* among others, or direct interaction with existing proteins. Finally, cell cycle arrest at G1 occurs as a result of p53 inducing transcription of the *p21(ARF)* gene which encodes a cyclin inhibitory protein. Through these interrelated pathways, *TP53* acts as a TSG responding appropriately to various signals by repair, halting replication, or apoptosis.

TP53 is mutated in both SCLS and NSCLC. The majority of mutations are missense in the DNA-binding region of the protein. Because many of the mutations are G-T transformations which have been linked to tobacco smoke, smoking is believed to play a causative role. The fact that the more smoking-related cancers, squamous cell carcinoma and SCLC, have a significantly higher rate of *TP53* mutation, 50% and 60%–75%, respectively, compared to adenocarcinoma (35%), supports this hypothesis (Olivier et al. 2002). p53 overexpression or mutation has been associated with worsened survival in NSCLC patients (Mitsudomi et al. 2000). The mechanism for this remains unclear as p53's role in chemo- and radioresistance is still being evaluated. In vitro studies of lung cancer cells have shown that mutations in specific regions of p53 can lead to radioresistance, but results of similar studies have varied (Bergqvist et al. 2003).

BCL-2: The *BCL-2* family of genes includes both pro- and antiapoptotic factors. Bcl-2 itself inhibits apoptosis and prolongs cell survival while Bax, Bad, and Bak among others, enhance the death signals. The exact mechanism of their action remains unknown but regulation occurs through homo- and heterodimerization of family members. The ratio of proapoptotic to antiapoptotic signals determines how the cell responds to apoptotic signals. Bcl-2 has been localized to the membranes of several cell organelles including mitochondria where it is believed to play its regulatory role in apoptosis (Kroemer 1997).

The *BCL-2* gene is overexpressed in the majority of SCLCs (71%) and to a lesser extent in NSCLC (35%). The rate of upregulation varies from 32% in squamous cell carcinoma to 61% in adenocarcinoma (Martin et al. 2003). The role of Bcl-2 overexpression in prognosis for lung cancer is unclear but meta-analysis has found an association with worsened survival in NSCLC but no association in SCLC (Martin et al. 2003). Resistance to both chemo- and radiotherapy has been noted in cells overexpressing Bcl-2, an observation which is believed to be a result of decreased apoptotic response to the given therapy.

1.1.6 Limitless Replicative Potential

Normal cells are preprogrammed to be limited to a finite number of possible replicative cycles independent of the intricate signaling pathways controlling growth and apoptosis. The loss of 50–100 bp of DNA from the chromosomal ends, the telomere, during each replication, is the mechanism for this barrier. Progressive replications lead eventually to the loss of protective segments of telomeric DNA causing genetic instability and cell death (Wong and Collins 2003). Malignant cells have almost invariantly become immortalized through mechanisms which add DNA to the telomeric regions either with overexpression of the enzyme telomerase or increased chromosomal exchange to this region.

Between 80% and 100% of both SCLC and NSCLC express telomerase (Hiyama et al. 1995). Although a frequent occurrence in lung cancer, telomerase expression does not appear to independently predict prognosis. Inhibition of the enzyme activity has been associated with enhanced chemotherapy-induced apoptosis in lung cancer cell lines (Misawa et al. 2002).

1.1.7 Sustained Angiogenesis

While this topic is covered in depth in Chap. 1.2, a brief overview will be presented here. Most cells require the presence of a capillary within 100 μm for requisite oxygen and nutritional support. The normally tightly regulated process of angiogenesis is necessarily disrupted in lung cancer allowing for unfettered growth of tumors. This occurs by mechanisms including overexpression of angiogenic stimuli such as vascular endothelial growth factor (VEGF) and cyclooxygenase-2 (COX-2), as well as matrix breakdown enzymes including the metalloproteinases (MMPs). VEGF is expressed in greater than 75% of both SCLC and NSCLC and appears to portend a worsened survival in both (Lantuejoul et al. 1998; Lucchi et al. 2002). COX-2 is overexpressed in over 70% of NSCLC but not in SCLC (Wolff et al. 1998). Inhibition of angiogenesis in vitro has been shown to decrease hypoxia, and lead to radiation sensitivity of lung cancer cells (Gorski et al. 1999).

1.1.8 Tissue Invasion and Metastasis

The majority of cancer deaths are caused by metastases. The process of metastasis requires a variety of steps from angiogenesis to invasion, embolization, adherence, extravasation, and finally to proliferation and further angiogenesis. Each of these steps requires its own acquired traits. Due to the complexity of the mechanisms underlying these numerous steps, the intricacies of the processes are only now beginning to be elucidated. Under normal growth conditions, cells interact with their environment through either cell–cell adhesion molecules (CAMs) or laminins linking cells to the extracellular matrix. Abnormalities in these interactions have been found in lung cancer cells. N-CAM, for example, is switched from an adhesive form to a repulsive form in over 90% of SCLC (Lantuejoul et al. 1998). This may help to explain the highly metastatic phenotype of SCLCs. The role of laminin expression is less clear. Laminins are proteins in the basement membrane and disruption of their function could lead to increased metastasis. Laminin-5 gene expression has been found to be reduced in both NSCLC (20%–60%) and SCLC (65%–85%) as a result of frequent epigenetic inactivation (Sathyanarayana et al. 2003). Other studies have found laminin-5 overexpression in NSCLC which was associated with shorter patient survival (Moriya et al. 2001). Finally, some of the alterations described in Sects. 1.1.3–1.1.5 have been shown to play a role in metastasis. Increased c-Myc expression, for example, has been observed in statistically significantly higher numbers of NSCLC patients with metastases as compared to those without (Volm et al. 1993). Akt also appears to play a role as constitutive activation is associated with decreased cell adhesion (Kraus et al. 2002).

1.1.9 Genetic Alterations in the Progression of Lung Cancer

As Hanahan and Weinberg (2000) describe, the actual order of molecular and genetic abnormalities that cancer cells accumulate to achieve the described hallmarks is likely highly variable. Accepting this, lung cancer is somewhat unique among cancers in that a significant portion of the patients have a well established carcinogenic exposure in the form of tobacco smoke. Efforts have been made to try to identify the relative appearance of the molecular abnormalities and to relate these to smoking (Osada and Takahashi 2002).

The various 3p lesions described in Sect. 1.1.4 are among the earliest abnormalities seen in the lung cancer development of smokers. Loss of the gene encoding *p16(INK4A)* and *p14(ARF)* on 9p21, and gain of telomerase expression are also noted early in lung cancer (Yashima et al. 1997). Mutations in the *RAS* gene may also be present in early lesions (Westra et al. 1996). Enhanced angiogenesis is thought to be a trait gained somewhat later in the cancer progression. As these characteristics accumulate, the tumor cells obtain the often lethal ability to invade and metastasize.

1.1.10 Therapeutic Targets

The role of many of these molecular abnormalities as targets for radiosensitization will be discussed in detail in Chap. 2.2.6, but their function as general therapeutic targets deserves mention. Inhibitors of the ERB-B family of receptors including cetuximab and gefitinib (EGFR) and trastuzumab (HER2/neu) have been developed and tested in lung cancer. Clinical studies in NSCLC have shown efficacy of cetuximab when combined with cytotoxic chemotherapy but the same has not been found with trastuzumab (Sridhar et al. 2003). Gefitinib used as a single agent has shown efficacy in patients with NSCLC who failed cisplatin based therapy, but showed no benefit in combination with cytotoxic chemotherapy (Kris et al. 2002). Imatinib was developed as an inhibitor of the c-Kit receptor, but has not proven to be an effective therapy in a population of SCLC patients unscreened for receptor expression (Johnson et al. 2003). Several drugs that inhibit Ras activation, known as farnesyltransferase inhibitors, have been developed and tested (Brunner et al. 2003). One of the more widely tested, tipifarnib, has failed to demonstrate activity in NSCLC as mono-therapy (Adjei et al. 2003). A drug, flavopiridol, has been developed which inhibits Cdk activity and thus cell cycle progression. While no responses were observed using flavopiridol in NSCLC patients, disease stabilization was noted (Shapiro et al. 2001). Inducement of apoptosis in lung cancer has been attempted through several mechanisms including gene therapy replacing wild-type *TP53*, where trials have shown only limited response in NSCLC patients, and oligonucleotide inactivation of Bcl-2 showing disease stabilizing effects in SCLC. Finally,

angiogenesis remains a major target of antineoplastic agents. Trials using VEGF inhibitors have suggested an increase in survival in NSCLC (Johnson et al. 2001). This diverse and multifaceted field of targeted therapies, only superficially addressed here, continues to develop and expand.

1.1.11 Conclusion

The highly integrated and complex circuitry of cellular signaling taking place in lung cancer remains only partially understood. Successful therapy will likely require not only a global understanding of each of the characteristics outlined here but also their interrelations. As a comprehensive view of these pathways is developed, several significant advances will likely be realized: (a) the development of molecular signatures for individual cancers that will guide therapeutic decision-making; (b) the continued discovery of molecular targets leading to the development of further targeted therapies and; (c) potential cancer prevention through identification and treatment of abnormalities seen early in the carcinogenic process.

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1.2 Angiogenesis and Lung Cancer

Dietmar W. Siemann, Susan M. Galbraith, and Wenyin Shi

CONTENTS

1.2.1 Introduction

Lung cancer is a significant public health problem in the US and the world. It ranks as the second most common cancer among both men and women in the US, where an estimated 171,900 new cases of lung cancer were diagnosed in 2003; a number representing approximately 13% of all new cancers diagnosed. Lung cancer is the most common cause of cancer-related deaths, accounting for 157,200 deaths in 2003 (American Cancer Society 2003). Although the incidence of lung cancer is now declining in men, the incidence in women continues to increase (Weir et al. 2003), probably due to changing smoking habits.

According to World Health Organization histologic classification schemes (World Health Organization 1979), there are four primary pathological types of lung cancer: small-cell carcinoma, squamous-cell carcinoma, adenocarcinoma, and large-cell carcinoma. However, for therapeutic purposes, lung cancer is generally divided into small-cell lung cancer (SCLC) or non-small-cell lung cancer (NSCLC). About 80% of patients present with NSCLC (Weir et al. 2003).

Although prevention and early detection are critical to improving treatment outcomes, these have proven difficult in lung cancer. A major reason is that only approximately 15% of lung cancers are discovered while still localized. Local treatment for early stage disease, particularly surgical interventions, can improve patient survival, yet less than 50% of patients are cured, principally due to the presence of undetected occult local or metastatic disease (Mountain and Hermes 2003; Downey 1999). Radiotherapy and chemotherapy typically are applied in more advanced disease. Still, survival in patients with lung cancer remains poor. The 5-year survival rate for all stages combined is only 5%–15% (Comis 2003; Richards et al. 2000). The majority of patients die from disease progression locally, at distant sites, or both.

Pathologic staging, which incorporates factors such as tumor size and grade, nodal status, and presence or absence of distant metastases, provides the best prediction of treatment outcome (Beadsmoore and Screaton 2003; Mountain 2000). However, because the growth of primary tumors and metastases is angiogenesis dependent (Folkman 1971, 2002), a great deal of attention has recently been paid to the role of this process not only in lung cancer formation, progression, and prognosis, but also in the development of novel therapeutic strategies for this disease.

1.2.2 Angiogenesis

Angiogenesis is a process that allows the development and formation of new blood vessels from a pre-

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existing vascular network. This process is complex and involves multiple sequential, interactive steps as well as a variety of cells, soluble factors and the extracellular matrix. The sequential steps include: degradation of basement membranes, migration and proliferation of endothelial cells, lumen formation, and stabilization of neovessels. Under physiological circumstances, angiogenesis is a rare event in adults, occurring almost exclusively in the female reproduction system (Folkman 1995; Risau 1997). It is normally suppressed and observed only transiently. However, angiogenesis can be activated in response to tissue damage, and it is associated with a variety of pathological conditions including cancer (Folkman 2002). While angiogenesis in itself is not sufficient for continued tumor growth, its absence severely compromises or halts the expansion of a tumor cell population. Indeed, it is believed that tumors can not grow to a size larger than a few cubic mm without initiating the angiogenic process (Folkman 1971, 1975, 2002). Furthermore, there is evidence that angiogenesis may be present in pre-malignant lesions such as epithelial dysplasia even prior to development of invasive cancer (Keith et al. 2000; Fontanini et al. 1999).

A balance of pro- and anti-angiogenic factors carefully regulates the angiogenic potential of endothelial cells. While tightly controlled under normal physiological conditions, this rigid control is absent in angiogenesis associated with tumors. Indeed, alterations of the expression and/or function of pro-angiogenic and anti-angiogenic molecules that disrupt the normal balance appear to be responsible for tumor angiogenesis. The regulatory factors involved may mediate any one of a cascade of steps in the process of angiogenesis. As a consequence, the characteristics of endothelial cells and associated perivascular structures (pericytes, vascular smooth muscle cells) can be dramatically altered.

Vascular endothelial growth factor (VEGF) is the most potent and specific growth factor for endothelial cells. VEGF can increase vascular permeability, induce endothelial cell proliferation and migration, activate proteases for extra-cellular matrix degradation, and inhibit apoptosis of endothelial cells (Senger et al. 1983; Connolly et al. 1989; Watanabe and Dvorak 1997; Ferrara 2002). VEGF is comprised of a family of five isoforms which bind with high affinity to tyrosine kinase associated receptors that are present on endothelial cells (Ferrara et al. 2003). Another class of endothelial cell specific molecules is the angiopoietin family. It includes at least four members (angiopoietins 1–4) of which Ang-1 and Ang-2 are best understood. Ang-1 binds to the specific receptor Tie-2 and acts as an agonist that stimulates endothelial cell differentiation, stabilization, and vascular remodeling (Papapetropoulos et al. 1999), whereas Ang-2 binds to Tie-2 and blocks the binding of Ang-1 (Holash et al. 1999).

In addition, there are numerous nonspecific angiogenic growth factors that can also affect endothelial cells. These include platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF/FGF-2), acidic fibroblast growth factor (aFGF/FGF-1), fibroblast growth factor-3 (FGF-3/int-2), fibroblast growth factor-4 (FGF-4/hst/K-FGF), hepatocyte growth factor/scatter factor (HGF/SF), transforming growth factor-β (TGF-β), transforming growth factor-α (TGF-α), tumor necrosis factor-α (TNF-α), granulocyte colony stimulating factor, interleukin-8, pleiotropin and angiogenin, to name just a few (Moore et al. 1998).

A growing number of endogenous anti-angiogenic factors have also been discovered. To date, these include endostatin, angiostatin, vasostatin, interferon-α,β,γ, METH-1 and METH-2, antithrombin III, and VEGF inhibitor (Kerbel 2000). These factors possess great structural diversity and activity. Some of the most notable, endostatin and angiostatin, are cleavage fragments of proteins that normally lack anti-angiogenic activity (O'Reilly et al. 1994, 1997). Table 1.2.1 lists endogenous factors that stimulate and inhibit angiogenesis.

1.2.3 Angiogenesis in Lung Cancer

The lungs are highly vascularized and highly dependent on intact vasculature for efficient function. Endothelial cells lining the lumen surfaces of blood vessels are not only a mechanical barrier but also play an essential role in the regulation of blood flow, vascular permeability, angiogenesis, and metastasis (Tuder et al. 2001; Paku 1998). Endothelial cells from normal and tumor tissues not only differ phenotypically but also in their gene expression profiles (St. Croix et al. 2000). Moreover, significantly different expression profiles of angiogenic proteins have been observed between different lung cancer types (Wong et al. 2000; Yamashita et al. 1999).

Typically, angiogenesis in tumors has been assessed indirectly by determining intratumoral microvessel density (MVD). Blood vessels are usually immunostained with a pan-endothelial marker, such as factor VIII-related antigen, and counted (Guidi et

Table 1.2.1. Endogenous regulatory factors involved in angiogenesis

Pro-angiogenic factors	Anti-angiogenic factors
Vascular endothelial growth factor (VEGF-A, B, C, D, E)	Angiostatin
Placental growth factor	Endostatin
Platelet-derived growth factor (PDGF)	Vasostatin
Basic fibroblast growth factor (bFGF/FGF-2)	Thrombospondin-1 and internal fragment
Acidic fibroblast growth factor (aFGF/FGF-1)	Vascular endothelial growth factor inhibitor
Fibroblast growth factor-3 (FGF-3/int-2)	Fragment of platelet factor-4
Fibroblast growth factor-4 (FGF-4/hst/K-FGF)	Derivative of prolactin
Hepatocyte growth factor / Scatter factor (HGF/SF)	Restin
Transforming growth factor-α (TGF-α)	Proliferin-related protein
Transforming growth factor-β (TGF-β)	SPARC cleavage product
Tumor necrosis factor-α (TNF-α)	Osteopontin cleavage product
Granulocyte colony stimulating factor	Interferon-α, Interferon-β
Interleukin-8	METH-1, METH-2
Pleiotropin	Angiopoietin-2
Angiogenin	Antithrombin III fragment
Proliferin	Interferon-inducible protein-10
Matrix metalloproteinases (MMPs)	Tissue inhibitors of metalloproteinases (TIMPs)
Angiopoietin-2	Prolactin
Prostaglandin E1 and E2	Interleukin 1, 6, 12
Thymidine phosphorylase (TP)-Platelet-derived endothelial cell growth factor (PD-ECGF)	VEGF soluble receptor

al. 1994). More recently, markers with an increased ability to highlight the entire tumor vasculature (CD31, CD34) have replaced factor VIII-related antigen as the most commonly used pan-endothelial markers (Miettinen 1993; Hasan et al. 2002). An international consensus on the methodology and criteria for evaluation of MVD has been put forth (Vermeulen et al. 1996). MVD is a measure of one feature of the tumor vasculature, the density of blood vessels in the regions of tumor with the highest concentration of blood vessels, referred to as 'hot spots'. While there is evidence, accumulated over the past 10 years, that correlates this parameter with angiogenic growth factor expression, tumor growth and the occurrence of distant metastases (Weidner et al. 1993; Takahashi et al. 1995; Mattern et al. 1996; McCulloch et al. 1995), there are important aspects of the process of angiogenesis that MVD does not reflect. For example, it does not measure the degree of vascular heterogeneity across the tumor, or the functions of the microvasculature such as blood flow or extent of tumor hypoxia.

Results from a number of clinical investigations now have indicated that increased MVD is associated with a poor prognosis. Indeed, MVD has been shown to be an independent prognostic factor in a variety of tumor types, including breast, bladder, ovarian, prostatic, pancreatic, melanoma, colorectal, and gastric carcinoma (Toi et al. 1993; Dickinson et al. 1994; Gadducci et al. 2003; Bono et al. 2002; Khan et al. 2002; Lee et al. 2002; Massi et al. 2002; Papamichael 2001; Tanigawa et al. 1996). Many studies also have associated the peak vessel density as measured by MVD with a poor prognosis in NSCLC (Macchiarini et al. 1992; Yamazaki et al. 1994; Fontanini et al. 1995; Angeletti et al. 1996; Giatromanolaki et al. 1996; Harpole et al. 1996; Kawaguchi et al. 1997; Fontanini et al. 1997; Matsuyama et al. 1998; Duarte et al. 1998; Yuan et al. 2000; Cox et al. 2000; O'Byrne et al. 2000; Dazzi et al. 1999). In addition, the incidence of node involvement increased with MVD, and MVD was an independent variable associated with lymph node metastasis (Fontanini et al. 1995). The role of MVD as a prognostic factor in locally advanced, completely resected NSCLC treated with postoperative radiotherapy and chemotherapy has also been reported (Angeletti et al. 1996). Since SCLC is rarely treated by surgery, this disease has not been as well studied. Still, despite the paucity of information in this class of tumors, it should be noted that available data suggest a similar correlation between MVD and prognosis for SCLC as has been reported in NSCLC (Lucchi et al. 2002; Fontanini et al. 2002).

However, not all lung cancer investigations have demonstrated relationships between vessel density and outcome. For example, in several recent studies MVD failed to be a predictor for survival in NSCLC (Pastorino et al. 1997; Apolinario et al. 1997; Chandrachud et al. 1997; Decaussin et al. 1999; Macluskey et al. 2000). These apparently contradic-

tory results may arise from differences in staining methods, tumor heterogeneity, and inter-observer variability. Interestingly, in tumors with an "alveolar pattern," where there is little parenchymal destruction and alveolar septa are present, prognosis is worse than in tumors showing an "angiogenic pattern" (Pezzella et al. 1997). This suggests that some lung cancers may be capable of utilizing the existing vascular bed and relying less on new vessel formation. In this circumstance, MVD is unlikely to be of prognostic utility. Also, while in general MVD is an important prognostic indicator, it has not yet been shown to be a useful measure for assessment of anti-angiogenic treatments (Hlatky et al. 2002). There are a number of potential reasons for this. Firstly, determination of treatment effect, rather than prediction of prognosis, requires serial measurement. Generally, only small samples of tumor can be obtained in a serial manner. Since MVD by definition measures the peak vessel density, use of small samples may affect accuracy and it is technically difficult to sample similar areas of tumor repeatedly. Secondly, while MVD reflects some aspects of the angiogenic process, it may not be a measure of the relative dependence of a particular tumor on angiogenesis, and changes in MVD do not necessarily correlate with changes in tumor growth rate.

The expression level of angiogenic factors, either quantified within tumor tissue or after secretion into body fluids, provides another indirect measure of tumor angiogenesis. The latter approach is particularly appealing as it provides a noninvasive means of investigating tumor angiogenic activity with potential diagnostic and prognostic implications. A number of such studies have been reported for lung cancer patients.

In NSCLC a significant role of increased VEGF and a correlation of VEGF expression with poor prognosis were found (Mattern et al. 1996, 1997; Volm et al. 1997a). VEGF receptor (KDR) expression by endothelial cells has also been associated with poor prognosis in NSCLC (Koukourakis et al. 2000). A similar association between VEGF expression and poor prognosis also was reported in SCLC (Salven et al. 1998; Ohta et al. 1996). In addition to determining tissue and tumor VEGF protein and mRNA expression, it is also possible to measure VEGF concentrations in body fluids. When this was done in lung cancer patients, serum or plasma VEGF levels were observed to increase with tumor stage progression (Matsuyama et al. 2000; Tamura et al. 2002; Takigawa et al. 1998). Also, patients with elevated serum or plasma VEGF levels at diagnosis had a poorer response to therapy and worse survival (Salven et al. 1998; Tamura et al. 2001). When measured in bronchoalveolar lavage fluid, raised VEGF levels were noted in patients with advanced NSCLC before and during treatment (Beinert et al. 1999; Ohta et al. 2002). However, other studies failed to find a relationship between NSCLC prognosis and serum VEGF level (Brattstrom et al. 1998). This is perhaps not surprising since there are pitfalls in the measurement of circulating VEGF levels. For example, platelets contain a large amount of VEGF, and depending on how samples are handled, varying amounts of platelet associated VEGF may be released. Consequently the use of plasma rather than serum samples for measurement of VEGF has been recommended (Webb et al. 1998). Since VEGF is one of the most potent and specific factors of tumor angiogenesis, the clinical possibilities of utilizing VEGF associated measurements as markers of tumor growth and/or response to therapy remains an area of intense interest, particularly for those therapies that target the VEGF pathway (Drevs 2003).

Basic FGF is another potent stimulator of angiogenesis that is often over-expressed in lung cancer patients (Berger et al. 1999). Indeed, high serum bFGF levels have been correlated with poorer prognosis (Strizzi et al. 2001; Ruotsalainen et al. 2002; Ueno et al. 2001; Brattstrom et al. 1998). However, there are also several conflicting findings regarding bFGF. These include the absence of a relationship between bFGF level and MVD (Strizzi et al. 2001; Ruotsalainen et al. 2002; Ueno et al. 2001; Brattstrom et al. 1998) and the lack of correlation between bFGF expression and survival (Volm et al. 1997b). Also, in NSCLC patients, serum bFGF did not differ between clinical stages (Ueno et al. 2001; Cherrington et al. 2000). Finally, one study has reported that elevated levels of serum bFGF in NSCLC patients were related to a better outcome (Brattstrom et al. 1998). In light of these observations it would appear that the value of bFGF as a surrogate marker for tumor angiogenesis in lung cancer remains uncertain.

Several other angiogenic molecules, such as matrix metalloproteinases, epidermal growth factor receptor, angiopoietin-2, thymidine phosphorylase and hepatocyte growth factor also have been investigated in NSCLC patients. In some of these studies these factors were found to be inversely correlated with prognosis (Brown et al. 1993; Fontanini et al. 1998; Tanaka et al. 2002; Koukourakis et al. 1997; Siegfried et al. 1998).

The measurement of circulating endothelial cells has also been investigated as a noninvasive method

for the assessment of angiogenesis. Some endothelial cells in tumors are recruited from circulating endothelial progenitors (CEP) originating in the bone marrow. Vascular trauma for instance, induces rapid but transient mobilization of VEGFR2+CD34+cells which also express AC133, a hemopoietic stem cell marker associated with a rise in plasma VEGF (Gill et al. 2001). Acute elevation of plasma VEGF in mice elicited similar mobilization of CEP. AC133 becomes downregulated as endothelial cells differentiate and mature. Bone marrow derived CEP are rapidly incorporated into tumor vasculature in proliferating tumors (Lyden et al. 2001), although the number of endothelial cells derived from CEP is tumor type dependent. Mancuso et al. (2001) have described an increase in circulating endothelial cells (CEC) in patients with cancer compared with healthy controls. In a mouse model of lymphoma, decreases in CEC were measured following continuous infusion of an angiogenesis inhibitor (Capillo et al. 2003). Therefore, there is considerable interest in CEC measurement as a potential marker of angiogenesis that may be applicable for serial assessment of anti-angiogenic therapy. However, additional data in a variety of cancers are needed to confirm the reproducibility of the methodology. In addition, the correlation of this parameter with clinical outcome needs to be determined to establish its utility.

Finally, a range of noninvasive imaging technologies including ultrasound, positron emission tomography (PET), computed tomography (CT), and nuclear magnetic resonance imaging (MRI) are available, or under development, that have the potential to measure various aspects of tumor vasculature, angiogenesis, and their relation to tumor metabolism, proliferation, and growth.

CT can be performed with contrast medium to measure vascular characteristics including blood flow, blood volume, mean fluid transit time and capillary permeability (Miles et al. 2000). However, sensitivity to physiological motion and radiation dose from serial scans remain disadvantages to the use of CT.

A variety of MRI methodologies have been used to investigate tumor vasculature. These include the use of gadolinium (Gd-DTPA) in dynamic contrast enhanced MRI (DCE-MRI) (Tofts et al. 1999), high molecular weight contrast agents to measure vessel permeability and blood volume, gradient-recalled echo sequences to measure a combination of blood oxygenation and blood flow (BOLD) (Griffiths et al. 1997; Robinson et al. 1995), and the change in BOLD signal seen while breathing high oxygen content gases to assess vessel maturity (Neeman et al. 2001). However, high molecular weight contrast agents are not yet clinically available so this technique has only been used in pre-clinical models, and the BOLD contrast method is dependent on the field gradient used, making both comparisons between measurements made on different MR machines and serial measurements difficult. DCE-MRI using Gd-DTPA is becoming increasingly widespread in microcirculation research (Hawighorst et al. 1999) and assessment of changes in microcirculation following treatment intervention (Jayson et al. 2002b; Beauregard et al. 1998; Morgan et al. 2003; Galbraith et al. 2003). Yet this method too has limitations. These are primarily the consequence of the inherent characteristics of Gd-DTPA, which result in the measured parameters reflecting a combination of blood flow, vessel permeability and surface area, rather than being able to discriminate these individual physiological parameters (Tofts et al. 1999). Finally, commonly used methods lack a directly measured arterial input function which affects accuracy and reproducibility of the technique (Galbraith et al. 2002).

The use of PET imaging in oncology is becoming widespread, principally using the uptake of ^{18}F labeled fluorodeoxy glucose (FDG) as a measure of tumor metabolism. This is proving to be useful in the assessment of tumor response to therapies, as changes in FDG uptake can be detected earlier than traditional assessment by CT (Kostakoglu and Goldsmith 2003). In NSCLC, PET has advantages over conventional imaging techniques in its ability to discriminate mediastinal lymphadenopathy, particularly for assessment of response following radiation therapy (Erdi et al. 2000).

PET methodologies useful for more direct assessment of tumor vasculature include ^{15}O labeled water for measurement of blood flow, and ^{11}C labeled carbon monoxide for measurement of blood volume (Hoekstra et al. 2002). Although the resolution obtained with PET is poorer compared with DCE-MRI or CT, it has the advantage that absolute blood flow measurements can be obtained. However, the very short half life of ^{15}O makes this technique feasible only where a cyclotron is on site. This method has been used for the assessment of response to treatment with agents that directly damage tumor vasculature (Anderson et al. 2003).

Collingridge et al. (2002) have used an ^{124}I iodinated monoclonal antibody VG67e which binds to human VEGF-A for assessment of tumor VEGF levels non-invasively. Similarly HuMV833, a fully human antibody to VEGF-A labeled with ^{124}I, allows imaging of VEGF distribution in tumors (Jayson et al. 2002a).

However, there has not been any comparison of tumor uptake by these methods with measurement of VEGF levels in tumor by alternative methods, and it is likely that the uptake of the imaging probe into tumor tissue is affected by the pharmacokinetic distribution of the probe in addition to the level of VEGF in tumor tissue.

Color Doppler ultrasonography can be used to measure flow velocity in tumor blood vessels. Parameters obtained include vascularity index, peak flow velocity and flow resistance index. These parameters have been used to improve discrimination between benign and malignant tumors (Strobel et al. 2000), to give prognostic information, and to monitor the changes in tumor vascularity after treatment (van der Woude et al. 1995). Alternatively, ultrasound techniques using microbubble contrast agents have also been developed for measurement of blood flow, and have potential utility in both preclinical and clinical settings (Leong-Poi et al. 2003; Kim et al. 2002). Still, the resolution of ultrasound, and the reduced blood velocity in smaller arterioles and capillaries mean that flow in these vessels is not measured by this technique. In addition, bulk tissue movements that produce artifacts can be a problem in some organs such as lung (Eriksson et al. 1991). Imaging tumors that are surrounded by aerated lung is also technically difficult. Finally, poor accessibility to anatomical areas for deep seated tumors, and operator dependence remain challenges for use of these ultrasound methodologies.

In several studies the potential correlation between the imaging parameters discussed above and MVD has been examined. While some studies demonstrate such a correlation (Peters-Engl et al. 1998; Hawighorst et al. 1997), others do not (Su et al. 2003). This is likely to be due to different aspects of the tumor vasculature being measured, some functional, some anatomical, rather than a reflection of the relative utility of the parameter concerned. Even when both are related to vascular structure such as blood volume and MVD they differ in the measurement method; MVD measures peak vascular density whereas blood volume measured by PET reflects a whole tumor assessment. Therefore, it is important to use each technique in an appropriate manner with an understanding of its inherent limitations. MVD is an anatomical technique that is clearly established as a useful prognostic tool. The noninvasive imaging techniques measure aspects of tumor vascular function, can be performed repeatedly, and sample a larger proportion of an individual tumor or several tumors within the same patient, so have potential for serial assessment of anti-angiogenic therapy. Confirmation of their utility in this regard will await completion of trials with effective anti-angiogenic therapies that produce improvements in patients' time to progression and overall survival and where changes in such endpoints are correlated with changes in the imaging parameters. In addition, more data are required to establish the reproducibility of each technique when used in a variety of settings in order to determine the significance of any changes measured following a therapeutic intervention.

1.2.4 Anti-angiogenic Therapy

The complex process of tumor angiogenesis offers many possible targets for anti-angiogenic strategies. Strategies vary from regulation of angiogenic factor expression in tumors, to endogenous inhibitors of angiogenesis. There are currently over 80 clinical trials employing such strategies (http://cancertrials.nci.nih.gov/). Based on their biological activities, these strategies can be categorized into several broad classes. One class of agents specifically targets angiogenic growth factors. It includes tyrosine kinase inhibitors of VEGF/bFGF, as well as antibodies or antisense oligonucleotides directed against pro-angiogenic growth factors or their receptors. A second class of agents includes those designed to inhibit endothelial cell function, such as thalidomide and endostatin. A third class consists of matrix metalloproteinase inhibitors, compounds that block the degradation of the basement membrane. Agents that target survival factors of neovascular blood supply, such as integrin antagonists, comprise yet another class.

1.2.4.1 Drugs That Block Angiogenic Factors

1.2.4.1.1 Inhibitors of VEGF and Its Receptors

The central role of VEGF and its receptor system in tumor angiogenesis has made it a promising target of anti-angiogenic therapies. Strategies include the use of: (a) specific VEGF antibodies to neutralize circulating VEGF, (b) antisense oligonucleotides or RNA to disrupt VEGF expression, and (c) VEGF receptor antibodies, or receptor associated tyrosine kinase inhibitors, to block VEGF signaling (Kim et

al. 1993; Shi and Siemann 2002; Witte et al. 1998; Solorzano et al. 2001).

Bevacizumab (Avastin), a recombinant humanized monoclonal antibody to VEGF, is the first anti-angiogenic therapy to have demonstrated a survival advantage when given to patients with cancer (Hurwitz et al. 2003). It is currently being investigated in a number of tumor types, including NSCLC. In Phase I studies, bevacizumab was generally well tolerated. Two patients had severe adverse events related to intratumoral bleeding and minor hemoptyses were also reported in other patients with pulmonary metastases. Systolic and diastolic blood pressures in patients treated at the 3- and 10-mg/kg dose levels increased by an average of more than 10 mm Hg at some point during therapy (Gordon et al. 2001).

The results of a Phase III trial of bevacizumab in combination with chemotherapy in patients with no prior therapy for metastatic colorectal cancer were recently reported. Patients treated with irinotecan, 5- fluorouracil, and leucovorin plus bevacizumab had a median overall survival of 20.3 months compared with 15.6 months for those receiving chemotherapy alone. Time to progression and response rate were also significantly improved in the combination arm (Hurwitz et al. 2003). In addition, bevacizumab as a single agent prolonged time to progression compared to placebo in patients with metastatic renal cancer, a tumor type which may have particular dependence on the VEGF pathway (Yang et al. 2003). Treatment was well tolerated in the renal cancer trial, with hypertension and asymptomatic proteinuria seen as the predominating adverse effects. No major bleeding episodes were seen, although 21% of patients in the 10-mg/kg q 2-week arm had grade 1 or 2 epistaxis, and 13% had grade 1 or 2 hematuria.

In a randomized Phase II study in NSCLC, patients with Stage IIIB or IV disease were randomized to standard therapy with carboplatin and paclitaxel alone or to the same chemotherapy plus bevacizumab 7.5 mg/kg or 15 mg/kg every 3 weeks (DeVore et al. 2000). The control group was allowed to cross over to the high dose arm following disease progression. Patients in the high dose arm had higher response rates and there was a trend to prolongation of time to progression and median survival. An unusual and unexpected toxicity was the development of life-threatening hemoptysis in six patients, resulting in four deaths, mainly in patients with central tumors and squamous cell histology. Such tumors are prone to central necrosis and cavitation even in the absence of treatment. The combination of their location close to major blood vessels and the propensity to central necrosis may explain why bleeding episodes, seen as a mild toxicity with bevacizumab in other tumor types, can be life threatening in this setting.

A Phase III trial of bevacizumab in advanced NSCLC is now ongoing through the Eastern Cooperative Oncology Group (ECOG). Patients with a history of hemoptysis or with squamous cell histology are excluded from study in view of the toxicity described in the Phase II study. The study randomizes patients between bevacizumab 15 mg/kg every 3 weeks or placebo with paclitaxel and carboplatin. Crossover of patients on the placebo arm is not allowed. Interim analysis for toxicity has shown no significant difference in fatal hemoptysis between the two arms although this was seen in the active treatment arm and the trial continues with further regular safety analyses planned (Shepherd and Sridhar 2003). A Phase II study of neoadjuvant bevacizumab, paclitaxel, and carboplatin in patients with stage IB, II, or IIIA resectable NSCLC is also currently recruiting and another ECOG Phase II pilot trial of cisplatin, etoposide and bevacizumab15 mg/kg is open in patients with advanced SCLC.

An alternative approach to interrupt VEGF activity that has received a great deal of attention is the use of small molecule compounds to inhibit VEGF receptor associated tyrosine kinases. SU5416 was one of the earliest to enter clinical trials. It inhibits VEGF receptor 2 as well as c-kit and has been shown in preclinical studies to inhibit VEGF-stimulated proliferation of human endothelial cells as well as the growth of primary and metastatic tumors in various models (Fong et al. 1999). Phase I studies showed that dose-limiting toxicity occurred at 190 mg/m^2 and consisted of headache, nausea, and vomiting. SU5416 was administered intravenously on a weekly schedule and had a short plasma terminal half-life of approximately 1 h. This is not ideal for an anti-angiogenic agent and is in contrast to the antibody bevacizumab, which has a prolonged half-life of 21 days. In addition, in a Phase II study in combination with gemcitabine and cisplatin significant vascular toxicities were observed with eight of 19 patients experiencing severe thromboembolic events. Analysis of variables of the coagulation cascade and of vessel wall activation was performed in three patients and showed significant increases in thrombin generation and endothelial cell perturbation in a treatment cycle-dependent manner. These toxicities led to the discontinuation of this trial and no further development of this compound is planned.

Several other VEGFR tyrosine kinase inhibitors have entered clinical trials. All of these are oral agents

with improved pharmacokinetic profiles compared with that of SU5416. Two are now in Phase III trials, vatalanib (PTK787/ZK 222584) and SU11248. These tyrosine kinase inhibitors have additional inhibitory activity on other kinase targets, some of which also influence angiogenesis. This may, in theory, be an advantage in improving efficacy over more specific therapies such as bevacizumab, but also potentially increases toxicity. It is not yet clear which specific toxicities are related to particular kinase inhibition, and multiple kinase inhibitors may well have other cellular targets as yet unknown, which are not mechanism related, but may result in toxicity. SU1148 is at the less specific end of the spectrum of kinase inhibitors, with inhibitory activity at low nanomolar concentrations against VEGFR2, FGF receptor 1, Flt-3, c kit, and PDGF receptor. In Phase I trials this compound has produced a number of objective tumor responses as a single agent, but also a range of toxicities including reversible yellow discoloration of the skin and urine, as well as depigmentation of hair (Raymond et al. 2002). In addition, some evidence of vascular toxicity was seen, with subungual splinter hemorrhages, thrombocytopenia felt to be due to microangiopathy and hypertension. Several patients had mucositis and erythema multiforme. The dose limiting toxicity was a debilitating asthenia which led to an intermittent regimen of 4 weeks on daily therapy followed by a 2-week break. Plasma concentration trough levels of 50–100 ng/ml were achieved at doses at or above 50 mg daily. These levels were associated with activity in pre-clinical models. The plasma half life was 40 h, and an active metabolite was produced with a half life of 80 h. A range of Phase II trials has been initiated, and SU11248 is now in Phase III in patients with gastrointestinal stromal tumors resistant to imatinib (Gleevec), as well as in renal cancer.

Vatalanib inhibits VEGFR1 in addition to VEGR2 at concentrations in the submicromolar range. It also inhibits other class III kinases but at higher concentrations (Wood et al. 2000). In Phase I trials it was well tolerated, with a dose-limiting toxicity of hypertension (Drevs 2003). This adverse event has now been reported with a number of therapies targeting the VEGF pathway, and is often seen more commonly in patients with higher baseline blood pressure. It generally appears to be controllable with standard anti-hypertensive medication. Another dose limiting toxicity seen was reversible ataxia. The peak plasma concentration at 1200 mg daily was 30 μM which is close to the IC50 reported in vitro (Morgan et al. 2003). As part of the Phase I trial, assessment of anti-angiogenic effects was performed using DCE-MRI. Significant reductions in DCE-MRI parameters including Ki (the rate constant for the inflow of contrast agent into the tissue) were seen in several patients. There was a significant negative correlation between the change in Ki and increase in dose and exposure. Patients with a best response of stable disease had a significantly greater reduction in Ki at both day 2 and at the end of cycle 1 compared with progressors. Similar findings have also been reported in a trial of vatalanib in renal cancer (de Bazelaire et al. 2003). While the data are preliminary, these studies do suggest that DCE-MRI may be a useful biomarker for use in dose and schedule selection with inhibitors of the VEGF pathway. Vatalanib is now in Phase III trials in colorectal cancer.

VEGFR tyrosine kinase inhibitors are also under investigation in lung cancer –ZD6474 is currently in Phase II clinical trials in this setting. In addition to VEGFR2, this compound inhibits the epidermal growth factor receptor (EGFR), although to a lesser extent, and, consistent with this activity, the dose limiting toxicities in Phase I included rash and diarrhea, as well as thrombocytopenia (Hurwitz et al. 2002). Randomized Phase II trials of ZD6474 are open in combination with docetaxel and as a single agent compared to gefitinib in platinum refractory NSCLC. A randomized Phase II trial examining ZD6474 in SCLC patients with limited or extensive disease who have achieved remission after induction chemotherapy and radiotherapy is also under development by the National Cancer Institute of Canada and will open shortly (Shepherd and Sridhar 2003).

Finally, ribozyme constructs that target VEGF receptor mRNA are also under development. Preclinical studies with these constructs induced inhibition of growth in both primary and metastatic Lewis lung carcinoma (Pavco et al. 2000; Oshika et al. 2000). Phase I trial of anti-Flt-1 ribozymes were carried out in patients with advanced cancer. Minor clinical responses were observed with 14 of 20 patients maintaining stable disease for 1–6 months (Fabbro and Manley 2001).

1.2.4.1.2 Non-specific Agents

Thalidomide has recently been shown to inhibit angiogenesis, though the mechanism of action is poorly understood. It may be mediated through inhibition of TNF-α VEGF, and bFGF expression by tumor cells, cell surface receptors to inhibition, and/or effects on the immune system (D'Amato et al. 1994; Li et al. 2003). Currently thalidomide is under evaluation in a

number of SCLC and NSCLC Phase II trials in which it is primarily used as maintenance therapy to arrest tumor growth and delay the onset of tumor relapse.

Cyclooxygenase 2 (COX2), an enzyme that is involved in prostaglandin synthesis, is frequently upregulated in NSCLC, and may be a marker of worse prognosis (Altorki et al. 2002). It also may promote angiogenesis, prevent apoptosis, and induce resistance to radiation therapy. Inhibitors of COX2 have been widely used for inflammatory conditions, and their anti-cancer activity has only recently begun to be explored. In pre-clinical models, celecoxib slowed the growth of NSCLC tumors (Gridelli et al. 2002). A Phase II study in combination with preoperative paclitaxel and carboplatin in patients with Stage I-IIIA NSCLC (Altorki et al. 2002) had encouraging response rates, but definitive demonstration of the potential benefit of such combinations awaits randomized trials.

1.2.4.2 Drugs That Inhibit Endothelial Cell Function

Endostatin, a 20-kDa C-terminal proteolytic fragment of collagen XVIII, has been identified as a potent endogenous inhibitor of angiogenesis. In murine models, the growth of Lewis lung tumors was markedly suppressed by systemic endostatin therapy. At a dose of 20 mg/kg once daily, there was almost complete regression of established primary tumors (O'Reilly et al. 1997). However, in patients, no clinical responses have been observed (Thomas et al. 2003). A few patients did demonstrate changes in their dynamic CT scans suggestive of a decline in microvessel density, but overall no consistent effect of endostatin on tumor vasculature was seen. Other studies have noted measurable effects of endostatin on tumor blood flow and metabolism and the induction of tumor and endothelial cell apoptosis, but again these occurred in the absence of demonstrable antitumor effects (Herbst et al. 2002a,c).

TNP-470, a synthetic analog of fumagillin, is an angiogenesis inhibitor that blocks the growth of new blood vessels by inhibiting methionine aminopeptidase, an enzyme critically important for endothelial cell proliferation (Sin et al. 1997). Preclinical studies, utilizing TNP-470 alone or in combination with chemotherapy, have resulted in tumor regressions, slowed tumor growth, and improved survival times (Teicher et al. 1994). In the clinic, partial responses were observed in 6 out of 16 NSCLC patients treated with TNP470 (Herbst et al. 2002b) suggesting that further evaluation of TNP-470, particularly in combination with chemotherapy, may be warranted.

Squalamine, an antiangiogenic aminosterol derivative originally isolated from the tissues of the dogfish shark, has been shown to inhibit mitogen-induced proliferation and migration of endothelial cells in vitro and cause inhibition of angiogenesis in vivo (Sills et al. 1998). Mechanistic studies have revealed that squalamine inhibits the sodium-hydrogen exchanger (isoform NHE3), causing changes in intracellular pH that lead to alterations in the shape and volume of endothelial cells (Akhter et al. 1999). In vivo, squalamine slowed the establishment of human lung cancer xenografts and enhanced the antitumor effects of systemic chemotherapy (Schiller and Bittner 1999). Tumor growth retardation and enhancement of antitumor effects by chemotherapeutic agents also were noted in the murine Lewis lung cancer model when treated with squalamine (Teicher et al. 1998). On the basis of the positive preclinical results obtained when combining this agent with cytotoxic agents and the demonstration of human safety (Bhargava et al. 2001), clinical trials have been initiated with squalamine in combination with chemotherapy in patients with late stage lung and ovarian cancer.

1.2.4.3 Drugs That Block Breakdown of Extracellular Matrix

To form new blood vessels, endothelial cells of existing blood vessels must degrade the underlying basement membrane and invade the stroma of the neighboring tissue. These processes of endothelial cell invasion and migration require the cooperative activity of plasminogen activators and matrix metalloproteinases (MMPs). The MMPs are a family of structurally related zinc-dependent endopeptidases collectively capable of degrading extracellular matrix. Their activities are controlled at different levels (Liekens et al. 2001): (a) their expression is up-regulated by angiogenic growth factors (Giuliani et al. 1999), (b) they need to be activated proteolytically (Murphy et al. 1999), and (c) their activities are negatively impacted by their inhibitors [tissue inhibitors of metalloproteinases (TIMPs)] (Blavier et al. 1999). Ultimately, an imbalance between MMPs and TIMPs is responsible for an invasive phenotype (Kossakowska et al. 1996; Gohji et al. 1996a,b). The inhibition of MMPs therefore has been extensively studied as an approach to inhibit the growth and invasion of neoplastic cells (Vihinen and Kahari

2002). Still, clinical outcomes with these agents have by and large been very disappointing.

Marimastat was the first orally-administrated synthetic MMP inhibitor and was the first to be evaluated in SCLC. It is relatively nonspecific, inhibiting the activity of MMP-1, 2, 3, 7, and 9. The principle toxicity of marimastat observed in several Phase I-II clinical studies was the appearance of a dose-limiting inflammatory polyarthritis that consisted of joint stiffness and pain (Steward 1999). Marimastat was tested in two Phase III SCLC studies in which patients were treated with chemotherapy with or without thoracic radiotherapy. After completing the cytotoxic therapy, patients were randomized to receive placebo or marimastat. The results showed no significant difference in survival of patients treated with placebo versus marimastat (Shepherd and Sridhar 2003). Similarly, Prinomastat (AG3340), a more selective MMP inhibitor with activity against MMP-2, 3, 9, and 14 failed to demonstrate efficacy in stage IIB/IV NSCLC patients (Smylie et al. 2001). A Phase I study with CGS 27023A (MMI270), an MMP inhibitor with activity against MMP-1, 2, 3, 9, and 13, that was carried out in patients with solid tumors, including lung cancer patients (Levitt et al. 2001), also resulted in no positive tumor responses. Finally, when BAY12-9566, an inhibitor of MMP-2 and 9 was evaluated in SCLC and stage III NSCLC patients, both trials were closed before reaching their accrual goal because the results showed a detrimental effect on patient survival (Hidalgo and Eckhardt 2001).

Studies with two other MMP inhibitors are ongoing. Neovastat (AE-941) is a naturally-occurring MMP inhibitor derived from shark cartilage extract that has shown antitumor/antimetastatic properties in animal models and few side effects in more than 800 patients (Gingras et al. 2003). Currently, a Phase III randomized study of induction platinum-based chemotherapy and radiotherapy with or without neovastat in patients with unresectable stage IIIA or IIIB NSCLC is in progress. BMS-275291 inhibits a broad range of MMPs known to be associated with the growth and spread of tumors (Poulaki 2002). BMS-275291 is in Phase II/III trials, as an adjunct to standard chemotherapy, in advanced or metastatic NSCLC patients.

1.2.4.4 Drugs That Target Survival Factors of Neovessels

A number of factors influence endothelial cell survival with VEGF being perhaps the most notable. Indeed, it is now recognized that anti-VEGF therapeutic approaches, in addition to their other actions (see Sect. 1.2.4.1.1), may directly affect endothelial cell survival (Gerber et al. 1998; Meeson et al. 1999; Bruns et al. 2000).

Another approach that also aims to affect endothelial cell survival targets integrins. Integrins are heterodimeric transmembrane proteins consisting of α and β subunits with large ectodomains and short cytoplasmic tails. They control cell motility, differentiation, and proliferation via interactions with extracellular matrix molecules. Integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$ are up-regulated on proliferating endothelial cells in angiogenic blood vessels (Brooks et al. 1995). The $\alpha_v\beta_3$ integrin, an adhesion receptor for extracellular matrix components with an exposed RGD sequence, is an attractive target for anti-angiogenic therapy because it is almost exclusively present on the cell surface of activated endothelial cells. It is considered a survival factor for angiogenic vessels (Eliceiri and Cheresh 1999). Antibodies against $\alpha_v\beta_3$ have been shown to inhibit adhesion-dependent signal transduction by angiogenic factors, leading to apoptosis of activated endothelial cells. Consequently, these agents block endothelial tube formation and angiogenesis in tumors (Brooks et al. 1994, 1995). Clinical studies with Vitaxin, a humanized monoclonal antibody against $\alpha_v\beta_3$ integrin, have begun (Gutheil et al. 2000).

1.2.5 Vascular Disrupting Therapies

An alternative to targeting tumor blood vessels on the basis of interfering with the process of tumor cell induced new vessel formation (i.e. anti-angiogenic therapies) is to develop agents that specifically compromise the function of existing vasculature in solid tumors. Such approaches aim to cause direct damage to the established tumor endothelium and thus lead to extensive secondary neoplastic cell death (Denekamp 1990; Siemann and Shi 2003). These vascular disrupting agents and their therapeutic application may be broadly divided into two categories, biological agents and small molecule drugs.

Biological approaches include targeted gene therapy, antibodies to neovascular antigens, and fusion proteins targeting specific endothelial cell receptors. Although investigations utilizing these approaches have, to date, been confined to preclinical investigations, encouraging results have been reported. For

example, endothelial cell specific promoter elements and vectors with restricted cellular tropisms have been examined (Trepel et al. 2000). The strategy of linking antibodies or peptides that recognize tumor-associated vasculature to toxins or pro-coagulant/pro-apoptotic effector molecules that can induce endothelial cell damage also has been explored. The utility of such ligand-directed targeting is supported by recent in situ studies in preclinical tumor models that demonstrated not only the localization of the therapeutic moiety to tumor vessels but also the induction of thrombi formation and the selective destruction of vasculature (Nilsson et al. 2001; Veenendaal et al. 2002).

In the category of small molecule drugs, two classes of agents that selectively disrupt the tumor vessel network have entered clinical trials. The first includes flavone acetic acid (FAA) and its potent analog 5,6-dimethylxanthenone-4-acetic acid (DMXAA) (Baguley 2003; Rewcastle et al. 1991). The mechanism of action of these agents appears to be largely indirect, through the induction of cytokines, particularly TNF-α (Ching et al. 1994; Philpott et al. 1995). The second class includes a group of tubulin-binding agents, most notably combretastatin A4 disodium phosphate (CA4DP) and the phosphate prodrug of N-acetyl-colchinol (ZD6126). The principal mechanism of action of this class of drugs is believed to be the selective disruption of the cytoskeleton of proliferating endothelial cells that leads to thrombus formation and a secondary ischemic tumor cell death (Kanthou and Tozer 2002; Galbraith et al. 2001).

Preclinical evaluations with vascular disrupting agents in rodent or human lung cancer models have been encouraging. Administration of CA4DP to animals bearing NSCLC significantly delayed the growth of the xenograft tumors and resulted in a survival benefit (Boehle et al. 2001). Other studies showed that this agent could inhibit the metastatic potential of the rodent Lewis lung cancer model (Griggs et al. 2001). Similarly AVE8062, a combretastatin analog, enhanced efficacy of cisplatin in the treatment of murine lung cancer (Morinaga et al. 2003) and ZD6126 treatment demonstrated efficacy in animals bearing primary human NSCLC xenografts as well as their metastases (Goto et al. 2002). On the basis of promising preclinical investigations, the lead vascular disrupting agents (DMXAA, CA4DP, ZD6126, AVE8062) have entered Phase I/II trials (http://cancertrials.nci.nih.gov/).

Optimal treatment strategies with agents that damage the existing tumor vessel network will ultimately likely combine such therapeutics with conventional therapies including radiotherapy and chemotherapy for maximum treatment effect (Siemann et al. 2002; Siemann and Shi 2003). In addition, preclinical investigations suggest that vascular disrupting approaches are likely to be complimentary to, rather than to duplicate anti-angiogenic strategies. Evidence suggests that anti-angiogenic agents may be especially well suited for micrometastatic disease or early stage cancer (Yoon et al. 1999; Lozonschi et al. 1999), whereas vascular disrupting agents may be particularly effective against large bulky and late stage tumors (Landuyt et al. 2001; Siemann and Shi 2003). Indeed, data are beginning to emerge that combining these two strategies may provide particularly beneficial therapeutic effects.

1.2.6 Conclusions

Angiogenesis plays a critical role in the progression and prognosis of lung cancer. Although still in early stages of development, therapeutic strategies directed against the tumor blood vessel network represents a promising advance in the management of lung cancer patients. The recent demonstration of improvement in survival in colorectal cancer with bevacizumab treatment is the first clinical validation of anti-angiogenic therapy, providing hope that similar benefits may be seen in other tumor types, including lung cancer. Ultimately, such endeavors are likely to incorporate both anti-angiogenic and vascular disrupting strategies in combination with conventional anti-cancer therapies.

Acknowledgements
This work was supported by PHS grants CA84408 and CA89655.

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1.3 Contemporary Issues in Staging of Lung Cancer

Frank B. Zimmermann

CONTENTS

1.3.1 Introduction

The prognosis of affected patients and the treatment concepts in lung cancer both depend on tumour histology and stage. The current TNM system adapted by the American Joint Committee for Cancer Staging in 1997 describes the anatomical spread of cancer by considering the tumour size and invasion, extent of lymphatic spread, and presence of metastatic disease (Mountain 1997). This anatomical basis has influenced current strategies for clinical and surgical staging procedures. Resectability of NSCLC is greatly determined by an accurate preoperative clinical staging and has important impacts on patients' survival (Park et al. 2000).

The choice of non-invasive, such as imaging, and invasive, such as surgical biopsy, diagnostic and staging investigations for detection of cytological and histological spread should be based on objective and subjective criteria describing patients condition and, therefore, feasible treatment options with high sensitivity and specificity. On the other hand, ideal diagnostic methods have to follow economic aspects as well. They should be easy to perform without discomfort and morbidity in order to alter the patients quality of life as little as possible (Grondin and Liptay 2002). Therefore, noninvasive imaging, the least invasive approach, typically forms the first line of investigation.

The staging of lung carcinoma is still progressing, with technology advances improving prognostic accuracy and changing pre-operative investigation algorithms. Noninvasive staging is based on spiral computer tomography (CT) with contrast enhancement, whereas mediastinoscopy and video-assisted thoracotomy have already been established as essential, minimally invasive diagnostic tools for invasive histological staging. In very early stages, diagnostics should give an accurate cytology and/or histology. Since cure can be obtained only in stages up to IIIA (5-year survival rate of 9%–13%) and some IIIB (T 4 N0–1) (5-year survival rate of 3%–8%) contralateral mediastinal lymph node staging is as essential as the clarification of pleural effusion and cardiac infiltration in locally more advanced tumours (Mountain 1997; Abner 1995).

Not only treatment concepts but also staging procedures should be determined in an interdisciplinary context, particularly when multimodal treatment strategies may be reasonable. Accurate preoperative imaging staging for stage III disease could avoid unnecessary surgical interventions, with NSCLC T4 or N3 having no benefit from surgical resection (Montin 1997; Park et al. 2000; Deslauries and Gregoire 2000; Quint and Francis 1999).

1.3.2 Anamnesis and Clinical Examination

Family history, profession (i.e. asbestos or Eternit exposure), and personal behaviour (smoking, former

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malignant disease) can give essential information on tumour type and may direct staging procedures and treatment policy. Disease-related symptoms can point to locoregional (hoarseness, haemoptysis, dysphagia) or systemic (paralysis, epilepsia) extent of disease, and might have prognostic and therapeutic relevance. Concomitant morbidity can limit therapeutic options and should be known before starting diagnostic procedures, since they may be reduced to a minimum due to restricted therapeutic applicability.

All lung cancer patients should undergo a complete physical examination, with special focus on all thoracic organs (pleural effusion, cardiac insufficiency, infiltration of supraclavicular or axillary lymph nodes, paralysis of nervus recurrens or phrenicus, Horner's syndrome) and on paraneoplastic syndromes (Lambert-Eaton syndrome, dermatomyositis, syndrome of inappropriate ADH-secretion, thrombosis). Symptoms and signs may identify up to 95% of NSCLC patients with advanced, inoperable disease (Grondin and Liptay 2002; Cromartie et al. 1980; Hyde and Hyde 1974). Laboratory evaluation should include basis blood account, coagulation factors, function of liver and kidney. LDH and AP can indicate an increased cell turnover or bone infiltration (Silvestri et al. 1995). Abnormal results in physical and laboratory evaluation are associated with an approximate 50% incidence of abnormal findings on subsequent imaging (Silvestri et al. 1995). On the other hand, without abnormal findings on clinical evaluation, there is little evidence supporting the use of routine imaging to detect extrathoracic metastases (Toloza et al. 2003a).

Tumour markers (CYFRA 21-1, CEA, NSE, proGRP) can be used to evaluate treatment response, but should not be ascertained before the malignancy has been cytologically or histologically determined.

1.3.3 Non-invasive Imaging in Lung Cancer

1.3.3.1 Chest Radiographs

Chest radiograph in two planes (125–140 kV) is the basis of radiological investigations. It is usually performed in patients with symptoms or as part of a general check-up, and can detect lesions of at least 10 mm in diameter including lung metastasis, describe pleural or pericardial effusion and atelectasis (Fig. 1.3.1). Above all, it is too insensitive and unreliable to detect or exclude centralized tumours like para- or retrocardial or mediastinal cancer and chest wall infiltration (MacDonald and Hansell 2003; Strauss and Dominioni 1999). The actual guidelines from the American College of Chest Physicians (ACCP) recommend further assessment (namely, CT of the chest) in virtually all lung cancer patients if it has therapeutic relevance (Silvestri et al. 2003). Therefore, CT and magnetic resonance imaging (MRI) are the most commonly applied imaging tools for preoperative staging of NSCLC (Park et al. 2000; Pugatch 1995; Hanson and Armstrong 1997; Ratto et al. 1991; Deslauriers and Gregoire 2000).

1.3.3.2 Computed Tomography of the Thorax

Despite recently available new imaging techniques like FDG-PET and MRI, CT of the chest is still the most popular and widely applied staging investiga-

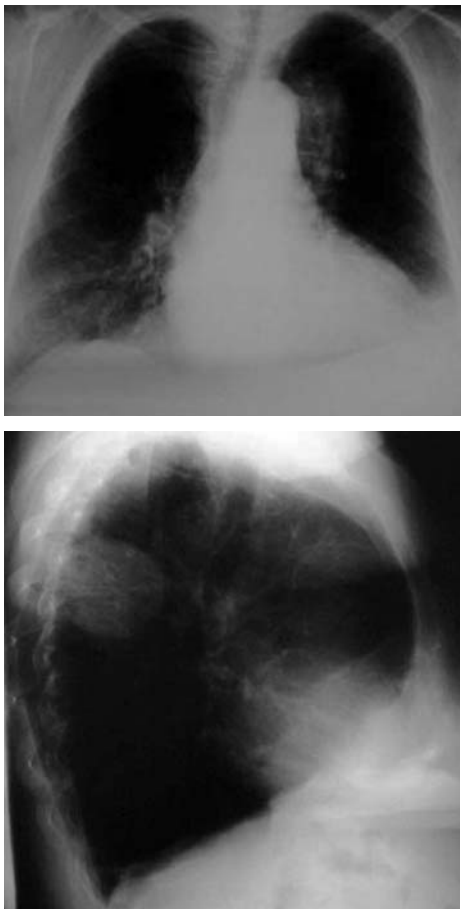

Fig. 1.3.1. Conventional chest radiography: tumor of the upper lobe

tion for lung cancer patients. New spiral multislice or helical CT scan can define the location, size, and anatomical characteristics of a tumour much better than a chest radiograph or older non-helical scans even in very small nodules of less than 5 mm in diameter (Fig. 1.3.2). Multiplanar reconstructed CT can give more information regarding the areas of superior sulcus, tracheo-bronchial tree, aorto-pulmonary window, and subcarinal and peri-diaphragm region (Touliopoulos and Costello 1995; Brink et al. 1994; Kuriyama et al. 1994). CT is useful for delineating the local extent and invasion of a lung tumour, lung atelectasis and pneumonitis. It can detect invasion into the chest wall or mediastinum, and

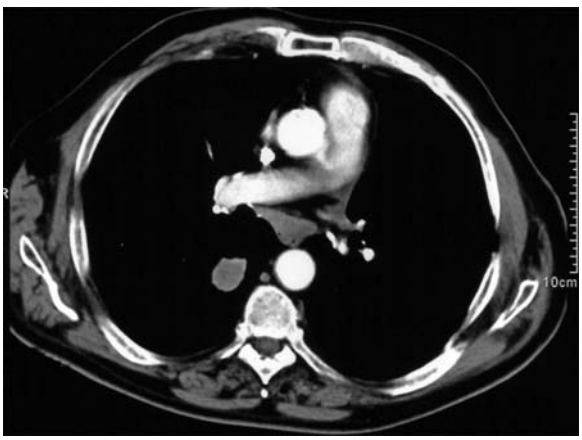

Fig. 1.3.2. CT-thorax: lung cancer with a diameter of 2.8 cm (T1-tumor) but suspected infrabifurcal lymph node infiltration, that could be excluded by PET and transesophageal ultrasound

permits 3-D reconstruction for better realizing the tumour morphology and for virtual bronchoscopy (Hollings and Shaw 2002). Nevertheless, it can not replace real bronchoscopy for locoregional staging, since mucosal abnormalities can not be detected, and histology or cytology are typically confirmed by real bronchoscopy. CT might not be reliable in distinguishing between T3 and T4 lesions with regard to mediastinal involvement, and has limited predictive value distinguishing between T2 and T3 lesions concerning pleural/chest wall invasion, with a sensitivity of between 38% and 87% and a specificity of only 40%–89% (Ratto et al. 1991; Glazer et al. 1985; Pennes et al. 1985). A certain criterion of invasion might be rib destruction by tumour mass extending into the chest wall (Glazer et al. 1985; Pearlberg et al. 1987; Haramati and White 2000). Nevertheless, large tumours can cause destruction just by pressure without proven infiltration, and, therefore, the accuracy was different in clinical studies (Pennes et al. 1985). Loss of extrapleural fat, length of pleural contact, and a tumour diameter of more than 9 mm seem to increase be predictive value of chest wall infiltration with a specificity beyond 80% and a sensitivity beyond 83% (Ratto et al. 1991). Pure pleural or chest wall thickening are not reliable indicators, nor is extrapleural soft tissue, which can be produced just by local inflammation or fibrosis, with an accuracy below 70% (Fig. 1.3.4) (Ratto et al. 1991; Glazer et al. 1985; Pennes et al. 1985; Pearlberg et al. 1987).

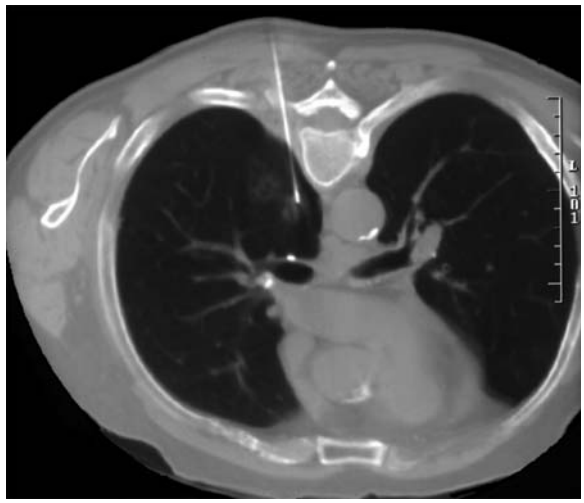

Fig. 1.3.3. Transthoracic CT-guided puncture of an area suspected to primary lung cancer

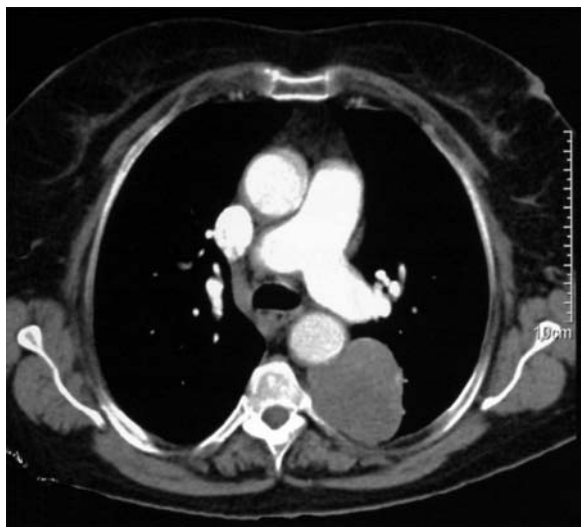

Fig. 1.3.4. CT-thorax: locally advanced lung tumor, with infiltration into the thoracic aorta and the thoracic wall suspected.

Some authors demand a cine-CT scan during respiration, to measure the tumour's mobility in comparison to those of the lungs and thoracic wall (Watanabe et al. 1991; Murata et al. 1994; Shirakawa et al. 1994).

Invasion into the mediastinum and mediastinal organs (aorta, heart) can be suspected on CT with high specificity (close to 100%) but very low sensitivity (around 40%) by thickened mediastinal pleura or pericardium, clouded fat tissue, circumferential contact of more than 90° of the mediastinal vessels, and deformation of a vascular outline (Glazer et al. 1989; Herman et al. 1994; White et al. 1994). Whether routine use of intravenous contrast medium supports the delineation of mediastinal lymph nodes and tumour infiltration into vascular structures is not yet confirmed in clinical trials (Patz et al. 1999). It is recommended but should be well-balanced with the risk of severe adverse reactions (Patz et al. 1999; Cascade et al. 1998). Sometimes, hypodense tumour mass can be discerned from contrast enhanced atelectasis. Nevertheless, even with optimal performance, CT has a sensitivity of only 52%, a specificity of only 86%, and an accuracy of only 71% in the specification of tumour status (Venuta et al. 1992). Therefore, a definite differentiation of T-stage with chest wall or mediastinal invasion is likely only possible by surgical intervention.

Although metastatic disease to hilar lymph nodes (LN) does decrease overall survival, it does not affect resectability. However, bulky mediastinal disease (N2 or N3) indeed influences the treatment concept, decisive being the most frequently used criterion defining resectability, and leading this large group of patients (21%–50% of NSCLC patients) (Martini et al. 1980; Dillemans et al. 1994; Nakanishi and Yasumoto 1996) over to neoadjuvant protocols (Mountain 1997; Park et al. 2000; Silvestri et al. 2003). Unfortunately, the only suspicious CT sign of mediastinal metastasis is LN enlargement with a short-axis diameter >1 cm on transverse CT scan, which is used by the majority of clinicians allowing the highest accuracy. Unfortunately, increased LN can occur in otherwise healthy people or patients with former infections as reactive hyperplasia (Mountain 1997; Deslauriers and Gregoire 2000; Martini et al. 1985; Choe et al. 1998; Murray et al. 1995; Martini et al. 1980; Gdeedo et al. 1997; Medina Gallardo et al. 1992). On the other hand, even up to 64% of LN normal in size can contain tumour in lung cancer patients (Hanson and Armstrong 1997; Deslauriers and Gregoire 2000; Webb et al. 1991; Arita et al. 1996). Therefore, with nodal size as the only criterion used, CT has a sensitivity of only 61% (41%–95%), a specificity of only 79% (25%–99), resulting in an accuracy of 53%–99%, and positive and negative predictive values of only 56% (14%–95)% and 83% (79%–96%) in mediastinal N2 nodal staging, respectively (Verschakelen et al. 2002; Gould et al. 2003; Toloza et al. 2003a), resulting in exclusion of more than 40% of patients from potentially curative resection. Thus, CT serves as a guide for further histological confirmation of critical LN in the mediastinum by other staging modalities before surgery, like transbronchial or transesophageal biopsy, mediastinoscopy and diagnostic thoracoscopy (Silvestri et al. 2003). Many recent studies including a meta-analysis have shown with strong evidence the superior accuracy of PET over CT for mediastinal staging with positive and negative predictive values of 79% and 93%, and the high accuracy of combined CT and PET with a sensitivity of 78%–93% and a specificity of 82%–95%, respectively (Toloza et al. 2003a; van Tinteren et al. 2002).

Standard CT protocols should include the upper liver and adrenal glands. By this means metastasis in these organs can be detected in 3%–10% of patients free of symptoms (Grondin and Liptay 2002).

1.3.3.3 Magnetic Resonance Imaging of the Thorax

Despite recent advantages in MRI techniques for imaging of the chest, the relevance of MRI in staging of lung cancer is restricted. Given disappointing sensitivity (52%–65%) and specificity (48%–79%) (Kernstine et al. 1999) without superiority to CT scan, clinicians do not routinely apply MRI in lung cancer staging. Scant experience with MRI and problems of motion artefacts and patient claustrophobia (LeBlanc et al. 2003), as well as cost, do not support broad application. Exceptional use may be considered in patients who are allergic to the intravenous contrast medium used for CT, have reduced renal function, or no peripheral venous access, since MRI can eliminate the need for contrast.

Another indication is given in superior sulcus tumour according to ACCP guidelines, for investigating possible neural or bone invasion (Silvestri et al. 2003). MRI with thin-section (5 mm) and multiplanar acquisition (coronal and sagittal images) is recommended due to its superior accuracy to CT (94% versus 63%) to detect tumour invasion of the vertebral body, brachial plexus, and spinal canal, thus precluding the necessity for surgery (Heelan

et al. 1989). There is no general use in mediastinal staging (Silvestri et al. 2003), though MRI might be more accurate than CT in diagnosing mediastinal invasion (Webb et al. 1991). The detection rate of mediastinal nodal metastasis by MRI is similar to CT (Webb et al. 1991; Martini et al. 1985; Thompson and Stanford 2000; Boiselle 2000), and MRI can guide histological confirmation of suspicious areas by invasive staging procedures in the subcarinal and aortopulmonary regions, which are difficult to assess in axial plane (Haramati and White 2000; Thompson and Stanford 2000; Levitt et al. 1985; Boiselle 2000).

Due to coronal and sagittal views MRI allows better assessment of the anatomical relationships in the apex, aortopulmonary window, and subcarinal region (Haramati and White 2000; Martini et al. 1985; Thompson and Stanford 2000). Therefore, MRI is better than conventional CT in realizing the extent of apical (Pancoast's tumour) and mediastinal tumours in this region (Thompson and Stanford 2000). Furthermore, MRI seems superior to CT in detecting tumour invasion of heart chambers, vena cava, and great pulmonary vessels (Fig. 1.3.5) (Haramati and White 2000; Thompson and Stanford 2000; Lloyd and Silvestri 2001). In contrast, MRI has restricted power to differentiate reactive inflammatory changes secondary to tumour extension and the true tumour invasion into the chest wall and mediastinum (Glazer et al. 1985; Stiglbauer et al. 1991), whereas it is sensitive in detecting pleural effusion (Deslauriers and Gregoire 2000; Stiglbauer et al. 1991). Nevertheless, pleural effusion can be benign or malignant, and, therefore, should be clarified by cytologic analysis before treatment (Quint and Francis 1999; Decker et al. 1978). Multislice contrast-enhanced CT, dynamic enhanced MRI (Hasegawa et al. 2003), MR angio- and lymphography (Bellin et al. 2000) for evaluating suspicious LN and vascular infiltration might be promising, but need further intensive clinical surgical controlled studies (Mountain 1997; Haramati and White 2000; Thompson and Stanford 2000; Macis et al. 2000; Ohno et al. 2002). Although it has various advantages over CT, MRI is and will be restricted to these specific rare clinical situations.

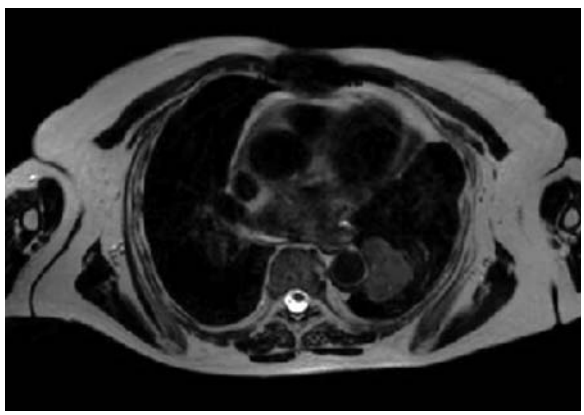

Fig. 1.3.5. MRI of the thorax: locally advanced lung tumor, but exclusion of an infiltration into the thoracic aorta.

1.3.3.4 Imaging for Extrathoracic Metastases Including Cervical Lymph Node Staging

Typical sites for metastasis from lung carcinoma are the brain, lung, liver, adrenal glands, and bone. The current investigations for metastases at these sites are CT or MRI scan of the brain, the lung including the liver and adrenal gland areas, ultrasound imaging of the upper abdomen, and radionucleotide bone scanning (Hyde and Hyde 1974). More recently, whole-body PET has been used increasingly with some good detection rate of extrathoracic metastasis (Bury et al. 1997; Valk et al. 1995).

By clinical and full radiological staging the number of unnecessary aggressive but "noncurative" thoracotomies or multimodal treatments might be reduced. Unfortunately, with extensive staging procedures (scanning of brain, liver, and adrenal glands), in contrast to pure routine chest CT and mediastinoscopy alone, it was found that in patients with previous normal clinical evaluation for distant metastasis the probability to find distant tumour spread is beyond 10% (Silvestri et al. 1995; Toloza et al. 2003a). This low prevalence of metastases in asymptomatic patients, and the relatively poor accuracy of the investigations moderate the demand of extensive staging (Grondin and Liptay 2002). Based on these results, the ACCP guidelines recommend a complete clinical evaluation for all lung cancer patients, and further extrathoracic diagnostic procedures appropriate to those with abnormal results (Silvestri et al. 2003). However, before excluding patients from curative treatment options, the suspicion should be confirmed by other more accurate means.

1.3.4 Invasive Imaging in Lung Cancer

Invasive staging procedures are often necessary for histological or cytological tissue confirmation of the

diagnosis, or to ensure the assumed stage where the clinical staging is often inaccurate (LeBlanc et al. 2003). The former situation requires an approach with a low false-negative rate, the latter a measure with a high sensitivity.

There is a variety of more or less invasive staging methods: bronchoscopy, mediastinoscopy, anterior mediastinoscopy (Chamberlain procedure), thoracoscopy (video-assisted thoracoscopic surgery), transbronchial needle aspiration (TBNA), transthoracic needle aspiration of the mediastinum or the primary tumour (TTNA), and endoscopic oesophageal or endobronchial ultrasound with fine needle aspiration (EUS-NA). Some of those means are only appropriate in specific situations that will be described in detail, with anticipated sensitivity, specificity, and particular risks.

1.3.4.1 Bronchoscopy and Transbronchial Biopsies (TBNA)

Fiberoptic bronchoscopy has a central role in staging of lung carcinoma, and is not exchangeable in obtaining the pathological diagnosis in suspected lung cancer by histological tissue from biopsy, forceps, or transbronchial needle biopsy. For cytological specification bronchoalveolar lavage, brushing, and endobronchial or transbronchial needle aspiration can be used. Bronchoscopy is safe, reliable, and widely accessible. In central lung tumours it allows direct visualization. Using forceps biopsies with sampling techniques bronchoscopy has a high sensitivity of about 80% (Mazzone et al. 2002), and is especially useful to distinguish centralized tumour by evaluating the proximity of the tumour to the carina, describing resectability in locally advanced cancer (T3) more reliably than with CT, and excluding curative resection in tumours infiltrating the carina. Bronchial brushing is frequently used, too, indicated in infiltrative or stenotic neoplasms, and gives a sensitivity of about 80%, slightly lower than with direct biopsy (Mazzone et al. 2002). In addition, transbronchial needle aspiration (TBNA) using a Wang needle is frequently used to detect central cancer, and to assess mediastinal lymphadenopathy, most frequently of subcarinal nodes as also suggested on CT scan (Govert et al. 1999; Wang 1995; Harrow and Wang 1996). The needle catheter is passed via the working channel of the bronchoscope, directed and progressed to the tracheobronchial area overlying the suspect lymph node to aspirate cells of the node. The feasibility of getting adequate specimens via TBNA is reported to be approximately 90% (Fritscher-Ravens et al. 2000; Savides et al. 2000; Wallace et al. 2001b), given a sensitivity of 80% in detecting the primary tumour and, by a meta-analysis, a sensitivity to detect lymph node metastasis of 76% and a specificity of 96% have been described (Mazzone et al. 2002; Toloza et al. 2003). Due to the insignificant morbidity it causes, TBNA can be done as an outpatient procedure. It can access even subcarinal nodes. The low sensitivity is caused by the blind procedure directed by previous CT scan alone. This problem might be solved with guidance by real-time imaging (CT, fluoroscopy, endobronchial ultrasound, or virtual CT-reconstructed bronchoscopy) (Rong and Cui 1998; Garpestad et al. 2001). The results coming from studies with a very high prevalence of N2 and N3 involvement can not be transferred to very early stages without extensive mediastinal involvement. In these situations the sensitivity is much lower, omitting TBNA from initial staging procedures, but reserving its primary role to confirm highly suspicious mediastinal involvement based on previous CT scan.

1.3.4.2 Transthoracic Needle Aspiration (TTNA)

Percutaneous transthoracic needle aspiration (TTNA) is an alternative to TBNA both for diagnosis and staging of the mediastinum, and allows the physician to assess nearly all mediastinal lymph nodes. It is regularly performed under CT or fluoroscopic guidance and does not need general anaesthesia. The procedure is well tolerated by most patients and relatively safe, but involves the risk of pneumothorax with rates of 10%–30% of patients requiring placement of a catheter for evacuation (Hyde and Hyde 1974; Fritscher-Ravens et al. 2001), an event which can be fatal in lung cancer patients also suffering from chronic airway disease and who are smokers or ex-smokers. A meta-analysis has demonstrated a sensitivity of 91% in mediastinal nodal staging (Toloza et al. 2003b). However, the FN rate is 20%–50%, and many lymph node stations may be inaccessible to TTNA because of their proximity to the heart or major thoracic vessels. Therefore, a non-cancer result cannot be counted on. TTNA remains a less-favoured staging investigation compared with procedures such as mediastinoscopy (Detterbeck et al. 2003), and should be reserved to confirm diagnosis by puncture of enlarged, suspected lymph nodes rather than to confirm the stage.

TTNA is used to confirm suspected interlobar pulmonary metastases, pleural metastases, and malignant pleural effusions by aspiration cytology. It is less invasive than video-assisted thoracic surgery and generally well tolerated. Nevertheless, there is still a risk of pneumothorax, and conclusive results are scarce compared with video-assisted thoracic surgery with diagnostic information on malignant spread in only 50%–65% of attempts in suspicious pleural effusions (DeCamp et al. 1997).

1.3.4.3 Transesophageal and Transtracheal Endoscopic Ultrasound and Needle Aspiration

Endoscopic ultrasound (EUS) based on a real-time ultrasound transducer on a fiberoptic oesophagoscope is a diagnostic procedure introduced in staging of oesophageal cancer, but increasingly used for staging of mediastinal lymph nodes also in other malignancies. It has an unlikely risk of severe complications, with negligible risk of infection or bleeding (<1%) (Wiersema et al. 2001; Fritscher-Ravens et al. 2000a; Schwartz et al. 2002; Patelli et al. 2002; Harrow et al. 2000). This technique offers almost exclusively but excellent access to the subcarinal, posterior mediastinal, retroperitoneal, and celiac axis lymph nodes. It offers a sensitivity of 78% and a specificity of 71% for qualitative assessment of mediastinal nodal status only (Toloza et al. 2003b), because even criteria such as echogenicity, size, and homogeneous or heterogeneous appearance are not proof of malignancy (Silvestri et al. 2003; White et al. 1994; Fritscher-Ravens et al. 2003). In clinical studies, EUS alone was superior to CT (84% vs. 49%) in the detection of metastatic lymph nodes (Gress et al. 1997), and even to PET (94% vs. 73%), but the specificity was higher in PET scanning (83% vs. 71%) (Fritscher-Ravens et al. 2003).

To date, there is no evidence regarding the feasibility of endoscopic ultrasound-guided transesophageal fine needle aspiration (EUS-FNA). The reported sensitivity is between 89% and 100% (Fritscher-Ravens et al. 1999, 2000b, 2003; Gress et al. 1997; Savides et al. 2000; Wallace et al. 2001b; Wiersema et al. 2001), and the false negative rate about 23% when an EUS-based needle aspiration is performed (Toloza et al. 2003b), though the majority of examined patients within clinical trials had clearly enlarged lymph nodes easy to puncture. Few definite available data on specificity show up to 100%, and it has been shown that severe toxicity is rare (Detterbeck et al. 2003; Fritscher-Ravens et al. 2000a,b; Harrow et al. 2000). Overall, the accuracy of EUS-FNA achieved results of 94%–100% in published series (Fritscher-Ravens et al. 1999, 2000a, 2003; Gress et al. 1997; Savides et al. 2000; Wallace et al. 2001b; Wiersema et al. 2001), being superior to CT and PET alone (Fritscher-Ravens et al. 2003; Gress et al. 1997; Wiersema et al. 2001), as well as the combination of both PET and CT (Fritscher-Ravens et al. 2003).

In treatment planning, EUS-FNA allows tissue confirmation in those patients, in whom bronchoscopy and associated methods could not confirm the disease (Fritscher-Ravens et al. 1999, 2000; Savides et al. 2000), and supplies the diagnostic staging of lung cancer with implications for further therapeutic management (Gress et al. 1997; Savides et al 2000; Wallace et al. 2001a; Wiersema et al. 2001). It makes an ideal adjunct to confirm lymph nodes suspicious on CT and/or PET.

The former blind nature of transbronchial and transtracheal biopsy with a moderate overall sensitivity and diagnostic accuracy (about 70%) may be improved by guidance with CT fluoroscopy or transbronchial ultrasound (Patelli et al. 2002; Harrow et al. 2000). Lymph nodes are localized by a 20-MHz miniature ultrasound probe placed in the trachea or central bronchus. After withdrawal of the ultrasound probe, a blind puncture follows. Real-time endobronchial ultrasound to control puncture directly is not yet available. There is access only to the pre-, para-tracheal, subcarinal lymph nodes, and partially the aortopulmonary window. Accuracy of EUS-FNA is 92% for the diagnosis of malignant mediastinal lymph nodes, while accuracy is 73% (Wiersema et al. 2002). Unfortunately, only small probes can be assessed, accounting for the relatively high false rate in lymph nodes carrying only small foci of malignancy. This problem might be solved in part by molecular techniques in combination with EUS-FNA (Wallace et al. 2003).

1.3.4.4 Mediastinoscopy

Mediastinoscopy performed under general anaesthesia is still the "gold standard" of invasive staging procedures for mediastinal staging of lymph node metastases and mediastinal infiltration (Barker and Silvestri 2002; Cybulsky and Bennett 1994). All of the pre- and left and right paratracheal (stations 1, 2R, 2L, 3, 4R, 4L) and the anterior subcarinal (sta-

tion 7) are accessible via suprasternal approach, and at least five nodal stations (stations 2R, 4R, 7, 4L, 2L) should be examined in principal, with no less than one node sampled from each station. It is considered minimally invasive and safe with low rates of morbidity and mortality (together about 2% and 0.7%, respectively: pneumothorax, left recurrent laryngeal nerve injury, bleeding, airway and oesophageal trauma, and infection) so that most patients can be discharged within 1 day of the procedure (LeBlanc et al. 2003; Cybulsky and Bennett 1994).

Areas that cannot be explored with this technique are the posterior subcarinal (station 7), inferior mediastinal (stations 8, 9), and aortopulmonary window and anterior mediastinal (stations 5, 6) nodes. Therefore, the sensitivity of conventional mediastinoscopy to ascertain tumour infiltration of mediastinal nodes was only 81% in a meta-analysis of 14 studies (Toloza et al. 2003), and the average false negative rate is about 10% mainly due to inaccessible nodes, in particular the posterior subcarinal, aortopulmonary window, and anterior and inferior mediastinal stations (Gdeedo et al. 1997; Hammoud et al. 1999; Kiernan et al. 2002; von Haag et al. 2002). Despite these problems, however, mediastinoscopy remains the standard approach for mediastinal staging with proven value in lung cancer. Mediastinoscopy is indicated in patients with pathological CT findings of mediastinal lymph nodes and otherwise eligible for surgery, with large or centrally located tumours infiltrating the mediastinum, and with histologically proven adenocarcinoma (Detterbeck et al. 2003; Canadian Lung Oncology Group 1995; Sugerbaker and Strauss 1993).

1.3.4.5 Aortopulmonary Window (APW) Lymph Node Assessment

Nodes in the aortopulmonary window (APW) (station 5) are typically infiltrated in locally advanced carcinoma of the left upper lobe, and represent the most important group of N2 nodes inaccessible by standard cervical mediastinoscopy. EUS-FNA is one method to evaluate these nodes, but it is restricted by a high false-negative rate. Other techniques are an extended cervical mediastinoscopy technique passing more laterally over the aortic arch (Ginsberg et al. 1987) also using a suprasternal incision, or an anterior mediastinotomy via the second or third intercostal space just to the left of the sternum, known as a Chamberlain procedure (Best et al. 1987). The extended cervical mediastinoscopy carries a small risk of bleeding and embolic stroke, but has the advantage of being able to perform a standard mediastinoscopy in the same sitting. The extended cervical mediastinoscopy has a reported sensitivity of about 50% and a negative predictive value of about 70%, increased in combination with standard cervical mediastinoscopy to 69%–76% and 82%–89%, respectively (Ginsberg et al. 1987; Freixinet et al. 2000). The Chamberlain procedure carries a lower risk of embolic stroke but needs an extra incision, may produce pleural injury and pneumothorax, and can hurt the left internal mammary artery (Toloza et al. 2003). Pure anterior mediastinotomy presents a sensitivity of 63%–86% to ascertain N2 invasion, and can be improved by a simultaneous standard cervical mediastinoscopy to 87% (Best et al. 1987; Deneffe et al. 1983). The Chamberlain or Ginsberg approaches are recommended by the ACCP guidelines in primary NSCLC tumours of the left upper lobe a soon as a standard cervical mediastinoscopy is required (Detterbeck et al. 2003), although the reliability of this procedure has not been extensively documented. It can also be used to assess local respectability.

1.3.4.6 Video-Assisted Thoracoscopy (VATS)

Video-assisted thoracic surgery (VATS) delivers a safe and reliable histological staging in lung cancer patients by visual evaluation of the extent of locoregional involvement including mediastinal organs, although it is in principle limited to only one side of the mediastinum (DeCamp et al. 1995; Roviaro et al. 1995; Loscertales et al. 2002), and is further improved by physical manipulation and digital palpation via instrument ports. VATS can be used to detect chest wall invasion, pleural effusion, and pleural tumour deposits, to define their extent, and to conduct drainage or even pleurodesis (Roviaro et al. 1995). All lymph node stations on the ipsilateral side down to the pulmonary ligament and paraesophageal stations, as well as the total pleural space, can be visualized and prepared for biopsy. The biopsy specimens allow a high quality of histological analysis, and result in diagnostic accuracy rates of VATS of 92%–100% (Sihoe and Yim 2003; Nakanishi et al. 1994; Ishida et al. 1996; Ghosn et al. 1994), comparable to those acquired with lymph node dissection via thoracotomy (Sagawa et al. 2002). VATS

might be useful in evaluating the response rates after neoadjuvant therapy in patients after previous mediastinoscopy, where repeated mediastinoscopy is difficult (Sonett and Krasna 2000), and in exploration for intrathoracic metastasis. There are no guidelines on the use of VATS. Nevertheless, due to the high precision in describing locoregional resectability, not only by pure visual inspection but also digital or instrument palpation, VATS is often recommended immediately before thoracotomy for lung cancer resection (Detterbeck et al. 2003; Sihoe and Yim 2003; Asamura et al. 1997; Roviaro et al. 1996; Yim 1996), which can spare a more radical approach in unresectable situations not detectable by non-invasive staging procedures and give some information on the optimum level for the thoracotomy (DeCamp et al. 1995).

1.3.4.7 Diagnostic Thoracotomy

Traditionally, the resection of the tumour and lymph nodes by thoracotomy for achieving a complete and accurate pathological staging has been recommended. Nevertheless, it is still debatable whether the extent of lymph node clearance should be as radical as possible to achieve an accurate staging and reduced remainder of malignant cells in the mediastinum, or just systematic to spare morbidity and perioperative disturbances of the immune system (Passlick et al. 2002; Izdicki et al. 1994; Grondin and Liptay 2002). An alternative may be the concept of sentinel node mapping within a video-assisted thoracoscopic procedure. The theory of sentinel node biopsy is supported by modern immunohistochemical staining techniques presenting micrometastases in more than 20% of lymph nodes previously thought to be benign (Kubuschock et al. 1999; Riquet et al. 1999), and the 20%–30% incidence of "skip metastases" in N2 nodes although the N1 nodes were free of malignant cells (Yoshino et al. 1996). Sentinel node mapping is performed by injecting a dye or radioisotope marker into the tumour during thoracotomy (Little et al. 1999; Liptay et al. 2000). The positive "sentinel" nodes carrying the marker are dissected. One initial study demonstrated feasibility in 82% of the patients and accuracy of 94% Micrometastases were found in 8% of patients, and "skip metastases" were found in 22% (Liptay et al. 2000). To date, this procedure can not be recommend outside of clinical studies, although this technique holds promise for the future.

Comprehensive, pure thoracoscopy is the standard invasive approach to evaluate pulmonary nodules and pleural effusions if less invasive procedures failed, and an adjuvant in the staging of ipsilateral mediastinal lymph nodes.

1.3.4.8 Other Staging Procedures

In patients with advanced disease, other than the previously explained invasive diagnostic procedures other than those previously explained might be indicated: needle aspiration of a supraclavicular lymph node, thoracentesis or thoracoscopy of a pleural effusion, or needle aspiration or biopsy of a metastatic site such as an enlarged adrenal or hepatic mass. Often these represent the easiest way to confirm the diagnosis of lung cancer. On the other hand, the policy to examine these sites of advanced disease takes into account that they are of imposing prognostic relevance both for life expectancy and quality of life.

An enlarged supraclavicular lymph node or a pleural effusion is probably carrying tumour cells: it has been estimated that up to 75% of NSCLC patients may have N3 nodal metastases at the time of presentation (Miller and Taylor 1965). A recent study reported that one-third of patients with mediastinal metastases on mediastinoscopy were also found to have occult cervical lymph node metastases (Lee and Ginsberg 1996). These scalene, supraclavicular, and cervical lymph nodes are easily accessible and, therefore, needle aspiration or surgical biopsy to diagnose an enlarged supraclavicular node are used either to confirm the diagnosis or to define the stage, although data on sensitivity, specificity, and false negative and false positive puncture rates are missing. Nevertheless, this approach is an attractive means of excluding patients from unnecessary surgery and risky invasive biopsy of the mediastinal nodes. Simple percutaneous FNA provides reliable biopsy results from palpable lymph nodes (Rohwedder et al. 1990), and guided by PET or ultrasound (using altered shape, internal architecture, vascular pattern, and echogenicity as criteria) even biopsy of impalpable cervical nodes can detect occult cervical node metastases in 8%–31% of lung cancer patients (Fultz et al. 2002; Sihoe and Yim 2003). On the other hand, routine open exploration of the supraclavicular areas is relatively invasive but can be done by extending of a routine cervical mediastinoscopy with subsequent exploration of the aortopulmonal window (Lee and Ginsberg 1996).

In patients with a suspected distant spread to liver, bone, or adrenal region an invasive procedure is indicated to accurately define the stage. The procedures used to assess possible distant sites are dictated primarily by technical and anatomic factors specific to the particular patient, in most cases CT-guided puncture, sometimes open resection. No data are available on the reliability of these staging procedures in patients with lung cancer. In general, procedures that can be performed on an outpatient basis and that carry a low risk of complications should be preferred, but they should also have a reasonable specificity.

1.3.4.9 Molecular Staging

Insight at the molecular level by means of molecular analysis in terms of carcinogenic process, mechanisms for growth, and evading apoptosis of lung cancer is increasing, and offers promise to finding molecular indicators of a tumour's particular "virulence" (Naruke et al. 2001; Jernal et al. 2002). At least one current preliminary study has proposed the prognostic value of molecular markers as being of even higher relevance than lymph node involvement (D'Amico et al. 2000). Tumour biology has been studied extensively, including carcinogenesis (oncogenes, tumour-suppressor genes, cell growth-regulating proteins), angiogenic factors, factors affecting tumour invasion (extracellular matrix metalloproteases), and markers of micrometastases. There is now increasing evidence that the synergy and interactions of the various molecular mechanisms represented may be at least as important as the individual prognostic significance of each molecular marker. The molecular markers among the multiple molecular, demographic, surgical, and pathological factors predicting local recurrence were K-ras mutation, positive p53 expression, and absent H-ras expression (Kwaitkowski et al. 1998). Five markers were found to be significant predictors of survival (erbB-2, Rb, p53, factor VIII, and CD-44), but the cumulative number of individual markers present could further stratify patients into different risk categories (D'Amico et al. 1999). Testing for an array of molecular markers may give more precise information on prognosis. Nevertheless, molecular staging still has to make an impact on clinical practice, because much of the evidence as yet falls short of the demands for clinical use, caused by problems within the research project published so far (non-standardized techniques, small and even contradicting studies) (Kwaitkowski et al. 1998; Iyengar and Tsao 2002; Lee et al. 1995). Despite these problems, however, molecular staging holds great promise for the future (Putnam 2001; D'Amico 2002). The prospects for accurately substaging patients may allow for highly individual prognoses and, accordingly, the determination of individualized therapy. The incorporation of molecular techniques into routine clinical practice will revolutionize lung cancer management.

1.3.5 General Recommendations

There are only a few guidelines in diagnostic evaluation of suspected lung cancer patients. The strategy depends on factors related to the patient (clinical presentation, co-morbidities, functional operability, compliance), to the tumour (localization and extent of the tumour, histology, and others), to the available facilities, and to the cost of procedures. Accurate definition of the diagnosis and stage allows the optimal treatment to be selected and is therefore recommended as precisely as possible. Diagnosis usually starts with the assessment of clinical presentation, risk factors, and radiographic appearance.

After initial investigation of the thoracic organs by chest radiograph and suspicion on lung cancer, flexible bronchoscopy and CT play a major role in the diagnosis of lung cancer bronchoscopy: they are applied initially to establish a tissue diagnosis with biopsy, brushings and/or washings, to localize the tumour and endobronchial extent, and to give an overview on suspicious locoregional lymph node infiltration. The overall output of bronchoscopy for the diagnosis of lung cancer varies from 30% to 90%. This mainly depends on the location of the tumour, with centralized tumours being histopathologically confirmed in close to 100% (Park et al. 2000; Pugatch 1995; Hanson and Armstrong 1997). Deep infiltrating tumours not specified by pure bronchoscopy will be defined further by bronchoalveolar lavage, brushing, endobronchial or transbronchial needle aspiration, or transbronchial biopsy when confirmation of the diagnosis is the primary aim. Lymph nodes can also be explored by these techniques. With CT, the size of the tumour, possible mediastinal involvement, and lymph node infiltration can be evaluated. The diagnostic approach can be extended to mediastinoscopy, trans-

esophageal ultrasound-based biopsy, or even thoracoscopy, if tumour is otherwise not confirmed.

Mediastinoscopy is preferred due to its low false negative rate (approximately 10%), if mediastinal involvement of lymph nodes or infiltration of the primary into the mediastinum should be clarified for further treatment planning, in particular if resection or a multidisciplinary approach are planned and offer a realistic cure. Mediastinoscopy is also recommended if the PET scan is positive in the mediastinum, or discrete enlarged lymph nodes exist. Transbronchial, transthoracic, or ultrasound-guided transesophageal approaches, as well as Chamberlain procedures or thoracoscopy, may be recommended under particular circumstances, for example if only lymph nodes of the paraesophageal region or aortopulmonary window seem to be involved. Transesophageal ultrasound can evaluate the posterior mediastinum including the infracarinal area with high precision, and allows tissue sampling by transesophageal puncture with high sensitivity (about 90%).

The optimal technique depends on expertise and should be chosen following multidisciplinary discussion.

When extensive infiltration of the mediastinum is documented already after radiological examination, meaning stage is clearly defined and bronchoscopy is unable to obtain tissue for histology or cytology, transbronchial, transtracheal, or transesophageal puncture should be preferred to mediastinoscopy, because they are less invasive and have a high sensitivity (about 90%) and low morbidity.

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Basic Treatment Considerations

2.1 Lung Cancer Surgery

Sidhu P. Gangadharan, Philip A. Linden, and David J. Sugarbaker

CONTENTS

2.1.1 Introduction

Lung cancer is the most common cancer in the world, with an incidence of 1.2 million cases and 1.1 million deaths in the year 2000 (Parkin et al. 2001). In the United States alone an estimated 171,000 new cases and 157,000 deaths from lung cancer occurred in 2003 (Jemal et al. 2003). It is estimated that lung cancer accounts for nearly 13% of cancers (excluding non-melanoma skin cancer) worldwide, comprising 18% of new cancers for men and 7% for women (Parkin et al. 1999). The United States has seen a modest improvement in 5-year survival to approximately 15% over the interval between 1974 and 1998, although death from lung cancer still exceeds that from all other cancers (Jemal et al. 2003).

The World Health Organization has classified the histologic subtypes of lung cancer (Brambilla et al. 2001). Surgical resection represents the best chance for cure of epithelial non-small-cell lung cancers. However, perhaps up to three-quarters of patients presenting with lung cancer have lesions that are unresectable because of locally advanced tumor or systemic spread (Anonymous 1995; Ginsberg et al. 1997). This chapter provides an overview of the important surgical aspects of lung cancer therapy, including preoperative assessment of resectability, operative strategy, adjuvant and neoadjuvant therapy, and challenging lung cancers, such as tumors invading the mediastinum or chest apex (superior sulcus tumors).

2.1.2 Preoperative Assessment

2.1.2.1 Diagnosis

Patients presenting with lung cancer are usually symptomatic, describing a history of cough, weight loss, or dyspnea in 60%–75% of cases (Beckles et al. 2003a). Hemoptysis, chest or bone pain, fever, or weakness occur somewhat less frequently (Beckles et al. 2003a). Physical examination may elicit signs of advanced disease including the following: lymphadenopathy in the supraclavicular or cervical regions, percussion dullness from an effusion, and neck vein distension from superior vena cava obstruction. After radiologic confirmation of the presence of tumor, a pathological diagnosis may be obtained by means of sputum cytology, bronchial washings or brushings, or fine needle aspiration. Bayesian theory has been applied to the undiagnosed pulmonary nodule

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to estimate likelihood of malignancy (Gurney et al. 1993; Gurney 1993; Cummings et al. 1986). This approach considers the resulting pre-test probability of malignancy, in conjunction with the patient's operative risk, and stratifies the patient into one of three categories: observation, further non-resectional diagnostic testing (e.g., sputum cytology, bronchial washings or brushings, fine needle aspiration, PET scan), or surgical resection (Ost et al. 2003). The patient's pre-test probability is highly dependent upon age, smoking history, and CT scan characteristics of the lesion (i.e., size greater than 2 cm, spiculations, and recent lesion growth).

2.1.3 Staging

Once the diagnosis of pulmonary malignancy has been made or, conversely, the pre-test probability is sufficient to warrant resection without preoperative tissue diagnosis, the patient undergoes a staging work-up to assign prognosis and determine the most appropriate therapy. The staging system for non-small cell lung cancer is based on TNM classification (Table 2.1.1) (Mountain 1997). Verification of stage is accomplished both invasively (i.e., fine needle biopsy, resection) and non-invasively (i.e., CT scan, PET scan). Stages I and II non-small cell lung cancers are treated with surgical resection. Patients with locally advanced Stage III tumors are potential candidates for surgery, depending on the specific aspects of local invasion (e.g., tumor infiltration into the chest wall or carina versus involvement of great vessels or heart) or level of nodal metastasis. Stage IV cancers exhibiting extensive metastatic spread are generally outside the realm of the thoracic surgeon, except for palliative measures, although solitary metastases may not preclude a potentially curative lung resection. Patients whose poor medical condition precludes a pulmonary resection may still benefit from interventions to restore and maintain airway patency through bronchoscopic debridement of tumor, photodynamic therapy, airway stenting, or brachytherapy.

Table 2.1.1. Non-small cell lung cancer staging

Stage	TNM subset
IA	T1N0M0
IB	T2N0M0
IIA	T1N1M0
IIB	T2N1M0 T3N0M0
IIIA	T1N2M0 T2N2M0 T3N1M0 T3N2M0
IIIB	T1N3M0 T2N3M0 T3N3M0 T4N0M0 T4N1M0 T4N2M0 T4N3M0
IV	Any T, any N, M1

2.1.3.1 T Stage

T1 tumors are less than 3 cm in diameter and exhibit invasion no more proximal than a lobar bronchus. These lesions are completely surrounded by lung parenchyma. T2 tumors are greater than 3 cm in diameter or exhibit invasion into the visceral, but not parietal, pleura. The extent of proximal invasion may be as far as a main stem bronchus, but no closer than within 2 cm of the carina. Atelectasis or pneumonitis resulting from T2 tumors may extend to the hilum, but not involve an entire lung.

T3 tumors are locally invasive and involve the parietal pleura, chest wall, diaphragm, mediastinal pleura, parietal pericardium, or a main stem bronchus less than 2 cm from the carina. There may be atelectasis or pneumonitis involving an entire lung.

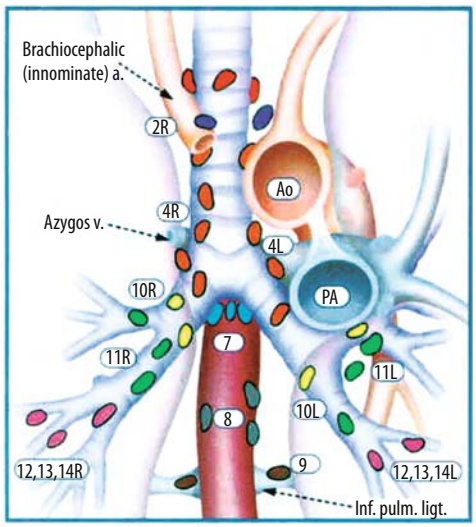
T4 tumors exhibit invasion of the carina, trachea, mediastinum, great vessels, heart, or esophagus. A malignant pericardial or pleural effusion conveys T4 status. In addition, satellite tumor nodules within the same lobe as the primary tumor are considered T4 lesions. There are two important points regarding resectability of T3/T4 tumors. First, it is essential to realize that an ipsilateral effusion termed T4 may not be a pathologic T4 tumor. Thoracoscopy with pleural biopsy often demonstrates a benign effusion secondary to lobar collapse. Second, clinical T4 tumors from a secondary nodule in the same lobe have a better prognosis (3-year survival of 66.5%) than other pathologic T4 tumors, and patients should be offered resection (Battafarano et al. 2002).

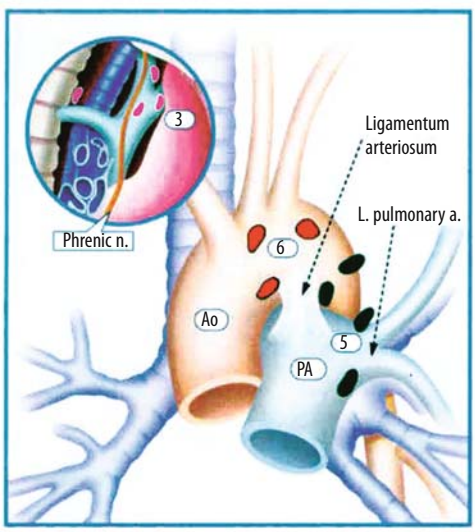
CT scanning has been considered a mainstay of tumor staging, but may incompletely distinguish the T1/T2 from T3/T4 tumors, a distinction that may affect the extent of surgical resection (Webb et al. 1991). Recent studies show that CT alone may incorrectly

stage tumors up to one-quarter of the time (Antoch et al. 2003; Lardinois et al. 2003). Integrated PET-CT scan may prove more accurate, yielding 98% correct tumor staging when compared to the final histopathological staging (Lardinois et al. 2003). In terms of airway invasion, although radiologic reconstruction of the bronchi and trachea are useful adjuncts to operative planning, our policy is to always perform bronchoscopy to assess the airway before any consideration of surgical resection. Determination of the proximal extent of endobronchial tumor invasion (i.e., distance from carina) may be accomplished, in addition to assessment for anatomic abnormalities, which might influence the surgical resection. Intraoperatively, frozen section analysis may be useful to determine extrapulmonary tumor involvement versus inflammation or adhesion in some cases (i.e., confirm T3 or T4 status).

2.1.3.2 N Stage

The lymph node drainage of the lung has been described previously (Asamura et al. 1999; Naruke et al. 1978). In 1997, a revised lymph node map was agreed upon by the American Joint Committee on Cancer (AJCC) and the Union Internationale Contre le Cancer (UICC) (Fig. 2.1.1) (Mountain and Dresler 1997). N0 cancers have no demonstrable metastases to regional lymph nodes. N1 represents metastasis to the ipsilateral peribronchial lymph nodes, ipsilateral hilar lymph nodes, or both, and intrapulmonary nodes involved by direct extension of the primary tumor (lymph nodes with double-digit numbering). N2 lymph nodes are metastases to ipsilateral mediastinal lymph nodes, subcarinal lymph nodes (single-digit lymph nodes), or both. N3 designates lymph





Superior Mediastinal Nodes

- 1 Highest Mediastinal
- 2 Upper Paratracheal
- 3 Pre-vascular and Retrotracheal
- 4 Lower Paratracheal (including Azygos Nodes)

N_2 = single digit, ipsilateral
N_3 = single digit contralateral or supraclavicular

Aortic Nodes

- 5 Subaortic (A-P window)
- 6 Para-aortic (ascending aorta or phrenic)

Inferior Mediastinal Nodes

- 7 Subcarinal
- 8 Paraesophageal (below carina)
- 9 Pulmonary Ligament

N_1 Nodes

- 10 Hilar
- 11 Interlobar
- 12 Lobar
- 13 Segmental
- 14 Subsegmental

Fig. 2.1.1. Regional lymph node staging system for non-small cell lung cancer. [Reproduced with permission from Mountain CF and Dresler CM (1977) Regional lymph node classification for lung cancer staging Chest June 111(6):1718–1723, Figure 1, p. 1719]

node metastasis to contralateral mediastinal or hilar lymph nodes, or ipsi- or contralateral scalene or supraclavicular lymph nodes.

Non-invasive lymph node staging can be performed using CT scan, PET scan, MRI, or endoscopic ultrasound (EUS). A meta-analysis of studies utilizing these various modalities revealed a pooled sensitivity of 57% for CT, 84% for PET, 100% for MRI, and 78% for EUS. Specificities were 89% for CT, 82%–95% for PET, 91% for MRI, and 71% for EUS. Further study of MRI is warranted, however, as the results were drawn from a single report of only 20 patients (Toloza et al. 2003). Currently, MRI would not be considered the standard imaging modality for evaluation of lymph nodes in lung cancer. The accuracy of CT or PET scan with regard to lymph node staging may be enhanced by the integration of these two technologies, although combined CT-PET scanners are not currently available in all facilities (Lardinois et al. 2003; Weng et al. 2000).

Invasive lymph node staging can be accomplished by transthoracic needle biopsy, EUS needle biopsy, mediastinoscopy, or thoracoscopy. Meta-analysis of the first four techniques reveals that cervical mediastinoscopy yields the best performance profile, with a sensitivity of 81% and negative predictive value of 91% (Toloza et al. 2003). Half of the nodes missed were not accessible through cervical mediastinoscopy, because this technique only permits evaluation of the paratracheal and subcarinal lymph node stations. Further enhancement of sensitivity may be accomplished with the addition of extended cervical or anterior mediastinotomy techniques (Ginsberg et al. 1987; McNeill and Chamberlain 1966). Therefore, mediastinoscopy is the recommended nodal staging technique except in the instance of extensive tumor infiltration into the mediastinum, where radiologic staging may suffice and needle aspiration or bronchoscopy may be enough to obtain pathologic confirmation of diagnosis (Kramer and Groen 2003; Detterbeck et al. 2003). The utility of thoracoscopic lymph node staging has not been fully elucidated (Gossot et al. 1996; Landreneau et al. 1993).

We use cervical mediastinoscopy as the last preoperative staging step before planned surgical resection. To minimize the likelihood that lymph nodes will read as falsely negative for tumor metastasis, we send the specimens for permanent section analysis by pathology, instead of relying on frozen section analysis. Thus, the planned pulmonary resection is deferred to a second operative setting. The surgical approach to cervical mediastinoscopy and lymph node sampling commences with a small incision above the sternal notch, followed by dissection between the strap muscles until the pre-tracheal fascia may be breached. Blunt dissection is then used to enter the mediastinum, and the paratracheal and subcarinal lymph nodes are exposed and removed with a biopsy forceps under direct vision (Reed and Sugarbaker 1996). The morbidity of the procedure is minimal (Park et al. 2003; Luke et al. 1986). Determination of IIIB disease (contralateral mediastinal lymph node involvement, N3) would preclude surgical resection. Our algorithm for positive N2 nodes involves preoperative chemoradiation or chemotherapy alone, followed by re-staging imaging to ascertain response. If there is no progression of disease, we recommend pulmonary resection with radical lymphadenectomy.

2.1.3.3 M Stage

M0 connotes no distant metastasis; M1 reports the presence of distant metastasis. A patient who is deemed to have M1 disease by virtue of a nodule in a separate lobe should be diagnosed by limited resection. The patient may be a candidate for curative resection, as these patients have a better prognosis than patients with distant M1 disease. In one study, the 3-year survival of T1-T2/N0/M1 resected tumors was 63.6% (Battafarano et al. 2002). The absence of clinical findings may preclude the need to extensively scan the asymptomatic early-stage lung cancer patient, as neither survival nor recurrence rates are affected (Tanaka et al. 1999; Ichinose et al. 1989). Some authors have recommended radiologic investigation for extrathoracic disease (e.g., bone scan, head CT, abdominal CT) only if it is warranted by clinical evaluation or in the case of advanced disease (stage IIIA or IIIB) (Silvestri et al. 2003). Unnecessary thoracotomy, however, may be prevented by routine extensive extrathoracic workup (Anonymous 2001). In addition to head CT, we have also started using whole body integrated PET-CT scanning to further clarify the presence of metastatic disease, and the effect of this new technology on survival and recurrence is yet to be prospectively determined.

Patients with either solitary brain metastases (Patchell et al. 1990; Burt et al. 1992; Magilligan et al. 1986) or solitary adrenal metastases (Luketich and Burt 1996; Porte et al. 2001) may benefit from surgical resection of the primary lung tumor in addition to the metastatic lesion. Our strategy is to combine a metastatic workup with cervical mediastinoscopy. If contralateral nodal disease is not found, then the patient may undergo resection of the solitary

brain or adrenal metastasis, followed by pulmonary resection as above.

2.1.4 Preoperative Fitness

Once a patient is determined to be resectable, it is imperative to assess overall fitness to undergo surgery. In addition to a careful history and physical that might reveal the presence of heart failure, coronary insufficiency, or other co-morbidities, all patients considered for surgical resection at our institution undergo pulmonary function testing (PFT) and determination of the diffusing capacity of the lung for carbon monoxide (DL_{CO}). In addition, a modified stair-climbing test is sometimes used to assess a patient's suitability for surgery (Brunelli et al. 2002, 2004).

A preoperative forced expiratory volume (FEV1) >2L (60% predicted) and DL_{CO} >60% predicted value suggest that the patient will tolerate pulmonary resection, including pneumonectomy. The threshold to tolerate a lesser resection is commensurately reduced: FEV1 >1L for lobectomy and FEV1 >0.6L for wedge resection (Miller et al. 1981). At our institution we rely heavily on the percent of predicted values, as these account for individual variability in age or size. Despite some variance in the literature regarding the efficacy of FEV1 or DL_{CO} in predicting outcome after lung surgery (Stephan et al. 2000; Ferguson et al. 1988), further testing to stratify postoperative risk should be undertaken if the FEV1 or DL_{CO} is less than the thresholds cited above (Datta and Lahiri 2003).

Calculation of a predicted postoperative FEV1 (ppoFEV1) may be accomplished either by estimation, using the formula of Juhl and Frost [ppoFEV1 = preoperative FEV1 × (1-[*S*×5.26]/100); *S*: number of segments to be resected] (Juhl and Frost 1975), or by quantitative VQ scanning modified after Wernly and colleagues (1980) [ppoFEV1 = preoperative FEV1 × (1-[% perfusion contributed by affected lung/100 × *S*/total number of segments in affected lung])]. A ppoFEV1 >40% predicted and DL_{CO} >40% predicted have been suggested as threshold values (Datta and Lahiri 2003; Beckles et al. 2003b). Our group has recently demonstrated that by using a variety of minimally invasive techniques, limited resections, and concomitant lung volume reduction, with advanced anesthetic and perioperative care, curative resections can be performed in patients with *preoperative* FEV1 <35% predicted with a mortality of 1% and serious morbidity under 5% (Linden et al. 2004). The determination of operability should be made by a thoracic surgeon skilled in these techniques. Exercise testing and calculation of VO_{2max} represents the next level of testing should the predicted postoperative values be below threshold values. VO_{2max} >20 ml/kg/min designates an acceptable risk group for surgery. VO_{2max} <10 ml/kg/min confers significantly increased risk for postoperative death or cardiopulmonary complications following lung surgery (Datta and Lahiri 2003; Beckles et al. 2003b).

In patients who are scheduled to undergo pneumonectomy or who may present with cardiac comorbidity, we obtain a preoperative echocardiogram to evaluate ventricular and valvular function, as well as to investigate any pre-existing pulmonary hypertension. Occasionally, right heart catheterization and pulmonary artery balloon occlusion are used to determine further a patient's physiologic response to lung resection.

2.1.5 Operative Strategy

2.1.5.1 Nomenclature and Anatomy

The scope of surgical resection ranges from 'wedge resection' to 'pneumonectomy'. The wedge resection represents a non-anatomic resection of the target lesion, with a variable margin of lung parenchyma. The terminology 'non-anatomic' refers to the lack of dissection of any of the branches of the three bronchopulmonary structures – pulmonary vein, pulmonary artery or bronchus – or the attendant draining lymphatics or lymph nodes. 'Segmentectomy' describes an anatomic resection of the bronchopulmonary segment (Fig. 2.1.2). The right upper lobe is comprised of apical, anterior, and posterior segments; the right middle lobe is comprised of the lateral and medial segments; and the right lower lobe is comprised of the superior segment, as well as the medial, anterior, lateral, and posterior basal segments. The left upper lobe is divided into the upper division comprising the apicoposterior and anterior segments, and the lingula, which contains a superior and inferior segment. The left lower lobe is comprised of the superior segment, and the anteromedial, lateral, and posterior basal segments. 'Lobectomy' entails removal of an entire lobe and its lobar pulmonary artery, pulmonary vein, and bronchus, with attendant lymphatic basin.

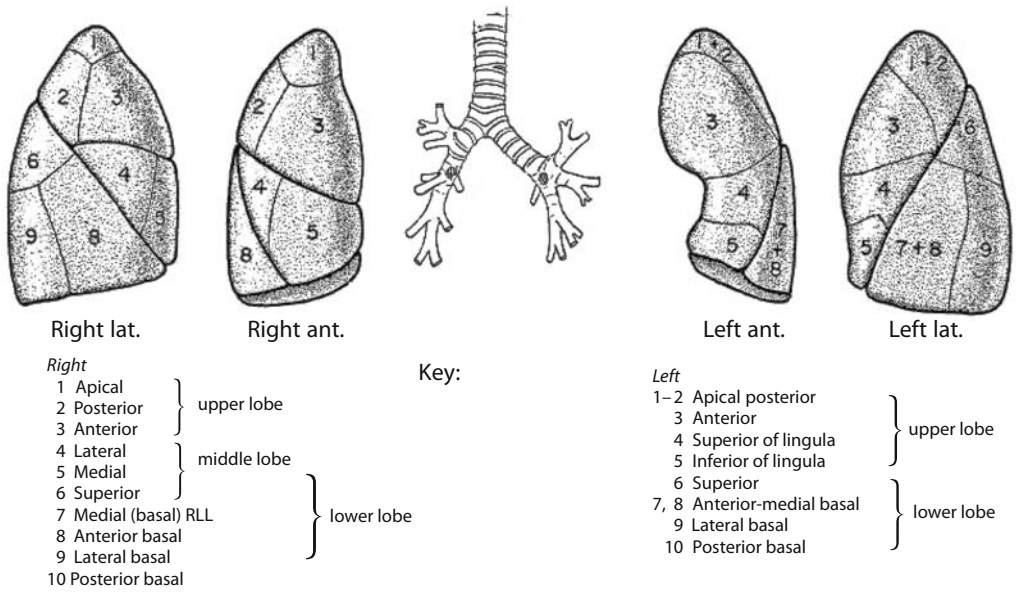


Fig. 2.1.2. Surgical anatomy of the lung. [Reproduced with permission from Elsevier Science, Inc, JB Putnam Lung (including pulmonary embolism and thoracic outlet syndrome) In: Townsend CM (ed) Sabiston Textbook of Surgery, 16th edition, Chapter 55, 2001. Figure 1]

'Bilobectomy' involves resection of two lobes from the same lung. 'Sleeve resection' denotes the removal of a circumferential portion of the airway in conjunction with the parenchymal resection. The remaining lung requires a bronchial anastomosis in order to re-establish airway continuity. A sleeve resection can also be performed on the pulmonary artery, should it be necessary to resect a circumferential portion of the vessel with the specimen. Similarly, bronchoplasty or arterioplasty in conjunction with a pulmonary resection describe the techniques by which the bronchus or pulmonary artery is reconstructed after removal of a non-circumferential portion of the structure during resection. Pneumonectomy can be intrapericardial or extrapericardial, in reference to the site of division of the pulmonary vessels. 'Extrapleural pneumonectomy' or 'pleuropneumonectomy' refer to the en bloc removal of the parietal pleura with the entire lung. En bloc chest wall resection describes the removal of a portion of the parietal pleura, ribs, and intercostal musculature attached to the primary specimen of resected lung.

2.1.5.2 Extent of Resection

The first lobectomy for lung cancer using a technique of individual ligation of the hilar structures was performed by Davies in 1912 (Davies 1913). Churchill refined lung resection with the introduction of the technique of individual ligation of the bronchopulmonary structures (Churchill and Belsey 1939). Graham reported the first successful pneumonectomy for lung cancer in 1933 (Graham and Singer 1933). Pneumonectomy remained the operation of choice for lung cancer until Churchill's report in 1950, which detailed long-term survival following lobectomy (Churchill et al. 1950). The issue of whether sub-lobar or non-anatomic resection might similarly suffice was raised by Jensik and colleagues in 1973. Subsequent investigators have concluded that a lesser resection in the setting of impaired cardiopulmonary reserve or advanced age might be justified (Landreneau et al. 1997; Errett et al. 1985). One argument against applying a strategy of limited resection more broadly to any patient with early stage lung cancer has been that it may understage cancers by virtue of inadequate lymph node sampling. Takizawa and colleagues (1998) found a 17% incidence of metastases to N1 and N2 lymph nodes with radical lymphadenectomy after resection of small (1.1-2.0 cm) peripheral lung adenocarcinomas, suggesting that an adequate assessment of the draining lymph node basin may be important even in these distal T1 tumors. The other area of contention is whether limited resection could effect a local and systemic cure. A randomized trial of lobectomy versus segmentectomy or wedge resection for T1 N0 non-small cell lung cancers was reported by the Lung Cancer Study Group in 1995. Although no statistically significant difference in survival was found, investigators did find that the overall recurrence rate

was increased 75% in the limited resection group, and that the locoregional recurrence was increased three-fold (Ginsberg and Rubinstein 1995). This increased recurrence after sub-lobar resection echoed the findings of Warren and Faber (1994). Landreneau and colleagues (1997) examined the outcomes of lobectomy and wedge resection, both video-assisted and via open thoracotomy, and found a significant improvement in 5-year survival curves after lobectomy, although this was explicable by an excess of non-cancer-related deaths in the limited resection group.

At our institution, we reserve pneumonectomy for cases in which tumors are too central to fully resect with lobectomy, and where bronchoplasty or sleeve resection still would not allow an adequate margin with parenchymal sparing. Similarly, extensive involvement of the pulmonary vessels may necessitate pneumonectomy, if arterioplasty is not feasible. Also, in cases where the cancer crosses the fissure on the left or crosses the major fissure, involving the upper and lower lobes on the right, pneumonectomy is considered in patients with suitable reserve.

Conversely, limited resection for lung cancer is reserved at our institution for patients with marginal medical status, advanced age, poor pulmonary reserve, or in some instances of second primary lung cancer. In all cases, the tumor stage is T1. Every effort is made to adequately stratify risk preoperatively, to ensure that all potential candidates for anatomic resection are identified.

2.1.6 Technique of Resection

We have previously described in detail the steps for the major pulmonary resections (Sugarbaker et al. 2001). In brief, after the induction of general anesthesia, bronchoscopy is performed to assess the airway for unexpected tumor progression or anatomic abnormality that would alter the planned resection. Subcutaneous heparin and prophylactic antibiotics are administered. Single-lung ventilation is then accomplished using a double-lumen endotracheal tube or single-lumen tube with a bronchial blocker. The patient is positioned in thoracotomy position – a lateral decubitus position – with the operative side up.

A number of incisions may be used to access the pleural space. For most anatomic resections, we utilize a posterolateral thoracotomy incision which begins at a point midway between the lower half of the scapula and the spine, and extends to the anterior border of the latissimus dorsi muscle. The serratus muscle is usually spared, the latissimus muscle is usually divided. The fifth intercostal space is entered at the superior border of the sixth rib. Occasionally the sixth space is used, or a rib may be removed partially or entirely in order to widen the access to the chest. An anterolateral thoracotomy, usually in the fourth intercostal space, is another alternative. Sufficient analgesia for these incisions is achieved with long-acting local anesthetic plus narcotic via a thoracic epidural catheter placed preoperatively.

The hilar structures are individually dissected and divided. Our preference is to divide both vessels and bronchi using a stapler. Smaller pulmonary arterial branches are doubly ligated if they are not amenable to stapler division. Incomplete fissures are also divided using a stapling device. Lymphadenectomy is performed.

The margins are inspected by a pathologist upon removal of the specimen to assure a negative bronchial margin. The integrity of the bronchial stump is checked by testing the stump with ventilatory pressure up to 30 cm of H_2O. When the patient has received neoadjuvant radiation or may receive postoperative radiation, it is our preference to buttress the bronchial stump with an intercostal muscle pedicle, a pericardial or pleural flap, or a thymic fat pad. We also buttress after pneumonectomy or bilobectomy.

2.1.6.1 Postoperative Course

Mortality for lung cancer surgery ranges from 2% to 4% in modern series, with postoperative morbidity occurring approximately 15%–30% of the time (Deslauriers et al. 1989; Ginsberg et al. 1983; Knott-Craig et al. 1997; Myrdal et al. 2001; Yano et al. 1997). Myrdal and colleagues (2001) reviewed their experience of 616 patients undergoing lung cancer surgery and found an overall 30-day postoperative mortality rate of 2.9%, with pneumonectomy conferring a higher risk (5.7%) than lobectomy (0.6%). The rate of major complication (defined as postoperative bleeding leading to exploration, respiratory failure, bronchopleural fistula, myocardial infarction, stroke, heart failure, or renal failure) was 8.8%, with a higher rate seen after pneumonectomy (18.5%) than lobectomy (5.7%). Minor events occurred in 22%, with supraventricular arrhythmias accounting for half of these complications (Myrdal et al. 2001). The mortality and complication rates after bilobectomy have been previously reported to be comparable to that of pneumonectomy (Deneuville et al. 1992). However,

more recent series do not report excess mortality or morbidity after bilobectomy (Damhuis and Schutte 1996; Cerfolio et al. 2000; Carbognani et al. 2001).

At the Brigham and Women's Hospital we use postoperative clinical pathways to standardize care after pulmonary resection and to reduce length of stay. Implementation of patient care pathways for lobectomy has been reported to reduce both length of stay and hospital cost (Cerfolio et al. 2001; Wright et al. 1997). Although 1-day stays after lobectomy have been reported (Tovar et al. 1998), a length of stay in the 5- to 7-day range is more common (Tschernko et al. 1996; Kirby et al. 1995). At our institution all patients are transferred to a specialized thoracic surgery intermediate care unit after lobectomy or lesser resection. After 1–3 days in this setting, to permit invasive hemodynamic monitoring, continuous oxygen monitoring, and frequent pulmonary toilet/ambulation, patients are transferred to a regular floor bed on the thoracic surgical unit, which provides continued specialized nursing care. After pneumonectomy, our patients are recovered first in a specialized thoracic intensive care unit, which allows even more extensive monitoring such as pulmonary artery catheterization, if indicated. Both hospital and surgeon-specific experience influence postoperative mortality for lobectomy and pneumonectomy, with higher volume correlating with better outcomes in several large studies (Birkmeyer et al. 2002, 2003; Hannan et al. 2002).

The 5-year survival for non-small cell lung cancer was reported by Mountain in 1997. For Stage I tumors the 5-year survival is 67% (T1N0) and 57% (T2N0). Stage II tumors are 55% (T1N1), 39% (T2N1), and 38% (T3N0). In Stage IIIA, the 5-year survival is 38% (T3N1) and 23% (T1-3N2). The rate drops in Stage IIIB to 3% (T1-3N3) and 6% (T4AnyN). M1 disease confers an overall 5-year survival of 1%.

2.1.7 Video-Assisted Thoracoscopic Surgery

Video-assisted thoracoscopic surgery (VATS) utilizes small port accesses to the chest and a videoscope for visualization, thereby avoiding a full thoracotomy incision. The ability to perform pulmonary resections with VATS techniques has provided a less invasive method to safely diagnose and treat lung cancers (DeCamp et al. 1995). Initial videoscopic thoracic surgery was diagnostic or limited to treatment of pneumothorax, pleural effusion, or other benign conditions (Kopp et al. 1979; Oldenburg and Newhouse 1979; Rodgers et al. 1979; Kapsenberg 1981; Boutin et al. 1982; Fritsch et al. 1975). VATS lobectomies for lung cancer were first reported in 1993 (Walker et al. 1993; Kirby and Rice 1993).

We have described our technique of VATS lobectomy in detail elsewhere (Sugarbaker et al. 2001). A small incision in the anterior seventh interspace is used to place a port for a 5- or 10-mm videoscope. The entirety of the pleural space and lung may be inspected for unexpected local or metastatic spread. For wedge resections, second and third ports are placed so that a triangulation is achieved over the tumor, and instruments can be introduced to retract, dissect, and staple the lung. For formal lobectomies or segmentectomies we use a 4- to 6-cm fourth interspace accessory incision in the anterior axillary line which allows access to the hilar structures. In addition, we employ one posterior port near the tip of the scapula for retraction. Dissection and division of the pulmonary vein, pulmonary artery, and bronchial structures are accomplished with endoscopic staplers in a similar manner to our open lobectomy. Mediastinal lymphadenectomy is also performed. The specimen is removed via an endoscopic bag to avoid seeding the port sites with shed tumor cells.

The operative mortality for wedge resection for lung cancer has been reported to be negligible (Landreneau et al. 1997; Kodama et al. 1997). For elderly patients undergoing VATS wedge resection, we have previously shown that the mortality is <1%, with a morbidity of 9%. VATS lobectomy also has been accomplished with minimal mortality and morbidity (Gharagozloo et al. 2003; Tatsumi and Ueda 2003; Morgan et al. 2003; Lewise et al. 1999; McKenna 1998). A recent representative report by Morgan and colleagues (2003) describes their experience with 158 patients undergoing VATS lobectomy. They report an 11% rate of conversion to open thoracotomy, secondary to extent of disease and bleeding in most cases. The in-hospital mortality rate was 0.6%, with an overall 30-day mortality rate of 1.8%.

The oncologic validity of VATS lobectomy has not been addressed in a randomized prospective trial, but retrospective studies report 5-year survival rates for Stage I and II non-small cell lung cancers ranging from 60% to 90%, and locoregional recurrence rates around 5% (Tatsumi and Ueda 2003; Walker et al. 2003; Sugi et al. 2000; McKenna et al. 1998). Freedom from cancer-related or associated death has been reported to be 78% for Stage I cancers, 51% for Stage II, and 29% for Stage III (Walker et al. 2003). An adequate lymph node dissection appears to be pos-

sible during VATS lobectomy (Asamura et al. 1999; Morikawa et al. 1998).

An initial randomized trial of VATS versus open lobectomy did not demonstrate a statistically significant difference in length of stay (Kirby et al. 1995). A subsequent randomized trial and several non-randomized trials, however, were able to show a reduction in length of stay with the minimally invasive technique (Tschernko et al. 1996; Demmy and Curtis 1999; Ohbuchi et al. 1998). These same trials have also reported a significant difference in the level of pain associated with VATS lobectomy (Tschernko et al. 1996; Morikawa et al. 1998; Demmy and Curtis 1999; Landreneau et al. 1993). Walker and associates (1996) have shown that the incidence of chronic pain following VATS lobectomy is 1.2%.

2.1.8 Radiation Therapy for Patients Undergoing Lung Resection – T3 Tumors

Adjuvant and neoadjuvant chemotherapy with or without radiation has been studied extensively for stage IIIA (N2) and stage IIIB (N3) disease. Radiation therapy, without chemotherapy, does little to help these patients. For locally invasive, T3, tumors, radiation therapy alone may make the difference between clear margins and positive margins. In general, T3 tumors invading the chest wall are treated with surgical excision with wide margins alone, without the need for radiation therapy. Several retrospective trials have shown either no benefit, or a detriment to adding preoperative radiation therapy to patients with simple chest wall invasion (Piehler et al. 1982; Albertucci et al. 1992). Exceptions to this finding are tumors abutting or involving the vertebral bodies. If the tumor is close to the vertebral body, the surgeon may consider preoperative radiation in order to shrink the tumor and lessen the chance that resection of the vertebral body will be required.

Superior sulcus tumors (Pancoast tumors) represent a unique subset of tumors which invade the chest apex. The tumor may involve vertebral bodies, subclavian vessels, or the brachial plexus. Pancoast tumors are preoperatively staged by CT, and sometimes MRI, as T3 or T4 depending on the level of invasion. Lymph node staging and metastatic workup are undertaken as for other non-small cell lung cancers. Positive N2 and N3 nodes are associated with a 5-year survival of less than 10% (Detterbeck 1997; Deslauriers et al. 1994).

Treatment of Pancoast tumors begins with neoadjuvant therapy. These tumors were initially approached with preoperative radiotherapy alone (Shaw et al. 1961). Recently, however, retrospective studies (Wright et al. 2002; Attar et al. 1998) as well as a prospective randomized trial (Martin et al. 2001) have shown potential benefit to combining chemotherapy with preoperative radiation for superior sulcus tumors.

Surgical approaches to superior sulcus tumors include extended posterolateral thoracotomy and anterior cervicothoracic incisions (Shaw et al. 1961; Dartevelle et al. 1993). Resection usually comprises the following steps: (1) resection of the chest wall including first rib and, at times, portions of involved vertebral bodies; (2) resection of involved nerve roots, up to the first thoracic nerve root; (3) resection of the thoracic sympathetic chain; (4) resection of upper lobe or wedge of involved lung; and (5) lymph node dissection. Incomplete resection yields a survival rate which is comparable to that of no resection (Rusch et al. 2000; Detterbeck 1997).

T3 tumors involving the mediastinum are very difficult to cure. Burt and colleagues (1987) reviewed 225 patients accrued over an 11-year period at Memorial Sloan Kettering. The 5-year survival for patients with T3N2 disease was 8%, which is similar to survival of patients with lower T stage tumors and N2 disease. Patients with T3N0 tumors invading the mediastinum fared no better, with 5-year survival of 10%. Although prospective trials do not exist, this subset of patients may very well benefit from neoadjuvant radiation or chemoradiation.

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2.2 Radiation Therapy

2.2.1 Radiobiology of Normal Lung Tissue and Lung Tumours

Yuta Shibamoto and Masaki Hara

CONTENTS

2.2.1.1 Introduction

Radiation biology has a history dating back almost 100 years. It began soon after Roentgen discovered X rays in 1895. In the early 1900s, Bergonie and Tribondeau formulated the famous rule that radiosensitivity of cells or tissues is correlated with the frequency of mitoses which they undergo and that poorly-differentiated and fast-proliferating tissues are more radiosensitive than well-differentiated and slow-proliferating tissues, from experiments using the testis of rats. Since then, biological studies have been carried out mostly using animals. In the 1950s, Puck and Marcus (1956) devised a colony formation method with which survival of cells became measurable in vitro. This facilitated tremendous progress in radiation biology at the cellular level. Most of the important biological phenomena at the cellular and animal levels appeared to have been clarified by 1980. More recently, advances in molecular biology have brought us much new knowledge on radiobiology of various normal tissues and tumours. Although molecular mechanisms for normal tissue reaction and tumour cell killing are not completely clarified yet, many cytokines have been identified that are involved in the pathogenesis of normal tissue reaction including radiation pneumonitis. Some of the more recent research efforts aim at identifying single nucleotide polymorphism of genes and oncogene expression that are possibly related to increased normal tissue reaction and radiosensitivity of tumours. In this article, we introduce recent investigations including our own on radiobiology of normal lung tissue and lung tumours.

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2.2.1.2 Biology of Irradiated Normal Lung Tissues

Previously, clonogenic death of target cells had been considered a major cause of normal tissue injury by irradiation. Regarding lung injury caused by irradiation, for example, the type II pneumocyte has been considered one of the most important target cells. The type II pneumocyte exhibited the earliest response to radiation and a decrease in lamellar bodies and a corresponding increase in alveolar surfactant were reported shortly after radiation (Penny et al. 1982). By 18–63 weeks, several type II cells underwent degeneration and sloughing into alveolar spaces. This would remain true, but recent researches have revealed that inflammatory cytokines are also involved in the pathogenesis of radiation pneumonitis. Rubin et al. (1995) demonstrated early and persistent elevation of cytokine production and gene expression following pulmonary irradiation in mice. Among these cytokines and genes are interleukin-1α/β, transforming growth factor-beta (TGF-β), platelet-derived growth factor, and collagen and fibronectin genes. The expression started shortly after irradiation and continued cascade-like for several months. They advocated that there is no latent period in a biologic sense for development of delayed

radiation pneumonitis. Anscher et al. (1994) reported that plasma TGF-β1 levels measured during radiation therapy for lung cancer may be useful in identifying patients who will or will not go on to develop symptomatic radiation pneumonitis. A subsequent study by the group suggested that changes in plasma TGF-β1 levels during radiotherapy may be a useful means by which to identify patients at risk for the development of symptomatic radiation pneumonitis, particularly in the subset of patients whose pre-treatment TGF-β levels are over 7.5 ng/ml (Anscher et al. 1997).

Chen et al. (2002) measured changes in plasma levels of IL-1α, IL-6, monocyte chemotactic protein 1, E-selectin, L-selectin, TGF-β1, and basic fibroblast growth factor in patients undergoing thoracic radiotherapy. They found that both IL-1α and IL-6 levels were significantly higher before, during, and after radiotherapy for those who had radiation pneumonitis. None of the other cytokines appeared to definitely correlate with radiation pneumonitis. Their results are different from those reported by other investigators (Rubin et al. 1995; Anscher et al. 1997), and further investigations with a larger number of patients are encouraged to determine cytokines most closely related to the development of radiation pneumonitis.

As a therapeutic approach, Rabbani et al. (2003) investigated soluble TGF-β type II receptor gene therapy to ameliorate acute pulmonary radiation injury in rats. They administered recombinant human adenoviral vector carrying this gene before 30 Gy of hemithoracic irradiation with an expectation that it might reduce availability of active TGF-β1 and thereby protect the lung. They observed a significant increase in the plasma level of TGF-β1 type II receptor after injection of the vector, and a significant reduction in respiratory rates at 4 weeks after treatment. These findings were supported by histological analyses of the irradiated lung tissue. Their study showed the ability of gene therapy to induce an increase in circulating levels of soluble receptors, to reduce the tissue level of active TGF-β1, and consequently to ameliorate acute radiation-induced lung injury.

Molecular aspects of radiation injury of the lung, including the role of respective cytokines and genes, are still to be clarified. Fruitful application of the molecular biology to therapeutic approaches may be expected in future. In the pathogenesis of radiation injury of normal tissues other than the lung, various cytokines have been reported to be involved (Chiang et al. 1997; Richter et al. 1997). Also, radiation-induced cellular senescence may be related to the development of late radiation morbidity (Peters 1996). In the near future, it is hoped that the relationship between clonogenic death of target cells, cytokine induction, and radiation-induced senescence is clarified at the molecular level.

2.2.1.3 Radiosensitivity and Proliferative Activity Testing of Primary Lung Cancers

The necessity for tailor-made cancer treatment based on the biological characteristics of each tumour has been advocated recently. For this purpose, prediction of tumour and/or normal tissue sensitivity to treatment is necessary. To estimate radiosensitivity of tumour cells, several types of predictive assays have been proposed. Among them, the SF-2 assay in which the surviving fraction of tumour cells at 2 Gy of in vitro irradiation is measured using colony formation or colorimetric methods has been most intensively investigated. The reliability of the SF-2 assay to predict radiosensitivity has remained rather controversial, but West et al. (1997), who made the greatest contribution to establishment of the SF-2 assay, reported a clear correlation between the SF-2 and the prognosis after radiation therapy in uterine cervical cancers; patients with tumours showing SF-2 values below the median had a better prognosis than those with tumours showing SF-2 values above the median. However, the use of the SF-2 assay for radiosensitivity prediction has not become a commonly used tool in clinics. One of the reasons for this may be the long waiting time before obtaining assay results.

We have tried to establish a more rapid assay of radiosensitivity using the cytokinesis-block micronucleus (MN) test. MN formation represents chromosomal damage and the MN frequency increases with radiation dose. Using this assay, we devised a method of simultaneously estimating radiosensitivity and proliferative activity of human tumours (Shibamoto et al. 1994, 1998). Estimation of tumour proliferative activity is also important in radiotherapy, since rapid growing tumours are considered to be resistant to protracted conventional radiotherapy. One of the important parameters of proliferative activity is the potential doubling time (Tpot). The Tpot, which is a doubling time in the absence of cell loss, is considered to represent repopulation rates during and after radiotherapy better than the volume doubling time. The assay involves determination of MN

frequency after radiation, the fraction of tumour cells undergoing mitosis in vitro (the dividing fraction, DF), and the extrapolated time for tumour cell nuclei to double in culture (in vitro Tpot).

After establishing the method in xenografted human and murine tumours (Shibamoto and Streffer 1991; Shibamoto et al. 1991), we have used this assay for primary human tumours. All the specimens were obtained at operation and not by biopsy. A total of 133 specimens of various human tumours were obtained from patients receiving no preoperative radiation or chemotherapy. The average weight of tumour specimens obtained was 2.0 g. The tumour tissues were minced with scissors and treated at 37°C for 2 h with 1 mg/ml collagenase/dispase solution. After filtering and centrifuging the tumour cell suspension, the cells were plated onto multiple collagen-coated dishes (20 cm^2). Whenever the cell yield was sufficient, $3–6\times10^5$ cells per dish were plated onto ten dishes. The culture medium used was Ham F12 supplemented with 20% foetal bovine serum and 0.2 mg/ml gentamicin sulphate. Within 1 h after plating, 2 or 4 Gy of irradiation was given to some of the dishes (usually two dishes per dose). Then, cytochalasin B dissolved in dimethyl sulfoxide was added to all dishes at the concentration of 1.5 µg/ml. This concentration of cytochalasin B appeared to be optimal in all of the human tumour cells tested in the previous study (Shibamoto et al. 1994). Cultures were terminated at various intervals, and the cells were fixed with 1% glutaraldehyde in phosphate buffer, treated with 5 N hydrochloric acid for 20 min and stained in the dark with Schiff's reagent for 1 h. Usually, unirradiated cells were fixed on days 1, 2, 3, 4, 6, and 8. By monitoring the increase in the number of binucleate cells (BNC) in the unirradiated dishes, the optimal days for fixing the irradiated cells were determined; these were usually days 4–6.

Tumour cells were distinguished from normal cells on the basis of morphological criteria such as nuclear irregularity, dense nuclear staining and a high nucleocytoplasmic ratio, and only those judged as tumour cells were scored. The cells with different numbers of nuclei (mononucleate, binucleate, trinucleate, etc.) and the micronuclei in the BNC were counted under a microscope at a magnification of 1000. At least 100 (250–300 whenever possible) cells were assessed per dish, and at least 50 (100–150 whenever possible) BNC were assessed to determine the MN frequency. BNC with three or more micronuclei were occasionally found, but all micronuclei were scored. Then, the percentage of multinucleate cells (MNC, cells with two or more nuclei), the average number of nuclei per cell, and the average number of micronuclei per single BNC (= MN frequency) were calculated. The DF (= maximal MNC percentage) and Tpot were estimated from the unirradiated group of cultures. The Tpot obtained with this assay was the extrapolated time for the nuclear ratio (the average number of nuclei per tumour cell) to reach 2.0. When the MN frequencies at different culture times (after day 3) were not significantly different from each other, these values were averaged for both unirradiated and irradiated cells.

Figure 2.2.1.1 shows a representative assay result for a squamous cell carcinoma of the lung. As shown, three sets of data, i.e. DF, Tpot and MN frequency, were obtained with this assay. The proportion of MNC appeared to reach a plateau within 4–6 days in all tumour cells investigated, and the DF was defined as the mean of the percent MNC at the plateau. The Tpot was obtained by fitting the initial part (for days 1–3) of the nuclear ratio curve to an exponential curve and extrapolating from it, when necessary. This extrapolation was necessary in nearly all tumours in which the nuclear ratio did not reach 2.0. In many tumours like the squamous cell carcinoma shown in Fig. 2.2.1.1, MN frequency at 4 Gy did not increase significantly as compared to that at 2 Gy. This phenomenon has already been reported in established murine and human cell lines by Abend et al. (1995), who attributed it to the development of apoptosis at higher doses.

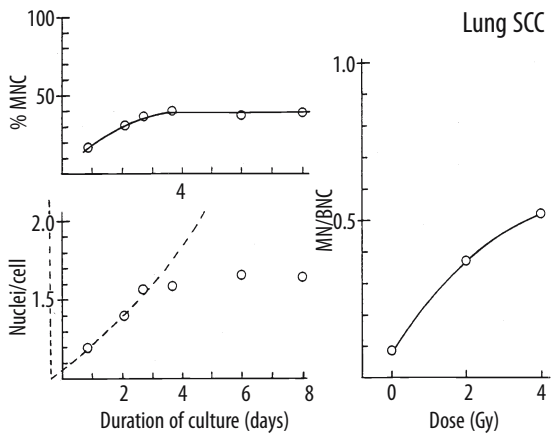

Fig. 2.2.1.1. Assay of a squamous cell carcinoma of the lung. *Left*, the percentage of multinucleate cells (*MNC*) and the average number of nuclei per cell as a function of culture duration. In the latter, an exponential curve was fitted to the three points obtained on days 1–3. *Right*, the average number of micronuclei (*MN*) per binucleate cell (*BNC*) as a function of the radiation dose

Of the 133 tumours tested so far, the DF and Tpot were obtained in 104 (78%) and the MN frequency could be evaluated in 93 (70%). Table 2.2.1.1 shows the assay data for lung cancers and other tumours. Among these tumours, metastases of pancreatic cancer had the highest DF and shortest Tpot values, while meningiomas had the lowest DF and longest Tpot. Among malignant tumours, bladder cancer appeared to have the lowest proliferative activity. Thus, the DF and Tpot values appear to reflect the degree of malignancy of each histological type of tumours. With regard to MN frequency, there was no great difference among these tumours. Especially, there was no difference in the MN frequency between adenocarcinoma and squamous cell carcinoma of the lung. This finding agrees with the data on uterine cancer showing similar values for the surviving fraction at 2 Gy in the two types of carcinomas (West et al. 1995). Small cell lung carcinomas are more radiosensitive than non-small cell carcinomas, but in this study, although the number of small cell carcinomas was small, the MN frequency after radiation for these tumours was similar to or only slightly higher than that for non-small cell carcinomas. Small cell carcinomas appear to die more often by apoptosis (Ohmori et al. 1993), and apoptosis and MN-related death are different events (Abend et al. 1995). This may explain our observation.

Table 2.2.1.1. Median values of the dividing fraction (DF) and potential doubling time (Tpot) and mean micronucleus frequency at 2 Gy of irradiation (after subtraction of the 0 Gy value) of various tumours

Tumour	n	DF (%)	Tpot (days)	MN/BNC (2Gy-0Gy)
Lung adenocarcinoma	41	23	7.7	0.15
Lung squamous cell carcinoma	14	25	8.5	0.17
Lung large cell carcinoma	3	27	6.5	0.16
Lung small cell carcinoma	4	30	7.0	0.20
Pancreatic cancer (metastasis)	6	49	4.6	0.16
Breast cancer (metastasis)	5	27	8.5	0.16
Bladder cancer	4	15	18	0.14
Malignant glioma	4	20	9.2	0.14
Osteosarcoma (lung metastasis)	4	20	13	0.21
Meningioma	4	8.2	53	0.08

To investigate whether there is any correlation between the DF/Tpot and clinical outcome, the patients with non-small cell lung cancer at each disease stage were divided into two groups according to the DF value (above or below median of each stage). Figure 2.2.1.2

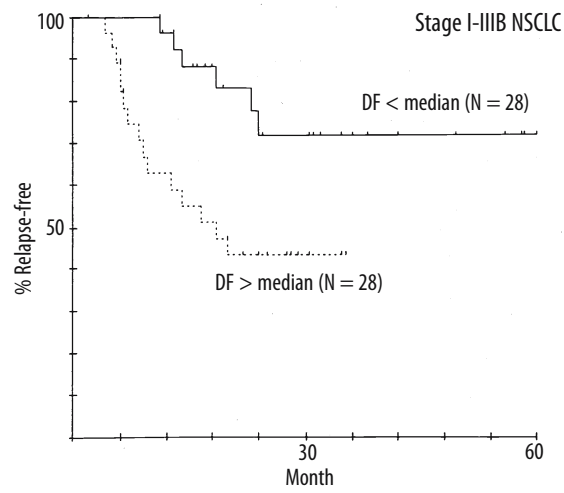

Fig. 2.2.1.2. Relapse-free survival curves according to the dividing fraction (> or < median for each stage) for patients with Stage I–IIIB non-small cell lung cancer. The stage distribution (I/II/IIIA/IIIB) was 15/4/6/3 for both groups. p=0.0077

shows postoperative relapse-free survival curves for the patients with Stage I–IIIB non-small cell cancer according to the DF value. The 28 patients with DF above median for each stage had significantly poorer relapse-free survival rate than the 28 patients with DF below the median (p=0.0077). Therefore, the DF seems to be a useful indicator of tumour proliferative activity and patient prognosis. The relationship between the DF and the growth fractions as determined by proliferation markers should be investigated, because the DF values obtained in our study do not differ significantly from the Ki-67 or proliferating cell nuclear antigen positivity rates reported for various types of tumours.

A total of 21 patients with Stage I–IIIB non-small cell lung cancer who underwent macroscopic curative surgery developed recurrence. In these patients, a correlation was found between the time to recurrence and their Tpot value (Fig. 2.2.1.3). Although we are not sure whether the regrowth rate of tumours after surgery is related to the Tpot, the Tpot obtained with this assay may also be useful in predicting the postoperative period at high risk for recurrence. The flow cytometry method is now being widely used to estimate the Tpot, but several methodological problems that make the obtained Tpot value inaccurate have been pointed out, including the influence of normal cell counts in diploid tumours and interlaboratory variations (Begg 1993). As an alternative, our method appears to be attracting attention recently.

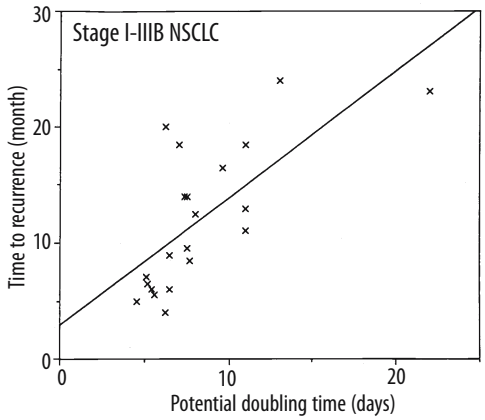

Fig. 2.2.1.3. Correlation between the potential doubling time (*Tpot*) and time to recurrence in 21 patients with Stage I–IIIB lung cancer. R=0.70, p=0.00044

Only some of the patients underwent postoperative radiation therapy, but in 18 patients, including those who had cancer other than that of the lung, the clinical response of the primary or metastatic lesions could be evaluated. Figure 2.2.1.4 shows the correlation between the tumour response to radiotherapy and the MN frequency at 2 Gy of in vitro irradiation (after subtraction of the value at 0 Gy). The tumour response was classified as complete response (CR), partial response (PR, > 50% regression in maximal tumour area), minor response (MR, < 50 > 25% regression) or no response (NR, < 25% regression). The MN frequency tended to be higher in tumours showing CR or PR than in those showing MR or NR.

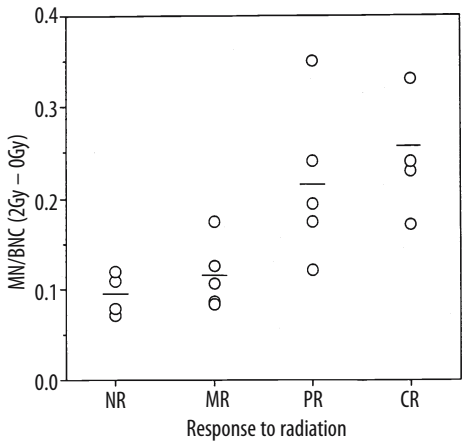

Fig. 2.2.1.4. Tumour response to radiotherapy and micronucleus frequency at 2 Gy after subtraction of that at 0 Gy. *MN/BNC*, mean number of micronuclei per binucleate cell; *NR*, no response; *MR*, minor response; *PR*, partial response; *CR*, complete response. *Bars* represent the mean for each group

In particular, tumours producing many micronuclei tended to show good response to radiotherapy. However, tumours producing few micronuclei varied in their response and were not necessarily radioresistant. Whether the MN frequency after radiation represents the radiosensitivity is a matter of controversy in laboratory studies. Some authors indicated a good correlation between the MN frequency and cell survival (Shibamoto et al. 1991; Mariya et al. 1997), while others found no such correlation (Bush and McMillan 1993; Villa et al. 1994). Since cell survival is not necessarily an absolute measure of radiosensitivity, such clinical studies as ours comparing the MN frequency with actual tumour response are necessary. Since it seems possible to evaluate apoptotic cells simultaneously, it may also be worthwhile to modify the method to include scoring of both micronucleated cells and apoptotic cells.

In summary, the cytokinesis-block assay is feasible in human tumour cells in primary culture. This assay provides three sets of data on the DF, Tpot, and MN frequency in approximately 1 week. The DF appears to be an index of tumour proliferative activity, and the Tpot obtained with this method was correlated with the time until recurrence. Whether or not the MN frequency after 2 Gy irradiation represents clinical radiosensitivity of the tumour is a topic of future investigation.

2.2.1.4 18F-Fluorodeoxyglucose Positron Emission Tomography Findings of Primary Lung Cancers

Positron emission tomography (PET) using 18F-fluorodeoxyglucose (FDG) is a useful tool to detect tumours with increased glucose metabolism. Although FDG uptake is observed in non-malignant lesions (Shreve et al. 1999), FDG-PET can detect small tumours of approximately 1 cm in the abdomen. We have used FDG-PET in patients with a lung nodule or suspected tumour. The majority of patients had lung cancers, but other patients with a lesion showing FDG uptake underwent surgery without preoperative histological confirmation and proved to have benign diseases. We have tried to characterise FDG-PET findings in these patients.

FDG-PET was performed using a GE Advance scanner (GE Medical Systems, Milwaukee, Wis., USA). The Advance unit produced 4.25-mm thick image planes (18 direct planes and 17 cross planes) with an image

matrix of 128×128. The resolution of the scanner at full width at half maximum was 5.5 mm and the longitudinal field view was 14.5 cm. All patients fasted for at least 6 h before imaging. A 3-min transmission scan was obtained before a 2-min emission scan by using a rotating germanium-68 pin source. Seven scans were usually performed to cover from head to thigh. Scans were started 60 min after administration of 185–170 MBq FDG.

Table 2.2.1.2 shows the standardised uptake value (SUV) of FDG and mass size in pulmonary adenocarcinoma, squamous cell carcinoma, small cell carcinoma, and tuberculoma. There was a trend whereby squamous cell carcinomas had a higher uptake than adenocarcinomas. This appeared to be partly related to the fact that adenocarcinomas are more frequently well-differentiated than squamous cell carcinomas. In adenocarcinomas, FDG uptake was higher in poorly-differentiated tumours than in well-differentiated ones, but this trend was not observed in squamous cell carcinomas. At present, we have no explanation for this discrepancy, and we will investigate further if there is any correlation between degree of histological differentiation and FDG uptake with larger numbers of patients. The SUV for small cell carcinomas were comparable to those for squamous cell carcinomas and poorly-differentiated adenocarcinomas.

Benign granulomatous diseases also showed increased FDG uptake. In our seven tuberculomas, the mean SUV was 2.5, which was comparable to that for well-differentiated and moderately-differentiated adenocarcinomas. Other benign lesions also had a moderate degree of FDG uptake, but 90% of their SUVs were below 3.0. Our results would suggest that a lesion with an SUV of 3.0 or higher is likely to be malignant. However, an SUV below 3.0 does not necessarily indicate that the lesion is benign. It appears difficult to differentiate benign nodules from well-differentiated adenocarcinomas on the basis of SUV for FDG.

Table 2.2.1.2. Standardised uptake ratio (SUR) of FDG in lung cancers and tuberculoma

		Longest diameter(mm)		SUV	
Histology	n	Mean	SD	Mean	SD
Adenocarcinoma	27	26	16	2.5	1.8
Well differentiated	19	22	13	1.8	1.4
Moderately differentiated	4	34	24	3.4	1.7
Poorly differentiated	4	39	12	5.1	1.4
Squamous cell carcinoma	17	40	19	6.9	2.6
Well differentiated	3	42	12	8.1	2.7
Moderately differentiated	8	30	14	6.3	2.4
Poorly differentiated	6	51	24	7.0	2.9
Small cell carcinoma	8	40	37	5.2	2.6
Tuberculoma	7	23	10	2.5	1.3

2.2.1.5 RadGenomics Project

The RadGenomics project started in April 2001 at the National Institute of Radiological Sciences in Japan (Iwakawa et al. 2002). This project promotes analysis of genes that are expressed in response to irradiation, identification of their allelic variants in the human population, development of an effective procedure for quantitating individual radiosensitivity, and analysis of the relationship between genetic heterogeneity and susceptibility to irradiation. Major groups of genes investigated in the project include DNA repair genes, genes for programmed cell death, genes for signal transduction, and genes for oxidative processes.

The outcome of the RadGenomics project should lead to improved protocols for individualised radiotherapy and reduction of adverse effects of treatment. The project will contribute to future research on the molecular mechanisms of radiosensitivity in humans and stimulate development of new high-throughput technology for a wider application of the biological and medical sciences. Identification of functionally important polymorphisms in the radiation response genes may determine individual differences in sensitivity to radiation exposure or radiotherapy.

We have initiated co-operative research with the National Institute of Radiological Sciences to investigate whether there is any correlation between specific single nucleotide polymorphism and normal tissue reaction to radiation therapy. Radiation pneumonitis is one of the major normal tissue reactions investigated in this collaboration. We will also investigate oncogene expression that is possibly related to radiosensitivity in lung cancers using a microarray.

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2.2.2 Radiation Time, Dose, and Fractionation in the Treatment of Lung Cancer

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CONTENTS

Radiation therapy has been an important component of potentially curative treatment of lung cancer for four decades. The radiosensitivity of normal tissues in the thorax, especially normal lung and esophagus, has led investigators to seek ways of enhancing the biological antitumor effects of radiation while reducing its acute and late effects on normal tissues. The focus in this chapter is on medically inoperable or locally advanced unresectable disease, specifically non-small cell lung cancer (NSCLC) classified as stage IIIB (T4 or N3) or stage IIIA that is unresectable because of bulky tumors or fixed N2 disease (according to the 1997 American Joint Committee on Cancer staging system) and small cell lung cancer (SCLC) confined to one hemithorax and the ipsilateral supraclavicular lymph nodes. Whether radiation therapy can be judged successful or unsuccessful depends on the endpoints used. The traditional assumption has been that distant metastasis is the major cause of death from lung cancer; however, that cause is actually uncontrolled tumor in the chest. Improvements in thoracic computed tomography (CT) scanning and fiberoptic bronchoscopy that allow better visualization of lung tumors led to the recognition that lack of local control is the main cause of treatment failure in lung cancer (Arriagada et al. 1991, 1997). Two independent randomized trials showed that improving local control, obtained by two different approaches, can affect overall survival rates in both SCLC and NSCLC (Saunders et al. 1997; Schaake-Koning et al. 1992).

The therapeutic ratio of radiation for the treatment of carcinoma of the lung can be improved by increasing the biological dose to maintain local control while protecting normal tissues. One way of doing so, and our emphasis in this chapter, is through the use of fractionation, i.e., manipulating the time interval and dose of irradiation to optimize the therapeutic ratio.

2.2.2.1. Non-Small Cell Lung Cancer

Local control of NSCLC, like that of SCLC, is directly related to survival. The ability to maintain local control of NSCLC has been far from satisfactory, and hence several attempts have been made to manipulate fractionation dose and schedule to escalate the biologically effective dose to the tumor and thus to improve outcome. Table 2.2.2.1 gives some definitions that are useful in reviewing the literature on time, dose, and fractionation in lung cancer.

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Table 2.2.2.1. Fractionation definitions for lung cancer[a]

Schedule	Dose per fraction (Gy)	Number of fractions per week	Intervals between fractions (h)	Total number of fractions	Duration of treatment (weeks)	Total dose (Gy)
Standard	1.8-2.75	4-6	24	25–40	5–8	55–75
Hypo	> 3.0	1–4	48–168[b]	↓	NC or ↓	NC or ↓
Hyper	0.7-1.3	10-25	2–12	↑	(↓) NC	NC (↑)
Rapid	> 2.5	5	24	↓	↓	↓
Accelerated	1.5–2.5	10–21	4–12	↓	↓↓	↓

[a] Numbers or symbols given assume a dose-rate of 2.0–6.0 Gy/min.
[b] Intervals longer than 168 h constitute a "split course."
↓ or ↑ indicate decreases or increases relative to values given for standard fractionation schedule.

2.2.2.1.1 Dose Escalation with Standard Fractionation

The single most influential study of dose escalation with standard fractionation was conducted by the Radiation Therapy Oncology Group (RTOG) (Perez et al. 1988). Patients were randomly assigned to one of four treatment groups. Three of these treatments involved standard fractionation (2.0 Gy per day given 5 days per week) to total doses of 40 Gy (in 20 fractions), 50 Gy (in 25 fractions), and 60 Gy (in 30 fractions); the fourth treatment used large-dose fractionation given in a split course (4 Gy per day for 5 days, followed by a 3-week interruption, and a second course of 4 Gy per day for 5 days) to a total dose of 40 Gy (in ten fractions over 5 weeks). The higher total radiation dose led to improved survival rates, but this effect came at the cost of some increase in toxicity. The RTOG investigators' conclusion that 60 Gy in 30 fractions was the most effective treatment became a standard for the RTOG, for other cooperative groups, and for radiation oncologists throughout the United States.

2.2.2.1.2 Large-Dose Fractionation

Advocates of large-dose fractionation emphasize the usefulness of this form of treatment (also called hypofractionation) in lessening the overall number of treatments and the corresponding burden on health care facilities, decreasing the stress on patients to adhere to a schedule of five visits per week over a period of 6 weeks, and possibly in increasing the biological antitumor effect. Thames and colleagues (1983) documented in the early 1980s that use of large dose fractions was associated with increased late effects in normal tissues; a comprehensive review of large-dose fractionation published 2 years later by Cox (1985) confirmed the increase in late effects but also drew attention to the possibility that this practice also had adverse effects on tumor control because it allowed repopulation of tumor cells between fractions.

In a subsequent study involving large-dose fractionation, Uematso and others (2001) used CT-guided frameless stereotactic radiation therapy to treat 50 patients with stage I NSCLC. Most of the patients in this study were given 50–60 Gy in 5–10 fractions for 1–2 weeks, and 18 patients had also undergone conventional radiation therapy (40–60 Gy in 20–33 fractions) before the stereotactic procedure. At a median follow-up of 36 months, 47 patients (94%) showed no evidence of local progression on follow-up CT scans, and the 3-year overall survival rate was 66%. No adverse effects definitively related to the stereotactic radiation therapy were noted except for minor bone fractures (two patients) and temporary pleural pain (six patients). On the basis of these results, the RTOG proposed a phase II trial (RTOG L-0236) of extracranial stereotactic radioablation for medically inoperable stage I NSCLC. The proposed dose is 60 Gy, to be given in three 20-Gy fractions with no more than two fractions per week.

2.2.2.1.3 Dose Escalation with Hyperfractionation

The potential for hyperfractionation to improve the therapeutic ratio for radiation in many malignant tumors was recognized in part from the failure of large-dose fractionation to improve local control and in part from the observation that use of smaller fractions was associated with fewer late effects in normal tissues. The RTOG conducted

a series of trials of hyperfractionated radiation therapy in which 1.2 Gy fractions were given twice daily and total doses were escalated (Diener-West et al. 1991). For cancer of the lung, the total doses ranged from 60 Gy (in 50 fractions over 5 weeks) to 79.2 Gy (in 66 fractions over 6.5 weeks). Improved survival rates were noted at a total dose of 69.6 Gy, given in 58 fractions, with no further improvement at higher doses. This dose fractionation regimen was subsequently investigated in a prospective trial in comparison with groups given either standard fractionation or induction chemotherapy followed by standard fractionation (Sause et al. 1995). In this trial, use of induction chemotherapy was associated with improved short-term survival but use of the hyperfractionated regimen was not.

2.2.2.1.4 Accelerated Fractionation

With its twice-daily doses of 1.2 Gy, the protocol in the RTOG study cited above (Diener-West et al. 1991) did involve some acceleration of treatment; however, the most thorough investigation of a markedly accelerated course of radiation therapy was conducted at Mount Vernon Hospital in the United Kingdom by Saunders and colleagues (Saunders et al. 1997; Saunders 2000). Their investigation of continuous hyperfractionated accelerated radiation therapy (CHART) involved use of three 1.5-Gy fractions per day for a total of 12 consecutive treatment days, with no interruptions for weekends. The total dose for this regimen was 54 Gy, given in 36 fractions over 12 days.

After CHART was found to be promising in comparison with the historical experience at Mount Vernon Hospital, a prospective randomized trial was undertaken to compare CHART (total dose of 54 Gy given in 36 fractions over 12 consecutive days) to standard fractionation (total dose of 60 Gy in 30 fractions, 5 days per week, for 6 weeks). The observed improvement in survival in the CHART group was considered to result largely from improved intrathoracic tumor control. A derivative benefit of this local tumor control from CHART was the lesser incidence of distant metastasis in the CHART group than in the standard-fractionation group (Saunders 2000). This finding suggests that metastasis from locally advanced lung cancer, like that at other cancer sites, may arise through secondary dissemination from residual local-regional tumor (Arriagada et al. 1995).

2.2.2.1.5 Reducing the Target Volume with Three-Dimensional Conformal Radiation Therapy

Some evidence exists to suggest that very high radiation doses (i.e., in excess of 70 Gy) for medically inoperable stage I disease have shown acceptable results in terms of local control and survival (Qiao et al. 2003). Such patients with small but inoperable tumors may be candidates for three-dimensional conformational radiation therapy, which can allow dose escalation if the high-dose radiation volume conforms closely to the size and shape of the tumor. The relationship between pulmonary toxicity, especially symptomatic toxicity, and the volume of irradiated lung is well established. With regard to maximum tolerated doses, studies of fractionated irradiation delivered either to both lungs or to one lung at a time (Cox et al. 1972) suggested that the limit was approximately 20 Gy at 1.5 Gy per fraction. With regard to the volume of lung subjected to radiation, Graham et al. (1995) used dose-volume histogram analysis to show that the percentage of normal lung volume receiving a total dose of 20 Gy (V20) or more, in standard daily fractions was strongly related to the risk of severe or life-threatening pulmonary toxicity.

That same group (Graham et al. 1995), among others (Bradley et al. 2003), led a prospective trial (RTOG 9311) of dose escalation with three-dimensional conformal radiation therapy in patients with inoperable NSCLC (Bradley et al. 2003). The trial was designed to escalate doses given on a standard fractionation schedule based on V_{20}; patients with V_{20} of less than 25% were given doses of 70.9 Gy in 33 fractions, 77.4 Gy in 36 fractions, 83.8 Gy in 39 fractions, or 90.3 Gy in 42 fractions. Toxic effects that occurred or persisted for more than 90 days after the start of radiation therapy were considered late effects. Estimated rates of grade 3 or higher late lung toxicity (according to the National Cancer Institute's Common Toxicity Criteria; Cancer Therapy Evaluation Program 1998) at 18 months for the four dose levels were 7%, 16%, 0%, and 13%, respectively. Details on esophageal toxicity were not available, although a fatal trachea-esophageal fistula was reported in the 90.3-Gy group (Bradley et al. 2003).

A second group of patients in this study, those with a V_{20} of 25% to 37%, were given doses of 70.9 Gy in 33 fractions or 77.4 Gy in 36 fractions. Estimated rates of grade 3 pulmonary toxicity at 18 months for these patients were 15% for both dose levels. Given these relatively high late toxicity rates (16% at 77.4 Gy for V_{20} <25% and a 15% at 70.9 Gy for V_{20} = 25%–37%), further dose escalation does not seem warranted, even with the use of three-dimensional conformal radiation therapy.

Other groups have attempted to reduce the volume to be irradiated by avoiding elective nodal irradiation, even for patients with T3 tumors (Emami 1998; Belderbos et al. 2003). By avoiding elective nodal irradiation for locally advanced lung cancer, some investigators have been able to increase the radiation dose to the tumor above 80 Gy (Belderbos et al. 2003). Another approach to decreasing target volumes is to use simultaneous positron emission tomography and CT scanning to more precisely delineate tumor volume, position, and size. One such approach, intensity-modulated radiation therapy, is discussed further in the following paragraphs.

2.2.2.1.6 Intensity-Modulated Radiation Therapy

Development of sophisticated software programs, combined with improvements in diagnostic imaging and image reconstruction, have allowed tumors to be visualized and delineated more precisely, improving the delivery of three-dimensional radiation therapy and opening the door for intensity-modulated radiation therapy (IMRT). Two sources of error in IMRT that could prevent successful delivery of optimal conformal treatment result from movement—movement of the patient, which can be addressed by careful immobilization, and the internal motion of thoracic tumors caused by respiration and heartbeat. Indeed, the main challenge in IMRT is to avoid increasing the integral dose to organs that lie in the path of the multiple fields that are focused on the target volume. In practice, the question in treating for thoracic tumors is whether IMRT can reduce the V_{20} (the percentage of lung receiving 20 Gy or more). Preliminary findings from Liu and colleagues (in press) suggest that IMRT is feasible but comes at the cost of exposing a much larger proportion of the lung to doses of 10 Gy or less. Furthermore, treatment with curative intent for thoracic tumors often involves concurrent chemotherapy, which can further increase the risk of normal tissue toxicity, especially pneumonitis, if large volumes of normal lung are exposed to low radiation doses.

2.2.2.1.7 Accounting for Tumor Motion

That intrathoracic tumors move in concert with respiratory and cardiac cycles has always been known, but the importance of accounting for this movement has been magnified with the advent of conformal and intensity-modulated radiation therapy. Lung tumors can move up to 15 mm in the inferior-superior directions with each breath (Seppenwoolde et al. 2002; Stevens et al. 2002). Motion in the anterior and posterior directions can also be as great as that in the superior-inferior plane. Moreover, the location and size of the tumor can change over the course of radiation therapy that lasts several weeks. The importance of recognizing and accounting for tumor motion over the course of radiation therapy is becoming increasingly apparent. Respiration-induced tumor motion changes during a course of radiation therapy can be more than 1 cm (Forster et al. 2003). Therefore, frequent monitoring of tumor motion and location may be required in order to insure that tumors remain within the high dose region throughout treatment.

2.2.2.1.8 Proton Therapy

At present, the best way of increasing the dose delivered to tumors in the thorax without increasing the dose to critical normal tissues seems to be proton therapy. Treatment planning methods are being developed that account for passive scattering (Moyers et al. 2001), and work has begun on the use of pencil beam scanning. Preliminary results suggest that good local control of small tumors can be achieved with little risk of acute or late toxicity (Shioyama et al. 2003). Clinical experience with proton beam irradiation is limited, particularly with regard to large tumors with lymph node involvement that would require high doses for control. Fractionation studies in the context of proton therapy are currently in their infancy.

2.2.2.1.9 Concurrent Chemotherapy

The use of concurrent weekly or daily cisplatin with radiation therapy has been mainly based on the results of a large randomized trial by the European Organization for Research and Treatment of Cancer (Schaake-Koning et al. 1992) that showed improved local control and overall survival from the use of concurrent chemotherapy and radiation. However, this trial was based on a fractionation scheme that may have been less than optimal in that 3-Gy fractions were given daily for 10 days, followed by an

interruption of 4 weeks and then daily 2.5-Gy fractions for 10 days. Randomized studies of fractionated radiation for locally advanced carcinomas of the upper respiratory and digestive tract (Fu et al. 2000) suggest that interruptions such as this quite likely permit proliferation of surviving clonogens, not only in normal tissues but also in the tumor. Also, a recent meta-analysis based on individual patient data raised some doubts about the magnitude of benefit, if any (Auperin and Le Pechoux 2003), from concurrent chemotherapy and radiation therapy and suggested that more randomized evidence was needed to support use of the combined approach.

The most extensive experience with altered fractionation with concurrent chemotherapy for NSCLC comes from work at the M. D. Anderson Cancer Center and the RTOG. Results from randomized phase II trials of a fractionation scheme developed by the RTOG (58 twice-daily 1.2-Gy fractions for a total dose of 69.6 Gy) used with concurrent chemotherapy seemed promising (Komaki et al. 1997). However, the most favorable outcomes seemed to be associated with a learning curve; specifically, institutions at which 5 or more patients received concurrent chemotherapy and twice-daily irradiation showed significantly better survival rates than institutions with less experience in this form of treatment (Lee et al. 2002). At M. D. Anderson, long-term follow-up of patients given 1.2 Gy twice a day with concurrent cisplatin and etoposide showed the most favorable 5-year survival rates reported to date, 26% (Liao et al. 2002).

2.2.2.2 Small Cell Lung Cancer

The current treatment strategy for limited-stage SCLC involves the use of chemotherapy, thoracic radiation therapy (Turrisi et al. 1999), and, for those who achieve a complete response, prophylactic cranial irradiation (PCI) (Auperin et al. 1999). Comparisons of chemotherapy plus thoracic radiation therapy with chemotherapy alone have shown that use of combination therapy improves survival rates; other trials have shown that concurrent chemotherapy and thoracic radiation therapy is superior to sequential or alternating chemotherapy and thoracic radiation therapy with regard to local-regional control and survival in limited-stage SCLC.

2.2.2.2.1 Use of Combined Chemotherapy and Thoracic Radiation Therapy

Because even initially localized SCLC tends to metastasize early in the course of the disease, chemotherapy is an essential component of the treatment regimen; intrathoracic failure becomes more important after distant metastases are controlled. Two separate meta-analyses have confirmed the value of adding thoracic radiation therapy to chemotherapy for SCLC in terms of decreasing the rate of local recurrence and improving survival. Warde and Payne (1992) analyzed results from 11 prospective randomized trials of chemotherapy with or without thoracic radiation therapy for patients with limited-stage SCLC and found that the addition of thoracic radiation therapy conferred an absolute increase of 5.4% in overall survival rate at 2 years (from 15% to 20.4%) and an absolute increase of 25% in local control rate at 2 years (from 15% to 40%). Pignon and colleagues (1992), in their analysis of data from 2,140 patients in 13 randomized trials of chemotherapy alone versus chemotherapy plus thoracic radiation therapy, found an absolute increase of 5.4% in overall survival rate at 3 years.

2.2.2.2.2 Concurrent Therapy

Potential advantages of delivering chemotherapy and radiation therapy concurrently are the ability to apply both modalities early in the course of treatment; the possible induction of synergistic effects; the enhanced accuracy of treatment planning owing to the absence of induction chemotherapy that might obscure the original tumor volume; and the short overall treatment time (high dose intensity), which prevents proliferation of clonogens. Potential disadvantages of concurrent therapy are enhanced toxicity to normal tissues, which could necessitate dose modification or treatment breaks; the inability to assess response to either modality; and possibly sensitization of normal tissues.

In 1990, McCracken and colleagues reported the results of a phase II trial of the Southwest Oncology Group in which two courses of cisplatin, etoposide, and vincristine were given concurrently with radiation therapy consisting of once-daily 1.8-Gy fractions given 5 days per week to a total dose of 45 Gy. The concurrent therapy was followed by additional chemotherapy with vincristine, methotrexate, and

etoposide alternating with doxorubicin and cyclophosphamide for 12 weeks. This study evaluated 154 patients. With a minimum observation period of 3 years, the 2-year survival rate was 42% and the 4-year survival rate was 30%. An updated analysis (Janaki et al. 1994) after a longer observation period showed a 5-year survival rate of 26%.

In 1999, the RTOG and the Eastern Cooperative Oncology Group (ECOG) (Turrisi et al. 1999) reported the results of a US nationwide randomized study of limited-stage SCLC treated with concurrent chemotherapy (etoposide and cisplatin) and thoracic radiation therapy (45 Gy given in twice-daily 1.5-Gy fractions or once-daily 1.8-Gy fractions); radiation was started on the first day of the chemotherapy cycle. The 2-year survival rate for the entire group was 44%. The 5-year survival rate was 16% for those given once-daily radiation and 26% for those given twice-daily radiation — a remarkable improvement over previously reported 5-year survival rates.

The Japanese Clinical Oncology Group (Goto et al. 1999) conducted a phase III study of concurrent versus sequential thoracic radiotherapy, given in combination with cisplatin and etoposide chemotherapy, for patients with limited-stage SCLC. Chemotherapy was given in either a 28-day cycle (the concurrent group) or a 21-day cycle (the sequential group). Thoracic radiation therapy was begun either on day 2 of the first cycle of chemotherapy in the concurrent group or after the fourth cycle of chemotherapy in the sequential group. The radiation therapy consisted of 45 Gy delivered to the thorax in twice-daily 1.5-Gy fractions over 3 weeks. PCI was given to patients who showed a complete or a near-complete response; the PCI consisted of 24 Gy given in twice-daily 1.5-Gy fractions given 5 days a week. The incidence of grade 3 or 4 leukopenia was significantly higher in the concurrent-therapy group (86.8% vs. 51.3%, $p< 0.001$), but the incidence of non-hematologic side effects was no different in the two groups. The 2- and 3-year survival rates in the sequential-therapy group were 35.4% and 20.7%, respectively, as compared with 55.3% and 30.9% in the concurrent-therapy group. Overall survival seemed to be superior in the concurrent group but this apparent trend was not statistically significant.

Arriagada and colleagues (1991) reported the results of two protocols involving 72 consecutive patients with limited-stage SCLC. Patients were given two cycles of induction chemotherapy followed by three 2-week cycles of thoracic radiation therapy that included chemotherapy with the same regimen as that used for the induction. Cisplatin and etoposide were used in the first trial, and cisplatin, etoposide, cyclophosphamide, and doxorubicin were used in the second trial. The results of this trial are among the most favorable reported in terms of long-term survival. The complete response rate was 87% and the overall survival rate was 26% at 3 years; the overall survival of patients who showed a complete response to the interdigitated therapy was 26% at 5 years.

Whether thoracic radiation therapy should be delivered early or late in the treatment course remains controversial. The National Cancer Institute of Canada Clinical Trials Group studied this issue in a randomized trial (Murray et al. 1993). In that trial, 308 patients were given six cycles of chemotherapy with cyclophosphamide, doxorubicin, and vincristine alternating with etoposide and cisplatin. Patients were randomly assigned to receive thoracic radiation therapy (40 Gy to the primary tumor site in 15 fractions over 3 weeks given concurrently with etoposide and cisplatin) beginning either at week 3 (the early group) or at week 15 (the late group). Those who showed a complete response were then given PCI (25 Gy in ten fractions over 2 weeks) after the completion of all chemotherapy and thoracic irradiation. Although the complete response rates were no different in the two groups, progression-free survival (p=0.036) and overall survival (p=0.008) were significantly better in the early-radiation group. Patients in the late-radiation group also had a significantly higher rate of brain metastasis (p=0.006). This study indicated that early use of thoracic radiation therapy with concurrent chemotherapy improved survival, possibly by eliminating the clonogens in the primary tumor.

Fractionation

The Intergroup study 0096 (Turrisi et al. 1999), conducted with the ECOG and RTOG, compared once-daily versus twice-daily radiation therapy in combination with concurrent cisplatin and etoposide. All patients received four 21-day cycles of chemotherapy. The once-daily fractionation group received a single 1.8-Gy fraction each day, to a total dose of 45 Gy in 25 fractions over 5 weeks. The twice-daily fractionation group received two 1.5-Gy fractions each day, with a 4- to 6-h interval between fractions, to a total dose of 45 Gy in 30 fractions over 3 weeks. Irradiation began during the first chemotherapy cycle. Patients who achieved a complete response then were offered PCI (ten 2.5-Gy fractions). Although accelerating the radiation improved median survival time (19 months

for the standard fractionation group to 23 months for the twice-daily group) and 2-year survival rates (41% vs. 47%), a statistically significant difference in survival was not apparent until 5 years (16% vs. 26%; p=0.04). The accelerated regimen also produced acute grade 3 esophagitis in 27% of cases as compared with 11% of those in the once-daily fractionation group.

The Japanese Clinical Oncology Group (Ariyoshi et al. 1994) reported a multicenter phase II trial of concurrent cisplatin–etoposide chemotherapy and thoracic radiation therapy for limited-stage SCLC. Thoracic irradiation was given in a split course, with 20 Gy given in ten 2-Gy fractions on days 2–12 of the first chemotherapy cycle and 30 Gy given in 15 2-Gy fractions delivered on days 29–47 of the second chemotherapy cycle. Some patients were then given a 10-Gy boost, bringing the total doses to 40–50 Gy over 7 weeks. PCI was given to those who showed a complete response. The split-course radiation therapy used in this study was not as effective as that used in Intergroup 0096; the median response duration was 8.7 months, the median survival time was 14.8 months, and the 2-year survival rate was 20%. The complete response rate was 40.7%.

Table 2.2.2.2. Intergroup Study 0096 versus RTOG 9712

	Intergroup Group 1	Intergroup Group 2	RTOG 9712
Thoracic radiation dose	45 Gy	45 Gy	61.2 Gy
Duration of radiation	5 weeks	3 weeks	5 weeks
Median survival time	19 months	23 months	—
Survival rates			
1 year	63%	67%	—
2 years	44%	47%	—
5 years	16%	26%[a]	—
Local failure rate	52%	36%	—
Incidence of grade 3 esophagitis	11%	27%	<40%

[a] Significantly different from Group 1 (p=0.01).

2.2.2.2.3 Radiation Dose to the Thorax

Arriagada and colleagues (1990) at the Institut Gustave-Roussy conducted three consecutive trials of 173 patients with limited SCLC treated with different thoracic radiation doses. All thoracic radiation was given in split courses alternating with chemotherapy; the total doses given were 45 Gy (i.e., doses split 15-15-15), 55 Gy (20-20-15), and 65 Gy (20-20-25). The corresponding 3-year local control rates were 66% for the group given 45 Gy and 70% for the two higher-dose groups; the 5-year survival rates were 16% for the 45-Gy group, 16% for the 55-Gy group, and 20% for the 65-Gy group. None of these apparent differences were statistically significant among the three groups. The overall incidence of lethal toxicity was 10%, and this rate was no different among any of the three radiation dose groups.

Choi and colleagues (1998) conducted a phase I study to determine the maximum tolerated dose of radiation in standard daily fractionation and hyperfractionated-accelerated twice-daily radiation schedules with concurrent chemotherapy for limited-stage SCLC. The maximum tolerated dose of hyperfractionated radiation therapy was 45 Gy given in 30 fractions over 19 days. However, in daily fractionation, the maximum tolerated dose was not reached at 66 Gy given in 33 fractions over 45 days, and thus patients were accrued for a third group to receive 70 Gy in 35 fractions over 47 days. The tumor response rates varied from 78% to 100%, and no difference was found among dose levels. Doses above 40 Gy did not significantly improve the local control rate. Esophagitis and granulocytopenia of grade 3 or higher were more common among patients given hyperfractionated and accelerated-fractionation treatments.

To clarify the maximum tolerated dose of thoracic radiation (in terms of acute esophagitis and pneumonitis) that could be given in combination with cisplatin and etoposide chemotherapy for patients with limited-stage SCLC, the RTOG conducted trial 9712 (Table 2.2.2.2) (Komaki et al. 2003). The findings of this phase I trial indicated that doses could be escalated to 61.2 Gy over 5 weeks through the use of a concomitant boost technique without more than 40% of patients developing esophagitis of grade 3 or higher. This total dose was given as follows. Eleven 1.8-Gy fractions were given to large fields once daily for 5 days a week, followed by 4 days of twice-daily radiation therapy in which one 1.8-Gy fraction was given in the morning to large fields and another 1.8-Gy fraction was delivered to boost fields 6 h later; for the final 5 days, twice-daily 1.8-Gy fractions were given to the boost fields.

Acknowledgment: Supported in part by National Cancer Institute grants CA 16672 and 06294 and the Texas Tobacco Settlement.

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2.2.3 Treatment Planning and Conformal Radiotherapy

Mary K. Martel

CONTENTS

2.2.3.1 Introduction

The goal of radiotherapy is to deliver therapeutic dose in a precise and accurate manner to the target volume while minimizing dose to surrounding normal tissue. Advancement in technology over the past several decades brings highly developed means to achieve this objective. Planning and delivery of radiation therapy has evolved to a multi-step process which is individualized for each patient. This process includes anatomy definition (including tumor and important normal structures), radiation beam design, delivery of the treatment plan, and verification of delivery. The complexity of the treatment process depends on many factors; of paramount importance is the level of dose prescription and whether the ultimate clinical intent is curative.

For treatment of non-small cell lung cancer (NSCLC), standard radiation therapy (RT) dose prescriptions range from 60 to 70 Gy at 1.8–2 Gy per fraction. However, it appears from clinical data that 70 Gy may translate to a tumor control probability (or local progression-free survival) of approximately 30% (Martel et al. 1999; Hazuka et al. 1993). Supporting this outcome data are results from other single institution trials (using standard doses) which show overall survival rates of 33%–43% (Armstrong et al. 1995; Graham et al. 1995; Sibley et al. 1995). In addition, however, several of these trials, along with the multi-institutional RTOG 8301 altered fractionation trial (Cox et al. 1990), saw an elevated incidence of high grade pneumonitis. These modest local control and survival rates coupled with undesired normal lung toxicity led to a rethinking of the radiotherapy treatment approach. Interest in RT dose escalation beyond 70 Gy launched a series of phase I trials aimed to determine the maximum tolerated dose (Robertson et al. 1997; Armstrong et al. 1997; Rosenzweig et al. 2000; Belderbos et al. 2003), with secondary endpoints to determine impact on local control and survival. However, given the dose-volume relationship for normal lung with toxicity (Martel et al. 1994; Oetzel et al. 1995; Graham et al. 1999; Marks et al. 1997; Kwa et al. 1998; Seppenwoolde et al. 2003), a novel dose escalation scheme (Ten Haken et al. 1993) was designed so that the prescribed dose would depend on the amount of normal lung volume irradiated, rather than escalate in the standard fashion. A normal tissue complication probability (NTCP) model for the calculation of risk of pneumonitis was used to set the dose levels so that, as the dose was escalated, the risk of toxicity increased in a predictable manner. Using this design, doses were escalated well above standard doses, achieving 84 to 102.9 Gy for many patients (Hayman et al. 2001) without the

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development of pneumonitis. For the subgroup of patients receiving doses greater than 92.4 Gy (Narayan et al. 2004b), survival rates improved. However, local control remained problematic, with progression occurring for many of the patients.

It has been hypothesized that one source of failure of high doses to control all tumors is due to the possible accelerated repopulation late in the treatment course of 8–10 weeks needed to deliver doses in excess of 80 Gy. Estimates predict a 1.6% loss of survival rate per day for treatment prolongation beyond 6 weeks (Fowler and Chappell 2000). Accordingly, dose escalation schemes that limit overall treatment time to 6 weeks or less provide a potential "radiobiological" avenue to explore for improvement of outcome. Several trials are already underway (Mehta et al. 2001; Belderbos et al. 2003; Timmerman et al. 2003). The subject of time, dose, and fractionation of radiation therapy is explored in depth (see Chap. 2.2.2) elsewhere in this book.

Another major source of failure is geographic miss of the tumor target volume by the planned radiation fields. This is mainly due to effects related to the anatomical site of the tumor in the lung, namely, respiration effects causing tumor movement, and the uncertainties of the radiation dose calculation due to the lower density of the lung. In addition, the treatment planning phase is highly dependent on how target volumes are determined for a given patient. Inadequate tumor definition from imaging studies leads to a target volume that does not cover the full extent of the disease, and geographic miss will occur. The solutions to eliminate geographic miss are technological in nature and will be discussed in this chapter. The basic and advanced technical aspects of treatment planning for radiation therapy will be covered, which will serve as an introduction to later chapters that describe target volume definition, normal tissue toxicity, respiration control, and advanced delivery techniques such as stereotactic radiotherapy and intensity modulated radiation therapy in greater detail.

2.2.3.2 Treatment Planning Process

2.2.3.2.1 Introduction

In simple terms, radiotherapy treatment planning can be defined as the process of arrangement of beams to irradiate a defined target volume to the prescribed dose. The accuracy of beam targeting improved in the 1980s with the advent of computerized image-based treatment planning which allowed the widespread use of dose calculations in three dimensions (3D) based on patient-specific 3D anatomy. For the anatomical site of the thorax, treatment planning is complicated by the number of normal organs (spinal cord, normal lung, esophagus and heart) located close to the tumor, which have limited tolerance to radiation. However, "3D" technology has allowed reduced irradiation of normal tissues by design of field shapes with the "beam's eye view" and arrangement of multiple non-coplanar, non-axial beam angles with 3D visualization tools (McShan et al. 1990). This allows dose to "conform" to the tumor/target volume while maximizing sparing of dose to surrounding normal tissue; this technique is called "conformal" therapy. Dose distributions calculated in 3D can be evaluated throughout the 3D patient volume, allowing for detailed analysis to facilitate achievement of the optimal plan. The intricacies of the treatment planning process for both standard and conformal radiotherapy techniques for lung cancer will be reviewed here. In addition, Senan et al. (2004) have an excellent review of literature-based recommendations for treatment planning for the lung.

2.2.3.2.2 Immobilization and Simulation

3D planning begins with the acquisition of an imaging volume data set with the patient in the treatment position. First, the patient is placed on a support table in a position that can be easily reproduced during treatment setup. For patients with lung cancer, the arms are positioned above their head so as not to restrict selection of beam angles and prevent treatment through the arms. A positioning (otherwise known as "immobilization") device is used to help duplicate the same position for each day of treatment. It is now common to make custom devices to fit individual patients. Custom foam cradles are used for immobilization of the thorax region. A foam mixture fills the space between a Styrofoam form and the patient, forming to the body shape, which is then attached with pegs to the treatment table. Well-made immobilization devices will reduce the magnitude of daily set-up uncertainty.

Localization of patient anatomy is performed using imaging studies. The simplest method is the use of a machine called a simulator that has the same geometrical features of a linear accelerator (identi-

cal isocentric gantry design and position of treatment table), but has a diagnostic X-ray generator in the head of the machine. It produces radiographs in two dimensional planes that visualize the intended anatomic area of treatment, but often using bony landmarks to approximate the location of soft tissue target volumes. Computed tomography (CT) scan information supplements, and, now more commonly, replaces the simulator X-rays for soft tissue volume delineation. Axial images are acquired with thin slices (3–5 mm) through the target area and adjacent normal structures, usually from vertebral bodies C4 to L1 at a minimum, and to include the entire volume of both lungs. A coordinate system must be established between the imaging studies and the treatment machine. This is accomplished through the use of an alignment system common to the simulator, CT scanner, and treatment rooms. Wall-mounted lasers project lines in three planes (axial, sagittal, and coronal) and intersect at the isocenter, defined as the focal point of the treatment linear accelerator's rotation at a point in space. In an X-ray simulator or CT simulator (a CT scanner with a laser system and localization software), the patient is aligned so that the approximate center of the tumor is positioned at the isocenter. An example of the placement of the isocenter during the CT simulation process is given in Figure 2.2.3.1. The field center and border can be display by the simulation software and the isocenter can be placed via software tools to the center of the tumor, using the coronal (left) and axial (right) reconstructed CT images as guidance. Since the lasers are aligned to point to the isocenter, the intersection of the lasers with the patient's skin surface is then marked in the simulator. These reference marks are used to re-align the patients at the time of daily treatment at the linear accelerator.

2.2.3.2.3 Planning Target Volume (PTV)

2.2.3.2.3.1 ICRU Guidelines

The imaging studies are used to construct a target volume, the first crucial step in the planning process. To promote systematic target volume definition, the International Commission on Radiation Units and Measurements (ICRU) has published nomenclature and guidelines (ICRU 1993, 1999). For target volume delineation, several concentric volumes are described. First, the extant of malignant cells visible on imaging studies, including any involved nodes, is called the gross tumor volume (GTV). Next, a margin around the GTV is added to account for potential local-regional subclinical extension, and is called the clinical target volume (CTV). The GTV and the CTV are based solely on anatomic and biological considerations. The final volume is the planning target volume (PTV). This volumetric expansion accounts for the uncertainties of the geographic position of the CTV from day-to-day. Specifically, a margin is added to compensate for physiologic changes in the size,

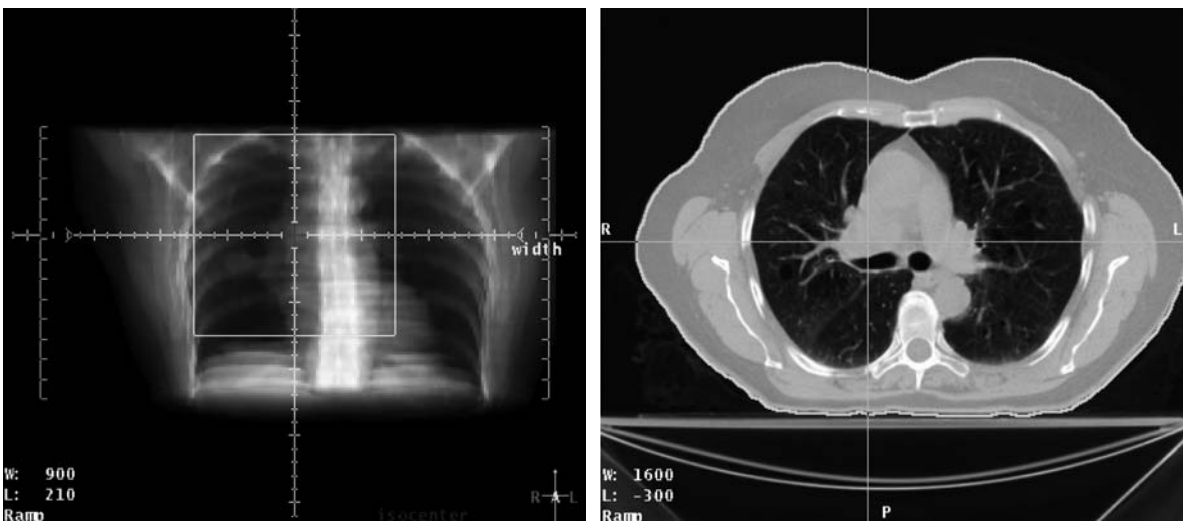

Fig. 2.2.3.1. Coronal digital reconstructed radiograph (DRR) (*left*) showing placement of an anterior field isocenter; and an axial CT slice with placement of the isocenter at depth in the patient

shape, and position of internal anatomy. Additional margins are added to account for patient movement (e.g., breathing) and differences in patient positioning from day to day (set-up uncertainty). The construction of the PTV is discussed below. In addition, target volume definition is discussed in Chaps. 2.2.4, and in the work of Armstrong (1998).

2.2.3.2.3.2 Use of CT for Gross Tumor Volume Delineation

CT imaging is the most common modality used for treatment planning. However, distinguishing tumor from surrounding normal lung and soft tissue is often not straightforward, even with the use of contrast, and there can be large variations in contoured volumes among clinicians and institutions (Senan et al. 1999; Bowden et al. 2002). Bowden et al. (2002) found that despite input from radiologists, significant variation up to 42% (on average 20%) occurred in the delineation of the 3D gross tumor volumes of NSCLC among oncologists. The authors propose standardization of the approach and give guidelines, which when followed, resulted in a reduction in the variation to 7%–22% (average 13%). Reduction of the contouring variation on CT is important since studies often relate clinical outcome to tumor size or volume. The recommended guidelines are given below, and are adapted from the procedure for the measurement of the volume of the primary tumor and involved lymph nodes from the TROG 99-05 study (Bowden et al. 2002): "Preparation: Volume measurements will be based on planning CT images, which should be contrast-enhanced. If the planning image does not have contrast, a recent (within 2 weeks of planning) diagnostic contrast-enhanced CT scan should be available for viewing alongside the planning CT scan. The planning CT scan should include all known tumor and all enlarged intrathoracic lymph nodes. Steps: (1) Identification of tumor and nodes: The contour should therefore closely hug the surface of the tumor and should not include a margin for suspected or microscopic spread. Opacities thought unlikely to represent tumor, but that a prudent radiation oncologist might include in the CTV because of lack of absolute certainty, should be excluded. The tumor, plus all hilar and mediastinal nodes with a diameter >1 cm, should be identified and outlined with a fine-tip felt pen by a diagnostic radiologist on the hard copy. (2) Initially the volume is contoured using mediastinal window (MW) settings (width 400 HU and level +20 HU). Because the density scale on commercial planning systems does not always correspond with Hounsfield units, it is recommended that the window settings be standardized for each individual department and that the same settings be used on every occasion. It is suggested that a diagnostic radiologist be asked to establish which settings most closely correspond with the range of Hounsfield units for both MWs and lung window (LW), as described in the report by Harris et al. (1993). For disease involving the mediastinum, the tumor/node edge should be defined by the interface between the tumor/node and fat or contrast-enhanced vessel using MW settings. (3) In practice, it is easiest to determine the tumor volume using the MW settings and then to enlarge this volume as required after changing to the LW settings. The LW should most closely correspond with a level of –750 HU and a window width of 850 HU. With these settings, the volume can only be contoured at the lung–tumor interface, because all mediastinal definition is lost. The maximal cross-sectional dimension of the tumor should be measured and recorded using the LW window image. Special situations: (1) Spicules: Only the solid portion of the tumor should be contoured. Fine spicules radiating into the surrounding lung should not be included, because the interpretation of their size and significance varies considerably among observers. (2) Cavitating tumor: If the tumor is cavitating, its volume will be taken to be that volume if no cavitation were present. (3) Atelectasis: Patients with adjoining atelectasis represent a special case. Sometimes the radiologist is able to distinguish atelectatic lung from tumor, especially if liver window settings are used (window width 150 HU, level 50 HU).

2.2.3.2.3.3 Addition of PET Scans

18-FDG-positron emission tomography (PET) has had a large impact on the delineation of the gross tumor volume for lung cancer because it images metabolically active tumor cells. In particular, PET has several advantages over CT in distinguishing tumor from collapsed lung or mediastinal structures, and benign from malignant lymph node enlargement. The merit of PET vs. CT in the definition of nodal involvement is reviewed by Gould et al. (2003). Data from 39 published studies showed that the sensitivity of PET vs. CT is 85% vs. 61%, and a specificity of 90% vs. 79%. A detailed discussion on the use of PET in lung cancer is given in Chap. 11.4..

A number of studies have evaluated the addition of PET to CT-based treatment planning, with results that suggest PET provides important additional in-

formation for treatment planning. The most common endpoints of the studies have been an analysis of the number of patients with volume changes based on the PET information, and the change in the margin or area of the treatment portals (Kiffer et al. 1998; Munley et al. 1999; Nestle et al. 1999; Vanuytsel et al. 2000; Mah et al. 2002; Erdi et al. 2002). For example, Kiffer et al. (1998) found with a qualitative assessment that PET activity was present in areas regarded as normal by CT and would have influenced the treatment field margin for four of 15 patients. Mah et al. (2002) found that in seven of 30 cases, PET information changed management strategy from radical to palliative treatment. In five of the remaining 23 cases, new nodes found on PET which were within 5 cm of the primary tumor were included in the PTV. The PTV that was defined using fused CT/PET would have been poorly covered by the CT-based treatment plan in up to 29% of the cases. The effect of FDG-PET on target definition varied with the physician, but led to a reduction in PTV in up to 70% of the cases and an increase in up to 76% of the cases. The relative change in PTV ranged from 0.40 to 1.86. It is clear from these studies that PET has significantly changed the treatment management of NSCLC patients, and is considered to be state-of-the-art for radiation treatment planning.

Issues remain with the use of PET in treatment planning, some of which were discussed in a recent journal editorial (Paulino and Johnstone 2004). For example, the determination of the edges of the tumor in the metabolically active area on PET is not straightforward. Most of the studies mentioned above used an arbitrary threshold value of the maximum intensity (30%–50%) in the PET-avid area or a standardized uptake value (ranging from 2 to 5). Figure 2.2.3.2 illustrates several problems with the lack of a unified approach to contouring on PET. On the left, the PET volume defined at the 50% threshold value is not contained within the CT defined volume, and may be due to respiration, motion issues, image registration, or other undetermined factors arising during PET acquisition that are not present during the CT scanning. On the right in Fig. 2.2.3.2, the choice of threshold value will yield ever-increasing volumes of the tumor. Several phantom studies have been published to determine optimal threshold values, with differing results. From Erdi et al. (1997), phantom data analysis for a set of spheres with volumes ranging from 0.4 to 5.5 ml was filled with F-18 activity (2–3 ìCi/ml) showed that image segmentation converged to a fixed threshold value (from 36% to 44%) for sphere volumes larger than 4 ml, but with the exact value depending on the source/background ratios. When applied to patient scans, the use of optimum threshold schema demonstrated a good correlation between the initial volume from CT and the final volume derived from the ^{18}FDG-PET scan. The mean difference for those volumes was 8.4%. Researchers from Beaumont Hospital (Black et al. 2004) performed a series of sphere phantom studies to determine an accurate and uniformly applicable method for defining a GTV with FDG-PET. They found a strong linear relationship between the threshold standardized uptake value (SUV) and the mean target SUV. The linear regressive function derived was: threshold SUV = 0.307×(mean target SUV) + 0.588. The background concentration and target volume indirectly affected the threshold SUV by way of their influence on the mean target SUV. The linear regressive function, as well as a fixed image intensity threshold (42% of maximum intensity) was applied to the sphere phantoms and 15 patients with NSCLC. The results indicated that a much smaller de-

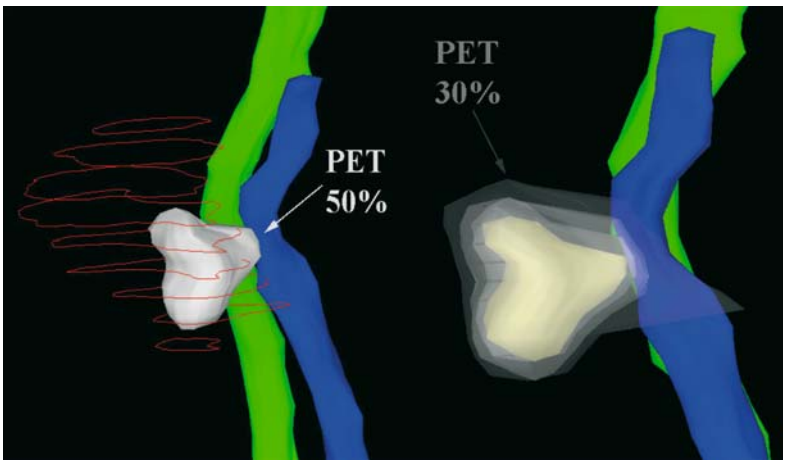

Fig. 2.2.3.2. The location and size of the PET tumor volume at the 50% (of maximum intensity) threshold (displayed in solid white) vs. the CT-defined tumor volume in *red* (*left*). PET volumes at various threshold values ranging from 30% to 60% of the maximum intensity value (*right*). (Image courtesy of Dr. Samir Narayan, University of Michigan)

viation occurred when the threshold SUV regressive function was utilized to estimate the phantom volume as compared to a fixed intensity threshold. The average absolute difference between the two methods was 21% with respect to the true phantom volume. The deviation became even more pronounced when applied to true patient GTV volumes, with a mean difference between the two methods of 67%. This was largely due to a greater degree of heterogeneity in the SUV of tumors over phantoms.

The PET (or other image datasets, such as MRI) information needs to be correlated to CT scans through the use of image registration software. Image data in the PET transmission/emission or PET/CT dataset can be aligned with the CT set by transforming the PET coordinate system to match the planning CT. Several types of algorithms exist to achieve this transformation (Pelizzari 1998). For example, one of the simplest techniques is to identify anatomical landmarks in each dataset and "tie" the two image sets together. A more complex registration method uses the entire volume of image data (i.e., intensities of the image voxels) for matching of "mutual information." Once the different image series are registered, image fusion software is used to display the two modalities simultaneously.

2.2.3.2.3.4 Microscopic Margin

Generally, the size of margin added to the GTV to account for microscopic extent (ME) has been somewhat arbitrary (i.e., 5 mm), or not used at all. However, Giraud et al. (2000)examined NSCLC surgical specimens with adenocarcinoma (ADC) and squamous cell carcinoma (SCC) histology. The mean value of ME was 2.69 mm for ADC and 1.48 mm for SCC. The usual 5-mm margin covers 80% of the ME for ADC and 91% for SCC. To have 95% confidence that all tumor is included in the clinical target volume, a margin of 8 mm and 6 mm must be chosen for ADC and SCC, respectively.

2.2.3.2.3.5 Setup Uncertainties

Sources of Error

Patient orientation at treatment may be different from the planned position. This is due in large part to random variation, but some systematic effects are present. Some sources of error are given below. For one, the location of the lasers used to indicate the isocenter may differ between the simulation and treatment room. Also, the patient may not be marked on the setup points in an exact manner in the CT simulation room. The patient may be imaged on the treatment machine before radiation is applied, which quantifies setup error, but there are limitations in the ability to visually read the portal image, as opposed to utilizing computer-aided graphic alignment tools. Also, based on the portal image, it is common to correct the position of the patient only when the needed shift exceeds 5 mm or greater. Furthermore, there may be limitations in the ability to make the proper shift in patient position. Finally, the patient may move on the table after imaging but before treatment commences.

Studies to measure patient setup errors should be carried out to estimate the margin to be used for the planning target volume definition. Study results will be dependent on the immobilization, simulation, and treatment techniques used at each individual institution. One such recent study (Schewe et al. 1996) measured overall setup errors in several anatomical sites, including the chest. Port films taken over the entire treatment course were compared to simulation films, using a curve matching graphical interface. In general, the average translations in patient position in the chest were: 1.3 mm±7.1 mm right-left, 3.3 mm±6.7 mm anterior-posterior, 2.1 mm±8.3 mm superior-inferior. This data is displayed on a patient-by-patient basis in Fig. 2.2.3.3. It is interesting to note some patients show much larger movement or setup error than others. Also, mean translations that differ from zero indicate systematic errors in setup. This study would indicate that if a population-based standard margin was to be used for each patient, at least 1 cm should be added to the CTV. However, such a margin would be too large for most patients in the study and would unnecessarily encompass too much normal tissue, but too small for the outliers, leading to geographic miss of the PTV. Portal imaging everyday (instead of the current once-per-week) will certainly decrease the setup uncertainty. An alternative method would be to image every day during the first week of treatment to determine an individualized margin for use during the remainder of the treatment. However, it is clear that regular observation and correction for patient setup is a necessity.

Accounting for Respiratory Motion

Tumor motion due to respiration must be included in the planning target volume definition, and can be determined at the time of imaging. Simulator X-

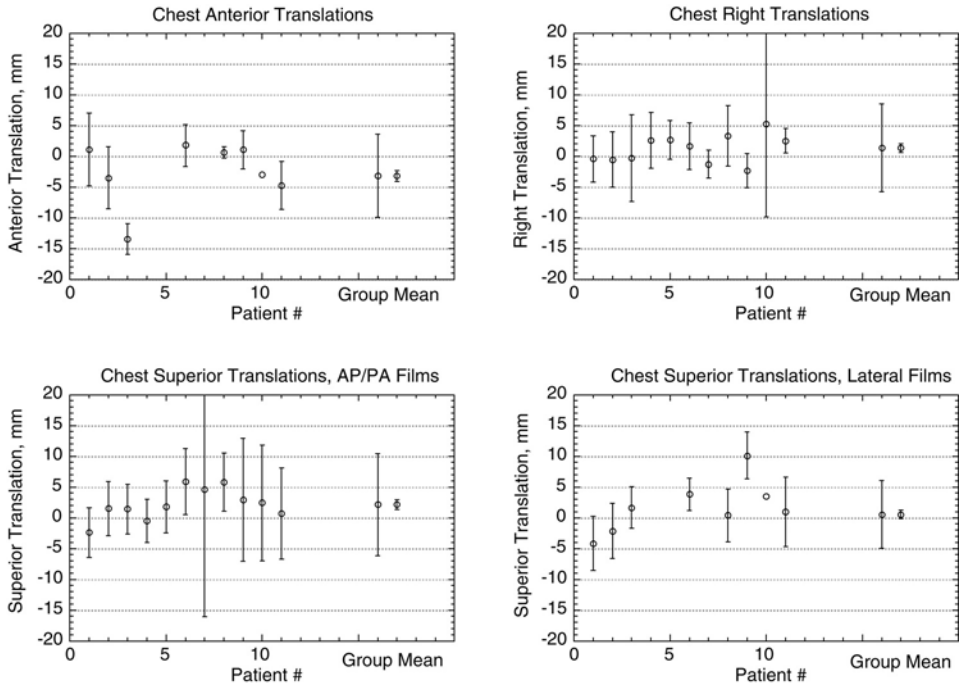

Fig. 2.2.3.3. Chest patient mean translations and standard deviations (Schewe et al. 1996)

ray films or planning CTs represent a "snapshot" of a point in time during the respiration cycle, which may not be at the same point under treatment conditions. On a conventional simulator, the tumor motion and/or diaphragm motion can be observed with fluoroscopy. Ekberg et al. (1998) observed tumor motion with fluoroscopy for a group of 20 patients. With quiet respiration, they observed maximum movements in the medio-lateral and dorsoventral direction of 5 mm, and in the cranio-caudal direction of 12 mm. A recent study by Sixel et al. (2003) used digital fluoroscopy to record a movie loop over several respiration cycles. The movie loop was registered with the simulation field films, and the maximum extent of the tumor motion was observed. The results showed movement ranging from 0 to 12.8 mm in the superior-inferior direction, 0–3.2 mm in the lateral direction and 0–4.4 mm in the anterior-posterior direction. Large variation in GTV motion from patient to patient was observed, especially in the superior-inferior direction, for which interpatient variability was >10 mm. Furthermore, the motion variability and magnitude were much larger in this dimension than in either the lateral or AP direction. There did not seem to be a relationship or pattern between the tumor location within the lung and the magnitude of motion. The authors reached the conclusion that the observed variability indicates the need for motion margins that are unique for each patient and in each dimension. A standard uniform PTV margin of 15 mm, as conventionally applied in the authors' clinic, was found to be inappropriate.

There are several drawbacks to the use of fluoroscopy for estimation of the PTV margin for motion. For example, the tumor can be difficult to see with fluoroscopy X-rays, the diaphragm motion may not correlate with tumor movement, and translation not shape change is measured. The use of CT simulators is now commonplace, and CT images may be acquired during different phases of the respiratory cycle. Allen et al. (2004) defined a composite GTV using a CT scan taken at deep inspiration and one at exhalation, representing the extremes of motion that may be expected during free-breathing at treatment time. Maximum excursion of the tumor averaged over all patients was: superior-inferior motion of 2.0 cm, lateral motion of 1.5 cm, and anterior-posterior motion of 1.7 cm. In addition, many of the tumors demonstrated shape deformation. An important conclusion reached was that a large variation in tumor movement about each axis was observed, and that motion could not be quantified as a class solution, or as a standard uniform (or non-uniform) margin.

Incorporation of a margin for motion will increase the planning target volume and, consequently, in-

crease the amount of normal lung that is irradiated. Alternatively, respiration can be suspended during the planning CT and treatment, as described by Wong et al. (1999), through the use of a device called active breathing control (ABC). This eliminates the PTV margin for motion since the GTV need only be defined at one point during respiration. A question remains, however, as to whether ABC will be tolerated by some patients with compromised lung function. Along similar lines to ABC, another emerging technology is respiratory gated therapy (Kubo et al. 2000), where radiation is delivered only at a certain phase of the respiration cycle when the target is in a known position. Gated therapy is discussed in detail in Chap. 11.2.

2.2.3.2.4 Radiation Beam Design and Delivery

2.2.3.2.4.1 Standard Beam Arrangements

After imaging data is complete for a given patient, the target volumes and normal anatomic structures must be defined. Each structure is circled or contoured on individual axial images, using image display workstations. The contouring process segments the image data into separate structures, each uniquely identified. Semi-automated and automated algorithms are available that will contour structures having the same density, allowing rapid definition of an entire 3D region. For example, lungs have one-third of the density of soft tissue and can be easily differentiated from surrounding tissue. Surfaces for each structure are generated from the segmented contours, and can be viewed in any plane that is generated through the surface. In Fig. 2.2.3.4, the planning target volume in green and the spinal cord volume in yellow are displayed as overlays on several reconstructed CT plans, such as the axial, sagittal, and coronal planes in the left panels. This type of display is useful during treatment beam design.

The next step in the planning process is the design of radiation beam field or aperture. In the treatment of lung cancer, relatively simple beam arrangements have been traditionally used. This is due in large part to the prophylactic treatment of hilar, mediastinal and in some cases, supraclavicular lymph nodes which may be at risk for harboring microscopic disease, which is called "elective"

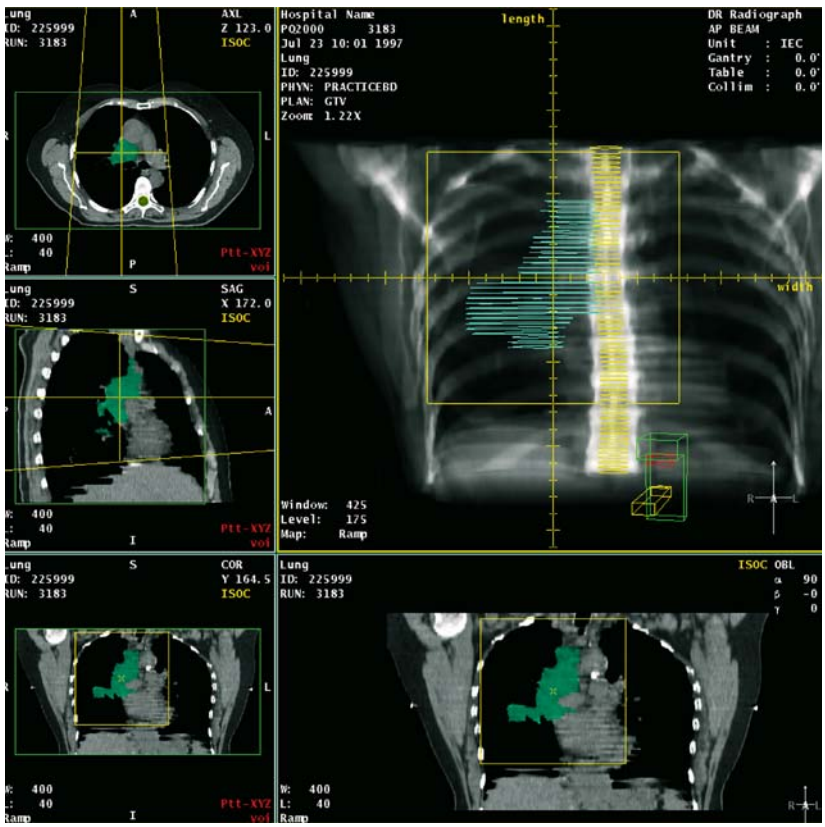

Fig. 2.2.3.4. Gross tumor volume (GTV) contours shown in *green* and spinal cord contours in *yellow* are overlaid on the coronal DRR (*upper right*), and on axial, sagittal, and coronal CT slices. The projection of the field borders on the patient is shown in *yellow* in each panel

nodal irradiation (ENI). Though the ENI volume is determined by anatomical landmarks located on simulator X-ray images or reconstructed coronal CT planes, it is rarely (if ever) contoured by the radiation oncologist as a separate structure. It is common to treat the "approximated" ENI volume, along with the contoured primary GTV/PTV, in large fields aimed from the anterior and posterior (AP/PA) direction of the patient in parallel-opposed fashion (see Fig. 2.2.3.4). Since the spinal cord is irradiated by the AP/PA fields, this beam arrangement can only be used until the tolerance dose of the cord is reached, generally 45–50 Gy at 1.8–2 Gy/fraction. Fields are then arranged "off-cord" to treat only the primary PTV. An example design of off-cord fields is shown in Fig. 2.2.3.5. Here, beam apertures are planned using 3D treatment planning software, called "virtual simulation." Initially, the radiation field borders are set in a rectangular fashion. Then, beam directions are selected by the use of the beam's eye view (BEV) tool. Target and normal structures are viewed from different directions in planes perpendicular to the beam's central axis using BEV (see Figs 2.2.3.4 and 2.2.3.5). Structures are distinguished from each other by use of different colors. In Fig. 2.2.3.5, the beam direction is angled away from the normal structure to separate the PTV structure from the spinal cord. The beam shape is then modified by designing a block that will allow full dose to the PTV but minimize dose to surrounding normal tissue. The block shape is represented by the outermost shape in the BEV in Fig. 2.2.3.5. Blocks consist of heavy metallic material mounted on a tray which is placed in the head of the machine, or a block substitute called a multileaf collimator (MLC). The MLC consists of a number of small leaves that move independent of each other to form the planned shape (displayed in the BEV in Fig. 2.2.3.6).

Once beam angles and shapes are designed, dose calculations are performed. Since it is not possible or practical to measure a 3D dose distribution for each patient situation, a general dose calculation system must be used to "predict" the dose in the patient. These calculations incorporate basic data that characterize the radiation beam energy and geometry, such as depth dose curves and isodose information for standard field sizes. The deposition of dose from photon irradiation results from the generation of secondary electrons. In the case of photon energies in the therapeutic range, electrons are primarily set in forward motion by Compton interactions (in which energy is both absorbed and scattered), which then penetrate deeper into tissue. Energy is deposited into tissue as these electrons slow down. Computerized algorithms have been developed to combine the dose distributions generated by combinations of beams, using individual patient information such as depth of the point of calculation, external body contour, and various densities of anatomical structures. Dose distributions are displayed with concentric curves for chosen dose levels (isodoses) which are displayed as overlays on anatomic structures. These curves are normalized to a reference dose, either at isocenter or to the lowest isodose curve that encompasses the PTV. Ideally, the 95% isodose curve will cover the planning target volume, or adjustments will be made in the field angles after evaluation of the dose distribution.

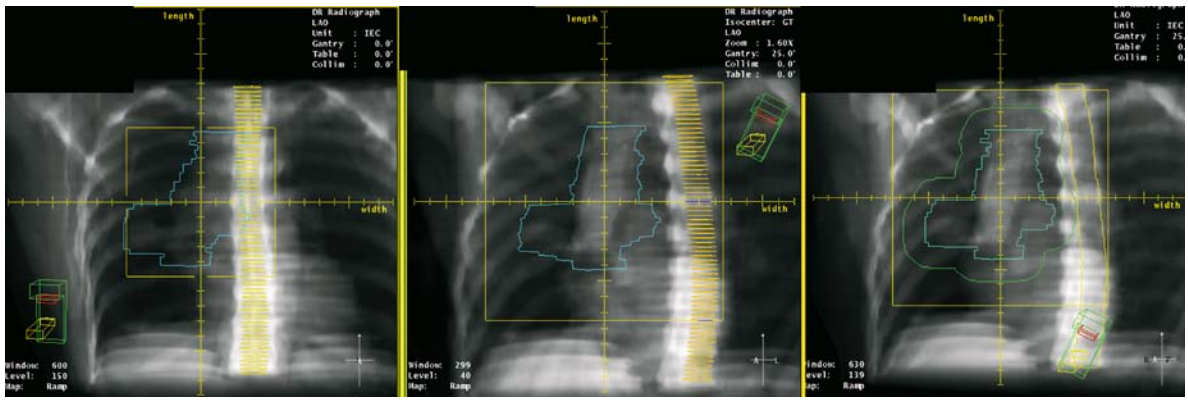

Fig. 2.2.3.5. To avoid delivering dose to the spinal cord (*yellow* contours) with the anterior field (*left*), the head of the machine must be rotated until the virtual simulation software shows "separation" of the cord from the tumor volume (outlined in *blue*; *middle*). Blocks to shield normal tissue are then drawn (outside *blue line*; *right*)

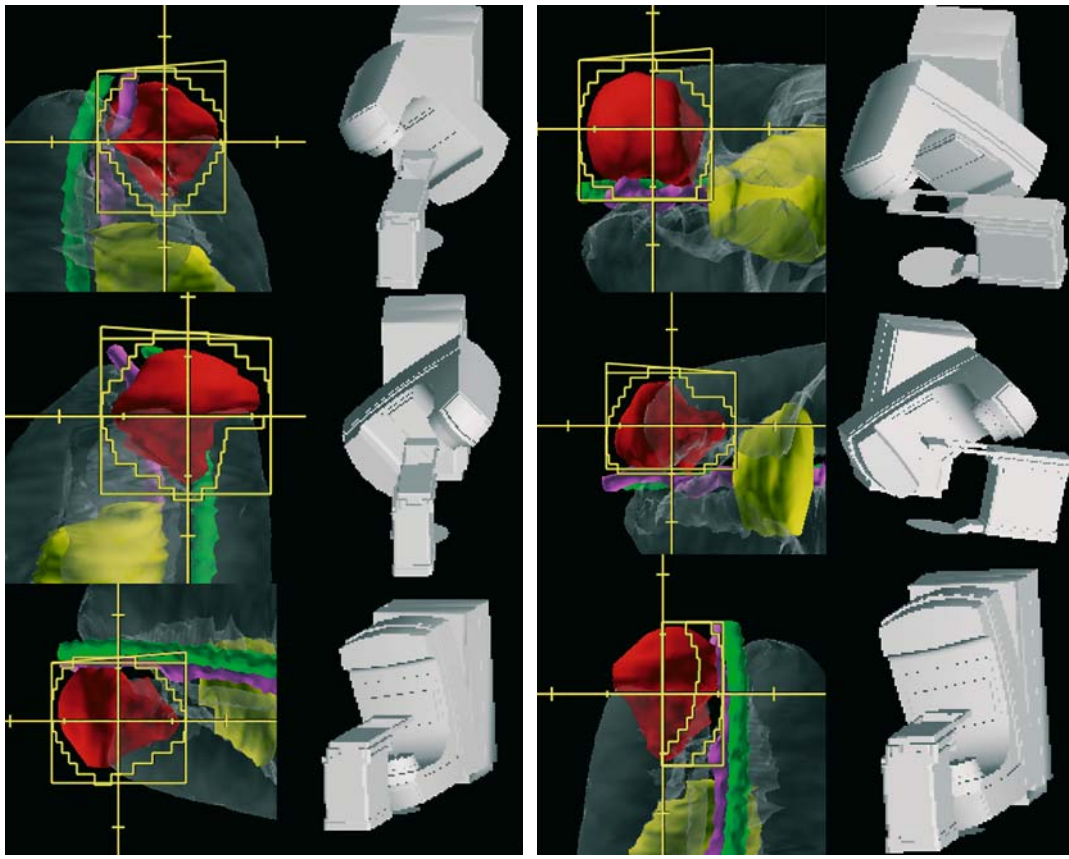

Fig. 2.2.3.6. Beam's eye view planning with non-coplanar and non-axial beams to avoid normal structures for an upper lobe tumor. (University of Michigan UMPlan)

2.2.3.2.4.2 Advanced Treatment Techniques

The fundamental rule of treatment planning is the use of multiple beams to concentrate the high isodose region at the isocenter and in the PTV. Two opposed beams, such as the AP/PA fields described above, will produce a more uniform dose distribution throughout the volume when compared to the use of a single beam. However, when more than two beams are used, the dose is further concentrated in the PTV and dose to normal tissues can be further reduced. An ideal treatment plan is both conformal (high dose wraps closely around the PTV with rapid fall-off to low doses) and homogeneous (±5% variability of dose within the PTV). Two example cases of conformal beam arrangements are given below. The first case is a tumor of the upper lobe, in Fig. 2.2.3.6. Normal tissue structures such as lungs, heart, esophagus, and spinal cord are contoured on CT, and are displayed as solid surfaces in 3D in a variety of BEV displays. The PTV, in red, is targeted by beams directed from five different machine gantry angles, and several different couch angles. These angles were chosen so that each normal structure is irradiated by only several, but not all, of the beams. For example, the spinal cord, in green, is contained within two of the six BEV fields. If the dose distribution for the PTV is not homogeneous, segments of fields may be placed to "boost" the dose; one such segment is shown in the lower right of Fig. 2.2.3.6.

The treatment plan can be evaluated as to whether it meets objectives of PTV coverage and normal tissue avoidance. A set of criteria for normal tissue tolerances (discussed in the next section) must be given to guide the treatment planner. Dose distributions for 3D volumes can be displayed and analyzed graphically with dose-volume histograms (DVH), generated for each structure. The cumulative form of the DVH is a plot of the volume of a given structure receiving a certain dose or higher as a function of dose. DVHs for the beam arrangement in Fig. 2.2.3.6 are displayed in

Fig. 2.2.3.7. The dose-volume histogram for normal lung is the addition of the dose distributions of both lungs but minus the dose distribution in the GTV. The GTV is selected instead of the PTV, since the PTV contains normal lung receiving high dose which influences the normal tissue toxicity rate.

The second case is shown in Fig. 2.2.3.8. The tumor is centrally located and in the lower lobe. Though the PTV is located near the spinal cord, dose to the cord is kept below tolerance by shielding the structure in two of the four fields. However, the PTV is also blocked, and the dose is boosted by adding a field segment, shown in the lower left panel. The dose volume histograms are shown in Fig. 2.2.3.9. Discussion of the analysis of the DVHs for both cases is given in the next section.

If the treatment plan does not meet the given dose-volume objectives, beam arrangements or other parameters are adjusted. This can include a change of beam energy, beam angle, or adjustment of the beam

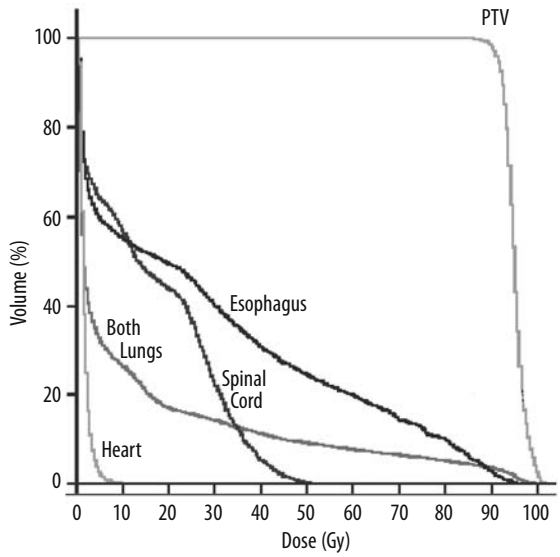

Fig. 2.2.3.7. Dose volume histograms for treatment plan shown in Fig. 2.2.3.6

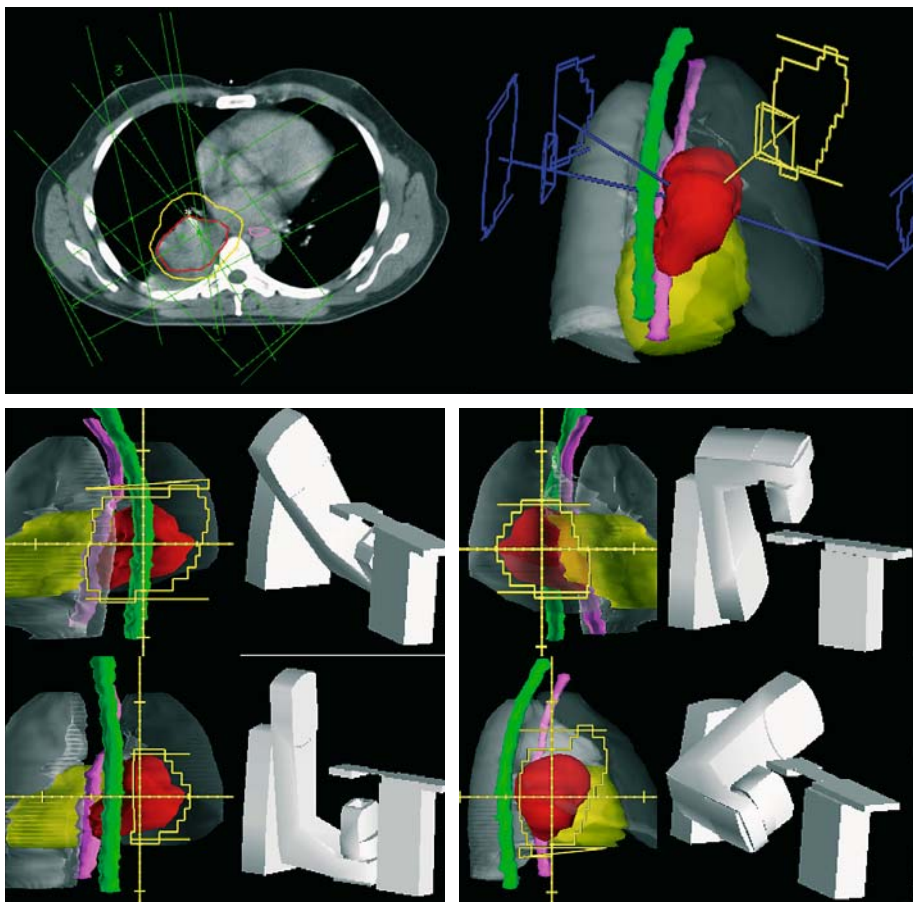

Fig. 2.2.3.8. Beam's eye view planning with non-coplanar and non-axial beams to avoid normal structures for a lower lobe tumor. (University of Michigan UMPlan)

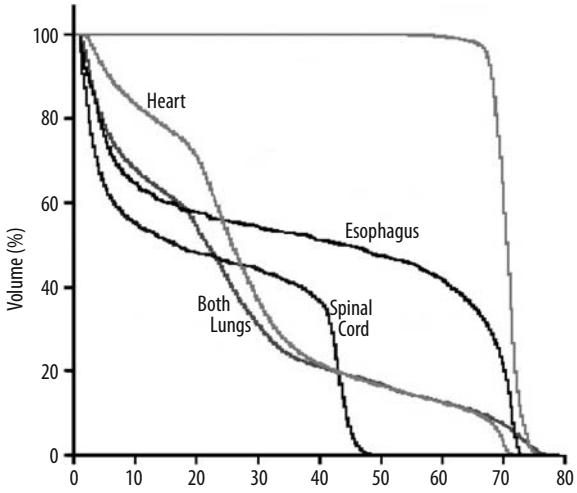

Fig. 2.2.3.9. Dose volume histograms for treatment plan shown in Fig. 2.2.3.8

intensity. For "forward-planned" conformal therapy, these adjustments are carried out manually, with changes made in an iterative fashion by the treatment planner. Normally, the beam intensity is uniform across the beam width and length. The simplest modification of the intensity is a wedged shape filter placed in the machine head. A more complex method is to break the field aperture into segments with varying beam-on times. Currently the most intricate form of intensity modulation achieves a checkerboard pattern with each square of a varying intensity. The delivery of this type of pattern is with a compensator or with a device called a multileaf collimator, which can move under computer control to shape segments of the field to deliver the intensity pattern. This is called intensity modulated radiation therapy (IMRT) and with this technique, there is potentially a high degree of control over the shaping of the dose distribution. Because the intensity pattern is so complex, a different type of computerized treatment planning is used, called inverse planning. The treatment planner defines the dose to be delivered to a target volume and the limiting dose to the surrounding normal tissues, and beam angles. The computer determines the corresponding intensity profiles to achieve the desired dose distribution. IMRT for lung cancer has recently being explored. There have been several theoretical treatment planning studies published, with findings that higher levels of tumor dose can be achieved while maintaining the same normal lung dose-volume indices (Derycke et al. 1998; van Sornsen de Koste et al. 2001; Grills et al. 2003; Marnitz 2002). IMRT for treatment of lung cancer is described in Chap. 11.1.

Once the final beams are designed, X-ray images in the form of digitally reconstructed radiographs (DRRs) are generated from the treatment planning CT to enhance the bony anatomy with high contrast, and are in the BEV plane. An example of a DRR of the lung is shown in Fig. 2.2.3.5. DRRs are used to compare to portal images taken before treatment, which are either films placed in the beam exiting the patient or with an electronic portal device. Verification of the radiation beam placement vis-à-vis the patient is carried out pre-treatment so that patient position can be adjusted accordingly. Beam delivery is carried out with the use of beam modifiers such as blocks, multileaf collimators, wedges, compensators, or IMRT.

2.2.3.2.5 Normal Tissue Tolerance and Treatment Planning Objectives

3D conformal therapy is now a mature technology in widespread use. However, it is still difficult to design the "best" plan, defined as a balance of achieving high dose delivery to the tumor with a low rate of normal tissue toxicity. A set of criteria for normal tissue tolerances should be established from published studies and adapted for local clinical use. A good starting point is the report by a National Cancer Institute-sponsored task force which carried out an extensive literature search and presented updated information on tolerance of normal tissues, with emphasis on partial volume effects (Emami et al. 1991). For uniform irradiation of normal lung, tolerance doses for a 5% chance of pneumonitis occurring within 5 years for uniform irradiation of 1/3 of the lung was 45 Gy, 2/3 was 30 Gy, and whole lung was 17.5 Gy. For the esophagus, the corresponding doses are: 60 Gy (1/3), 58 Gy (2/3) and 55 Gy (whole) for an endpoint of clinical stricture/perforation. For the heart: 60 Gy (1/3), 45 Gy (2/3), and 40 Gy (whole) for the endpoint of pericarditis. The 50% chance of a complication occurring in 5 years was also given for each organ. These tolerance data show that the complication probability may be a function of irradiated volume and dose. Preferably, biological models that use 3D dose and volume information (and often, fractionation effects) could be employed within the framework of the treatment planning system to predict normal tissue complications and tumor control rates. Parameters for these models are determined by fits to clinical data. The model can then be interpolated or extrapolated beyond the range of the data and is useful during design of 3D treatment plans to estimate

and help limit normal lung toxicity. For example, an empirical methodology was developed (Lyman 1985) to parameterize normal tissue complication probability (NTCP) under conditions of uniform irradiation to whole or partial organs. The relationship among these three variables (NTCP, partial volume, and dose) was modeled. Tolerance data was used by Burman et al. (1991) to provide best-fit estimates of those parameters. Subsequently, the parameterization can be used to estimate the complication probability as a function of any dose and fractional volume for the uniform irradiation of a partial organ volume. With the Lyman model, a single number for fractional volume must be determined. The DVH, which summarizes the non-uniform distribution of dose for a particular treatment plan throughout an organ, can be "reduced" to a one-step DVH that represents uniform dose to a partial volume. The assumption is that, when plugged into the Burman-Lyman NTCP parameterization, the transformed DVH would predict the same NTCP as the original DVH. The Kutcher (Kutcher et al. 1991) reduction method gives a final histogram with a single "effective" volume (Veff) for irradiation of a single reference dose.

The Emami tolerance data summary was one of the early efforts towards the use of objective criteria in evaluating treatment plans. However, the tolerance doses given were based on limited volumetric dose data publications and on "guesstimates" based on clinical experience. As 3D dose distributions for normal lung became available, dosimetric parameters could be correlated with complication data. Martel et al. (1994) reviewed the 3D dose volume histograms for lung for patients with Hodgkin's disease or lung cancer vs. the development of acute pneumonitis. A reasonable prediction was found for low versus high risk of pneumonitis when examining risk groups stratified according to the effective volume parameter for lung (Veff). There were also differences in the mean lung dose (MLD) between patients with complications (MLD of 18–21 Gy) versus no complications (24–26.1 Gy). Oetzel et al. (1995) demonstrated good correlation for the pneumonitis risk with observed complication rates for ipsilateral lung DVHs. Mean lung dose varied for patients with and without complications (23.8 Gy vs. 20.1 Gy). Marks et al. (1997) found the volume of normal lung receiving greater than 30 Gy (V30) was a strong predictor of pneumonitis. Graham et al. (1999) reported the best predictor of acute pneumonitis was the volume of total lung receiving >20 Gy (V20). Kwa et al. (1998) found a relationship between the incidence of radiation pneumonitis and the mean lung dose in an analysis of pooled data of 540 patients from five institutions of the previously listed studies. Increasing mean lung dose correlated well with increasing pneumonitis rate. Figure 2.2.3.10 illustrates this relationship and can be used to reliably predict the risk of pneumonitis when mean lung dose is evaluated from a treatment plan DVH. A more thorough investigation of a variety of dosimetric parameters (Seppenwoolde et al. 2003) confirmed that the underlying local dose–effect relation for radiation pneumonitis was linear (mean lung dose), rather than a step function (V20, V30, etc.). Each of these studies provides dosimetric parameters (Veff, V30, V20, MLD) that can be extracted from the 3D dose distribution to give the clinician a guide for safe treatment. Treatment-related toxicity is discussed in detail in Chaps. 8.2–8.4. It should be noted that current toxicity data does not include the effect of concurrent chemotherapy.

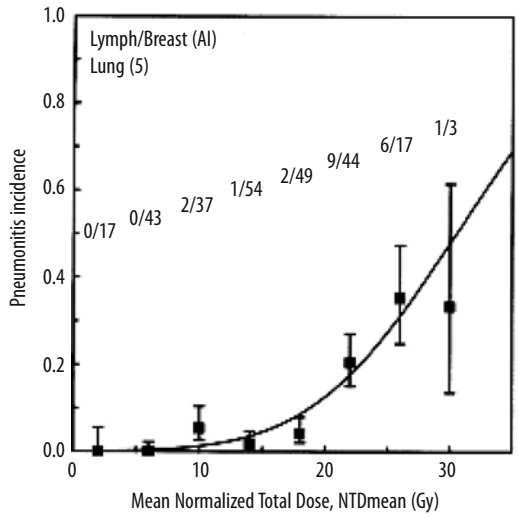

Fig. 2.2.3.10. The incidence of radiation pneumonitis as a function of the mean normalized total dose (*NTDmean*), representing mean lung dose (Kwa et al. 1998)

Complication data such as those discussed above has helped in the design of several dose escalation trials. As discussed in the introduction, one of the first trials in the 3D treatment planning era used a novel dose escalation scheme (Ten Haken et al. 1993; Hayman et al. 2001) at the University of Michigan. Because of the observed dose–volume relationship for normal lung with toxicity, the prescribed dose depended on the volume of lung (Veff) irradiated by the plan, rather than escalated in the standard fashion with all patients regardless of the amount of lung irradiated receiving the same level of dose. The normal tissue complication probability (NTCP) model from

Lyman was used to set the dose levels so that, as the dose was escalated, the risk of pneumonitis increased in a predictable manner. The Netherlands Cancer Institute (Belderbos et al. 2003) has a similar approach but uses mean lung dose to stratify patients into dose groups. The Radiation Therapy Oncology Group's (RTOG) trial (RTOG 1993) has three levels of stratification according to V20. The use of 3D conformal therapy is a requirement for these studies.

The University of Michigan trial set constraints for dose to normal tissue. All doses were corrected for the effects of lung density. For example, the maximum dose to the spinal cord is 50 Gy. The Veff computed for the esophagus with a normalization dose of 80 Gy must be less than 33%. The Veff for the heart with a normalization dose of 40 Gy and 65 Gy must be less than 100% and 33%, respectively. The Veff computed for both lungs minus the GTV for the prescription dose must be less than 40%. This means that, for the esophagus and heart, the probability of a complication must be no greater than the risk associated with uniform irradiation of one third of the esophagus, one third of the heart, and the whole heart to 80, 65, and 40 Gy, respectively. These dose levels were adapted from the Emami et al. (1991) data. The two patient cases given in Figs. 2.2.3.6 and 2.2.3.8 were entered on the trial. The first case has a GTV of 169 cc and a PTV of 429 cc. With sophisticated beam arrangements, the normal lung (both lungs minus GTV) Veff was 13%, with a prescription dose of 92.4 Gy, achieving a dose much higher than standard fractionation. All normal tissue doses were well within constraints with the spinal cord maximum dose of 49 Gy, and the esophagus and heart Veffs of less than 5%. The second case had a smaller GTV of 105 cc and PTV of 308 cc. However, because of the central location, the normal lung Veff was 37% with a prescription dose of 69.3 Gy.

2.2.3.2.6 Dose Calculation Issues

2.2.3.2.6.1 Effects of Lung Density

It is still common that most clinics, and many clinical trials, have not taken the effects of lung density into account when prescribing dose to the PTV. In computer calculations, lungs are assigned a density of 1, which is equivalent to water, instead of approximately 0.2–0.4 that is reality. This means that the attenuation of photons per unit length is lower in low density lung tissue compared with unit density water-equivalent tissue. Orton et al. (1998) mentions several reasons for the lack of use of density corrections: the inability of treatment-planning computers to make adequate calculations of density-corrected doses; the lack of consensus as to which density-correction algorithms were best, or at least "acceptable"; the lack of evidence that corrections for lung density were necessary in clinical trials; and, probably most importantly, the realization that because all clinical experience so far had been with uncorrected doses, to start making density corrections would require that prescription doses be increased by an "unknown" amount so that past and future protocols could be compared. When dose was measured in a benchmark test phantom to a point in between two lungs, there was increased dose ranging from 5%–14% relative to a phantom of unit density (Table 2.2.3.1). The effect decreases as the photon energy increases. The use of high energy beams could be used to minimize the dose correction discrepancies. However, studies (Mackie et al. 1985; Rice et al. 1988) have shown that higher energy beams tend to "spare" the surface of the tumor when traversing through the lung. Also, higher energies will have an increased range of secondary electrons in lung tissue, which further spreads out the low isodoses relative to a water-equivalent tissue (Ekstrand and Barnes 1990). When a clinically relevant phantom study was performed (Klein et al. 1997), dose delivered to the PTV with 6 MV was within 5% of predicted, but low by 11% with use of 18 MV. It is generally recommended to use density corrections and low energy photon beam for treatment planning of lung cancer.

Table 2.2.3.1. Lung density correction factors measured in the benchmark problem phantom at energies ranging from ^{60}Co (1.25 MeV) up to 24 MV. [From Orton et al. (1998)]

Photon energy	Laterals	AP/PA fields	Overall
Co-60	1.3	0.98	1.14
4 MV	1.25	0.98	1.11
6 MV	1.22	0.98	1.10
10 MV	1.16	0.99	1.08
15 MV	1.15	0.99	1.07
18 MV	1.14	0.99	1.07
24 MV	1.11	0.99	1.05

2.2.3.2.6.2 Calculation Algorithms

Current treatment-planning computer systems have the capability of incorporating the effect of lower lung density into the dose calculation, and there are several density-correction algorithms. However, because of the variety of treatment situations for lung cancer, it is

difficult to take into account all effects, such the build-up and scattering of secondary electrons. Such effects depend on, for example, how much lung is traversed, beam energy, and beam field size. Correction-based algorithms such as the equivalent path length (EPL) model, the generalized Batho, and equivalent-tissue-air ratio (ETAR) methods are available commercially. The limitation of these algorithms is that the increased lateral electron scatter in lung tissue is not accounted for. Calculation algorithms have become more sophisticated in the past decade and practical to use with the increase in computer calculation power. For example, the convolution-superposition (CS) method can predict the lack of lateral electron transport in the calculation. The effect of the more accurate CS algorithm vs. the EPL algorithm is shown in Fig. 2.2.3.11 (de Jaeger et al. 2003). The patient's original plan using EPL shows that the 95% isodose line is enclosing the PTV (left panels). Recalculation of the dose distributions with the CS model shows that the 95% isodose line constricts into the PTV, causing a reduction of dose particularly in the region of the PTV that is embedded in lung, due to the penumbra broadening in the low-density lung tissue. This effect is less at the mediastinal boundary with the PTV. Overall, the mean lung dose as determined by the CS and EPL algorithms differed on average by 17%, and the V20 differed on average by 12% (Fig. 2.2.3.12) (de Jaeger et al. 2003).

Model-based calculation techniques, such as the convolution-superposition and more recently, Monte Carlo methods, offers a physics-based approach found to be more accurate than correction-based methods

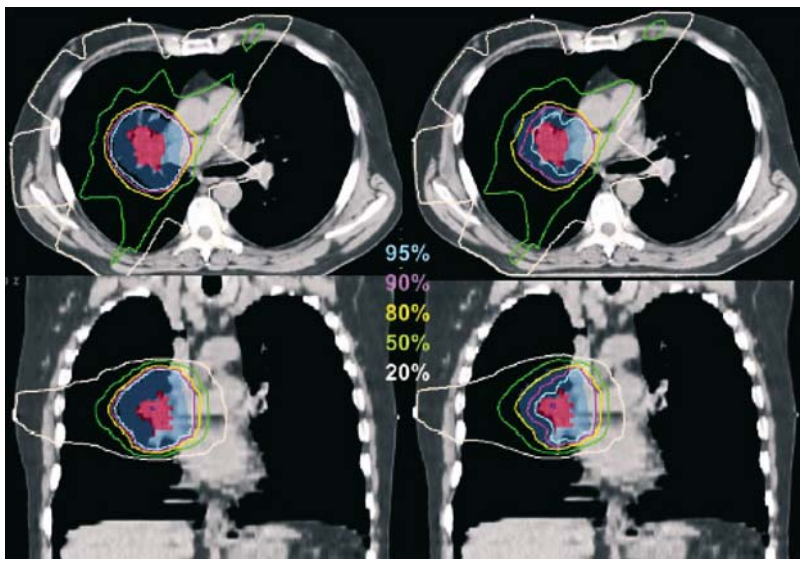

Fig. 2.2.3.11. Isodose distributions in transverse and coronal views through the dose specification point of a five-field treatment plan for a right hilar NSCLC, computed using the EPL algorithm (*left*) and the CS algorithm (*right*). The isodose levels displayed are: *blue*, 95%; *pink*, 90%; *yellow*, 80%; *green*, 50%; *white*, 20%. The color washes in *red* and *blue* represent the GTV and the PTV, respectively. Note the difference in the computations of the 95% isodose line in the PTV (de Jaeger et al. 2003)

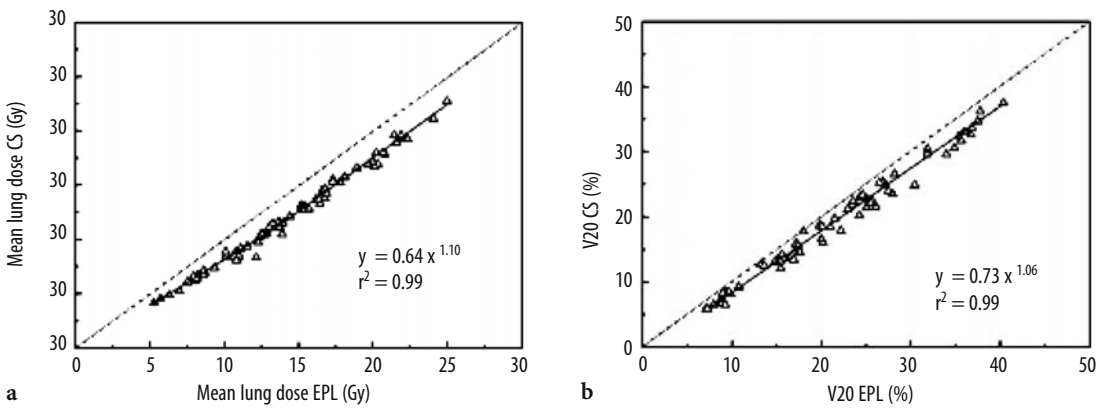

Fig. 2.2.3.12. The mean lung dose computed with the CS and EPL algorithm (**a**). Each triangle represents data of an individual patient. The *dashed line* indicates the line of identity. Also shown is a fit of the data using a power-law relationship. Similarly, (**b**) represents the comparison between CS and EPL calculations of V20. The data were also fitted using a power-law relation (de Jaeger et al. 2003)

for calculating the dose in inhomogeneous media. The Monte Carlo method is the only method that explicitly transports photons and electrons within a material and is therefore likely to provide more accurate results at material interfaces and within lower density material (Chetty et al. 2003). A wide range of experiments have been conducted in both unit density and low density geometries to validate user-specific Monte Carlo codes developed for clinical treatment planning. Results of one such validation experiment is given in Fig. 2.2.3.13 (Chetty et al. 2003). Depth dose curves are shown for unit density material in the two upper left panels, for small field sizes where the calculation is the least accurate for other algorithms,

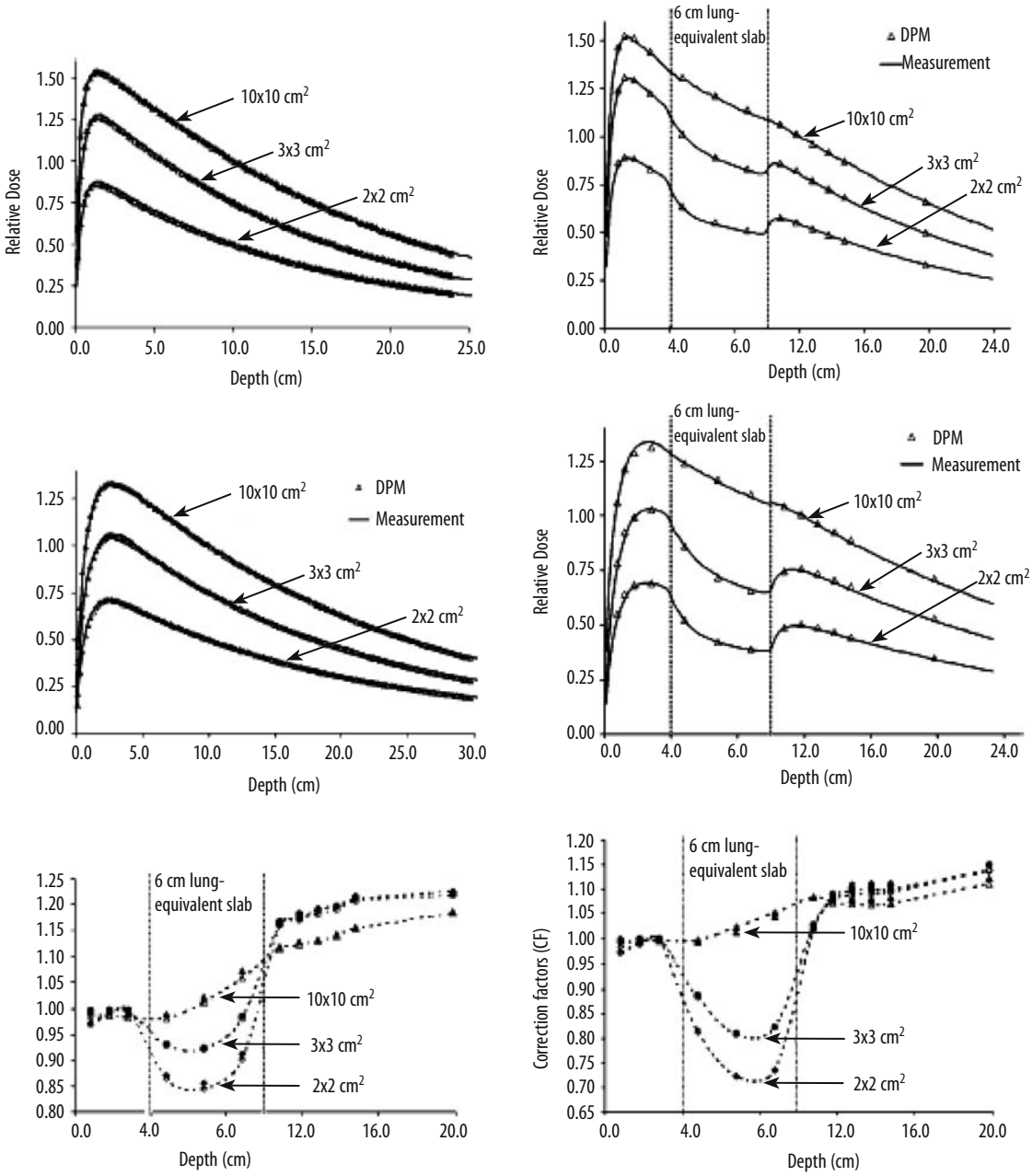

Fig. 2.2.3.13. Relative central axis depth dose for 6 MV (*upper left*) and 15 MV (*middle left*) photons in a water phantom. Relative central axis depth dose for 6 MV (*upper left*) and 15 MV (*middle right*) photons in the inhomogeneous solid-water/lung/solid-water phantom. Depth dose curves have been normalized to the doses, for the respective field sizes, at 10 cm depth in the homogeneous phantom. Correction factors (CF) as a function of depth for 6 MV (*lower left*) and 15 MV (*lower right*) photons. The CF is defined as the ratio of dose in the inhomogeneous phantom to that in the homogeneous water phantom, at a given field size and depth (Chetty et al. 2003)

and for two energies of 6 MV and 18 MV. The Monte Carlo calculation, represented as a line in the two upper right panels, is in very good agreement with the measurement points when lung material is placed in the beam. Note the decrease of dose within the lung, relative to the unit density curve, and the "re-buildup" of the dose in the unit density material (solid tumor) located past the lung. Though this effect is difficult to model, the Monte Carlo method prediction is accurate. The correction factors as a function of depth for (lower left) 6 MV and (lower right) 15 MV photons are also given. When Monte Carlo was used to recalculate patient cases (Wang et al. 2002), the calculated dose distributions were again characterized by reduced penetration and increased penumbra due to larger secondary electron range in the low-density media, not as accurately accounted for in the pencil beam algorithm compared to Monte Carlo. It was concluded that it would be optimal to either use a Monte Carlo once fast algorithms are developed.

2.2.3.3 Conclusion

Technological advances have become commercially available in the past decade. In particular, 3D conformal therapy has become the first step in improving the targeting of dose to the tumor while sparing dose to normal tissue, and has facilitated radiation dose escalation. Though local control and survival has not yet dramatically improved with recent dose escalation trials, this may possibly be due to geographical misses because of poor target definition, movement of the tumor due to respiration, and dose/fractionation levels. Improved construction of the planning target volume is an important first step in improving the treatment planning process. Further improvements can be gained by sophisticated beam arrangement planning, made possible with an intelligent choice of clinically relevant normal tissue tolerance criteria. Finally, algorithms to account for the effects of lower lung density have become available and will facilitate the accurate and realistic calculation of dose to the PTV and the lung. The next step in the coming decade is to determine the impact of new technology on treatment outcome.

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2.2.4 Target Volumes in Non-Small Cell Lung Cancer

Frank Lagerwaard and Suresh Senan

CONTENTS

2.2.4.1 Introduction

Only the use of three-dimensional (3D) treatment planning is appropriate for high-dose radiotherapy in non-small cell lung cancer (NSCLC) as major errors in target coverage have been reported in more than 15% of patients planned using two-dimensional (2D) techniques (Rosenman et al. 2002). However, even with 3D conformal radiotherapy (3DCRT) techniques, local control and overall survival are suboptimal in both early-stage and locally-advanced NSCLC (Lagerwaard et al. 2002a; Qiao et al. 2003; Senan et al. 2002a). Trials evaluating more intensive radiotherapy schemes (Saunders et al. 1997) and combined chemo-radiotherapy (Schaake-Koning et al. 1992; Furuse et al. 1999; Curran et al. 2003) have all shown improved survival, but at the cost of increased normal tissue toxicity. By improving the sparing of normal tissues, 3DCRT enables a reduction in treatment-related toxicity, but its clinical use in lung cancer remains disappointingly low (Movsas et al. 2003). In order to facilitate the use of 3DCRT in lung cancer, literature-based recommendations have now been developed by the European Organization for Research and Treatment of Cancer (Senan et al. 2004).

In order to standardize the use of target volumes for radiotherapy, the International Commission on Radiation Units and Measurements (ICRU) reports 50 (ICRU 1993) and 62 (ICRU 1999) have recommended specific definitions for delineation of the gross tumor volume (GTV), the clinical target volume (CTV), the internal target volume (ITV) and planning target volume (PTV), respectively (Table 2.2.4.1). However, application of the ICRU criteria is not always clear-cut in lung cancer. Traditionally, both the GTVs and CTVs

Table 2.2.4.1. Recommendations on target volume description from the International Commission on Radiation Units and Measurements (ICRU) Reports 50 and 62

Gross tumor volume (GTV)	The clinically macroscopic disease, including that which is visible on imaging modalities
Clinical target volume (CTV)	An expansion of the GTV in order to account for the spread of sub-clinical disease
Planning target volume (PTV)	A 3D expansion of the CTV to account for motion of the target volume, external setup variability and other uncertainties, and which defines the final volume to be treated
Internal target volume (ITV)	An expansion of the CTV in order to specifically incorporate tumor movement into target definition

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are derived from a single planning CT scan performed during quiet respiration. Standard 'population-based' margins are subsequently added in order to account for mobility in the generation of ITVs. However, the need to use separate margins for internal movement and external setup uncertainty, as proposed by the ICRU 62, has been questioned as the use of such margins could complicate the treatment planning process. It has therefore been proposed that ITVs should only be used where this clearly benefits the treatment planning for a particular situation (Craig et al. 2001). As the different causes of geometric uncertainties should be added in quadrature rather than in a linear fashion, it may be more straightforward to derive the PTV directly from the CTV. In fact, several models have been described that allow the calculation of CTV to PTV margins based on the requirement that, e.g. 99% of the CTV is on average irradiated to 95% of the dose (Stroom et al. 1999; van Herk et al. 2000).

In 3DCRT, radiation dose distributions generally tightly conform to the tumor volume, making the accurate delineation of target volumes crucial for preventing geographical misses. As intra-fractional mobility is an important problem in the thorax, 'non-standard' imaging techniques are required for optimal definition of target volumes for NSCLC. Treatment planning based upon the use of a single CT scan performed during quiet respiration is a suboptimal method for defining the GTV for lung tumors (van Sornsen de Koste et al. 2001; Shimizu et al. 2000). Recent work indicates that the only the use of individualized (i.e. 'patient-based') margins is appropriate for radiotherapy of lung tumors rather than 'population-based' CTV to PTV margins (Stevens et al. 2001; van Sornsen de Koste et al. 2003a; Sixel et al. 2003). Several approaches which directly allow for the determination of ITVs, including the use of slow CT scans, multiple planning CT scans, or planning scans performed in different phases of respiration, have been introduced into clinical practice (Stevens et al. 2001; Yamada et al. 2002; van Sornsen de Koste et al. 2003b).

This chapter will highlight potential clinical pitfalls in defining the target volumes for NSCLC, and evaluate the newer clinical approaches used for individualized determination of target mobility.

2.2.4.2 Defining the GTV of Primary Tumors

CT scans for treatment planning should ideally be performed under identical conditions as for the actual treatment delivery. In contrast to diagnostic CT scans which are obtained during breath-hold, radiotherapy planning scans are commonly performed during quiet respiration. If recent diagnostic CT scans are available, use of intravenous contrast is not necessarily indicated for treatment planning CT scans unless, for example, a primary tumor is adjacent to the mediastinum or hilus. It is essential to realize the CT scanning procedure inherently introduces errors in the visualization of location, size, and shape of mobile tumors and normal organs (Booth and Zavgorodni 2001). An extreme example of such imaging-induced errors in tumor visualization is illustrated in a patient with a highly mobile lung tumor in the right lung (Fig. 2.2.4.1). The different approaches for addressing tumor mobility are reviewed in greater detail below.

A literature review found that the inter-clinician variability in contouring the GTV is a major contributing factor responsible for the uncertainty in treatment planning for lung cancer (Weiss and Hess 2003). Appropriate training in radiology, clear instructions for target contouring, the use of optimal imaging techniques, and a close liaison with experienced radiologists have all been proposed as measures to ensure a more accurate and consistent definition of target volumes (Senan et al. 1999). As the size of the GTV within the lung parenchyma or the mediastinum is highly dependent on the window width and level chosen to analyze CT slices (Harris et al. 1993), standard window-level parameter settings should be specified in contouring protocols. It is recommended that these settings be preset in treatment planning workstations in order to improve the consistency in target contouring.

Although some reports suggest that the use of fluorodeoxyglucose (^{18}FDG) positron-emission tomography (PET) scans could improve the definition of the GTV when atelectasis is present (Caldwell et al. 2001; Nestle et al. 1999), further studies are required before PET scans are used for this purpose. Inflammation or infection can also increase ^{18}FDG uptake (Bakheet et al. 2000), and hypoxic or necrotic tumor regions may show decreased ^{18}FDG uptake. As such, a correlation of PET findings with pathology is needed in order to establish the threshold of detection for microscopic tumor deposits. This contrasts to the large body of data showing the negative predictive value of PET in excluding metastases to mediastinal lymph nodes. As the spatial resolution of ^{18}FDG PET scans is modest, and image registration of CT and PET investigations remains cumbersome, use of integrated CT-PET scanners, preferably with

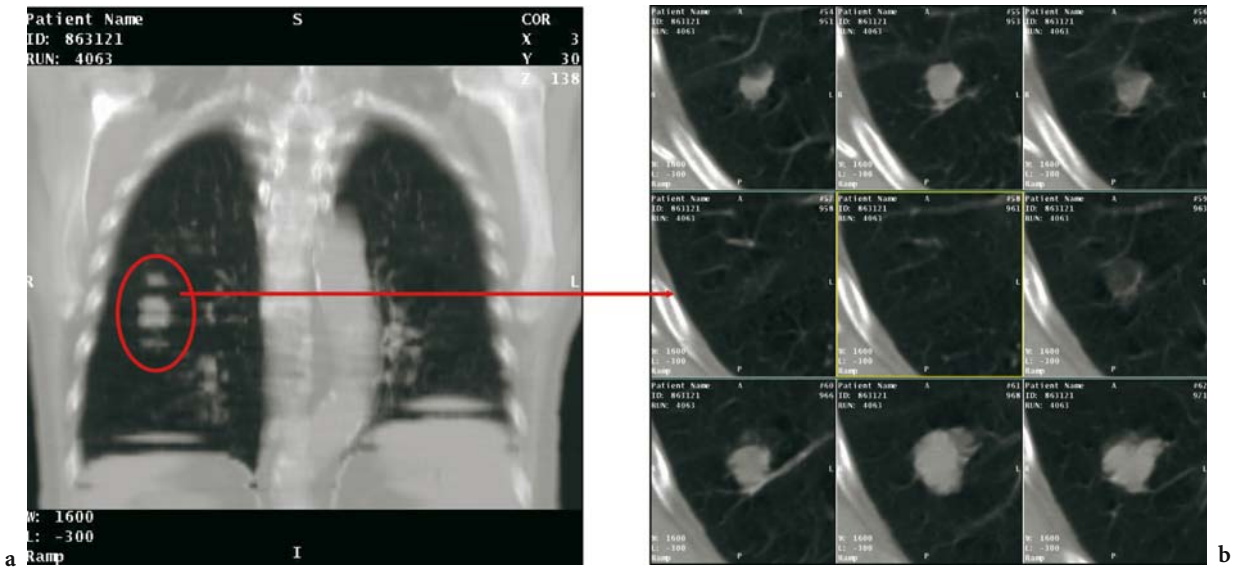


Fig. 2.2.4.1. a Distorted image of a peripheral lung tumor captured on a spiral CT scan (1 s/slice). **b** Tumor movements during scan acquisition account for the 'missing' tumor volume in intermediate slices

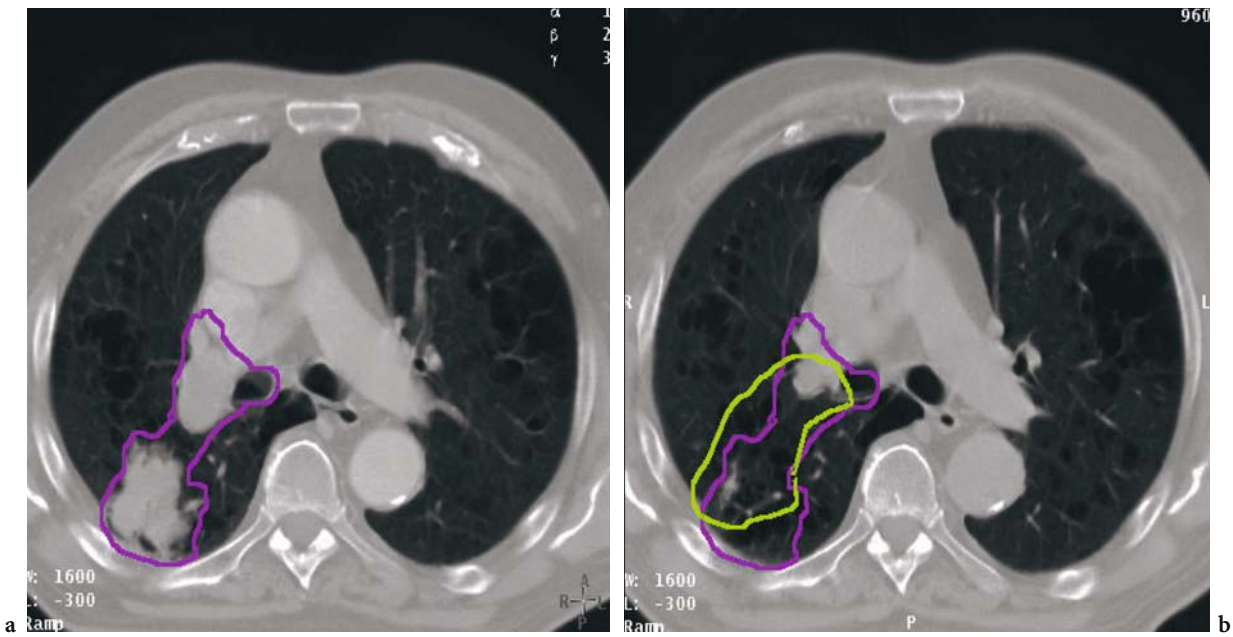


Fig. 2.2.4.2a,b. Target contouring on co-registered pre- (**a**) and post-chemotherapy (**b**) CT scans. The *pink contour* represents the GTV (tumor and hilar nodes) contour using 3D image registration. The *green contour* represents the contour drawn by a clinician, using non-matched hard copies of the pre-chemotherapy CT scans

respiration-gated acquisition protocols, may prove to be more advantageous for primary lung tumors (Nehmeh et al. 2002; Goerres et al. 2003; Beyer et al. 2003).

When radiotherapy is preceded by induction chemotherapy, the question of the correct target volume to be irradiated is unclear, although many centers have opted to irradiate the pre-chemotherapy GTV. The latter can generally be accurately reconstructed only by using coregistration of pre- and post-chemotherapy CT scans (Rosenman et al. 1998; Lagerwaard et al. 2002a) (Fig. 2.2.4.2).

2.2.4.3 Defining the GTV for Nodal Disease

Identifying metastases to the hilar and/or mediastinal lymph nodes is critical for radiotherapy planning as these sites must receive full tumoricidal doses in order to ensure local control. As the presence of nodal metastases in localized NSCLC implies a need for systemic therapy, there has been major interest in accurate pre-operative staging of the mediastinum. Increasingly, patients who are referred for chemoradiotherapy, both as a definitive procedure and as pre-operative induction treatment, have already undergone histological staging of their mediastinum.

The modified Naruke/ATS-LCSG nodal map (Mountain and Dresler 1997), which is routinely used by surgeons, pathologists, and radiologists, is also recommended for radiotherapy planning. The use of intravenous contrast may not be required for identifying enlarged lymph nodes if a recent contrast-enhanced diagnostic CT scan is also available (Cascade et al. 1998; Patz et al. 1999). Planning CT scans with a slice thickness of less than 5 mm are recommended as these enable better recognition of nodal structures. A short-axis diameter of 10 mm on CT scans is commonly used to define the upper limit of normal nodes, and the short transverse plane is preferred as this shows a smaller variation than the mean long transverse diameter (Glazer et al. 1985; Kiyono et al. 1988). For subcarinal (N7) nodes, however, a short-axis diameter of 12 mm can be normal (Kiyono et al. 1988). However, anatomic criteria do not correlate well with metastatic involvement (de Leyn et al. 1997; Arita et al. 1996). In patients who did not receive prior induction therapy, up to 44% of nodes found to contain metastases were less than 10 mm (Prenzel et al. 2003).Conversely, 18% of patients with pathologically-confirmed N2 disease had no nodes >10 mm.

A cervical mediastinoscopy is generally considered to be the standard procedure for excluding mediastinal nodal metastases. However, only the anterior mediastinum including pre-tracheal, para-tracheal, and anterior subcarinal nodal regions are accessible to cervical mediastinoscopy. In addition to the risks associated with a general anesthetic, a complication rate of up to 5% has been reported (Hujala et al. 2001), which includes pneumothorax, hemorrhage, and recurrent laryngeal nerve palsy (Coughlin et al. 1985).

The resolution of modern FDG-PET scanners allows for the detection of tumor in nodes of less than 1 cm in size (Gupta et al. 2000). FDG-PET is significantly more accurate than CT alone in the detection of metastases to the lymph nodes, with a mean sensitivity of 0.79 for PET scans versus 0.60 for CT scans, and a mean specificity of 0.91 versus 0.77 for PET and CT, respectively (Dwamena et al. 1999). The negative predictive value was 93% and 85%, respectively, for PET and CT scans. The high negative predictive value of PET in excluding mediastinal N2 or N3 disease has led to the omission of mediastinoscopy in surgical candidates who have negative mediastinal PET images (Vansteenkiste et al. 1997; Gupta et al. 2001). False negative nodes on PET scans are usually found in the proximity of the primary tumor, and generally show only minimal lymph node invasion, i.e., intracapsular disease in only one nodal level (Vanuytsel et al. 2000). Conversely, up to 24% of PET scans may be falsely positive in detecting mediastinal lymph node metastases (Roberts et al. 2000), and histological verification is a requirement in surgical trials.

However, the lack of anatomical landmarks, and the limited spatial resolution of PET images, makes correlation with CT images necessary for localizing abnormalities (Osman et al. 2003). Clinically significant inaccuracies in locating lesions were reported to be uncommon in a study in which visual correlation of CTs and PET scans were performed (Vansteenkiste et al. 1998). However, in a prospective study with histopathologic correlation, integrated CT-PET systems provided additional information on 41% of patients with lung cancer, over that provided by conventional visual correlation of both studies (Lardinois et al. 2003). This suggests that integrated CT-PET systems should be preferred for radiotherapy planning, as high spatial resolution is crucial in curative radiotherapy.

2.2.4.4 Defining CTVs for the Primary Tumor

Pathologic examination of surgical specimens can reveal the margins that have to be added for subclinical tumor extension. A detailed histologic study of 70 surgical specimens reported a mean microscopic tumor extension of 2.69 mm in adenocarcinomas, and 1.48 mm in squamous cell carcinomas (Giraud et al. 2000). However, in order to ensure incorporation of 95% of all microscopic tumor extent, the authors recommend the use of margins of 8 mm for adenocarcinomas, and 6 mm for squamous cell carcinomas.

Giraud et al. (2000) also correlated the pathological findings with pre-operative CT scans, and they de-

scribed a significant correlation between radiological and histological sizes for only macroscopic tumor, but not for microscopic extension. The latter may be related to the fact that CT measurements were made in soft tissue (mediastinal) setting, and not using lung settings (Giraud 2000). However, even measurements on CT scans in the appropriate lung parenchyma settings can underestimate the microscopic extension in lung parenchyma. In a study where a diagnosis of T1N0 NSCLC was made in 47 lesions on the basis of CT scans, pathologic upstaging to T2 disease was observed in 13 cases (Shennib et al. 2000).

In summary, the available evidence suggests that it is reasonable to use margins of between 5 and 8 mm in order to account for subclinical tumor extension. The use of software tools to generate these 3D margins around contoured GTVs or CTVs is preferred as this has been shown to reduce inter-clinician variations in contouring (Senan et al. 1999).

2.2.4.5 CTV for Nodal Disease: Is Elective Nodal Irradiation Required?

Traditional radiotherapy fields have encompassed the radiologically normal mediastinum, and sometimes also the supraclavicular region, in order to treat potential subclinical disease. This approach is referred to as elective or prophylactic nodal irradiation (ENI). However, advances in the non-surgical assessment of the mediastinal involvement, together with analyses of recurrence patterns following involved-field radiotherapy (IFRT), have questioned the need for routine ENI. A recent analysis of 1705 patients from four RTOG trials for the adequacy of coverage of elective nodal regions at different radiation doses, found that neither in-field progression nor the 2-year survival were affected by the adequacy of nodal coverage of the mediastinum, ipsilateral supraclavicular area and, contralateral hilum (Emami et al. 2003).

In stage I NSCLC, omitting ENI has resulted in a remarkably low incidence of regional recurrences (Slotman et al. 1996; Krol et al. 1996; Lagerwaard et al. 2002b). The low incidence of isolated mediastinal recurrences contrasts with the nearly 23% incidence of occult mediastinal nodal metastases seen in patients with clinical stage I tumors after a lymph node dissection (Oda et al. 1998), a finding that may partly be explained by the suboptimal local control and the high incidence of non-cancer mortality in patients who are unfit for surgery. In the absence of evidence to support ENI, recent reviews have recommended using only involved-fields when irradiating stage I NSCLC (Sibley 1998; Qiao et al. 2003).

In stage III NSCLC, prospective data from clinical trials in which ENI has been omitted show that isolated nodal failures outside the PTV occur in less than 6% of patients (Hayman et al. 2001; Rosenzweig et al. 2001; Senan et al. 2002; Belderbos et al. 2003), despite the fact that only one of these trials used information from FDG-PET scans for radiotherapy planning. As pathological complete responses were obtained in less than 20% of patients with locally advanced NSCLC after high-dose radiotherapy alone (Le Chevalier et al. 1992), treatment intensification to the GTV should remain the priority. With the advent of 3DCRT and better understanding of dosimetric parameters that influence lung toxicity (Graham et al. 1999; Tsujino et al. 2003), it has become evident that the delivery of higher radiation doses to the GTV is not feasible if the regional lymph nodes are to receive "prophylactic" radiation (Williams et al. 2000; Grills et al. 2003).

In stage III NSCLC, omitting ENI results in a significant sparing of the esophagus, e.g., a reduction in the mean esophageal dose, the volume encompassed by the 50 Gy isodose, and the NTCP of between 38%--74% (Grills et al. 2003). Reducing the dose to the esophagus is crucial for reducing the toxicity of concurrent chemo-radiotherapy (Hirota et al. 2001). Similarly, performing ENI will significantly increase the dose to pulmonary tissue (McGibney et al. 1999; Jenkins et al. 2003; Grills et al. 2003). Treating only involved mediastinal nodes resulted in relative reductions in the lung V_{20}, mean dose, and NTCP of 30%, 30%, and 60%, respectively, when compared to plans incorporating ENI (Grills et al. 2003). The incorporation of PET scans into radiotherapy planning greatly improves the ability to accurately stage the regional nodes, and further reduces the risks of geographic miss with involved fields.

Proponents of the use of ENI point out that occult metastases are found in more than 50% of hilar and mediastinal nodes in patient with NSCLC, i.e., metastases missed by conventional histopathologic techniques but which were identified using immunohistochemistry (Chen et al. 1993; Passlick et al. 1996; Maruyama et al. 2000). This, they argue, indicates that ENI could contribute to the cure of some patients. However, the presence of these occult nodal metastases correlates with an increase in both local regional and distant metastases in most (but not all) reports, indicating a need for effective systemic chemotherapy. Proponents of ENI suggest

that the presence of any proven or suspected mediastinal node metastasis is an indication for elective irradiation of the 'entire mediastinum,' but not the uninvolved contralateral hilar or any supraclavicular nodes (Kiricuta 2001). Although some authors have attempted to reconstruct the doses to elective nodal regions after the use of involved-fields (Rosenzweig et al. 2001), there is little data available to suggest how elective nodal volumes should be defined in 3D for radiotherapy planning. Two recent articles have suggested approaches for 3D field-definition for ENI (Slanina and Laubenberger 2002; Kiricuta 2001), partly using data derived from systematic nodal dissections in early-stage NSCLC (Naruke et al. 1999).

In the absence of clinical data from prospective clinical trials to indicate a survival benefit for ENI, the increased toxicity associated with elective nodal irradiation indicates that this approach should not be used unless additional data is forthcoming from randomized clinical trials.

2.2.4.6 Incorporating Tumor Mobility

No clear correlation exists between the extent of tumor mobility and the anatomical location in the lung (van Sornsen de Koste et al. 2003; Sixel et al. 2003). Therefore, an individualized determination of the margins needed to incorporate mobility is more appropriate for high-dose radiotherapy than is the application of 'standard' population-based margins. Several alternative approaches have been used clinically to derive individualized mobility margins, including those discussed in the following sections.

2.2.4.6.1 Full Characterization and Incorporation of Internal Mobility

Characterizing and incorporating all intra-fractional tumor mobility is a commonly used approach. An obvious disadvantage of this method is that target volumes may be unnecessarily large, particularly if the extremes of mobility (deep inspiration and deep expiration) are incorporated. Fluoroscopy only allows for a limited assessment of mobility to be obtained (if at all) on superior-inferior and medio-lateral movements (Halperin et al. 2002; Stevens et al. 2001), and is not an optimal method for characterizing mobility in high precision radiotherapy. An even more important drawback of fluoroscopy is that the observed mobility cannot be accurately linked to the geometry of planning CT scans.

The fusion of target volumes generated on 'two-phase' CT scans, obtained at either deep or quiet inspiration and expiration, has also been used to characterize internal mobility (Aruga et al. 2000; Onimaru et al. 2003; Stevens et al. 2001; Yamada et al. 2002). It has been suggested that use of 'two-phase' treatment planning, instead of using unnecessary large population-derived mobility margins, allows for a reduction in the irradiation of normal tissue, and also improves the reliability of patient data for DVH modeling (Yamada et al. 2002). However, the summation of target volumes generated at deep inspiration and deep expiration may lead to an overestimation of the actual target volume (Senan et al. 2002b). Furthermore, the reproducibility of such target volumes is questionable (Ozhasoglu and Murphy 2002).

Another method for obtaining individualized ITVs is by summation of target volumes captured on multiple random planning CT scans. Figure 2.2.4.3 illustrates an example of ITV generation by the summation of six GTVs for a highly mobile tumor of the right lower lobe. The exact number of CT scans needed for generating optimal ITVs is unclear.

Another approach used for peripheral lung tumors is the generation of "slow" GTVs from CT scans, performed with a prolonged revolution time of 4 s/slice (Lagerwaard et al. 2001; van Sornsen de Koste et al. 2001). Target volumes derived from slow CT scans are located in a central position relative to target volumes that were derived from six random planning CT scans during quiet respiration. Being centrally located, GTVs generated using a single slow CT scan will encompass the six-scan volume if a symmetrical 3D margin of 5 mm is applied (van Sornsen de Koste et al. 2003b). A full breathing cycle has been reported to range from between 1.5--3.5 s and 3.6±0.85 s in patients with lung cancer (Seppenwoolde et al. 2002; Chen et al. 2001), and the need for an additional margin (of 5 mm) to account for mobility may reflect factors such as variations between respiratory cycles.

Respiration-correlated (or 4D) CT scans represent a major recent breakthrough in imaging as it generates both spatial and temporal information on organ mobility (Ford et al. 2003; Vedam et al. 2003; Keall et al. 2003). In this technique, the respiratory waveform is synchronously recorded with CT acquisition, and multiple CT slices are acquired at each table position for at least the duration of one full respiratory cycle. This yields CT datasets for up to 20 phases of the respiratory cycle (Fig. 2.2.4.4). Multi-slice CT scanners

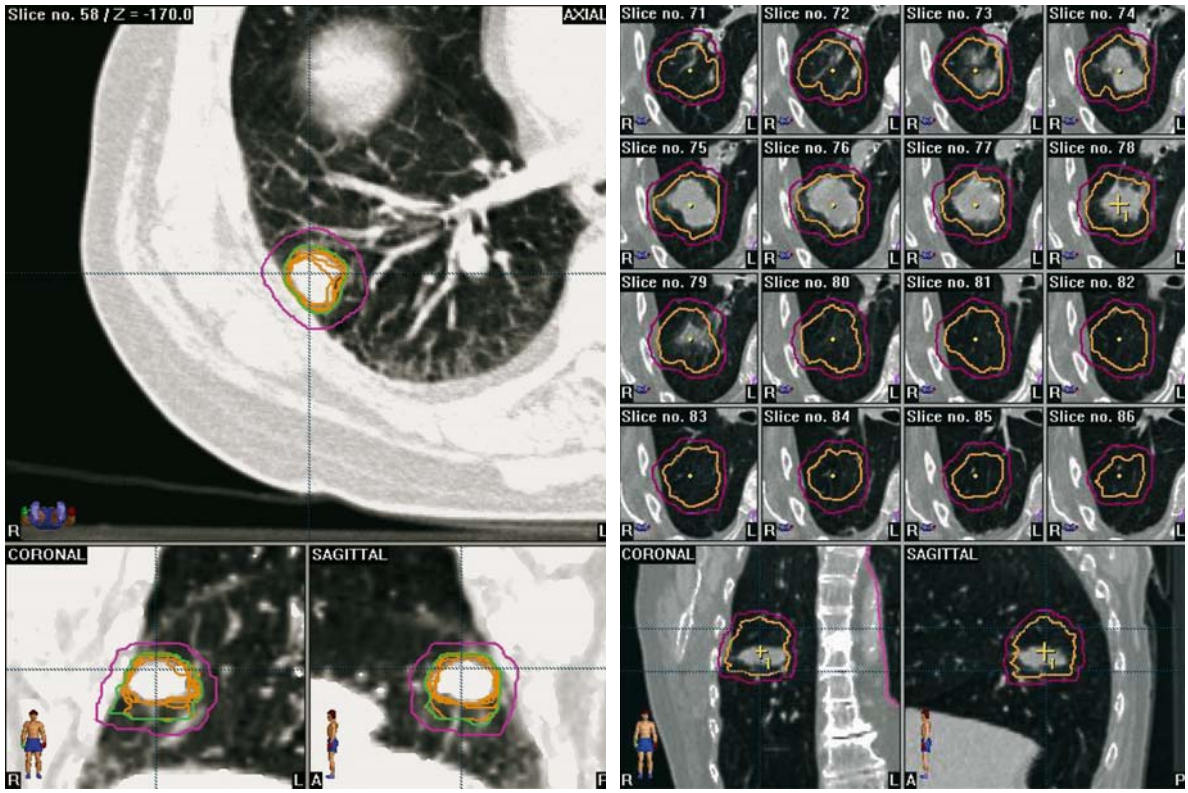


Fig. 2.2.4.3. A technique for generating an ITV (*green line*) for a lung tumor the summation of all GTVs (*yellow contours*) from six consecutive rapid scans. The resulting PTV is shown in pink

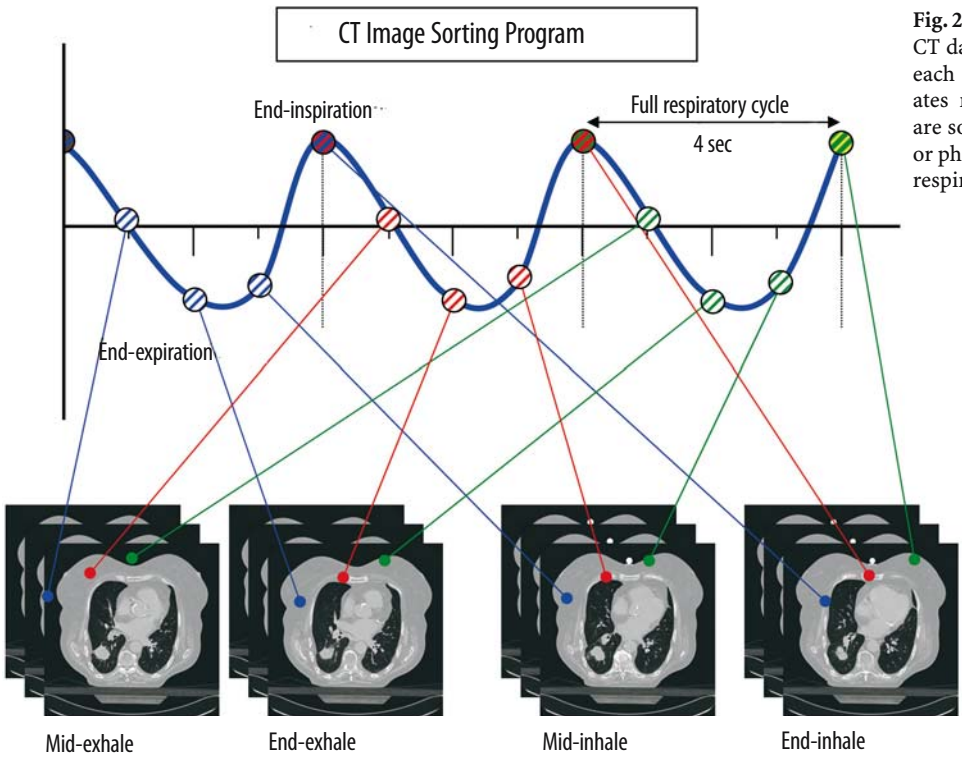


Fig. 2.2.4.4. Processing of 4D CT datasets: Oversampling at each couch position generates multiple images, which are sorted into up to 20 'bins' or phases of the co-registered respiratory cycle

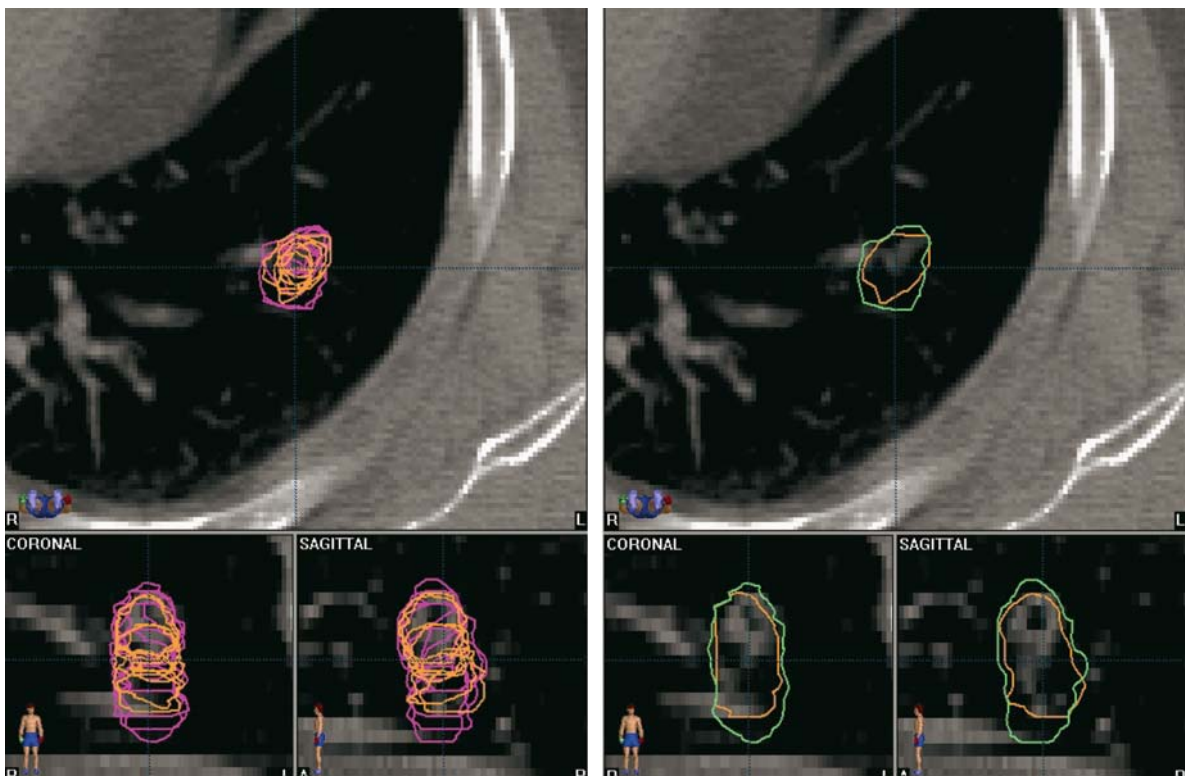
equipped with respiratory gating hardware, and 4D imaging software are now commercially available. Preliminary studies indicate that a single 4D CT scan is sufficient to replace the use of six rapid CT scans for generating the ITV of mobile peripheral lung tumors (Fig. 2.2.4.5).

2.2.4.6.2 Minimizing Respiratory Motion

Patient breath-holding, usually at end-inspiration, has been used as a method for minimizing the mobility of lung tumors (Murphy et al. 2002; O'Dell et al. 2002). Although theoretically attractive, the drawbacks of this approach include the fact that patients have to be coached in order to generate reproducible results, and that an individualized assessment is required for each patient. In addition, a considerable number of patients with medically inoperable lung cancer cannot tolerate breath-holding (Murphy et al. 2002; Hara et al. 2002; Barnes et al. 2001). When performing breath-hold, some residual mobility persists due to variations in breath-holding and cardiac action, and drifts in tumor position have been reported during breath-hold (Murphy et al. 2003). The use of active breathing control has been shown to achieve reproducible lung volumes and diaphragmatic positions (Wong et al. 1999), but residual tumor mobility may not permit significant reductions in margins for the mobility of lung tumors (Cheung et al. 2003). An approach using a patient self-breath-holding system, which is based on the control of the radiation beam by patients themselves, has also been described (Onishi et al. 2003). When planning CT scans were repeated three times during self-breath-holding, the target volumes obtained were reproducible within 2 mm's distance.

2.2.4.6.3 Respiratory Gating

The use of respiratory gating has many advantages over breath-holding techniques, but advanced gating equipment at both the CT scan and linear accelerator are mandatory. The generation of target volumes using "prospective gating", i.e. performing respira-



a b

Fig. 2.2.4.5. a A comparison of GTVs derived using six rapid CT scans (*yellow contours*) and all ten bins from a 4D CT scan (pink contours) in a highly mobile tumor. **b** Corresponding ITVs from six scans (*yellow*) and a 4D CT (*green contour*).

tion-triggered CT scans for radiotherapy planning, has major limitations (Ford et al. 2002). CT sessions will be time-consuming as only a single CT slice is acquired at each table position per breathing cycle. In addition, the respiratory phase at which the scan is to be performed has to be predetermined before image acquisition, or alternatively, multiple CT scans of similar duration would be required if many respiratory phases are to be imaged. The long image acquisition time for each CT set increases the likelihood of patient movement during the scanning process. However, respiration-gated radiotherapy will be simplified with the availability of 4D CT scans derived using a multi-slice CT scan, which permits evaluation of all 'bins' of the 4D dataset for 'retrospective gating' (Vedam et al. 2003).

2.2.4.6.4 Tumor-Tracking Radiotherapy

An advanced approach for solving the problem of mobility is real-time tumor-tracking radiation therapy (RTRT) (Murphy 2002; Shirato et al. 2000, 2003). The technique requires bronchoscopic insertion of radio-opaque markers in (or near) the tumor, and robustness of treatment planning is dependent upon a constant relationship between the fiducial markers and tumor position. Using fluoroscopic tumor tracking, the system triggers the linear accelerator to irradiate only when the marker(s) are located within a predetermined coordinate range. The use of RTRT has a number of limitations, including difficulty in accurate insertion of fiducial markers in tumors. Bronchoscopic implantation of markers in centrally-located lung tumors is often unsuccessful due to problems with early displacement, and the insertion of markers is restricted to small peripheral bronchi in or adjacent to the tumor (Shirato et al. 2003; Harada et al. 2002). One report found that it was only possible to insert markers in the proximity of tumors in five (of seven) patients with T1 lung tumors (Seppenwoolde et al. 2002). Transthoracic insertion of markers for lung lesions is associated with a substantial risk for pneumothorax (Whyte et al. 2003), a complication that may be life-threatening in patients with compromised pulmonary function. Ideally, four fiducial markers are required in order to accurately detect tumor rotation and volumetric changes during treatment (Murphy et al. 2002), and this is not feasible in the majority of patients with lung cancer.

2.2.4.7 Deriving Margins for Mobility of Mediastinal Nodes

The addition of a margin of 5 mm to individual mediastinal nodes is necessary in order to account for variations in both contouring and mobility (van Sornsen de Koste et al. 2002).

2.2.4.8 Defining Target Volumes for Postoperative Radiotherapy

Since the topic of postoperative radiotherapy (PORT) is the subject of another chapter (see Chap. 3.1.2), only some aspects of target volume definition in resected NSCLC will be briefly considered here. PORT has been considered in the following situations: (1) after a microscopic or macroscopic incomplete excision, (2) when carcinoma in situ is present at the bronchial resection margins, and (3) for completely excised stage II and III disease. As no data is available from prospective randomized clinical trials to support the use of PORT in most of these situations, the proposals contained below on appropriate target volumes are not uniformly accepted.

2.2.4.8.1 Target Volumes After an Incomplete Excision

Microscopic tumor at the proximal bronchial extension has been reported to correlate with poorer survival, and also was found to correlate with lymph node metastases (Kara et al. 2000). In addition, peribronchial tumor extension occurs more frequently than mucosal or submucosal tumor extension, and only the former has been reported to correlate with poor survival (Massard et al. 2000; Snijder et al. 1998; Soorae and Stevenson 1979). Furthermore, the risk of tumor recurrence at the bronchial margin was reported to correlate with the distance to the proximal tumor (Verleden et al. 1990). Given the effectiveness of PORT in reducing local recurrence at tumor sites, e.g., for head, neck, and breast cancer, radiotherapy to only the bronchus stump may be justified.

The appropriate management of carcinoma in situ in a patient who has recently undergone a major pulmonary resection for NSCLC is unclear. Carcinoma in situ may be multifocal, and it is not an uncommon

finding in patients who have coexisting tumors of the head and neck, and lung. Spontaneous regressions have been reported (Massard et al. 2000), although other reports suggest that progression to invasive cancer develops in the majority of patients with carcinoma in situ (Venmans et al. 2000). Given the competing causes of mortality in these patients, follow-up using autofluorescence bronchoscopy, CT scans, and possibly PET scans may be preferred to immediate PORT.

2.2.4.8.2 PORT in Patients Undergoing a Complete Surgical Excision

The PORT meta-analysis found a deleterious effect for PORT in N0-1 disease, and a lack of survival benefit for resected N2 disease (PORT Meta-Analysis Group 1998). These findings were criticized by the proponents of PORT and readers are referred to a comprehensive response to the criticisms in a recent paper (Arriagada et al. 2003). It is noteworthy that complete mediastinal lymph node dissections have also not been shown to improve survival in patients with NSCLC (Keller 2002), and the following issues must be kept in mind when designing future studies to evaluate adjuvant treatment in this setting:

Limited reductions in local control after PORT: In the relatively recent GETCB trial, only a 29% reduction in local recurrences was achieved with PORT (Dautzenberg et al. 1999). The ECOG 3590 trial reported in-field recurrence rates of 12%--13% after PORT, with or without chemotherapy (Keller et al. 2000). Such tumor recurrences may be related to the inadequacy of mediastinal target coverage when standard 'off-cord' radiotherapy techniques are used, as these have be shown to result in inadequate coverage of the contralateral mediastinum, and in some cases, the subcarinal region (DiBiase et al. 2000). Surprisingly, such 'off-cord' techniques are still considered by some to be compatible with modern radiotherapy.

Field definitions: It is not clear whether inclusion of the 'entire mediastinum' in the target volume is required (e.g. Machtay et al. 2001). A need to fully treat contralateral mediastinal nodes implies that clinically significant damage to the adjacent lung will result. Similarly, treating stations N8--9 will increase cardiac irradiation, even when CT-based planning is used. Many patients are currently staged using a combination of CT and PET scans, EUS and intra-operative sampling, or nodal dissection. It is questionable whether nodal stations showing no evidence of metastases after such evaluation should still be irradiated. Future protocols should provide a clear justification for the choice of fields and also define target volumes using the Naruke-ATS scheme (Mountain and Dresler 1997). Careful follow-up of patients treated in adjuvant trials, both with and without radiotherapy, will reveal useful information about the adequacy of local fields.

2.2.4.9 Conclusion

The definition of target volumes for NSCLC remains a controversial topic as tradition-based approaches of the past are being critically evaluated in the light of the use of 3DCRT approaches, by awareness of the poor local control achieved using current treatment fields and radiation doses, and by the major improvement in non-invasive staging that enable GTVs to be established with greater accuracy. Implementation of these renewed concepts may allow for the therapeutic ratio of concurrent chemo-radiotherapy in NSCLC to be improved significantly.

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2.2.5 Target Volumes in Small Cell Lung Cancer

Yolanda I. Garces and James A. Bonner

CONTENTS

2.2.5.1 Introduction

Advances have been made in the last 30 years in the treatment of limited-stage small cell lung cancer (LSSCLC). Cisplatin-based chemotherapy, the integration of radiotherapy concurrent with chemotherapy, and the incorporation of prophylactic cranial irradiation into the curative treatment of this group of patients have been responsible for these advances. However, key issues related to planning and delivery of radiotherapy remain unsettled. These interwoven issues include radiobiology, timing, dose, fractionation, and the volume of disease treated with radiotherapy. The focus of this chapter is on the evolution of treatment volumes over time and the controversies surrounding radiation target volumes for patients with LSSCLC. The possible considerations for radiation oncologists wanting to encompass appropriate treatment volumes for patients with LSSCLC are reviewed.

Initially, radiation was the treatment of choice for LSSCLC. However, systemic recurrences of disease were commonplace, and eventually the pendulum swung to chemotherapy as the main treatment. In the 1970s and early 1980s, it was noted that the addition of radiotherapy to chemotherapy improved overall survival and local control in the chest, and this was confirmed by meta-analyses reported in the early 1990s (Pignon et al. 1992; Warde and Payne 1992). More recently, radiation in the form of prophylactic cranial irradiation has also been shown to improve survival (Aupérin et al. 1999); thus, both radiotherapy and chemotherapy are integral components in the successful treatment of LSSCLC. Thoracic radiation was typically directed at the primary tumor, ipsilateral hilum, entire mediastinum, and supraclavicular fossae bilaterally. This was the treatment for LSSCLC as long as radiation was delivered to a "tolerable" radiation field. Elective nodal irradiation for LSSCLC has not been the subject of clinical trials or retrospective studies except possibly when treating the supraclavicular areas. Therefore, the focus of this chapter is on radiotherapy tumor volumes, specifically prechemotherapy versus postchemotherapy volumes in the treatment of LSSCLC.

2.2.5.2 Tumor Volume Definitions

First, to discuss radiotherapy treatment volumes adequately, some standard definitions have to be reviewed. Report number 62 (a supplement to report number 50) of the International Commission on Radiation Units (ICRU) and Measurements (1999) provides guidance and makes recommendations for the use of radiotherapy. The report provides

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radiation oncologists, physicists, and dosimetrists with a common language and standard definitions so that radiation doses conform to uniform guidelines from study to study. The gross tumor volume (GTV) can consist of the primary tumor, the nodal volumes, or metastatic disease that is grossly evident on clinical examination or the Tumor Node Metastasis American Joint Committee on Cancer (TNM AJCC)-approved imaging modalities used for staging (Greene et al. 2002). The clinical target volume (CTV) contains the GTV or any microscopic or subclinical extension (or both) and is the volume that must be treated for radical therapy. The CTV can encompass the entire GTV, whereby the GTV is within the CTV. Alternatively, the CTV can be separate from the primary GTV. This could occur, for example, in a patient who has a lung tumor in the right lower lobe (GTV) and an elective nodal site (mediastinal nodes), which would be called "CTV II"; therefore, the two volumes may not be contiguous [GTV (or CTV I) and CTV II]. However, the lymphatics that drain the peribronchial lymph nodes may also be at risk and may need to be included as an additional intervening CTV. The planning target volume (PTV) includes the GTV and CTV volumes as well as margins to allow for physiologic movement (internal margin) and set-up errors (set-up margin). It is a geometric concept used by physicists and dosimetrists. This volume becomes the volume that allows one to select the beam angles and energies needed to deliver the appropriate dose to the CTV.

These definitions are relatively recent and are currently being incorporated into the standard treatment of LSSCLC. They should be used for newly designed trials as well as for studies of dose escalation so that comparisons can be made between studies that likely use widely different treatment planning techniques and three-dimensional conformal radiation fields. Certainly, these definitions have not been used in most of the studies that have been reported on LSSCLC. Therefore, in the rest of this chapter, we will review the field design with respect to gross disease within lung parenchyma as well as nodal regions intended to be included within the radiation field and will not focus on GTV, CTV, or PTV.

2.2.5.3 Case Example

An example of a case is given in Figs. 2.2.5.1–2.2.5.4. This is the case of a 61-year-old man who stopped smoking 18 years earlier. He presented with cough, left scapular pain, and mild shortness of breath. He was otherwise healthy and had not lost weight. The Karnofsky performance score was 90. The findings on physical examination, including a detailed examination of the lungs and lymph nodes, were entirely normal. Computed tomography (CT) showed a large left upper lobe mass (Fig. 2.2.5.1a,b). Pulmonary function studies demonstrated a forced expiratory volume in 1 s of 3.24 (81% of predicted); the diffusing capacity of lung for carbon monoxide was 35.5 (122% of predicted). Bronchoscopy disclosed erythema and mucosal nodularity in the distal left main bronchus and complete obstruction of the apical posterior segment of the left upper lobe by an extrinsic process. Brushings from the bronchial tree and biopsy specimens from the precarinal region and left upper lobe bronchus were positive for small cell carcinoma. The staging work-up was completed and was negative. The diagnosis was LSSCLC.

Physicians in radiation and medical oncology were consulted and treatment options discussed. The patient elected to participate in an ongoing North Central Cancer Treatment Group (NCCTG) study. He received two cycles of chemotherapy (topotecan and paclitaxel) and was reevaluated 1 month later (Fig. 2.2.5.1c,d). He had a partial response to chemotherapy. Next, he received concurrent chemotherapy (cisplatin and etoposide) and radiotherapy. The radiotherapy was given, according to protocol, to the postchemotherapy volume. However, for illustrative purposes, we fused the prechemotherapy CT scan with the radiation-planning scan. The prechemotherapy volume was outlined. Next, we used the postchemotherapy CT data set (radiation-planning scan) and planned a treatment for the prechemotherapy and postchemotherapy volumes. This enabled us to use the same CT data for the lung volumes. This is how one typically would treat the prechemotherapy volume. Figure 2.2.5.2 shows a digitally reconstructed radiograph with the prechemotherapy volume outlined in red and the postchemotherapy volume indicated with a wire frame in green. No field borders are shown on these digitally reconstructed radiographs; the fields included the superior mediastinum, GTV, ipsilateral hilum, and subcarinal region. A 1.5-cm margin was used for gross disease and a 1.0-cm margin for the lymph node regions. Inferiorly, the field edge was 5 cm below the carina. For this study, the supraclavicular fossae were not included in either treatment plan; whether they should be is a matter of controversy. Both plans were designed to treat with

a total dose of 54 Gy. Figure 2.2.5.3 shows the two plans just above the level of the carina, with one treatment plan based on the prechemotherapy volume (Fig. 2.2.5.3a) and the other based on the postchemotherapy volume (Fig. 2.2.5.3b). The dose volume histograms for treatment of prechemotherapy volumes and postchemotherapy volumes are shown in Fig. 2.2.5.4. The lung V20 was calculated by dividing the volume of lung receiving 20 Gy or more by the total volume of the lung.

This case demonstrates that the difference in V20 would be significant if one were to treat the prechemotherapy volume and the postchemotherapy volume with a V20 of 36% and 28.6%, respectively. It is also possible that if non-coplanar beams had been chosen and a CTV had been used, the V20 would have been even lower. Non-coplanar beams were not allowed for the study in which this patient participated. Concurrent chemotherapy and radiotherapy began 6 weeks after two cycles of induction chemotherapy.

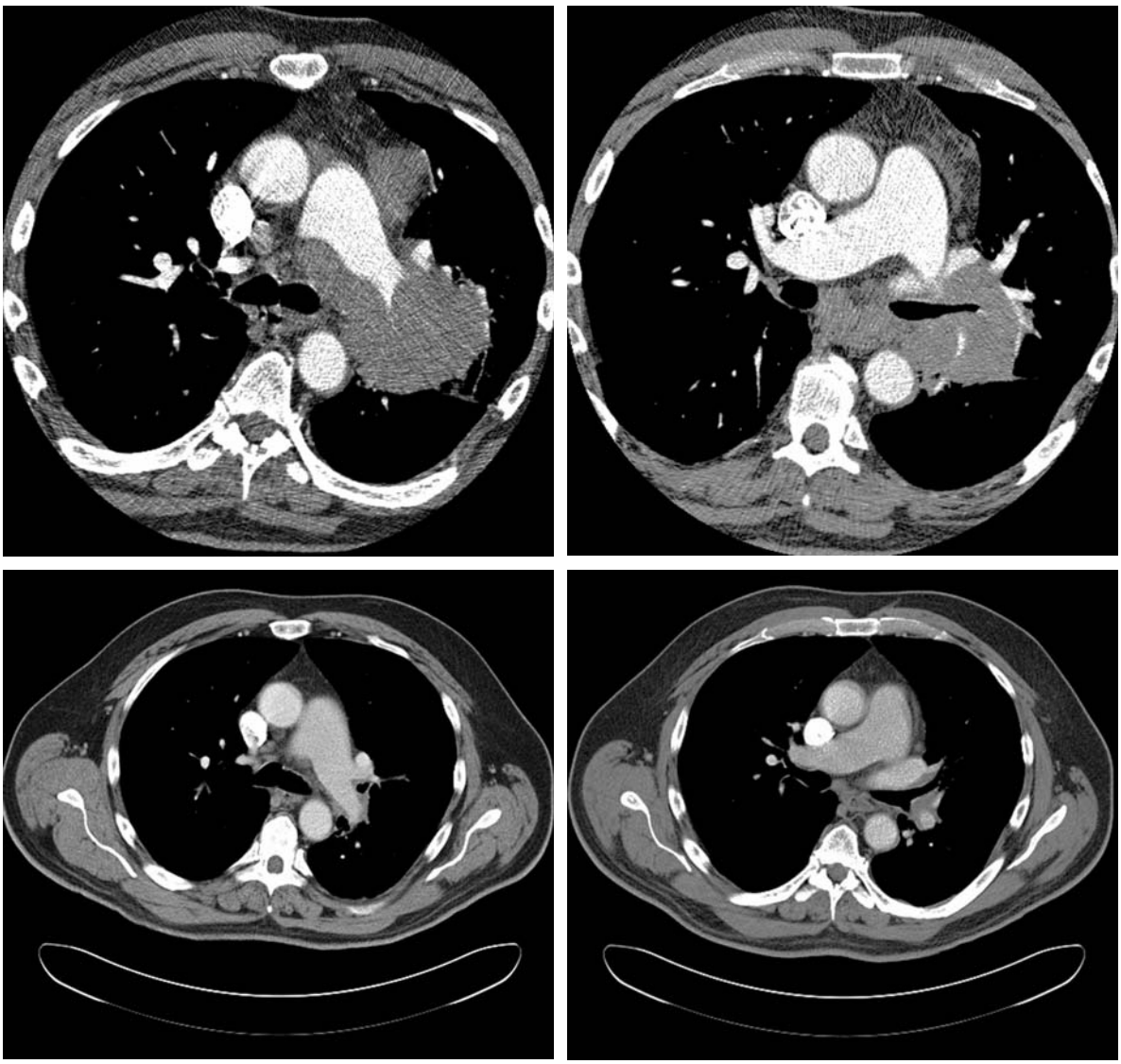
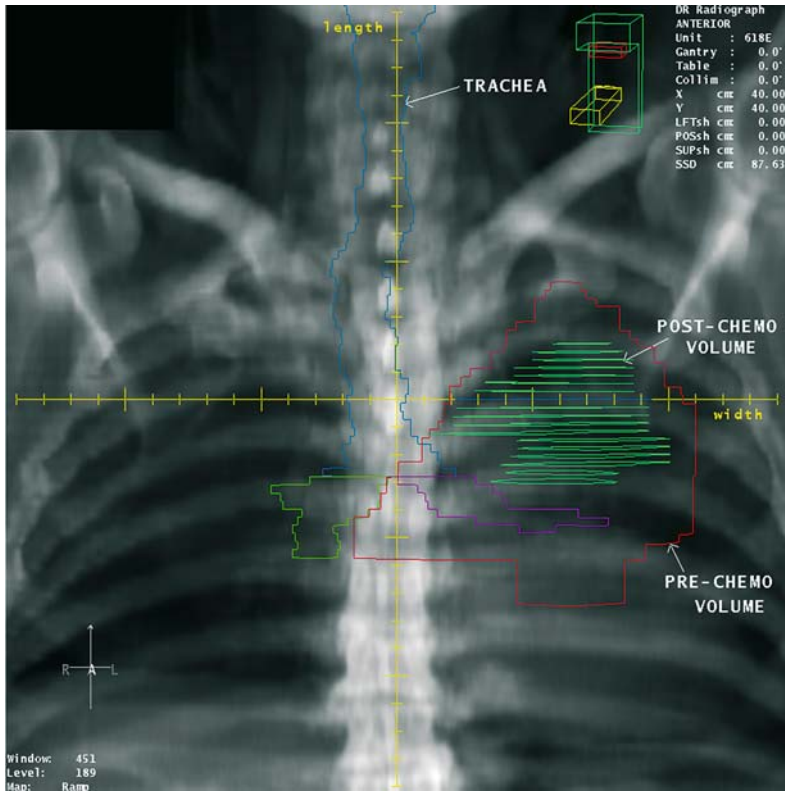
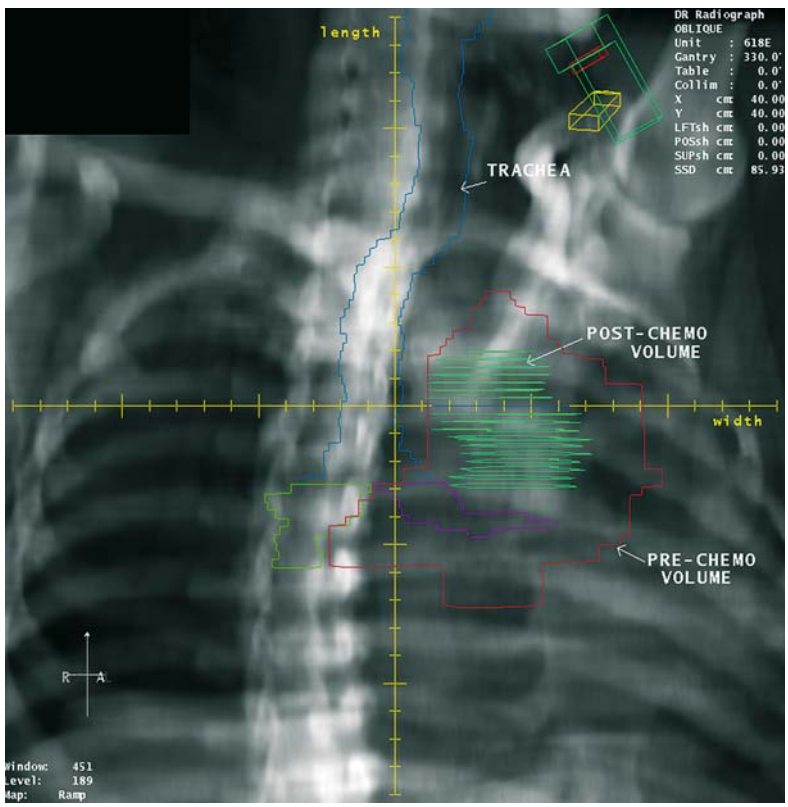


Fig. 2.2.5.1a–d. Prechemotherapy CT at the level of (**a**) the carina and (**b**) the hilum. Postchemotherapy CT scan (6 weeks) at the level of (**c**) the carina and (**d**) the hilum

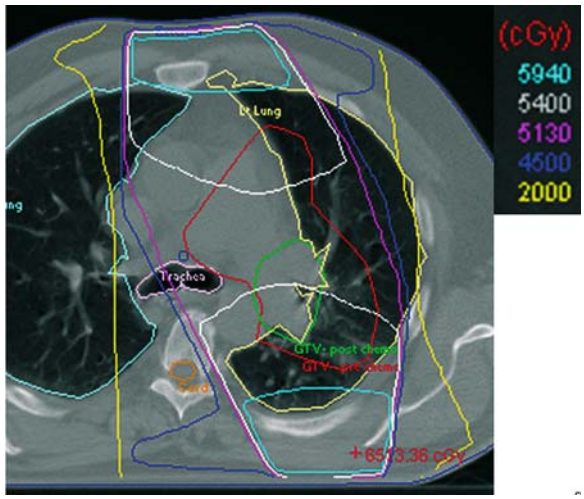


a

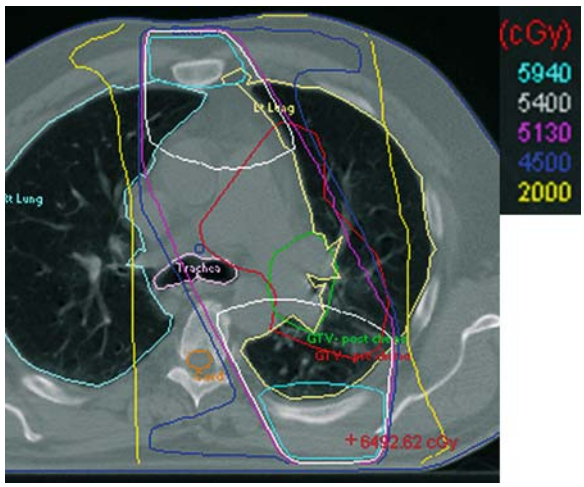


b

Fig. 2.2.5.2a,b. Digitally reconstructed radiograph (DRR) demonstrating the prechemotherapy volume (*red outline*) and postchemotherapy volume (*green wire-frame outlines*) on an anterior-posterior simulation DRR (**a**) and oblique DRR (**b**)



a



b

Fig. 2.2.5.3a,b. Isodose curves demonstrating a radiotherapy plan both to 5,400 cGy: one plan is based on the prechemotherapy volume (**a**, *red*) and the other is based on the postchemotherapy volume (**b**, *green*)

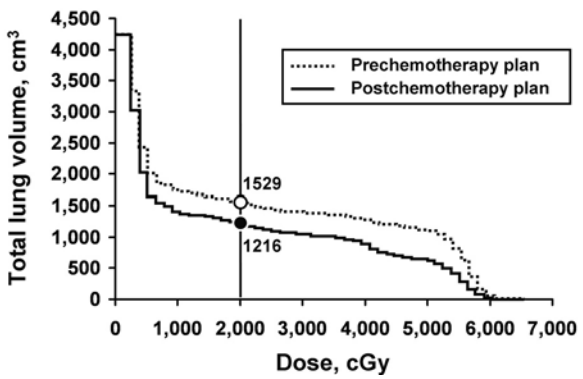


Fig. 2.2.5.4. Dose volume histogram of the left and right lungs. The *vertical line* represents lung volume

2.2.5.4 Prechemotherapy vs. Postchemotherapy Volumes

The treatment volumes of radiotherapy for LSSCLC have not been studied extensively. This topic needs further thought and should be incorporated into clinical trials. Only one randomized study has addressed this issue, and few retrospective studies have focused on it. In the following sections, the randomized study, the retrospective studies, and some observations about this issue are reviewed, including the advantages and disadvantages of treating the prechemotherapy or postchemotherapy volumes.

2.2.5.4.1 Randomized Study

In a Southwest Oncology Group (SWOG) study, all patients were treated initially with vincristine, methotrexate, doxorubicin, and cyclophosphamide for 6 weeks (Kies et al. 1987). After chemotherapy, the disease was restaged to determine if the patient had a complete response, partial response (a decrease in tumor mass by 50% in the largest cross-sectional diameter), stable disease (less than a partial response, but no progressive disease), or progressive disease. Patients with a complete response were assigned randomly to split-course thoracic radiation (48 Gy) or to continuation of chemotherapy without thoracic radiation. Patients with a partial response or stable disease were given the same split-course radiation as those with a complete response, but the randomization was based on prechemotherapy or postchemotherapy volumes as determined from chest radiography. This study showed that among the eligible patients with a partial response or stable disease (n=191), there were no differences in failure or survival patterns between those randomly assigned to the prechemotherapy volume and those randomly assigned to the postchemotherapy volume. Toxicity, specifically the risk of radiation pneumonitis, was also similar for the two groups. The frequency of life-threatening or fatal leukopenia was slightly higher in the prechemotherapy volume group (17 of 93 patients) than in the postchemotherapy volume group (8 of 98 patients). The amount of lung tissue spared by the use of postchemotherapy volumes was not quantified.

Although the SWOG study failed to show differences in outcomes for those in the prechemotherapy and postchemotherapy volume groups, the conclusions should be viewed circumspectly. The chemotherapy was not cisplatin-based, and it was not given

concurrently with radiotherapy. The recurrence of disease was defined as "intrathoracic" or "systemic." The authors stated that the port films and follow-up chest radiographs were reviewed again in only a small proportion of cases and may not reflect "in-field" radiation failures (Kies et al. 1987). The imaging studies and treatment planning were crude by current standards. Chest radiographs were required and lung tomograms were optional for initial staging. These chest radiographs were used to establish the prechemotherapy and postchemotherapy radiation volumes. Because the study was conducted before CT fusion could be accomplished, there possibly was underdosing of prechemotherapy volumes or inaccurate field designs (or both). We have some evidence that even with CT fusion for non-small cell lung carcinoma (NSCLC) the interobserver differences in treatment volumes can be large (Lagerwaard et al. 2002). Also, the patients who had a complete response were randomly assigned to different treatments from those who had a partial response or stable disease, thus leading to questions about the exact volumes that were used for the patients with a complete response. Despite these limitations, this study was important and warrants further consideration in the design of future studies (Wagner 1997). In the future, patterns of disease recurrences need to be collected prospectively and correlated with the radiation volumes so that marginal recurrences and intrathoracic recurrences (in and out of the radiation field) can be described and reported.

2.2.5.4.2 Retrospective Studies

Several retrospective studies have focused on treatment volumes and patterns of recurrences. They all have the limitations of retrospective studies, but the information they provide is valuable and contributes to the small body of literature on this subject.

Liengswangwong and colleagues (1994) reviewed the cases of 67 consecutive patients. Of these patients, adequate information was available for 59, who were not treated according to any research protocol at Mayo Clinic from 1982 through 1990. Most of these patients received two or three cycles of induction cyclophosphamide-based chemotherapy before thoracic radiotherapy, which was given concurrently with chemotherapy to 55 of the 59 patients. Treatment of the prechemotherapy or the postchemotherapy volume was at the discretion of the treating radiation oncologist, and all treatment planning was based on CT scans. A double split course of radiotherapy was used for 51 patients, with two 3-week intervals separating the 15 Gy in five fractions, for a total dose of 45 Gy in 15 fractions. The local recurrences were reviewed retrospectively and categorized as "in-field," "marginal" (±1 cm out of the margin of the field), or "outside the field of radiation."

The two comparison groups consisted of 31 patients in whom the prechemotherapy volume was treated and 28 patients in whom the postchemotherapy volume was treated. On average, the postchemotherapy volumes were about 2.5 cm smaller than the prechemotherapy volumes (range, 0.5–5.0 cm). As first site of recurrence, ten of the 31 patients in the prechemotherapy group had in-field failures compared with nine of the 28 patients in the postchemotherapy group. The 14 patients who were assigned to the prechemotherapy group because they did not have a response to chemotherapy may have had a worse prognosis; these patients were analyzed separately. There were no differences in outcomes between the 14 patients in the prechemotherapy group who had no response and the 14 who had a complete and/or partial response. Furthermore, there were no differences in disease-specific or overall survival among the three groups. However, the study had some limitations: (1) The chemotherapy was not cisplatin-based; (2) split-course radiotherapy was used – however, it was used uniformly in the majority of patients; (3) the study was small, resulting in even smaller subgroups. Despite these limitations, the study suggested that treating the postchemotherapy volume does not lead to marginal recurrences.

A large multicenter randomized clinical trial was conducted by the NCCTG. Building on the off-study experience of Liengswangwong and colleagues (1994), the NCCTG study used postchemotherapy volumes in a prospective manner (Bonner et al. 1999). This trial compared split-course hyperfractionated radiotherapy with once-a-day radiotherapy for LSSCLC, in which all patients had the postchemotherapy volume treated following three cycles of chemotherapy. The authors retrospectively evaluated in-field and out-of-field recurrences. Among 90 patients who had local progression of disease as a component of their initial progression, only seven had out-of-field recurrences. Two of these recurrences were less than 2 cm from the field edge and would have been included had prechemotherapy volumes been treated. Thus, this study strongly suggested that postchemotherapy volumes were appropriate and safe for treating LSSCLC, minimizing the amount of normal lung volume irradiated without compromising disease control.

Brodin and colleagues (1990) retrospectively reviewed the cases of 53 of their patients who received cyclophosphamide-based chemotherapy followed by a continuous course of radiation (40 Gy in 2-Gy fractions). The radiation was delivered only to the primary tumor with a 1.5-cm margin and included only the adjacent mediastinum. No effort was made to treat all the nodal areas or the supraclavicular fossa unless they were involved. Two of the authors reviewed the radiation simulation films and the prechemotherapy and postchemotherapy chest radiographs. They determined if the prechemotherapy or postchemotherapy volume was covered or if neither volume was covered (protocol violation). The authors reported cure rates and local control rates for patients with limited-stage disease (n=23). Among the 13 patients who had the prechemotherapy volume treated, seven were cured locally, six had in-field recurrences, and none had marginal or out-of-field intrathoracic recurrences. Among the six patients who had the postchemotherapy volume treated, one was cured locally, four had in-field recurrences, none had marginal recurrence, and one had an intrathoracic recurrence outside the radiation field. Among the four patients in the protocol violation group in whom neither the prechemotherapy nor postchemotherapy volume was covered adequately, two were cured locally, one had in-field recurrence, none had marginal recurrence, and one had intrathoracic out-of-field recurrence. The unique feature of this study was that an autopsy was performed on 76% of the subjects, providing reliable data about treatment failure. However, the authors acknowledged it occasionally was difficult to distinguish between recurrent tumor and radiation fibrosis; also, the total dose of radiation was low, which could have led to the increased number of in-field recurrences.

In contrast to the report of Brodin and colleagues (1990), Mira and Livingston (1980) showed that the majority of intrathoracic recurrences in their study originated outside the radiation field. These authors reviewed the cases of 45 patients treated at their institution over a 2-year period, including the years 1976 and 1977. This retrospective review included 34 patients who had chemotherapy and radiotherapy as well as follow-up notes and chest radiographs adequate for focusing on the patterns of failure. In total, 17 of the patients had limited-stage disease. Chemotherapy was administered first, followed by radiation to the primary tumor, mediastinum, and both supraclavicular fossae with a 1- to 2-cm margin. The radiation dose varied, but most patients received 3 Gy per day to a total dose of 30–45 Gy (with a split course for the latter). Nine patients died of chest complications, seven of whom had recurrent tumor in the chest. The majority of the recurrences were intrathoracic but outside the radiation field. Similar to the other retrospective studies, the study of Mira and Livingston (1980) was limited by the small number of patients, the limited imaging modalities, the radiation techniques used, and the lack of cisplatin-based chemotherapy.

Arriagada and colleagues (1991) reviewed their experience at Institut Gustave-Roussy with two phase II trials that evaluated induction chemotherapy followed by thoracic radiotherapy and additional maintenance chemotherapy between 1980 and 1983. In both studies, thoracic radiotherapy was delivered as a split course. In one study, 15 Gy was given in six fractions over 10 days (three sessions every 4 weeks, for a total dose of 45 Gy); in the other study, a higher total dose (55 Gy) was given. In all, 62 patients with complete remission were included in the review for in-field and marginal recurrences. Twenty-two local recurrences were observed: 16 in-field and six marginal. The authors also reviewed the fields to determine if it was evident whether coverage of the initial tumor volume was adequate ("safety" margin of at least 1 cm) or inadequate (initial tumor area not included in the radiation field). Of the 62 patients with complete remission, 50 had inadequate coverage, which was attributed to the reluctance of the radiation oncologist to treat the prechemotherapy volume after significant shrinkage had occurred with induction chemotherapy. There was no difference in outcomes between the patients who had adequate coverage and those who had inadequate coverage, which can be considered to represent prechemotherapy or postchemotherapy volumes, respectively. The study of Arriagada and colleagues (1991) had many of the same limitations as the other studies with regard to the difficulty with assessing volumes retrospectively, the lack of cisplatin-based chemotherapy, the small number of patients, and the split-course radiotherapy.

Perez and colleagues (1981) reported on a randomized trial of patients with LSSCLC in a Southeastern Cancer Study Group trial of chemotherapy followed by radiotherapy versus radiotherapy followed by chemotherapy at the time of progression. In contrast to the studies mentioned above, Perez et al. (1981) found, in retrospect, that patients who had inadequate coverage of the radiation volume had an intrathoracic recurrence rate of 69% (9/13 patients) compared with 33% (13/50 patients) for those who had adequate coverage (p=0.026). "Inadequate coverage" was not defined clearly, but the authors stated that

this was primarily because of the lack of inclusion of the contralateral hilum or mediastinum. These findings are consistent with those of Liengswangwong and colleagues (1994), because most failures occurred centrally. It is not clear whether these regions were the initial sites of disease, elective nodal areas, or areas that were not treated initially in the radiation field. Nonetheless, the study of Perez and colleagues (1981) stressed the importance of adequate coverage of disease. The patients were treated with posterior spinal cord blocks, which can lead to underdosing of the midline mediastinal structures; this would not be done with contemporary radiation planning.

2.2.5.5 Advantages and Disadvantages of Prechemotherapy and Postchemotherapy Treatment Volumes

Treatment of either the prechemotherapy or postchemotherapy volume has potential advantages and disadvantages. An advantage of treating the prechemotherapy volume is that all sites initially involved by disease would be included because it could be hypothesized that microscopic disease may remain in all areas of initial gross disease and, hence, may benefit from radiotherapy. However, when postchemotherapy volumes have been used after the initial therapy was chemotherapy alone, no significant increase in marginal recurrences has been found. The majority of the retrospective studies discussed above have shown that patients in the postchemotherapy volume group tend to have a preponderance of central recurrences. Therefore, the above hypothesis would be correct only if it is assumed that in previous studies marginal recurrences had gone undetected.

Furthermore, some authors have suggested that the radiation should be administered early in the course of treatment because there may be a survival advantage with early radiotherapy (Murray 1998; Williams and Turrisi 1997). By necessity, the prechemotherapy volume must be included when radiotherapy is given with the first cycle of chemotherapy. In this case, the tumor volume will be evident on the radiation-planning CT scan. However, prechemotherapy volume radiotherapy has possible disadvantages if the initial treatment is chemotherapy alone. If radiotherapy is started after the second or third cycle of chemotherapy, it could be difficult to delineate the prechemotherapy target volume on the treatment-planning CT scan. This would require additional time for the radiation oncologist to fuse the initial study or to transpose the prechemotherapy volume onto the planning CT, which could lead to errors (Lagerwaard et al. 2002). Another disadvantage is that normal structures, including the lung and possibly the heart or esophagus, may receive additional treatment that could exceed tolerance levels; however, there is no evidence, other than theoretical concerns, that this additional treatment volume is necessary. In some centers, the radiation-planning CT scan is performed at the same time as the first cycle of chemotherapy, and radiotherapy is initiated with the second cycle of chemotherapy. Thus, the prechemotherapy volumes are treated; however, if the tumor has shrunk, then a substantial volume of normal lung and other healthy structures may be treated, possibly leading to untoward toxicity. The patient's V20 may appear to be lower than it actually is had the radiation oncologist scanned the patient again and planned with the prechemotherapy volumes on a postchemotherapy planning CT scan.

Possible advantages of treating the postchemotherapy volume have been alluded to above. We favor this approach if the initial treatment has been chemotherapy. The advantages of treating the postchemotherapy volume include minimized toxicity, the possibility for dose escalation of smaller volume disease, and, because radiotherapy has not been given with the initial chemotherapy cycles, the medical oncologist will know whether the patient has a response to a particular chemotherapeutic agent.

Possible disadvantages of treating the postchemotherapy volume include underdosing of microscopically involved areas, which could lead to marginal recurrences. Although this has not been demonstrated in the studies described above, they were mainly retrospective and included a small number of patients. Another disadvantage could be the possible decrease in efficacy if the radiation is delivered "too late" after the start of treatment. The question "How late is too late?" has not been answered, as evidenced by a discussion of presentations at the 10th World Conference on Lung Cancer (Bonner et al. 2003; Fried et al. 2003; James et al. 2003; Komaki et al. 2003; Kubota et al. 2003; Schild et al. 2003).

2.2.5.6 Our Treatment Model

Our treatment strategy for LSSCLC is complex. All eligible patients are invited to participate in a clinical

trial. If they are not interested in participating and have small-volume disease, medially located tumors, or disease in which toxicity of normal tissue is not a concern because the radiation fields would likely not change substantially even after chemotherapy, we favor early treatment. We typically would use the Intergroup regimen of 45 Gy twice daily (Turrisi et al. 1999). The volume consists of the prechemotherapy volume and includes the primary tumor, ipsilateral hilum, and mediastinum. We do not treat the supraclavicular fossae unless they are involved. However, the ipsilateral supraclavicular fossa should be considered in the target volume for upper lobe lesions or for patients with high mediastinal nodal involvement. If the patient has large-volume disease that may possibly shrink with chemotherapy, allowing for significantly less irradiation of healthy tissue, we favor treating with between two and three cycles of induction chemotherapy, after which we offer once-daily radiotherapy to 50.4–54 Gy to the postchemotherapy volume with concurrent chemotherapy. Usually, the postchemotherapy volume is the target. The NCCTG multicenter trial showed only two out-of-field failures that could have been "in-field" if a prechemotherapy volume had been treated. However, these two cases were complicated by atelectasis and scarring and the postchemotherapy volume was difficult to discern (reviewed by J.A.B.) (Bonner et al. 1999). Thus, for patients who have not had a response, the prechemotherapy volume is the target. We offer once-a-day radiation as a viable alternative to twice-daily radiation because a prospective multicenter NCCTG study with once-daily treatments achieved results similar to those of the Intergroup trial, with results reported out to 8 years (Schild et al. 2003).

2.2.5.7 Factors for a Radiation Oncologist to Consider

The following is a list of possible factors that a radiation oncologist should consider when making decisions about prechemotherapy volume or postchemotherapy volume radiation:

1. *The volume of gross disease at diagnosis and the volume of normal structures that would be treated to cover the volume of disease adequately.* If the volume of disease is small and the fields are not likely to change significantly with chemotherapy, early radiotherapy to the prechemotherapy volume should be considered. If the volume of disease is large and chemotherapy will shrink the tumor volume significantly, allowing for less of a radiation dose to normal structures, then one to three cycles of chemotherapy followed by radiotherapy to the postchemotherapy volume should be considered.
2. *Elective nodal irradiation*. Elective nodal irradiation involves the treatment of nodal stations that have a high risk of harboring microscopic disease. Historically, the field design for LSSCLC included comprehensive treatment of bilateral supraclavicular regions (the inferior mediastinum, superior mediastinum, and ipsilateral hilar and subcarinal regions). Recently, the trend has been to exclude the supraclavicular regions bilaterally unless they have been shown radiographically or histologically to be involved. Some investigators have even suggested that a viable option may be not to treat elective sites, as in NSCLC, to allow for dose escalation studies (Williams and Turrisi 1997).
3. *Current lung function and overall functional status.* If the patient has poor lung function or poor performance status, chemotherapy alone may be considered as the initial therapy. This choice may allow patients the opportunity to participate in a lung rehabilitation program and to stop smoking if they currently are cigarette smokers. Most aggressive combined modality studies have been performed primarily with patients who had good performance scores, and this should be considered when making treatment decisions.
4. *Any urgent need for radiation or impending need for early radiation*. If there is an urgent or impending need for early radiation, radiation should be given.
5. *Referral pattern*. A radiation oncologist needs to be involved as early as possible so that multidisciplinary decisions about treatment management can be made in order to plan for optimal integration of various treatments. With all the recent studies on LSSCLC and NSCLC favoring the use of concurrent chemotherapy and radiotherapy, it is mandatory that the radiation oncologist review the patient's case before treatment is initiated. Management is complex and requires a fully functional multidisciplinary team.
6. *Disease location*. It is important to consider sites of initial involvement and to ensure that those sites are included in your initial fields and boost volume so that you do not underdose areas that have experienced a complete response. Using the AJCC staging manual's lymph node map as a guide to treat the entire nodal station is helpful when

outlining nodal areas that have had a complete response (Greene et al. 2002). For example, if the pleura appears to be involved initially, the radiation oncologist needs to ensure good coverage of this area because microscopic disease will likely remain even if the patient has had a complete response. However, if a lymph node station group initially projected into the lung tissue and the patient has a partial response after chemotherapy, we believe it is reasonable to target the smaller mass or the nodal region and not "overexpose" the lung unnecessarily. Another unsettled issue concerning disease location is complete response of a peripheral tumor nodule. In this situation, we are inclined to treat the prechemotherapy volume if the patient's lung function studies suggest that this treatment is feasible.

2.2.5.8 Conclusions

Tumor volumes for LSSCLC are an evolving field that requires future study. The topic is neither straightforward nor simple. The clinical situations vary greatly from patient to patient. With limited class I evidence to guide treatment decisions, whether the prechemotherapy or postchemotherapy volume should be the target volume still depends on the radiation oncologist's best judgment.

Acknowledgments
We would like to thank Pamela R. Lemish for her radiation planning skills and providing the prechemotherapy and postchemotherapy plans for our comparison. We also would like to thank Jessica A. Gardner for her assistance with manuscript preparation and Dr. Paul D. Brown for his review and comments about the manuscript.

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2.2.6 Radioprotectors and Chemoprotectors in the Management of Lung Cancer

Ritsuko Komaki, Joe Chang, Zhongxing Liao, James D. Cox, K. A. Mason, and Luka Milas

CONTENTS

2.2.6.1 Introduction

Lung cancer is the leading cause of cancer death in most developed countries. Almost one million new cases of lung cancer occur worldwide each year (Jemal et al. 2004), and the prognosis remains poor with an overall survival at 5 years of only 15% (Jemal et al. 2004). Between 70% and 85% of all cases are histologically classified as non-small cell lung carcinoma (NSCLC), comprised of squamous cell, adenocarcinoma, large cell, or undifferentiated histology, while the remaining belong to small cell histology (Jemal et al. 2004). At the time of diagnosis the majority of patients present with locally advanced disease and many of them have overt metastatic dissemination. Radiation therapy has traditionally been the treatment of choice for locally advanced disease but has provided limited benefits both in terms of local tumor control and patient survival, with 2- to 5-year survival commonly not exceeding 10% (National Cancer Institute Cancer Gov 2002). However, adding cytotoxic drugs to radiotherapy considerably improves treatment outcome, so that the combination of chemotherapy with radiotherapy has currently become a common practice in the treatment of advanced lung cancer. The addition of chemotherapy to radiotherapy has two principal objectives, to increase the chance of local tumor control and to eliminate metastatic disease outside of the radiation field. The former can be achieved by reducing cell burden in tumors undergoing radiotherapy or by interfering with tumor cell radioresistance factors, thereby rendering tumor cells more susceptible to destruction by radiation. Factors which contribute to tumor radioresistance include the failure of tumor cells to undergo cell death after radiation, the cells' ability to efficiently repair DNA damage, continued cell proliferation during the course of radiotherapy, cell radioresistance secondary to hypoxia that commonly develops in solid tumors, and the presence in tumor cells of various abnormal molecular structures or dysregulated processes linked to cellular radioresistance (Milas et al. 2003a).

Addition of induction (neoadjuvant) chemotherapy to radiotherapy results in an increase in median survival time by approximately 4 months, and the overall survival rates at 2 years range from 10% to 15% (NCI 2002; Milas et al. 2003a,b; Dillman et al. 1990; LeChevalier et al. 1991). These therapeutic gains have been improved by using concurrent chemoradiotherapy, i.e., by administering cytotoxic drugs during the course of radiation treatment (NCI 2002; Milas et al. 2003a; Komaki et al. 2002a,b; Schaake-Koning et al. 1992; Curran et al. 2003). This combined treatment approach results in median survival times of 13–14 months, and in survival rates at 5 years as high as 15%–20%. These improvements have been achieved by using standard chemotherapeutic agents, primarily cisplatin-based drug combinations. Since direct comparison trials between induction and concurrent chemoradiotherapy have clearly demonstrated therapeutic superiority of the latter approach (Schaake-Koning et al. 1992; Curran et al. 2003), concurrent chemoradiotherapy can be regarded as the current standard of care

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for local-regionally advanced lung cancer. Still, the poor overall survival of lung cancer patients necessitates the introduction of treatment strategies that would further improve local tumor control, patient survival rate, and quality of life.

Many factors, known and unknown, limit therapeutic success of radiotherapy or chemoradiotherapy for lung cancer, with one major factor being the level of tolerance of normal tissues to the damage by these agents. Toxicities associated with chemotherapy and radiotherapy may limit the dose and duration of the treatment, adversely affect both short and long-term patient quality of life, be life-threatening, and increase costs of patient care. Normal tissue toxicities are more common and more serious after chemoradiotherapy than radiotherapy alone, and may be particularly excessive in concurrent chemoradiotherapy. Because of the increased toxicity, the dose of chemotherapeutic agents in the setting of concurrent chemoradiotherapy is significantly reduced, which may lower drugs' ability to exert their effects on both local-regional tumor and disseminated disease.

Because normal tissue toxicity is a major barrier to radiotherapy and chemoradiotherapy of lung cancer, every effort must be taken to avert or minimize the injury to critical normal tissues or other side effects of these treatments. Improvements are being sought primarily through better delivery of radiation therapy or the use of chemical or biological radio- or chemoprotective agents. Technical improvements in radiotherapy include three-dimensional treatment planning, conformational radiotherapy, or the use of protons. These normal tissue sparing strategies may allow administration of higher doses of radiation, chemotherapeutic drugs, or both, directed towards achieving superior treatment outcome.

This chapter overviews a selection of relevant preclinical findings and limited clinical data on the use of radio- and chemo-protective agents to prevent or reduce injury to normal tissues that limit radiotherapy of lung cancer. We particularly focused our discussion on protection with amifostine, and presented the results of our recent clinical trial. Additional information can be found in other reviews on this topic (Murray and McBride 1996; Nieder et al. 2003).

2.2.6.2 Thiols as Radioprotective Agents

Both preclinical and clinical investigations on chemical protectors in radiotherapy have been dominated by thiols. The most effective compounds have those with a sulfhydryl, –SH, group at one terminus and a strong basic function, an amino group, at the other terminus. Some of the important radioprotective thiols are listed in Table 2.2.6.1. The general structure of these aminothiols is $H_2N(CH_2)_xNH(CH_2)_ySH$, and among them, phosphorothioates (such as WR 2721, WR-3689, WR-151327) are the most effective and least toxic (Murray and McBride 1996). Various mechanisms have been proposed for the thiol-mediated radiation protection of normal tissues. Thiols (RSH) and their anions (RS-) rapidly bind to free radicals such as OH and prevent them from reacting with cellular DNA. This type of protection from DNA damage by scavenging free radicals is oxygen dependent (Travis 1984). Another mode of protection occurs via H-atom donation (the fixation-repair model). Thiols compete with oxygen for radiation-induced DNA radicals. DNA radicals are "fixed" (not repaired) by reacting with oxygen and potentially harmful hydroxyperoxides may be generated. However, DNA radicals can be chemically repaired when they react with thiols by donation of hydrogen (Durand 1983). Furthermore, intracellular oxygen can be depleted as a result of thiol oxidation (Durand and Olive 1989) that would decrease the rate of oxygen-mediated DNA damage fixation. Finally, thiols induce DNA packaging that may decrease accessibility of DNA sites to radiolytic attack. This mechanism may be oxygen independent and may explain the protection from densely ionizing radiation such as neutrons (Savoye et al. 1997).

2.2.6.2.1 Amifostine: Preclinical Findings

Amifostine (Ethyol) is a thiol-containing compound that has long been recognized for its strong radioprotective properties and has already been used in clinical trials (Brizel 2003). Amifostine does not readily cross the cell membrane because of its hydrophilicity. The drug is rapidly dephosphorylated to its active metabolite WR-1065 and cleared from plasma with a half-life of 1–3 min following iv administration (Shaw et al. 1999a). In contrast to its brief systemic half-life, there is prolonged retention of the drug in normal tissues (Yuhas 1980). In the first 30 min following administration, drug uptake into normal tissues such as salivary gland, liver, kidney, heart, and bone marrow has been demonstrated to be up to 100-fold greater than in tumor tissues (Yuhas 1980). Bio-distribution studies show that the highest tissue levels of amifostine and its metabolites are found in salivary glands (Rasey et al. 1986).

Table 2.2.6.1. Radioprotective thiols and phosphorothioates. [Reprinted from Kirk-Othmer (1996), with permission]

Compound	CAS Register Number	Structure
	Thiols	
Dithiothreitol (DTT)	[27565-41-9]	$HSCH_2CH(OH)CH(OH)CH_2SH$
2-Mercaptoethanol (WR-15504)	[60-24-2]	$HOCH_2CH_2SH$
Cysteamine (MEA, WR-347)	[156-57-0]	$H_2NCH_2CH_2SH$
2-((Aminopropyl)amino)ethanethiol (WR-1065)	[31098-42-7]	$H_2N(CH_3)_2NHCH_2CH_2SH$
WR-255591	[117062-90-5]	$CH_3NH(CH_2)_3NHCH_2CH_2SH$
WR-151326	[120119-18-8]	$CH_3NH(CH_2)_3NH(CH_2)_3SH$
	Phosphorothioates	
WR-638	[3724-89-8]	$H_2NCH_2CH_2SPO_3H_2$
WR-2721	[20537-88-6]	$H_2N(CH_2)_3NHCH_2CH_2SPO_3H_2$
WR-3689	[20751-90-0]	$CH_3NH(CH_2)_3NHCH_2CH_2SPO_3H_2$
WR-151327	[82147-31-7]	$CH_3NH(CH_2)_3NH(CH_2)_3SPO_3H_2$

WR, Walter Reed Army Institute of Research.

During the 1970s and 1980s extensive animal studies explored the ability of amifostine to protect a variety of normal tissues against acute and late radiation injury and whether the drug improves therapeutic ratio of radiotherapy. A radioprotective effect was observed for acute injury of the bone marrow, esophagus, jejunum, colon, hair follicles, testis, and immune system (Murray and McBride 1996; Milas et al. 1988). Amifostine was also a potent radioprotector of late responding tissues such as lung and subcutaneous tissues (Milas et al. 1988; Travis et al. 1985; Vujaskovic et al. 2002a,b; Lockhart 1990; Hunter and Milas 1983). Protection of the lung was achieved against both single and fractionated radiation, and was assessed by biochemical testing such as reduction in hydroxyproline content of lung tissue and functional assays such as breathing frequency (Travis et al. 1985; Vujaskovic et al. 2002a). Amifostine treatment was associated with reduction in accumulation of macrophages in irradiated lung and profibrogenic cytokine activity (Vujaskovic et al. 2002b). Interestingly, while systemic application of amifostine was radioprotective for the lung tissue (Travis et al. 1985; Vujaskovic et al. 2002a,b), inhaled amifostine was ineffective (Lockhart 1990). In contrast to the near universal protection of acutely responding tissues and lung, amifostine was not effective in protecting brain from radiation injury, which was attributed to the inability of the hydrophyllic drug to cross the blood–brain barrier (Utley et al. 1984). Wide variation in the degree of radioprotection existed among various tissues, with protection factors for murine normal tissues ranging from 1.2 for hair follicles to greater than 2 for jejunum and bone marrow (Murray and McBride 1996; Milas et al. 1988). The degree of radioprotection was dependent on the drug dose and time of administration in relation to radiation exposure. In general, higher doses of amifostine produced better protection up to a maximum dose of about 400 mg/kg (Murray and McBride 1996; Milas et al. 1982, 1988) Maximum radioprotection was achieved when amifostine was given 10–30 min before radiotherapy (Murray and McBride 1996; Milas et al. 1982, 1988). In addition to normal tissue radioprotection, a number of studies have examined whether amifostine protects tumors as well. Although some studies documented a small degree of tumor radioprotection, primarily of microscopic tumor foci, most studies showed no tumor protection (Murray and McBride 1996; Milas et al. 1982, 1988; Wasserman et al. 1981). Therefore, preclinical studies support the notion of selective or preferential normal tissue protection resulting in increased therapeutic gain of radiotherapy.

The mechanism of amifostine's selective or preferential protection of normal tissues is related to several factors. Amifostine undergoes preferential rapid uptake into normal tissues but negligible or slower uptake into tumor tissues. While normal tissues actively concentrate amifostine against the concentration gradient, solid tumors generally absorb amifostine passively (Yuhas 1980). This selectivity results, in part, from differences in pH and alkaline phosphatase at the level of the capillary endothelium, both being higher in normal tissues compared to tumors (Yuhas 1980; Rasey et al. 1985, 1986). The acidic tumor microenvironment inhibits alkaline phosphatase necessary for uptake and conversion

of amifostine to the active protective thiol, WR-1065 (Calabro-Jones et al. 1985), a condition absent in normal tissues. Once inside the cell, WR-1065 acts as a scavenger of oxygen free radicals (Ohnishi et al. 1992), which is reduced under hypoxic conditions commonly present in solid tumors. In addition, amifostine may be less available to tumors because of their defective vascular network.

Overall, a large body of preclinical data shows that amifostine preferentially protects the majority of normal tissues, including the lung, from the effects of DNA damaging agents, such as radiation. In addition to interaction with radiation, amifostine has been shown to exert independent antimetastatic and antiangiogenic activity (Grdina et al. 2002; Giannopoulou and Papadimitriou 2003). Thus, these preclinical data provide a strong rationale for the clinical development of combined modality cancer treatment with amifostine and radiotherapy.

2.2.6.2.2 Amifostine: Clinical Studies

Clinical trials with amifostine began in the 1980s and showed that the drug is generally well tolerated. Its administration is associated with a number of transient side effects including nausea, vomiting, sneezing, mild somnolence, hypotension, a metallic taste during infusion, and occasional allergic reactions (Kligerman et al. 1988; Schuchter and Glick 1993). Hypotension appeared to be the most clinically significant side effect that could curtail treatment. A number of trials showed that amifostine reduces the severity of toxicity of radiotherapy or chemotherapy (Kligerman et al. 1988; Brizel et al. 2000; Kemp et al. 1996). Brizel et al. (2000) reported a randomized trial showing that amifostine reduces both severity and duration of xerostomia in head and neck cancer patients treated with radiotherapy. This study led to FDA approval of amifostine for this clinical indication.

A number of clinical trials have been performed using amifostine in combination with chemoradiotherapy for lung cancer (Koukourakis et al. 2000; Antonadou et al. 2001, 2003; Movsas et al. 2003; Senzer 2002; Leong et al. 2003), including one at the University of Texas M. D. Anderson Cancer Center (MDACC) (Komaki et al. 2002a,b, 2004). Antonadou et al. (2001, 2003) conducted a randomized phase III trial of concurrent chemotherapy (either paclitaxel or carboplatin) and radiation treatment plus/minus daily amifostine given iv at 300 mg/m^2 15–20 min before each fraction of radiotherapy and before chemotherapy in patients with locally advanced lung cancer. The results showed that amifostine significantly reduced radiation-induced pneumonitis (>= grade 3 from 56.3% to 19.4%, $p<0.002$), and esophagitis (>= grade 3 from 84.4% to 38.9%, $p<0.001$) without compromising antitumor efficacy (Antonadou et al. 2003). Movsas et al. (2003) recently reported preliminary results of a phase III RTOG 98-01 trial in which 243 patients with stage II-IIIA/B NSCLC were treated with induction chemotherapy (paclitaxel and carboplatin) followed by concurrent chemotherapy and hyperfractionated radiotherapy (69.6 Gy with 1.2 Gy/fraction, BID). Patients were randomized to receive amifostine i.v. 500 mg four times/week between the BID radiotherapy or no amifostine treatment. Although amifostine did not significantly reduce grade 3 or higher esophagitis, both weight loss from baseline and swallowing dysfunction were lower in the amifostine group.

At MDACC we investigated the ability of amifostine to reduce the severity and/or incidence of acute toxicities of concurrent chemotherapy and radiation therapy for NSCLC (Komaki et al. 2002a, 2004). A total of 64 patients with inoperable stage II or III NSCLC were treated with concurrent chemoradiotherapy. Both groups received thoracic radiation therapy (TRT) with 1.2 Gy/fraction, 2 fractions per day, 5 days per week for a total dose 69.6 Gy. All patients received oral etoposide (VP-16), 50 mg Bid, 30 min before TRT beginning day 1 for 10 days, repeated on day 29, and cisplatin 50 mg/m^2 iv on days 1, 8, 29, and 36. Patients in the study group received amifostine, 500 mg iv, twice weekly before chemoradiation (arm 1); patients in the control group received chemoradiation without amifostine (arm 2). Patient and tumor characteristics were distributed equally in both groups. Of the 64 patients enrolled, 62 were evaluable (31 in arm 1, 31 in arm 2) with a minimum follow-up of 24 months. Important findings from this study on the incidence and severity of a number of chemoradiotherapy-induced toxicities are shown in Figs. 2.2.6.1 and 2.2.6.2. As shown in Fig. 2.2.6.1, amifostine treatment increased the incidence of mild esophageal toxicity from 23% to 48%, but conversely it markedly reduced the incidence of severe esophageal toxicity from 35% to 16% (p=0.021). The reasons for this divergent effect of amifostine on mild and severe toxicity are not yet understood. Amifostine significantly reduced the incidence of constipation, pneumonitis, and neutropenic fever (Fig. 2.2.6.2). Of important note, severe, grade 3, pneumonitis occurred in 16% of patients treated with chemoradiotherapy alone but in no patients that received amifostine in addition to chemoradiotherapy. The most significant side effect of amifostine was hypotension occurring in 65% of pa-

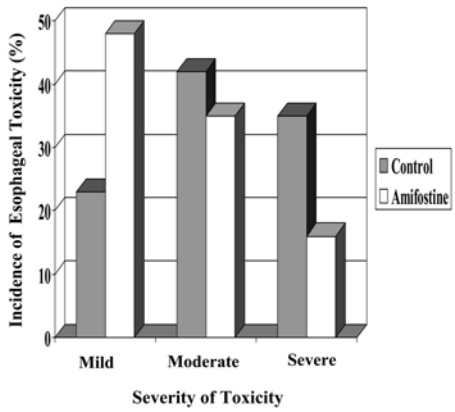

Fig. 2.2.6.1. Effect of amifostine on esophageal toxicity induced by chemoradiotherapy in patients with NSCLC. [Modified from Komaki et al. (2004) with permission]

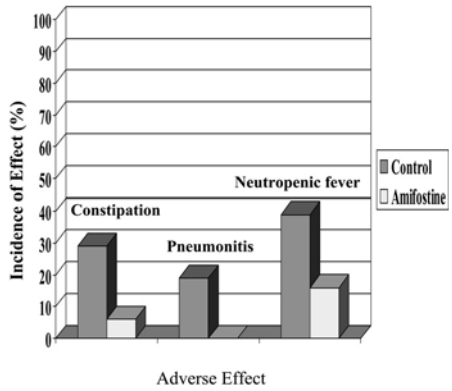

Fig. 2.2.6.2. Effect of amifostine on constipation, pneumonitis, and neutropenic fever caused by chemoradiotherapy in patients with NSCLC. [Modified from Komaki et al. (2004) with permission]

tients, consistent with findings from other similar clinical studies. Figure 2.2.6.3 shows that amifostine had no significant effect on tumor response to chemoradiotherapy, as determined by percent of local regional control, percent of distant metastases free survival and overall patient survival. We concluded that amifostine reduced the severity and incidence of the acute esophageal, pulmonary, and hematologic toxicity resulting from concurrent cisplatin-based chemoradiotherapy, but had no apparent effect on tumor response to therapy. Another study from MDACC showed that amifostine can partially reverse the reduction of lung diffusion capacity caused by chemotherapy and/or radiotherapy (Gopal et al. 2002), further documenting amifostine-induced radioprotection of normal tissues during thoracic radiotherapy. The results of randomized clinical trials with iv amifostine in lung cancer are summarized in Table 2.2.6.2.

Although the iv route of amifostine administration has been most commonly used in clinical trials, the practical advantages of sc administration have led to a clinical trial directly comparing routs of administration. A study comparing the relative bioavailability of amifostine administered sc and iv was conducted in normal male volunteers. Amifostine was given either iv at a dose of 200 mg/m^2 or sc at a fixed dose of 500 mg. The sc dose resulted in an area under the concentration–time curve for the bound form of WR-1065 of 68% compared to that after iv administration. There was greater inter-patient variability in drug concentration following sc administration (Shaw et al. 1999b; Bonner and Shaw 2002).

Koukourakis et al. (2000) conducted a randomized Phase II study in 140 patients receiving radiotherapy to assess the feasibility, tolerance, and cytoprotective efficacy of sc amifostine. Patients (n=70)

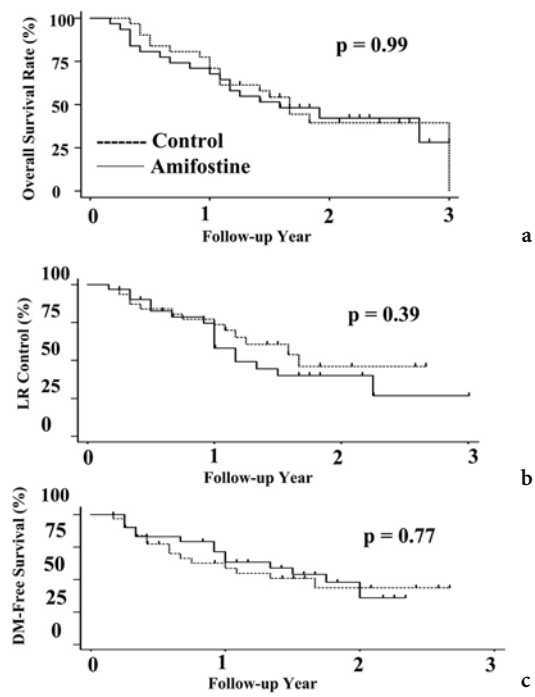

Fig. 2.2.6.3. Kaplan-Meier survival curves showing the effect of amifostine on (**a**) overall survival rate, (**b**) locoregional (LR) tumor control, and (**c**) distant-metastasis (DM)-free survival after chemoradiotherapy in patients with NSCLC. [Modified from Komaki et al. (2004) with permission]

received 500 mg of amifostine as a single sc injection 20 min prior to each radiotherapy fraction. The regimen was well tolerated, effectively reduced early toxicity of radiotherapy, and prevented treatment-induced delays. Patients reported a reduction in hypotension and nausea as compared with the iv administration. A phase III multi-center randomized trial to compare iv vs sc amifostine vs no amifostine in pa-

Table 2.2.6.2. Randomized trials with amifostine in lung cancer. [From Komaki et al. (2004) with permission]

Reference	Radiation dose	Chemotherapy	Amifostine dose	Comments
Movsas et al. 2003 *n*=242	69.6 Gy @ 1.2 Gy b.i.d. day 43	Induction P+Cx2; concurrent weekly C	500 mg IV 4x/week between b.i.d. RT fractions	No difference by NCI-CTC esophagitis Swallowing diaries (p=0.03) & weight loss (p=0.05) favor amifostine (Median survival, 15.6 and 15.8 months)
Leong et al. 2003 *n*=60	60–66 Gy @ 2.0 Gy q.d. day 43	Induction P+Cx2; concurrent weekly P	740 mg/m2 with each chemo (d 1, 22, 43, 50, 57, 64, 71, 78)	Esophagitis grade 2–3: 43% in amifostine, 70% in control (not significant) (median survival, 12.5 and 14.5 months)
Senzer et al. 2002 *n*=63	64.8 Gy @ 1.8 Gy q.d. day 1	Concurrent P+C q wk x 7; gemcitabine & cisplatin x 3 after chemoradiation	500 mg IV before weekly chemo; 200 mg IV daily before RT	No difference in toxicity, no survival data (ongoing trial)
Antonadou et al. 2001 *n*=146	55-60 Gy @ 2.0 Gy	None q.d.	340 mg/m2 daily before RT	↓ pneumonitis; ↓ esophagitis (no survival data)
Antonadou et al. 2003 *n*=73	55-60 Gy @ 2.0 Gy q.d.	Concurrent weekly P or C	300 mg/m2 daily before Chemo/RT and RT	↓ esophagitis (p<0.001) ↓ pneumonitis (p=0.009) (no survival data)
Komaki et al. 2004 *n*=62	69.6 Gy @1.2 Gy b.i.d. day 1	Concurrent cisplatin IV d 1, 8, 29, 36 Etoposide p.o. d 1-5	500 mg IV 1st, 2nd day each wk before chemo & 1st RT fraction	↓ degree of esophagitis, ↓ pneumonitis ↓ neutropenic fever 8–12, 29–33, 36–40 (median survival, 19 and 20 months)

P, paclitaxel; C, carboplatin; RT, radiation therapy; NCI-CTC, NCI common toxicity criteria.

tients with locally advanced NSCLC receiving concurrent chemoradiotherapy is ongoing. A phase II study of the efficacy of s.c. administration of amifostine in surgically resected NSCLC patients treated with postoperative radiotherapy is ongoing at MDACC.

2.2.6.3 Prostanoids, COX-2, and COX-2 Inhibitors

In response to physiological signals, stress or injury including radiation injury, cells produce prostanoids [prostaglandins (PGs) and thromboxanes (TBX)], a family of diverse, highly biologically active lipids derived from enzymatic metabolism of arachidonic acid by COX-1 or COX-2 enzymes. COX-1 is ubiquitous and responsible for prostanoid production in normal tissues where prostanoids exert numerous homeostatic physiological functions. In contrast, COX-2 is an inducible enzyme involved in prostaglandin production in pathologic states, particularly in inflammatory processes and cancer. COX-2 is induced by various factors including inflammatory cytokines (such as TNF-α, IL-1β, and platelet activity factors), oncogenes, growth factors, and hypoxia. Prostanoids play a role in the pathogenesis of various pathological states including inflammation, where PGE2, a potent vasodilator and an immunosuppressive substance, is the major prostaglandin involved. PGE2, produced in abundance by pro-inflammatory mononuclear cells such as macrophages, mediates the typical symptoms of inflammation due to its vasodilatory action. This augments edema formation caused by substances that increase vascular permeability such as histamine. PGE2 is also involved in the development of erythema and heat at the site of inflammation. Since radiation-induced lung injury is characterized by inflammatory tissue reactions, PGE2 and other PGs, as well as pro-inflammatory cytokines, are produced in injured tissue in abundance. Because different prostanoids have complementary or antagonistic activities, the final biological effect on tissues depends on the balance of similar and opposing actions of the prostanoids involved.

Production of PGE2 and other pro-inflammatory prostanoids can be suppressed by non-steroidal anti-inflammatory drugs (NSAIDs), which inhibit both isoforms of COX enzyme, or by selective COX-2 inhibitors. Since selective COX-2 inhibitors do not inhibit prostanoid production in normal tissues, they are less toxic

than commonly used NSAIDs. Interestingly, both prostanoids and their inhibitors have been reported to exert radioprotective actions on normal tissues. Exogenous administration of PGE2, other PGs, or PG analogs prior to irradiation of mice was shown to protect a variety of tissues including hematopoietic tissue, jejunal mucosa, dermis, and testis (reviewed in Hanson 1998; Milas and Hanson 1995). PGs vary widely in their radioprotective ability; however, the PG analog misoprostol was amongst the most effective. Paradoxically, inhibiting PGs by NSAIDs has also been shown to protect many tissues, including the lung, against radiation injury (Milas and Hanson 1995; Michalowski 1994). For example, Milas et al. (1992) reported that the NSAID indomethacin can protect mouse lung from radiation damage, but the protection was limited to the early pneumonitis phase of injury. Preliminary investigations in our laboratory using the selective COX-2 inhibitor SC-236 did not demonstrate significant protection from radiation-induced pneumonitis when the drug was administered a few days before and after lung irradiation. Subsequent experiments, using a different COX-2 inhibitor, celecoxib, provided suggestive evidence that giving the inhibitor during the development phase of acute pneumonitis may reduce either the latency or severity of lung injury. It should be emphasized that even in the absence of lung radioprotection by COX-2 inhibitors, therapeutic gain is still improved by their administration because of their potent enhancement of tumor radioresponse. The ability of COX-2 inhibitors to selectively enhance tumor radioresponse has been reviewed in detail elsewhere (Milas 2001; Milas et al. 2003b; Choy and Milas 2003).

Corticosteroids are highly potent anti-inflammatory drugs used for symptomatic treatment of radiation-induced pneumonitis. They inhibit production of all prostanoids because, in addition to their ability to inhibit COX enzymes, they prevent release of arachidonic acid from membrane phospholipids by stimulating the generation and secretion of lipocortins. Ward et al. (1992a) showed that steroid administration to rats at the time of radiation delivery protected rats from lung interstitial edema, delayed or suppressed radiation-induced alveolitis, but did not affect development of pulmonary fibrosis.

2.2.6.4 Growth Factors and Cytokines

Growth factors and cytokines play a critical role in pathogenesis of radiation injury, including that to the lung. Radiation alters the magnitude and dynamic activity of factors already present in affected tissues. Response to radiation occurs within minutes or hours after irradiation and can persist for days and months, influencing the pathogenesis of both early and late radiation damage. The principal action of growth factors and cytokines is on cell and tissue proliferation, as well as cell loss. Hence, growth factors affect all of the major determinants of cell and tissue radioresponse: total number of clonogenic cells, cell cycle redistribution, cell repopulation, cellular repair mechanisms, and tissue microenvironment such as tumor hypoxia and acidity. Many growth factors may be affected upon tissue irradiation, those that have cytotoxic actions and those that have cytoprotective ability, so that the extent of tissue damage depends on the interaction of cytokines with similar or opposing activities. Involvement of growth factors and cytokines in pathogenesis of lung radiation damage is discussed in more detail in Chap. 11.6.

Since some growth factors and cytokines may act protectively, attempts have been made to protect tissues that are at risk from lung cancer radiotherapy. Basic fibroblast growth factor (b-FGF) was found to protect endothelial cells both in vitro (Haimovitz-Friedman et al. 1991) and in vivo (Haimovitz-Friedman et al. 1991; Fuks et al. 1994) from radiation. To confer radiation resistance in vitro, b-FGF had to be present at the time of radiation exposure and/or within several hours after irradiation. This protective effect was abolished by treatment with anti-b-FGF antibodies. The radioprotective effect of b-FGF was attributed to its ability to increase cellular repair. A subsequent study by the same group (Fuks et al. 1994) showed that mice could be protected from lethal doses of whole lung irradiation if given iv b-FGF immediately before or within 2 h after irradiation. The effect was attributed to the protection of endothelial cells against radiation-induced apoptosis. Histology of irradiated lung tissue, but not of lungs exposed to both b-FGF and radiation, showed apoptotic changes in the endothelial cell lining of the pulmonary microvasculature within 6–8 h after radiation exposure. Also, histological features of radiation-induced pneumonitis were absent in mice treated with b-FGF. These results were not confirmed in a subsequent study by Tee and Travis (1995) that assessed the radioprotective action of b-FGF in two strains of mice having different susceptibilities to radiation-induced lung injury. The reasons for the discrepancy are unclear, but some differences in experimental conditions such as radiation dose, field size of radiation, and mouse strain could have accounted for this disparity.

Keratinocyte growth factor (KGF) is another cell growth factor that has been investigated for its ability to protect against radiation-induced lung damage. Although a member of the FGF family (FGF-7), KGF's cell growth stimulatory activity is confined to epithelial cells (Rubin et al. 1989; Miki et al. 1992). KGF was shown to be a good stimulator of proliferation of type II pneumocytes in vitro and in vivo (Panos et al. 1993; Ulich et al. 1994), a type of cells considered to play an important role in repair of injured lung tissue. Yi et al. (1996) showed that intratracheal administration of KGF to rats 2 or 3 days before exposure of rats to 18 Gy bilateral thoracic irradiation reduced severity of radiation-induced pneumonitis and fibrosis observed histologically. However, there was no significant improvement in rat survival. In contrast, KGF was highly effective both in preventing development of bleomycin-induced fibrosis and in improving the survival of treated animals. Significant protection was also rendered against the damage inflicted by the combined bleomycin plus radiation treatment. A more recent study (Terry et al. 2004) showed that a single intratracheal administration of rHuKGF to normal mice increased proliferation of alveolar epithelial cells 3–7 days later. This treatment afforded significant protection against lethality from radiation-induced pneumonitis when the mice were irradiated at day 7 after administration of rHuKGF.

Regarding radioprotective abilities of cytokines, it is worth mentioning that sc administration of recombinant IL-11 (rIL-11) rendered significant protection to mice from fatal thoracic irradiation (Redlich et al. 1996). The observed radioprotection was attributed to the rIL-11-induced inhibition of radiation-induced expression of TNF mRNA as well as TNF production by macrophages.

2.2.6.5 Pentoxifylline

Pentoxifylline (Trental), a methylxanthine derivative, is hemorheologic agent capable of reducing or ameliorating late radiation sequelae. In humans, pentoxifylline is used to treat persistent soft tissue ulcerations and necrosis. It has a variety of physiological activities including inhibition of platelet aggregation, regulation of tissue damaging cytokines such as tumor necrosis factor alpha (TNFα), and enhances blood flow in injured microvasculature. The drug may increase radioresponse of solid tumors by increasing tumor oxygenation (Lee et al. 2000), and as such was tested in a clinical phase III trial in NSCLC in combination with radiotherapy (Kwon et al. 2000). This study showed that pentoxifylline was modestly effective, increasing median time to relapse by 2 months and median survival time from 7 to 18 months. Though pentoxifylline has been shown to modestly improve tumor radioresponse, it has most often been used to reduce normal tissue radiation injury. Preclinical studies in experimental animals have, in general, shown pentoxifylline to be radioprotective but the degree of protection was highly variable. As an illustration, Lefaix et al. (1999) reported striking regression of subcutaneous fibrosis induced by radiation to the skin surface of pigs using a combination of pentoxifylline and alpha-tocopherol (vitamin E). On the other hand, pentoxifylline has also been shown to have little or no effect on acute skin or lung injuries (Dion et al. 1989; Koh et al. 1995; Rube et al. 2002; Ward et al. 1992b). With respect to lung injury, pentoxifylline inhibited the radiation-induced increase in TNFα mRNA during the acute phase of radiation injury, pneumonitis, but the impact of this biochemical change on lung injury was unclear (Rube et al. 2002). In another study (Ward et al. 1992b), pentoxifylline was found to further increase radiation-induced production of prostanoids (PGI2 and TXA2), while decreasing endothelial dysfunction accompanied by increases in lung wet weight, protein, and hydroxyproline content in the irradiated lung. A recent randomized clinical trial, however, using prophylactic pentoxifylline showed a significant reduction in both early and late radiation-induced lung toxicities in patients with breast and lung cancer (Ozturk et al. 2004).

2.2.6.6 Angiotensin Converting Enzyme (ACE) Inhibitors

Angiotensin converting enzyme (ACE) converts angiotensin I to angiotensin II, which is a potent vasoconstrictor and hypertensive factor. Captopril is an inhibitor of ACE that has been shown to protect against radiation injury of a number of tissues including the lung. In addition to inhibition of ACE, captopril is a free radical scavenger (Chopra et al. 1989) and exhibits superoxide dismutase (SOD)-like activity (Roberts and Robinson 1995). Captopril reduces radiation-induced pulmonary endothelial dysfunction (Ward et al. 1988), pulmonary fibrosis (Ward et al. 1990a, 1992c), and delays radiation-induced pulmonary arterial hypoperfusion in rats (Graham et al. 1988). Moreover, ACE inhibitor prophylaxis in rats receiving whole lung radiation was found to reduce radiation-induced activation of ACE, plasminogen ac-

tivator, and production of prostaglandins, and thromboxane (Ward et al. 1988). When added to the feed after irradiation, captopril reduced early lung reaction in rats receiving fractionated hemithoracic irradiation (Ward et al. 1993). In addition to pulmonary protection, ACE inhibition also protects against radiation injury of other tissues including kidney (Moulder et al. 1993), skin (Ward et al. 1990b), jejunum (Yoon et al. 1994), and heart (Yarom et al. 1993). With respect to the heart, Yarom et al. (1993) showed that captopril ameliorated the decrease in capillary function, increase in mast cells, fibrosis, number of atrial granules, and changes in nerve terminals, but it failed to prevent the progressive functional deterioration of the heart following irradiation. Mechanisms of captopril-mediated radioprotection are not fully understood, but are at least partially related to its antihypertensive activity and its thiol-like function.

Based on promising preclinical observations on radioprotection by ACE inhibitors, several clinical studies were performed. Wang et al. (2000) reported a retrospective clinical study of ACE inhibitors given for the management of hypertension in patients with lung cancer treated with definitive radiotherapy. The study showed ACE inhibitors given at a dose within the range used to treat hypertension did not decrease the incidence or delay the onset of symptomatic radiation pneumonitis. Currently, a phase II RTOG randomized clinical trial using captopril is ongoing. The primary goal of this study is to test whether captopril given after completion of radiotherapy can reduce the incidence or severity of pulmonary damage after aggressive definitive chemoradiotherapy.

2.2.6.7 Radioprotective Gene Therapy: Superoxide Dismutase (SOD)

The manganese superoxide dismutase (MnSOD) located within the mitochondria is one of nature's most efficient catalysts. The enzyme protects redox machinery within the mitochondria from the superoxide radical produced during normal respiration. In many pathological conditions, such as inflammation caused by radiation-induced free radical damage, superoxide is abundantly produced and may overwhelm the cell's ability to efficiently remove thus leading to tissue injury. Via its antioxidant activity, MnSOD inactivates superoxide and hence has potential to protect against free-radical induced injury. Early studies showed that systemic administration of SOD can prevent radiation injury (Petkau 1987) and can even reduce preexisting radiation-induced fibrosis (Delanian et al. 1994). When given prior to radiation the activity of SOD has generally been attributed to its radical scavenging effects, whereas when given after radiation the effects are most likely related to its anti-inflammatory and or immunostimulatory properties (Murray and McBride 1996). Another SOD, recombinant CuZnSOD was shown to protect the lung of hamsters from radiation-induced damage as evidenced by the absence of severe histopathologic tissue changes 4–16 weeks after irradiation and the prevention of elevation of total protein content in bronchoalveolar lavage (Breuer et al. 2000).

More recently, a novel approach has been advanced for radioprotective gene therapy using the antioxidant manganese superoxide dismutase delivered to specific target organs such as lung and esophagus by gene transfer vectors including plasmid/liposomes (PL) and adenovirus (Greenberger et al. 2003). Radiation protection by MnSOD transgene overexpression at the cellular level has been demonstrated to be localized to the mitochondrial membrane. Intraesophageal administration of MnSOD-PL prior to irradiation induces transgene expression for 48–72 h, and an associated decrease in radiation-induced expression of inflammatory cytokine mRNA and protein and esophagitis (Epperly et al. 2001, 2003). Intratracheal injection of adenovirus containing MnSOD protected against radiation-induced organizing alveolitis in mice (Epperly et al. 1999). In addition, intratracheal MnSOD-PL gene therapy reduced radiation induced inflammatory cytokines without rendering protection to orthotopic Lewis lung cancer (Guo et al. 2003). Preclinical animal studies suggested that radioprotective gene therapy reduces the radiation toxicities and may facilitate dose escalation protocols to improve the therapeutic ratio of lung cancer radiotherapy. However, the efficacy and specificity of this approach need further investigation. Application of MnSOD-PL gene therapy in the setting of fractionated chemo-radiotherapy is being tested in clinical trials for prevention of esophagitis in patients with non-small cell lung cancer. The gene therapy approach to specifically deliver agents to targeted tissues is not limited to MnSOD but has high potential for delivery of a wide array of agents including both cytotoxic and radioprotective agents.

2.2.6.8 Concluding Remarks

Normal tissue damage remains a major limiting factor in cancer radiotherapy, and chemoradiotherapy

where the improvement in tumor control and survival of patients is accompanied by increased rate and severity of treatment related toxicity. For many years scientists have explored various approaches to minimize damage to tissues, including the use of chemical and biological radioprotective agents. As elaborated in this chapter, many of these agents exert significant radioprotection and chemoprotection in experimental animal models and some of them have been tested in clinical trials. Amifostine has undergone the most extensive investigation, both preclinical and clinical. A number of clinical trials, including a recent one from MDACC described in Sect. 2.2.6.2.2, provided encouraging results both with respect to reduction of the incidence and/or severity of esophagitis and pneumonitis. Agents discussed have complex mechanisms of action, and affect a variety of radiation-induced tissue reactions both directly and indirectly. Radiation elicits the release of many substances, such as growth factors, cytokines and prostanoids, which can have both radioprotective and radioenhancing properties. Since the final outcome of treatment critically depends on the balance between these competing processes, the use of radioprotective agents may act on only some of the many factors involved. This is likely one of the reasons for the inconsistency in the literature on radioprotection. Rapid achievements in recombinant technology and genetic engineering are opening possibilities to upregulate or downregulate cellular expressions of diverse factors involved in tissue responses to radiation and to select appropriate factors to achieve a predetermined response. For example, redirecting the actions or optimizing the concentrations of a given response factor may become useful in increasing the therapeutic ratio of radiotherapy by enhancing tumor radioresponse, or by reducing damage of normal tissues with radioprotectors.

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2.3 Lung Cancer Chemotherapy for Radiation Oncologists

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CONTENTS

2.3.1 Introduction

Non-small cell lung cancer (NSCLC) accounts for 80%–85% of all cases of lung cancer (Jemal et al. 2003). The remainder of patients have small cell lung cancer (SCLC), which appears to be declining in incidence in recent years. Sensitivity to chemotherapy was initially noted in SCLC, with reports of complete responses in patients treated with combination chemotherapy (Maurer et al. 1980; Ettinger and Lagakos 1982). Subsequently, several studies conducted over the past two decades have demonstrated improved outcome from systemic chemotherapy for both SCLC and NSCLC (Schiller et al. 2002; Fossella et al. 2003; Wozniak et al. 1998; Sandler et al. 2000; Roth et al. 1992; Fukuoka et al. 1991; Belani et al. 1998). In addition to the benefits from chemotherapy for patients with advanced lung cancer, recent evidence supports the use of chemotherapy even in patients with earlier stages of disease (LeChevalier 2003; Kato et al. 2003). More recently, several novel chemotherapeutic agents have contributed to the development of combination regimens that have favorable toxicity profiles and have paved the way for incorporation into multi-modality treatment of lung cancer. In addition, improvements in both quality of life and survival have also been demonstrated with chemotherapy in lung cancer, but the benefits are modest in magnitude (Schiller et al. 2002; Fossella et al. 2003). As we move forward into the twenty-first century, the main focus will be on early detection, continued optimization of systemic therapy, development of novel molecularly-targeted agents, and identification of patient selection methods to individualize treatments.

2.3.2 Non-Small Cell Lung Cancer

Approximately 35%–40% of all patients with NSCLC have advanced or metastatic disease at the time of diagnosis (Jemal et al. 2003). Such patients are not candidates for surgical resection or definitive combined chemoradiotherapy. Systemic chemotherapy is the mainstay of treatment for advanced NSCLC. The advent of the platinum compounds opened the doors to effective chemotherapeutic intervention for advanced NSCLC.

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2.3.2.1 Platinum Compounds

Cisplatin and carboplatin are the two commonly used platinum compounds for the treatment of NSCLC. Though both these drugs exert anti-cancer activity by similar mechanisms, they have distinctly different toxicity profiles. Cisplatin is associated with high emetogenicity and also causes nephrotoxicity, ototoxicity, and neurotoxicity. Carboplatin, a better tolerated platinum compound, has the dose-limiting toxicity of myelosuppression, especially thrombocytopenia. The platinum compounds have single agent response rates of 10%–20% in patients with untreated advanced NSCLC (Woziak et al. 1998; von Pawel et al. 2000; Gatzemeier et al. 2000; Bonomi et al. 1989). However, when combined with a novel third generation chemotherapeutic agent (taxanes, gemcitabine, vinorelbine, irinotecan), they result in response rates of 30%–40% (Woziak et al. 1998; Lilenbaum et al. 2002; Sederholm 2002; Negoro et al. 2003).

Initial randomized trials compared the efficacy of cisplatin-based combination regimens against best supportive care alone (Rapp et al. 1988). A meta-analysis (NSCLC Collaborative Group 1995) of 52 randomized trials in lung cancer demonstrated a 10% improvement in 1-year survival rates and a 27% reduction in the risk of death for patients with advanced NSCLC treated with cisplatin-based combinations when compared to supportive care alone (NSCLC Collaborative Group 1995). The improved response rates and survival noted in such studies led to the adoption of cisplatin-based regimens as the cornerstone of therapy for advanced NSCLC. Though cisplatin and carboplatin have not been directly compared against each other as single agents, randomized trials have evaluated the efficacy of combination regimens consisting of cisplatin and carboplatin (Schiller et al. 2002; Fossella et al. 2003; Rosell et al. 2002). Klastersky et al. (1990) compared the efficacy of cisplatin-etoposide combination against carboplatin-etoposide for patients with untreated, advanced NSCLC. Though the response rate was higher on the cisplatin arm (27% vs 16%, P = 0.07), the overall survival was comparable between the two regimens. The carboplatin-etoposide arm was associated with a more favorable toxicity profile. In another study, Rosell et al. (2002) compared cisplatin-paclitaxel combination against carboplatin-paclitaxel regimen in advanced NSCLC. The study was designed to demonstrate non-inferiority for the carboplatin arm. Response rate, which was the primary endpoint, was 25% in the carboplatin arm and 28% in the cisplatin arm (p=0.45). The median survival, a secondary endpoint, favored the cisplatin arm, which led the investigators to conclude that cisplatin-based regimen was more efficacious for the treatment of advanced NSCLC. However, 34% of the patients randomized to the carboplatin arm received a carboplatin dose of AUC = 4.9 mg/ml.min as opposed to the planned dose of AUC = 6 mg/ml.min, due to miscalculation of the dose. A study by the Eastern Cooperative Oncology Group demonstrated comparable efficacy between cisplatin-paclitaxel and carboplatin-paclitaxel (Schiller et al. 2002). However, paclitaxel was administered as a 24-h infusion in the cisplatin arm and as a 3-h infusion in the carboplatin arm. Thus, there is continued controversy regarding the superiority for one over the other platinum compound. The favorable toxicity profile of carboplatin supports the use of carboplatin-based regimen for the treatment of advanced NSCLC, where the primary goal of therapy is palliation.

Attempts to improve the efficacy of cisplatin-based combinations by using higher doses of cisplatin have not been successful. Though a study by Gralla et al. (1981) demonstrated improved survival with high dose cisplatin (120 mg/m^2/cycle) when combined with vindesine, a subsequent prospective, large randomized trial (Klastersky et al. 1986) failed to show an advantage with high-dose cisplatin. The South West Oncology Group compared a dose intense schedule of cisplatin (100 mg/m^2 on days 1 and 8 of each cycle) for four cycles versus conventional dose of cisplatin (50 mg/m^2 on days 1 and 8 of each cycle) for eight cycles (Gandara et al. 1993). Both schedules were associated with similar efficacy, thus documenting the lack of dose-response effect with cisplatin in the treatment of advanced NSCLC.

2.3.2.2 Combination Chemotherapy

The combination of a platinum compound with a third generation chemotherapeutic agent such as the taxanes (paclitaxel, docetaxel), gemcitabine, vinorelbine and irinotecan has become the current standard of care for the treatment of advanced NSCLC (Bunn 2002). The third generation agents demonstrated response rates of 20%–40% when used as single-agents in previously untreated NSCLC patients (Ramalingam and Belani 2003). Subsequent studies have evaluated combination regimens consisting of one of the newer agents with in combination with a platinum compound (Table 2.3.1).

Table 2.3.1. Cisplatin vs. cisplatin-based doublet combination for NSCLC

Author (number of patients)	Regimen	Response rate	Median survival (months)	1-Year survival
Wozniak et al. (1998) (432)	Cisplatin	12%	6.0	20%
	Cisplatin Vinorelbine	26%[a]	8.0[a]	36%
Gatzemeier et al. (2000) (414)	Cisplatin (high dose)	17%	8.6	36%
	Cisplatin Paclitaxel	26%[a]	8.1	30%
Von Pawel et al. (2000) (446)	Cisplatin	14%	6.4	23%
	Cisplatin Tirapazamine	28%[a]	8.0[a]	34%
Sandler et al. (2000) (522)	Cisplatin	11%	7.6	28%
	Cisplatin Gemcitabine	30%[a]	9.1[a]	39%

[a] Indicates differences that are statistically significant.

A randomized study compared the combination of cisplatin and vinorelbine versus cisplatin alone for the treatment of advanced NSCLC (Wozniak et al. 1998). Improvements in response rate, time to progression and overall survival were noted with the combination arm. Similarly, cisplatin-paclitaxel combination was compared to treatment with high-dose cisplatin alone in a study by Gatzemeier et al. (2000). Patients in the combination arm experienced a superior response rate and time to progression, though the overall survival was comparable between the two arms. The lack of survival benefit with combination chemotherapy arm could be explained by the fact that a higher proportion of patients in the cisplatin alone arm received subsequent salvage chemotherapy. The combination of cisplatin and gemcitabine was compared against cisplatin alone in a randomized clinical trial (n=522 patients) for patients with advanced NSCLC (Sandler et al. 2000). Though hematological toxicity occurred at a higher frequency, all the efficacy parameters were superior with the combination arm. In another study designed along similar lines, therapy with cisplatin alone was compared with the combination of cisplatin and tirapazamine in advanced NSCLC (n=446 patients) (von Pawel et al. 2000). This study also demonstrated superior efficacy with the combination. The above randomized studies demonstrated that combination regimens consisting of cisplatin were superior to therapy with cisplatin alone. Thus cisplatin alone is not recommended for first-line treatment of advanced NSCLC.

2.3.2.3 Comparison of Platinum-Based Combination Regimens

Initial chemotherapy combinations for NSCLC included alkylating agents (cyclophosphamide, ifosfamide), mitotic spindle toxins (vindesine, vinblastine), topoisomerase inhibitors (etoposide) and anti-tumor antibiotics (doxorubicin) with a platinum compound. In recent years, various platinum-based combinations have been compared to identify the optimal regimen for the treatment of advanced NSCLC (Table 2.3.2).

The Eastern cooperative oncology group (ECOG) conducted a three-arm randomized clinical trial for patients with advanced NSCLC (n=599 patients) (Bonomi et al. 2000). Patients in the control arm received chemotherapy with cisplatin and etoposide. The two experimental arms were: cisplatin and paclitaxel (135 mg/m^2 of paclitaxel); cisplatin and paclitaxel (250 mg/m^2). Growth factor support was utilized for patients in the high dose paclitaxel arm. Paclitaxel was administered as a 24-h infusion in both the arms. The study demonstrated higher objective response rate and 1-year survival rate for patients treated with the paclitaxel regimens as compared to cisplatin-etoposide. There was no difference in efficacy between the two paclitaxel arms, though the high-dose paclitaxel arm was associated with increased myalgias, neurotoxicity, and, possibly, increased treatment-related cardiac events. Belani and colleagues (1998) compared the regimen of carboplatin and paclitaxel to cisplatin and etopo-

Table 2.3.2. Comparison of doublet combinations in advanced NSCLC

Author (number of patients)	Regimen	Response rate	Median survival (months)	1-Year survival
Belani et al. (1998) (369)	Cisplatin Etoposide	14%	9.0	37%
	Carboplatin Paclitaxel	22%	7.8	32%
Schiller et al. (2002) ECOG 1594 (1105)	Cisplatin Paclitaxel	21%	7.8	31%
	Cisplatin Gemcitabine	21%	8.1	36%
	Cisplatin Docetaxel	17%	7.4	31%
	Carboplatin Paclitaxel	15%	8.2	35%
Fossella et al. (2003) (1218)	Cisplatin Vinorelbine	25%	10.1	41%
	Cisplatin Docetaxel	32%	11.3	46%
	Carboplatin Docetaxel	24%	9.1	38%
Kelly et al. (2001) SWOG 9509 (408)	Cisplatin Vinorelbine	28%	8.0	36%
	Carboplatin Paclitaxel	25%	8.0	38%
Niho et al. (1999) (199)	Cisplatin Vindesine	22%	10.0	41%
	Cisplatin Irinotecan	29%	10.0	36%

side for the treatment of patients with advanced NSCLC. Carboplatin was administered at a dose of AUC = 6 mg/ml.min and paclitaxel was given at 225 mg/m^2 (3-h infusion). The study included 369 patients with advanced NSCLC who had not received prior chemotherapy. Though the response rate was superior with carboplatin-paclitaxel combination 22% vs 14%, (p=0.059), the overall survival was similar between the two arms of the study. However, there was a lower incidence of vomiting (3.7% vs 10%, p=0.021), febrile neutropenia (3.7% vs 8.4%, p=0.077) and diarrhea with the carboplatin-paclitaxel combination.

Four different chemotherapy combinations were compared in a study by the ECOG (ECOG 1594) in an attempt to identify the optimal regimen for the treatment of patients with advanced NSCLC (Schiller et al. 2002). The control arm consisted of treatment with cisplatin and paclitaxel (24-h infusion). The three experimental arms were: cisplatin-docetaxel, cisplatin-gemcitabine and carboplatin-paclitaxel (3-h infusion). An interim analysis suggested a higher incidence of toxicity for patients with ECOG performance status of 2 in all four arms (Sweeney et al. 2001). The study was subsequently amended to exclude participation of patients with ECOG performance status of 2. The overall response rate for the 1155 eligible patients was 19% with a 1-year survival rate of 33%. There were no differences between the four arms in response rate or overall survival. Distinct differences in toxicity were noted between the treatment regimens. The occurrence of grade 3/4 nausea and vomiting was lower in the carboplatin-paclitaxel arm, while alopecia was lower in the cisplatin-gemcitabine arm.

The carboplatin-paclitaxel regimen has also been compared with the approved regimen of cisplatin-vinorelbine in a randomized trial by the SouthWest Oncology Group (SWOG) for patients with advanced NSCLC (Kelly et al. 2001). Both regimens were associated with a similar efficacy with response rates of 28% and 25% for the cisplatin-vinorelbine and carboplatin-paclitaxel arms, respectively. The median survival was 8 months for patients on both the arms of the study. There were no differences in quality of life scores between patients in the two groups, though there were differences in toxicity profiles with the two regimens.

The efficacy of docetaxel in the first-line treatment of advanced NSCLC was demonstrated by a large randomized three-arm clinical trial (Fossella et al. 2003). The three arms of the study were: cisplatin-vinorelbine, cisplatin-docetaxel and carboplatin-docetaxel. The efficacy of the cisplatin-docetaxel arm was superior, whereas carboplatin-docetaxel was similar to the control arm of cisplatin-vinorelbine. Platinum-docetaxel regimens are also reasonable first-line regimens for advanced NSCLC. Thus, all of the above studies have established the efficacy of platinum-based two-drug combinations for the first-line treatment of patients with advanced NSCLC. The comparable efficacy of all the regimens evaluated thus far allows for selection of therapy for patients based on toxicity profile, frequency of administration and cost.

2.3.2.4 Two-Drug Combinations Versus Single-Agent Therapy

The addition of a platinum compound (cisplatin or carboplatin) to a third generation chemotherapeutic agent has repeatedly been shown to improve outcome as compared to the same agent administered alone (Table 2.3.3). The Cancer and Leukemia Group B (CALGB) compared carboplatin-paclitaxel combination against therapy with paclitaxel alone for patients with advanced NSCLC (Lilenbaum et al. 2002). Though the toxicity profile favored the single agent arm, both the response rate and median survival were higher with the combination. Even patients with ECOG performance status of 2 who were included in the study derived a higher degree of benefit from the two-drug combination compared to single agent therapy. Studies that were conducted along similar lines have also established the superiority of carboplatin-gemcitabine combination over gemcitabine alone and cisplatin-docetaxel combination over docetaxel therapy alone (Sederholm 2002; Georgoulias et al. 2003). In a randomized study conducted in Japan, the combination of cisplatin-irinotecan has also demonstrated higher efficacy over therapy with irinotecan alone (Negoro et al. 2003). The improvement in survival and response rate with the addition of a platinum compound to the third generation agent was consistent across these trials. Thus, single agent therapy cannot be recommended for first-line use in patients with good performance status.

2.3.2.5 Two-Drug Versus Three-Drug Combinations

Efforts to improve the outcome of two-drug combinations by the addition of a third cytotoxic agent have not met with much success. The Spanish Lung Cancer Group randomized patients with advanced NSCLC to one of the following three arms: Arm A, cisplatin-gemcitabine; Arm B, cisplatin-gemcitabine-vinorelbine; Arm C, sequential therapy with three cycles each of vinorelbine-gemcitabine followed by ifosfamide-vinorelbine (Alberola et al. 2003). There was no significant difference in response rates or survival between the three arms. The incidence of grades 3/4 neutropenia, thrombocytopenia, and febrile neutropenia were higher in the three-drug

Table 2.3.3. Single agent vs. doublet combination therapy in advanced NSCLC

Author (number of patients)	Regimen	Response rate	Median survival (months)	1-Year survival
Lilenbaum et al. (2002) (561)	Paclitaxel Carboplatin	29%	8.6	37%
	Paclitaxel	17%	6.8	33%
Sederholm (2002) (334)	Gemcitabine Carboplatin	30%	11.0	44%
	Gemcitabine	12%	9.0	32%
Georgoulias et al. (2003) (308)	Docetaxel Cisplatin	36%[a]	10.0	45%
	Docetaxel	0%	8.0	40%
Masuda et al. (2003) (259)	Irinotecan Cisplatin	43%	12.0	49%
	Irinotecan	21%	11.0	44%

[a] p=0.003.

combination arm. Similar results were noted with another trial that compared a doublet regimen with a triplet combination (Rudd et al. 2002). The doublet combination of carboplatin-gemcitabine was compared to a cisplatin-ifosfamide-mitomycin regimen in a randomized study that included 422 patients. While the response rates were similar between the two arms, 1-year survival and median survival were superior with the carboplatin-gemcitabine combination. The incidence of nausea, vomiting, alopecia, and constipation were higher with the three-drug combination, while thrombocytopenia was more common with the carboplatin-gemcitabine doublet. Based on these studies, it is apparent that the therapeutic index of doublet combinations is superior to triplet chemotherapy combinations. Hence the combination of three cytotoxic agents should not be used in the routine care of patients with advanced NSCLC.

2.3.2.6 Non-Platinum Regimens

Combination regimens without a platinum compound have been studied with the objective of improving the toxicity profile (Table 2.3.4). This notion was supported by initial phase II clinical trials that demonstrated comparable efficacy and lesser toxicity with non-platinum regimens (Isla et al. 2001; Iaffaioli et al. 2000; Kakolyris et al. 2001). In a randomized phase II clinical trial, Georgoulias and colleagues (2001) compared the efficacy of cisplatin-docetaxel combination with a non-platinum regimen consisting of gemcitabine and docetaxel. This study demonstrated comparable efficacy between the two regimens. However, important differences were noted between the two arms in terms of toxicity. The non-platinum arm was associated with a lower incidence of grades 3/4 nausea, vomiting, diarrhea, and a trend towards lower occurrence of asthenia and neurotoxicity. Another interesting observation from the study was related to differences in efficacy of non-platinum regimen based on tumor histology. The non-platinum combination was associated with better efficacy in patients with adenocarcinoma where as patients with non-adenocarcinoma histology derived greater benefit from platinum–docetaxel regimen. Since the analysis to delineate differences between the various histological sub-types were not prospectively planned as part of the study, this observation has to be confirmed in prospective randomized trials. Kosmidis and colleagues (2002) demonstrated comparable efficacy between carboplatin-paclitaxel combination and a non-platinum doublet of gemcitabine–paclitaxel in a randomized study for patients with previously untreated NSCLC. No major differences in toxicity were noted between the two arms. The cost of therapy was also similar between the two arms of the study. The enthusiasm to utilize non-platinum regimens for patients with advanced NSCLC was, however, diminished by the results of the three-arm randomized EORTC trial for patients

Table 2.3.4. Non-platinum combinations in the treatment of advanced NSCLC

Author (number of patients)	Regimen	Response rate	Median survival (months)	1-Year survival
Smit et al. (2003) (480)	Cisplatin Paclitaxel	31%	8.1	35%
	Cisplatin Gemcitabine	36%	8.8	32%
	Paclitaxel Gemcitabine	27%	6.9	26%
Georgoulias et al. (2001) (441)	Cisplatin Docetaxel	35%	10.0	42%
	Gemcitabine Docetaxel	33%	9.5	37%
Gridelli et al. (2002) (502)	Gemcitabine Vinorelbine	25%	8.0	31%
	Control[a]	30%	9.5	37%
Kosmidis et al. (2002) (509)	Carboplatin Paclitaxel	28%	10.4	42%
	Gemcitabine Paclitaxel	35%	9.8	41%

[a] Control arm consisted of therapy with cisplatin-vinorelbine or cisplatin-gemcitabine.

with advanced NSCLC (Smit et al. 2003). The experimental arms were cisplatin-gemcitabine and a non-platinum arm consisting of paclitaxel-gemcitabine. The control arm consisted of therapy with cisplatin-paclitaxel. Though the overall survival was not statistically different between the three arms, there was a trend towards inferior efficacy with the non-platinum regimen of paclitaxel-gemcitabine. It is to be noted that the dose of paclitaxel used in this study (175 mg/m^2) was lower than the dose used in other randomized studies that evaluated a paclitaxel-containing regimen. Surprisingly, no major differences in toxicity was noted between the three arms besides myelosuppression.

Lack of differences in toxicity between platinum-based doublet and non-platinum regimens can be attributed to improved supportive care measures and better patient selection for combination chemotherapy. A large, randomized clinical trial conducted in the US by the coalition of cooperative groups will hopefully answer this important question regarding the role of non-platinum regimens in the treatment of advanced NSCLC (Treat et al. 2003). The three arms of this ongoing study include carboplatin-paclitaxel, carboplatin-gemcitabine, and paclitaxel-gemcitabine. Projected accrual for this study is approximately 1100 patients. Interim results of the study demonstrated comparable efficacy between the three arms.

2.3.2.7 Duration of Chemotherapy

Until recently, there were no established guidelines regarding the duration of chemotherapy for patients with advanced NSCLC. Most oncologists have used six courses of chemotherapy for patients who achieved an initial response or disease stabilization with chemotherapy. However, randomized trials conducted recently have demonstrated that administration of chemotherapy beyond three to four cycles does not add to the benefit (Socinski et al. 2002; Smith et al. 2001). In a randomized study by Smith and colleagues (2001), patients with advanced NSCLC were randomized to treatment with either three or six courses of chemotherapy with mitomycin C, vinblastine and cisplatin. Of the 155 patients randomized to three courses, 72% of patients completed the chemotherapy according to plan. However, only 31% of patients randomized to six courses received the planned therapy. There were no differences between the two groups in overall survival, response rate and time to progression. However, there was a significant increase in the incidence of fatigue and a trend toward increase in nausea and vomiting with continued chemotherapy beyond the third course, among patients randomized to six courses of treatment. Responses were most likely to occur during the first three courses and there was no significant increase in response rate beyond the third course. Similar results were noted in a study that evaluated a modern doublet regimen consisting of carboplatin and paclitaxel by Socinski and colleagues (2002). As part of their study, patients with advanced NSCLC were randomized to four courses of chemotherapy (arm A) or continuation of chemotherapy beyond four courses until progression of disease (arm B). The response rate and overall survival were similar between the two arms of the study. Interestingly, the median number of courses of chemotherapy that was administered to patients in arm B was also four. There was an increase in the incidence of neuropathy with continuation of chemotherapy beyond four courses. The results of these two randomized clinical trials have demonstrated lack of sufficient therapeutic benefit to offset the increased cost, toxicity and patient inconvenience beyond three to four courses of chemotherapy with both cisplatin-based and carboplatin-based regimens for patients with advanced NSCLC. Continuation of chemotherapy beyond four courses is appropriate for patients who have an ongoing response at the end of four courses of chemotherapy. The role of maintenance chemotherapy continues to evolve and at present is not well established.

2.3.2.8 Second-Line Chemotherapy

It is estimated that approximately 50% of the patients with advanced NSCLC will be eligible for second-line chemotherapy. Though a variety of cytotoxic agents with activity against lung cancer have been developed, few randomized trials have been conducted to evaluate their efficacy in the second-line setting (Table 2.3.5). Docetaxel is the only approved second-line therapeutic option for advanced NSCLC in the US. The efficacy of docetaxel as second-line therapy was demonstrated in two randomized clinical trials (Shepherd et al. 2000; Fossella et al. 2000). Shepherd and colleagues (2000) randomized patients with advanced NSCLC who had progressed following prior platinum-based chemotherapy to treatment with docetaxel or supportive care alone. Patients who had received a taxane in the first-line setting were excluded from the

Table 2.3.5. Second-line therapy for advanced NSCLC

Author (number of patients)	Treatment	Response rate	Median survival (months)	1-Year survival
Fossella et al. (2000) (373)	ocetaxel 100 mg/m^2	2%	5.7	21%
	ocetaxel 75 mg/m^2	7.5%	5.5	32%
	Vinorelbine or Ifosfamide	1%	5.6	19%
Shepherd et al. (2000) (204)	Docetaxel 100 mg/m2	6.3%	5.9	19%
	Docetaxel 75 mg/m^2	5.5%	7.5	37%
	Best supportive care	0	4.6	19%
Hanna et al. (2003) (571)	Pemetrexed	9.1%	8.3	30%
	Docetaxel 75 mg/m^2	8.8%	7.9	30%

study. Two different doses of docetaxel (75 mg/m^2 and 100 mg/m^2) were evaluated as part of the study. Therapy with docetaxel was associated with improvements in overall survival and time to progression, despite the fact that the response rate was only 7%. Stabilization of disease was noted in 43% of the patients treated with docetaxel. The survival benefit with docetaxel was more pronounced in the 75 mg/m^2 dose level due to more favorable therapeutic index when compared to the 100 mg/m^2 dose. Eleven patients developed febrile neutropenia (24%) with the higher dose of docetaxel compared to only 1 patient (1.8%) at the lower dose. Benefit from docetaxel for patients with platinum-refractory NSCLC was also demonstrated by a randomized trial by Fossella and colleagues (2000). In their study, 363 patients who were either refractory to or relapsed following platinum-based chemotherapy were randomized to one of the three following treatment arms: docetaxel 100 mg/m^2, docetaxel 75 mg/m^2, or treatment with vinorelbine or ifosfamide. Unlike the Shepherd study, patients who had received prior therapy with paclitaxel were included in this study. The response rates in the three treatment arms were 10.8%, 6.7%, and 0.8%, respectively. The 1-year survival rate was superior in the docetaxel arm that utilized 75 mg/m^2 compared to the control arm of vinorelbine or ifosfamide (32% vs 19%, p=0.025). Disease stabilization was noted in approximately 35% of the patients treated with docetaxel. Prior therapy with paclitaxel did not impact the efficacy of docetaxel. The survival advantage noted in these two studies with docetaxel, despite the low response rates can primarily be attributed to stabilization of disease that occurred in 35%–45% of the patients. Thus, achievement of disease stabilization is a meaningful therapeutic outcome with second-line therapy for patients with advanced NSCLC. The results of these two studies led to the approval of docetaxel by the Food and Drug Administration for second-line therapy of patients with advanced NSCLC in the United States. Because of the higher incidence of toxicity with the 100 mg/m^2 dose, the recommended dose of docetaxel for second-line therapy is 75 mg/m^2 administered every 3 weeks.

Pemetrexed, a multi-targeted antifolate agent, has also recently shown to be effective in second-line therapy of advanced NSCLC. A randomized clinical trial compared pemetrexed with docetaxel in the second-line treatment of advanced NSCLC (Hanna et al. 2003). Patients with an ECOG performance status of $\leq$2 were eligible for the study. Approximately 25% of the patients had received prior therapy with a taxane. All patients randomized to the pemetrexed arm received vitamin B12 and folic acid supplementation, an intervention that reduces toxicity of pemetrexed. The efficacy was similar between docetaxel and pemetrexed for the 571 patients enrolled to the study. The 1-year survival was 30% for patients on both arms of the study. However, there were some differences in the hematological toxicity profiles of both agents. The incidence of febrile neutropenia was lesser with pemetrexed (1.9% vs 12.7%, p<0.001). Hospitalizations due to febrile neutropenia occurred less frequently with pemetrexed. Based on the results of this study, pemetrexed represents another second-line treatment option for patients with advanced NSCLC and it will likely get FDA approval for use in this setting. Studies that have evaluated two-drug combinations in the second-line setting have demonstrated a higher incidence of toxicity without an appreciable increase in the efficacy of the regimen. Thus, single agent chemotherapy with docetaxel, and more recently pemetrexed, constitutes standard therapy for patients with advanced NSCLC who have progressed following platinum-based chemotherapy.

2.3.2.9 Management of Elderly NSCLC Patients

Approximately 40% of patients with advanced NSCLC are above the age of 70 years at the time of diagnosis (Langer et al. 2002). Co-morbid illnesses that tend to be common among elderly patients, could impact the choice of chemotherapy. Physiological changes that occur with aging, such as alterations in renal function, may also pose challenges to administration of recommended doses of chemotherapy. Such factors have resulted in under-representation of elderly patients in clinical trials, thus limiting the ability to extend the data from clinical trials to making treatment decisions for elderly patients. During recent years, clinical trials have been conducted exclusively for elderly NSCLC patients to evaluate various chemotherapeutic agents. The ELVIS trial (Elderly Lung Cancer Vinorelbine Italian Study) randomized elderly NSCLC (age >70 years) to treatment with best supportive care alone versus single agent chemotherapy with vinorelbine and supportive care (Elderly Lung Cancer Vinorelbine Italian Study Group 1999). Though the study was closed early due to slow accrual, patients in the chemotherapy arm experienced improved survival and lung cancer symptoms-related quality of life. The response rate and median survival with chemotherapy were 19% and 27 weeks, respectively. In another study conducted for elderly patients, patients were randomized to treatment with vinorelbine alone, gemcitabine alone or the combination of vinorelbine and gemcitabine (Gridelli et al. 2003). This large (n=698) study demonstrated comparable efficacy between all three arms of the study. However, the combination arm was associated with a higher degree of toxicity. These two studies have demonstrated that elderly patients with a good performance status tolerate single agent chemotherapy without excessive toxicities.

The role of platinum-based chemotherapy has undergone limited evaluation in elderly patients with NSCLC. Lilenbaum et al. (2002) conducted a randomized clinical trial (CALGB 9730) that compared treatment with paclitaxel alone versus treatment with carboplatin and paclitaxel for patients with advanced NSCLC. The study was designed to include age as a stratification factor. Approximately 26% of the patients enrolled to the study were above the age of 70 years. No significant differences were noted in the efficacy of chemotherapy between patients who were above the age of 70 years versus younger patients (<70 years) in both arms of the study. Elderly patients tolerated the carboplatin-paclitaxel combination as well and the survival benefit with doublet therapy was maintained. A retrospective analysis of the ECOG 1594 trial that evaluated the outcome in elderly patients also substantiated the findings of the CALGB 9730 trial (Langer et al. 2003a). In this analysis, the outcome for elderly patients were similar to that of the younger patients in all four arms of the study. A slight increase in the incidence of grades 3 and 4 hematological toxicity was noted in the elderly sub-group. From the above studies it is clear that elderly patients with a good performance status (ECOG < 2) benefit from platinum-based combinations as much as younger patients without any major increase in toxicity.

2.3.2.10 Management of NSCLC Patients With Poor PS

Several studies have documented poor performance status as a negative prognostic factor for advanced NSCLC (Albain et al. 1990). A study conducted by the ECOG demonstrated a median survival of 10 weeks for NSCLC patients with poor PS and a toxic death rate of 10% upon treatment with one of four different combination chemotherapy regimens (Ruckdeschel et al. 1986). The ECOG 1594 trial initially included patients with PS 2. However, the study was closed to this sub-group of patients after 68 patients with PS 2 were enrolled due to a high incidence of toxicity. Of the 64 evaluable patients with PS 2, the response rate was 14% with a median survival of 4.1 months, which are inferior compared to that seen in patients with a good PS (Sweeney et al. 2001). The overall toxicity rate was not different in patients with poor PS compared to patients with PS<2. The results of this study led to a prospective trial for NSCLC patients with poor PS, the only one of its kind so far (Langer et al. 2003b). The study randomized patients to treatment with cisplatin-gemcitabine versus carboplatin-paclitaxel. These two arms were chosen based on the results from ECOG 1594, which demonstrated more favorable toxicity profile with carboplatin-paclitaxel arm and better efficacy with the cisplatin-gemcitabine arm for patients with PS 2. The doses of paclitaxel, gemcitabine, and cisplatin were reduced in an attempt to decrease the toxicities associated with these regimens. The median survival for patients in both arms was approximately 6 months. No differences in efficacy were noted between the two regimens. The worst grade 3/4 toxicity occurred in 80% of the patients on both arms of the study. This study documented the feasibility of administering

platinum-based combination at attenuated doses to patients with PS 2.

Thus the treatment of NSCLC patients with a poor PS continues to be a subject of debate. The survival duration of these patients is poor, despite treatment with combination chemotherapy. Novel approaches such as incorporating molecularly targeted agents with appropriate single agent chemotherapy may in fact prove to be optimal for the treatment of NSCLC patients with poor PS. Furthermore, differences in the reasons contributing to the poor PS, such as cancer-related versus non-cancer related factors may also be important determinants of outcome.

2.3.2.11 Molecularly Targeted Therapy for NSCLC

The ability to interrupt cell-signaling pathways with agents that are selective against specific molecular targets represents an important advance in the treatment of cancer. Increasingly, new molecular targets and novel agents that selectively modulate these targets are being developed for several malignancies. Some of the treatment modalities currently under study in NSCLC are: Inhibitors of signal transduction pathway such as epidermal growth factor receptor (EGFR), HER-2/Neu, protein kinase C; anti-angiogenic agents such as monoclonal antibodies against the vascular endothelial growth factor (VEGF), matrix metalloproteinase inhibitors (MMPI); novel retinoids; gene therapy and vaccines such as p53, GVAX; and agents with multi-pronged effects such as the cyclooxygenase-2 inhibitors.

Gefitinib, an inhibitor of the EGFR tyrosine kinase has recently been approved for the treatment of patients with advanced NSCLC who are refractory to chemotherapy. Two randomized trials documented the anti-tumor activity of gefitinib in advanced NSCLC (Table 2.3.6) (Fukuoka et al. 2003; Kris et al. 2003). In the Iressa Dose Evaluation in Advanced Lung Cancer I (IDEAL 1) trial, patients with advanced NSCLC who had received prior therapy with a platinum-based regimen were randomized to therapy with two different dose levels of gefitinib (250 mg or 500 mg administered orally on a daily basis) (Fukuoka et al. 2003). The study demonstrated a response rate of 18% and median survival of 7.6 months. Improvement in symptoms were noted in approximately 40% of the patients. There were no differences in efficacy between the two dose levels of gefitinib. However, the incidence of grade 3 diarrhea and skin rash, the principal toxicities associated with the use of gefitinib, were higher at the 500 mg dose level. In a similar study conducted in the US (IDEAL II), Kris and colleagues (2003) included NSCLC patients who had received prior first- and second-line chemotherapy. Patients were randomized to the two dose levels of gefitinib as in IDEAL 1. The study documented a response rate of 11% with a symptom improvement rate of 40%. Based on available data, no clear correlation between the EGFR expression status and response to therapy with gefitinib has been established. Though gefitinib is effective as a single agent in advanced NSCLC, randomized clinical trials that compared the combination of gefitinib with chemotherapy versus chemotherapy alone in chemotherapy-naive NSCLC patients failed to demonstrate an advantage to the gefitinib combination (Herbst et al. 2003). Erlotinib, which is another orally administered inhibitor of the EGFR also has single agent activity in advanced NSCLC (Perez-Soler et al. 2001). In a phase II study for patients who progressed with first-line chemotherapy, treatment with erlotinib resulted in a response rate of 11%. The study included patients whose tumors overexpressed EGFR (>1+ by immunohistochemistry). An interesting observation from the study was that the median survival was better for patients who experienced skin rash as an adverse event. However, combination of chemotherapy with erlotinib also failed to improve outcome compared to chemotherapy alone (Tarceva press release,

Table 2.3.6. EGFR inhibitors for recurrent NSCLC

Author (number of patients)	Treatment	Response rate	Overall survival (months)	Disease control rate (PR+SD)
Fukuoka et al. (2003) (210)	Gefitinib 250mg	18%	7.6	54%
	Gefitinib 500mg	19%	7.9	51%
Kris et al. (2003) (216)	Gefitinib 250mg	12%	6.5	43%
	Gefitinib 500mg	9%	5.9	35%
Perez-Soler et al. (2001) (57)	Erlotinib 150 mg	11%	9.0	45%

2003). Identification of predictive factors of response to therapy with gefitinib will lead to optimal utilization of gefitinib for the treatment of advanced NSCLC patients. Initial observations have included improved efficacy with EGFR inhibitors in female patients, adenocarcinoma histology, lifetime non-smokers and patients who experience a skin rash upon initiation of therapy (Perez-Soler et al. 2001; Shah et al. 2003). Two prospective clinical trials have evaluated the efficacy of EGFR inhibitors for the treatment of bronchioloalveolar carcinoma (BAC). It is estimated that approximately 3%–4% of patients with NSCLC have BAC histology. Initial studies with gefitinib demonstrated objective responses in patients with BAC histology. Subsequently SWOG conducted a phase II study of gefitinib for patients with BAC histology. Approximately two-thirds of the patients enrolled to the study (n=145) were chemotherapy-naive (West 2003). The study reported response rate of 22% in previously untreated patients and about 14% in patients who had received prior chemotherapy. In another study by Miller et al. (2003), erlotinib was evaluated for the treatment of BAC. Preliminary results from the study demonstrated objective responses in 26% of the patients (n=50). The mechanisms that underlie the increased efficacy of EGFR inhibitors in BAC are unclear at present. It also appears that NSCLC patients who have never smoked cigarettes during their lifetime have a higher likelihood of responding to therapy with gefitinib (Shah et al. 2003). Thus emerging evidence suggest that efficacy of EGFR inhibitors can be improved with appropriate patient selection. Studies to determine specific genetic and proteomic profiles of tumors that predict response to therapy are underway and will hopefully lead to improved patient selection methods for treatment with selective agents such as EGFR inhibitors.

2.3.2.12 Chemotherapy for Early Stage NSCLC

Approximately 25% of the patients present with early stage NSCLC that is amenable to surgical resection (Harpole et al. 1995; Smythe 2001). In addition to the stage of disease, feasibility of surgical resection is also determined by co-morbid illnesses and extent of pulmonary function. The 5-year survival rates following surgery are 61%, 38%, 34%, 24%, and 9%, respectively, for patients with clinical stages IA, IB, IIA, IIB and IIIA NSCLC (Mountain and Dresler 1997). Presence of micrometastatic disease appears to be an important determinant of outcome following surgical resection (Passlick et al. 1999; Pantel et al. 1993). Therefore, eradication of micrometastatic disease is an important therapeutic goal for the treatment of patients for patients with early stage NSCLC.

Systemic chemotherapy has been evaluated by several clinical trials as adjuvant therapy following surgical resection of early stage NSCLC (Feld et al. 1993; Wada et al. 1999; Keller et al. 2000; Dautzenberg et al. 1995). Initial clinical trials that evaluated platinum-based chemotherapy as adjuvant treatment yielded disappointing results. Many such studies were underpowered to detect a modest benefit from chemotherapy. Furthermore, delivery of planned doses of chemotherapy in the postoperative setting was limited in part due to toxicity. In fact, in several studies, only 60%–70% of the planned doses of chemotherapy was administered postoperatively. A meta-analysis of several randomized clinical trials in the adjuvant setting demonstrated a 5% improvement in 5-year survival rate and a 13% decrease in relative risk of death with platinum-based chemotherapy for patients with early stage NSCLC (Non-Small Cell Lung Cancer Collaborative Group 1995).

The Intergroup-ECOG conducted a randomized clinical trial for patients with stage II and IIIA NSCLC who underwent surgical resection (ECOG 3590) (Keller et al. 2000). Patients (n=488) were randomized to treatment with four cycles of cisplatin and etoposide administered concurrently with radiation (50.4 Gy) or radiotherapy alone. There were no differences in overall survival between the two arms of the study. The incidence of both local and distant recurrence of cancer was also similar between the two groups. Only 69% of the patients assigned to the chemoradiotherapy arm completed the planned four cycles of chemotherapy. Toxicity was higher for patients treated with chemoradiation. Since patients in both arms of the study received postoperative radiotherapy, the ability to make conclusions regarding the true impact of chemotherapy as adjuvant treatment was limited in this study.

Two Japanese clinical trials have demonstrated survival advantage with UFT following surgical resection for patients with stage I NSCLC. Wada and colleagues (1996) randomized patients with resected stage I, II and IIIA NSCLC to observation, treatment with cisplatin, vindesine and UFT, or UFT alone (400 mg daily for 1 year). The 5-year survival rates for the three groups were 49%, 61%, and 64%, respectively. Multivariate analysis of the study demonstrated higher efficacy with UFT in patients with adenocarcinoma histology compared to patients with squamous cell carcinoma. Subsequently Kato et al. (2003) con-

ducted a randomized study for patients with resected stage I adenocarcinoma. Patients (n=979) were randomized to observation versus UFT (250 mg daily for 2 years). Approximately 50% of the patients completed the prescribed 2-year course of treatment. The 5-year survival rate favored the UFT arm (87.9% for UFT arm vs 85.4% for observation arm, p=0.035). The absolute improvement in survival was 10% higher for patients with stage T2N0, where as the benefit was not present for patients with T1N0 stage.

The Adjuvant Lung Project Italy (ALPI) study evaluated the role of adjuvant chemotherapy (mitomycin, vindesine and cisplatin) for patients with resected stages I, II and IIIA NSCLC (Scagliotti et al. 2003). Patients were randomized to observation alone or treatment with three cycles of systemic chemotherapy (n=1209). Postoperative radiotherapy (50–54 Gy) was administered at the discretion of the participating center. The median overall survival was 55.2 months and 48 months for the chemotherapy arm and control arm, respectively. However, this difference was not statistically significant. The progression-free survival, which also favored the chemotherapy arm, did not reach a level of statistical significance. Only 69% of the patients assigned to chemotherapy completed the three cycles of planned treatment. This could in part have been due to excessive toxicity from the use of a three-drug chemotherapy combination. The International Adjuvant Lung Trial (IALT) evaluated a platinum-based two-drug combination as adjuvant therapy for resected NSCLC (LeChevalier 2003). Patients (n=1867) with stages I, II, and IIIA NSCLC were randomized to three to four cycles of chemotherapy or observation following surgical resection. Cisplatin was administered in combination with one of the following four drugs: etoposide, vinorelbine, vinblastine, or vindesine. Approximately 30% of patients in both experimental and control arms received adjuvant radiotherapy. Treatment was tolerated well overall with grade 4 toxicities being reported in approximately 23% of the patients (neutropenia, 17%; thrombocytopenia, 3%; vomiting, 3%). With a median follow up of 56 months, the 5-year survival was superior (44.5% vs 40.4%, p<0.03) for patients in the chemotherapy arm. Approximately 74% of the patients in the chemotherapy arm received a cumulative dose of cisplatin of $\geq$240 mg/m^2. The IALT is the first randomized study to demonstrate survival advantage with postoperative cisplatin-based chemotherapy for patients with resected NSCLC. While the survival advantage noted in this study is relatively modest, it provides the foundation on which further improvements can be made. The use of third generation chemotherapeutic agents in combination with platinum may result in improved treatment tolerance and a greater ability to deliver the planned doses of chemotherapy in the postoperative setting.

Another approach to eradication of micro-metastatic disease involves the use of pre-operative chemotherapy for patients with resectable NSCLC. Two randomized clinical trials demonstrated survival advantage with pre-operative chemotherapy for patients with stages IIIA NSCLC (Roth et al. 1994; Rosell et al. 1994). Both studies included approximately 60 patients and were closed prematurely based on the superior survival noted with pre-operative chemotherapy. The French Thoracic Oncology Group conducted a randomized study of pre-operative chemotherapy for patients with stages I, II, and IIIA NSCLC. Patients were randomized to therapy with two cycles of chemotherapy (mitomycin, ifosfamide and cisplatin) followed by surgery versus surgical resection alone (Depierre et al. 2002). The response rate to chemotherapy was 64%. The median survival for the pre-operative chemotherapy and surgery alone arms were 37 months and 26 months respectively (p=0.15). A multivariate analysis demonstrated that the benefit from pre-operative chemotherapy was restricted to patients with a nodal status of N0 or N1 (relative risk 0.68, p=0.027). There was a significant reduction in distant recurrence of cancer in patients treated with pre-operative chemotherapy.

Benefit with pre-operative chemotherapy has also been noted in a phase II study conducted in the US. The Bimodality Lung Oncology Team (BLOT) conducted a study for patients (n=134) with stages I, II, and IIIA (N2 negative) NSCLC (Pisters et al. 2000). Patients received a total of five cycles of carboplatin and paclitaxel peri-operatively, with at least two cycles delivered in the pre-operative period. The response rate to chemotherapy was approximately 56% and 94% of the patients underwent planned surgery. There was no evidence of excessive operative mortality attributable to administration of pre-operative chemotherapy. The 5-year survival rate was 46% for the 94 patients who received two cycles of pre-operative chemotherapy. Based on the results of this study, a randomized clinical trial is being conducted by the SouthWest Oncology Group (SWOG 9900). Patients with stages I, II, and IIIA (N2 negative) will receive three cycles of chemotherapy with carboplatin and paclitaxel followed by surgery or undergo surgical resection alone. The results of this ongoing study will hopefully provide definitive answers regarding the role of pre-operative chemotherapy in the treatment of early stage NSCLC.

The results of the studies with pre-operative chemotherapy have demonstrated the following: (1) improved ability to deliver planned doses of chemotherapeutic agents in the pre-operative setting; (2) tumor and nodal downstaging can be achieved; (3) pre-operative chemotherapy provides an in vivo assessment of the effects of chemotherapeutic agents; (4) identification of patients with rapidly progressive disease, who may not benefit from aggressive surgery.

Systemic chemotherapy should be considered for patients with early stage NSCLC based on the results of the studies mentioned above. Research efforts should focus on development of predictive methods to identify patients at risk of relapse following surgery. Improvements are also necessary to enhance the efficacy of systemic therapy in the peri-operative setting. This includes the evaluation of novel chemotherapeutic agents and molecularly targeted approaches. Comparative studies to evaluate the differences between preoperative and postoperative chemotherapy are also warranted.

2.3.2.13 Treatment of NSCLC: Conclusions

Systemic chemotherapy improves both survival and quality of life for NSCLC patients with a good performance status. The benefits from chemotherapy also extend to fit elderly patients. Though several novel chemotherapeutic agents have become available in recent years, it appears that a chemotherapy efficacy-plateau has been reached. For patients with locally advanced unresectable disease, chemotherapy has been successfully integrated with radiation therapy resulting in improved outcome. Management of early NSCLC calls for a multi-disciplinary approach and incorporation of systemic therapy in the treatment of all stages of this disease. Development of molecularly targeted agents and methods to incorporate them into existing treatment paradigms represents the next major advance and challenge for the treatment of NSCLC.

2.3.3 Small Cell Lung Cancer

Small cell lung cancer (SCLC) accounts for approximately 15%–20% of all lung cancers (Osterlind et al. 1983). As is the case with non-small cell lung cancer, the majority of patients with SCLC present with extensive stage disease at the time of diagnosis (Aisner 1996). SCLC follows an aggressive course with median survival of approximately 6 weeks for patients with untreated extensive stage SCLC (SCLC-ED). The role for chemotherapy was identified in the 1970s when responses were noted with chemotherapeutic agents such as cyclophosphamide, methotrexate, vincristine, and procarbazine. A few small randomized trials compared chemotherapy with placebo for patients SCLC-ED (Agra et al. 2003). In one study, patients were treated with either ifosfamide or placebo. In the second study, the three treatment arms were placebo, ifosfamide alone, and ifosfamide in combination with CCNU. Both studies documented improvement in survival with chemotherapy. Another study compared treatment with cyclophosphamide versus placebo for SCLC (Green et al. 1969). This study demonstrated a doubling of the median survival for patients treated with cyclophosphamide. Such observations led to the evaluation of combination chemotherapy regimens for the treatment of SCLC. Initial trials evaluated cyclophosphamide-based combination regimens (Hong et al. 1989; Messeih et al. 1987). The emergence of the platinum compounds led to the development of platinum-based combinations that were studied in several randomized trials in the 1980s. Combination chemotherapy results in response rates of 60%–80%, and a median survival of 8–10 months (Hanna and Einhorn 2002). The following section will focus on the treatment of SCLC-ED. Detailed discussion on incorporating local therapy with systemic treatment for SCLC-ED will be discussed in subsequent chapters.

2.3.3.1 Platinum-Based Combinations

The combination of cisplatin and etoposide was chosen for evaluation based on reports of pre-clinical synergy between the two drugs (Schabel et al. 1979). In addition, studies with cyclophosphamide-based regimens performed earlier had demonstrated improved response rates when etoposide was added to the combination (Messeih et al. 1987). Phase II studies that evaluated the combination of cisplatin and etoposide demonstrated response rates of >80% for patients with SCLC-ED (Boni et al. 1989; Evans et al. 1985). Hence the combination of cisplatin and etoposide was evaluated extensively in randomized clinical trials (Table 2.3.7). Fukuoka and colleagues (1991) conducted a randomized study that compared the

Table 2.3.7. Chemotherapy for SCLC-ED

Author (number of patients)	Regimen	Response rate	Median survival (months)
Fukuoka[a] et al. (1991) (300)	CAV	55%	9.9
	EP	78%	9.9
	CAV/EP	76%	11.8
Roth et al. (1992) (437)	CAV	51%	8.3
	EP	61%	8.6
	CAV/EP	59%	8.1
Noda et al. (2002) (154)	EP	68%	9.4
	IP	84%	12.8
Skarlos[a] et al. (1994) (147)	EP	50%[b]	12.5
	ECb	64%[b]	11.8

EP, etoposide/cisplatin; CAV, cyclophosphamide/adriamycin/vincristine; ECb, etoposide/carboplatin; EP, irinotecan/cisplatin.
[a] Study included patients with SCLC-ED and SCLC-LD.
[b] Response rate in SCLC-ED.

combination of cisplatin and etoposide (EP) to cyclophosphamide, adriamycin and vincristine (CAV). A third arm in this study included alternating courses of CAV and EP. Treatment cycles were repeated every 3–4 weeks. The response rates were superior for the two treatment arms that included EP (78%, 76% vs 55%). The median survival for the CAV, EP and CAV/EP arms was 8.7, 8.3, and 9 months, respectively, for patients with SCLC-ED. The toxicity profiles were comparable between the three arms with no significant differences. Roth and colleagues (1992) conducted a study of similar design for patients with ED-SCLC. The three treatment arms of the study were EP, CAV, or alternating cycles of CAV and EP. The response rates for patients in this study were 61%, 51%, and 59% for EP, CAV and CAV/EP respectively. The median survival was 8.6 months, 8.3 months, and 8.1 months, respectively, for the three arms. In both of these studies, patients who failed to respond to initial CAV chemotherapy demonstrated modest responses when they crossed over to treatment with EP. There was a trend towards more favorable hematological toxicity profile for patients with EP in both studies. The higher response rates and the favorable hematological toxicity profile were the important factors that led to the adoption of EP as the commonly used regimen for SCLC-ED.

Recently, the Japanese Cooperative Oncology Group conducted a randomized clinical trial to compare the efficacy of cisplatin and irinotecan (IP) with EP for patients with SCLC-ED (Noda et al. 2002). Patients with SCLC-ED were randomized to treatment with IP (irinotecan 60 mg/m^2 on days 1, 8, and 15; cisplatin 60 mg/m^2 on days 1; cycles repeated every 4 weeks) or EP (etoposide 100 mg/m^2 on days 1, 2, and 3; cisplatin 80 mg/m^2, day 1; cycles repeated every 3 weeks). The study was closed early as a statistically significant improvement in survival for patients in the IP arm was noted during an interim analysis. The median survival for patients in the IP and EP arms were 12.8 months and 9.4 months, respectively (p=0.002). The 2-year survival rate for the two arms were 19% and 5%, respectively. Diarrhea was the principal toxicity associated with the IP regimen. The provocative results of this study led to a confirmatory trial in the US to test the efficacy of the IP regimen for SCLC-ED that is currently underway. Another study that compared a slightly modified regimen of IP (Irinotecan 65 mg/m^2 on days 1 and 8; cisplatin 30 mg/m^2 on days 1 and 8; cycles repeated every 3 weeks) with EP for SCLC-ED has completed accrual and the results are awaited. It is possible that IP will replace EP as the new standard of care for SCLC-ED.

2.3.3.2 Cisplatin Versus Carboplatin

The favorable non-hematological toxicity profile associated with the use of carboplatin in comparison with cisplatin led to the evaluation of the carboplatin-etoposide (ECb) combination for the treatment of SCLC-ED. Phase II studies that evaluated ECb demonstrated response rates of 50%–85% for patients with untreated SCLC-ED (Ellis et al. 1995; Katakami et al. 1996; Pfeiffer et al. 1995). Based on the encouraging efficacy of ECb regimen, the Hellenic Cooperative Oncology Group conducted a randomized clinical trial to compare EP with ECb for patients with untreated SCLC (Skarlos et al. 1994). This small study included 30 and 31 patients with SCLC-ED on the two treatment arms, respectively. No significant differences were noted in response rate or median survival for patients with SCLC-ED in the two arms. However, leukopenia, neutropenic infections, nausea, vomiting and neurotoxicity were more frequent and/or severe in the EP group. No other randomized trial has compared the efficacy of EP with ECb. Another randomized clinical trial compared the combination of teniposide and vincristine with either cisplatin or carboplatin (Lassen et al. 1996). The study noted no significant differences between the cisplatin-based and carboplatin-based regimens in efficacy. Thus, the favorable toxicity profile of ECb makes this an acceptable first-line regimen for patients with SCLC-ED in whom palliation is the primary goal. The ECb

regimen is also well suited for elderly patients with SCLC-ED (Byrne and Carney 1994). However, for patients with limited stage SCLC in whom treatment is administered with a curative intent, EP still remains the standard regimen.

2.3.3.3 Dose-Intensive Chemotherapy

Randomized clinical trials have evaluated dose-intense chemotherapy regimens to improve the efficacy of combination chemotherapy for the treatment of SCLC-ED (Ihde et al. 1994; Pujol et al. 1997; Johnson et al. 1987). Johnson and colleagues (1987) compared treatment with conventional doses of CAV with a dose-intense regimen of CAV. After the first three cycles of therapy, all patients received standard doses of CAV. Though the occurrence of complete responses were more frequent in the high dose arm (22% vs 12%), the overall response rate and median survival were comparable between the two arms. However, the incidence of life-threatening neutropenia and infections were significantly higher in the high dose chemotherapy arm. Murray and colleagues (1999) conducted a study for patients with SCLC-ED to increase overall relative dose-intensity by delivering four drugs at standard intensity rather than increasing the delivery of two or three drugs within a combination above standard intensity. Patients were randomized to treatment with cisplatin, vincristine, doxorubicin, and etoposide (CODE) or alternating cycles of CAV and EP. Though the response rate was higher with CODE (87% vs 70%, P=0.006), the overall survival was similar between the two arms. The incidence of deaths during chemotherapy was higher with CODE (8.2% vs 0.9%). Furuse and colleagues (1998) administered CODE with growth factor support for patients with SCLD-ED in another randomized trial. Patients in the control arm received alternating cycles of CAV and EP. Overall response rates were 77% for the CAV/PE arm and 84% for the CODE arm, respectively (15% complete response in both arms). The median survival times were 10.9 months with CAV/PE and 11.6 months with CODE (p=0.1). The achieved dose-intensity for CODE was approximately twice that for CAV/PE for those drugs common to both arms. The incidence of leukopenia did not differ between the two arms, but anemia and thrombocytopenia were more frequent in the CODE arm. Four treatment-related deaths from neutropenic fever occurred in the CODE arm. Several other randomized trials have also evaluated the utility of dose-intense regimens for the treatment of SCLC-ED. From the results of these studies, it is clear that there is no enhancement of efficacy with dose-intense chemotherapy for SCLC-ED, though the toxicity is higher.

2.3.3.4 Maintenance Chemotherapy

Prolonged administration of chemotherapy has been evaluated as a strategy to maintain responses for SCLC-ED patients following response to initial chemotherapy. Randomized trials evaluated continuation of the same chemotherapeutic regimen following initial induction treatment, whereas other trials evaluated the use of a different chemotherapeutic agent(s) for maintenance therapy (Giaccone et al. 1993; Spiro et al. 1989; Lebeau et al. 1992). There was no consistent benefit with maintenance chemotherapy in a majority of these studies. The Eastern Cooperative Oncology Group recently evaluated the utility of topotecan as maintenance chemotherapy following initial treatment with EP (Schiller et al. 2001). In their study, patients with SCLC-ED were treated with four cycles of EP as induction therapy. Patients with an objective response or stable disease were randomized to observation alone versus four cycles of therapy with topotecan. A total of 213 patients were randomized to maintenance therapy. The progression-free survival was significantly better in the maintenance therapy arm (3.6 months vs 2.3 months, p<0.001). However, there was no difference in overall survival between the two arms (9.3 months vs 8.9 months, p=0.43). Therefore maintenance chemotherapy cannot be recommended for patients with SCLC-ED.

2.3.3.5 Second-Line Chemotherapy

Despite initial response to chemotherapy, nearly all patients with SCLC-ED will develop recurrent disease. Patients who develop progression at least 90 days after completion of first-line chemotherapy (sensitive relapse) are more responsive to salvage therapies compared to patients who relapsed within 90 days of initial therapy or those who did not experience objective response with initial treatment (refractory patients) (Hanna and Einhorn 2002). Phase II clinical studies have evaluated several chemotherapeutic agents as salvage treatment of recurrent SCLC (Einhorn et al. 1990; Masuda et al. 1992; Ardizzoni

et al. 1997). The drugs that have been evaluated in this setting include etoposide, topotecan, gemcitabine, paclitaxel, docetaxel, and vinorelbine (Kelly 2001; Shihabi and Belani 2001; Chiappori and Rocha-Lima 2003; Thatcher et al. 2003). Topotecan is approved for second-line treatment of SCLC in the US. The efficacy of topotecan was studied by a phase III clinical trial that randomized patients with recurrent, but sensitive SCLC to treatment with topotecan or CAV (von Pawel et al. 1999). Patients who had relapsed after at least 60 days of initial chemotherapy were eligible for the study. The response rate for patients in the topotecan and CAV arms were 24% and 18%, respectively (p=0.285) Median times to progression and survival were similar for patients in both the groups. However, the proportion of patients who experienced symptom improvement was greater in the topotecan group than in the CAV group for four of eight symptoms evaluated, including dyspnea, anorexia, hoarseness, and fatigue, as well as interference with daily activity (p<0.043). The improvement in symptoms noted with topotecan for patients with relapsed SCLC was the principal reason behind its approval for second-line treatment.

2.3.3.6 Future Directions in SCLC Therapy

Treatment of SCLC remains a major challenge despite the remarkable initial efficacy of chemotherapy. Various strategies such as dose-intense regimens, dose-dense therapy, maintenance therapy, alternating chemotherapy and newer, more aggressive combination regimens have all failed to improve the outcome for SCLC-ED. Imatinib, an inhibitor of the C-Kit tyrosine kinase enzyme was evaluated in a phase II clinical trial for patients with SCLC-ED (Johnson et al. 2003) based on the rationale that C-Kit is expressed in approximately 70% of SCLC tumors. However, no objective responses were noted for the 19 patients who were enrolled to the study. A recent study that evaluated G3139, an antisense oligonucleotide against the BCL-2, demonstrated encouraging activity in combination with chemotherapy for patients with SCLC (Rudin et al. 2003). Other targeted approaches that are under evaluation for the treatment of SCLC include anti-angiogenic agents, proteasome inhibition, inhibitors of the mTOR (mammalian target for rapamycin) pathway and vaccines (Bunn et al. 2003). With continued evaluation of novel strategies and efforts to enroll patients in clinical trials, hopefully the treatment of SCLC will move to the next level.

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2.4 Radiotherapy and Chemotherapy

Fundamentals and Pre-clinical Data

A. William Blackstock and Kevin P. McMullen

CONTENTS

2.4.1 Introduction

Beginning with the original work of McGrath and Williams (1966), we have known ionizing radiation produces a myriad of lesions in the deoxyribonucleic acid (DNA). Considerable evidence indicates that ionization energy deposited in the nucleus results in DNA double strand breaks (DSBs) and clusters of damaged bases (Ward 1994), both of which are probably the most important lesions in the cell responsible for cell lethality resulting from chromosomal aberrations. With the chromosomal aberrations comes the loss of genetic material after the cells divide and mitotic-linked cell death. The serious investigation of chemotherapy for malignancy started with the observation of unusual reactions in soldiers exposed to chemicals used in World War II. Among the unexpected results from this observation was the development of the highly toxic, but therapeutically useful, mustard gas derivative, nitrogen mustard [methyl bis(betachloroethyl) amine]. This compound was the first modern anti-tumor drug to regularly produce responses in malignant diseases in humans. Since that time a plethora of drugs with a variety of mechanisms of action to disrupt cellular function have been developed and investigated.

There are three major approaches to sequencing radiation and chemotherapy in the treatment of lung cancer: (a) sequential, in which one modality is completed prior to the start of the other; (b) concurrent, where radiation and chemotherapy are given on the same days, and (c) alternating, in which courses of radiation and chemotherapy are alternated so that administration of the two modalities is completed over the same overall time period without their concurrent administration. Recent studies have attempted to combine agents sequentially and concurrently, whether it is induction chemotherapy followed by concurrent chemo-radiation or chemo-radiation followed by consolidative/maintenance chemotherapy. This chapter will focus on a review of the fundamentals of combined modality therapy with an emphasis on concurrent chemo-radiation. It will attempt to discuss the rationale along with the inherent difficulties of achieving a therapeutic benefit when combining a local modality (radiation) and a systemic therapy (chemotherapy) concurrently. While the initial attempts to combine traditional cytotoxic chemotherapy with radiation were rather empirical, we will illustrate the importance of understanding the mechanism of the interaction as we develop future chemo-radiation strategies. This work will highlight the progress made in our pre-clinical understanding of the often complex interactions between ionizing radiation and chemotherapy and the need for continued investigations and understandings from the laboratory. And finally, a discussion of how we are integrating recently developed compounds against specific cellular targets (targeted therapies) with

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traditionally cytotoxic agents in to our current and evolving – combined modality treatment regimens.

2.4.2 Basic Principles of Chemoradiation

When radiation and chemotherapy are administered together, one essential element of this strategy is to achieve a therapeutic gain (Fig. 2.4.1). Regardless of whether the radiation is enhancing the effects of the chemotherapy or vice versa, one hopes to see the tumor control curve move to the left while not affecting the normal tissue complication curve. This would then result in a differential effect between tumor and normal tissue; an increase in the tumor control probability without an unacceptable increase in normal tissue damage.

Expanding on this concept are the theoretical types of interaction between radiation and chemotherapy postulated by Steel and Peckam. "Spatial cooperation" in this discussion proposes the delivery of optimal radiation and optimal systemic chemotherapy, with an assumption that there is no interaction between the two modalities. Most chemotherapeutic agents active in lung cancer, however, tend to interact with radiation, making spatial cooperation often difficult to achieve. "Toxicity independence" allows for administration of both treatment modalities at the maximally tolerated dose not compromised by dose reductions necessitated by increased toxicity. Given that radiation and a number of chemotherapeutic agents possess overlapping toxicities, this concept is also difficult to apply in lung cancer. "Protection of normal tissues" postulates that an agent would protect normal tissues (and not the tumor) from the effects of radiotherapy or chemotherapy, resulting in an ability to deliver higher doses of radiotherapy or administer more aggressive chemotherapy regimens. With a few limited exceptions (Amifostine), establishing this concept in our management of lung cancer has been unsuccessful. While growth factors are not protecting in nature, but stimulate the bone marrow, the expanded use of growth factors in lung cancer has been successful in allowing more aggressive chemotherapeutic regimens to be studied in conjunction with radiation. And finally and most related to this review, a "direct interaction" between radiation and chemotherapy within the radiation field will increase the local efficacy of the treatment. This enhancement of the effect or response may be additive, infra-additive, or supra-additive (synergistic). Table 2.4.1 outlines the definitions for these possible interactions and provides examples. In terms of a quantitative assessment of these effects, the isobologram, introduced by Loewe (1953, 1957) and later utilized and described by Gessner and Cabana (1970) has been employed to demonstrate among combinations of agents tested in different fixed ratios, some were additive, some were subadditive, and others were superadditive (Fig. 2.4.2). The isobologram, when accompanied by an appropriate statistical analysis, is the method most clearly tied to the classical definition of additivity and has been described as the "gold standard" for evaluating drug–drug (Tallarida et al. 1989) or drug–radiation interactions.

A subset of a supra-additive effect would include "sensitization" or "potentiation," meaning when two agents are combined with one having no effect other

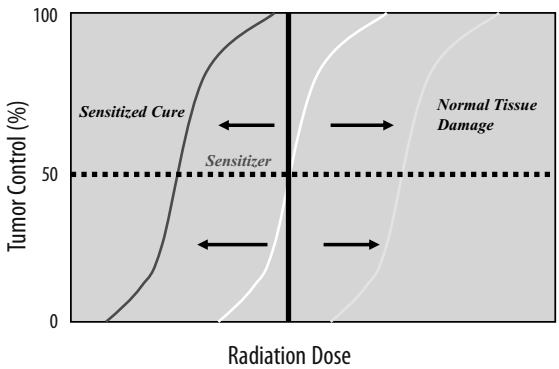

Fig 2.4.1. Adapted from a concept from Ged Adams/Elaine Zeman

Table 2.4.1.

Synergistic or superadditive	The effect of two independent agents results in a greater effect than each agent individually, or the sum of the individual effects. The presence of one therapy en-hances the effects of the second	2 + 1 = 4
Additive	The effect is one in which the effect of two independent agents is the sum of the effects that they would have if acting alone	2 + 1 = 3
Subadditive	The effect of two independent agents results in a lesser effect than each agent individually, or the sum of the individual effects. The presence of one therapy diminishes the effects of the second	2 + 1 = 2.5

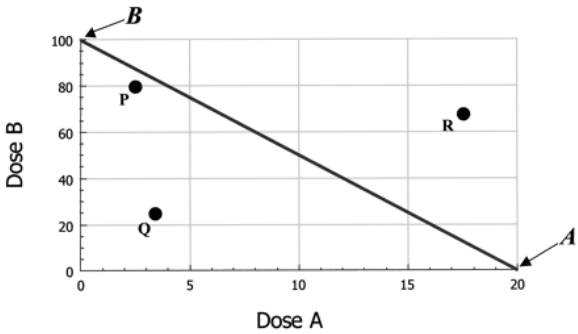

Fig 2.4.2. Isobologram (illustration) for some particular effect (e.g., 50% of the maximum) in which the dose of drug A alone is $A = 20$ and drug B alone is $B = 100$. The *straight line* connecting these intercept points (additivity line) is the locus of all dose pairs that, based on these potencies, should give the same effect. An actual dose pair such as point Q attains this effect with lesser quantities and is superadditive (synergistic), while the dose pair denoted by point R means greater quantities are required and is therefore subadditive. A point such as P that appears below the line would probably be simply additive. A suitable statistical analysis is required to demonstrate the nature of the interaction. From Tallarida (2001)

than to increase the effect of the other. One of the best examples of an attempt to exploit differences between normal organ physiology and tumor physiology is the existence of tumor hypoxia, to be discussed later, and the acceptance that hypoxic tumor cells are more resistant to DNA damage by ionizing radiation than are oxic cells (Hall 1988). This has led to the development of hypoxic cell sensitizers and cytotoxins such as Tirapazamine, a bioreductive drug that exhibits greatly enhanced cytotoxicity in hypoxic tumor cells and RSR-13, (2-[4-[2-[(3,5-dimethylphenyl)amino]-2-oxoethyl]phenoxy]-2-methylpropanoic acid monosodium salt), a compound that allosterically modifies hemoglobin to increase tumor pO(2).

2.4.3 Biologic Interactions – Cell Cycle Effects

When combining radiation and conventional chemotherapy, optimizing the interaction between the agents is critical for the desired effect. Terasima and Tolmach (1963) showed for the first time that there is a very large variation in radiosensitivity during the cell cycle. The organization of the growth and division phases of cells in a population, so that all cells divide at the same time, refers to cell synchronization. The synchronization of tumor cells may subsequently increase the efficacy of one specific agent by placing cells into either a chemotherapy sensitive or radiation sensitive portion of the cell cycle.

There are a variety of anti-chemotherapeutic agents used in the treatment of lung cancer that likely interact with radiation through cell cycle perturbations. The taxanes act by stabilizing microtubules, thereby causing a G2-M cell cycle arrest. Unlike other known mitotic spindle inhibitors (Vinca alkaloids, colchicine, and podophyllotoxin) that inhibit tubulin polymerization, taxanes markedly enhance microtubule assembly and disrupt the transition of a cell through mitosis. Two well established agents used in the treatment of lung cancer today include paclitaxel and docetaxel. Both chemotherapeutic agents have been studied as radiosensitizers because of the arrest of cells at G2-M, which is a particularly radiation sensitive phase of the cell cycle (Choy et al. 1993; Geard et al. 1993) Vinorelbine a semisynthetic vinca alkaloid that binds to tubulin and is a potent inhibitor of mitotic microtubule polymerization has also been shown to possess radiation sensitizing properties in a NSCLC cell line (Edelstein et al. 1996). Like the taxanes, the mechanism is at least in part, through the Vinorelbine-induced block at the G2/M point of the cell cycle (Zhang et al. 2004).

While it is clear that Gemcitabine has significant radiation sensitizing properties, the importance of cell cycle effects to this end has been inconsistent (Tolis et al. 1999; Bandala et al. 2001; Cappella et al. 2001). Merlin et al. (1998) observed that low concentrations (IC50 values) of gemcitabine caused an arrest in early S phase of the cell cycle. In contrast, higher concentrations of gemcitabine caused an arrest in the G1 phase of the cell cycle. Pauwels et al. (2003) observed a clear S-phase block, and increasing concentrations of gemcitabine resulted in a shift of this arrest to early S phase and finally a blockade of cells at the G1/S border.

DNA damaging agents such as cisplatin and carboplatin have also been shown to perturb cell cycle progression at either G_1, S, or G_2 phase, although the G_1 arrest is only seen in cells expressing the wild-type p53 tumor suppressor protein. The significance of cell cycle arrest/cell synchronization and radiation sensitization with platinum compounds is likely less important than other mechanisms to be discussed.

Perhaps less well studied, but equally important, are the chemo-sensitizing effects of ionizing radiation as it relates to the cell cycle. When cells are exposed to ionizing radiation, they initiate a complex response that includes the arrest of cell cycle progression in G1 and G2 (Maity et al. 1994). As reported by Giocanti et al. (1993) cells arrested in G2 following

radiation proved hypersensitive to the cytotoxic effects of Etoposide, an agent important in the treatment of NSCLC and SCLC.

2.4.4 Biologic Interactions – DNA Damage and Repair

During the past 75 years, concepts of radiation damage to cells have evolved from target theory (Blau and Altenburger 1922; Dessauer 1922; Lea 1955) to indirect action from free radicals, and then to a modified target theory that includes both ionization clusters directly in critical targets (DNA double strand breaks) within the cell. The rejoining kinetics for radiation-induced total DNA strand breaks varies among mammalian cell lines, but can occur over the course of minutes to hours. The phenomenon of "split-dose recovery" relative to cell killing, later attributed to sublethal damage repair, was first described in 1957 (Jacobson 1957). While the molecular basis for sublethal damage repair is still not fully understood, it refers to a kind of damage that was not initially lethal by itself (first insult), but was present and could interact with a second additional insult such that together, the damage becomes lethal. If a significant time interval (several hours), is allowed to elapse before the second insult, survival increases because the cells are able to repair themselves during this period of quiescence.

Carboplatin and cisplatin, drugs active in lung cancer, have both been shown to interact in this fashion with radiation. As reported by Dolling, cells treated with cisplatin prior to radiation experienced a subsequent inhibition of DNA double strand break rejoining (repair) (Dolling et al. 1998). The authors suggest this phenomenon may indicate cisplatin-radiation induced double strand breaks may be more difficult to process because the excision repair machinery processing the cisplatin adduct may block access of double strand break repair proteins to the nascent double strand break. What is clear, platinum appears to reduce the sparing effect of split-dose radiation exposures and inhibits the repair of potentially lethal damage (Amorino et al. 2000).

Our group and others previously explored the use of gemcitabine, a nucleoside analog, either alone or in combination with radiation (Shewach and Lawrence 1996; Lawrence et al. 1997, 1999, 2001; Blackstock et al. 2001). The rationale for such studies was the observation that nucleoside analogs, as inhibitors of DNA replication and DNA chain termination (Tseng et al. 1982; Huang et al. 1990; Yang et al. 1992; Catapano et al. 1993) would poison DNA repair in radioresistant tumor cells. Studies from Huang et al. have demonstrated that gemcitabine effectively inhibits chromosome repair after irradiation, thus increasing the frequency of residual chromosome breaks (Huang and Hittelman 1995).

CPT-11 is a semi-synthesized derivative of camptothecin that is active both in NSCLC and SCLC and is under investigation in conjunction with thoracic radiation. SN-38 is the active metabolite of CPT-11, and plays a key role in the action of the pro-drug. Omura et al. (1997) have investigated the role of potential lethal damage repair in spheroids treated with SN-38. Spheroids were incubated in conditioned medium in the absence and presence of SN-38 after irradiation. The survival of spheroids exposed to radiation increased 2.5-fold during the 24-h incubation but decreased in the presence of SN-38. Suggesting to the investigators that SN-38 not only inhibits potential lethal damage repair, but also fixes the potential lethal damage when the culture conditions are favorable for repair.

While the reports are more limited, radiation has been shown to augment the activity of a variety of platinum analogs. Yang et al. (1995) has shown that intracellular carboplatin concentrations increased linearly with radiation dose under both hypoxic and oxic irradiation conditions and that irradiation significantly increased the binding of carboplatin to double strand DNA under hypoxic conditions (Yang et al. 1995). Data from Richmond and Mahtani (1991) would suggest the chemosensitizing interaction between cisplatin and radiation is at least, in part, mediated through enhanced formation of toxic platinum intermediates in the presence of radiation induced free-radicals.

2.4.5 Biologic Interactions – Apoptosis

In addition to the type of cell killing referred to prior as "mitotic-linked" death that can be delayed and is caused principally by chromosome fragment loss, there has been an intense interest over the past decade in the process known as apoptosis and in the extent to which the induction of this important process is relevant for ionizing radiation-induced cell

death (Kerr et al. 1972; Dewey et al. 1995). Evidence has been presented that radiation-induced apoptosis can occur through p53-dependent and independent mechanisms (Strasser et al. 1994) from damage in either the nucleus or the cytoplasm/membrane (Guo et al. 1997; Haimovitz-Friedman 1998). This damage results in cells undergoing apoptosis during interphase either without attempting division, or several hours after they have divided one or more times or during an aberrant mitosis (Vidair et al. 1996; Forrester et al. 1999; Endlich et al. 2000). From the viewpoint of radiation oncology, alterations in radiation-induced apoptosis must be evaluated quantitatively in terms of concomitant alterations in reproductive cell death.

The importance of apoptosis in radiation-chemotherapy interactions has also been studied but is less clear. Flavopiridol, a cyclin-dependent kinase inhibitor currently under development by the National Cancer Institute, significantly enhanced the induction of apoptosis by irradiation in both the human colon HCT-116 cell line and the MKN-74 gastric cell line as measured by quantitative fluorescent microscopy, caspase-3 activation, poly(ADP-ribose) polymerase cleavage, and cytochrome C release (Jung et al. 2003). Dey et al. (2003) also observed that low-dose fractionated radiation (<1 Gy) used in combination with Paclitaxel, overcame the anti-apoptotic effects of BCL-2 and nuclear factor kappa B. In contrast, Chen et al. (2000) compared the cytotoxic and radiosensitizing effects of gemcitabine in colon cancer cells which differed in their p53 status. In terms of the effect of dFdCyd on radiation sensitivity, the investigators found that both minimally cytotoxic concentrations dFdCyd failed to radiosensitize either RKO-P cells containing wild-type p53 and in RKO-E6 cells possessing a disruption of p53 function, whereas at cytotoxic concentrations equal sensitization was produced. These results do not support an important role for p53 in apoptosis mediated radiosensitization with gemcitabine.

2.4.6 Biologic Interactions – Tumor Hypoxia

Tissue hypoxia results from an inadequate supply of oxygen (O2) that compromises biologic functions. Hypoxia in tumors is primarily a pathophysiologic consequence of structurally and functionally disturbed microcirculation and the deterioration of diffusion conditions. Tumor hypoxia appears to be strongly associated with tumor propagation, malignant progression, and resistance to therapy, and it has thus become a central issue in tumor physiology and cancer treatment (Hockel and Vaupel 2001). Although it had been appreciated for several years that lowering the oxygenation of tissues made them more resistant to damage by ionizing radiation (Crabtree and Cramer 1933), it was the pioneering studies of Gray and colleagues (1953) soon after World War II that established the universality of the radiation resistance conferred by hypoxia as well as providing early insight into the mechanism of action. The difference in radiation sensitivity between the aerobic and hypoxic cells, which is known as the oxygen enhancement ratio and is defined as the ratio of doses to produce the same level of cell kill under hypoxic to aerobic conditions, is normally in the range 2.5–3 for mammalian cells. The reason for the universality of this effect is that oxygen reacts chemically with the fundamental biological lesion produced by ionizing radiation, a radical in DNA. Oxygen, being the most electron-affinic molecule in the cell, reacts extremely rapidly with the free electron of the free radical, thereby "fixing" the damage. In the absence of oxygen, much of the radical damage can be restored to its undamaged form by hydrogen donation from nonprotein sulfhydryls in the cells. For a more expanded discussion, see recent reviews by Hockel and Vaupel (2001) and Brown (1999).

While hypoxic cells in vitro are resistant to ionizing radiation, this is not universally true for conventional chemotherapy (Tannock and Guttman 1981; Teicher et al. 1990). Exceptions are bleomycin and neocarzinostatin, which, like radiation, are more toxic toward oxygenated cells, and bioreductive drugs that are more toxic toward hypoxic cells. As observed in a variety of solid tumor models, a number of factors associated either directly or indirectly with tumor hypoxia contribute to resistance to chemotherapy. Hypoxia (and associated deficiencies in nutrients) causes cells to stop or slow their rate of progression through the cell cycle (Pallavicini et al. 1979; Amellem and Pettersen 1991). This effect is not the result of a generalized decrease in ATP or energy status of the cell but is likely to be caused by specific proteins induced under hypoxic conditions (Sciandra et al. 1984; Heacock and Sutherland 1986; Price and Calderwood 1992; Graeber et al. 1994). Most chemotherapeutic agents are more effective against rapidly proliferating cells than slowly or nonproliferating cells, this slowing of cell proliferation with increasing distance from the vasculature likely leads to decreased cell killing at these increased

distances. Second, the concentration of anticancer drugs will be higher closer to blood vessels than further away. This is a consequence not only of the geometry, in which the drug being provided by a central vessel has to diffuse out over a much greater volume at the periphery of the cord, but also of the fact that many chemotherapeutic agents, because of their reactivity, will be limited in their diffusion from the blood vessel. This is particularly true for agents that physically bind to DNA, such as intercalators (Kerr and Kaye 1987; Durand 1989).

There are a number of related ways in which hypoxia might contribute to drug resistance: amplification of genes conferring drug resistance (Rice et al. 1986), induction of various hypoxic stress proteins that appear to be responsible for resistance to etoposide (Hughes et al. 1989) and cisplatin (Murphy et al. 1994).

There are additional compelling evidence for the importance of oxygenation and chemotherapy activity. Teicher et al. (1997) have investigated whether the administration of PEG-hemoglobin could enhance the efficacy of a variety of chemotherapeutic agents in a solid tumor model. The investigators were able to demonstrate that the administration of PEG-hemoglobin was effective in decreasing hypoxia in the 13762 mammary carcinoma and further, that PEG-hemoglobin given prior to each dose of chemotherapy increased the tumor growth delay produced by the panel of agents, including paclitaxel. In related studies, Kovacs et al. (1999) evaluated tirapazamine, an agent that is activated specifically at the low oxygen levels and exhibits preferential cytotoxicity towards hypoxic cells in combination with cisplatin. Combining the compounds under hypoxic conditions resulted in an increase in cisplatin-induced DNA interstrand cross-links with kinetics suggesting tirapazamine inhibited or delayed the repair of the DNA cross-links. The investigators postulate the mechanism may be through a potentiation of cisplatin-induced DNA interstrand cross-linking.

Viewed in its whole, the combination of conventional cytotoxics with radiation clearly represents a very complex process that involves a multitude of interactions.

2.4.7 Important Clinical Translational Principles

Almost by definition, the goals of a phase I chemoradiation trial in lung cancer are to identify the toxicities associated with combining thoracic radiation with a particular chemotherapeutic/targeted agent, and to define a safe regimen for phase II testing. In the context of a phase I trial investigating a concurrent chemotherapy and radiation strategy, the recommended phase II regimen is defined as the doses and schedules of both the systemic therapy and local radiation therapy. This recommended phase II dose is not necessarily equivalent to the maximally tolerated dose of the systemic agent alone plus a standard dose and schedule of radiation. The schedule used when the systemic agent is combined with radiation may be substantially different from that of the systemic agent by itself or when it is used with other systemic agents.

In addition, if an agent's purported mechanism of action and toxicity depend on metabolism of that agent in the hypoxic region or overexpression of a unique cellular receptor, determination of the recommended phase II dose may require that eligibility for the phase I trial be restricted to patients with appropriately hypoxic tumors or tumors that overexpress that receptor to adequately define the relevant toxicity, and further, to define early efficacy.

Radiation toxicity is incrementally cumulative over the duration of the treatment, therefore toxicity assessment for each dose level should include evaluation during the entire radiation period rather than only during the first course or cycle of combined therapy. The window of evaluation should be specifically defined, e.g., up to 30 days after completion of radiation. Subsequent cohorts generally should not be treated until that evaluation window is closed. Collection of late toxicity data should be prospectively included in the trial design, despite the fact that it is impractical to use late toxicities to define the maximum tolerated dose. Under certain circumstances, these data may provide a rationale for choosing a recommended phase II dose other than that defined by the acute maximum tolerated dose.

The definition of dose-limiting toxicities (i.e., type, grade, and duration of adverse event) for chemoradiation trials will necessarily be different than those for chemotherapy trials. Patients are not typically exposed to recurring risks in chemotherapy plus radiation trials because therapy is not cyclical; the dose-limiting toxicity is often organ- and site-confined as determined by the port of radiation, and phase I chemoradiation trials are often performed in a potentially curative, rather than palliative, setting.

2.4.8 Biologic Interactions – Molecular Targeted Therapies

As recently discussed by Lawrence et al. (1997, 1999, 2001), the discovery that cancers result from genetic changes such as the activation of an oncogene or the loss of a tumor suppressor gene has offered new opportunities for targeting. More specifically, the finding that overexpression of growth factor signal transduction pathways can drive uncontrolled tumor cell growth presents the opportunity to target specific genetic alterations that produced and support the growth of that cancer. This discovery has led to generation of antibodies and small molecules aimed at inhibiting aberrant growth factor receptor activation. It is reasonable to expect that these therapies will be selective for malignant cells compared to normal cells given that the expression of these targets is not usually increased in normal tissues. As implied from the data below, the impact of these novel therapies may be greatest in the multimodality treatment of lung cancer.

2.4.8.1 Epidermal Growth Factor Receptor

The epidermal growth factor receptor (EGFR) autocrine pathway contributes to a number of processes important to cancer development and progression, including cell proliferation, apoptosis, angiogenesis, and metastatic spread. The critical role this receptor plays in cancer has led to an extensive search for selective inhibitors of the EGFR signaling pathway. The results of a large body of preclinical studies and the early clinical trials thus far conducted suggest that targeting the EGFR could represent a significant contribution to cancer therapy. A variety of different approaches are currently being used to target the EGFR; monoclonal antibodies to prevent ligand binding and small molecule inhibitors of the tyrosine kinase enzymatic activity to inhibit autophosphorylation and downstream intracellular signaling.

Studies in lung cancer have indicated EGFR is expressed in 81% to 93% of patients; overexpression (as measured by 20% of cells staining positive for the receptor) was found in 45%–70%, and was more common in squamous cell carcinoma (57%–92%) than in non-squamous cell tumors (36%–58%) (Rusch et al. 1993; Fontanini et al. 1995; Rusch et al. 1997) Inhibition of EGFR with EGFR monoclonal antibodies or agents that inhibit tyrosine kinase, a key component of the EGFR signaling pathway, is believed to result in inhibition of cell-cycle progression, angiogenesis, DNA repair after chemotherapy or radiation, and increased apoptosis.

In addition to effects on cell proliferation and the cell cycle, EGFR activation likely influences the cell's sensitivity to ionizing radiation. The pre-clinical data for ZD 1839 as a radiation sensitizer are limited but compelling. In data recently reported by Huang et al. (2002), human squamous carcinoma cell lines exposed to ZD 1839 before radiation significantly reduced cell survival compared with control – radiation only treated cells. Williams et al. (2002) in a human colorectal tumor model observed that the tumors in animals treated with 100 mg kg ZD 1839 for 14 days combined with fractionated radiation, showed a significantly better response to treatment than those treated with radiation or drug alone. As recently reviewed by Raben et al. (2002), the data indicating ZD 1839 has significant radiation sensitizing properties continues to accumulate.

Given these compelling pre-clinical data, two representative clinical trials currently underway evaluating concurrent radiation, conventional chemotherapy and ZD 1839 are shown in Table 2.4.2 .

Table 2.4.2.

	Induction chemotherapy	Chemoradiation	Consolidative chemotherapy	Maintenance
Cancer and Leukemia Group B 30106	Paclitaxel, carboplatin q 21 days, daily Iressa	Weekly paclitaxel, weekly carboplatin, daily Iressa, 66 Gy thoracic radiation	–	Daily Iressa until progression
Wake Forest University / Research Base	–	Weekly docetaxel, daily Iressa, 70 Gy thoracic radiation	Docetaxel q 21 days, daily Iressa	Daily Iressa for 1 year or until progression
RTOG 0213	–	Daily celecoxib, 66 Gy thoracic radiation	–	–

2.4.8.2 Biologic Interactions – Vascular Endothelial Growth Factor (VEGF)

VEGF (vascular endothelial growth factor) stimulates vascular endothelial cell growth, survival, and proliferation. It plays a central role in the development of new blood vessels (angiogenesis) and the survival of immature blood vessels (vascular maintenance). Tumor expression of VEGF leads to the development and maintenance of a vascular network, which promotes tumor growth and metastasis. VEGF expression correlates with poor prognosis in many tumor types including lung cancer. VEGF exerts its effects by binding to and activating two structurally related membrane receptor tyrosine kinases, VEGF receptor-1 (VEGFR-1 or flt-1) and VEGFR-2 (flk-1 or KDR), which are expressed by endothelial cells within the blood vessel wall. VEGF also interacts with the structurally distinct receptor neuropilin-1. Strategies to inhibit VEGF have successfully controlled tumor growth, dissemination, and distant metastasis by a variety of VEGF agents such as neutralizing anti-VEGF antibodies, anti-sense VEGF, cDNA, and soluble VEGF receptors.

To evaluate the potential radiation sensitizing effects of anti-VEGF therapy, Kozin et al. (2001) treated mice bearing two different human tumor xenografts with anti-vascular endothelial growth factor receptor-2 antibody (DC101) and fractionated radiation. DC101 significantly decreased the dose of radiation necessary to control 50% of tumors locally. The decrease was 1.7- and 1.3-fold for the moderately radiosensitive small cell lung carcinoma 54A and the highly radioresistant glioblastoma multiforme U87, respectively. In conjunction with the observation, was no significant decrease of tumor oxygenation by the 1–2 doses of DC101, despite the anti-vascular effect of the antibody (Prewett et al. 1999; Hansen-Algenstaedt et al. 2000; Klement et al. 2000). As discussed in the manuscript, a comparison of these findings with those using TNP-470 suggests that different antiangiogenic agents may have different effects on tumor oxygenation (Murata et al. 1997). Thus, inhibitors of the VEGF pathway that either block VEGFR2 (as described in this study) or neutralize VEGF may be preferable to angiogenesis inhibitors such as TNP-470 in this respect (Lee et al. 2000). However, the changes in oxygenation may also depend on tumor type as well as duration and dose fractionation of both antiangiogenic and radiation treatments (Hansen-Algenstaedt et al. 2000; Lee et al. 2000). The investigators suggest that tumor cell apoptosis by DC101 could be one possible mechanism contributing to the improved tumor response seen with combined DC101 and radiation (Carmeliet and Jain 2000; Klement et al. 2000). These findings support the notion that different antiangiogenic agents should be evaluated in combination with radiation if we are to proceed with rationale strategies that are likely to be successful in future clinical trials.

2.4.8.3 Biologic Interactions – Cyclooxygenase Enzyme II (COX-II)

Cyclooxygenase (COX) is a key enzyme that catalyzes the conversion of arachidonic acid to prostaglandins and other prostanoids. Two isoforms of COX have been identified. COX-1 is expressed constitutively in a number of cell types and is involved in the homeostasis of various physiological functions, whereas COX-2 is an inducible enzyme of which the expression is regulated by a variety of factors, including cytokines, growth factors, and tumor promoters (Herschman 1991; Williams et al. 1999). Selective COX-2 inhibitors have been reported to prevent carcinogenesis and reduce the growth rate of tumor cells grown in vitro and in vivo (Elder et al. 1997; Sheng et al. 1997; Liu et al. 1998; Taketo 1998).

As reviewed and discussed by Pyo et al. (2001) the underlying mechanism responsible for the antitumor effect of COX-2 inhibitors has not been clearly defined, although several possibilities have been proposed, including regulation of angiogenesis, alteration in cell cycle progression, and inhibition of PG-induced immunosuppressive activity (Furuta et al. 1988; Milas et al. 1990, 1999; Milas 2003). In addition, induction of apoptosis is one of the most widely investigated and consistently supported potential mechanisms for the antineoplastic effect of COX-2 inhibitors.

Studies conducted at Vanderbilt to investigate the radiosensitizing effect of the selective COX-2 inhibitor, NS-398 were performed in NCI-H460 human lung cancer cells, which express COX-2 constitutively, and HCT-116 human colon cancer cells, which lack COX-2 expression (Pyo et al. 2001). NS-398 enhanced radiosensitivity in the H460 human lung cancer cells with a dose enhancement ratio of 1.8 but protected HCT-116 cells from the effects of radiation. Radiation-induced apoptosis was also enhanced by NS-398 in the H460 cells but not in the HCT-116 cells. NS-398 enhanced the effect of radiation on H460 tumors in vivo by an enhancement factor of 2.5; however, it did not

enhance the radiosensitivity of HCT-116 tumors. The group suggests these data would indicate the sensitizing effect may be attributable to enhancement of radiation-induced apoptosis and that selective COX-2 inhibitors may have potential as radiosensitizers for the treatment of human cancers. As reflected in table 2, an RTOG trial is underway evaluating celecoxib in conjunction with radiation in patients with stage III NSCLC.

2.4.9 Summary

Clearly the management of lung cancer, particular as it relates to combing radiation with conventional chemotherapy or recently developed targeted therapies, requires a understanding of the interaction in the laboratory. Mason et al. (1999), suggested from normal tissue studies performed in a mouse model, that while gemcitabine was a potent radiation sensitizer, it also potentiated the radiation effects in surrounding normal tissues. It would appear this observation is relevant to a number of clinical trials in lung cancer demonstrating increased pulmonary toxicity with the addition of gemcitabine to a course of thoracic radiation. Clearly these data should not deter the effort to continue to investigate this combination in lung cancer, but that we as investigators remain mindful of the therapeutic index, and that the strategy incorporating future novel conventional chemotherapy agents and radiation should result in an increase in efficacy with an acceptable increase in toxicity.

Data from MacRae et al. (2002) in a review of 115 patients with locally advanced NSCLC receiving concurrent paclitaxel ± carboplatin and radiation therapy, observed that a decline in hemoglobin during chemoradiation correlated with an overall worse survival. These data support the work reported by Nabid et al. (2002), in which the synthetic allosteric hemoglobin modifier RSR13, which reduces hemoglobin oxygen binding affinity and increases tumor oxygenation, was combined with a standard regimen of chemoradiation. The investigators observed an encouraging response rate of 89%, and 1- and 2-year survival rates of 67% and 40%, respectively. While strategies attempting to minimize tumor hypoxia during combined modality therapy clearly warrant further exploration, the recent reports of erythropoietin given during radiotherapy in an effort to this end, resulted in worse local control and survival, reflecting the need for a better understanding of this process and continued, well-designed clinical trials.

The recent introduction of molecularly targeted therapies into conventional chemotherapy and concurrent radiation trials in lung cancer are evolving and potentially exciting. These studies, for the most part, have been built on solid pre-clinical rationale and have incorporated the "translational" aspect of clinical trial design needed in lung cancer research. Integrating the basic principles of chemo-radiation discussed in this chapter with our better understanding of the interactions between the active agents in lung cancer will likely result in improved therapies in the near future for patients with lung cancer.

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Current Treatment Strategies in Non-Small Cell Lung Cancer

3.1 Early Stage in Non-Small Cell Lung Cancer

3.1.1 Radiotherapy in Early Stage Non-Small Cell Lung Cancer

Branislav Jeremić

CONTENTS

3.1.1.1 Introduction

There is a world-wide standard policy to offer surgery to patients with early stage (I/II) non-small cell lung cancer. This treatment modality offers the best results and has not changed substantially in the past two decades. In the international staging system classification (Mountain 1986), the 5-year survival rates for pathological stage I/II were 68.5% for T1N0, 59% for T2N0, 54.1% for T1N1 and 40.0% for T2N1. When clinical staging is used, however, these results become inferior: 61.9 % for T1N0, 35.8% for T2N0, 33.6% for T1N1 and 22.7% for T2N1 tumours. A similar analysis was carried out in the mid-1990s for the purposes of second staging classification (Mountain 1997). Since the patients in T3N0 subgroup had very similar outcomes (pathological stage: 5-year survival, 38%; clinical stage: 5-year survival, 22%) to that of T2N1 patients, they were from stage IIIA to stage IIB. Stage I has now been subdivided into IA (T1N0) and IB (T2N0), while the stage II also has two subdivisions, IIA (T1N1) and IIB (T2N1 and T3N0).

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The pathological staging is considered an ultimate one because it gives the best correlation with outcome and therefore represents the best indication of what adequate surgical candidates could be offered. However, there are also data from surgical series on patients with early stage non-small cell lung cancer when clinical staging is used (Mountain 1986; Naruke et al. 1988). Although comparison of treatment outcome based on pathological and clinical data has not been so frequently observed in recent years, there is still a subset of patients in whom clinical staging is used. These patients, although technically resectable, do not undergo surgery for various reasons. The vast majority of these patients are medically inoperable due to pre-existing comorbidity, mostly cardiopulmonary. This comorbidity prohibits surgery due to presumed high peri- and post-operative risk. Another group of patients not undergoing surgery are elderly, and are not surgical candidates due to restricted cardiopulmonary reserve, which can be expected to occur even without overt cardiopulmonary disease. Finally, the smallest group of patients not undergoing surgery, and possibly the group of patients for whom radiation oncology is most important, are the patients who refuse surgery, regardless of grounds, mostly stated to be anticipated morbidity and peri-operative mortality, as well as a substantial decrease in quality of life of potential long-term survivors. This may nowadays range from as low as nil to as high as >20% in elderly patients treated with pneumonectomy (Whittle et al. 1991; Au et al. 1994; Mizushima et al. 1997). These three groups of patients are those mostly offered radiation therapy alone, being frequently considered "standard" treatment approach in this setting. Unfortunately, the patients who undergo radiation therapy alone for early stage non-small cell lung cancer mostly constitute negative selection, materialised in their serious concomitant diseases. Additional disadvantages are the use of not pathological staging but rather clinical staging, as well as insufficient staging. It is, therefore, quite clear that the results of radiation therapy in this population cannot be meaningfully

compared to those of surgery, even when one uses the results from the surgical series using clinical staging. Additional reasons for the observed bias in reporting radiation therapy versus surgical series include institutional/investigator bias and the different process of decision-making (patients versus physicians), the latter one materialised in great variance across the studies with respect to the proportion of patients refusing surgery.

There are no prospective randomised studies comparing radiation therapy alone with other treatment modalities in patients with early stage non-small cell lung caner, including observation (no treatment). While one recent report (McGarry et al. 2002) showed no advantage for radiation therapy over observation-only, serious flaws in that particular report, both methodological and statistical, led to increased concern (Jeremic et al. 2002) that observation alone should not be practised in any case with early stage non-small cell lung cancer today. In addition, indirect evidence supporting active treatment came from the recent study (Henschke et al. 2003) which showed that even the smallest tumours (i.e. stage I) measuring 6–15 mm, 16–25 mm, and 26–30 mm, when untreated, had an 8-year fatality rate of 87%, 94% and 88%, respectively. Although that study focused on the role of surgery versus observation, it is not unrealistic to expect the same or similar from radiation therapy alone in this disease. This chapter, therefore, summarises achievements of radiation therapy alone in early stage NSCLC, highlights its advantages and underlines its disadvantages, and aims to enable better insight in a number of pre-treatment and treatment characteristics in this setting, especially focusing on curative radiation therapy. This is the main intention of this chapter because radiation therapy alone is the treatment of choice in technically operable but medically inoperable patients with early stage non-small cell lung cancer, including elderly and those who refuse surgery.

3.1.1.2 Overall Results of Radiation Therapy

Numerous studies unequivocally documented the outcome of patients with operable non-small cell lung cancer in the last four decades, including mostly patients with early (I/II) stage disease. It seems that the history of radiation therapy in early stage non-small cell lung cancer starts with the report of Morrison et al. (1963) who obtained the overall survival of 7% at 5 years in 28 patients with operable lung cancer treated with 45 Gy. This should come as no surprise due to the lack of modern diagnostic and planning tools (computerised tomography). Similarly, Coy and Kennelly (1980) provided similar results (5-year survival of 10%) in 141 patients with T1-3 NX tumours using doses of 50–57.5 Gy, although Smart (1966) indicated great potential for radiation therapy alone in this disease obtaining a 5-year survival of 22% and a median survival of approximately 24 months with 40–55 Gy in 40 patients. Of the studies that followed later on (Morrison et al. 1963; Smart 1966; Coy and Kennelly 1980; Cooper et al. 1985; Haffty et al. 1988; Noordijk et al. 1988; Zhang et al. 1989; Talton et al. 1990; Sandler et al. 1990; Ono et al. 1991; Dosertz et al. 1992; Kupelian et al. 1996; Cheung et al. 2000) some enrolled patients without specifying results according to the tumour stage, while others also enrolled a proportion of patients in stage III NSCLC (Cooper et al. 1980; Zhang et al. 1989; Talton et al. 1990; Dosoretz et al. 1992; Kupelian et al. 1996; Cheung et al. 2000). There was a substantial variation in the diagnostic tools used over the time and in the first reports computerised tomography scanning for diagnostic and therapeutic (planning) purposes was not used. It is, therefore, quite clear that those studies covering longer periods of time were likely to include a number of patients with more (locoregionally) advanced disease (Morrison et al. 1963; Smart 1966; Coy and Kennelly 1980; Cooper et al. 1985; Haffty et al. 1988; Noordijk et al. 1988; Zhang et al. 1989; Talton et al. 1990; Sandler et al. 1990; Ono et al. 1991; Dosoretz et al. 1992; Kupelian et al. 1996; Cheung et al. 2000). To further extend this, of those cited above, even some of the reports published in the 1980s and 1990s suffered from the very same drawback, frequently explained by the long time periods covering the study report (Cooper et al. 1980; Zhang et al. 1989; Talton et al. 1990; Haffty et al. 1988; Noordijk et al. 1988; Sandler et al. 1990; Ono et al. 1991). This may be one of the crucial issues in interpretation of the overall results, since Sandler et al. (1990) documented an improvement in survival in patients with "excellent" staging (chest CT scan, including the liver, and bone scan) when compared to those having "good" staging (conventional tomography, liver-spleen scan and a bone scan), and particularly to those being staged less vigorously. This issue should not present a problem nowadays, but is still a good reminder to those adopting a nihilistic approach in this patient population, which frequently results in inadequate treatment decision-

making based on insufficient staging, particularly in among elderly patients. The characteristics of patients enrolled into contemporary studies, as well as the outcome of studies, are given in Table 3.1.1.1.

Radiation therapy characteristics have also varied greatly with time. Doses as low as 18 Gy were sometimes given, but went up to 80 Gy, while all fractionation regimens were used: standard (1.8–2.0 Gy per fraction), hypofractionated (up to 4 Gy per fraction), split-course (1 or 2 weeks split), or hyperfractionated (1.2 Gy b.i.d. fractionation). Equipment used to deliver irradiation included a range of machines from orthovoltage X-rays through cobalt-60 to either low- or high-megavoltage X-rays of linear accelerators; treatment prescription/dose specification, patients positioning, number of irradiated treatment fields per day, etc., also varied significantly.

Whatever the differences and variances in the aforementioned studies and the interpretation of their respective results may have led to, radiation therapy alone has been capable of producing a median survival time of up to >30 months (>40 months in T1N0) since the mid-1980s. with 5-year survival rates of up to 30% in stage I non-small cell lung cancer (40% in T1N0) and up to 25% in stage II non-small cell lung cancer.

Besides the differences in radiation therapy characteristics in the aforementioned studies, these results were also achieved in a cohort of substantially differing patient populations (Table 3.1.1.2). An important underlying issue, namely, the reason for not undergoing surgery, was considerably different across the studies, particularly when one considers patient refusal which only recently started to gain more attention. While the percentage of such patients

Table 3.1.1.1. Patient and treatment characteristics and outcome of contemporary studies

Author	(*n*)	Median age (years)	Stage	Chest CT	Dose (Gy)	MST (months)	OS (5-year)	CSS (5-year)
Haffty et al. (1988)	43	64	T1-2N0-1	9%	54–60	28	21%	-
Noordijk et al. (1988)	50	74	T1-2N0	100%	60	27	16%	-
Zhang et al. (1989)	44	57	T1-2N0-2	-	55–70	>36	32%	-
Talton et al. (1990)	77	65	T1-3N0	20%	60	~16[a]	17%	-
Sandler et al. (1990)	77	72	T1-2N0	16%	<50–>60	20	10%[a]	17%[a]
Ono et al. (1991)	38	-	T1N0	24%	39–70	~40	42%	-
Dosoretz et al. (1992)	152	74	T1-3N0-1	Most	<50–>70	17	10%	15%
Hayakawa et al. (1992)	64	-	T1-2N0-1	24%	<60–>80	19	24%	-
Rosenthal et al. (1992)	62	68	T1-2N1	Most	18–65[b]	17.9	12%	
Kaskowitz et al. (1993)	53	73	T1-2N0	100%	<50–>70	20.9	6%	13%
Slotman and Karim (1994)	47	75	T1-2N0	55%	32–56	20	15%	32%
Graham et al. (1995)	103	67	T1-2N0-1	76%	18–60[b]	16.1	14%	-
Gauden et al. (1995)	347	70	T1-2N0	87%	50	27.9	27%	-
Krol et al. (1996)	108	74	T1-2N0	86%	60–65	~24	15%	31%
Slotman et al. (1996)	31	75	T1-2N0	100%	48	33	8%	-
Kupelian et al. (1996)	71	-	T1-4N0	100%	<50–>60	~16	12%	32%
Morita et al. (1997)	149	75	T1-2N0	100%	55–74	27.2	22%	-
Jeremic et al. (1997)	49	63	T1-2N0	100%	69.6	33	30%	-
Sibley et al. (1998)	141	70	T1-2N0	90%	50–80	18	13%	32%
Hayakawa et al. (1999)	36	-	T1-2N0	67%	60–81[c]	~33[a]	23%	39%
Jeremic et al. (1999)	67	60	T1-2N1	100%	69.6	27	25%	-
Cheung et al. (2000)	102	71.5	T1-3N0-1	93%	50–52.5	24	16%	27%
Zierhut et al. (2001)	60	69	T1-2N0-1	-	60	20.5	-	-
Hayakawa et al. (2001)	114	69	T1-2N0-1	-	60–80	-	12%	16%
Cheung et al. (2000)	33	72	T1-2N0	97%	48	22.6	46% (2-year)	54% (2-year)
Lagerwaard et al. (2002)	113	-	T1-2N0	100%	<66–70	20	12%	30%
Firat et al. (2002)	50	69	T1-2N0	100%	31–77	13[a]	5%	33%

CT, computerised tomography; MST, median survival time; OS, overall survival; CSS, cause-specific survival.
[a] Estimated from the available survival curve; [b] median dose, 60 Gy; [c] one patient irradiated with 48 Gy.

Table 3.1.1.2. Reasons for not undergoing surgery

Author	Number of patients (median age in years)		Morbidity	Age	Refusal	Other	Intercurrent deaths	MST (months)	OS (5-year)	CSS (5-year)
Coy and Kennelly (1980)	141	-	33%	20%	8%	39%	-	-	11%	-
Cooper et al. (1985)	72	(66)	66%	22%	12%		-	9	6%	-
Haffty et al. (1988)	43	(64)	86%		14%		-	28	21%	-
Noordijk et al. (1988)	50	(74)	68%	16%	14%	2%	22%	27	16%	-
Zhang et al. (1989)	44	(57)	73%		27%		14%	>36	32%	-
Sandler et al. (1990)	77	(72)	78%	5%	17%		13%	20	10%[a]	17%[a]
Ono et al. (1991)	38	-	55%	13%	11%	21%	-	~40	42%	-
Dosoretz et al. (1992)	152	(74)	85%		8%	7%	11%	17	10%	15%
Kaskowitz et al. (1993)	53	(73)	81%		19%		27%	20.9	6%	13%
Slotman and Karim (1994)	47	(75)	94%		6%		-	20	15%	32%
Graham et al. (1995)	103	(67)	-	-	-	-	28%	16.1	13%	
Gauden et al. (1995)	347	(70)	64%				-	27.9	27%	
Krol et al. (1996)	108	(74)	89%		5%	6%	30%	~24	15%	31%
Slotman et al. (1996)	31	(75)	88%	-	6%	6%	42%	33	8%	
Kupelian et al. (1996)	71	-	-	-	-	-	28%	16	12%	32%
Morita et al. (1997)	149	(75)	55%	28%	17%		21%	27.2	22%	
Jeremic et al. (1997)	49	(63)	60%		40%		12%	33	30%	
Sibley et al. (1998)	141	(70)	99%		1%		33%	18	13%	32%
Hayakawa et al. (1999)	36	-	56%	33%	11%		-	~33[a]	23%	39%
Jeremic et al. (1999)	67	(60)	65%		35%		6%	27	25%	
Cheung et al. (2000)	102	(71.5)	76%		12%	12%		24	16%	27%
Lagerwaard et al. (2002)	113	(74)	83%	7%	10%		27%	20	12%	30%[b]

MST, median survival time; OS, overall survival; CSS, cause-specific survival.
[a] Estimated from survival curve; [b] at 3 years.

was usually around 10%, there are also several studies in which it was >20% (Zhang et al. 1989; Morita et al. 1997; Jeremic et al. 1997, 1999). Interestingly, the highest median survival times (up to 33 months) were observed in these particular studies. This was coupled with the highest 5-year survival rates (up to 32%). It became widely accepted opinion that these patients represent the population which seems to be the one most likely to give true insight in the effectiveness of radiation therapy in this disease, simply because they are those resembling surgical candidates the most. In this patient population, using overall survival as an endpoint is more meaningful, because there are less cancer-unrelated events. In other patient popula-

tions, the use of cancer-specific survival or disease-specific survivals must be mandatory to correct for events other than cancer-related. Indeed, when 5-year cancer-specific or disease-free survival rates were reported (Sandler et al. 1990; Kaskowitz et al. 1993; Slotman and Karim 1994; Krol et al. 1996; Sibley et al. 1998; Cheung et al. 2000), they were usually twice as high as those of overall survival, as presented in the same studies, the difference being approximately 10%–20% in favour of the former. Additionally, it is a well recognised fact that patients' refusal inversely correlates with the incidence of intercurrent deaths (6%–16%) (Zhang et al. 1989; Sandler et al. 1990; Jeremic et al. 1997, 1999).The incidence of intercurrent deaths, on the other hand, are directly dependent on increasing age and pre-existing comorbidity (21%–43%) (Noordijk et al. 1988; Kaskowitz et al. 1993; Slotman and Karim 1994; Morita et al. 1997; Sibley et al. 1998). These several important facts play a complicated framework which has largely been underestimated in the past. Contemporary studies must take these facts into account and adapt the study designs and data presentation to enable better insight into the effectiveness of radiation therapy in this disease and to enable easier comparison across the studies.

3.1.1.3 Tumour Dose

A good starting point for properly addressing the question of effectiveness of radiation therapy in early stage non-small cell lung cancer, is the radiation therapy dose itself. In the previous section it was already mentioned that tumour doses used during the radiation therapy course ranged from as low as 18 Gy to as high as 80 Gy. This wide range of tumour doses should somehow make it possible to obtain information regarding the anticipated dose-response (effect) issue in this setting. This issue, however, cannot artificially be detached from the issue of tumour stage/size, since one of the long-lasting biological premises in radiation oncology is that larger tumour volumes (presumably higher stage) require higher tumour doses.

Impact of tumour dose was evaluated by a number of investigators. It has usually been observed that higher doses carry favourable outcome. Some studies used somewhat lower cut-off values (e.g. 40 or 50 Gy) which enabled comparison of palliative versus curative treatments (Cooper et al. 1985; Sandler et al. 1990; Kupelian et al. 1996). It was Cooper et al. (1985) who first noted improved survival with the higher dose (>40 Gy compared to <40 Gy). Haffty et al. (1988) noted an advantage of continuous course (59 Gy) over split course (54 Gy) regimen, not only regarding overall survival, but local control as well. The dose effect upon survival was also evaluated in the study of Zhang et al. (1989) who found that higher doses (69–70 Gy) were more efficient that the lower ones (55–61 Gy). However, Sandler et al. (1990) could not confirm this, presumably due to a somewhat narrow dose range in their study. Hayakawa et al. (1992) and Dosoretz et al. (1992) also confirmed importance of higher doses on overall survival and disease-specific survival, but warned of the use of very high doses (>80 Gy) when conventional tools were used for treatment planning/delivery (Hayakawa et al. 1992) due to increased risk of treatment related toxicity and mortality. Slotman and Karim (1994) did not find an impact of the higher (48–56 Gy) versus lower (32–40 Gy) doses of radiation therapy on either overall survival or disease-specific survival in stage I non-small cell lung cancer. Kaskowitz et al. (1993) and Sibley et al. (1998) both observed better overall survival, though not statistically significant, for higher doses ($\geq$65 Gy and $\geq$64 Gy, respectively). Graham et al. (1995) used tumour/dose/fractionation calculations as a measure of the effectiveness of radiation therapy to document better outcome with increasing tumour/dose/fractionation values in multivariate analysis. Also, Kupelian et al. (1996) and Morita et al. (1997) showed impact of the dose on local response/control, which was not always translated into a better survival (Morita et al. 1997). Stage I/II non-small cell lung cancer should represent tumours with the smallest burden of tumour cells, although imprecise staging currently used allows that even small-volume tumours are placed in the higher staging category (e.g. stage III) when invading certain intrathoracic/mediastinal structures. Also, although analyses from the available data sometimes favoured even lower doses of radiation therapy, it would still be preferable to recommend/use the doses traditionally considered as "curative", being in the order of >65–70 Gy with standard fractionation or its equivalent when altered fractionation is used. This suggestion should be even more valid nowadays when three-dimensional treatment planning and delivery is becoming a new standard of treatment planning and delivery in radiation oncology world-wide, because it should enable better therapeutic benefit when compared to two-dimensionally planned and executed radiation therapy used in the past.

3.1.1.4 Tumour Stage and Size

A number of studies have evaluated the impact of tumour stage and/or size on treatment outcome. It was mostly observed that smaller tumours and/or lower stage of disease carry an improvement in survival (Table 3.1.1.3). Cut-off sizes mostly used in the studies were <3 cm or <4 cm and these tumours were frequently compared to larger ones as was T1 stage versus T2 stage with regard to overall survival, disease-specific survival and local control. To strengthen possible findings, multivariate analyses were also used to investigate if there was an independent influence of T stage, frequently documenting that T stage was the only prognosticator of the treatment outcome (Kaskowitz et al. 1993; Graham et al. 1995; Gauden et al. 1995; Jeremic et al. 1997). Additionally, better outcome for T1 versus T2 or for tumour size ≤3 cm versus >3 cm (Morita et al. 1997; Slotman et al. 1996; Sibley et al. 1998) was observed, although without statistical significance. Contrary to these, there are also studies that evaluated both T stage and particular tumour size, with conflicting results. In the study of Kupelian et al. (1996), T stage did not influence either overall survival or disease-specific survival or local control. Interestingly, however, when tumour size was used as a variable, it was found that tumours <5 cm had better disease-specific survival and those <4 cm had better local control, confirmed in both cases using multivariate analysis. While it is reasonable to expect impact of tumour stage/size on the outcome, this should happen first at local/regional level, and then on the overall survival, providing causal relationship between local control and overall survival. It seems, therefore, that local/regional-recurrence free survival or disease-specific survival must be included in the analysis as important initial endpoints, as well as the distant metastasis-free survival, to provide better insight into the events other than those occurring locoregionally. The patterns of failure (detailed later in Sect. 3.1.1.5) were shown to heavily depend on local/regional tumour control in this disease.

Important obstacles for clear and precise definition of the role of tumour stage/size are staging systems widely used in the last 20 years (Mountain 1986, 1997). As briefly mentioned in the preceding section, these surgical systems do not relate only to a tumour size, but also to a particular tumour location, leading to confusion when this (surgical) staging system is applied to a non-surgical setting, having different biological premises. A practical example of such a problem is as follows: a tumour of 1 cm would be, by virtue of its size, placed into T1 category, but if it involves main bronchus at ≥2 cm distal to the carina, it would be designated as T2. This may be even more so in the case of a tumour of the same size invading chest wall, being automatically placed into the T3 category. This issue may be an important one owing to the log-cell kill nature of anticancer action of radiation therapy. There are requests for continuous revision of the current international staging system, which should make both T and N staging more specific/detailed and, therefore, easier to interpret/compare.

3.1.1.5 Treatment Volume

Another issue which must be considered in this context is the "optimal" treatment volume. Unfortunately, as with preceding issues, shortcomings in the literature also apply here. Nevertheless, it seems that the issue focuses on the question of elective nodal irradiation. This would mean elective radiation therapy of hilum with or without a part or whole of the mediastinum in cases of stage I, or a part or whole of the mediastinum in stage II non-small cell lung cancer. To properly address this issue, one must consider it together with the irradiation dose used for elective treatment. Some studies used doses of 40 Gy in 20 daily fractions (Zhang et al. 1989; Talton et al. 1990; Hayakawa et al. 1992, 1999; Slotman et al. 1996; Morita et al. 1997) which can not be considered as adequate to treat microscopic disease. While some were using 45 Gy in 20–22 fractions (Morrison et al. 1963; Haffty et al. 1988; Kupelian et al. 1996), which can be considered standard practice, it is of unproven efficacy in lung cancer. Furthermore, if we extrapolate the data from squamous cell carcinoma of the head and neck, then one would need 50 Gy given with 2.0 Gy standard fractionation to treat microscopic disease successfully. Close to this level were doses used by Kaskowitz et al. (1993), by Morita et al. (1997) in part of their patients, and by Jeremic et al. (1997, 1999), with hyperfractionated radiation therapy dose of 50.40 Gy using 1.2 Gy b.i.d. fractionation applied by the latter. Finally, because of the fear that there may be an increased risk of subclinical nodal spread in some lymph node regions, others have also adapted otherwise strict institutional policy and included some nodes at risk into the limited field RT, giving it, therefore, a form of "electively-lim-

Table 3.1.1.3. Effect of tumour stage/tumour size

Author	Number of patients	Stage	Stage/size effect	Remarks
Coy and Kennelly (1980)	141	T1-3 N2	+	<3 cm better than other sizes (OS)
Noodijk et al. (1988)	50	T1-2 N0	+	≤4 cm better than >4 cm and T1 better than T2 (OS) (p=0.06)
Zhang et al. (1989)	44	T1-2 N0-2	+	T1 N0 better than T2 N0 (OS)
Sandler et al. (1990)	77	T1-2 N0	+	≤3 cm better OS and DSS, but not LRFS
Rosenthal et al.(1992)	62	T1-2 N1	-	T1 vs T2, better, but not significantly (OS)
Dosoretz et al. (1992)	152	T1-3 N0, 1	+	T1 better than T2 (DFS) <3 cm better than other sizes in locally uncontrolled tumours <3 cm better DMFS in locally controlled tumours
Kaskowitz et al. (1993)	53	T1-2 N0	+	T1 better than T2 (OS) (only prognostic factor)
Slotman and Karim (1994)	47	T1-2 N0	+	Smaller size better DSS (<0.001) and OS (0.08) (multivariate analysis)
Gauden et al. (1995)	347	T1-2 N0	+	T1 better than T2 (only prognostic factor) (OS)
Graham et al. (1995)	103	T1-2 N0-1	+	T stage independent prognosticator (multivariate analysis) (OS)
Slotman et al. (1996)	31	T1-2 N0	-	T1 vs T2 (not significant) (OS)
Krol et al. (1996)	108	T1-2 N0	+	<4 cm better OS, CSS and CR
Kupelian et al. (1996)	71	T1-4 N0	- +	T stage for OS, DSS and LC <5 cm better DSS; <4 cm better LC (multivariate analysis)
Morita et al. (1997)	149	T1-2 N0	- +	T1 better than T2, but not significantly (OS) <4 cm better than >4 cm (OS and CR)
Jeremic et al. (1997)	49	T1-2 N0	±	T1 better than T2 (OS and RFS), but not on multivariate analysis
Sibley et al. (1998)	141	T1-2 N0	-	≤3 cm better than >3 cm (OS, CSS, PFS), but not significantly
Jeremic et al. (1999)	67	T1-2 N1	+	T1 better than T2 (multivariate analysis) (OS)
Cheung et al. (2000)	102	T1-3 N0-1	-	Tumour volumes (≤10, 11–50, and ≤50 cm³) not significant for RFS
Lagerwaard et al. (2002)	113	T1-2 N0	±	T2 adverse prognosticator of CSS and DMFS, but not OS or LRFS (multivariate analysis)
Firat et al. (2002)	50	T1-2 N0	-	T size <4 cm and T1 vs T2 both not significant on OS

OS, overall survival; DSS, disease-specific survival; LRFS, local recurrence-free survival; DFS, disease-free survival; DMFS, distant metastasis-free survival; LC, local control; CR, complete response; RFS, relapse-free survival; PFS, progression-free survival.

ited" RT, usually based on primary tumour location (central tumour location or tumour adjacent to the mediastinum (Senan et al. 2002; Lagerwaard et al. 2002).

Unfortunately, the choice and number of treatment fields, as well as the dose prescription, were not always clearly specified, leaving some room for less precise interpretation of the data. This relates in particular to the second part of the radiation therapy course, which, by using various combinations of radiation therapy fields to treat visible tumour only (mostly obliques and/or laterals), provides an unintentional treatment contribution to the nodal areas at risk. This contribution for a particular radiation therapy plan is not documented at all and is therefore unknown. However, Martel et al. (1999) showed that three-dimensional conformal radiation therapy used to deliver starting doses of 69.3–84 Gy to gross tumour volume resulted in 100% of the ipsilateral hilum, 59% of the low paratracheal region, 57% of the aortopulmonary region, 97% of the subcarinal region and 57% of the contralateral hilum receiving ≥50 Gy. Another report from the same institution (Hayman et al. 2001) showed no isolated elective nodal fail-

ures when three-dimensional conformal radiation therapy was used in patients with non-small cell lung cancer, although there were three (6%) failures in the lymph nodes outside the planning target volume. Rosenzweig et al. (2001) also used similar three-dimensional conformal radiotherapy (range, 50.4–81 Gy; median, 68.4 Gy) without elective nodal RT to observe 2-year rate of elective nodal control in 88% patients with tumours locally controlled. With unintentional nodal radiation therapy, a dose of >40 Gy was delivered to the ipsilateral superior mediastinum in 34% patients, to the inferior mediastinum in 63% patients and to the subcarinal region in 41% patients. It is, therefore, obvious that not just conventional radiation therapy but also three-dimensional conformal radiation therapy (using "limited" radiation therapy fields, e.g. those covering only macroscopically/radiographically visible tumour) frequently result in higher dose to the nodal regions that one may initially assume. If one intends to document the necessity of elective nodal radiation therapy in this setting, a policy of clear documentation of the dose to the regions presumably harbouring microscopic spread must be mandatory. Unfortunately, even the most recent publications on the use of three-dimensionally conformal radiation therapy in inoperable non-small cell lung cancer, including cases of early stage non-small cell lung cancer, do not document incidental nodal irradiation, yet claiming that no elective irradiation was performed (Belderbos et al. 2003; Bradley et al. 2003; Lagerwaard et al. 2002).

In some studies institutional policy regarding elective nodal irradiation did not change over time (Jeremic et al. 1997, 1999], while some studies (Sandler et al. 1990; Graham et al. 1995) did not provide results according to radiation therapy volume. While Dosoretz et al. (1992) found no impact of elective nodal irradiation on the treatment outcome, Kupelian et al. (1996) and Sibley et al. (1998) found better overall survival, disease-specific survival and local control in patients undergoing elective nodal irradiation, though insignificant, probably due to a small number of events. Morita et al. (1997), however, clearly documented superior complete response rates and overall survival in patients undergoing elective nodal irradiation and a lower distant metastasis rate in patients undergoing elective nodal irradiation.

The issue of elective nodal irradiation must be considered together with the incidence of occult lymph node (hilar and/or mediastinal) metastasis. If the initial clinical staging based on computerised tomography scanning is ultimately verified during operation, the incidence of nodal metastases in stage I non-small cell lung cancer may be as high as 26% (Glazer et al. 1984; Heavey et al. 1986; Black et al. 1988; Conces et al. 1989), supporting, thus, a consistent finding over the decades that surgical/pathological upstaging is seen in approximately 25% of cases of T1N0 and approximately 35% of cases of T2N0 cases (Martini and Beattie 1977; Naruke et al. 1988; Ginsberg and Rubinstein 1995). Recent surgical data also showed similar incidence of unsuspected lymph node metastasis when T1 stage was broken by tumour size, 18% in T1a (<2 cm) and 23% in T1b (2–3 cm) tumours (Koike et al. 1998). They effectively support the findings of earlier surgical studies in early stage non-small cell lung cancer which provided the evidence that incidence of lymphatic invasion/metastasis rises with increasing size of the tumour (<1.0 cm, 1.1–2.0 cm and >2.0 cm had approximately 0%, 17% and 38% of such incidence, respectively) (Ishida et al. 1991). When immunohistochemical staining was used in patients with peripheral adenocarcinoma of $\leq$2.0 cm, occult nodal (hilar and/or mediastinal) (micro)metastases were detected in 20% of patients (Wu et al. 2001). On multivariate analysis, nodal micrometastasis was an independent prognosticator of survival, which was in agreement with previous studies (Chen et al. 1993; Passlick et al. 1996; Dobashi et al. 1997; Maruyama et al. 1997). Also, occult nodal metastases were significantly more frequent in poorly differentiated tumours, confirming previous findings (Takizawa et al. 1998). Although direct comparison between surgery and radiation therapy regarding this issue is not likely to be performed, nevertheless, adopting exact philosophy of the surgical approach suggested as preferred/mandatory treatment for T1N0 patients (i.e. lobectomy) would include systematic removal of all hilar and mediastinal lymph node content (Ishida et al. 1991; Ginsberg and Rubinstein 1995), equivalence of which would be larger radiation therapy fields instituted to treat some, if not all, lymph node regions (hilar and/or mediastinal).

Contrary to that suggestion, recent review of the data on the patterns of recurrence after radical radiation therapy in early stage non-small cell lung cancer available in the literature (Jeremic et al. 2002) showed that the predominant type of failure remains local, being reported as either isolated or initial in approximately 11%–55% cases (ultimately up to 75%). An isolated/initial regional failure was reported to occur in only 0%–7% cases (ultimately up to 15% cases), while the distant metastasis mostly lies between these two (isolated/initial in 3%–33% cases and ultimately in up to 36% cases) (Table 3.1.1.4). These findings

Table 3.1.1.4. Pattern of failure

Author	Number	Stage	Hilum RT	Mediastinum RT	Tumour dose (Gy)	Failures					
						Local		Nodal		Distant	
						Initial/ isolated	Ultimate	Initial/ isolated	Ultimate	Initial/ Isolated	Ultimate
Cooper et al. (1985)	72	T1-3 N0-1	?	?	<30–<40		75%				
Noodijk et al. (1988)	50	T1-2 N0	-	-	60		70%				
Haffty et al. (1988)	43	T1-2 N0-1	+	88%	54–59		40%				
Zhang et al. (1989)	44	T1-2 N0-2	+	+	55–70	16%	27%	7%	7%	7%	11%
Sandler et al. (1990)	77	T1-2 N0	90%	90%	<50–>60	44%	56%				
Dosoretz et al. (1992)	152	T1-3 N0-1	Most	Most	<50–>70	41%	44%			14%	20%
Rosenthal et al. (1992)	62	T1-2 N1	+	+	18–65[a]	55%				31%	
Kaskowitz et al. (1993)	53	T1-2 N0	83%	85%	<50–>70	42%	45%	0%	8%	17%	32%
Slotman and Karim (1994)	47	T1-2 N0	71%	71%	32–56	19%	25%			17%	21%
Slotman et al. (1996)	31	T1-2 N0	-	-	48		6%	3%	6%	10%	16%
Krol et al. (1996)	108	T1-2 N0	-	-	60–65	28%	66%	2%	15%	3%	33%
Jeremic et al. (1997)	49	T1-2 N0	+	-	69.6		45%	0%	11%		25%
Sibley et al. (1998)	141	T1-2 N0	14%	73%	50–80	16%	19%	3%	5%	15%	20%
Hayakawa et al. (1999)	36	T1-2 N0	28%	28%	60–81[b]	11%	19%	3%	8%	33%	36%
Jeremic et al. (1999)	67	T1-2 N1	+	+	69.6	42%	46%	0%	12%	27%	34%
Cheung et al. (2000)	102	T1-3 N0-1	-	-	50–52.5	30%	42%	4%	11%	15%	20%

[a] Median dose, 60 Gy; [b] one patient irradiated with 48 Gy.

could support the use of more localised fields, because it was stressed that the major concern should be the gross tumour burden and not a microscopic one (Williams et al. 2000). Recent use of positron emission tomography scanning in lung cancer has shown that it may be successful not just in detecting subclinical distant spread (MacManus et al. 2001) but also in detecting a subclinical regional spread. Farrell et al. (2000) investigated 84 patients without hilar or mediastinal lymph node enlargement on computed tomography. Histopathological N0 disease was confirmed in 73 patients, 63 of whom had no hilar or mediastinal activity on fluorodeoxyglucose-positron emission tomography scan (86%) while hilar or mediastinal lymph node activity and distant metastases were found in 3, 6 and 1 patient, respectively. Thus positron emission tomography rather overestimated more advanced disease in 12% of the patients as compared to chest tomography with false negative findings in 11 patients (13%). In a series by Marom et al. (1999) nodal staging by computerised tomography, positron emission tomography and histopatho-

logical analysis disclosed N0 status in 42, 29 and 32 patients, respectively. However, with regards to hilar lymph node involvement, both computerised tomography and positron emission tomography were positive in six patients, three of which were confirmed by pathological analysis. Hence, the rates of false negative staging by computerised tomography and false positive staging by positron emission tomography were due to differences in mediastinal lymph node assessment which is of particular importance when assessing the role of positron emission tomography in stage I/II lung cancer. These findings are supported by a study by M. Saunders et al. (1999). They assessed the rate of N2 and N3 mediastinal lymph node involvement by positron emission tomography and computerised tomography in a series of 97 patients under consideration for surgery. True negative findings were observed in 65 and 62 patients for positron emission tomography and computerised tomography, respectively. However, the rate of false negative findings differed substantially with five patients by positron emission tomography and 12 patients by computerised tomography. Thus positron emission tomography apparently offers particular advantages of computerised tomography imaging with regards to exclusion of mediastinal lymph node involvement while assessment of hilar nodal disease may be equally difficult by computerised tomography and positron emission tomography. It is, therefore, expected that positron emission tomography may help better delineate the tumour itself, exclude possible areas of regional/distant spread, and enable dose-escalation which seems to be possible in the cases with limited lung volume included in the radiation therapy fields. An additional advantage of positron emission tomography is that it can be used for the purpose of treatment planning, owing to increased capability of image fusion (with computerised tomography).

However, more information on the biological properties and differences between various subgroups of patients/tumours (e.g. histology, tumour grade), must be gathered before one can embark on investigation of various radiotherapeutic issues in this disease. One such attempt has been recently published by Sawyer et al. (1999) using data obtainable from 346 patients undergoing complete resection of early clinical stage (I/II) non-small cell lung cancer to identify predictors of subclinical nodal involvement. By using findings of preoperative bronchoscopy, tumour size, tumour grade and histology to create risk groups for N1/N2/local/regional recurrence, they have found that the risk of subclinical nodal involvement was at least 15.6% in the best (low risk) subgroup (n=32), while all other patients (n=295) had at least 35% of such a risk. Increasing risk correlated with increasing size and grade of tumour, accompanied with positive findings of bronchoscopy. Suzuki et al. (2001) used a similar approach to determine predictors of lymph node and intrapulmonary metastasis in 389 patients with clinical stage IA non-small cell lung cancer undergoing major lung resection and complete mediastinal lymph node dissection. In total, 88 patients (23%) had pathological lymph node involvement or intrapulmonary metastases. Significant predictors of local or regional spread included grade of differentiation and pleural involvement. With both risk factors present, more than 40% of clinical stage IA non-small cell lung cancer patients had pathologic involvement of lymph nodes or intrapulmonary metastases. The same group (Suzuki et al. 1999) previously investigated clinical predictors of N2 disease in 379 patients with clinical N0–N1. There were 68 (17.9%) patients with pathologic N2 stage. Multivariate analysis showed that tumour size, high serum CEA level and adenocarcinoma histology were significant predictors of N2 disease.

Owing to somewhat conflicting results, no reliable recommendations can be made concerning elective nodal irradiation. There seems to be a subgroup of patients with increased risk of developing nodal metastasis, identification of which must be one of the priorities of research in this field. Contrary to that, it is reasonable to assume that small, peripheral, low-grade tumours would be the best candidates for limited radiation therapy treatment fields (omitting elective nodal irradiation), due to lowest incidence of occult nodal metastasis. However, more information regarding biology of these tumours is needed because identification of potential factors contributing to higher incidence of subclinical regional lymph node metastasis would help optimise radiation therapy fields and enable successful dose-escalation at the primary tumour level.

3.1.1.6 Prognostic Factors

In previous sections some of the radiation therapy-related factors have been discussed in detail. In addition to these, there were also attempts to investigate the influence of various pre-treatment, both patient- and tumour-related, prognostic factors on either overall survival or cause-specific survival/disease-specific survival. Gender seems not to play a major role in the outcome of patients (Coy and Kennelly

1980; Sandler et al. 1990; Hayakawa et al. 1992; Rosenthal et al. 1992; Slotman and Karim 1994; Gauden et al. 1995; Morita et al. 1997; Jeremic et al. 1997, 1999; Lagerwaard et al. 2002).

Similarly, most of the reports observed no influence of age on treatment outcome (Morrison et al. 1963; Noordijk et al. 1988; Sandler et al. 1990; Kaskowitz et al. 1993; Krol et al. 1996; Jeremic et al. 1997, 1999; Hayakawa et al. 1992; Slotman and Karin 1994; Slotman et al. 1996; Gauden et al. 1995; Rosenthal et al. 1992). In contrast, Morita et al. (1997) found a detrimental effect of age of >80 years on overall survival, though not providing data on other endpoints such as cause-specific survival. Sibley et al. (1998), however, used both uni- and multivariate analysis to show that younger age positively correlated with overall survival and cause-specific survival. Both studies, however, provide no explanation at all, nor even a hypothesis, for such a finding. The same holds true for the report of Lagerwaard et al. (2002) who found a detrimental effect of increasing age (patients were grouped as aged <70 years, 70–75 years, and >75 years) on overall survival, but not on cause-specific survival or local and distant tumour control. Similar findings were observed by Firat et al. (2002) in a univariate analysis, but these were not confirmed by the multivariate analysis. Recent analyses focusing on elderly with early stage non-small cell lung cancer (Furuta et al. 1996; Hayakawa et al. 2001; Gauden and Tripcony 2001) showed similar outcome for this patient population when treated with radiation therapy alone, which may go as high as 36% when 5-year cause-specific survival was used as an endpoint (Furuta et al. 1996).

An investigation of the influence of performance status on treatment outcome is controversial. While Dosoretz et al. (1992), Slotman and Karim (1994), Kaskowitz et al. (1993) and Gauden et al. (1995) found no influence of performance status on either overall survival or disease-specific survival, Rosenthal et al. (1992), Hayakawa et al. (1992), Kupelian et al. (1996), and Jeremic et al. (1997, 1999) did note its effect on either overall survival and/or disease-specific survival/relapse-free survival as well. In the study by Lagerwaard et al. (2002), the World Health Organization performance status score was an independent prognosticator of OS, and the same was observed in the study of Firat et al. (2002) using the Karnofsky performance status score in an univariate analysis. Likewise, conflicting results are seen with weight loss.

Regarding histology, only Sibley et al. (1998) found an improvement in cause-specific survival for squamous histology, while Gauden et al. (1995) observed the same for mixed (adenocarcinoma/squamous cell carcinoma) histology using both overall survival and relapse-free survival as endpoints. Lagerwaard et al. (2002), meanwhile, observed an independent and favourable influence of unknown histology (versus squamous cell histology and non-squamous cell histology) on overall survival. All other studies observed no such effect (Sandler et al. 1990; Dosoretz et al. 1992, 1993; Hayakawa et al. 1992; Rosenthal et al. 1992; Slotman and Karim 1994; Slotman et al. 1996; Jeremic et al. 1997; Firat et al. 2002). Finally, only Hayakawa et al. (1992) observed influence of tumour location (better for tumours located in the upper lobes or the superior segment of the lower lobes) on outcome of these patients, all other studies excluding its possible effect when comparing central versus peripheral location (Ono et al. 1991; Slotman and Karim 1994; Slotman et al. 1996; Jeremic et al. 1997; Cheung et al. 2000; Lagerwaard et al. 2002).

Besides clinical prognostic factors, a number of biological and molecular characteristics of lung cancer may influence treatment outcome. While these have been investigated in surgical patients (Slebos et al. 1990; Tateishi et al. 1991; Fontanini et al. 1992; Pastorino et al. 1997), these data are basically lacking in medically inoperable early stage non-small cell lung cancer patients treated with radiation therapy alone.

3.1.1.7 Toxicity

Although one case of oesophageal haemorrhage after dilatation and one case of pulmonary fibrosis (2; 7%) leading to treatment-related deaths have already been documented in one of the first reports on radiation therapy in early stage non-small cell lung cancer (Morrison et al. 1963) after 45 Gy given in 20 daily fractions over 4 weeks, this issue has not been systematically addressed over the years. Authors often did not provide information on toxicity at all (Coy and Kennelly 1980; Cooper et al. 1985; Zhang et al. 1989; Rosenthal et al. 1992; Krol et al. 1996), while others only mentioned either absence or rarity of, mostly "serious", toxicity (Noordijk et al. 1988; Sandler et al. 1990; Dosoretz et al. 1992; Gauden et al. 1995; Slotman et al. 1996; Morita et al. 1997; Hayakawa et al. 1999). When data were provided without specifying the toxicity criteria, there was usually no reporting on high-grade ($\geq$3) toxicity.

Mild to moderate (corresponding to grades 1 and 2) esophagitis was seen in up to two-thirds of patients, while mild to moderate pneumonitis was seen in approximately one-fifth of patients. These results were obtained regardless of tumour/dose fractionation pattern or whether elective nodal radiation therapy was used or not. However, Hayakawa et al. (1992) described four out of 13 (31%) patients dying of pulmonary insufficiency due to bronchial stenotic changes after receiving >80 Gy in 2-Gy daily fractions at the proximal bronchi.

There were only five studies that reported on toxicity using grading systems. Graham et al. (1995) reported on mild to moderate acute toxicity in 103 patients with early stage non-small cell lung cancer treated with 18-60 Gy (median primary dose, 60 Gy in 30 fractions), of whom 80% received elective nodal radiation therapy. One patient-developed grade 3 pneumonitis according to the European Organization for the Research and Treatment of Cancer/Radiation Therapy Oncology Group (Cox et al. 1995), and there were also only three cases of late grade 2 lung toxicity. Jeremic et al. (1997) treated 49 patients with stage I non-small cell lung cancer with hyperfractionated radiation therapy doses of 69.6 Gy via 1.2 Gy b.i.d. fractionation, of whom 33 were older than 60 years. They have also used Radiation Therapy Oncology Group toxicity criteria (Cox et al. 1995) to show only 2 (6%) grade 3 acute toxicities (bronchopulmonary and oesophageal) and three (9%) grade 3 late toxicities (bronchopulmonary, oesophageal and osseous), although the ipsilateral hilum was electively treated to a 50.40-Gy dose with the same fractionation. Jeremic et al. (1999) again used Radiation Therapy Oncology group (Cox et al. 1995) toxicity criteria to report on the same hyperfractionated radiation therapy regimen (69.6 Gy using 1.2 Gy b.i.d. fractionation) in 67 stage II non-small cell lung cancer patients, of whom 40 were ≥60 years old. Although elective mediastinal irradiation was used in all cases, there were only two bronchopulmonary and two oesophageal acute grade 3 toxicities (total n=4; 6%) and only one bronchopulmonary and two oesophageal late grade 3 toxicities (total n=3; 4%). Sibley et al. (1998) observed two (1.5%) grade ≥3 complications, one being fatal pneumonitis 2 months after the completion of 66 Gy in 2 Gy fractions, the other being severe oxygen-dependent pneumonitis unresponsive to steroids after 64 Gy in 2 Gy fractions. Both patients had their mediastinum region encompassed. However, no information on grading system used in that study was provided. Finally, Lagerwaard et al. (2002) observed grade 1–2 esophagitis according to the Radiation Therapy Oncology Group in 16% patients with no symptoms consistent with late oesophageal toxicity. Grade 2 or higher on the Southwest Oncology Group scale was observed in 6% patients. In the latter group of reports (Jeremic et al. 1997, 1999; Graham et al. 1995; Sibley et al. 1998), high-grade (≥3) acute esophagitis and pneumonitis were documented in up to 3% of cases, and the same applies to the high-grade late toxicity, with no apparent differences between various radiation therapy regimens, although Lagerwaard et al. (2002) used multivariate analysis to document the detrimental effect of radiation dose of 70 Gy or more on the incidence of acute esophagitis.

In none of these series was it reported that these toxic events may have happened in elderly patients. When, however, the study population was confined to elderly with early stage non-small cell lung cancer only, it was observed that no significant radiation therapy-related complications were found and that incidence of both acute and late high-grade (3 and 4) toxicity was similar among all age groups (Gauden et al. 1995; Gauden and Tripcony 2001). When radiation therapy-related deaths occurred (Hayakawa et al. 2001), again, there was no difference between elderly (5%) treated with the highest dose levels (80 Gy) and their non-elderly counterparts (4%) treated the same way.

A substantial problem with all these reports is a great variety of both pre-treatment and radiation therapy-related factors, such as the total dose, fractionation or treatment fields, not just between the institutions, but intra-institutionally, too. This greatly obscures the overall picture and prohibits firm conclusions. While it is a well established premise that higher total dose, higher dose per fraction and larger volume of the lung irradiated should lead to more toxicity (Moss et al. 1960; Holsti and Vuorinen 1967; Rubin and Casarett 1968; Mah et al. 1987; McDonald et al. 1995), both acute and late, it is unknown to what extent other, radiation therapy-unrelated factors such as pre-existing comorbidity, infections, or simply natural processes such as sclerosis present in elderly patients, may add to the occurrence of toxicity (Rubin and Casarett 1968; Braun et al. 1975; Prasad 1978; Garipaoglu et al. 1999). Some, however, have observed that concomitant chronic obstructive pulmonary disease did not increase the risk of radiation pneumonitis (Prasad 1978). Acute high-grade toxicity may also be interesting from the standpoint of treatment interruptions which may adversely influence treatment outcome (Cox et al. 1993; Chen et al. 2000; Jeremic et al. 2003b).

In the first-ever analysis devoted to this issue exclusively in early stage non-small cell lung cancer (Jeremic et al. 2003a), of 116 patients treated with total tumour doses of 69.6 Gy, 1.2 Gy b.i.d. fractionation, 44 patients refused surgery while 72 patients were medically inoperable due to existing co-morbid states. Patients who were medically inoperable had worse KPS (p=0.0059) and more pronounced weight loss (p=0.0005). Among them, 12 patients experienced high-grade toxicity and 11 of them with either acute (n=6) or "consequential" late (n=5) high-grade toxicity requested interruption in the hyperfractionated radiation therapy course (range, 12–25 days; median, 17 days). Superior survival was observed in patients who refused surgery when compared to those who were medically inoperable (p=0.0041), as well as superior local recurrence-free survival (p=0.011), but no difference was observed in distant metastasis-free survival (p=0.14). Cause-specific survival also favoured patients who refused surgery (p=0.004). Multivariate analysis showed independent influence of the reason for not undergoing surgery on overall survival (p=0.035), but not on local recurrence-free survival (p=0.084) or cause-specific survival (p=0.068). Patients who refused surgery did not experience high-grade toxicity (0/44), whereas 11 of 72 patients with medical inoperability and co-morbid states experienced high-grade toxicity and had treatment interruptions to manage toxicity (p=0.0064). Patients without treatment interruptions had significantly better overall survival (p=0.00000), local recurrence-free survival (p=0.00000) and cause-specific survival (p=0.00000) than those with treatment interruptions. When corrected for treatment interruptions, the reason for not undergoing surgery independently influenced overall survival (p=0.040), but not local recurrence-free survival (p=0.092) or cause-specific survival (p=0.068). In contrast to this, treatment interruption was an independent prognosticator of all three endpoints used (p=0.00031, p=0.0075 and p=0.00033, respectively). When 11 patients with treatment interruptions were excluded, the reason for not undergoing surgery still affected overall survival (p=0.037) and cause-specific survival (p=0.039) but not local recurrence-free survival (p=0.11). Multivariate analyses using overall survival, cause-specific survival and local recurrence-free survival showed that the reason for not undergoing surgery affected overall survival (p=0.0436), but neither cause-specific survival (p=0.083) nor local recurrence-free survival (p=0.080). Late high-grade toxicity becomes also interesting from the standpoint of prolonged survival of these patients. Prolonged follow-up is, therefore, necessary. It may also be advantageous in terms of detecting second cancers, both lung and non-lung, that occur in long-term survivors after the first radiation therapy (Jeremic et al. 2001). If diagnosed at an early stage, these patients may experience similar outcome as with the first radiation therapy.

Reporting of toxicity poses an additional problem, because only rarely scoring systems have been used. Additionally, such reporting was almost always done on an actual (crude) basis, and not on the actuarial one. While the former method may be acceptable, although not preferable, for acute toxicity, it should be strongly discouraged as totally inappropriate for late toxicity.

With the wide introduction of computerised three-dimensional treatment planning in recent years, it is now widely possible to tailor the dose to tumour and spare surrounding healthy tissues. In particular, the use of dose-volume histograms enabled a preliminary step in quantitative assessment of competitive treatment plans and a screening tool to select "the best" available plan (Drzymala et al. 1991), usually coupled with other quantitative indices such as normal tissue complication probability and tumour control probability (Kutcher and Burman 1987; Lyman and Wolbarst 1987; Burman et al. 1991). These may enable an increase in the dose delivered to tumour, necessary for better tumour control (Armstrong et al. 1993; Robertson et al. 1997). They can also give useful data for characterisation of the dose-volume relationship and the development of pneumonitis (Martel et al. 1994; Oetzel et al. 1995; Kwa et al. 1998; Graham et al. 1999) and reduced dose to not just lung (Graham et al. 1994), but other critical normal tissues as well (Maguire et al. 1999; Bahri et al. 1999).

3.1.1.8 Quality of Life

The quality of life in patients treated with radiation therapy becomes an increasingly important issue in lung cancer, but no clear data exist in early non-small cell lung cancer treated by radiation therapy alone. Movsas et al. (1999) recently used a quality-adjusted survival time model which takes into account survival as well as toxicity by weighting the time spent with a specific toxicity as well as local or distant tumour progression. Each of the number of toxicities was weighted with increasing severity as the toxicity increased in grade. A total of 979 patients

with stage II-IIIB (vast majority with stage III; no stage I) inoperable non-small cell lung cancer were enrolled on six prospective phase II and III studies that ranged from standard radiation therapy (60 Gy), hyperfractionated radiation therapy (69.6 Gy), induction chemotherapy followed by standard radiation therapy, induction chemotherapy and concurrent radiochemotherapy and concurrent chemotherapy and hyperfractionated radiation therapy. Patients aged <60 years old had improved survival with more aggressive therapy (with chemotherapy added to radiation therapy), while those aged >70 years old achieved the best quality-adjusted survival time with standard radiation therapy alone. The same authors used the quality-adjusted time without symptoms (Q-Twist) in the same group of patients enrolled during Radiation Therapy Oncology Group studies in locally advanced non-small cell lung cancer, a minority of whom were stage II (Movsas et al. 2000). A quality-adjusted survival analysis subtracted from survival time spent with toxicity and/or relapse. While an overall benefit in Q-Twist was seen with the addition of chemotherapy to radiation therapy, the advantage of more aggressive therapy was limited to patients aged <70 years old. In patients aged >70 years, no radiation therapy/chemotherapy regimen had a superior Q-Twist than radiation therapy alone. None of these analyses provided separate analysis for patients with early stage non-small cell lung cancer.

A study by Langendijk et al. (2000) on the pre-treatment quality of life in inoperable non-small cell lung cancer (stage I, 21%; stage II, 1%) disclosed that World Health Organization performance status, weight loss and age were all significantly associated with quality of life. Among the different respiratory symptoms assessed by the European Organization for the Research and Treatment of Cancer quality of life questionnaire-C30 score, dyspnea was the only item significantly correlated with global quality of life. Furthermore, changes of dyspnea subsequent to treatment were also significantly associated with global quality of life. Unfortunately, neither analysis of treatment-related toxicity and quality of life was included in this study nor was there a separate analysis relating to early stage non-small cell lung cancer.

3.1.1.9 Novel Approaches

High precision radiation therapy in the form of stereotactic radiosurgery was successfully used in cases of brain metastasis, including those originating from primary lung cancer (Sturm et al. 1987; Flickinger et al. 1994; Alexander et al. 1995). It had also been shown that stereotactic fractionated radiation therapy is an effective treatment approach for both malignant and non-malignant neoplasms because it combines the accurate focal dose delivery of stereotactic radiosurgery with the biological advantages of fractionated radiation therapy (Dunbar et al. 1994; Kooy et al. 1994; Varlotto et al. 1996). It was also indicated that stereotactic fractionated radiation therapy can be advantageous over stereotactic radiosurgery in tumours >3 cm or those located in the vicinity of critical organs (Dunbar et al. 1994; Varlotto et al. 1996). This experience led to application of stereotactic techniques in numerous extracranial tumour sites, including that of lung (Blomgren et al. 1995; Umeatsu et al. 1998, 2001; Fukumoto et al. 2002; Nagata et al. 2002; Hara et al. 2002; Hof et al. 2003; Onimaru et al. 2003; Whyte et al. 2003; Lee et al. 2003; Timmerman et al. 2003). While initial studies included patients with lung metastasis and those with early stage non-small cell lung cancer, more recent reports concentrated exclusively on the latter. What these studies provided is new impetus for radiation therapy in early stage non-small cell lung cancer using one or more high-dose fractions with different planning and execution systems, mostly used alone, i.e. without additional external beam radiotherapy in, mostly again, unfavourable patient populations, sometimes being worse that that usually seen in similar studies with external beam radiation therapy alone. Initial results are indeed impressive. Local tumour control was obtained in at least 85% of patients, while 2- to 3-year survivals went up to 60%–70%, all accompanied with very low toxicity. These results await longer follow-up and possible comparison with traditional, external beam radiation therapy, before wide clinical application.

3.1.1.10 Conclusions

Early stage non-small cell lung cancer undergoes radiation therapy alone for several reasons. Although this patient population must be considered unfavourable, radiation therapy alone appears to be an efficient treatment method in these patients which are frequently named as technically operable, medically inoperable early stage non-small cell lung cancer patients. Although survival figures are still lower than

those obtainable with surgical candidates, even when clinically staged, with high-dose radiation therapy the median survival times of up to 30 months and 5-year survival of up to 30% have been obtained. These figures are even better when cause-specific survival is used. Various radiation therapy characteristics are examined showing that there seems to be a favourable effect of high doses on outcome, as well as there seem to be favourable effects of smaller size/lower stage. While there is no general agreement on the use of elective nodal irradiation, some tumours (e.g. small, peripheral lesions) seem the most suitable for limited radiation therapy. Unfortunately, discrepancies between surgical and radiotherapeutic series regarding the staging procedures, treatment procedures in this disease as well as the documentation of the pattern of failure make any conclusion unreliable. However, they call for more cooperation between technology and biology in order to more selectively apply one or other approach. Suggesting that limited field radiation therapy must be used for the sake of dose escalation (leading to better tumour control and/or less toxicity) would inevitably lead to misuse of these technologies and false interpretation of the results. The pattern of failure after radiation therapy alone clearly identified local component as predominant, while observed rare isolated nodal relapses are in contrast with surgical findings in the same disease. Of a number of pre-treatment patient and tumour characteristics occasionally examined gender and age probably do not influence survival. Performance status and weight loss may exert its influence on survival, but possible effects of tumour location and histology remain controversial. Reported toxicity of radiation therapy is confined to mild to moderate bronchopulmonary and oesophageal toxicity. Although it is reported as a rare event, except in cases with very high doses when given after conventional planning, it's reporting needs to be substantially improved and systematically addressed. Quality of life is an issue completely underrepresented and needs to be focused upon, especially with expected increase in the long-term survivors with the use of sophisticated tools for treatment planning and delivery which will enable further dose escalation in this disease.

Some, if not all, of the issues discussed above could have been settled in the case of existing prospective randomised studies. Unfortunately, they are lacking, although patients with early stage non-small cell lung cancer were sometimes included in prospective studies evaluating the effect of various altered fractionated regimens, alone or with concurrent chemotherapy, mostly, however, without specifying its outcome. Pure hyperfractionated radiation therapy alone or with either induction or concurrent chemotherapy (Cox et al. 1990; Sause et al. 1995; Lee et al. 1996; Komaki et al. 1997), accelerated radiation therapy via concomitant boost (Byhardt et al. 1993) were used, but without specifying the outcome in this patient population. When accelerated hyperfractionated radiation therapy using concomitant boost was used with doses as high as 73.6–80 Gy, the median survival time for patients with stage I/II was 34 months and the median local progression-free survival was 23 months (Maguire et al. 2001). In an Australian study (Ball et al. 1999), patients randomised to concurrent carboplatin versus conventionally fractionated radical radiation therapy (60 Gy) alone achieved the median survival time of 41.6 months versus 19.5 months and an estimated 2-year survival of 77% versus 27%, p=0.042), although stage was not an independent prognosticator in that study involving a majority of stage III non-small cell lung cancer patients. In a recent subset analysis (Bentzen et al. 2000) of 169 patients with stage I–IIA non-small cell lung cancer initially enrolled in the continuous hyperfractionated accelerated radiotherapy study (Saunders et al. 1999) there was a benefit of 13% at 2 years (37% vs. 24%) and 6% at 4 years (18% vs. 12%), for continuous hyperfractionated accelerated radiation therapy (54 Gy) over conventionally fractionated radical radiation therapy (60 Gy), respectively. It showed again that the community of radiation oncologists dealing with lung cancer must use prospective randomised trials to ask simple and meaningful questions and to obtain answers which may be used instantly in the clinic, a task of major importance in this disease.

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3.1.2 Postoperative Radiotherapy for Non-Small Cell Lung Carcinoma

Jeffrey C. Haynes and Mitchell Machtay

CONTENTS

in 12% of patients with stage I disease, but 41% of patients with stage II disease. A cooperative group experience (the Ludwig Lung Cancer Study group) found that 41% of first failures were intrathoracic, while 34% were extrathoracic (Anonymous 1987). The most common intrathoracic site was the bronchial resection line (16% of all patients), followed by the ipsilateral nodal region (13%), the contralateral intrapulmonary region (12%), and the ipsilateral intrapulmonary region (11%).

These studies suggest that local failure is a considerable problem among patients with resected non-small cell lung cancer (NSCLC) and that local failure often occurs as the first site of failure. These data imply that postoperative radiation therapy (PORT) might improve local-regional control and therefore could lengthen the survival of patients with lung cancer, particularly among stage II+ patients. The patterns of failure data have served as the primary rationale for the use of PORT over several decades of radiation oncology.

3.1.2.1 Patterns of Failure Following Surgery Alone

While lung cancer is considered a "systemic disease," local recurrences after definitive surgery are not uncommon. In one series of stage I patients, 39% of first failures were intrathoracic (26% ipsilateral) (Feld et al. 1984). A series from the Mayo Clinic found that 19% of first recurrences in stage I NSCLC were local failures (Pairolero et al. 1984). Immerman et al. (1981) found that local failure only occurred

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3.1.2.2 Results of PORT in Patients with Pathologic Stage I NSCLC

Patients with completely resected stage I NSCLC have a relatively favorable prognosis with surgery alone, and postoperative radiotherapy (PORT) has not proven beneficial. Only one randomized study in the literature has demonstrated a significant survival benefit (Trodella et al. 2002). A randomized study published in 1980 demonstrated that survival among stage I (pN0) patients is shortened by PORT (24% vs. 43% at 5 years) (van Houtte et al. 1980). A second randomized study published more recently (1996) showed no benefit to PORT and potential detriment among the subset of stage I patients with T2N0 disease (Lafitte et al. 1996). One more recent small randomized study, however, does show a significant local-regional control and survival advantage to the use

of PORT in a highly selected population (Trodella et al. 2002).

These mixed results are not extremely surprising, since (as noted above), historical series have shown that local-regional recurrences are relatively uncommon after definitive surgery. Since distant metastatic failure is substantially more likely than local-regional failure, the addition of a local modality such as postoperative radiotherapy can not be expected to improve survival.

3.1.2.3 Results of PORT in Stage II and III (Node-Positive) NSCLC

3.1.2.3.1 Non-Randomized Studies

Sawyer et al.'s (1997) retrospective review of the Mayo clinic experience showed a dramatic benefit to PORT among N2 patients. Patients receiving PORT had an actuarial 4-year survival of 43% versus 20% for the surgery-alone group. The two groups were well balanced with respect to gender, age, histology, tumor grade, involved N1 lymph node number, and number of mediastinal lymph node stations dissected or involved. These results appear to confirm the data from other retrospective reports published in the 1980s (Choi et al. 1980; Chung et al. 1982; Kirsh et al. 1976). However, these papers can be criticized as falling short of the high level of evidence demanded by modern evaluators of medical therapeutics.

3.1.2.3.2 Randomized Controlled Trials

The results of major randomized trials of postoperative radiotherapy for NSCLC are described in Table 3.1.2.1. The best known of these studies is probably the Lung Cancer Study Group (LCSG) Trial, published in 1986 (Weisenburger et al. 1986). This trial found that PORT had no impact on survival but dramatically reduced the rate of local recurrence. Patients with pathologic N2 disease had a reduction in the overall rate of recurrence as well. Importantly, only selected N2 patients were eligible for the LCSG trial; the most superior mediastinal node had to be proven negative after a thorough mediastinal lymph node dissection. In community practice many surgeons sample only a few mediastinal lymph nodes and thus many patients may have occult N2 disease. Therefore, the LCSG finding that PORT is of little benefit for N1 patients may perhaps not be generalized to all communities.

Table 3.1.2.1. Results of selected randomized trials of postoperative radiotherapy (PORT) for NSCLC

Study	Number of patients	Stage	XRT dose (Gy)	Survival with XRT	Survival without XRT	LRF with XRT	LRF without XRT
Belgium (van Houtte et al. 1980)	202	I--III	60	24%[a]	43%[a]	2%	11%
LCSG773 (Weisenburger et al. 1986)	230	II,III	50	40%	40%	3%[a]	21%[a]
CAMS (Feng et al. 2000)	317	II,III	60	43%	41%	13%[a]	33%[a]
Lille (Lafitte et al. 1996)	163	I	45--60	35%	52%	15%	17%
MRC LU11 (Stephens et al. 1996)	308	II,III	40	25%	25%	18%[a]	29%[a]
Austria (Mayer et al. 1997)	155	I--III	50--56	30%	20%	6%	24%
GETCB (Dautzenberg et al. 1999)	720	I--III	60	30%[a]	43%[a]	28%	34%
Slovenia (Debevec et al. 1996)	74	III	30	32%	20%	[b]	[b]
Italy (Trodella et al. 2002)	104	I	50	67%[a]	58%[a]	2%[a]	22%[a]

[a] Statistically significant difference ($p \leq 0.05$) [b] Data not available.

Several other randomized controlled trials (RCTs) demonstrated an improvement in local control but never more than a trend towards improved survival. The MRC Lung Cancer Working Party trial found an increase in the time to "definite" local recurrence (Stephens et al. 1996). Mayer et al. (1997) found that PORT offered a significant improvement in local control and almost twice the recurrence-free survival (p=0.07 for the latter).

The outcome of one RCT stands in stark contrast to those of the others. The trial by Dautzenberg et al. (1999) not only failed to show any significant benefits to PORT; it showed a dramatically inferior 5-year survival rate in the PORT arm (30% vs. 43%, p=0.002). This study was not limited to patients with node-positive disease; approximately 30% of the patients in the trial had pN0 disease, and the study did not stratify by stage or nodal status. In addition, many of the deaths in the trial likely resulted from suboptimal radiation technique. Patients were treated to 60 Gy, a high dose usually reserved for gross disease, in daily fractions as large at 2.5 Gy. Given the association between fraction size and toxicity to the heart and lungs (Stewart et al. 1995; Movsas 1995), it is not surprising that "non-cancer-related deaths" in this study were noted to occur at a higher rate in those patients treated with >2 Gy per fraction (26% vs. 16%–18%) (Dautzenberg et al. 1999). Furthermore, the authors note that "an additional dose of 20 Gy was delivered by lateral and/or oblique fields." As noted later in this chapter, lateral fields may increase serious pulmonary complications. The results of the Dautzenberg trial can probably not be generalized to modern radiotherapy for stage II and III patients.

3.1.2.4 The PORT Meta-analysis

In response to the lack of statistical power of the existing RCTs, the PORT Meta-analysis Trialists Group attempted to bring together all the existing randomized data in an effort to settle the question of PORT in NSCLC (PORT 1998). It should be noted that the Dautzenberg trial (described in the meta-analysis as being two trials) weighs heavily in the meta-analysis, accounting for 728 of the 2128 patients considered. The meta-analysis found that PORT had a significant adverse effect on survival, with a hazard ratio of 1.21 (95% CI 1.08–1.34) (PORT 1998). This result translates into a 7% decrease in absolute survival, from 55% to 48%. Subgroup analysis reveals that the survival disadvantage is concentrated in the N0 and N1 patients. Among patients with pathologic N2 disease, a statistically insignificant trend toward better survival with PORT was observed (hazard ratio=0.96).

There are a number of problems with the design and interpretation of the PORT meta-analysis; these shortcomings have been detailed elsewhere (Machtay et al. 1999). Briefly, these problems include the following:

- Inappropriate lumping (including patients with pathologic stage I disease along with node-positive disease in the same meta-analysis).
- Unexplained exclusion of at least one randomized trial that appeared to demonstrate a trend toward improved outcome with PORT (Mayer et al. 1997).
- Limited information to confirm that patients in the randomized trials included in the meta-analysis met the usual medical criteria to safely receive PORT.
- Limited information regarding the surgical techniques used in the randomized trials included in the meta-analysis; as shown in Table 3.1.2.2, an unusually large number of patients underwent pneumonectomy.
- Fifth and most importantly, the studies in the meta-analysis probably utilized radiotherapy techniques that would today be considered outdated and unsafe. These include the use of lateral radiation fields, Cobalt-60 source radiotherapy, large daily radiation fraction size, and high total PORT doses.

All of these biases conspire to efface any possible survival benefit of PORT for NSCLC in the meta-analysis. Even apart from the question of bias, a meta-analysis should not be regarded as the final word on a subject. The history of meta-analysis makes clear the fallibility of the process (LeLorier et al. 1997). The meta-analysis of PORT for breast cancer found that postmastectomy irradiation for breast cancer worsened survival (Cuzick et al. 1987). Subsequent well-designed randomized trials have subsequently demonstrated a survival benefit when patients are appropriately selected and treated with modern techniques (Ragaz et al. 1997; Overgaard et al. 1997). The postmastectomy example is not unique. In the treatment of lung cancer with chemotherapy, a summary of studies using suboptimal chemotherapy (i.e. alkylator agents alone) showed a decremental effect on survival, while treatment with modern (cisplatin-based) chemotherapy shows an advantage (Stewart 1995).

Table 3.1.2.2. Type of surgery used in selected randomized trials of postoperative radiotherapy (PORT) for NSCLC

Study	Surgical procedure (%)		Radical hilar/mediastinal lymph node dissection? (yes/no/unknown)
	Less than Pneumonectomy	Pneumonectomy	
Belgium (van Houtte et al. 1980)	60	40	Unknown
LCSG773 (Weisenburger et al. 1986)	45	55	Yes; most cephalad node removed must be negative
Lille (Lafitte et al. 1996)	80	20	Yes
MRC LU11 (Stephens et al. 1996)	48	52	No
GETCB (Dautzenberg et al. 1999)	58	42	No
Slovenia	58	42	Yes
Austria (Mayer et al. 1997)	76	24	Yes
Italy[5]	91	9	Yes

Finally, even though no randomized study shows a clear survival advantage to PORT for patients with stage II and III disease, PORT may provide benefits that can not be measured in a meta-analysis. Specifically, the prevention of local-regional relapse may be an important component of quality of life for patients with cancer. Mediastinal relapse can cause airway obstruction, hemoptysis, dysphagia, and/or chest pain and is rarely controllable.

3.1.2.5 Subacute/Late Toxicity of PORT

While the acute toxicity of PORT is relatively modest (Keller et al. 2000), the potential for subacute and/or late toxicity (cardiopulmonary) appears to be significant. Despite all of the problems with the PORT meta-analysis described above, the data strongly suggest an unrecognized, important potential for severe toxicity with PORT. In the meta-analysis, 19% of 548 coded deaths in the PORT group were due to causes other than lung cancer (PORT 1998). In contrast, in the non-PORT group, only 11% of 522 coded deaths were due to causes other than lung cancer. The Dautzenberg trial reported that at 5 years, the rate of death from intercurrent disease (DID) was 32% for PORT vs. 8% (surgery alone control group) (Dautzenberg et al. 1999). It is plausible that some cases of serious radiation pneumonopathy were mistaken for bronchopneumonia or other forms of cardiorespiratory failure.

Second, careful examination of the survival curves in the meta-analysis reveals that the survival curves begin to separate at 3 months following treatment and continue to widen until the 1-year mark, after which they remain parallel. Death between 3 and 12 months following radiotherapy is consistent with radiation pneumonopathy (see Fig. 3.1.2.1) and perhaps the development of radiation cardiac injury.

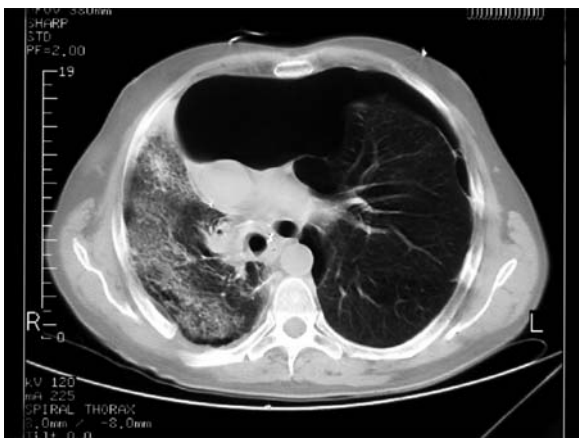


Fig. 3.1.2.1. This patient was treated to 60 Gy postoperatively after lobectomy revealed pathologic stage T3N1M0 disease with a positive resection margin. Several months after completing PORT, he began having progressive respiratory insufficiency, culminating in severe respiratory distress. The thoracic CT scan shown here demonstrates severe radiation pneumonitis and evolving fibrosis of the ipsilateral lung and a contralateral pneumothorax. The patient was treated with corticosteroids, antibiotics, and contralateral chest tube placement and recovered satisfactorily after hospitalization

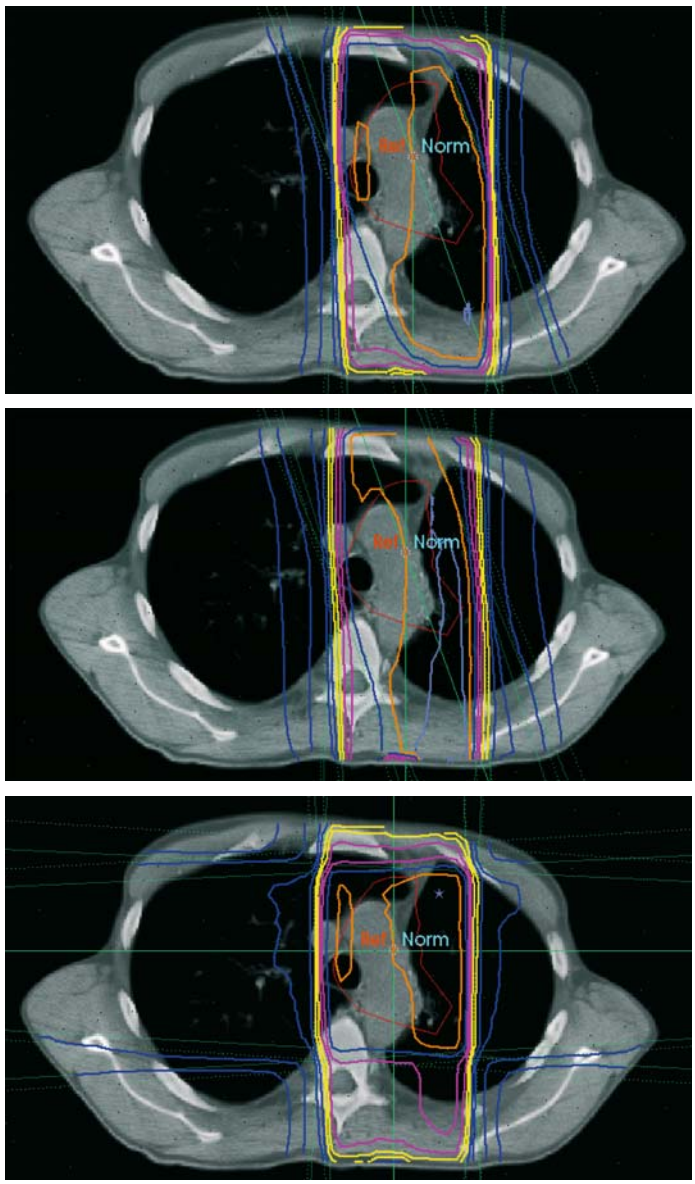
These data strongly suggest that potential benefits of PORT (reduction of local recurrence and improved lung cancer-specific survival) have been offset by life-threatening toxicity, particularly in stage I and II NSCLC. This pattern was also observed in early randomized studies of postmastectomy chest irradiation for breast cancer (Cuzick et al. 1987; Marks and Prosnitz 2000).

If severe toxicities from postoperative radiotherapy can be prevented, it is possible that the oncologic benefits of PORT may be better realized. Non-randomized data suggest that with the use of modern radiotherapy techniques, the risk of intercurrent deaths after PORT is comparable to that seen in an age-matched population (Machtay et al. 2001).

3.1.2.6 Proper Radiotherapy Techniques for PORT

3.1.2.6.1 Fields

The currently accepted field arrangement delivers approximately 40 Gy in opposed AP/PA fields and then spares the spinal cord by delivering the remaining dose with opposed oblique fields offset 20°–35° from midline (see Fig. 3.1.2.2). Linear accelerator based therapy is utilized; retrospective data suggest that the use of Co-60 source radiotherapy is associated with a higher rate of death from non-cancer cause (Philips et al. 1993), perhaps related to increased scatter to normal lung



a
b
c

Fig. 3.1.2.2a–c. These images depict radiotherapy dosimetry for typical postoperative treatment to 54 Gy. **a** Treatment with 40 Gy via AP-PA technique, followed by an opposed-oblique boost to 54 Gy, all treatment administered via 6-MV photons from a linear accelerator. **b** The identical treatment plan administered via Co-60 photons; note the increased radiation dose scatter into uninvolved lung parenchyma, despite less satisfactory clinical target volume coverage as determined by dose volume histogram analysis. **c** The use of a lateral radiotherapy beam as part of the boost field is shown; although target volume coverage is adequate, excessive uninvolved lung parenchyma is exposed

tissue. Field arrangements should not include lateral fields. Lateral fields dramatically increase the volume of irradiated lung tissue, which is generally considered the pivotal factor in the prediction of radiation pneumonopathy (Graham et al. 1999; Marks et al. 1997). Graham et al. (1999) strongly recommend that the V20 (the volume of lung irradiated to 20 Gy or above) be kept <25% to maintain a low risk of radiation pneumonopathy and warns that when the V20 exceeds 35%, the risk of life-threatening pneumonopathy rises exponentially. These criteria are likely to be particularly relevant to the postoperative patient, who already has impaired pulmonary reserve due to the rigors of surgery, missing lung tissue, and probable underlying chronic lung disease.

In order to minimize the volume of lung irradiated, the clinical target volume (CTV) for PORT should not include large portions of the lung parenchyma but instead focus on the bronchial stump, the ipsilateral hilum, and mediastinum. These correspond to the sites most at risk for local recurrence, particularly the most highly symptomatic and unsalvageable types of local recurrence.

More controversial is the question of whether or not to irradiate the ipsilateral supraclavicular fossa. Supraclavicular nodal involvement is not uncommon when rigorously assessed by imaging (Fultz et al. 2002) and is strongly related to the presence of positive mediastinal nodes. An autopsy study of 203 patients with NSCLC who died within 1 month after definitive surgery showed that 5% harbored occult supraclavicular disease (Matthews et al. 1973). However, most studies have been unable to conclude a benefit to elective supraclavicular irradiation. In a retrospective study of over 1000 patients with inoperable NSCLC treated with radiotherapy on RTOG protocols, Emami et al. (2003) showed that the failure to adequately irradiate the supraclavicular fossa rarely resulted in clinical supraclavicular recurrence (2%). In the Chinese randomized trial of PORT, the rate of supraclavicular nodal failure was the same in the irradiated versus unirradiated groups (13.4% vs. 11.7%) (Feng et al. 2000). In that study, supraclavicular irradiation was used in the PORT arm only if the very high (level 1--2) mediastinal nodes were positive. The decision on whether or not to include the supraclavicular fossa should be highly individualized.

3.1.2.6.2 Radiotherapy Dose

Because many patients would not suffer local recurrence even if no radiotherapy were given, a goal in PORT is to minimize cardiopulmonary complications. Higher doses to the heart have been clearly associated with cardiac mortality amongst Hodgkin's disease patients (Hancock et al. 1993; Zinzani et al. 1996). In canine models radiation damage to myocardial connective tissue increases significantly above a threshold dose of 62 Gy in 2-Gy fractions and heart failure ensues (McChesney et al. 1992). As noted above, radiation pneumonopathy is closely related to radiotherapy dose-volume relationships (Graham et al. 1999). Table 3.1.2.1 shows that the randomized trials that showed statistically significant detrimental effect of PORT used the highest radiotherapy doses (60 Gy).

A study at the University of Pennsylvania suggested that while overall there was no significantly increased risk of death from intercurrent disease (DID) after PORT (compared with the expected rate for age-matched controls), there was a trend toward more DID in patients treated to higher cumulative radiotherapy doses. The crude risk of death by intercurrent disease was 2% among patients treated to <54 Gy but 17% among those treated to >=54 Gy, which bordered on significance (p=0.06) (Machtay et al. 2001).

In the Penn experience, there was no noticeable relationship between the rate of local-regional control and radiotherapy dose. In another retrospective series, Emami et al. (1987) found a trend toward better local-regional control with 60+ Gy, but the results were not statistically significant (p=0.53).

We currently recommend a dose of approximately 50 Gy in standard fractionation for most patients treated with PORT. The LCSG randomized trial utilized this dose and had excellent local-regional control (Weisenburger et al. 1986). This dose was also used in the recent Intergroup randomized trial and demonstrated a high rate of local-regional control (Keller et al. 2000). Selected patients felt to be at particularly high risk for local-regional recurrence may be considered for additional boost radiotherapy dose if carefully given via highly conformal techniques.

3.1.2.6.3 Time Interval Between Surgery and Radiotherapy

Hypothetically, a longer interval between surgery and radiotherapy is detrimental. The tumor cells would have a greater opportunity to repopulate, and radiation is less effective against a larger mass of tumor cells. Data from sites other than the lung suggest a

detrimental effect from a long interval; a review of the literature by Huang et al. (2003) found that there was strong evidence of a decrease in local control with long intervals in radiation in breast cancer or head and neck cancer (Huang et al. 2003).

However, the only study to examine the question in NSCLC found that a longer delay (>36 days versus <36 days) after surgery resulted in a higher probability of local-regional control and lung cancer-specific survival (Wurschmidt et al. 1997). This study was retrospective, and it is possible that selection bias accounted for patients with more negative prognostic factors being referred to start PORT more rapidly.

3.1.2.6.4 Follow-Up/Supportive Care

Close follow-up is probably important after PORT for NSCLC. Prompt recognition and treatment of radiation pneumonopathy could reduce morbidity and mortality. A patient who presents with pulmonary symptoms greater than grade 1 after recent thoracic irradiation should undergo an intense diagnostic workup to identify pulmonary infection, pulmonary embolism, or recurrent cancer. This may include high-resolution CT scan, bronchoscopy, and/or PET scan. If grade 2 or greater radiation pneumonitis is diagnosed, corticosteroids should be started promptly and the patient referred to a pulmonologist for help in management (Movsas et al. 1995; Machtay 2004). Particular attention and prophylactic medications should be used to prevent steroid-related complications including infection, diabetes, gastritis, and osteoporosis.

3.1.2.7 PORT – Special Cases

3.1.2.7.1 Sublobar Resection

Some patients are medically unable to undergo a lobectomy and thus undergo sublobar resection such as wedge resection or segmentectomy. Attempts at these lesser resections have been associated with high rates of local recurrence, as documented in a randomized trial by the LCSG (Ginsberg and Rubinstein 1995). A prospective non-randomized trial by the CALGB investigated the use of PORT (Bogart et al. 2000). While the postoperative radiotherapy treatment was feasible, it was felt that the amount of lung irradiated in order to cover the operative bed (staple line and surrounding tissue) was excessive for this fragile patient population and further prospective studies of this design are not planned (Bogart et al. 2000).

Several studies have attempted intraoperative brachytherapy to improve local control following sublobar resection. Lee et al. (2003) implanted iodine-125 seeds along the resection margin after limited resection in 33 stage I patients who were not candidates for lobectomy or pneumonectomy. After a median follow-up of 51 months, the authors observed a 5-year survival of 67% for T1N0 patients and 39% for T2N0 patients, with two local recurrences in the group. Encouraging results with sublobar resection plus brachytherapy were also reported by Chen et al. (1999), and the American College of Surgeons Oncology Group (ACOSOG) is developing a phase II multicenter randomized trial to rigorously assess this technique.

3.1.2.7.2 Positive Margin

There are very little data analyzing the role of PORT for patients who underwent resection with a positive resection margin(s). While common sense would dictate that PORT should be mandatory after incomplete resection, results have been inconsistent (Law et al. 1982; Kaiser et al. 1989; Gebitekin et al. 1994). Techniques similar to that described above would seem appropriate, with boost to as small a radiotherapy field as possible to approximately 59.4 Gy in standard fractionation. A retrospective review of the University of Pennsylvania experience suggested no significant differences in outcomes between patients irradiated for positive versus negative margins (Machtay et al. 1998).

3.1.2.7.3 Chest Wall Invasion

Patients with chest wall invasion but negative nodes (T3N0) are still candidates for aggressive resection, but they do not appear to gain significant benefit from external beam radiotherapy. A small retrospective study of 35 patients with chest wall invasion found that those receiving radiation had a higher survival than those treated with surgery alone (56% vs. 38%, no *p* value published) (Patterson et al. 1982). While patients were not randomly assigned to radiation,

the radiated patients were more likely to have residual disease or mediastinal node involvement. In the Sloan-Kettering series of 69 patients with chest wall invasion from Pancoast tumors, the addition of brachytherapy resulted in a trend towards improved survival following complete resection (35% vs. 54% at 5 years, p=0.15) (Ginsberg et al. 1994).

3.1.2.8 Postoperative Radiotherapy in the Era of Chemotherapy

Until the 1990s, NSCLC was considered highly chemoresistant and the role of chemotherapy was primarily for palliation of visceral metastatic disease. However, the role of chemotherapy in combination with radiotherapy for inoperable stage III disease has been unequivocally confirmed (Marino et al. 1995), and data suggest that preoperative chemo or chemoradiation for resectable stage III disease improves survival over local therapy alone (Rosell et al. 1994).

The data have been more controversial in the postoperative setting. Several trials have investigated postoperative chemoradiation versus PORT alone in NSCLC. These studies, including a meta-analysis (Stewart 1995) and a subsequent large US Intergroup randomized trial (Keller et al. 2000), have shown no significant benefits to postoperative combined modality therapy over PORT alone. Subgroup analysis of a randomized European trial comparing pre-PORT multiagent chemotherapy to PORT alone suggested improved disease-free survival among 137 patients with pathologic N2 disease (Dautzenberg et al. 1995).

In 2003, results became available from the largest randomized study ever done comparing adjuvant chemotherapy versus control for resected NSCLC (LeChevalier 2003). This study, the International Adjuvant Lung Trial (IALT) did not specify the use or non-use of PORT but did stratify appropriately for its use in its statistical design. The IALT showed a statistically significant improvement in overall survival with adjuvant chemotherapy, with an absolute benefit of approximately 4.5% at 5 years. All stages of disease appeared to have similar gains; most patients with pathologic N2 disease received PORT in this study.

Further clinical trials of chemotherapy with PORT are ongoing. The RTOG recently completed a phase II trial combining PORT (50.4 Gy) with concurrent and consolidation carboplatin/paclitaxel for stage II and IIIA resected NSCLC (Graham et al. 2003). The 3-year actuarial survival was 61%, which compares quite favorably with the results from the previous US Intergroup study (Keller et al. 2000) (52%) and the IALT study (LeChevalier 2003) (45%).

As an alternative to delivering therapy after surgery, some centers aggressively try to identify patients with resectable stage IIIA/N2 disease preoperatively and offer them induction therapy. This induction or neoadjuvant therapy may include chemoradiotherapy (Albain et al. 1997, 2003) or chemotherapy alone (Rosell and Felip 2001; Roth et al. 1998). If chemotherapy alone is used preoperatively, the question remains whether or not to utilize postoperative radiotherapy. A retrospective study at M. D. Anderson considered PORT in combination with preoperative chemotherapy and showed that PORT improved local-regional control (81% vs. 54% at 5 years, p =0.07) (Taylor et al. 2003). However, survival was not improved, and was actually numerically lower in the PORT group, perhaps reflecting adverse selection bias (patients with a large amount of residual cancer after preoperative chemotherapy/surgery were more likely to be offered PORT).

3.1.2.9 Summary/Future Directions

The outcomes of currently published randomized trials of PORT could probably be improved upon simply by using modern treatment and planning equipment and adhering to the techniques outlined in this chapter. However, there remains a severe lack of high-level medical evidence to demonstrate an improvement in survival by adding PORT to complete surgical resection for NSCLC, particularly for early stage disease. Available data strongly suggest that PORT is contraindicated after complete resection of pathologic stage I NSCLC. Outside of the clinical trials settings, the use of PORT should probably be limited to patients with pathologic N2 disease or N1 disease characterized by one or more high risk factors for local recurrence such as the absence of a complete mediastinal lymph node dissection. Additional prospective trials studying PORT, perhaps postoperative chemoradiotherapy versus chemotherapy alone for selected patients, are indicated.

Future trials investigating PORT, in combination with systemic therapy, are clearly indicated but must utilize meticulous radiotherapy techniques. Gains in PORT could be obtained by reducing the potential for cardiopulmonary toxicity by strictly minimizing

the volume of heart and lung irradiated. This might be achieved by using improved radiotherapy planning techniques (e.g. multifield 3-D and/or intensity modulated radiation therapy) and/or improvements in radiotherapy delivery (e.g. respiratory gating technology). These technological advances must be combined with better means of predicting which patients harbor the greatest risk of local-regional recurrence, as identified via conventional and/or molecular prognostic markers.

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3.1.3 Photodynamic Therapy

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CONTENTS

3.1.3.1 Clinical Background

The cure rate among lung cancer patients has remained dismal at ≈13% due to the advanced disease stage at which the majority are diagnosed (Benfield 1991; Weir 2003). Cure will not be possible and the presence of either detected or unforeseen nodal or distant metastasis will ultimately cause morbidity and lead to cancer death. Advances of staging procedures, e.g. positron emission tomography (PET) scan have led to better pre-treatment assessment leading to a more tailored approach (van Tinteren et al. 2002). Because patients cohorts are more properly identified regarding their disease status, improvements of outcome in the various early stage cohorts only reflect stage migration, since the majority of patients still have advanced disease at presentation.

Advanced stage lung cancer poses a serious threat to quality of life, due both to local problems and distant metastasis. Central airway obstruction may lead to imminent suffocation and requires immediate intervention (Bollinger 2002; Dumon et al. 1984; Sutedja and Postmus 1994). Techniques that can achieve immediate results to restore airways passage are therefore appropriate. Obstruction may be caused by intraluminal tumor growth, extraluminal tumor compression or a combination of both. Coagulation to prevent bleeding followed by tumor debulking in combination with stent placement in the case of significant (residual) airway compression are key issues for interventional pulmonologists. There is agreement among experts with regard to several aspects of interventional pulmonology for both palliation and treatment with curative intent for early stage lung cancer (Sutedja and Postmus 1994; Bolliger et al. 2002; Colt and Dumon 1995; Mathur et al. 2003; Furuse et al. 1993; van Boxem et al. 1999; Mathur 2003). Treatment plans must be diligently considered to offer the optimal therapy. Patients referred to interventional pulmonologists are at risk because end-stage recurrences have usually failed chemo-radiotherapy. In addition imminent and poor physical condition reduce ventilation capacity much further, while one still has to solve the problems of central airways' obstruction (Dumon et al. 1984; Sutedja and Postmus 1994; Bolliger et al. 2002; Colt and Dumon 1995).

For operable patients, surgery and lymph node dissection are considered the standard approach. However, the risk of developing subsequent primaries (field cancerization) and the fact that many individuals may have limited pulmonary capacity (e.g. COPD), justify considering less invasive and morbid interventional strategies (Mathur et al. 2003; Furuse et al. 1993; van Boxem et al. 1998, 1999). Early detection may lead to a significant stage shift by finding more subjects with N0 lung cancer (Petty 2000; Lam et al. 1993). The integration of early diagnosis with minimally invasive procedures to preserve quality of life with optimal cost effectiveness are keys for success (Hayata 1996; Kato 1999). Diligent work-up is necessary, as currently the exact pathological TN status can be frequently only be determined retrospectively (Nagamoto et al. 1989; Usuda et al. 1993; Sutedja 2001). However, new staging and imaging procedures hold great promise for accurate assessment prior to intervention (Sutedja et al. 1996, 2001; Miyazu et al. 2002; Herder et al. 2001). Based on previous surgical and pathological data (Nagamoto et al. 1989; Usuda et al. 1993; Endo et al. 1998), certain patients cohorts with favorable prognosis can be identified, in whom a less aggressive intervention is warranted.

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Medically inoperable early stage lung cancers can be treated successfully with bronchoscopic therapy such as PDT (Hayata 1996; Sutedja et al. 1994; Vonk Noordegraaf et al. 2003), and non-lung cancer related morbidities and death remain important factors to be taken into account (Marcus 2000). The choice for a tailored approach for each particular patient is a valid one (Furuse 1993; Kato 1985; 2003). The role and limitations of photodynamic therapy (PDT), also in comparison with alternative bronchoscopic techniques, will be discussed.

3.1.3.2 Photodynamic Therapy

The concept of phototherapy was rediscovered by Western civilization at the beginning of the twentieth century through the Dane Niels Finsen and the Germans Oscar Raab and Herman von Tappeiner (Daniell and Hill 1991). This concept has raised much interest regarding "selective" approach of target tissues such as in malignancies. Dougherty et al. (1985) was the great initiator for research in photodynamic therapy (PDT) and Hayata et al. (1996) were the first to apply PDT in the treatment of lung cancer, especially with regard to centrally located tumor.

After administration of photosensitizers and allowing the sensitizer molecules to accumulate in the target tissue, illumination with light of the appropriate wavelength induces a photochemical reaction (Sutedja and Postmus 1996). The formation of toxic radicals, e.g., singlet oxygens, leads to immediate vascular thrombosis in the vascular bed, causing secondary hypoxia and tissue necrosis (Gomer et al. 1989; Nelson et al. 1988). The use of photosensitizers in correspondence with light in the infrared region for deeper penetration is desirable for treating bulky tumor mass (Braichotte et al. 1996). In contrast, early cancer consists of several cell layers thick only, justifying the use of a different wavelength in the case of using Photofrin II® for achieving superficial necrosis to prevent deep eschar formation, as clinical data failed to show that selective uptake of photosensitizers is clinically relevant (Kawaguchi et al. 1998; van Boxem et al. 2001; Grosjean et al. 1996; Wagnieres et al. 1998). Indeed, even with the use of new photosensitizer molecules, the issue of selective damage remains rather obscure. Local illumination is therefore the most probable reason for "selective" local damage of the target tissue, even with the use of new generation photosensitizers (Borle et al. 2003).

Many studies have used Photofrin II (di-hematoporphyrin ether) for lung cancer treatment (Sutedja and Postmus 1996). Hematoporphyrin derivatives such as Photofrin II are mixtures of poorly defined active components with moderate phototoxicity (Gomer et al. 1989). Sensitizer molecules are retained in the skin causing all patients to be potentially skin photosensitive for several weeks (Dougherty 1990).

Although new sensitizers have been developed to increase efficacy and reduce skin toxicity, there are still limitations for PDT in clinical practice. The two-step approach of injecting the sensitizers first and performing light illumination afterwards, precludes intervention for emergency cases such as in patients threatened with imminent suffocation. Late necrosis after PDT requires an additional bronchoscopic procedure for tissue debulking and prolonged skin toxicity limits patient mobility. PDT is therefore difficult to justify for treating end-stage cancers with limited life expectancy and is not the treatment method for imminent suffocation (Bolliger et al. 2002). Currently, many bronchoscopic techniques are available which can achieve immediate benefit. Therefore, the necessity for PDT should be carefully considered in each particular case.

Based on these factors, PDT can be compared with techniques such as cryotherapy and brachytherapy, in which the stepwise approach can be applied for non-emergency cases for treating symptomatic obstruction. Several studies in which PDT is compared to or used as an adjunct, have shown prolonged responses (Barber et al. 2002; Diaz-Jimenez et al. 1999). However, cost-effectiveness studies are lacking in which the skin-toxicity issue has been taken into account (Kato 1999). It is therefore understandable that immediate coagulation (Nd-YAG laser, electrocautery, and argon plasma coagulation) combined with mechanical tumor debulking, are the most applied techniques in many institutions. For treating extraluminal obstruction, stent placement is the only choice (Bolliger et al. 2002; Colt and Dumon 1995).

Several studies have shown the efficacy of PDT for treating early stage lung cancer (Edell 1992; Furuse 1993; Sutedja et al. 1994; Hayata et al. 1996; Sutedja and Postmus 2001; Grosjean et al. 1996; Awadh et al. 1997; Kato 2003). Many patients were treated because of medical inoperability (e.g., poor lung function, cardiac status). Surgery requires relatively wasteful removal of healthy lung parenchyma

because many centrally located cancers involve the bronchial spurs. The strategy in using PDT prior to surgical exploration, to enable less extensive resection, is based on the same principle (Edell and Cortese 1992; Cortese et al. 1997; Kato et al. 1985). Many data have shown the efficacy of PDT for treating early stage lung cancers, mainly in using hematoporphyrin derivatives, e.g., Photofrin II, as sensitizers (Sutedja and Postmus 1996, 2001). Recently mono-L-aspartyl chlorine e6 or NPE6 by Kato and co-workers seemed to achieve similar efficacy with less skin toxicity (Kato et al. 2003). Maier et al. (2002) in comparing 5-ALA – 5-amine levulinic acid which is converted by the tumor tissue itself to active sensitizers of photo-porphyrin IX – for treating more advanced cancers in comparison to hematoporphyrin derivatives, obtained less satisfactory results. In contrast, the results obtained by Awadh et al. (1997) in using 5-ALA in a limited number of early cancer patients seem quite promising. This underscores the basic principles of PDT and the exploitation of light-tissue physics to optimize efficacy (Braichotte et al. 1996). Clinical data using tetra(m-hydroxyphenyl)chlorine (m-THPC) and 5-ALA are scanty (Grosjean et al. 1996; Awadh et al. 1997; Kato et al. 2003; Maier et al 2002). Again the vascular effects of PDT may be the most important reason for achieving more profound tumor necrosis considering the use of systemic injection of photosensitizers in contrast to local application only. This may suggest the important aspect of angiogenesis in (pre-)neoplastic tissues regarding carcinogenesis (Keith et al. 2000).

Other bronchoscopic techniques have become increasingly popular with the recognition that accurate staging rather than technique per se is the most important determinant for cure (van Boxem et al. 1999, 2001). Supported by surgical and pathological databases showing the correlation between smaller tumor size and higher response rates (Nagamoto et al. 1989; Usuda et al. 1993; Endo et al. 1998) – also with regard to PDT data (Hayata et al. 1996) – combined with better staging methods, e.g., autofluorescence bronchoscopy, HRCT, endobronchial ultrasonography, and PET scan (Sutedja et al. 2001; Miyazu et al. 2002; Herder et al. 2001), the choice of a more tailored treatment without overkill will become the optimal strategy.

The curative potential of PDT for early stage cancer has been tested in a prospective study to define its role as an alternative for surgical resection (Edell and Cortese 1992; Cortese et al. 1997). PDT proved to be an effective modality, in which 43% of the patients were spared surgery and considered cured. However, as mentioned previously, phase II data using alternative bronchoscopic techniques seem equally promising (Mathur et al. 2003; van Boxem et al. 1999).

3.1.3.3 Alternatives to PDT

Several alternatives for treating intraluminal tumor are currently available based on arguments discussed above for obtaining immediate palliation and for treatment with curative intent. Lasers (Nd-YAG laser, Argon, CO2), electrocautery, argon plasma coagulation, cryotherapy, and brachytherapy are feasible and details of these techniques have been extensively reviewed (Sutedja and Postmus 1994; Bolliger et al. 2002; Mathur et al. 2003; van Boxem et al. 1999; Ono 1995; Deygas 2001). Generally speaking – again from the clinical perspective of dealing with imminent suffocation – one can obtain immediate symptomatic relief by tumor coagulation followed by debulking quicker than applying techniques that obtain secondary or late effects (cryotherapy, PDT, and brachytherapy). All these techniques have been shown to be effective in achieving palliation, i.e., restoring airway passage with symptomatic relief of dyspnea, hemoptysis, and obstructive pneumonia (Sutedja and Postmus 1994; Bolliger et al. 2002). The effectiveness of stenting also for end-stage terminal cancers has been shown (Bolliger et al. 2002; Colt and Dumon 1995).

Arguments have been raised that the limited number of patients with occult cancer treated in the various bronchoscopic studies does not justify the role of local bronchoscopic treatments for treatment with curative intent. However, less extensive surgical resection, e.g., segmentectomy and surgical bronchoplasty for patients considered high risk surgical candidates is considered legitimate (Kato 1985; Endo et al. 1998; Fujimura 2000). As early cancers in the central airways are only several cell layers thick (Auerbach 1961), the use of a fiberoptic bronchoscope under local anesthesia is an attractive and cost effective alternative to local intraluminal treatment for superficial early stage lung cancer in comparison to the more morbid surgical intervention (Pasic et al. 2004). The potential of various bronchoscopic techniques has been reviewed and guidelines have been published (Mathur et al. 2003; van Boxem et al. 1999). Early cancer is often diagnosed incidentally and many are missed during routine bronchoscopy

(Sato et al. 1998). Even in cases with positive sputum cytology, the extreme burden of repeat bronchoscopies is necessary to localize the lesions, while the average delay of almost 2 years before proper treatment can be given is also counterproductive for stage shift efforts. However, new strategies such as sputum examinations, autofluorescence bronchoscopy, high resolution CT scan, and endobronchial ultrasonography have increased the detection rate and accuracy in staging (Sutedja 2001, 2003; Miyazu 2002). New techniques also seem better in predicting the likelihood of malignant development than the conventional morphology classifications of pre-neoplastic lesions (Jeanmart et al. 2003; Pasic et al. 2003).

So far, inoperable patients with early stage cancer were the main candidates for bronchoscopic treatment. However, any bronchoscopic modality is potentially curative (Table 3.1.3.1), as long as "occult" N0 cancers have been staged properly (van Boxem et al. 1999, 2001; Sutedja et al. 2001; Miyazu et al. 2002). This is quite obvious, as true occult cancers are only several cell layers thick (3-mm range) (Auerbach 1961). Local treatment cannot achieve cure when regional lymph nodes already contain metastasis. Bronchoscopic treatment, be it PDT or other techniques, can only be successful for accessible cancer defined as ≈1-cm^2 surface area, ≤3-mm thickness and with distinct borders (Nagamoto et al. 1989; Usuda et al. 1993; Hayata et al. 1996; Edell and Cortese 1992; Corese et al. 1997; Fujimura et al. 2000). In retrospect, PDT data already indicated the limitations of bronchoscopic treatment as response rates were strongly correlated to tumor dimension (Sutedja et al. 1994; Hayata et al. 1996). Tumor growth in the deeper layers of the bronchial mucosa and nodal disease are limitations for any kind of local therapy. Therefore, there is no theoretical argument why intraluminal bronchoscopic treatment is not justifiable in carefully selected cases. The cutting edge of the scalpel will be combined with the cutting edge capacities of bronchoscopic treatment with clearly less morbidity and better outcome in terms of quality of life (Endo et al. 1998; Nakamura et al. 2001). New imaging facilities beyond the visible threshold of our eyes are currently being investigated in early clinical trials (Sutedja 2003). Recent studies using autofluorescence bronchoscopy, high resolution CT scan, and endobronchial ultrasound showed that bronchoscopic treatment with curative intent is a justifiable strategy in a carefully selected patient population (Sutedja et al. 1996, 2001; Miyazu et al. 2002; Herder et al. 2001). Extension proximal to the maximally feasible resection plane can be initially treated bronchoscopically to allow less extensive surgical removal (Kato et al. 1985).

Table 3.1.3.1. "Early stage" lung cancer in the central airways treated with curative intent using photodynamic therapy and other bronchoscopic treatment methods

Reference	Methods and number of patients	Response	Survival (months)
Hayata et al. (1996)	PDT (HpD) 123 lesions	CR 93% if <1 cm! CR 45% if >1 cm!	<60
Cortese et al. (1997)	PDT (Photofrin II) 21 patients with *23 resectable* lesions	Nine patients (43%) spared surgery!	>24
Grosjean et al. (1996)	PDT (m-THPC) 12 patients	CR 13/16 (81%)	3–38
Awadh et al. (1997)	PDT (δ-ALA) Six patients	CR 5/6 (83%)	
Ono et al. 1995	*HDR brachytherapy* 34 patients	CR 30/34 (88%)	3–30
Deygas et al. (2001)	Cryotherapy	CR 32/35 (91%)	20% failure >4 years
Vonk Noordegraaf et al. (2003)	Electrocautery	CR 31/32 (97%)	Median 5 years (2–10 years)
van Boxem et al. (1998)	Electrocautery 13 patients, 15 lesions	CR 80%: 10 patients 12 lesions	16–43

PDT, photodynamic therapy; HDR, high dose rate; CR, complete response = radiographically occult cancers with negative histology/cytology at follow-up.

3.1.3.4 Summary

With the introduction of managed care, the cost-effectiveness issue has rightfully become important in the management of lung cancer. Photodynamic therapy has catalyzed research activities in minimally invasive bronchoscopic techniques and proved that local treatment for a more cost-effective palliation and treatment with curative intent are valid principles (Sutedja and Postmus 1994; Kato 1999; Pasic 2004). Some bronchoscopic treatment methods are relatively cheap. Lasers and brachytherapy are more elaborate and only available in large institutions. Especially when the success rate is also determined by other factors such as accurate staging and costs, the integrated use of simple procedures such as electrocautery, argon plasma coagulation, and cryotherapy is inevitable. Implementation into daily clinical practice is much easier if techniques are simple additions to standard facilities without requiring complex logistics.

Therefore, both in the management of imminent suffocation and central early stage lung cancer, several cost-effective alternatives are available. One should not forget that screening programs are offered only to those considered surgically resectable (van Klaveren et al. 2002). Availability of minimally invasive techniques may not only justify early intervention for the medically inoperable individuals, but can provide an acceptable local treatment alternative with curative intent for those not considered surgical candidates (Vonk Noordegraaf et al. 2003). Treatment at the earliest stage such as in patients with carcinoma in situ is warranted (Venmans et al. 2000). The emergence of minimally invasive techniques provides us with cost-effective alternatives, rather than having to rigidly rely on conventional strategies as standard strategies. The way is clear to implementing early treatment intervention in a cost-effective manner. Especially because in lung cancer due to field cancerization, individuals remain at risk to develop subsequent primaries (Woolner 1984). The challenge is now to prove that screening and early detection can obtain significant stage shift and will remain cost-effective in reducing lung cancer mortality despite the issue of overdiagnosis (Black 2000).

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3.2 Locally Advanced Non-Small Lung Cancer

3.2.1 Radiochemotherapy in Locally Advanced Non-Small Cell Lung Cancer

Branislav Jeremić and Aleksandar Dagović

CONTENTS

3.2.1.1 Introduction

Locally advanced non-small-cell lung cancer (LA-NSCLC) represents a heterogeneous group of patients. According to the two staging systems widely adopted in the community of thoracic oncologists (Mountain 1986, 1997), this is synonymous to stage III, although numerous, mostly non-surgical reports, included also a proportion of patients with stage II disease into this group of patients. It should be noted that these staging systems are surgical, i.e. the major principle is surgical extirpation of the tumour and lymph nodes. The only issues which matter in these systems are the size of the tumour (e.g. 3 cm or 5 cm in largest diameter), its location (e.g. 2 cm or more from the carina), and extent of invasion into neighbouring structures (e.g. chest wall or heart). These systems do not take tumour volumes into account at all! That said, one major principle of anticancer action of both radiation therapy and chemotherapy, log-cell kill, is not considered to any extent. This is an extremely important issue, especially in a number of tumours which could have similar tumour volume, but which could have been assigned a different stage in the case of a different location or invasion of neighbouring structures. This has necessitated a revision of current staging systems, in order to take also tumour volume into account, as well as other factors such as presence or absence of pleural effusion, etc.

Another problem is that surgical systems used in the last two decades have grouped a number of T and N designations into the same stage. Even with a subdivision (to IIIA and IIIB), made in the first system used (Mountain 1986), there were still a number of various T and N designations. After moving T3No to stage IIB, in the recent staging system revision (Mountain 1997), there is still a total of 11 different designations; four in stage IIIA (T3N1, T3N2, T1N2, and T2N2) and seven in stage IIIB (T4N0, T4N1, T4N2, T4N3, T1N3, T2N3, and T3N3)! However, there has been no full investigation, even in cases of big multi-institutional, cooperative group trials, into outcome results of these various T and N substaging designations, i.e. there is no data on whether, e.g. T1N3 is better than T4N1, or indeed whether they were similar in outcome. This applies for all other staging designations in both surgical and non-surgical studies. We are, therefore, left without crucial information: what is the real impact of increasing T and N substage and is there a "trade-off" when the adverse effect of increasing T stage is, perhaps, levelled-off with decreasing N stage, or perhaps which one of these two substaging designations may be more important than the other one and if so, then when exactly? As a result of not solving these crucial questions, a community of thoracic oncologists continues to use surgical system in the design, performance and reporting of clinical studies. The change of staging system currently used and its better definition, followed by proven validity and utility, must be one of the priorities of future clinical work. Hopefully, this will provide more details regarding

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impact of a particular T and N substaging designation and lead to more precise evaluation of the outcome of both non-surgical treatment modalities.

LA-NSCLC has been the major battleground for investigating various treatment options. While surgery (e.g. in very selected T4N0), radiation therapy (altered fractionation regimens with curative intention in stage III or palliative hypofractionated regimens in mostly stage IIIB patients) and chemotherapy (in stage IIIB in numerous clinical studies investigating effect of various chemotherapeutic agents) can all be used alone in this disease, this is not such frequent practice nowadays in the majority of patients who can tolerate more intensive (combined) treatment approaches owing to the mounting evidence that the vast majority of patients should be treated with such a combined modality approach. In practice this means, a bimodality (radiochemotherapy) or a trimodality approach, the latter being detailed in Chap. 3.2.2.

3.2.1.2 Radiation Therapy Alone

Traditionally, LA-NSCLC has been managed by radiation therapy alone. Because radiation therapy was relatively well tolerated and offered good palliation, and because there have been few alternatives, there have been only a few studies validating its efficacy. The Veterans' Affairs group reported on a study where radiation therapy had been compared to best supportive care for LA-NSCLC. There was an improvement in the median survival time with radiation therapy, although no 2-year survivors were seen in either arm (Roswit et al. 1968). It should be clearly stated that at the time of this study staging procedures were rather primitive and it is likely that many patients in both arms probably had Stage IV disease (if modern imaging had been used). Also, radiation therapy techniques used in this study should also be considered outdated. More recently, similar results were obtained in a randomised study. The 2-year survival was 18% with radiation therapy dose of 50 Gy versus 0% for observation with palliative radiotherapy when severe local symptoms developed (Reinfuss et al. 1999). In another randomised cooperative group study from the US, patients were randomised to radiation therapy versus single agent vindesine (Johnson et al. 1990), while the third arm comprised both modalities. The study showed no survival advantage for radiation therapy. Again, however, it should be stressed that there was a substantial crossover in this trial, with many patients in the vindesine arm ultimately receiving thoracic radiotherapy. This study suggested no survival advantage to "early" radiation therapy but this should not be interpreted to imply no advantage at all for radiation therapy.

In spite of the shortcomings of these studies, radiation therapy has been considered as the mainstay of therapy for locally advanced non-small cell lung cancer. In the benchmark trial, continuous-course RT of 50- to 60-Gy doses has been shown to be superior to the 40-Gy split-course or continuous-course schedule (Perez et al. 1986) Consequently, the 60-Gy continuous-course schedule has been adopted as the standard radiation therapy in many radiotherapeutic centres all over the world, especially in the US. However, the results obtained with radiation therapy alone are unsatisfactory for locally advanced non-small-cell lung cancer, since the median survival time was approximately 9–10 months and the overall 5-year survival rate was only 3%–6% in prospective randomised trials (Holsti and Mattson 1980; Petrowich et al. 1981; Perez et al. 1987). Various retrospective and prospective randomised studies have revealed that both local and systemic failure play an important role in the poor survival of these patients (Petrowich et al. 1977; Cox et al. 1979; Perez et al. 1986). Thus, various means of increasing the likelihood of both local and systemic control were sought.

Various altered fractionation RT regimens have been used in order to improve local control (Cox et al. 1993; Saunders and Dische 1990; Byhardt et al. 1993). The Radiation Therapy Oncology Group (Cox et al. 1990) has investigated hyperfractionated radiation therapy with 1.2 Gy b.i.d. fractions and reported improved survival in a subgroup of patients with favourable prognostic factors treated with hyperfractionated radiation therapy with doses ≥69.6 Gy compared to that obtained with the standard treatment (60 Gy/30 fractions over 6 weeks). Continuous hyperfractionated accelerated radiation therapy was tested against standard fractionation radiation therapy in inoperable non-small cell lung cancer, including a proportion of stage I/II patients and it is shown to carry some benefit (Saunders et al. 1999). Unfortunately, this treatment design was extremely complicated for daily clinical practice which has prevented it from widespread use, even in the UK. Current attempts to modify it include the omission of weekend days or neoadjuvant chemotherapy, both of which effectively destroy its underlying principle, namely, accelerated fractionated radiation therapy to combat accelerated tumour clonogenic proliferation. Attempts have been seen in recent years to combine acceleration and hy-

perfractionation in a less demanding regimen, such as hyperfractionated accelerated radiation therapy which also proved to be effective in this setting. More data, however, are needed before widely accepting it in clinical practice.

What these altered fractionated regimens confirmed is the duality of failure patterns, with both local and distant failure playing an important role in ultimate outcome of patients treated with radiation therapy alone. These facts were recognised several decades ago and, coupled with poor survival figures, they stressed the need for inclusion of chemotherapy to better control this disease. The reason for adding chemotherapy to radical radiation therapy was to improve local/regional control while, at the same time, addressing the issue of possible distant spread, not addressed by radiation therapy. Unfortunately, the results were not encouraging and not different from that obtained with radiation therapy alone. Chemotherapy was usually given as an adjuvant (i.e. post-radiation therapy) and it consisted of non-platinum based drugs (Reynolds and O'Dell 1978; White et al. 1982). Failure of these studies was usually explained by radiation therapy-induced fibrotic changes in lungs that prevented successful blood/drug perfusion and, therefore, drug supply to the tumour-bearing area, and/or relative inefficiency of drugs available at that time, mostly non-platinum based chemotherapy (Reynolds and O'Dell 1978; White et al. 1982).

Regardless of this, radiation therapy and chemotherapy, mostly platinum-based, were considered as necessary components of successful treatment. And they have been increasingly practised around the world in the last two decades. A number of possible combinations have arisen, largely exploiting different aspects of such combinations, and frequently focusing on the issue of scheduling. Induction (neo-adjuvant) chemotherapy followed by radical radiation therapy (Dillman et al. 1990; Sause et al. 1995), "sandwich" chemotherapy and radiation therapy (LeChevalier et al. 1992), as well as concurrent radiochemotherapy (Schaake-Koning et al. 1992; Jeremic et al. 1995, 1996, 1998) have all gained widespread use, sometimes with very similar results obtained with these different approaches. To further obscure the overall picture, both radiation therapy and chemotherapy have evolved over the years. A number of different time/dose/fractionation radiation therapy regimens have been used (Cox et al. 1990; Byhardt et al. 1993; Saunders and Dische 1990). They paralleled the introduction of the third generation of drugs, namely paclitaxel (Johnson et al. 1996; Herscher et al. 1998), docetaxel (Millward et al. 1996; Mauer et al. 1998), vinorelbine (LeChevalier et al. 1994; Masters bet al. 1998), gemcitabine (Manegold et al. 1997; Vokes et al. 1998), irinotecan (Fukuoka et al. 1992; Oshita et al. 1997) and topotecan (Lynch et al. 1994; Perez-Soler et al. 1996).

3.2.1.3 Neoadjuvant (Induction) Chemotherapy Followed by Radiation Therapy

As stated many times, the major aim of this type of radiochemotherapy is to decrease tumour burden and to combat micrometastatic disease, believed to be present from the outset. When radiation therapy follows induction chemotherapy, the effects of chemotherapy may permit delivery of radiation to a reduced tumour volume. Increased drug delivery with less overall toxicity is also possible compared to concurrent administration. Potential disadvantages of induction treatment include a prolonged overall treatment time, excessive toxicity due to chemotherapy preventing or delaying the delivery of radiation and chemotherapy-induced tumour cell resistance resulting in reduced radiation efficacy, as well as accelerated tumour clonogenic repopulation, also expected to occur during the chemotherapy phase of the combined treatment (Byhardt et al. 1998; Byhardt 1999). There have been many phase II trials designed to evaluate whether or not survival is improved with the addition of induction chemotherapy to radiation therapy in patients with locally advanced non-small cell lung cancer versus radiation therapy alone. Although these trials have had conflicting results, several phase III trials (Table 3.2.1.1) and three meta-analyses have demonstrated a survival benefit, confirmed with recent updates providing long-term data.

In North America, the Cancer and Leukemia Group B (CALGB) 8433 trial is the landmark study of sequential radiochemotherapy versus radiation therapy alone for the treatment of locally advanced non-small cell lung cancer (Dillman et al. 1990). Between 1984 and 1987, 155 patients with clinical or surgical T3 or N2 and M0 non-small cell lung cancer were randomised to induction chemotherapy followed by radiation therapy or radiation therapy alone. All patients had a good performance status and minimal weight loss prior to study entry. Induction chemotherapy consisted of cisplatin (100 mg/m^2, days 1 and 29) and vinblastine (5 mg/m^2, days 1, 8, 15, 22 and 29).

Table 3.2.1.1. Randomised trials of induction chemotherapy followed by radiation therapy versus radiation therapy alone

Author	CT	RT dose (Gy)	MST (months)	p Value	3-Year survival
Dillman et al. (1990)	VP	60	13.7	0.012	23%
		60	9.6		11%
Sause et al. (1995)	VP	60	13.8	0.03	NR
		60	11.4		NR
LeChevalier et al. (1991)	VCPC	65	12.0	NR	21%[a]
		65	10.0		14%[a]
Cullen et al. (1997)	MIC	50[b]	13.0	0.056	14%
		50[b]	9.9		10%

CALGB, Cancer and Leukemia Group B; MRC, Medical Research council; CT, chemotherapy; RT, radiation therapy; MST, medians survival time; VP, vinblastine, cisplatin; VCPC, vindesine, cyclophosphamide, cisplatin, lomustine; MIC, mitomycin, ifosfamide, cisplatin; NR, not reported.
[a] 2-Year survival; [b] median radiation therapy dose.

Radiation therapy to a total dose of 60 Gy in 30 fractions was the same in both arms and began on day 50 in the combined-modality arm. The addition of chemotherapy did not impair the ability to deliver radiation therapy, with 88% of patients in the combined-modality arm and 87% of patients on the radiation therapy alone arm completing radiation therapy per protocol. Although there were no treatment-related deaths on either arm, the addition of chemotherapy increased the number of hospital admissions for vomiting (5% vs. 0%) and infection (7% vs. 3%). In the initial report, induction chemotherapy improved median survival (13.8 vs. 9.7 months, p=0.0066) and doubled the number of long term survivors with 23% of patients treated with radiochemotherapy surviving 3 years compared to 11% of those treated with radiation alone, prompting early closure of the study. Long-term 7-year follow-up confirmed that induction chemotherapy improves long-term and median survival (13.7 vs. 9.6 months, p=0.012) compared to radiation therapy alone (Dillman et al. 1996). Three other modern cisplatin-based trials have confirmed the CALGB experience.

The Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group trial randomised 458 eligible patients with good performance status, minimal weight loss and locally advanced non-small cell lung cancer to receive once-daily radiation therapy to 60 Gy in 2-Gy fractions with or without induction cisplatin and vinblastine (Sause et al. 1995). Patients randomised to a third arm received radiation therapy twice daily to a total dose of 69.6 Gy. Median survival was statistically superior (p=0.03) for the combined modality arm (13.8 months) versus either the standard radiation therapy arm (11.4 months), or the twice daily radiation therapy arm (12.3 months). Final results of this study confirmed an improvement in median survival for combined-modality therapy, but 5-year survival rates remained poor at less than 10% (Sause et al. 2000).

French experience with induction chemotherapy followed by radiation therapy was provided in a trial with radiation alone versus combined chemoradiation (LeChevalier et al. 1991). In this phase III trial, 353 patients with unresectable locally advanced squamous cell or large cell lung carcinoma were randomised to receive either radiation therapy alone (65 Gy in 2.5-Gy fractions) or three monthly cycles of cisplatin-based chemotherapy followed by the same radiation therapy regimen. There was a significant decrease in distant metastases for the combined-modality arm and the median (12.0 vs. 10.0 months) and 2-year survival rates (21% vs. 14%, p=0.02) were also improved (LeChevalier et al. 1992). Re-analysis revealed that only 8% of patients had continued local control at 5 years (Arriagada et al. 1997). Five-year survival rates remained poor at 6% and 3%, likely secondary to the high rate of local failure on both arms.

The Medical Research Council randomised 447 eligible patients with good performance status and localised, inoperable non-small cell lung cancer to receive radiation therapy alone or cisplatin-based induction chemotherapy followed by radiation therapy (Cullen et al. 1997). On both arms, the median radiation therapy dose was low at 50 Gy. Median survival was improved with the addition of chemotherapy (13.0 vs. 9.9 months, p=0.056), although this difference was of borderline significance.

As demonstrated by the above randomised trials, the addition of platinum-based induction che-

motherapy to radiation therapy results in improved survival versus radiation therapy alone. This is particularly true for short-term survival, but modest improvements in long-term survival have also been observed. Several smaller randomised trials have failed to confirm a survival benefit for the addition of induction chemotherapy, but these trials may have lacked the power to detect small differences in survival (Mattson et al. 1988; Morton et al. 1991; Crino et al. 1993; Planting et al. 1996). Three large meta-analyses have demonstrated a small but consistent survival benefit for the addition of induction chemotherapy to radiation therapy for locally advanced non-small cell lung cancer (Non-Small Cell Lung Cancer Collaborative Group 1995; Marino et al. 1995; Pritchard and Anthony 1996).

Since it was recognised that this type of combined radiation therapy and chemotherapy may bring an increase in the locoregional failures, attempts were made to include a more intensive latter (radiation therapy) part of the treatment. In such an attempt, Clamon et al. (1999) compared induction chemotherapy consisting of cisplatin/vinblastine followed by standard radiation therapy (60 Gy in 30 daily fractions) with or without concurrent 100 mg/m^2/week of carboplatin. There was no difference between the radiosensitized and non-radiosensitized groups regarding overall survival (the median survival time: 13.4 vs. 13.5 months; 4-year survival: 13% vs. 10%; p=0.74). These results showed a more sobering picture about induction cisplatin/vinblastine followed by standard radiation therapy that does not necessarily obtain good and lasting results, being inferior in the study of Clamon et al. (1999) to that expected from previous two studies (Dillman et al. 1990; Sause et al. 1995). They showed that even when sensitised by carboplatin, standard fraction radiation therapy can not compensate for accelerated proliferation of surviving tumour clonogenics which occurs during the induction (chemotherapy) phase of treatment. Furthermore, the results of the study by Clamon et al. (1999) do not differ from those obtained by hyperfractionated radiation therapy alone in the Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group study (Sause et al. 1995) or the same hyperfractionated radiation therapy (69.6 Gy using 1.2 Gy twice-daily) in the study of Jeremic et al. (1996).

More recently, in an attempt to further intensify the second part (radiation therapy) of the combined treatment, Vokes et al. (2002) reported on a randomised phase II study by the Cancer and Leukemia Group B (9431) which used two cycles of induction chemotherapy (cisplatin/gemcitabine or cisplatin/paclitaxel or cisplatin/vinorelbine) followed by two cycles of the same chemotherapy concurrently with conventionally fractionated radical radiation therapy (66 Gy) in 175 patients with unresectable stage III non-small cell lung cancer. Response rates were 74%, 67% and 73% for the three arms, respectively. While the median survival time for all patients was 17 months, 3-year survival rates for the three groups were 28%, 19% and 23%, respectively. Authors concluded that the use of concurrent radiochemotherapy could have led to the improvement in outcome when compared to previous Cancer and Leukemia Group B experience with induction treatments (Dillman et al. 1990, 1996; Clamon et al. 1999).

3.2.1.4 Concurrent Radiochemotherapy

This combined modality approach denotes the administration of both modalities at the same time, meaning that chemotherapy is given during the radiation therapy course. A number of variations exist, including chemotherapy being administered on a 3-weekly basis, bi-weekly, weekly, or daily, although concurrent radiochemotherapy employing third generation drugs (e.g. paclitaxel) also involved administration of the drug twice or thrice weekly. Whatever the design of concurrent radiochemotherapy, its main aim is to address the issue of locoregional and distant disease at the same time, from the outset of the treatment as intensively as possible. This, unfortunately, may lead to increased toxicity (mostly acute) which may require dose reductions or treatment interruptions, both adversely influencing treatment outcome. On the other hand, with this approach three radiobiological premises, namely spatial cooperation, independent cell kill and synergistic action, as postulated by Steel and Peckham (1979), can be exploited.

The initial question regarding the effectiveness of concurrent radiochemotherapy was whether it is more effective than radiation therapy alone. In a number of studies radiation therapy alone was tested against concurrent radiochemotherapy, the latter aiming mostly on an improvement at local tumour control. Prospective randomised phase III studies investigating this issue are outlined in Table 3.2.1.2 (Soresi et al. 1988; Schaake-Koning et al. 1992; Trovo et al. 1992; Blanke et al. 1995; Jeremic et al. 1995, 1996; Bonner et al. 1998; Ball et al. 1999; Groen et al. 2004). Some of the negative studies may be criticised because of a relatively low total radiation

Table 3.2.1.2. Randomised studies of RT versus RT and concurrent platinum-based CHT

Author	RT (dose/fractionation)	CHT drugs/timing	MST (months)	Survival	
				2-year	3-year
Soresi et al. (1988)	50.4 Gy in 28 fx	-	11		
	Same	P, 15 mg/m^2, weekly	16		
Schaake-Koning et al. (1992)	55 Gy split course	-	12	19%	2%
	Same	P, 30 mg/m^2, weekly	12	30%	13%
	Same	P, 6 mg/m^2, daily	14	31%	13%
Trovo et al. (1992)	45 Gy in 15 fx	-	10	13%	
	Same	P, 6 mg/m^2, daily	10	13%	
Blanke et al. (1995)	60–65 Gy in 30–33 fx	-	10	13%	
	Same	P, 70 mg/m^2, day 1, 22, and 43	11	18%	
Jeremic et al. (1995)	64.8 Gy (1.2 Gy b.i.d.)	-	8	25%	6.6%
	Same	C, 100 mg, day 1,2; E, 100 mg, E, day 1–3; weekly	18	35%	23%
	Same	C, 200 mg, day 1,2; E, 100 mg, day 1-5; weeks 1, 3, 5	13	27%	16%
Jeremic et al. (1996)	69.6 Gy (1.2 Gy b.i.d.)	-	14	26%	11%
	Same	C/E, each 50 mg, daily	22	43%	23%
Bonner et al. (1998)	60 Gy in 30 fx	-	8.6		5%
	60 Gy in 40 fx split +/- CHT	P, 30 mg/sqm; E, 100 mg/sqm, day 1–3 and 28–30	11.6		22%
Ball et al. (1999)[a]	60 Gy in 6 weeks	-	13.8	26%	10%
	Same	C, 70 mg/m^2 x 5 days, weeks 1 and 5	17.0	29%	8%
	60 Gy in 3 weeks	-	14.4	28%	13%
	Same	C, 70 mg/m^2 x 5 days, week 1	15.0	20%	5%
Groen et al. 2004	60 Gy in 30 fx	-	11.7		
	Same	C, 840 mg/m^2, CI, 6 weeks	11.8		
Cakir and Egehan 2004	64 Gy in 32 fx	-	9[b]		2%
	Same	P, 20 mg/m^2 x 5days, weeks 1 and 6	16[b]		10%

RT, radiotherapy; CHT, chemotherapy; MST, median survival time; P, cisplatin; C, carboplatin; E, etoposide; fx, fractions.
[a] Includes patients with early stage; [b] estimated from the available survival curve.

therapy dose (Soresi et al. 1988; Trovo et al. 1992) and chemotherapy being given in an insufficient total dose (Soresi et al. 1988). All three positive studies used protracted chemotherapy dosing. While an European Organization for Research and Treatment of Cancer study (Schaake-Koning et al. 1992) tested both daily and weekly cisplatin with split-course radiation therapy, showing superior outcome for daily cisplatin/radiation therapy, Jeremic et al. first used bi-weekly, and weekly (Jeremic et al. 1995), and then daily (Jeremic et al. 1996) carboplatin/etoposide with hyperfractionated radiation therapy doses of 64.8 (Jeremic et al. 1995) and then 69.6 Gy (Jeremic et al. 1996). In these two consecutive studies, the best results were obtained with low-dose daily chemotherapy given during the hyperfractionated radiation therapy course, with very encouraging 4- to 5-year survival rates being approximately 20% (Jeremic et al. 1995, 1996). As a rule, survival advantage in these three studies was a consequence of an advantage at local tumour level. Obviously, low-dose daily chemotherapy acted synergistically with radiation therapy, and enhanced its effects on local tumour level. As expected, no influence on distant metastasis control was noted. Recently, Cakir and Egehan (2004) provided additional evidence that concurrent radiation therapy (64 Gy in 32 daily fractions) and cisplatin (20 mg/m^2, days 1–5, weeks 2 and 6) offers survival advantage over the same radiation therapy alone. At 3 years, 10% patients survived in the combined group while only 2% survived in the radiation therapy lone group. The combined treatment approach also of-

fered better locoregional control (p=0.0001) and disease-free survival (p=0.0006), confirming previous observations of superiority of combined radiation therapy and platinum chemotherapy over radiation therapy alone.

Additionally, those studies/arms which used high-dose chemotherapy concurrently with radiation therapy observed no impact either on distant metastasis control, or on a local level. Another advantage of low-dose concurrent chemotherapy over high-dose chemotherapy and concurrent radiation therapy is that the former type of concurrent radiochemotherapy leads to less high-grade acute toxicity and, consequently, better treatment compliance, less treatment interruptions, which influence treatment outcome (Cox et al. 1993).

3.2.1.5 Neoadjuvant (Induction) Chemotherapy Followed by Radiation Therapy Versus Concurrent Radiochemotherapy

The induction chemotherapy studies showed a survival advantage for the combined approach owing to the improvement in the distant metastasis control, a finding in contrast to that of the concurrent approach studies, which unequivocally showed improvement in survival owing to the improvement in locoregional tumour control. Putting these data into the perspective of exploitable mechanisms of combined radiation and chemotherapy (Steel and Peckham 1979), one must identify the induction regimens as those enabling the therapeutic benefit due to spatial cooperation only. No independent cell kill can be noted because there was no significant difference in locoregional tumour control, as one may expect if such independent cell kill would have happened. Also, no enhancement of tumour response can be noted for the same reason. Contrary to these findings, in concurrent studies, spatial cooperation did not work, while both independent cell kill and enhancement of tumour response may have occurred. In the low-dose (daily) chemotherapy arms of the concurrent studies, however, it seems unlikely that independent cell kill occurred (and if so, then to a much lesser degree), thus leaving enhancement of tumour response as the only viable alternative.

Confirmation of these premises was recently provided by El Sharouni et al. (2003) who investigated the influence of waiting times for radiotherapy after induction chemotherapy by comparing CT scans done at the end of induction chemotherapy and those done for the purpose of radiotherapy planning. In 41% of potentially curable tumours they turned into incurable ones, with the median potential tumour doubling time being 29 days, much less than previously thought.

Since both of these approaches proved to be feasible and effective in practice, the next logical step, therefore, was to compare induction chemotherapy followed by radical radiation therapy with concurrent radiation therapy and chemotherapy. Currently, there are only two prospective randomised phase III studies evaluating concurrent versus induction chemotherapy and radiation therapy. Furuse et al. (1999, 2000) were the first to compare mitomycin, cisplatin, and vindesine chemotherapy given as either induction followed by radiation therapy (56 Gy) and the same mitomycin, cisplatin, and vindesine given concurrently with radiation therapy. Their first publication showed superior median survival time and 5-year survival (the median survival time, 16.5 vs. 13.3 months; 5-year survival, 16% vs. 9%; p=0.039) for concurrent regimen (Furuse et al. 1999). Subsequent data analysis, focusing on patterns of failure, identified an improvement in local tumour control (median time, 10.6 vs. 8.0 months; 5-year, 34% vs. 20%; p=0.0462) as a reason for an improvement in survival (Furuse et al. 2000). More recently, Curran et al. (2000) and Komaki et al. (2000) reported on the Radiation Therapy Oncology Group study 9410 which evaluated the same induction chemotherapy followed by radiation therapy as used by the Cancer and Leukemia group B 8433 (Dillman et al. 1990) and the Radiation Therapy Oncology Group 8808/Eastern Cooperative Oncology Group 4508 (Sause et al. 1995). It was compared with either standard fraction radiation therapy (60 Gy) and cisplatin/etoposide or hyperfractionated radiation therapy (69.6 Gy) and cisplatin/etoposide. Both the standard radiochemotherapy and hyperfractionated radiochemotherapy arms had better median survival times than the induction arm (17.0 vs. 16.0 vs. 14.6 months), although only standard radiochemotherapy was statistically significantly better than induction chemotherapy (Curran et al. 2000). Pattern of failure analysis showed that the best local control was in the hyperfractionated radiochemotherapy arm, confirming indirectly the observations of Jeremic et al. (1995, 1996) that high-dose hyperfractionated radiation therapy is an advantageous approach. Furthermore, and contrary to studies using low-dose chemotherapy concurrent with high-dose radiation therapy, it was shown once

again that high-dose chemotherapy bears a risk of exceptional acute toxicity when given with high-dose standard or hyperfractionated radiation therapy. This finding is not just limited to the Radiation Therapy Oncology Group 9410 but was also seen in similar studies (Byhardt et al. 1995; Lee et al. 1996; Komaki et al. 1997). Confirmation of more frequent high-grade toxicity recently came from preliminary results from the recent Canadian meta-analysis (Rakowitch et al. 2004). In that analysis, radiation therapy and concurrent low-dose, daily chemotherapy carried somewhat lower risk of acute toxicity, including high-grade neutropenia when compared to that observed with radiation therapy and concurrent high-dose chemotherapy, another advantage of radiation therapy and concurrent low-dose, daily chemotherapy.

3.2.1.6 Optimisation of Concurrent Radiochemotherapy

These two large prospective randomised trials solved the question of the "standard" treatment option in locally advanced non-small cell lung cancer. Additional evidence that concurrent radiochemotherapy should be the standard of care in locally advanced non-small cell lung cancer comes from the recent Southwest Oncology Group phase II study by Albain et al. (2002) which used two cycles of cisplatin/etoposide concurrently with conventionally fractionated 45 Gy in pathologic Stage IIIB non-small cell lung cancer. In the absence of progressive disease, an additional 16 Gy was administered with two additional cycles of cisplatin/etoposide. The median survival time was 15 months and 5-year survival was 15%. However, grade 4 neutropenia was observed in 32% patients, grade 3–4 anaemia in 28% patients and grade 3–4 esophagitis in 20% patients.

Recent attempts to refine concurrent radiation therapy and platinum-based chemotherapy include reports by Jeremic et al. (1998, 2001) and Lau et al. (2001) who both tried to address the issue of somewhat poorer distant metastasis control by increasing the dose of chemotherapy. While Jeremic et al. (1998) tested the addition of weekend carboplatin/etoposide to concurrent hyperfractionated radiation therapy (69.6 Gy) and low-dose daily carboplatin/etoposide in phase II study leading to a promising median survival time of 29 months and 5-year survival in 25%, the results of their subsequent prospective randomised trial showed no advantage for weekend chemotherapy when compared to no weekend chemotherapy (MST, 22 vs. 20 months; 5-year survival, 23% vs. 20%; p=0.57) (Jeremic et al. 2001). Lau et al. (2001) used concurrent radiation therapy (61 Gy) and chemotherapy consisting of twice weekly paclitaxel for 6 weeks and once weekly carboplatin for 6 weeks. Two cycles of consolidation paclitaxel and carboplatin were offered to patients who achieved a complete response, partial response, or stable disease. The median survival time was 17 months and 2-year actuarial survival rate was 40%. More recently, and quite encouragingly, the South West Oncology Group reported a trial in which concurrent cisplatin/etoposide/radiation therapy was followed by three cycles of adjuvant high-dose docetaxel (Gandara et al. 2003). The median survival in this phase II study was an extremely impressive 26 months, and this has become the basis for ongoing South West Oncology phase III studies. Most recently, Sakai et al. (2004) reported on a phase II study which employed bi-weekly docetaxel and carboplatin with concurrent radiation therapy (60 Gy in 30 daily fractions) followed by consolidation chemotherapy with docetaxel plus carboplatin in patients with stage III unresectable NSCLC. Among 32 evaluable patients, an impressive response rate of 91% was obtained. The median survival time was 27 months and a 2-year survival was 61%. High-grade toxicity was low.

It is likely that we will witness more similar studies in the future and for that reason we believe more emphasis should be placed on the patterns of failure during such treatments, especially because these treatment approaches would need further confirmation in prospective randomised fashion. By virtue of their intervention, they all have two parts, a concurrent one and a consolidation one, with the same or different drugs being administered during the latter part of combined treatment. Regardless of the underlying principle for such an intervention, these studies nicely outlined overall results, relapse-free survivals and clearly documented toxicity. The latter was divided between the concurrent and the consolidation part and we have all been able to learn more about the exact toxicity which the first or the second parts of the treatment were leading to. Unfortunately, this did not happen with the patterns of failure. While these studies presented very detailed patterns of failure in general, this was done for the whole time period of the study (treatment plus follow-up). This way we only learned about the total patterns of failure and not about which type of failure was observed

when, i.e. after concurrent or after consolidation part, and more particularly in which patients after the concurrent part, although some studies mandated consolidation chemotherapy in non-progressing patients.

Why is an exact pattern of failure important? It is important from several standpoints, some of which are briefly outlined here. Firstly, there are several types of patients after the initial (concurrent) part of radiochemotherapy and they can easily be separated regarding the response. While it is extremely unlikely that those achieving a stable disease (SD) would benefit from the consolidation chemotherapy, those with either a complete response (CR) or a partial response (PR) seem likely candidates (although not all of them) to benefit from the consolidation chemotherapy. Separation, therefore, of pattern of failure occurring in likely (CR and PR) and unlikely (SD) candidates could be used for further studies of similar design with respect to, e.g. eligibility criteria. Secondly, and more importantly, among likely candidates (CR and PR) to benefit from consolidation chemotherapy, a distinction should be made between those achieving CR and those achieving PR after concurrent radiochemotherapy. This is so since different mechanisms (precisely, different location) of action of consolidation chemotherapy would be expected. In the CR patients, consolidation chemotherapy would target microscopic disease both intrathoracically and extrathoracically, while in the PR patients, it would have to deal with clinically overt intrathoracic disease and a microscopic one extrathoracically. It is obvious that pattern of failure in these two distinct groups of patients would then clearly show how and where consolidation chemotherapy is actually acting and to what extent (clinical versus subclinical). Of additional importance is that with a clear pattern of failure, we would be able to open the door to investigating the determinants of treatment outcome such as cross-resistance between drugs or drugs and radiotherapy. This would also lead to investigating more of the inherent nature of these treatment modalities such as total dose or fractionation (for radiotherapy) or one or more drug(s) combination(s) (e.g. the same or different drugs in the concurrent and the consolidation part of the treatment), especially important due to the forthcoming generation of drugs waiting to enter wide clinical practice.

Although identifying patterns of failure in patients achieving different responses after concurrent radiochemotherapy may require some additional measures and likely place additional burden on investigators and hospitals, this effort would ultimately be rewarding. This way we would be able to discriminate between different patients and different options and to proceed (or not) with a consolidation therapy in one or more patient subsets, an approach which would ultimately lead to a better patient-tailored treatment sequence, a must for any clinical research into lung cancer in the future.

One of the unsolved question on "optimisation" of concurrent radiochemotherapy, particularly from the standpoint of radiation oncology, is the type of fractionation; conventional, once daily or altered fractionation, employing multiple fractions per day (hyperfractionation). The Radiation Therapy Oncology Group 8311 study (Cox et al. 1990) showed a possible advantage only for a hyperfractionated radiation therapy dose of 69.6 Gy, 1.2 Gy b.i.d. fractionation (but not beyond it) over standard 60 Gy given in 30 daily fractions in a favourable subset of locally advanced non-small cell lung cancer. The Radiation Therapy Oncology Group study 9410, while not statistically designed to directly compare standard vs. altered fractionation, appeared to show no survival difference between conventional, once daily and hyperfractionated radiation therapy when both given with concurrent chemotherapy. Interestingly, when compared to conventionally fractionated radiation therapy, hyperfractionated radiochemotherapy offered better local control in the Radiation Therapy Oncology Group 9410, but this did not translate into a difference in survival. Another study came to the same conclusion, albeit of somewhat different treatment approach. In the North Central Cancer Treatment Group/Mayo Clinic phase III study (Schild et al. 2002) conventionally fractionated radiation therapy (60 Gy) was compared to split-course hyperfractionated radiation therapy using 30 Gy given in 20 fractions on 10 treatment days for 2 weeks with a 2-week break after which another 30 Gy were given using the same fractionation. Both conventionally fractionated and hyperfractionated radiation therapy groups received concurrent cisplatin/etoposide. No difference in toxicity was seen and no statistically significant difference in treatment outcome, although hyperfractionated radiation therapy offered numerically slightly better survival, and local control.

More recently, the Eastern Cooperative Oncology Group completed a randomised trial comparing standard fractionation radiation therapy versus hyperfractionated accelerated radiation therapy. All patients in both arms received induction chemotherapy with carboplatin/paclitaxel, though concur-

rent chemotherapy was not used. Unfortunately, the study did not meet its accrual goals and was closed early; nonetheless 111 patients were analysed and the results suggest a slight though statistically insignificant advantage to hyperfractionated accelerated radiation therapy (median survival and 2- and 3-year actuarial survival: 22.2 months, 48% and 20% vs. 13.7 months, 33% and 15%, respectively) (Belani et al. 2003).

Further attempts to optimise the treatment approach in this disease include radiation therapy given concurrently with "third generation" drugs. While all "third generation" drugs have been tested in this setting, prospective randomised phase III studies are lacking. Nevertheless, it seems that paclitaxel/carboplatin combination has similar efficacy and likely less toxicity than either cisplatin- or other multiagent-based chemotherapy (Kelly et al. 2001; Schiller et al. 2002). A number of phase II studies tested this combination (Choy et al. 1998, 2000; Lau et al. 2001) with promising results. The first prospective study comparing radiation therapy/paclitaxel versus radiation therapy alone showed an advantage for radiation therapy/paclitaxel (the median survival time, 15.2 vs. 12 months; p=0.027) (Ulutin and Pak 2003). Testing paclitaxel/carboplatin combination and standard-fraction radiation therapy (63 Gy) in three schedules, Choy et al. (2002) used either pre-radiation therapy chemotherapy followed by radiation therapy (arm 1), pre-radiation therapy and concurrent radiochemotherapy (arm 2) and concurrent radiochemotherapy and post-radiation therapy chemotherapy (arm 3). Although this phase II randomised study was not designed to statistically compare treatment arms, the best results were nevertheless achieved in arm 3 (the median survival time, 16.1 months; 2-year survival, 33%). Also, in arm 2 there was suboptimal compliance with concurrent radiochemotherapy after induction chemotherapy. It is expected that a number of ongoing or recently completed studies bring new insight into the issue of optimisation of radiation therapy and chemotherapy in this disease.

3.2.1.7 New Approaches in Radiation Therapy and Chemotherapy of Locally Advanced Non-Small Cell Lung Cancer

Some of the newer approaches regarding chemotherapy have been mentioned above. It is also expected that additional new drugs will become more readily available in the future and that the process of their initial clinical testing (phase I–III) will include testing for their radioenhancing potentials which would go parallel to their testing for anticancer chemotherapy purposes. In this way, we would be able to learn about drug properties earlier, both alone or in combination with radiation therapy and to address important issues of optimal sequencing radiation therapy and chemotherapy in locally advanced disease.

Regarding radiation therapy, wide application of powerful computers has made a substantial impact on treatment planning and delivery. Three-dimensional conformal radiation therapy is now increasingly being practised world-wide. With radiation therapy fields tailored to include only detectable tumour, more focused and escalated radiation therapy doses can be given. Phase I/II studies have shown that radiation therapy doses to the order of $\geq$80 Gy are frequently being used with acceptable toxicity (Armstrong et al. 1993, 1997; Robertson et al. 1997), and that the radiation therapy concept of the necessity of elective nodal irradiation may be challenged. It should, however, be mentioned that even with limited field radiation therapy in three-dimensional conformal radiation therapy, some incidental elective nodal irradiation always occurs, and may approach 45–50 Gy, considered as the radiation therapy dose necessary for elective treatment (Martel et al. 1999; Rosenzweig et al. 2001). In addition to increasing target coverage and allowing radiation dose escalation, the use of three-dimensional conformal radiation therapy also allows more accurate prediction of toxicity of a given course of radiation therapy (Graham 1997; Kwa et al. 1998).

Intensity-modulated radiotherapy has also been used in locally advanced non-small cell lung cancer and potential advantages of intensity-modulated radiation therapy become evident when one compares the three-dimensional conformal radiation therapy and intensity-modulated radiation therapy plans (Yorke 2001). With intensity-modulated radiation therapy, the prescription dose could be increased in the majority of cases. This was coupled with the decreased lung dose and improved planning target volume uniformity, as well as significantly reducing cumulative radiation therapy dose to the oesophagus, while maintaining the same or higher dose to gross disease (Giraud et al. 2001). While extracranial stereotactic radiosurgery and stereotactic fractionated radiation therapy were initially used only for small (early stage) (Uematsu et al. 1998; Hara et al. 2002; Fukumoto et al. 2002; Nagata et al. 2002;

Whyte et al. 2003; Hof et al. 2003; Timmerman et al. 2003; Onimaru et al. 2003) tumours, its application is slowly extending to tumours classified as locally advanced. It is not unrealistic to expect that extracranial stereotactic radiosurgery and stereotactic fractionated radiation therapy will play an important role in metastatic non-small cell lung cancer, particularly in cases with favourable characteristics (response to chemotherapy, single metastatic lesion, small primary tumours, etc.). However, it should be clearly emphasised that proper selection of patients remains a prerequisite for the use of these new technologies in locally advanced and/or metastatic non-small cell lung cancer.

Although hardly termed a "new approach", the use of radioprotectors attracted renewed clinical interest in the protection of radiation therapy-induced toxicity. Several studies reported on the use of amifostine during radiation therapy and chemotherapy in lung cancer. Antonodou et al. (2001) performed a randomised phase III trial of radiation therapy with or without daily amifostine in patients with advanced stage lung cancer. The incidence of pneumonitis $\geq$2 was significantly lower in the amifostine group as well as incidence of esophagitis $\geq$grade 2, and the protective effect of amifostine also produced lower incidence of late damage, with no effect on treatment outcome. Further evidence came from Komaki et al. (2002) who administered amifostine twice weekly before treatment in patients with inoperable non-small cell lung cancer treated with concurrent radiochemotherapy. They observed that Morphine intake to reduce severe esophagitis was significantly lower in the amifostine arm, as well as was the incidence of acute pneumonitis in the treatment arm. Finally, a randomised double-blind study (Leong et al. 2003) showed a trend for fewer patients showing toxicity in the amifostine group. The Radiation Therapy Oncology Group has just reported preliminary results of the study Radiation Therapy Oncology Group 98-01, which randomised patients to intensive chemoradiation (induction carboplatin/paclitaxel followed by hyperfractionated radiation therapy to 69.6 Gy with concurrent weekly carboplatin/paclitaxel) with or without amifostine four times per week during radiation therapy. Although there was no difference in the rate of grade 3 esophagitis, patient-reported area-under-the-curve swallowing dysfunction scores were significantly lower in the amifostine group (Movsas et al. 2003). It is expected that more studies addressing the issue of optimal protection with amifostine will provide more data on further optimisation before becoming a standard adjunct to radiation therapy or radiochemotherapy treatments in the future.

3.2.1.8 Conclusions

Locally advanced non-small cell lung cancer is one of the major targets for clinical research in lung cancer. While it has to date accounted for approximately 40% of all cases, it is expected that widespread use of positron emission tomography (leading to more precise staging of patients) will likely decrease the number of patients falling into stage III non-small cell lung cancer. This is because patients clinically or even pathologically staged as IIIB and a minority of those staged as IIIA will actually have metastatic burden from the outset, undiagnosed with current diagnostic tools. This is supported by simple observation of the natural history of this disease, regardless of the treatment: there are always some patients who fail distantly several months or a year after the diagnosis. These patients are likely to be ones who would be upstaged by the use of positron emission tomography and moved to stage IV (metastatic disease). On the other hand, it is expected that a proportion of patients with early stages (I and II) non-small cell lung cancer will also be upstaged, and will likely increase the number of patients actually having stage III (locally advanced) disease. Whatever predominates, locally advanced non-small cell lung cancer will remain one of the major focuses of clinical research in lung cancer simply because major improvements occurred here and they have occurred owing to optimised combined modality treatments, notably combined radiation therapy and chemotherapy. His is even more so since it had been shown that patients with clinical stage IIIA non-small cell lung cancer treated with concurrent radiochemotherapy have equivalent outcome when compared to those treated with induction chemotherapy followed by surgical resection (Taylor et al. 2004). These results largely confirmed the Integroup trial 0139 preliminary data presented during ASCO 2003 (Albain et al. 2003) in which both approaches (induction treatment included radiotherapy as well!) were deemed as feasible. The surgical arm achieved superior progression-free survival but this was achieved at the expense of an increase in treatment-related deaths in this group. The latter fact accompanied with the substantial effects of radiation therapy added to preoperative chemotherapy, led authors to suggest that longer follow-up is necessary to give better insight into this issue. Nevertheless, radiation therapy and chemotherapy will further evolve in the near future and will bring us to the exiting era of more successful clinical research, leading ultimately to better outcome in this disease.

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3.2.2 Chemotherapy or Chemoradiotherapy Followed by Surgical Resection for Non-Small Cell Lung Cancer

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CONTENTS

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The integration of chemotherapy with or without radiotherapy together with surgery in a combined-modality approach for non-metastatic non-small cell lung cancer has been the focus of intense clinical research over the past two decades. Many questions are debated, including whether preoperative therapy should be used at all in early stage disease or whether a surgical resection should ever be performed after combined-modality treatment of more advanced stage III cancers. If the answer to either of these is 'yes,' then questions remain regarding which patient population should be treated and with what specific induction regimen.

Induction therapy followed by surgery is discussed for two distinct patient populations with different rationales and expectations. The first group involves patients with stages I, II and selected early stage III NSCLC. The standard of care in this group of patients has been surgical resection. However, despite complete resection of all known disease, many of these patients remain at high risk for relapse and death. Distant metastases are the most common site of relapse in this patient population. The addition of systemic therapy prior to surgery in this patient population has the aim of decreasing the rate of distant spread and thus improving their survival. Radiation therapy plays limited role in this group of patients.

The second large group for which a combined-modality treatment plan that incorporates surgery may be beneficial includes patients with locally advanced disease, for whom the current standard of care is concurrent chemotherapy and radiotherapy (chemoRT). Cure rates produced with this chemoRT alone are modest, with long-term survival in reported randomized phase III trials between 8%–15% (Sause et al. 2000; Dillman et al. 1996). Both local and distant failure rates are very high. The rate of persistent local disease was reported to be as high as 83% after treatment with chemotherapy and full-dose radiotherapy (Arriagada et al. 1991). Persistent locoregional disease is a major problem, not only because of the local effects of the

uncontrolled tumor but also as a potential source of metastatic seeding. Persistence of local disease after completion of treatment portends especially poor prognosis (Andre et al. 2001). It is hypothesized that surgical removal of residual disease should render a proportion of these patients disease-free.

The optimal sequence of chemotherapy, radiotherapy, and surgery is uncertain. Compliance with induction therapy (same as older term "neoadjuvant") is generally higher than with adjuvant treatments (either chemotherapy or RT), due to poor tolerance of therapy in patients recovering from thoracotomy. Other potential advantages of early administration of systemic therapy include improved respectability, organ sparing (less frequent need for pneumonectomy) and the opportunity for in vivo chemosensitivity testing. Perhaps the most important, yet not fully validated, advantage of the induction therapy option is the delivery of systemic therapy in the moment of the lowest micrometastatic burden. The disadvantages to a neoadjuvant strategy include compromised nutritional and immunological status prior to major surgery, complications arising from the induction regimen causing a delay of definitive surgery, early tumor progression, technically challenging surgery (especially if RT is incorporated in the induction program), and poor postoperative healing.

In this chapter we review the development and current status of combined-modality treatment programs that include surgical resection. A large number of phase II trials and several phase III trials involving bimodality or trimodality treatment have been completed, and a few more are ongoing. Direct comparison of these studies is impossible due to differences in methodology and patient population entered in these trials. Some of the studies enrolled advanced stage patients with the dual aims of decreasing systemic spread while improving the resection rate. Other trials enrolled patients with lower volume disease technically amenable to upfront resection. Pathological staging of the mediastinum was not uniformly mandated across trials, and the induction regimens varied greatly regarding specific chemotherapy and RT prescriptions. Criteria proceeding to a post-induction resection were also not uniform. Eligibility for thoracotomy was in some studies reserved only for patients with a response while other studies required resection of "stable" disease as well. Data regarding local and distant relapse, postoperative morbidity and mortality, late causes of death and predictors of favorable outcome were not always reported. Nevertheless, much can be learned from the trials conducted to date.

3.2.2.1 Radiotherapy as Sole Induction Modality

Early induction trials focused on preoperative radiotherapy alone because effective chemotherapy did not exist. A large randomized study published in 1975 found no difference in overall survival (Warram 1975). Patients enrolled were initially considered to be operable, and were assigned to either preoperative radiotherapy or immediate surgery. Even though 27% of the patients had no tumor in the resected specimen, resectability rates were not improved and overall survival was identical. The last randomized trial that used radiotherapy alone as induction treatment was CALGB 9134 (Elias et al. 2002). This trial closed early due to poor accrual and long-term results were not encouraging. Given the propensity of NSCLC for distant spread, the induction strategy consisting only of local treatment is no longer considered appropriate and induction radiotherapy alone has been largely abandoned.

3.2.2.2 First-Generation Induction Trials Incorporating Chemotherapy

The initial set of small pilot studies was conducted in the 1980s. These trials were primarily aimed to define the feasibility and safety of pre-surgery induction treatment. Patients enrolled had stage III disease, mostly based on clinical staging, and pathologic conformation of mediastinal disease was not universally required. Some trials enrolled patients with high-volume disease, while the others enrolled only low-burden disease. The designs of the trials are reviewed in Table 3.2.2.1 (Skarin et al. 1989; Eagan et al. 1987; Bitran et al. 1986; Elias et al. 1994; Darwish et al. 1994). Radiotherapy varied from preoperative, postoperative, or both, and in most cases was sequenced after the chemotherapy.

The outcomes of these trials, reviewed in Table 3.2.2.2., were highly variable but in general demonstrated safety and feasibility of combined-modality treatment in conjunction with surgery.

Table 3.2.2.1. Designs of first-generation phase II induction trials for NSCLC

Investigators	Stage subsets/ tumor volume	Treatment program	Number of patients	Biopsy-proven N2/N3 disease (%)
Dana Farber I (Skarin et al. 1989)	T3 or low-volume stage III(N2)	CAP × 2 → RT → surgery → RT → CAP × 3	41	68
LCSG 831 (Eagan et al. 1987)	T3 or low-volume stage III(N2)	CAP × 3 with split RT → surgery	39	51
University of Chicago (Bitran et al.1986)	High-volume T3 or T4N2 or N3	VdEP × 2→ surgery → RT	21	100
Dana Farber II (Elias et al. 1994)	T1-3N2 (mixed low and high volume)	CAP × 4 + RT→ surgery → RT	54	94
Perugia (Darwish et al. 1994)	T1-3N2 (clinically high tumor volume)	EP × 2–3 → surgery → variable RT	42	0

LCSG, Lung Cancer Study Group; C, cyclophosphamide: A, doxorubicin; P, cisplatin; RT, radiotherapy: Vd, vindesine; E, etoposide; RT, radiotherapy.

Table 3.2.2.2. Results from first-generation phase II induction trials for NSCLC

Investigators	Response rate (%)	Resection rate (% original n)	Median survival (months)	Long-term survival
Dana Farber I (Skarin et al. 1989)	43	88	32	31%, 3-year
LCSG 831 (Eagan et al. 1987)	51	33	11	8%, 2-year
University of Chicago (Bitran et al. 1986)	70	14	8	34%, 1-year
Dana Farber II (Elias et al. 1994)	39	56	18	22%, 5-year
Perugia (Darwish et al. 1994)	82	72	24	24%, 3-year

LCSG, Lung Cancer Study Group.

3.2.2.3 Second-Generation Phase II Induction Trials

3.2.2.3.1 Chemotherapy as the Sole Induction Modality

Induction trials conducted following the first-generation efforts were larger and designed with better staging and in more homogenous patient populations. Studies in which the induction regimen consisted of chemotherapy alone are outlined in Table 3.2.2.3. All of these required pathological confirmation of N2 disease, but the disease burden or tumor volume varied. Three of the studies used the MVP regimen (mitomycin-C, vinblastine, cisplatin), one incorporated vinblastine plus cisplatin and the last trial tested continuous infusion cisplatin and 5-fluorouracil with leucovorin rescue (Wagner et al. 1994; Martini et al. 1993; Burkes et al. 1992; Elias et al. 1997; Sugarbaker et al. 1995). Postoperative RT was a part of the treatment plan in all except the LCSG and Toronto trials. In the Dana-Farber and CALGB trials, the postoperative RT dose was 54 Gy for completely resected patients and 60 Gy after an incomplete resection. In the Memorial study, postoperative RT was recommended, but not mandated, for patients with persistent mediastinal nodal disease at the time of surgery. In that study, some of the patients with incompletely resected tumors received radioactive iodine seed implant.

The outcomes of these studies are summarized in Table 3.2.2.4. The LCSG 881 trial was a two-arm phase II randomized trial, in which one arm was assigned preoperative chemotherapy and the other received

Table 3.2.2.3. Design of second-generation trials of induction chemotherapy for pathologic stage IIIA (N2) NSCLC

Investigators	Number of patients	Local disease burden	Treatment schema
LCSG 881 (Wagner et al. 1994)	26	High volume	MVP x 2 → Surgery or 44 Gy → Surgery
Memorial (Martini et al. 1993)	136	Mixed volume	MVP x 2–3 →Surgery → Radiotherapy for persistent N2
Toronto (Burkes et al. 1992)	39	Mixed volume	MVP x 2 → Surgery → MVP x 2 for responders
Dana Farber III (Elias et al. 1997)	34	Mixed volume	PFL (continuous infusion) x 3 → Surgery → Radiotherapy
CALGB 8935 (Sugarbaker et al. 1995)	74	High volume	VP x 2 → Surgery → VP x 2 → Radiotherapy

LCSG, Lung Cancer Study Group; CALGB, Cancer and Leukemia Group B; M, mitomycin-C; V, vinblastine; P, cisplatin; F, 5-fluorouracil: L, leucovorin.

Table 3.2.2.4. Results of second-generation trials of induction chemotherapy for pathologic stage IIIA(N2) NSCLC

Investigators	Response rates (%)[a]	Complete resection rates (%)[a]	Treatment-related mortality (%)[a]	Operative mortality (%)[c]	pCR[b] rates (%)	pCR[b] in mediastinal nodes (%)[a]	Median survival (months)
LCSG 881 (Wagner et al. 1994)	65	68	14.5	18	4	Not stated	12
Memorial (Martini et al. 1993)	78	65	5	5	14	32	19
Toronto (Burkes et al. 1992)	71	51	18.0	9	8	Not stated	21
Dana Farber III (Elias et al. 1997)	65	62	0	0	15	44	18
CALGB 8935 (Sugarbaker et al. 1995)	64[d]	62	2.7	3.2	0	Not stated	15

LCSG, Lung Cancer Study Group; CALGB, Cancer and Leukemia Group B.
[a] Percent of all enrolled patients.
[b] Pathological complete response.
[c] Percent of patients subjected to surgery.
[d] Includes stable disease.

preoperative radiotherapy. The results were reported for the entire group of patients and not separately for each treatment arm. Resection rates (of the entire denominator) were 51%–68%. Pathological complete response rates ranged from 0% to 15%. Postoperative mortality ranged from 0% to 18%. The causes of death were predominantly pulmonary or cardiopulmonary. Postoperative radiotherapy did not provide additional benefit in the Memorial study (p=0.24), however the selection of patients receiving radiotherapy was based on unfavorable response to neoadjuvant chemotherapy, not by randomized assignment. Pulmonary complications attributable to mitomycin-C in the Memorial study, including the three lethal ones, all occurred after the cumulative dose of 24 mg/m2. The studies that did not use mitomycin-C had lower perioperative death rates. In the Dana-Farber study, all mediastinal downstaging to N0 or N1 occurred in patients with low-volume disease. The CALGB study noted that there was no correlation between radiographic response to the induction regimen and pathological downstaging at the time of surgery.

Survival outcomes were highly variable, with median survival ranging from 12 to 21 months, due to differences in the study eligibility and design, as re-

viewed above. In the Dana Farber study and CALGB trial 8935, 15% and 41% of first relapses occurred in the brain, respectively.

3.2.2.3.2 Chemotherapy and Radiotherapy as Induction Modalities

Another group of second-generation trials conducted during a similar time period used chemotherapy given concurrently with radiotherapy (chemoRT), such that radiotherapy commenced on day 1 of chemotherapy (Albain et al. 1995; Weiden and Piantadosi 1992; Faber et al. 1989; Strauss et al. 1992; Vora et al. 2000). The designs of these studies are presented in Table 3.2.2.5. Patients eligible for these trials had stage III disease, and the proportion of pathologic N2-positive disease was 38%–87%. All of the trials used cisplatin-based induction chemotherapy, with the addition of etoposide, 5-fluorouracil, vinblastine, or a combination of these drugs. Radiotherapy was delivered in continuous fashion in all trials, except in the Rush Presbyterian study, in which 40 Gy were delivered over 7 weeks (split course). In the LCSG 852 trial, only the patients with a clinical response were eligible for thoracotomy, but some of the non-responders underwent surgery off the protocol. Postoperative treatment was variable. In the SWOG 8805 trial, patients with positive node, positive surgical margins, or unresectable tumors received two more cycles of chemotherapy with an additional 14 Gy. The Tufts University study gave postoperative chemotherapy with either cisplatin/etoposide or carboplatin/paclitaxel. The CALGB study mandated one more cycle of chemotherapy concurrent with 30 Gy of thoracic radiotherapy for all patients.

All the trials except the CALGB study allowed the inclusion of the IIIB subset, and the proportion varied from 6% to 53% of patients per trial. The SWOG 8805 and LCSG 852 trials were specifically designed for patients with a high-volume disease burden, whereas the others included a mix of high and low burden presentations.

The outcomes of these studies are summarized in Table 3.2.2.6. Clinical response or "response plus stable" (in one study) rates ranged from 56% to 92%. Complete resection rates ranged from 52% to 79% and pathologic complete response rates (pCR) ranged from 9% to 21% of the initial number of patients entered on the studies. In the SWOG 8805 trial, there were 30 patients who had stable disease at the time of presurgical evaluation, and 26 of those underwent a complete resection. Of those 26 patients, 45% had pCR or only rare microscopic foci. The Rush-Presbyterian trial also found discrepancies between the clinical response to the induction therapy and pathological findings at the time of surgery. Thus, a substantial proportion of patients with a residual mass and/or nodal enlargement on the post-induction CT scan has, in fact, a major response, and surgical exploration should not be withheld from them just on the basis of lack of response on the CT scan.

The operative mortality rates in these trials were 0%–15%. The majority of the events were pulmonary, similar to chemotherapy-alone induction trials. The

Table 3.2.2.5. Design of second-generation trials of concurrent induction chemoradiotherapy (standard fractionation) in NSCLC

Investigators	Number of patients	Disease burden	IIIA(N2) (%)	T3N0-1/T4 or N3 (%)	Biopsy of N2 or T4 Required?	Treatment schema
SWOG 8805 (Albain et al. 1995)	126	High volume	60	0/40	Yes	EP × 2 + 45 Gy → Surgery → EP × 2 + 14 Gy if persistent N2/incomplete resection
LCSG 852 (Weiden et al. 1992)	85	High volume	85	0/13	No	PF × 2 + 30 Gy → Surgery
Rush-Presbyterian (Faber et al. 1989)	85	Mixed volume	73	21/6	Yes	PF or PEF + 40 Gy (split course) → Surgery
CALGB I (Strauss et al. 1992)	41	Mixed volume	80	20/0	Yes	PVF × 2 + 30 Gy → Surgery → PVF × 1 + 30 Gy
Tufts (Vora et al. 2000)	42	High volume	66	2/45	No	EP × 2 + 59.4 Gy → surgery → PE × 4 or Carbo T × 4

SWOG, Southwest Oncology Group; LCSG, Lung Cancer Study Group; CALGB, Cancer and Leukemia Group B; E, etoposide; P, cisplatin; F, 5-fluorouracil; V, vinblastine; Carbo, carboplatin; T, paclitaxel; Gy, gray.

Table 3.2.2.6. Results of second-generation trials of induction chemoradiotherapy in NSCLC

Investigators	Response rate (%)[a]	Complete resection rate (%)[a]	Treatment-related mortality (%)[a]	Operative mortality (%)[b]	pCR (%)[a]	PCR in N2 (%)[a]	Median survival (months)
SWOG 8805 (Albain et al. 1995)	59	71	10	8	15	38	15
LCSG 852 (Weiden and Piantadosi 1992)	56	52	8	7	9	Not stated	13
Rush-Presbyterian (Faber et al. 1989)	92[a]	71	3.5	5	20	26	22
CALGB I (Strauss et al. 1992)	64[c]	61	15	10	17	Not stated	16
Tufts (Vora et al. 2000)	69[a]	79	0	0	21	59	30

SWOG, Southwest Oncology Group; LCSG, Lung Cancer Study Group; CALGB, Cancer and Leukemia Group B.
[a] Percentage of the original number.
[b] Percentage of patients subjected to surgery.
[c] Includes stable disease.

cause of death often resembled the adult respiratory distress syndrome (ARDS). The Tufts study was unique in that the ARDS was not observed, despite the high preoperative radiation dose. These investigators used a rigid protocol to limit fluids intraoperatively and postoperatively, and had the patients ventilated for at least 48 h.

Median survivals for the second-generation studies of concurrent chemoRT ranged from 13 to 26 months. Studies that limited enrollment to patients with high-burden disease reported shorter median survivals than those that enrolled mixed-burden disease.

A common observation in many of these trials was a high incidence of brain relapse. In Tufts university study, the brain was the first site of failure in 50% of recurrences, and the only site of recurrence in 36% of patients. The LCSG investigators noted that in patients who had complete resection, 28% of first recurrence sites were in the brain, in contrast to only 7% in patients who did not undergo surgery. In patients who experienced a recurrence in the brain, in almost one third that was the sole site of recurrence. Similar findings were noted by the SWOG 8805 study. The CALGB protocol called for prophylactic cranial irradiation (PCI) in patients with non-squamous histologies who completed all the treatment, but about a third of eligible patients did not receive it. None of 13 patients who received PCI developed brain metastases, compared to one out of seven who were eligible but did not receive it. In SWOG 8805, PCI was optional, and there was no significant difference in rates of brain recurrence in the irradiated subset, although numbers were too small to reach a definitive conclusion about this issues.

The Tufts trial utilized a higher dose of preoperative RT, a prescription similar to those used for standard concurrent chemoRT without surgery. Thus most of the allowable dose of RT was given upfront without a break. In the other trials, truncation of the RT occurred at around 45–50 Gy to plan for the surgery. Thus, patients with residual disease or unresectable disease could only receive full dose RT via an interruption of several to many weeks, depending on time to recovery from surgery. However, a high dose of RT in the preoperative setting results in increased fibrosis that may increase the risk of surgical complications (as will be discussed later), so it cannot be universally recommended without additional prospective study.

3.2.2.3.3 Long-Term Survival in the Second-Generation Induction Trials

Long-term outcomes of selected second-generation studies with a minimum of three years of follow-up are summarized in Table 3.2.2.7. The direct comparison of outcomes between those studies is impossible due to differences in methodology and patient populations entered on these trials. Nevertheless, the long-term outcomes were encouraging and provided support for subsequent phase III trials.

Table 3.2.2.7. Long-term survival in selected second-generation phase II induction trials in NSCLC

Investigators	Disease burden	Included T3N0 or N1?	Biopsy proof of N2 status required?	Selected stage IIIB included?	Long-term survival
Memorial (Martini et al. 1993)	Mixed volume	No	Yes	No	28%, 3-year; 17%, 5-year
Toronto (Burkes et al. 1992)	Mixed volume	No	Yes	No	26%, 3-year
SWOG 8805 (Albain et al. 1995, 1999)	High volume	No	Yes	Yes	27%, 3-year, 20%, 6-year, stage IIIA (N2); 24%, 3-year, 22%, 6-year, stage IIIB
CALGB I (Strauss et al. 1992)	High volume	Yes	No	No	28%, 3-year 22%, 7(+)-year
CALGB 8935 (Sugarbaker et al. 1995)	High volume	No	Yes	No	23%, 3-year
Rush-Presbyterian (Faber et al. 1989)	Mixed volume	Yes	No	Yes	40%, 3-year
Tufts (Vora et al. 2000)	High volume	Yes	No	Yes	37% 5-year

CR, complete response; SWOG, Southwest Oncology Group: CALGB, Cancer and Leukemia Group B.

3.2.2.4 Third-Generation Phase II Studies of Induction Chemotherapy plus Concurrent Hyperfractionated Radiotherapy

Three phase II trials were conducted with an induction regimen that consisted of platinum-based chemotherapy and hyperfractionated radiotherapy. In one of these trials, the radiation schedule included a planned break, while in the other two, the radiation was intensified by delivering it in an accelerated fashion. The designs of the trials are summarized in the Table 3.2.2.8. The MGH study enrolled 42 patients to a preoperative regimen consisting of split course, hyperfractionated radiotherapy concurrent with chemotherapy (Choi et al. 1997). All patients had N2 disease confirmed histologically prior to treatment. Thirty three percent of patients enrolled on this study

Table 3.2.2.8. Third-generation phase II trials of concurrent induction chemoradiotherapy with hyperfractionation in NSCLC

Investigators	Stage subset(s)/number of patients	Disease burden	Chemotherapy	Radiotherapy
MGH (Choi et al. 1997)	Biopsy-proven stage IIIA(N2), n=42	Mixed volume	PVF × 2 concurrent with RT → surgery → PVF × 1 concurrent with RT	42 Gy split (1.5 bid × 7 → 10 day rest → 1.5 bid × 7); postoperative 12–18 Gy 1.5 bid)
West German Cancer Center (WGCC) (Eberhardt et al. 1998)	Mediastinoscopy required: – 6, advanced T3 N0/1; – 46, 2 or more N2 nodes; – 42, IIIB (T4) or contralateral N3) Total n = 94	High volume	EP × 3 → reduced dose EP × 1 with RT → surgery	45 Gy (1.5 Gy bid over 3 weeks); PCI later in trial
German Lung Cancer Cooperative Group (GLCCG) (Thomas et al. 1999)	– N2, 25; (all biopsy-proven) – T4 or N3, 29; Total n=54	High volume	ICE x 2 → PVd × 1 + RT → surgery	45 Gy (1.5 Gy bid over 3 weeks)

MGH, Massachusetts General Hospital; n, number of patients; P, cisplatin: V, vinblastine; F, 5-fluorouracil; E, etoposide; I, ifosfamide, C, carboplatin; Vd, vindesine; Gy, gray; PCI, prophylactic cranial irradiation.

had mediastinal lymph nodes smaller than 1 cm on a pretreatment CT, and in 19 % the lymph nodes were greater than 2 cm. The volume of mediastinal disease was thus mixed in this study. Twelve Gy of postoperative RT was given for either complete response or microscopic disease only, and 18 Gy for residual disease or positive margins, concurrent with chemotherapy.

The West German Cancer Center study used 3 cycles of induction chemotherapy, followed by continuous hyperfractionated accelerated RT concurrent with chemotherapy (Eberhardt et al. 1998). Patients eligible for enrollment had to have either surgically unresectable disease, or more than 1 ipsilateral mediastinal lymph node involved, or positive contralateral mediastinal lymph nodes. This study mandated repeat mediastinoscopy at the completion of induction treatment. Only those patients whose mediastinal tumor burden was downstaged (defined as a negative mediastinal biopsy or only one positive lymph node) were offered surgical resection. Thus, all patients with stable disease were not mandated to proceed to thoracotomy. Patients who did not undergo resection of residual disease were given additional RT to a total of 60 Gy. These investigators reported a high incidence of isolated brain relapse and introduced prophylactic cranial irradiation (PCI) in the third year of the study. The PCI dose was 30 Gy in 2 Gy fractions over 3 weeks starting 1 day after the last chemotherapy administration.

The German Lung Cancer Cooperative Group trial accrued 54 patients to a regimen that consisted of 2 cycles of induction chemotherapy, followed by hyperfractionated accelerated RT concurrent with chemotherapy, followed by resection (Thomas et al. 1999). Eligibility criteria included either biopsy-proven N2 disease or clinical T4 or N3 disease. Patients who had a tumor response or stable disease were eligible for surgery. Patients who did not have complete resection received additional 16 Gy of radiotherapy.

The results of these trials are presented in the Table 3.2.2.9. Treatment-related mortality was 7%, 6% and 9% and postoperative mortality 5%, 7% and 8% (of patients who underwent thoracotomy) in the MGH, WGCC and GLCCG trials, respectively. The main perioperative complication seen in both WGCC and GLCCG trials was bronchial stump insufficiency, most often after right-sided resections. Both groups started reinforcing bronchial stumps with tissue later in each trial, reducing the incidence of this problem to zero.

A complete resection with negative margins was accomplished in 81% of all patients in the MGH trial. The median survival was 25 months and overall survival was 66%, 37% and 37% at 2, 3 and 5 years, respectively. The preoperative size of mediastinal nodes (<= 1 cm vs >1 cm) did not influence the survival,

Table 3.2.2.9. Results from third-generation trials of induction chemoradiotherapy with hyperfractionation in NSCLC

Investigators	Number of patients	Resection rate (%)[a]	Treatment related deaths (%)[a]	Postoperative deaths (%)[b]	Survival	Predictors of favorable outcome
MGH (Choi et al. 1997)	42	93%	7	5	37%, 5-year	• Downstaging to N0 (79% 5-year survival) • Complete resection
West German Cancer Center (WGCC) (Eberhardt et al. 1998)	94	53%a (60% IIIA, 45% (IIIB)	6	7	28%, 4-year (31% IIIA 26% IIIB)	4-year survival from registration: • complete resection[c] 46% vs 11%, p=0.0001 • N2/3 → N0 38% vs 15%, p=0.11 • LDH $\leq$ 240 or not 37% vs 0%, p=0.003 • PCI Decrease in first brain metastases, p=0.005
German Lung Cancer Cooperative Group (GLCCG) (Thomas et al. 1999)	54	63% (R0)	9	8	30%, 3-year	• > 90% histological regression (3-year survival 48% vs. 9%, p=0.007) • Complete resection (p=0.009)

MGH, Massachusetts General Hospital; CR, complete response; p, pathologic; PCI, prophylactic cranial irradiation.
[a] Percentage of the original number of patients.
[b] Percentage of patients subjected to surgery.
[c] Resection not mandated if persistent T4 or N2/N3 disease.

but the sample size was very small. Four patients had pCR, three of whom showed only a partial response on postinduction CT. Five-year survival was 79% if the nodes were downstaged to N0.

Of patients entered on the West German Cancer Center study, 64% were eligible for surgery after the induction regimen and 53% had complete resection with negative margins. Twenty-four (26%) had complete pathological response. Among 29 patients with radiographically stable disease after the induction treatment, about a third was completely resected and three had pathological complete response. Median survival was 20 and 18 months and 3-year survival were 36% and 31 % for stages IIIA and IIIB, respectively (no statistical difference). No differences were observed for the different TNM categories and T (T1/2 vs. T3/4) and N (N0/1 vs. N2/3) subgroups. The complete resection rates were 60% for IIIA and 45% for IIIB. Of 8 patients with T4N0-1, 6 were able to have a complete resection. Prophylactic cranial irradiation markedly reduced the incidence of brain relapse, but the difference in median survival (26 months with PCI and 20 months without) did not reach statistical significance, possibly because the follow-up period for the first group was shorter.

A complete resection with negative margins was achieved in 63% of patients enrolled on the GLCCG trial. Over a half of these exhibited a major histological response, defined as necrosis or fibrosis of more than 90 % of tumor cells. Seven (13%) had pathological complete response. Preoperative assessment of response (complete/partial) did not correlate with the degree of tumor regression. Approximately 25% of patients who relapsed had only a local recurrence, whereas 35% had a distant-only relapse. The median survival for the whole group was 20 months, with 2- and 3-year survival 40% and 30%, respectively. Median survivals for stages IIIA and IIIB (25 vs. 17 months) showed no statistical significance, as did 2- and 3-year survivals (52% and 35% vs. 30 and 26%).

The MGH study had higher resection rate and overall survival than the two German studies but also enrolled patients with less advanced disease. The two German trials had similar patient populations, treatment and outcome. The authors of those studies credit the accelerated radiation schedule for the fact that many of their patients with advanced, high-volume disease were able to undergo resection. However, second-generation trials with concurrent chemoRT in patients with high-volume tumor burdens (described above, e.g., SWOG 8805) also achieved high resection rates.

3.2.2.5 Predictors of Favorable Outcome in Second- and Third-Generation Phase II Studies

Several of the phase II studies discussed above also reported prognostic factors, although many of the studies were underpowered for robust statistical analyses. These trials are summarized in Table 3.2.2.10. Favorable factors included postinduction pathological complete response, complete resection, T3N0 and T3N1 disease, T4N0 or T4N1 disease and pathological clearance of the initial mediastinal nodal involvement. Not all of these factors were assessed in each study.

The only factor predictive of intermediate survival (2-3 years) in the SWOG 8805 trial was pathological clearance of nodal disease (Albain et al. 1995). Complete resection rate, pathological complete response and multiple other factors did not reach statistical significance. However, complete resection later emerged as a predictor of long-term (six-year) survival, along with nodal pathological clearance (Albain et al. 1999). The six -year survival was 33% in patients with pathological complete response in the nodes, compared to 11% for those who did not have the pathological nodal clearance. The 6-year survival for complete resection yes vs no was 29% and 0%, respectively. The Tufts, MGH and WGCC trials also found mediastinal downstaging to be of prognostic importance. SWOG 8805 was the only second-generation induction study that assessed the nodal downstaging in a multivariate model.

Clinical response to neoadjuvant therapy in most of the trials did not correlate with the degree of tumor regression on pathology. However, clinical response to treatment was a favorable outcome predictor in the Memorial and WGCC trials. Pathological complete response or major regression (only microscopic residual disease) was an important predictor for survival in the Memorial, Tufts and GLCCG trials. In the WGCC study, tumor persistence in the resected specimen was not associated with adverse prognosis, but all patients with stable disease did not undergo a resection in this trial.

Metastatic disease remains the most difficult therapeutic problem in NSCLC, so it is critical to identify predictors of which patients will benefit from a surgical resection. Mediastinal downstaging may be a marker of chemosensitivity of the metastatic clones of tumor cells. This theory may explain why mediastinal downstaging, but not pathological complete response in the primary tumor, carries a prognostic significance. Conversely, the presence of persistent

Table 3.2.2.10. Predictors of favorable outcome in trials of induction therapy

Study Group	Favorable outcome predictors
Memorial (Martini et al. 1993)	• Major response to chemotherapy (5-year OS 19% vs. 7%) • Complete resection (5-year OS 27% vs. 12%) • Complete pathological response (5-year survival 61%)
SWOG 8805 (Albain et al. 1995, 1999)	• Pathological mediastinal clearance (3-year survival 44% vs. 18%, p=0.05) • Complete resection
CALGB 8935 (Sugarbaker et al. 1995; Kumar et al. 1996)	• Complete resection (3-year survival 46% for complete resection vs. 23% for incomplete resection vs. 0 for non-resected)
Tufts (Vora et al. 2000)	• Complete resection • Complete pathological response • Mediastinal clearance
Rush-Presbyterian (Faber et al. 1989; Reddy et al. 1992)	• Resection (3-year OS 47% vs. 17%, p=0.0001) • Pathological complete response
MGH (Choi et al. 1997)	• Pathological nodal clearance (p=0.04) • Complete resection (p=0.02)
WGCC (Eberhardt et al. 1998)	• Clinical response • Complete resection (median survival 42 vs. 13 months, p=0.0001) • Pathological nodal downstaging
GLCCG (Thomas et al. 1999)	• Pathological tumor regression >90% (3-year survival, 56% vs. 9%, • Complete resection (p=0.009)

OS, overall survival.

disease in the mediastinum may indicate unresponsive distant disease. Whether this marker can be reliably assessed without major morbidity, and if so, can it be used in selecting patients who might derive the most benefit from surgical resection is uncertain. Second look mediastinoscopy is technically difficult. Molecular markers, such as p53 or K-ras, as well as more recently-described gene expression profiles, on specimens obtained pre-and post-induction treatment, are being studied as ancillary projects within several of these trials and other ongoing studies. Also, investigations regarding the role of PET scan "response" in the mediastinal nodes are underway on a large and prospective scale, based upon encouraging results in small pilot studies. However, PET scanning may not be sensitive enough to detect residual nodal microscopic disease.

3.2.2.6 The Stage IIIB Subset in Induction Trials

Although several of the second-generation trials (LCSG 852 and the Rush Presbyterian study) allowed the inclusion of the IIIB subset, the sample sizes were too small to allow for independent statistical analysis. The SWOG 8805 study was designed to include a sufficient sample of the stage IIIB subgroup to allow independent assessment of outcome (Albain et al. 1995). Six-year survival for T4N0-1 was 49% versus 20% for the IIIA(N2) subset and 18% for T4N2 or TanyN3 (Albain et al. 1999). These long-term survival data are a major improvement over results from trials of chemoRT without surgery in any stage III subset. Another intriguing stage IIIB subset result from SWOG 8805 pertained to N3 disease. Among patients with contralateral mediastinal (N3) involvement no one survived 2 years, whereas 35% of patients with N3 disease due to supraclavicular involvement survived at least 2 years.

The Tufts University trial also reported IIIB group separately, but unlike SWOG 8805, pathological determination of IIIB status was not required (Vora et al. 2000). Nevertheless, the Tufts investigators also noted excellent survival among patients with resected T4N0 tumors at initial staging, with a median survival of 51 months. The resection rates were 76% and 76% for stage IIIA, and 63% and 50% for stage IIIB in the Tufts and SWOG trials, respectively.

The two- and three-year survivals in the SWOG 8805 trial were identical for stage IIIA(N2) and IIIB subsets (Albain et al. 1995, 1999). Similar observations were made in the West German Cancer Center and the German Lung Cancer Cooperative Group studies (Eberhardt et al. 1998; Thomas et al. 1999).

In the WGCC trial, 4-year survival was 31% and 26% in stages IIIA and IIIB, respectively (p=0.59). In the GLCCG, 3-year survival was 35% and 26%, for stages IIIA and IIIB (p=0.33).

Grunenwald et al. (2001) prospectively studied 40 patients with IIIB disease, of whom 30 had T4 disease and 18, N3. Five patients had T4N0 tumors and one had T4N1. Eligible patients had disease judged to be potentially resectable after a course of preoperative therapy. All patients underwent pretreatment surgical staging. Induction treatment consisted of 5-FU, cisplatin and vinblastine for 2 cycles. A total of 42 Gy of external radiotherapy was given split in two 21 Gy courses, 1.5 Gy BID, with 10 days of rest between the courses. Radiotherapy began on the first day of chemotherapy. Response was assessed a month after completion of all therapy. Patients who responded to the induction regimen underwent thoracotomy. A clinical response was obtained in 73% of patients and in 60% resection was performed. The resection was complete in all but one patient who underwent thoracotomy. Four patients (10%) had complete pathological response. Of the patients with N2 or N3 disease, 30% had complete mediastinal clearance. There were 5 treatment-related deaths and 7 additional patients suffered serious morbidity. Median survival was 15 months and five-year overall survival was 19%. Thirty percent of overall patient number had locoregional relapse and 50% had distant relapse. Pathological mediastinal nodal downstaging was the only significant favorable prognostic factor in a multivariate analysis (5-year survival 42% for post-induction N0/1 vs. 12 % for postinduction N2/3 for resected patients). All long-term survivors had persistent viable tumor cells in the primary tumor but 6 of 7 were postinduction N0-1.

Pitz et al. (2002) treated patients with stage IIIB NSCLC with neoadjuvant gemcitabine and cisplatin, followed by surgery in responding patients. No preoperative RT was given. Twelve of the patients had T4N0 tumors, 21 had T1-3N3 and the remaining had T4N2 disease. Patients with supraclavicular lymph node involvement were excluded from the protocol. A repeat mediastinoscopy was required however it was possible to complete in only a fraction of patients, and was falsely negative in some. Patients received postoperative radiotherapy for persistent nodal involvement, positive margins or incomplete resection. The investigators reported a response rate of 66%, resection rate of 44% and perioperative mortality of 2.4%. Median survival for all patients was 15.1 months and 3-year survival was 15%. The investigators found no difference in outcome between T4N0 and N2/N3 subsets. However, only patients with a response after induction chemotherapy were considered for surgical resection.

Collectively, these trials support the feasibility of induction therapy in stage IIIB NSCLC, and underscore the potential importance of resection of both responding and stable disease. They highlight the T4N0/1 substage as a group that does particularly well with trimodality therapy.

3.2.2.7 Patterns of Failure in Second- and Third-Generation Phase II Induction Trials

Patterns of failure were reported in most trials, either as a percentage of the entire number of patients or as a percentage of patients with resected disease, as summarized in Table 3.2.2.11. The preponderance of relapses is distant, especially among patients who underwent resection, however the number of locoregional relapses is not insignificant.

All patients who experienced a local-only failure in the Memorial study had an incomplete resection. The patterns of failure in the Rush-Presbyterian and SWOG trials were unaffected by nodal downstaging. In studies that analyzed the patterns of failure between patients with resected and unresected disease separately, locoregional failures occurred less frequently in those patients who had a complete resection.

A high incidence of brain relapse was noted universally across these trials. For many patients, this was the only site of relapse. In the Dana Farber and CALGB 8935 studies, 15 % and 41% of first relapses occurred in the brain, respectively. In LCSG 852 trial, 28% of initial recurrences among patients with a complete resection occurred in the brain, compared with 7% among patients with no or incomplete resection.

3.2.2.8 Randomized Trials of Surgery Alone Vs Induction Therapy Followed by Surgery in Resectable IIIA NSCLC

The trials included in this section generally involved patients with low bulk or minimal N2 disease. The control arm in these studies was surgery alone. The experimental arm used induction chemotherapy

Table 3.2.2.11. Patterns of failure in second- and third-generation phase II trials

Investigators	Disease burden	Local or locoregional only failure (%)	Combined local-and distant failure (%)	Distant-only failure (%)	Denominator
Dana-Farber III (Elias et al. 1997)	Mixed volume	30	22	48	All patients
CALGB I (Strauss et al. 1992)	Mixed volume	36	18	36	All patients
MGH (Choi et al. 1997)	Mixed volume	15	10	75	All patients
SWOG 8805 (Albain et al. 1995)	High volume	11	28	61	All patients
GLCCG (Thomas et al. 1999)	High volume	25	41	34	All patients
Rush-Presbyterian (Faber et al. 1989; Reddy et al. 1992)	Mixed volume	26	18	56	All patients
Toronto (Burkes et al. 1992)	Mixed volume	25	13	62	Resected patients only
Memorial (Martini et al. 1993)	Mixed volume	26	0	74	Resected patients only
LCSG 852[a]	High volume	33	11	50	All patients
(Weiden et al. 1992)		0	17	67	Resected patients only
CALGB 8935	High volume	25	44	31	All patients
(Sugarbaker et al. 1995; Kumar et al. 1996)		4	39	57	Resected patients only
WGCC	High volume	43	11	46	All patients
(Eberhardt et al. 1998)		22	6	72	Resected patients only

[a] Does not include four cases of second primary tumor.

with or without RT. The design of these studies is presented in Table 3.2.2.12.

Patients with a higher-volume disease burden were enrolled in the NCI (multiple N2 nodes on mediastinoscopy) and the Japanese (clinically bulky) trials. (Pass et al. 1992; Yoneda et al. 1995) The NCI study had the most homogenous population since it required histological documentation of N2 disease and excluded N3 disease. However, only 28 patients were accrued and the trial closed prematurely. Radiotherapy (54-60 Gy) was given postoperatively in non-chemotherapy arm, but not in chemotherapy arm. The pattern of failure in the surgery-RT arm was predominantly distant (>90%), while in chemotherapy-surgery arm was about 67% locoregional and 33% distant. The results of this very small trial were nevertheless provocative regarding the potential benefit of induction chemotherapy in resectable disease.

Two frequently discussed trials of preoperative chemotherapy in patients with early stage III disease were conducted by the investigators from the MD Anderson Cancer Center and Spain (Roth et al. 1994, 1998; Rosell et al. 1994). The accrual to each of these trials was a halted at 60 patients per trial because of early emergence of increased survival in the induction chemotherapy arm. The Spanish trial was critiqued because of the very poor survival in the control group (8 months median survival, with no patient surviving 2 years), more consistent with that of stage IV patients treated with chemotherapy. The MD Anderson trial was updated in 1998 (Roth et al. 1998). The advantage of the perioperative chemotherapy arm was maintained, although the statistical significance became borderline (p=0.056, log-rank test; p=0.048, Breslow-Gehan-Wilcoxon test).

The French Thoracic Cooperative Group Trial enrolled patient with stage IB to IIIA disease (Depierre et al. 2002). All patients were judged to have resectable disease before any induction treatment. Staging was clinical (radiographic) and pre-surgery mediastinoscopy was not required. An excess of patients with N2

Table 3.2.2.12. Reported phase III trials of surgery with or without induction therapy in resectable NSCLC

Investigators	Stage subset(s)	Disease burden	Chemotherapy	Radiotherapy	Patient No.	2–3 Year survival		
						No ChT	ChT	*p* Value
NCI (Pass et al. 1992)	IIIA(N2) by biopsy	High volume	EP 2 cycles preop EP 4 cycles postop	Postoperative in no-ChT arm only (54–60 Gy)	28	21%	46%	0.12
Japan (Yoneda et al. 1995)	Clinical IIIA and IIIB	High volume	VdP pre-operative	Concurrent with CT	83	40%	37%	NS
M.D. Anderson (Roth et al. 1994, 1998)	IIIA(N2) not required; node biopsy not required; some IIIB	Low volume	CEP pre- and postoperative	Postoperative only if residual disease	60	15%	56%	<0.05
Spain (Rosell et al. 1994)	IIIA(N2) not required; node biopsy not required	Low volume	PIM preoperative	Postoperative for both arms	60	0%	30%	<0.05
French Thoracic Cooperative Group (Depierre et al. 2002)	Clinical T2N0, II, IIIA	Low volume	MIP × 2 pre-operative; also postoperative, if objective response	Postoperative to 60 Gy, if pT3 or pN2 for both arms	355	41%[a]	52%[a]	p = 0.15[b]

E, etoposide; P, cisplatin; V, vinblastine; I, ifosfamide; Vd, vindesine; M, mitomycin, C; C, cyclophosphamide; NS, not significant; NCI, National Cancer Institute; ChT, chemotherapy.
[a] In N0-1 disease p=0.027, in N2 disease p=0.85.
[b] 3-Year survival.

disease was accrued to the chemotherapy arm (12%), but the difference was not statistically significant (p=0.065). Complete resection rate was 92% in the induction chemotherapy arm, and 86% in surgery alone arm. Postoperative radiotherapy to 60 Gy was delivered for pathologic T3 or N2 status, or if the resection was incomplete. Forty-one percent of patients in surgery alone arm and 23% in induction chemotherapy arm received postoperative RT. The 1-, 2-, 3- and 4-year survivals were 77%, 71%, 59% and 44%, respectively, in the induction chemotherapy arm and 73%, 52%, 41% and 35% in the surgery alone arm. The difference did not reach statistical significance (p=0.15). Stage-adjusted relative risk of death was 0.80 in the chemotherapy arm (p=0.089). In a subset analysis, there was a benefit to induction for patients with N0-1 disease (RR 0.68, p=0.027), but not for patients with N2 (RR 1.04, p=0.85). There was excess risk of deaths within the first 5 months after the surgery in the induction chemotherapy arm (RR 1.32, p=0.37), but the curves crossed at 5 months and the RR in the induction chemotherapy arm decreased to 0.74 after these first 5 months. There was a non-significant excess of mortality (10% vs. 5%) in the induction chemotherapy arm, consisting of pneumonia, empyema, fistula and pulmonary embolism. Induction chemotherapy reduced the risk of distant relapse (RR=0.54, p=0.01). Locoregional relapses were not significantly different between the treatment arms.

The MD Anderson and Spanish studies are often quoted in support of induction chemotherapy in early, low-volume stage III NSCLC. Their results are indeed provocative, but both of these studies had very small numbers of patients so that even a minor imbalance in prognostic factors between the two arms could have resulted in a major difference on the outcome. There was an excess of tumors with K-ras mutation and aneuploidy in the control arm of the Spanish study, a factor associated with an adverse prognosis. In the MD Anderson trial, there were more T4 tumors in the surgery alone arm, although this difference was not statistically different. Thus, the encouraging results of these trials must be confirmed in larger phase III trials conducted in homogenously staged and treated patient populations.

3.2.2.9 Radiotherapy as a Component of the Induction Regimen

Radiotherapy hypothetically plays an important role in patients with locally advanced tumors in increasing

rates of downstaging and resectability. Radiotherapy may also be beneficial, either preoperatively or postoperatively, in sterilizing microscopic mediastinal disease that cannot be completely removed during the surgery. In patients with microscopic N2 disease who have disease that is resectable upfront, the role of RT is much less certain.

Despite this, the utility of RT in neoadjuvant regimens in high-volume disease has been questioned. The only randomized trial to date that addressed the necessity of radiotherapy in the induction regimen was that of Fleck et al., conducted in Brazil and reported only in abstract format (Fleck et al. 1994). The investigators randomized 96 patients between induction MVP therapy followed by surgery or to cisplatin/5-FU concurrent with RT followed by surgery. Patients entered on the trial had largely advanced, high volume stage III NSCLC. The 5-year survival was improved in chemoradiotherapy arm, 31% vs. 15%, p=0.05. While the MVP regimen was commonly used at the time the study was conducted, mitomycin-C has been avoided in more recent trials due to its association with high rates of pulmonary complications. The 5-year survival in the MVP-surgery arm was very similar to the results obtained with induction chemotherapy followed by definitive radiotherapy (Dillman et al. 1996).

A radiotherapy dose prescription of 40-45 Gy is favored in most induction regimens because it is efficacious but does not result in excessive perioperative and postoperative morbidity. Trials that used higher doses of RT had greater rates of postoperative complications, especially in association with pneumonectomy (Fowler et al. 1993; Yashar et al. 1992; Deutsch et al. 1994). One exception is the Tufts study that did not report any deaths after a neoadjuvant regimen that included 59.4 Gy of radiotherapy (Vora et al. 2000).

The optimal sequence of radiotherapy relative to surgery is also an unresolved issue. In patients with large, locally-advanced tumors, preoperative radiotherapy will likely improve respectability and may synergize with chemotherapy. Also, there is more certainty that the patient will receive the entire planned dose when the RT is given within the induction treatment plan. The advantage of postoperative radiotherapy is that it can be given to a higher dose, which may be important in patients for whom a complete resection is not possible. One of the shortcomings of most induction chemoRT protocols is that eligibility for surgical resection practically must be determined before fibrosis sets in, usually 3-4 weeks after the completion of the induction with lower-dose RT. Those patients who cannot have surgery but still have localized disease are then usually treated with additional RT after the protocol-induced break. This may prevent achievement of the optimal benefit from RT, since treatment breaks during radiotherapy have been associated with decrease in survival (Cox et al. 1993; Jeremic et al. 2003). However, postoperative RT programs often report poor compliance and many patients do not receive the planned therapy (Sugarbaker et al. 1995).

The schedule of radiotherapy in trimodality programs also remains undefined. The hyperfractionated accelerated schedule intensifies the effect of RT, which may be important in locally advanced tumors. This schedule was tolerated well and was not associated with excessive rate of perioperative complications in 3 prospective phase II trials (Choi et al. 1997; Eberhardt et al. 1998; Thomas et al. 1999). A recently completed phase III German trial built upon the phase II results and when completely analyzed, it will shed light on the role of RT in the induction versus postoperative RT (Thomas et al. 2004). This trial randomized patients with stage IIIA disease to preoperative induction chemotherapy followed by hyperfractionated accelerated RT plus chemotherapy, then surgery versus preoperative chemotherapy followed by surgery followed by standard fractionation postoperative RT. Since both of the arms included RT, this trial does not test whether RT is necessary for improved survival. However, it will provide important information on the impact of RT on the pathologic response rate, nodal downstaging, morbidity and resectability. It will address the question of whether nodal downstaging is in and of itself an important predictor of long-term survival.

3.2.2.10 Phase III Trials of Chemoradiotherapy With or Without Surgery

Several prospective, randomized trials involving trimodality therapy were conducted in stage III NSCLC. These trials asked different questions, and all but one closed early without reaching the planned accrual target. They are summarized in Table 3.2.2.13.

3.2.2.10.1 Induction Chemotherapy Followed by Surgery vs Radiotherapy Alone

A small NCI Canada study randomized 31 patients to RT alone versus induction cisplatin and vinblastine

Table 3.2.2.13. Reported phase III induction trials for NSCLC

Investigators	Stage subset	Question	Study design	Number of patients	Outcome comment
NCI Canada (Shepherd et al. 1998)	Biopsy-proven state IIIA(N2)	Postinduction surgery vs RT?	PV → Surgery vs RT	31	Closed early due to radiotherapy alone arm; survival curves superimposed at 2 years
RTOG 89-01 (Johnstone et al. 2002)	Biopsy-proven stage IIIA(N2)	Postinduction surgery vs RT?	MVP or VP ↓ Surgery vs RT ↓ MVP or VP	73	Closed early due to slow accrual; p=0.62 for overall survival; 4-year: 22% for surgery vs 22% for RT
CALGB (Elias et al. 2002)	Biopsy-proven stage IIIA(N2)	Induction RT or chemo?	RT → Surgery → RT vs PV → Surgery → PV → RT	57	Closed early due to slow accrual; median survival 24 months (RT/S/RT) and 18 months (CT/S/CT) (p=0.4)
INT 0139 (Albain et al. 2003)	Biopsy-proven IIIA (N2)	Postinduction surgery vs. chemo RT alone?	PE/RT → Surgery → PE vs PE/RT → RT → PE	392	Preliminary results: 3-year OS: CT/RT/S 38%, CT/RT 33%, p 0.51 Med OS: CT/RT/S 22 mo., CT/RT 21 mo. 3-year PFS: CT/RT/S 29%, CT/RT 19%, p 0.02 Med PFS: CT/RT/S 14 mo., CT/RT 12 mo.

P, cisplatin; F, 5-fluorouracil; M, mitomycin-C; V, vinblastine; E, Etoposide; RTOG, Radiation Therapy Oncology Group; CALGB, Cancer and Leukemia Group B.

chemotherapy followed by and surgery (Shepherd et al. 1998). The study was halted after a CALGB randomized trial showed the superiority of combined chemoRT over RT alone as definitive treatment of stage III NSCLC (Dillman et al. 1996). The RT-alone alone arm was no longer appropriate (suboptimal therapy). In the analysis of patients accrued up to that point, there was no difference in median survival (16.2 vs. 18.7 months) or long-term survival (Shepherd et al. 1998).

3.2.2.10.2 Induction Chemotherapy vs Induction Radiotherapy

A CALGB trial randomized 57 patients with pathologically documented N2 disease to induction RT to 40 Gy followed by surgery, followed by 14-20 Gy of additional RT vs. induction of 2 cycles of platinum/vinblastine (PV) followed by surgery, followed by 2 more cycles of PV followed by RT to 54-60 Gy (Elias et al. 2002). There were only 2 pathological complete responses in the induction chemotherapy arm and none in the induction RT arm. Patients in the induction radiotherapy arm experienced better local control (76% vs. 50%, p=0.014). Less than half of patients were able to complete the adjuvant portion of the chemotherapy. The trial was closed early due to poor accrual. There was no difference in survival between the arms (median 24 months in RT induction vs. 18 months in chemotherapy induction, p=0.46).

3.2.2.10.3 Induction ChemoRT Followed by Surgery vs Definitive ChemoRT Alone

Two studies have been conducted to date, one of which was terminated early and the other was completed and recently reported.

The RTOG 8901 study accrued 73 patients to two treatment arms: induction chemotherapy with cisplatin, vinblastine, and mitomycin-C followed by surgical resection, versus the same chemotherapy followed by RT to 64 Gy (Johnstone et al. 2002). Patients in both arms received consolidation cisplatin and vinblastine chemotherapy. The original accrual goal was 244 patients, but the trial closed early due to poor accrual even though the protocol was amended to omit mitomycin-C after the first 16 patients. Pathologic documentation of N2 disease was required and the patients were stratified by volume of disease. In all, 29 patients were randomized to sur-

gery and 33 patients to RT. There was no difference in median survival (19.4 vs. 17.4 months) or in 1-, 2- or 4-year survival (70% vs. 66%, 48% vs. 34%, 22% vs. 22%, respectively).

The largest phase III trial to date that addresses the potential worth of surgery in stage IIIA(N2) NSCLC is the Intergroup 0139 trial, chaired by RTOG (Albain et al. 2003). The entry criteria for this study included T1-3 primary tumor, pathologically confirmed N2 disease, feasible resection from a surgical standpoint and medical ability to undergo resection. Patients were stratified by performance status, T1–2 vs. T3, and whether contralateral mediastinal nodes required biopsy or not (mandated if nodes were visible on CT scan), and randomized between the trimodality versus the bimodality arm. The induction regimen was identical in both arms: 45 Gy of external radiotherapy given in a once daily fraction, concurrent with day 1 of induction chemotherapy, which was cisplatin, 50 mg/m2 on days 1, 8, 29, 36 and etoposide, 50 mg/m2 days 1–5 and 29–33. Patients were reevaluated by a CT scan 2–4 weeks after completion of the induction regimen in the surgical arm, and in the RT arm, a week before completion of treatment. Those patients with no progression proceeded with their assigned treatment. In the surgical arm, the treatment consisted of resection of all known disease and mediastinal nodal sampling. In the RT arm, the radiotherapy continued to 61 Gy without a break. In both arms, consolidation chemotherapy (two cycles of cisplatin and etoposide) was given to all patients. The study initially was designed to accrue 510 patients, but the Data Safety and Monitoring Board recommended closure with 429 accrued patients due to sufficient events based on the slower than anticipated accrual.

The first interim results were recently presented (Albain et al. 2003). At a median follow-up of 69 months, 392 patients were analyzable. Induction treatment was delivered as per the protocol equally in both arms. In the surgical arm, a thoracotomy was performed in 96% and a complete resection was accomplished in 88% of patients for whom the data were available. There were 18% pathologic complete responses (T0N0) and 46% with pathologic nodal clearance. The chemoRT toxicity was similar in both arms, with the exception of esophagitis which was more common in the chemoRT arm. Consolidation chemotherapy was not administered to 42% of patients undergoing surgery and 21% of those not having undergone surgery ($p<0.001$). Conversely, RT was delivered according to protocol in 81% on the chemoRT arm versus 97% on the surgery arm ($p=0.002$). Three patients (1.6%) in chemoRT arm and 14 (7%) patients in chemoRT-surgery arm died from treatment-related toxicity. In the latter group, ten of these deaths were caused by postoperative complications. Most of the deaths occurred in patients who underwent pneumonectomy (especially right-sided), and the most frequent cause of death was acute respiratory distress syndrome (ARDS).

Median progression-free survival was 14.0 months and 11.7 months in the chemoRT-surgery arm and chemoRT arm, respectively. Three-year progression free survival was 29% in the chemoRT-surgery arm vs. 19% in chemoRT arm (log rank $p=0.02$). The median overall survival was 22.1 months versus. 21.7 months and the 3-year survival was 38% vs. 33% in the chemoRT-surgery and ChemoRT arms, respectively (log rank $p=0.51$). The overall survival curves cross over and begin to separate at 22 months. By 3 years, there was a 5% absolute survival benefit in the surgical arm, but the confidence intervals are wide and overlap. More patients died of treatment complications in the surgical arm, but more are alive without progression in the same treatment arm. Sites of relapse were also analyzed: 13% of patients in the chemoRT-surgery arm had locoregional relapse only versus 21% in the chemoRT arm ($p=0.07$). Relapse in the primary site was three times more common in the non-surgical arm. Brain was a common site of first relapse in both arms (10% versus 18 % in the chemoRT and chemoRT-surgery arm, respectively, $p=0.08$).

Pretreatment factors predictive of favorable outcome were lower T stage, less than 5% weight loss and younger age. Female sex and normal LDH did not reach statistical significance. After the induction treatment, patients who achieved complete response in the mediastinal nodes had median survival of 36.7 months and 3-year survival of about 50%, regardless of the response in the primary tumor.

3.2.2.11 Phase II Trials of Induction Regimens That Incorporated Third-Generation Chemotherapy Agents

Recent investigations tested third-generation chemotherapy agents within the induction therapy prescription. Selected studies with larger numbers of patients are presented below (see Table 3.2.2.14). One of the trials included patients with stages IB, II and "early" IIIA, three studies enrolled patients with N2

biopsy-positive but resectable stage IIIA disease, and the last one included high-volume, advanced unresectable stage IIIA and IIIB disease. The diversity of patients prevents comparisons among studies as well as conclusions regarding an improvement over second-generation induction programs.

Preoperative carboplatin and paclitaxel chemotherapy was tested by the BLOT group (Bi-modality Lung Oncology Team) in 90 patients with stages IB, II, and selected IIIA NSCLC (Pisters et al. 2000). Initially, 94 patients with stages IB through IIA (no N2) were administered two cycles (paclitaxel 225 mg/m2 and carboplatin AUC 6) preoperatively and three postoperatively. The "major response" rate was 56%. At the time of thoracotomy, 86% of the original number of patients was able to undergo complete resection. There were two deaths related to surgery and one related to induction therapy, for a total mortality of 3%. Pathologic complete response was observed in six patients (6%). Only 43% were able to receive the planned postoperative chemotherapy. After this initial analysis, the protocol was amended to three preoperative cycles of the same chemotherapy and 40 additional patients were accrued. The results were presented recently (Pisters et al. 2003). Five year-survival for the cohort receiving two cycles of preoperative chemotherapy was 46%. The patients who received three cycles of preoperative therapy had 48% 3-year survival, but the follow-up was shorter. The diversity of stages included in this trial precludes comparing the outcome of this trial to other studies. It is uncertain whether these results represent a survival improvement over second-generation induction chemotherapy, but tolerance to treatment was extremely good.

The Swiss Group for Clinical Cancer Research (SAKK) enrolled patients with stage IIIA disease due to biopsy-proven ipsilateral mediastinal nodal involvement that were considered potentially operable (Betticher et al. 2003). The induction regimen consisted of cisplatin 40 mg/m2 on days 1–2 plus docetaxel 85 mg/m2 on day 1 for three cycles. All patients except those with progressive disease underwent thoracotomy. Postoperative RT to 60 Gy was administered for a positive resection margin and/or involvement of the uppermost mediastinal lymph node. Postoperative chemotherapy was not given. A total of 90 patients were enrolled, 18% of whom did not have mediastinal nodal enlargement on CT scan. The protocol was later amended to increase the cisplatin dose to 100 mg/m2 per cycle.

The overall clinical response was 66%. Complete resection was accomplished in only 48% of the entire patient group. An additional 43% underwent incomplete resection with positive margins and/or positive highest mediastinal lymph node. It is of note

Table 3.2.2.14. Design and results of completed phase II trials using third-generation chemotherapy drugs within the induction regimen

Investigators	Stage subset	Study design	Patients (*n*)	Response rate	Resection rate (R0)[a]	pCR	Survival
BLOT (Pisters et al. 2000, 2003)	IB-IIIA (no N2)	TC × 2 → Surgery → TC x3 TC × 3 → Surgery → TC x3	94 40	56% 40%	86%	6%	3-Year 63%, 5-year 46% 3-year 48 %
SAKK (Bettincher et al. 2003)	IIIA (pN2), mixed bulk	PD × 3 → Surgery → variable RT	90	66%	48%	16%	3-Year 33%
De Marinis et al. (2003)	IIIA (pN2), bulky	GTP × 3 → Surgery→ variable RT	49	74%	55%	16%	Median 23 months
ILCP (Capuzzo et al. 2003)	IIIA, IIIB (clin) bulky	GP × 4 → Surgery → variable RT	129	62%	29%	2%	Median 19 months
EORTC (Splinter et al. 2000; van Zandwijk et al. 2000; O'Brien et al. 2003)	IIIA (pN2), bulky	GC → Surgery TC → Surgery	47 52	70% 64%	71% 80%	NR	NR

T, paclitaxel; C, carboplatin; P, cisplatin; D, docetaxel; G, gemcitabine; NR, not reported.
[a] Of the original number of patients.

that the median overall cisplatin dose-intensity in patients with negative resection margins was higher than in patients with positive resection margins (96 vs. 80 mg/m2/cycle, p=0.034). There were two treatment-related deaths (3%). About a third of patients received postoperative radiotherapy. There were 14 patients (16%) with a complete pathologic response, and 45 (60%) had pathologic nodal clearance. The median survival was 27.6 months and 3-year survival 33%. Among treatment-related variables tested in multivariate analysis, mediastinal downstaging was the most powerful independent favorable prognostic factor (p=0.0003). Patients with mediastinal downstaging had a 3-year survival rate of 61% compared to 11% for those who did not. Complete resection was also predictive of favorable outcome (p=0.006).

De Marinis et al. (2003) enrolled 49 patients biopsy-documented N2 disease in an induction protocol consisting of 1000 mg/m2 gemcitabine, 125 mg/m2 paclitaxel, and 50 mg/m2 cisplatin given on days 1 and 8 for three cycles (De Marinis et al. 2003). All the patients enrolled had multiple enlarged nodes on chest CT scan. Patients with at least stable disease after the induction regimen underwent attempted surgical resection. Postoperative RT was given to 59.4 Gy for patients with persistent N2 disease or incomplete resection. Patients whose disease did not respond received RT alone, and the patients whose disease responded but did not undergo thoracotomy received three more cycles of the same chemotherapy followed by RT. The response rate was 73.5 % based on radiographic criteria. The complete resection rate was 55%. Mediastinal nodal disease clearance occurred in 35% of cases, and complete pathological response in 16%. There was one death during the induction. After a short median follow-up of 16 months, median survival and progression-free survival were 23 months and 18 months, respectively. The brain was the most common metastatic site (16%). Postoperative complications were not detailed.

The EORTC is conducting a phase III trial (EORTC 08941) of induction chemotherapy followed by either radiotherapy or surgery for those patients with at least partial clinical response to induction (Splinter et al. 2000). The trial design allows a menu of induction combination chemotherapy as long as it includes cisplatin at 100 mg/m2 or carboplatin at 400 mg/m2. Two reports of feasibility and toxicity have been published to date of induction approaches, while the phase II trial is ongoing (van Zandwijk et al. 2000; O'Brien et al. 2003). The first pilot study was reported by van Zandwijk et al. (2000) in which gemcitabine 1000 mg/m2 and cisplatin 100 mg/m2 were used. The dose of gemcitabine had to be reduced or omitted in more than half of the patients, mainly due to thrombocytopenia. Responses were observed in 70%. O'Brien et al. (2003) reported the use of induction paclitaxel, 200 mg/m2, and carboplatin, AUC of 6. Over 90% of patients were able to complete all induction treatment per protocol. The response rate was 64%. One patient died of postoperative complications. In the two studies, resection rates of 71% and 80%, respectively, were reported.

The Italian Lung Cancer Project completed a phase II trial in unresectable, locally advanced stage IIIA and IIIB NSCLC (Cappuzzo et al. 2003). The induction regimen consisted of four cycles of gemcitabine 1000 mg/m2 on days 1 and 8, and cisplatin 70 mg/m2 on day 2. The trial accrued 129 patients. The response rate was 80%, but the resectability rate was only 29%. Postoperative RT to 44–46 Gy was given for positive mediastinal lymph nodes and was continued to 60 Gy if the disease was unresectable. There was no perioperative mortality and minimal morbidity. The median progression-free survival was 11 months and median survival was 20 months.

3.2.2.12 Treatment-Related Morbidity and Mortality in Trials of Induction Therapy Followed by Surgery

The toxicity of combined-modality therapy that includes surgery is not insignificant. Each modality carries its own set of toxicities, which interact with each other so that it is often difficult to attribute a particular toxicity to just one modality. It is important to note that the patients enrolled in clinical trials had to have good performance status, reasonable pulmonary function, and little comorbidity. This is frequently not the case with general patient populations diagnosed with lung cancer. The extent of morbidity and mortality reported in the literature is likely to be an underestimate when applied to the general population.

Treatment-related mortality reported in the second-generation phase II trials ranged from 0% to 18%, and perioperative mortality in most trials was between 5% and 10%. Mitomycin-C, an agent with recognized pulmonary toxicity, was commonly used in some of the earlier induction regimens and likely contributed to some of the deaths. In three out of five phase II trials using third-generation chemotherapy regimens, there were no perioperative deaths re-

ported and 1%–2% mortality related to the induction therapy (de Marinis et al. 2003; van Zandwijk et al. 2000; Cappuzzo et al. 2003). The randomized phase III Intergroup 0139 trial had 5% perioperative mortality in the surgical arm. Without the induction therapy, the mortality risk for a lobectomy is about 1%–2% and for a pneumonectomy 3%–6% (Harpole et al. 1996; Ginsberg et al. 1983; Mitsudomi et al. 1996). Taken together, these data indicate that the surgical risk is probably slightly increased after the induction therapy.

Treatment-related toxicity noted during the induction part of the treatment mainly consists of myelosuppression, which was short-lived and rarely life-threatening. Other acute toxicities include nausea/emesis, mucositis, diarrhea, and malaise. Moderate esophagitis was quite common in trials using a hyperfractionated accelerated schedule, occurring in about 40% of patients, with severe esophagitis in up to 14% (Choi et al. 1997; Eberhardt et al. 1998; Thomas et al. 1999). In regimens using single daily RT fractions, the incidence of severe esophagitis was in general below 10%. Radiation pneumonitis usually occurs after the completion of RT and can interfere with postoperative recovery and delivery of additional chemotherapy.

Surgical issues in association with neoadjuvant therapy were recently reviewed (Liptay and Fry 1999). It is generally agreed that post-induction resections usually pose a greater technical challenge and require more vigilance in postoperative care. Patients going into surgery after completing an induction regimen may have compromised immunological and nutritional status and decreased renal reserve. Fibrotic reaction from radiotherapy may obliterate resection planes. Reactive changes may be indistinguishable from the tumor and result in inappropriately extensive resection. To minimize the effect of fibrotic reaction, surgery should be performed within 4–6 weeks after completion of induction regimen. Right pneumonectomy carries the highest morbidity and mortality risk, attributed to greater alveolar content of the right lung.

Preoperative radiation therapy is known to increase the risk of bronchial stump insufficiency and tissue coverage of bronchial stumps in all patients receiving neoadjuvant therapy is advocated (Faber and Piccione 2000). The major impact of the experience of the multidisciplinary medical team that cares for these patients is exemplified by the two studies which noted several cases of bronchial stump insufficiency after an induction regimen that included hyperfractionated radiotherapy occurring early in the study course (Eberhardt et al. 1998; Thomas et al. 1999). This problem was eliminated when the surgeons incorporated a bronchial stump protection protocol for all future patients.

ARDS was reported in many studies, and was responsible for the majority of perioperative deaths in the Intergroup 0139 trial. The incidence of this complication in the absence of induction therapy appears to be lower, and studies regarding its pathogenesis and prevention are needed (Deslauriers et al. 1998).

The adequacy of postoperative pulmonary reserve should be tested not only by standard pulmonary function tests but also by assessing exercise tolerance and functional level. Postoperative predicted DLCO greater than 50% is usually recommended as a guideline. Specific recommendations for patients undergoing post-induction resection include restriction of intravenous fluids perioperatively, reinforcing bronchial stumps with tissue, pain control via epidural/paravertebral catheter, early use of broad spectrum antibiotics, aggressive pulmonary toilet, and monitoring/prevention of supraventricular tachycardia (Liptay and Fry 1999).

3.2.2.13 Strategies to Reduce Radiotherapy-Related Morbidity in Trimodality Treatment of Non-Small Cell Lung Cancer

Induction RT likely helps improve resection rates, especially in locally advanced tumors, but at the same time contributes to surgical morbidity and mortality. Two well recognized morbid effects of RT are radiation pneumonitis (usually occurring within 6 months from completion of radiation) and late fibrosis. These complications are likely to be more devastating in patients who undergo a lobectomy or pneumonectomy. The occurrence of clinical radiation pneumonitis has been correlated with the volume of lung receiving over 20 Gy (V20) (Graham et al. 1999). However, impairment of diffusion capacity and perfusion can and do occur at lower doses (Gopal et al. 2003; Marks et al. 1997; Seppenwoolde et al. 2000). By fitting patient data into a mathematical model, Gopal et al. suggested a sharp loss in local DLCO occurring with radiation doses above 13 Gy (Gopal et al. 2003). These data suggest that it is prudent to limit the volume of lung receiving even low-dose radiation.

There are several strategies that can be used to limit the radiation effect on the normal lung; how-

ever, none have been studied in the context of a trimodality approach. Three-dimensional conformal radiotherapy technique can ensure adequate radiation dose to the tumor and areas of risk, and limit the irradiation of the healthy tissue. Limiting the mediastinal target volume to only those areas positive on positron emission tomography (PET) scan will reduce the volume of irradiated lung and should be considered for future studies. Irradiation of contralateral uninvolved lung should be avoided to the maximum extent possible, especially in patients who are likely to require pneumonectomy. Ideally, the irradiated volume should include as little lung outside the area destined to be resected as possible. The chemical protector amifostine was reported to protect from radiation-induced decrease in pulmonary diffusion capacity as well as to decrease the risk of radiation pneumonitis and could be studied in trimodality settings (Gopal et al. 2001; Antonadou et al. 2003).

3.2.2.14 Ongoing and Planned Phase III Trials Worldwide

Several phase III trials investigating combined-modality therapy are ongoing at this time. For example, three major trials address the role of surgery. The EORTC has just completed accrual to a phase III trial (EORTC 08941) of induction chemotherapy followed by either radiotherapy or surgery (EORTC 08941) (Splinter et al. 2000). The trial enrolled stage IIIA(N2) NSCLC patients, considered unresectable pre-treatment with positive N2 nodal biopsy or ipsilateral vocal cord or diaphragm paralysis. Patients are given any combination chemotherapy regimen that contains cisplatin at 100 mg/m2, or carboplatin at 400 mg/m2. Upon completion, patients are reassessed for response, and those achieving either complete or partial response are randomized to either radical RT or surgical resection. Postoperative RT is given either for positive surgical margins of persistent N2 disease at surgery. This trial was opened in 1994 and first survival results are anticipated soon.

The German/French consortium has opened a new phase III trial based on encouraging pilot data of a novel trimodality regimen (W. Eberhardt, 2004, personal communication). Patients with advanced stage III disease (two or more N2 levels involved, large-volume N2 disease, selected IIIB subsets) are treated with induction cisplatin plus paclitaxel followed by (if no progression) hyperfractionated RT plus concurrent cisplatin plus vinorelbine. Upon restaging, patients with operable disease are randomized to either surgical resection or to a boost chemoRT program of cisplatin plus vinorelbine plus single daily fraction RT to 75 Gy.

A phase III Nordic trial is ongoing for patients with biopsy-proven N2 disease. The randomization is to either carboplatin plus paclitaxel for three cycles followed by RT to 60 Gy (single daily fraction), or, to the same induction therapy followed by surgical resection and then followed by RT to 60 Gy (single daily fraction).

Examples of large, ongoing or planned phase III trials that test the role of RT in the induction regimen are those conducted by the SAKK group (trial 16A/2000) and the North American Intergroup. Both trials enroll/will enroll patients with low volume N2 disease that is proven by biopsy and with resectable primary tumors. The SAKK trial prescribes three cycles of cisplatin plus docetaxel followed by restaging. If a response or stable disease occurs, patients will be randomized to either surgical resection or to daily RT (with a novel hyperfractionated imbedded boost) followed then by surgical resection. The North American Intergroup will also test induction cisplatin and docetaxel, but the randomization will be to concurrent daily RT or not. Both arms then receive surgical resection, followed by additional chemotherapy in all patients. This study will also have multiple important correlative studies, including PET scan questions, molecular biologic predictors and proteomics.

Many phase III trials are ongoing or planned that address the role of induction chemotherapy in earlier stage disease versus surgery alone. At this writing, these trials are all in a state a flux, given very recent reports of large survival benefits from adjuvant chemotherapy (Arriagada et al. 2004; Winton et al. 2004; Strauss et al. 2004; Hamada et al. 2004). Thus, studies with a surgery-alone control group are no longer feasible. However, the question of the sequence – chemotherapy then surgery vs surgery then chemotherapy – is still a critical one to answer in early stage NSCLC.

3.2.2.15 Conclusions

In summary, induction therapy is feasible and can result in long-term survival over and above that ex-

pected from first-generation, single-modality treatments. Depending on substage and disease burden, 15%–49% of patients will remain free of recurrence long-term. Clinical response to induction therapy is not necessarily predictive of the pathologic response after surgery, so that surgery should not be withheld in the absence of radiographic change. Downstaging of mediastinal nodal disease appears to be the best predictor of long-term survival across studies. However, surgery after induction therapy is technically more demanding with a somewhat increased risk of perioperative mortality, with more studies needed to understand and prevent these problems. Induction therapy programs with chemoRT do not necessarily result in worse quality of life (Schumacher et al. 2004), but close monitoring for perioperative ARDS is necessary. Most relapses following induction therapy/surgery are distant, with brain as the most common single site. Strategies to decrease this problem are needed.

After this review of reported results of multiple clinical trials, the debate regarding combined-modality therapy that involves surgery can be readdressed. Should resection of early stage NSCLC always be preceded by neoadjuvant chemotherapy? And should chemoradiotherapy in high-volume, advanced stage III NSCLC always be followed by surgical resection? The International Association for the Study of Lung Cancer (IASLC) issued a consensus statement after its meeting in September, 2002 (before the results of INT 0139 and the recent adjuvant trials were known). This consensus statement reaffirmed surgical resection alone and chemoradiation alone as standards of care for early and locally advanced NSCLC, respectively (Eberhardt et al. 2003). Another recommendation was more recently made by the National Comprehensive Cancer Network (2004). Its current clinical practice guidelines recommend induction chemotherapy with or without radiation therapy, followed by surgery for patients with T1–T2, N2 positive patients. For patients with T3N2 disease, the NCCN-recommended treatment is chemoradiation, although no prospective trial specifically addresses this issue.

Since the recent adjuvant therapy results were released, many experts now recommend adjuvant administration of platinum-based chemotherapy to resected patients with early stage NSCLC (Arriagada et al. 2004; Winton et al. 2004; Strauss et al. 2004; Hamada et al. 2004). This creates a conundrum regarding whether the same chemotherapy administered in a preoperative setting would be as or more efficacious. Trials are planned or underway to address this question. The IASLC consensus statement must be revised, given that surgery alone is now considered to be inferior treatment.

The debate regarding surgery in high-volume disease is not settled. The large North American Intergroup trial 0139 at its first survival analysis showed that for patients with locally advanced NSCLC, surgical resection after induction therapy increases disease-free survival, but this advantage is offset by increased non-cancer mortality, ultimately resulting in the same overall survival (Albain et al. 2003). It is possible that with longer follow-up the advantage in disease-free survival will translate into improvement in overall survival. Chemotherapy as the sole induction modality in this group is problematic, given resection rates are generally lower when the tumor burden is higher. However, until more data are available, trimodality treatment should not be routinely offered to this patient population outside a clinical trial without a detailed, informed discussion of risks versus benefits. One exception appears to be stage T4N0/1 NSCLC. Data (albeit very small subsets or series) collectively suggest that surgical resection markedly improves the long-term outcome for this subgroup, with 5-year survival rates of almost 50%. Ideally, a phase III trial to validate these observations should be done, but most likely will not be feasible. Thus, routine use of a published trimodality program in this uncommon subset appears to be reasonable.

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3.2.3 Palliative External Beam Thoracic Radiotherapy

Jason Lester and Fergus Macbeth

CONTENTS

3.2.3.1 Introduction

Non-small cell lung cancer (NSCLC) continues to be a major health problem in many countries. Despite advances in diagnosis and treatment, 90% of patients are incurable at presentation, and the overwhelming majority will die of their disease. Most of these patients will develop thoracic symptoms at some point during their illness, and the challenge facing heath professionals is to provide effective palliation while avoiding unacceptable toxicity. Management decisions involve balancing possible treatment benefits against side effects, and this is often difficult to do because many lung cancer patients are advanced in age and also have significant co-morbidity.

Palliative thoracic radiotherapy can be defined as radiotherapy given in less than radical doses to control symptoms from intrathoracic disease. It has long been used in the management of NSCLC patients; fractionation schedules and indications for their use have evolved over time, based on empirical observations rather than clinical evidence. Comparative studies of clinical practice have shown that policies about when to employ palliative radiotherapy and about the fractionation schedules thought appropriate differ between health care systems (Priestman et al. 1989; Maher et al. 1992). A survey of practice from one American radiotherapy centre (Lutz et al. 1997) reported that only 12% of lung cancer patients received low dose palliative radiotherapy, whereas a typical British centre would treat a greater proportion of patients in this way (Macbeth, unpublished observation). Despite the increasing use of chemotherapy over the last decade, radiotherapy continues to play an important role in palliating NSCLC patients, particularly those with symptoms predominantly from intrathoracic disease.

In this chapter, we will discuss the clinical evidence available to guide us on when and how to use palliative thoracic radiotherapy in NSCLC. The studies referred to in this chapter were identified through a search of MEDLINE up to September 2003, and through hand-searching of relevant journals and conference abstracts.

3.2.3.2 Treatment Effectiveness

3.2.3.2 1 How Effective Is Radiotherapy at Palliating Thoracic Symptoms Related to NSCLC?

Despite its widespread use, there have been no randomised controlled trials (RCTs) comparing palliative radiotherapy with supportive care alone in symptomatic patients. The best information we have is from RCTs comparing different radiotherapy treatment schedules, and from a few other published non-randomised series (Table 3.2.3.1).

Symptom palliation is a difficult end point to measure accurately, because by definition, assessment of symptom severity is subjective; it will differ between individual patients as well as between clinicians. In addition, evidence suggests that doctors underesti-

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Table 3.2.3.1. The effect of palliative radiotherapy

Author	No. of patients	Symptom assessment	Cough	Hemoptysis	Chest pain	Dyspnea	Anorexia
Simpson et al. (1985)	409	clinician	99/180(55)	71/75(95)	67/134(50)	63/171(37)	NR
Collins et al. (1988)	96	clinician	58/86(67)	42/48(87)	28/39(72)	45/85(53)	24/59(41)
Teo et al. (1988)	255	clinician	Overall symptom control 146/255(57)				
MRCLCWP (1991)	369	clinician	206/341(60)	144/172(84)	162/208(78)	156/255(61)	141/213(66)
MRCLCWP (1992)	235	clinician	114/220(52)	80/109(73)	90/137(66)	84/198(42)	77/148(52)
Muers and Round (1993)	289	clinician	(72)	(98)	(82)	(82)	NR
MRCLCWP (1996)	509	patient	210/404(52)	NR	188/289(65)	146/255(57)	NR
Rees et al. (1997)	216	patient	107/168(64)	78/81(95)	78/89(88)	78/128(72)	NR
Erridge and Murray (2003)	149	clinician	64/118(54)	61/66(92)	35/53(66)	66/117(56)	NR

Number of patients with palliation/number with symptoms (%); NR, not recorded.

mate the severity of physical symptoms (Stephens 1997) compared to patients. Some symptoms, in particular hemoptysis, may be intermittent and self-limiting, making any response to treatment difficult to assess. Most NSCLC patients will be on medication such as analgesics and antitussives before starting radiotherapy. Altering a drug dose during treatment may give misleading results when evaluating effectiveness. An increase in morphine use, for example, may result in reduced pain, cough and dyspnea all of which may be attributed to radiotherapy unless any change in medication is recorded very carefully. Consequently, there are no well validated universally accepted methods in use to measure symptomatic response to treatment, and the studies in Table 3.2.3.1 used a variety of techniques to do this. For this reason, attempting to combine the numerical data in Table 3.2.3.1 would be inappropriate.

It can be seen, however, that palliative radiotherapy results in symptom improvement in the majority of patients. Hemoptysis and chest pain are particularly well palliated and over half of all patients in each study had improvement in cough. The results for dyspnea are less good, probably reflecting the varied causes of this particular symptom in patients with NSCLC.

3.2.3.2.2 What Are the Most Effective Dose Regimens?

Patients with incurable NSCLC have a poor prognosis, and the aim of any therapeutic intervention should be to improve disease-related symptoms and maintain quality of life. To date there have been 14 randomised trials, ten published (Table 3.2.3.2) and four in abstract form (Table 3.2.3.3) comparing different palliative radiotherapy fractionation schedules in incurable NSCLC. Overall, it seems that short radiotherapy schedules of 1 or 2 fractions are as effective in palliating thoracic symptoms as more prolonged treatment schedules. Only three published trials to date have shown significantly improved survival with a more fractionated, higher dose regimen.

The first is the Medical Research Council Lung Cancer Working Party trial (MRC LCWP 1996) which randomised 235 patients to 36 or 39 Gy in 12 or 13 daily fractions (36 Gy/12 fractions or 39 Gy/13 fractions) or 17 Gy in 2 fractions over 8 days to the primary site and mediastinal lymph nodes. All the patients in this trial were of good performance status (WHO 0-2), and had disease too advanced for radical radiotherapy, but no evidence of metastatic disease outside the locoregional volume. The median survival was significantly greater in the 13-fraction arm (9 months vs 7 months, p=0.003). The 2-fraction schedule did however result in more rapid palliation of symptoms, with significantly less acute esophagitis.

This difference in survival may be explained by the significantly lower incidence of distant metastases in the higher dose arm (64% vs 77% at 12 months). It is reasonable to conclude that higher doses of palliative thoracic radiotherapy can delay the development of systemic metastases if disease is confined to the chest and can be encompassed within a single treatment field. This translates into a small but significant survival advantage to patients of good performance

Table 3.2.3.2. Published randomised trials comparing different regimens of palliative radiotherapy

Author	Patient number and PS	Regimens	Palliation	Survival	Esophagitis
Teo et al. (1988)	273, any PS	45 Gy/18 fx 31.2 Gy/4 fx/4 weeks	Better with 45 Gy	No difference	No difference
Simpson et al. (1985)	316, KPS=>60	40 Gy/20 fx 30 Gy/10 fx 40 Gy/10 fx	No difference	No difference	No difference
Abratt et al. (1995)	84, PS 0–2	35 Gy/10 fx 45 Gy/15 fx	No difference	No difference	Worse with 45 Gy
MRC (1991)	369, any PS	30 Gy/10 fx 17 Gy/2 fx	No difference	No difference	No difference
MRC (1992)	235, PS 2–4	17 Gy/2 fx 10 Gy/1 fx	No difference	No difference	Worse with 17 Gy
MRC (1996)	509, PS 0–1	36–39 Gy/ 12-13 fx 17 Gy/2 fx	No difference	Better with 39 Gy 9% vs 12% at 2 years	Worse with 39 Gy
Rees et al. (1997)	216, any PS	17 Gy/2 fx 22.5 Gy/5 fx	No difference	No difference	NR
Reinfuss et al. (1999)	240, KPS=>50	50 Gy/25 fx 40 Gy/10 fx 20-25 Gy/5 fx	NR	Better with 50 Gy 2-year survival 18% vs 6% vs 0%	No difference
Nestle et al. (2000)	152, KPS=>50	36 Gy/15 fx(b.i.d.) 60 Gy/30 fx 17 Gy/2 fx	No difference	No difference	Worse with 60 Gy
Bezjak et al. (2002)	230, PS 0–3	10 Gy/1 fx 20 Gy/5 fx	Better with 20 Gy	Better with 20 Gy MS 4.2 vs 6 months	No difference

PS, performance status; KPS Karnofsky performance status; NR, not recorded; MS, median survival, fx, fraction(s).

Table 3.2.3.3. Randomised trials comparing different regimens of palliative radiotherapy – abstract only

Author	Patient number and PS	Regimens	Palliation	Survival	Esophagitis
Gaze et al. (2001)	148, PS 0–3	30 Gy/10 fx 10 Gy/1 fx	Better with 30 Gy	No difference	No difference
Sundstrom et al. (2001)	407, any PS	17 Gy/2 fx 42 Gy/15 fx 50 Gy/25 fx	No difference	No difference	Worse with 17 Gy at 2 weeks
Senkus-Konefka et al. (2001)	100, any PS	16 Gy/2 fx 20 Gy/5 fx	No difference	No difference	Worse with 20 Gy
Kramer et al. (2003)	297, PS 2-4	16 Gy/2 fx 30 Gy/10 fx	NA	Mean survival better with 30 Gy 26 vs 35.4 weeks	NA

NA, not available; fx, fraction(s).

status. This is supported by the randomised trial reported by Reinfuss et al. (1993), which showed a significant survival advantage when treating good performance status (PS) stage III patients with more a prolonged treatment schedule.

A National Cancer Institute of Canada (NCIC) trial (Bezjak et al. 2002) also showed a significant survival difference for a higher dose regimen. A total of 230 patients were randomised to either 20 Gy/5 fractions over 5 days or 10 Gy/1 fraction. Both regimens were effective in palliating symptoms, and resulted in limited toxicity, but a significant survival advantage was reported in the higher dose arm (median survival 6 months vs 4.2 months, p=0.0305). Subsequent sub-

group analysis showed this difference persisted in patients with good PS (WHO 0-1) and localised cancer stage, but was not seen in poor PS patients or those with metastatic disease.

The first MRC LCWP RCT (MRC LCWP 1991) randomised 369 patients to 17 Gy in 2 fractions over 8 days or 30 Gy in 10 fractions over 12 days (or 27 Gy in 6 fractions over 8 days). Patients with poor PS were included, and nearly one third had metastatic disease at the time of randomisation. The schedules were equivalent with respect to symptom palliation, survival and toxicity. In an attempt to simplify treatment even further for patients with poor PS (WHO 2-4), MRC LCWP (1992) randomised 235 patients to 17 Gy in 2 fractions over 8 days or 10 Gy in 1 fraction. There were no significant differences in palliation or survival between the two arms, although there was a higher incidence of esophagitis with the 2-fraction schedule. The conclusion from the MRC LCWP (1991, 1992) trials was that patients with poor PS and/or more extensive disease can be effectively palliated with one or two treatments; longer and higher dose fractionation schedules are unnecessary and offer no survival advantage.

The Norwegian Lung Cancer Study Group (NLCSG) randomised 407 patients to one of three palliative regimens; 17 Gy in 2 fractions over 8 days, 42 Gy in 15 fractions over 3 weeks or 50 Gy in 25 fractions over 5 weeks (Sundstrom et al. 2002, abstract only). There were no significant differences in symptom palliation or survival between the three arms. In contrast to the MRC LCWP (1996) trial, subgroup analysis did not show any survival advantage with the higher dose regimens when looking at stage IIIa disease alone. This may be explained by the distribution of performance status in the two trials. In the MRC 1996 trial, 76% of patients were WHO PS 0–1 compared to only 25% in the NLCSG trial. It is probable that poorer performance status patients do not live long enough to benefit from a higher dose of thoracic radiotherapy.

Gaze et al. (2001, abstract only) randomised 149 patients to 30 Gy in 10 fractions over 12 days or 10 Gy in 1 fraction. Both regimens were effective in palliating thoracic symptoms, and there was no significant difference in survival between the two arms. The 10-fraction regimen resulted in a greater proportion of patients having improvement in dyspnea, and was associated with less anxiety. But the symptoms were scored by the doctors, raising the question of bias, and results therefore should be interpreted with caution. The reduction in anxiety with the 10-fraction regimen may simply have been due to more contact with hospital staff over the course of treatment.

In a Dutch RCT (Kramer et al. 2003, abstract only) 297 patients with stage III disease and poor PS, or stage IV disease, were randomised to 30 Gy in 10 fractions over 12 days or 16 Gy in 2 fractions over 8 days. *Mean* life expectancy was significantly greater in the higher dose arm (35.4 weeks vs 26 weeks, $p<0.02$). This is the only randomised study to date to claim a survival advantage with a higher dose regimen in patients of poor PS or metastatic disease, but the statistical methods used are open to question. Mean (or average) values are rarely used in the analysis of survival, as a small number of long term survivors can skew results. Median values (time at which 50% of patients are alive) are not affected in the same way, and are generally felt to give a more accurate estimate of survival. It is possible that a handful of long term survivors in the 10-fraction arm resulted in the apparent difference seen. In addition, if the survival difference is a true one, what explains it? Poor performance status patients would not live long enough to benefit from the higher dose, and it seems unlikely that increased local control with the higher dose would result in a survival advantage in patients with established metastatic disease.

Overall, the evidence suggests that two principles can be applied when treating symptomatic NSCLC patients with palliative thoracic radiotherapy:

- 1. Poor PS patients and those with metastatic disease are effectively palliated with 1 or 2 fractions of radiotherapy and do not benefit from more fractionated regimens.
- 2. Patients with relatively localised disease and good PS may derive a modest survival advantage with higher doses.

3.2.3.2.3 Treatment-Related Toxicity

It is well recognised that palliative thoracic radiotherapy can be associated with significant acute and long term toxicity. Transient anorexia and nausea are common, as is dysphagia secondary to radiation esophagitis. These symptoms were investigated in detail in the three MRC LCWP trials. All three used patient-held daily diary cards to record significant symptoms. Overall, the proportion of patients suffering some degree of nausea or anorexia following radiotherapy was about 20% and 35%, respectively, and these symptoms were usually mild. The incidence, severity and duration of dysphagia depended on the ra-

diotherapy regimen used. With 30 Gy in 10 fractions over 12 days and 17 Gy in 2 fractions over 8 days, dysphagia started on day 7, peaking around day 17 when about 40% of patients reported moderate to severe symptoms, and falling to pre-radiotherapy levels by day 28. The 10-Gy/1-fraction regimen resulted in virtually no additional cases of dysphagia above pre-radiotherapy levels. As expected, the higher dose 36- and 39-Gy regimens resulted in more frequent (70% of patients) and prolonged dysphagia.

It has only relatively recently been recognised that palliative thoracic radiotherapy can be associated with other acute symptoms. Stevens and Begbie (1995) noted that 5/38 patients treated with 17 Gy in 2 fractions over 8 days developed acute chest pain. Devereux et al. (1997) asked 118 patients to complete a questionnaire within 24 h of having their first fraction of palliative radiotherapy to the chest. The majority of patients were treated with 8.5- or 10-Gy fractions Chest pain was reported by 54 (45.8%) of patients after their first fraction of radiotherapy. In over 75% of cases, this was within 12 h of the treatment, and on 23 occasions lasted less than 2 h. In addition, 43 (36.4%) of patients reported one or more systemic symptoms (rigors, sweating, fevers). In the majority of cases, systemic symptoms occurred within 12 h of treatment and lasted less than 2 h. Only 49 (41.6%) reported no immediate side effects. The timing of symptoms suggests radiotherapy is the most likely cause, but the mechanism is not clear. Of interest is that prophylactic steroids did not prevent chest pain in the Stevens and Begbie (1995) series.

Acute radiation pneumonitis consisting of cough, shortness of breath and patchy radiological changes is a well recognised side effect of thoracic radiation given at radical doses. Using palliative radiotherapy regimens, symptoms are uncommon, usually mild, and resolve completely without long term sequelae.

The most serious late toxicities from thoracic radiotherapy are pulmonary fibrosis and myelopathy. Pulmonary fibrosis occurs as a consequence of tissue injury repair within a radiation field. It becomes clinically evident 9 to 12 months after radiotherapy, and may cause progressive shortness of breath. Pulmonary fibrosis seems to depend, amongst other factors, on the volume of lung irradiated above a threshold of 20–30 Gy in 2-Gy fractions. However, large fraction sizes cause disproportionately more late toxicity, and certainly both 10 Gy in 1 fraction and 17 Gy in 2 fractions over 8 days have the potential to cause significant fibrosis. It is not usually a problem in this context as field sizes are generally not too large, and most patients do not survive long enough to develop late complications from radiotherapy.

Radiation myelopathy (RM) is a rare but potentially disastrous late effect of thoracic radiotherapy. Clinical experience has demonstrated that regimens such as 30 Gy in 10 fractions over 12 days and 20 Gy in 5 fractions over 5 days are within the tolerance of the spinal cord. Higher dose regimens, and those using large doses per fraction have been associated with an unacceptable risk of RM. Macbeth et al. (1996) reported on the cumulative experience from the three MRC LCWP trials, in which five cases of probable RM were identified from the 1048 patients randomised. The time of onset ranged from 8 to 42 months from the start of treatment. Three occurred in the 524 patients treated with 17 Gy in 2 fractions over 8 days, and two in the 159 treated with 39 Gy in 13 fractions over 17 days. The estimated cumulative risks for RM at 2 years were 2.2% for the 17-Gy group, and 2.5% for the 39-Gy group.

3.2.3.3 The Asymptomatic Patient

The majority of patients with incurable NSCLC referred for palliative radiotherapy will have symptoms related to their tumour. A proportion of patients referred will, however, be asymptomatic, or the presenting symptom will have resolved and will no longer be troubling them. Is immediate palliative radiotherapy beneficial in this group of patients, or should treatment be deferred until the onset of thoracic symptoms?

The MRC LCWP (2002) trial randomised 230 people with previously untreated, incurable NSCLC and minimal thoracic symptoms to immediate radiotherapy or radiotherapy deferred until symptoms developed. The schedules used were 17 Gy in 2 fractions over 8 days or 10 Gy in 1 fraction. In the immediate radiotherapy group, 90% of patients received treatment, compared to 42% in the deferred arm. There were no significant differences in survival or quality of life between the two arms. These findings seem to suggest that about half of patients with unresectable disease and minimal thoracic symptoms will never need palliative radiotherapy during the course of their illness. However, 68% of patients in this trial were PS 0–1, and only 12% had distant metastases. This trial was begun before the results of the MRC LCWP (1996) trial were known. It is probable that a proportion of patients in this trial with good PS and

no evidence of metastases would have been suitable for 39 Gy in 13 fractions over 17 days or 36 Gy in 12 fractions over 16 days which has been shown to improve survival in this group. An earlier study reported by Carroll et al. (1986) looked at 48 patients who were treated with thoracic radiotherapy only when symptoms developed. Of 48 patients, 22 (46%) died without needing treatment, supporting the findings of the MRC LCWP (2002) trial.

Reinfuss et al. (1993) randomised 240 patients of good PS with stage III, unresectable, asymptomatic NSCLC to one of three arms: 50 Gy in 25 fractions over 5 weeks, 40 Gy in 10 fractions over 2 weeks split course, or deferred radiotherapy. Median survival was significantly greater with the 5-week regimen compared to the other two arms (12 months, 9 months and 6 months, $p<0.05$). The results of this study do not support the use of deferred radiotherapy in asymptomatic patients of good PS with locally advanced disease. The survival advantage seen with the 50-Gy regimen supports the use of higher doses in this group of patients, as would be expected, given the results of the MRC LCWP (1996) trial.

The available evidence therefore indicates that a policy of deferred radiotherapy in relatively asymptomatic, poor performance status patients is reasonable. Patients of good performance status with relatively localised incurable disease should be considered for higher dose palliative thoracic radiotherapy even in the absence of symptoms, because survival may be improved.

3.2.3.4 Radiotherapy, Chemotherapy or Both?

In the last 10 years, the use of chemotherapy in advanced and metastatic NSCLC has increased significantly. Despite its wide use, there is very little data about the effectiveness of chemotherapy in palliating lung cancer symptoms. A meta-analysis carried out by the Non-Small Cell Lung Cancer Collaborative Group (NSCLCCG) using data from 11 RCTs has shown a modest improvement in median survival with cisplatin-based palliative chemotherapy over supportive care alone of around 2 months (NSCLCCG 1995). To date, there are no randomised trials which have compared palliative radiotherapy with palliative chemotherapy. In addition, it is not known how best to combine these treatment modalities. For example, are the survival gains additive if good PS patients with no evidence of metastases are treated with both chemotherapy and high dose palliative radiotherapy? Which modality should be used first, or should they be used together? At present, there is no evidence supporting the use of one treatment modality over the other.

3.2.3.5 Appropriate Treatment Strategies

The decision on how best to treat a patient with palliative intent can be complex, because the potential benefits of any intervention must be carefully weighed against the risks of toxicity. Any treatment plan must take into account the patient's performance status, symptoms, stage of disease, and individual wishes. A critical step in this decision making process is the assessment of performance status. The five-point World Health Organisation PS scale is a simple measure of functional impairment, which has consistently been shown to be a major prognostic factor in NSCLC.

The evidence suggests symptomatic poor PS patients and/or those with metastatic disease are effectively palliated with 1 or 2 fractions of chest radiotherapy and do not benefit from more prolonged regimens. The MRC LCWP (1992) trial showed that the 10-Gy/1-fraction regimen is as effective, and associated with less oesophagitis than 17 Gy in 2 fractions over 8 days. Although nausea and, rarely, vomiting can occur with 10 Gy in 1 fraction, it does not seem to be more frequent than with other regimens, and can be simply managed with antiemetics which can be given prophylactically if felt necessary. With the short fractionation regimens, there may be a greater risk of chest pain and systemic symptoms such as rigors occurring within 24 h of radiotherapy, but the prophylactic use of analgesics and antipyretics is usually sufficient to control these effects. In addition, the short fractionation regimens have the advantage of reducing travelling time for patients who are often very frail.

The MRC LCWP (1996) and NCIC (Bezjak et al. 2002) trials showed that patients with good PS may derive a modest survival advantage with a higher dose regimen given over a more prolonged period, although at the expense of greater toxicity and no better palliation. These issues should be discussed with the patient before deciding on a particular radiotherapy regimen.

The spinal cord damage reported by Macbeth et al. (1996) with 17 Gy in 2 fractions over 8 days and 39 Gy in 13 fractions over 17 days means these regimens

should be used with caution. A pragmatic approach would be to reduce the total dose given to a safer level based on previous experience, for example 16 Gy in 2 fractions over 8 days and 36 Gy in 12 fractions over 16 days. In some cases, it is also possible to shield the spinal cord towards the end of treatment, minimising the chance of RM. The use of 16 Gy in 2 fractions in a total of 126 patients has been reported (Lupattelli et al. 2000; Senkus-Konefka et al. 2001) and found not be associated with myelopathy.

In addition, patients should be assessed for chemotherapy. This decision should take into account PS, co-morbidity, bone marrow, kidney, liver and heart function along with the treating health professional's subjective opinion as to whether the patient is likely to cope with chemotherapy. Patients should be counselled about the relative advantages and disadvantages of all treatment options for which they are potentially suitable, allowing an informed choice to be made that takes into account their personal wishes. Table 3.2.3.4 broadly outlines a strategy for managing patients with incurable NSCLC, using the available evidence as outlined above. Finally, large fraction chest radiotherapy should be used cautiously in patients with stridor and significant tracheal obstruction. Hatton et al. (1997) have shown that palliative radiotherapy is associated with a measurable decrease in respiratory function. This may be made worse with large fractions, and so caution would suggest that more fractionated regimens (e.g. 20 Gy in 5 fractions or 30 Gy in 10 fractions) are preferable in this clinical situation

Table 3.2.3.4. A treatment strategy for locally advanced and metastatic NSCLC

	Poor PS	Good PS
Locally advanced:		
Chest symptoms	16 Gy/2 fx or 10 Gy/1 fx	Chemotherapy or 36 Gy/12 fx (? or both)
No chest symptoms	Delayed 16 Gy/2 fx or 10 Gy/1 fx	Chemotherapy or 36 Gy/12 fx (? or both)
Metastatic:		
Chest symptoms	10 Gy/1 fx	Chemotherapy or 10 Gy/1 fx
No chest symptoms	Delayed 10 Gy/1 fx	Chemotherapy or delayed 10 Gy/1 fx

3.2.3.6 Conclusion

With chemotherapy playing an increasing role in the management of advanced and metastatic NSCLC, it is important not to forget that palliative thoracic radiotherapy remains an effective treatment in this setting. Research carried out over the last 15 years has given us valuable information on the most appropriate radiotherapy treatment regimens to use, has highlighted the risks of toxicity, and how best to minimise them. There has been a tendency for recent research to concentrate solely on the role of chemotherapy; however there are still many important unanswered questions. It is not clear which modality may be most beneficial for a given situation, how best to select patients to ensure they gain the most benefit, and whether combining treatment options is useful.

Patients with this disease have a limited life expectancy, and often suffer from many disease-related symptoms. It is the desire of all health professionals to apply what is known to make the experience of terminal lung cancer as symptom-free as possible. Appropriate, coordinated research will hopefully help us achieve this aim.

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3.2.4 Intraoperative Electron Beam Radiotherapy in Lung Cancer

Methodology, Clinical Experience, and Long-Term Institutional Results

Javier Aristu, Leire Arbea, and Felipe A. Calvo

CONTENTS

3.2.4.1 Introduction

The majority of patients with non-small cell lung cancer present locally advanced or metastatic disease at diagnosis and 5-year survival rates range from 5%–15% (Bulzebruck et al. 1992). A substantial percentage of these patients will locally relapse with or without metastatic disease. However, local failure rates as first site of recurrence may be underestimated because in many institutions the follow-up is based mainly upon radiological tests. A recent RTOG study reported a lack of information on the patterns of failure of 27%–58% of dead patients (Komaki et al. 1998). Le Chevallier et al. (1991) observed a local persistence-relapse rate near to 80% in a series of patients treated with induction chemotherapy and radiotherapy when they were evaluated through bronchoscopy and biopsy.

There is a well-known dose response relationship in non-small cell lung cancer (NSCLC) (Perez et al. 1987). Pérez et al. showed that the 3-year intrathoracic relapse was 38% for a total radiation dose of 40 Gy in split or 50 Gy continuously, 48% for 50 Gy, and 27% for 60 Gy. It is likely that intrathoracic disease control is associated with increased survival (Perez et al. 1986). The potential benefit of dose escalation above 60 Gy with conventional techniques has been questioned due to the increased risk of toxicity in the lung parenchyma, spinal cord, heart, and esophagus. On the other hand, doses in the range of 60 Gy are inadequate to eradicate locally advanced solid tumors.

Contemporary pattern of failure data show that 40%–70% of patients with non-small cell lung cancer stages II–IIIB are expected to relapse locally. The failure rate seems to depend more on the disease stage than on the treatment modality used (Komaki et al. 1998; Le Chevalier et al. 1991; Perez et al. 1986; Stanley et al. 1981; Kumar et al. 1996).

Local control in non-small cell lung cancer continues to be an unresolved issue and the introduction of new radiation techniques to intensify the local dose is justified. Intraoperative electron radiation (IOERT) is a sophisticated radiation modality well explored in the treatment of abdominopelvic tumors, but is scarcely used in thoracic tumors .The therapeutic gain in IOERT procedures is obtained with the displacement of radiosensitive organs away from the electron beam or with the shielding of fixed structures with lead sheets. Target definition is done following surgical resection jointly with the thoracic surgery team.

IOERT has been integrated into multidisciplinary programs as a boosting modality that completes the

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total dose given with fractionated external beam radiation therapy (ISIORT'98 1998). This treatment has the advantage of the radiobiological effects of fractionation over the primary volume that includes the primary tumor and the draining areas while the tumor bed is boosted with single dose electrons.

This chapter describes the methodology and clinical results of a retrospective analysis including the prognostic factors related with local control and survival in a large institutional experience generated at the University Clinic of Navarre (Pamplona, Spain) with non-small cell lung cancer patients treated with an IOERT component within a multidisciplinary treatment program.

3.2.4.2 Tissue Tolerance Studies – Mediastinal IOERT

The tolerance of mediastinal structures to IOERT has been prospectively analyzed in experimental animal studies. In a dose-escalation study (Barnes et al. 1987) delivering 20, 30, and 40 Gy to two separated intrathoracic IOERT fields which included collapsed right upper lobe, esophagus, trachea, phrenic nerve, right atrium, and blood vessels, pathologic changes were observed at 30 Gy in the trachea and esophagus, with severe ulceration and peribronchial and perivascular chronic inflammation in the normal lung. A dose of 20 Gy over the atrium showed medial and adventitial fibrosis, obliterative endarteritis of the vasa vasorum, and severe coagulative necrosis. Acute pneumonitis was seen at all doses, and changes in the contralateral lung were detected using 12-MeV electrons.

De Boer et al. (1989) studied the effects of 20, 25, and 30 Gy in mediastinal structures. The bronchial stump healed in all dogs. Severe tissue damage was seen at all doses and included bronchovascular and esophagoaortic fistulas and esophageal stenosis.

At the National Cancer Institute, an experimental program evaluated the tolerance of surgically manipulated mediastinal structures to IOERT in 49 adult foxhounds in a limited phase I clinical trial (four patients with stage II or III NSCLC). Normal healing of the bronchial stump was found after pneumonectomy and IOERT doses of 20, 30, and 40 Gy, but there were late changes with tracheobronchial irradiation damage at all doses (5–10 months after treatment). Two out of four receiving 20 Gy developed esophageal ulceration at 6 months without late stricture. In dogs given 30 and 40 Gy, esophageal damage was severe (esophagoaortic fistula and stenosis) and one dog developed carinal necrosis. The same institution reported the results of five dogs reserved for long-term studies and one stage II NSCLC patient alive at 5 years. They conclude that IOERT in the mediastinum may be safe at dose levels that do not exceed 20 Gy (Tochner et al. 1992).

Additional experimental analysis of canine esophagus tolerance to IOERT has been reported by the NCI investigators (Sindelar et al. 1992). After right thoracotomy with mobilization of the intrathoracic esophagus, IOERT was delivered to include a 6-cm esophageal segment using a 9-MeV electron beam with escalating single doses of 0, 20, and 30 Gy. Dogs were followed clinically with endoscopic and radiologic studies and were electively sacrificed at 6 weeks or 3, 12, or 60 months after treatment. Transient mild dysphagia and mild esophagitis was observed in all dogs receiving 20 Gy, without major clinical or pathological sequelae except in one dog that developed achalasia requiring a liquid diet. At a dose of 30 Gy, changes in the esophagus were pronounced with ulcerative esophagitis and chronic ulcerative esophagitis inducing gross stenosis after 9 months.

Zhou et al. (1992) analyzed the acute responses of the mediastinal and thoracic viscera in nine canines sacrificed after they received single IOERT doses of 25, 35, and 45 Gy. No pathological changes were found in the spinal cord and vertebra. Microscopic examination of trachea, esophagus, and lung showed mild or severe histological changes at 30 days at the level of 25 Gy versus 35–45 Gy, respectively. Severe and unrepaired histologic changes were found in the heart and aorta receiving 35–45 Gy.

Based on these data, active clinical programs using thoracic IOERT agree that 20 Gy is the upper single-dose limit that can be safely tolerated by mediastinal and thoracic viscera (Table 3.2.4.1) with IOERT

Table 3.2.4.1. Clinical and pathologic findings observed in animal experimental models

IORT doses	Bronchial stump	Esophageal damage	Lung damage	Pathologic changes in heart and vessels
20 Gy	Normal healing	Transient mild dysphagia	Mild	Moderate
30 Gy	Normal healing	Chronic ulcerative esophagitis	Moderate	Moderate–severe
40 Gy	Normal healing	Esophageal perforation, esophageal stricture	Severe	Severe

alone. There are no reported experimental normal-tissue tolerance studies of IOERT used in combination with EBRT.

3.2.4.2.1 Technical Considerations

IOERT requires the adaptation of linear accelerator with multienergetic electron beam capability (energies recommended from 6 to 20 MeV), through the development of specially designed applicators for electron beam conformation (cone sizes recommended from 5 to 12 cm diameter) (Figs. 3.2.4.1, 3.2.4.2). The clinical program combines the efforts of surgeons, anesthesiologists, physicists and radiation oncologists to adequately select patients for IOERT indications, perform the surgical procedure (tumor resection plus normal tissue protection), transport and monitor the patient for and during intraoperative irradiation and finally decide the radiotherapeutic parameters for treatment prescription (Fig. 3.2.4.3, 3.2.4.4). In general, IOERT during lung cancer surgery involves the coordination of 10–15 health professionals, prolongs the surgical time approximately 30–45 min (depending upon transportation time) and induces a 2-h gap of time availability in the linear accelerator for outpatient treatment.

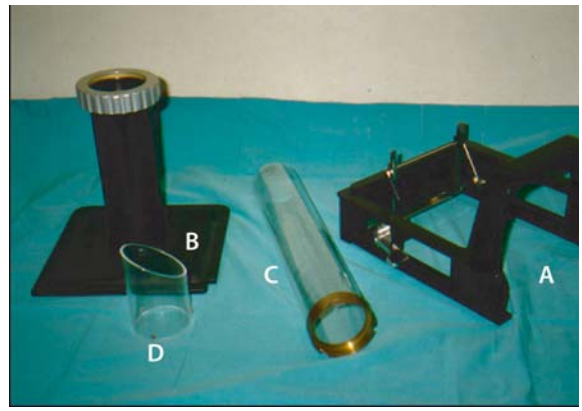


Fig. 3.2.4.1. Equipment used in an IOERT procedure: gantry adapter with mirror-carrier (*A*); intermediate element (*B*); transparent methacrylate applicator with a metric reference (*C*); distal section of a beveled applicator (*D*)

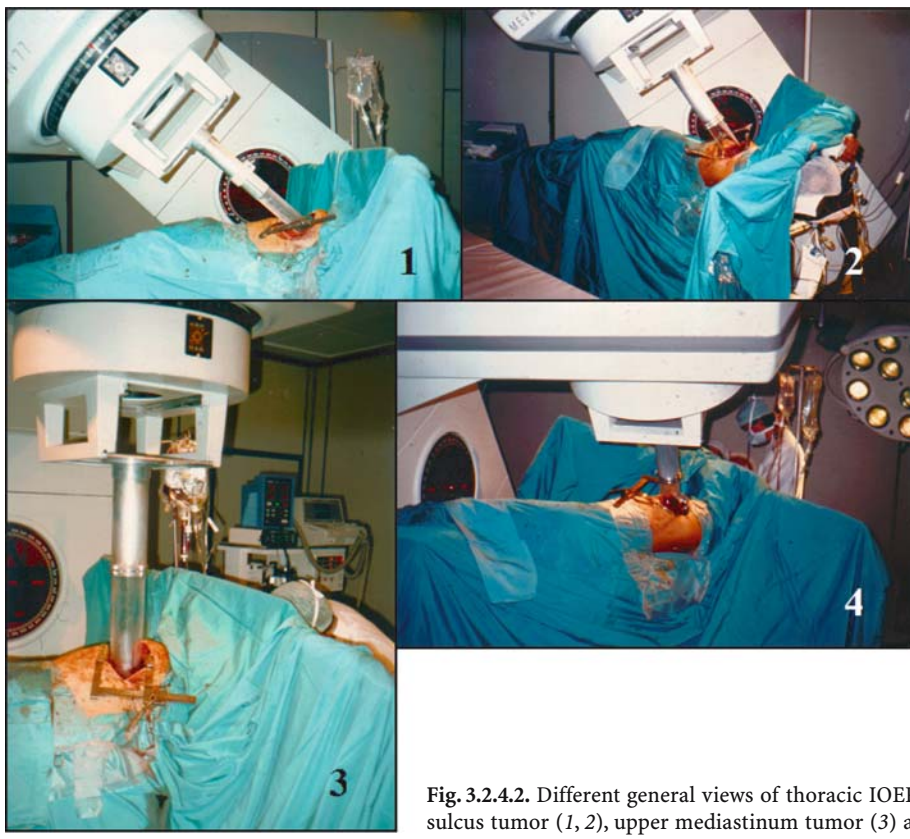


Fig. 3.2.4.2. Different general views of thoracic IOERT with electrons in superior sulcus tumor (*1*, *2*), upper mediastinum tumor (*3*) and left hilium tumor (*4*)

Fig. 3.2.4.3a–c. Simulation for applicator selection (size, beveled angle, positioning, and maneuvers for normal tissue protection) after right superior lobectomy: The IOERT target volume includes right mediastinum and bronchial stump; the remaining normal lung is mobilized out of the electron field (**a**). Postresection simulation for a Pancoast tumor. The target volume includes the tumor bed region (posterior and superior chest wall and paravertebral space), and the remaining normal lung is mobilized out of the intraoperative field (**b**). IOERT applicator positioning during exploratory thoracotomy for an unresectable right-lobe NSCLC (**c**)

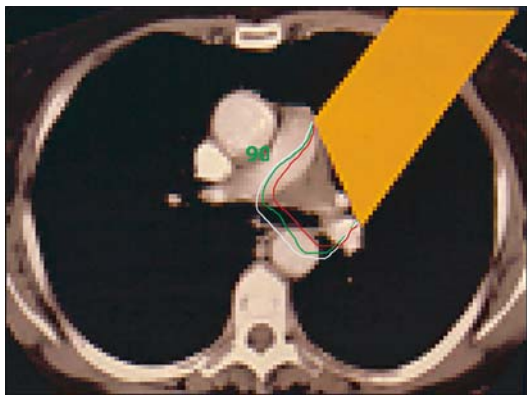


Fig. 3.2.4.4. Simulation for isodose distribution using 15-Mev electrons and a 30º beveled applicator 7 cm in diameter to treat a mediastinal partially resected tumor

3.2.4.2.2 Clinical Indications

IOERT at the time of thoracotomy for a surgical approach to lung cancer has been employed in three different situations:

- Treatment of unresectable hilar and/or mediastinal disease
- Treatment of post-resected residual disease (chest wall, mediastinum and/or bronchial stump)
- Adjuvant treatment of mediastinum

Conceptual indications for IOERT in thoracic surgery have been the treatment of residual disease at the primary site and/or nodal regions, or adjuvant treatment of high risk of recurrence without proven cancer residue after induction therapy and surgery. IOERT is a superselective radiation boost component available for integration in conventional radiotherapy programs for lung cancer. Lung parenchyma is the normal tissue that may benefit the most from IOERT.

Esophagus, trachea, aorta, and heart are difficult to displace from the IOERT beam, particularly in the treatment of mediastinal regions or left lower chest cavity. In the case that the bronchial stump is included in the IOERT field, tissue coverage with a vascularized pleural or pericardial flap is recommended to promote bronchial healing.

3.2.4.3 International IOERT Clinical Experiences and Results

The clinical experience of IOERT in lung cancer is still limited and the available data regarding treatment of NSCLC were obtained in phase I–II trials in a small series of patients. Abe and Takahashi (1981) in the initial Japanese experience did not use IOERT in lung neoplasms because of the early systemic dissemination of disease.

3.2.4.3.1 NCI Series

Based on a previous canine experimental model involving the use of pneumonectomy and IOERT doses

of 0, 20, 30, and 40 Gy, a limited phase I National Cancer Institute (NCI) clinical trial demonstrated considerable toxicity with 25 Gy of IOERT to two separated fields encompassing the superior and inferior mediastinum following pneumonectomy (Pass et al. 1987). Early complications were described in three out of four patients: one case of bronchial stump dehiscence, one bronchopleural fistula, and one case of reversible esophagitis. Three patients with late complications showed one case of irreversible radiation esophagitis. Only one long-term survivor is free from disease (at more than 3 years). The retrospective analysis of toxic events detected overlapping of the fields in one toxic case. This study recognized the feasibility of IOERT during lung cancer surgery and recommended a decrease in the IOERT dose to 15–20 Gy.

3.2.4.3.2 Graz University Experience

More recently, combined IOERT (10–20 Gy) and postoperative EBRT (46–56 Gy) were used in 21 inoperable tumors at the University Medical School of Graz (Austria) (Jeuttner et al. 1990). The analysis included 12 patients with N0 disease. The radiosensitive mediastinal structures such as the heart, spinal cored, esophagus, and large vessels could be mobilized or protected from the IOERT beam by shielding maneuvers.

The response rates in 14 evaluable patients 18 weeks after they completed IOERT and EBRT was excellent with three complete responses (21%) and ten partial responses (71%). Ten patients are alive and well at a range of 5–20 months (median 12 months).

The same institution updated the results of this program in two consecutive studies (Arian-Schad et al. 1990; Schmolle-Juettner et al. 1994). The IOERT procedure was generally well tolerated, but fatal intrabronchial hemorrhage related to IOERT occurred in two cases with tumor involvement of the pulmonary artery. Local failure was seen in three patients and the 5-year overall and recurrence-free survival rates were 15% and 53%, respectively.

3.2.4.3.3 Montpellier Series

The Centre Regional De Lutte Contre Le Cancer in Montpellier (France) reported results in 17 patients: three stage I, seven stage II, and seven stage IIIA (personal communication). The treatment protocol involved the use of IOERT with doses in the range 10–20 Gy and 45 Gy EBRT in 20–25 fractions with or without a 3-week rest period following a complete surgical excision. Microscopic residual disease in the mediastinal nodes or pleura-chest wall was seen in 12 and five patients, respectively. The median follow-up time for the entire group of patients alive was 59 months, with follow-up ranging from 40+ to 120+ months.

Disease control and survival results were as follow. Local control was obtained in 13 out of 17 patients (76%) and central recurrence in the IOERT field has been demonstrated in four patients. Three patients are alive without disease at 5.5, 8, and 11 years. A total of 14 patients are dead: seven from distant metastases, four from loco-regional recurrence, one patient developed a second cancer, and two patients had a local recurrence in the EBRT field. The median survival time for the entire group was 36 months and the actuarial survival rate is 18% projected at 11 years.

3.2.4.3.4 The Allegheny University Hospital:

3.2.4.3.4.1 Graduate Hospital of Philadelphia Experience

This unique experience in the US was preliminarily reported in 1994 (Fisher et al. 1994a). The present update includes 21 patients treated from June 1992 to September 1997 as a part of a pilot feasibility experience for stage I (n=1), II (n=2), and III (n=18) NSCLC patients managed by surgical resection, IOERT (10 Gy), and EBRT (45.0–59.4 Gy, 16 preoperatively and five postoperatively). Chemotherapy was administered to all patients. The median survival time for the alive patients is 33 months. Patterns of relapse have shown three (14%) thoracic and 12 (55%) systemic. Actuarial 5-year survival is 33%.

3.2.4.3.4.2 Instituto Madrileño de Oncología (Madrid, Spain)

From February 1992 to July 1997, 18 patients with stage III non-small-cell lung cancer (11 Pancoast tumors) received IOERT as a part of a multidisciplinary program including surgical resection in all cases, chemotherapy in 13, preoperative EBRT in seven, and postoperative

EBRT in seven. Tumor residue at the time of surgery was macroscopic (gross) in eight cases. The median survival time for the entire series is 14 months. Intra thoracic recurrence has been identified in two patients. Five-year actuarial survival is projected as 22% (cause-specific 33%). Long-term toxicity observed included neuropathy (two cases) and esophageal structure one case (Calvo et al. 1999).

3.2.4.4 Experience at the University Clinic of Navarra

3.2.4.4.1 Patients and Methods

Patients with histologically proved non-small cell lung cancers stages IIB–IIIB were treated with IOERT during the period 1984–1993. Selection criteria included CT measurable disease, Karnofsky performance status equal or greater than 60, no prior oncologic treatment, no prior diagnosis of cancer and normal hematological, hepatic, and renal profile. Patients were initially evaluated with complete history and physical, CBC, blood electrolytes, serum creatinine, and liver enzyme profile. Radiological tests for diagnosis and staging work up included chest X-ray, chest CT, upper abdominal CT, brain MRI and bone scan. The histological diagnosis was obtained with biopsy or cytology through bronchoscopy or fine needle aspiration depending on the location and tumor accessibility. All the patients signed an informed consent before the initiation of the treatment. Patients were treated according to one of the three following treatment protocols:

1. Patients treated with surgery, IOERT, and postoperative external beam radiation.
2. Patients treated with neoadjuvant chemotherapy, surgery, IOERT, and postoperative radiation therapy.
3. Patients treated with neoadjuvant chemotherapy, preoperative external beam radiation therapy, followed by surgery and IOERT.

The neoadjuvant chemotherapy consisted of cisplatin 120 mg/m^2 i.v. on day 1, mitomycin C 8 mg/m^2 i.v day 1 and vindesine 3 mg/m^2 (maximum dose 5 mg/m^2) i.v on days 1 and 14 (MVP) or the same treatment regimen where the cisplatin administration was replaced by intraarterial carboplatin 150 mg/m^2. The cycles of chemotherapy were repeated every 28 days for three to five treatments until maximum response was achieved (3–5 cycles). Patients who documented a clinical response or with stable disease and considered resectable were referred to surgical resection 5 weeks after the last cycle of chemotherapy. The bronchial stump was protected with a pleural or pericardial flap in order to prevent anastomotic leak. After surgical resection IOERT was applied over the surgical bed and the hilar and mediastinal regions depending on tumor location. Total administered dose varied between 10 and 15 Gy depending on microscopic or macroscopic residual tumor. A detailed description of the IOERT methodology for thoracic tumors has been published previously (Calvo et al. 1990, 1991, 1992; Aristu et al. 1997; Martínez-Monge et al. 1994). Postoperative external beam radiation therapy was started 4–5 weeks after surgical resection.

Tumors that were not considered resectable after neoadjuvant chemotherapy were treated with preoperative external beam radiation therapy using the same total dose and fractionation than with postoperative external beam radiation therapy described above. All patients received concurrent chemotherapy with preoperative radiation using the same chemotherapy combination used as neoadjuvant or with cisplatinum 20 mg/m^2 or carboplatinum 55 mg/m^2 combined with 5-fluorouracil 1000 mg/m^2 (maximum daily dose 1500 mg) for 3–5 days over the first and last week of external beam radiation therapy. At 4–6 weeks after the completion of the preoperative chemoradiation course the patients were referred for surgical resection and IOERT, when feasible.

3.2.4.5 Results

3.2.4.5.1 Patient Characteristics

The present analysis includes 104 patients treated from October 1984 to December 1993. A total of 22 patients were treated with surgery, IOERT, and postoperative radiation therapy, 46 patients were treated with neoadjuvant chemotherapy, surgery, IOERT, and postoperative radiation, and 36 patients received neoadjuvant chemotherapy, preoperative radiotherapy, surgery and IOERT (19 of the later subset of patients had superior sulcus tumors). The median age was 60.5 years (range 27–79 years) and 97% of the patients were male. In all, 15 patients (14%) had a Karnofsky performance status equal to or lower than 70% and 10% of the patients had a weight loss

at diagnosis greater than 5%. Of the patients, 66 had squamous cell carcinoma (63.5%), 26 adenocarcinoma (25%), and 12 patients had other histologic subtypes (11.5%) including mixed tumors, large cell carcinoma, or undifferentiated tumors. The clinical stage more frequently observed was IIIB with 58 patients (56%) followed by stage IIIA with 28 patients (27%) and IIB with 18 patients (17%).

Table 3.2.4.2 shows patient characteristics according to the treatment administered . No statistically significant differences were observed among the three treatment groups in relation to age, Karnofsky performance status, histologic subtype, or stage. There is a trend towards statistical significance (p=0.052) in patients with adenocarcinoma treated with preoperative radiation therapy.

Table 3.2.4.2. Patient and tumor characteristics according to the treatment group (University Clinic of Navarra experience 1984–1993; ARITUS 2000)

	Number of patients (%)			
	S-RT	CT-S-RT	CT-RT-S	p
Number of patients	22	46	36	
Age			0.318	
Mean	61.5	61	59.5	
Range	44–78	27–79	33–75	
Gender				
Male:female	22:0	45:1	34:2	
KPS >70%	15 (68)	38 (83)	27 (75)	0.989
Histology				0.052
Epidermoid carcinoma	15 (68)	35 (76)	16 (44)	
Adenocarcinoma	3 (14)	7 (15)	16 (44)	
Others	4 (18)	4 (9)	4 (12)	
Primary tumor				0.284
Tx	1 (4.5)			
T1		1 (2)	1 (3)	
T2	1 (4.5)	7 (15)		
T3	y8 (36)	19 (41)	16 (44)	
T4	12 (54.5)	19 (41)	19 (53)	
Regional lymph nodes				0,152
N0	12 (54.5)	16 (35)	21 (58)	
N1		2 (4)	1 (3)	
N2	10 (45.5)	24 (52)	11 (30.5)	
N3		4 (9)	3 (8.5)	
Stage				0.072
IIB	5 (23)	5 (11)	8 (22)	
IIIA	5 (23)	17 (37)	6 (17)	
IIIB	12 (54)	24 (52)	22 (61)	

S, surgery; RT, radiotherapy; CT, chemotherapy; p, statistical significance, Ji2 test.

3.2.4.5.2 Treatment Characteristics

Of the 104 patients, 89 underwent surgical resection (86%) while 15 patients (14%) were deemed unresectable. The type of surgical procedure most frequently performed was a lobectomy (65%) followed by segmentectomy (6%). The surgical resection was considered complete in 57 patients (54%) and incomplete in the rest. At total of 40 patients (38.5%) had positive resection margins. The rate of complete resection was 89% for stage IIB, 57% for stage IIIA, and 43% for stage IIIB (p=0.003). Within the same treatment group and histologic subtype, the probability of undergoing a complete resection was 9.5 times lower in patients stage IIIB compared with IIB and 4.36 times lower in stage IIIA compared with stage IIB. The probability of leaving gross residual tumor was seven times higher in patients with stage IIIB. Superior sulcus tumors had a higher probability of complete tumor resection (p=0.025) than non-superior sulcus tumors comparing the same stage and histology. Of eighty-two patients, 32 (39%) that received neoadjuvant treatment had complete pathological response (pT0) or near complete pathological response (pTmic). Patients treated with the MVP chemotherapy combination and CMP combination had a probability of pT0-pTmic response rate of 28% and 50%, respectively (p=0.002). Superior sulcus tumors had a probability of pT0-pTmic response rate of 68% versus 30% for those patients with non-superior sulcus tumors (p=0.001). There were no differences in the pathological response rate among the different histologic subtypes or stages. The IOERT median dose was 10 Gy with a range from 10 Gy to 24 Gy. Patients were treated in this study with 130 IOERT fields resulting in 78 single fields and 26 double fields. In patients treated with two IOERT fields an effort was made to avoid overlapping. The majority of patients were treated with electron beam energy ranging from 9 MeV to 12 MeV and applicator diameters ranged from 7 cm to 8 cm. IOERT treatment regions were the hilum, mediastinum, and thoracic wall depending on tumor location. IOERT treatment characteristics are shown in Table 3.2.4.3. In 15 patients with unresectable tumors the IOERT beam was placed directly over the gross tumor. The surgical residual tumor was considered microscopic in 34% (considered as no evidence of tumor or close macroscopically positive margins) and gross in 64% of the patients, respectively.

Table 3.2.4.3. IOERT characteristics (Aritus 2000)

	Number	(%)
Number of beams		
Single	78	(75)
Double	26	(25)
Total	**130**	
Dose (Gy)		
10	101	(78)
12.5	7	(5)
15	20	(15)
24	2	(2)
Electrons energy (MeV)		
6	9	(7)
9	60	(46)
12	41	(31)
15	8	(6)
18	6	(5)
20	6	(5)
Applicator diameter (cm)		
5	4	(3)
6	19	(15)
7	20	(15)
8	31	(24)
9	34	(26)
10	19	(15)
12	3	(2)
Treatment region[a]		
Hilum	67	(42)
Mediastinum	53	(34)
Chest wall	38	(24)

[a] More than one region can be treated in the same procedure.

3.2.4.5.3 Pattern of Failure

A total of 13 patients were excluded from the failure analysis due to early death (without clinical or radiological evidence of disease recurrence) or progression of the disease during the treatment or in the postoperative period. In 23 patients (25%) local relapse was the only site of failure, 18 patients (20%) had local and distant relapse, and 19 patients (21%) presented metastatic disease. Overall, local failure was observed in 45% of the patients with a medium time to local progression of 22 months. Distant metastasis was observed in 41% of the patients. Local relapse within the IOERT field was observed in 33 patients (36%). In all, 31 patients (31%) did not show evidence of disease progression . Table 3.2.4.4 describes the patterns of failure according to the treatment group.

3.2.4.5.4 Analysis of Local Relapse

Table 3.2.4.5 shows the univariate analysis of different variables in relation to the IOERT local disease free. The Cox multivariate analysis demonstrated statistically significant differences in local control for stages IIB and IIIA compared to IIIB (p=0.002) in N0/N1 patients with respect to N2 or N3 patients (p=0.001).) and in patients undergoing complete resection compared to patients undergoing incomplete resection (p=0.001). Patients with stage IIB or IIIA had a probability of relapse three times slower than patients with stage IIIB regardless of the degree of pathologic response, stage, type of resection, and presence of superior sulcus presentation. Patients with N2/N3 stage had a probability of local progression four times higher than patients with N0/N1 stage for the same pathological response, stage, type of resection or presence of superior sulcus location. Patients with tumors completely resected had a probability of local relapse slower than patients with tumor incompletely resected regardless the degree of pathological response, N stage, overall stage, and presence of superior sulcus location (Table 3.2.4.6).

Table 3.2.4.4. Patterns of failure according to the treatment group (Aritus 2000)

	Number of patients (%)				
S-RT	CT-S-RT	CT-RT-S	Pancoast	Total	
Control of disease	4 (4)	12 (13)	1 (1)	11 (12)	28 (31)
Local	4 (4)	13 (14)	5 (5)	1 (1)	23 (25)
Distant	5 (5)	6 (7)	4 (4)	4 (4)	19 (21)
Mixed	4 (4)	9 (10)	5 (5)		18 (20)
Unknown		1 (1)	1 (1)	1 (1)	3 (3)

S, surgery; RT, radiotherapy; CT, chemotherapy.

Table 3.2.4.5. IOERT local disease free survival at 1, 2, 3, 5, and 10 years according to the different variables (Aritus 2000)

Variable	Local control at IOERT (%)					Mean (CI 95%)	*p*
	1 year	2 years	3 years	5 years	10 years		
Histology							0.48
Epidermoid carcinoma	76	48	41	41	41	24 (14–34)	
Adenocarcinoma	79	69	63	63	63	—	
Other	74	49	49	49	49	16	
KPS ≤70%							0.07
No	78	58	53	53	53	—	
Yes	80	0				15 (12-18)	
Stage							0.003
IIB	100	100	100	100	100	—	
IIIA	79	57	57	57	57	—	
IIIB	69	44	29	29	29	18 (13-23)	
Pancoast tumor							0.006
No	73	46	38	38	38	21 (12-30)	
Yes	92	92	92	92	92	—	
Regional Lymph Nodes							0.006
N0/N1	84	72	68	68	68	—	
N2/N3	70	38	30	30	30	18 (12-24)	
Neoadjuvant CT (NCT)							0.92
No	71	71	59	47	47	28	
Yes	78	51	48	48	48	34	
Response to (NCT)							0.59
Partial	83	40	44	44	44	24 (3–45)	
No changes/progression	68	60	60	60	60	—	
Postoperative RT							0.28
No	73	48	40	40	40	—	
Yes	79	64	59	59	59	21 (11–31)	
Simultaneous CT/RT							0.27
No	80	47	40	40	40	21 (12-30)	
Yes	72	63	59	59	59	28	
Response to CT/RT							0.76
No	91	72	61	61	61	—	
Yes	64	64	64	64	64	—	
IOERT dose >10 Gy							0.66
No	78	51	45	45	45	25	
Yes	71	64	57	57	57	—	
Equivalent tumor dose							0.34
≤63	81	54	48	48	48	34	
>63	617	59	52	52	52	—	
Pathologic response							0.02
PT0/pTmic	89	67	67	67	67	—	
pT+	69	46	35	35	35	19 (8–30)	
Pathologic lymph nodes							0.70
pN0	85	62	55	55	55	—	
pN+	86	64	32	32	232	21 (13–29)	
Surgical residue							0.003
Microscopic	96	77	71	71	71	—	
Macroscopic	72	40	40	40	40	16 (11–21)	
Surgical resection							<0.001
Partial	53	30	20	20	20	14 (8–20)	
Complete	93	70	67	67	67	—	

p, Statistical significance between actuarial survival curves (log rank test).

Table 3.2.4.6. Cox multivariate regression model (Aritus 2000)

Variables	Hazard Ratio	CI 95%	*p* value Likelihood Ratio test
Stage			0,002
IIB/IIIA	1 (ref)		
IIIB	3.65	1.64–8.10	
Lymph nodes			<0.001
N0/N1	1 (ref)		
N2/N3	4.10	2.05–8.25	
Surgical resection			
Complete	1 (ref)		0.001
Incomplete	0.33	0.17–0.64	

3.2.4.5.5 Patient Outcome

Two patients were lost to follow-up and two patients died at home with incomplete information about the cause of death. Most of the remaining patients (62%) died of tumor progression. In all, 11 patients (10.5%) are alive and without evidence of disease with a median of 97 months in surviving patients (59–143 months).

3.2.4.5.6 Analysis of Survival

With a median follow-up of 109 months, the overall survival at 1, 2, 3 and 5 years was 62%, 37%, 25%, and 20%, respectively. Median survival time was 15 months. Different variables evaluated in the univariate survival analysis are statistically significant including histologic subtype, Karnofsky performance status, presence of superior sulcus tumor location (Figure 3.2.4.5), pathological response (Figure 3.2.4.6), and type of surgical resection (Figure 3.2.4.7). Patients who remained locally controlled had a statistically significant survival benefit compared with patients who had local failure. After multivariate analysis the only independent prognostic factor that remained statistically significant is local control. Patients undergoing local failure had lower survival rates (Figure 3.2.4.8).

3.2.4.5.7 Risk Groups for Local Control and Survival

The multivariate analysis was able to discriminate three independent prognostic factors for local control: stage IIIB versus IIB or IIIA, N0/N1 versus N2/N3 and patients with tumors incompletely resected versus completely resected. We have identified four

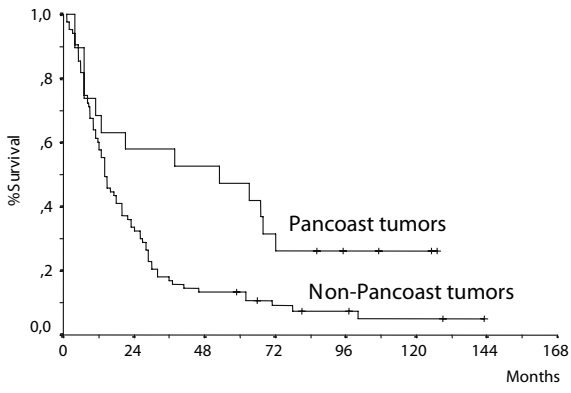


Fig. 3.2.4.5. Overall survival in Pancoast tumors and non-Pancoast tumors (p<0.009). [University Clinic of Navarra experience 1984–1993, Aristu (2000)])

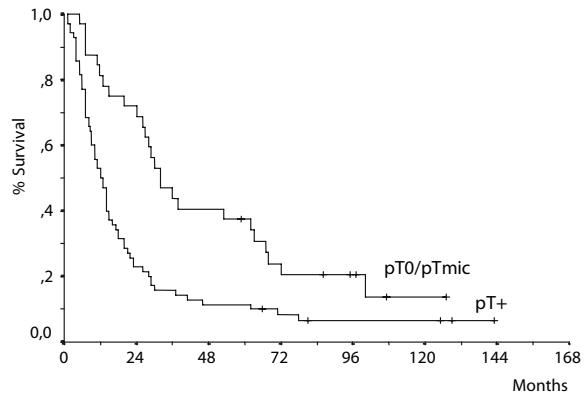


Fig. 3.2.4.6. Overall survival according pathologic response (p<0.001). *pT0/pTmic*, complete or near complete pathologic response; *pT+*, viable tumoral cells in the resected specimen (Aristu 2000)

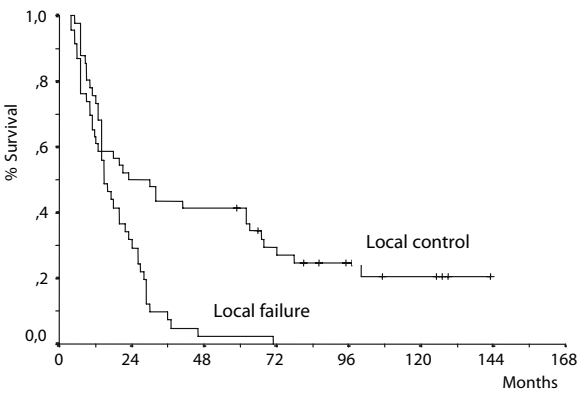


Fig. 3.2.4.7. Overall survival in patients with tumors completely or incompletely (p<0.001) (Aristu 2000)

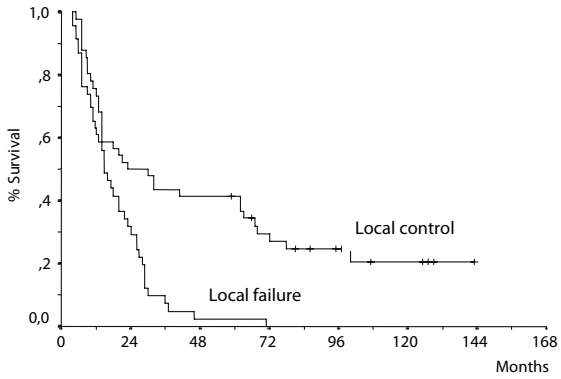


Fig. 3.2.4.8. Overall survival in patients who achieve local control or patients with local failure ($p<0.001$) (Aritus 2000)

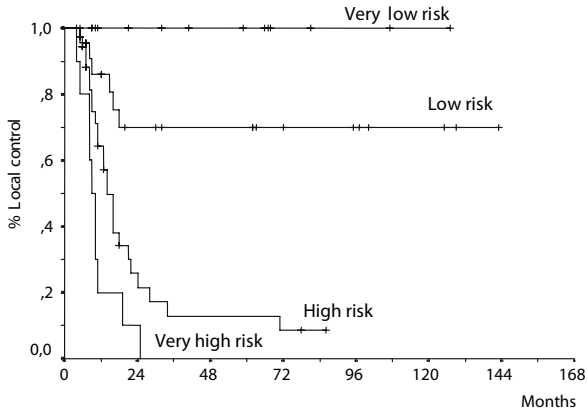
Table 3.2.4.7. Local control depending on prognostic groups ($p<0.001$) (Aritus 2000) (see also Fig. 3.2.4.9)

Number of prognostic factors	Prognostic group	Local control (%) MST			
		2 y	5 y	10 y	(CI 95%)
0	Very low risk	100	100	100	Not reached
1	Low risk	70	70	70	Not reached
2	High risk	21	13	8	14 (11–17)
3	Very high risk	10	0	0	9 (7–11)

risk groups for local relapse depending on the number of prognostic factors present in each patient. Very low risk patients for local recurrence are those without any unfavorable risk factor. Low risk patients are those with one risk factor. High risk patients are those with two risk factors and very high risk patients are those with three risk factors. The local control analysis for each group shows statistically significant differences ($p<0.001$) (Fig. 3.2.4.9 and Table 3.2.4.7). Using the same model for the analysis of overall survival we have identified two risk groups depending on the number of prognostic factors present. Low risk patients for survival are those who present zero or one prognostic factor (5-year survival 37%) and patients with high risk for survival are those who have two or three prognostic factors (5-year survival 5%) ($p<0.001$).

3.2.4.6 Summary and Final Considerations

The retrospective nature of most clinical experiences with IOERT for lung cancer patients does not enable definitive conclusions to be drawn on the impact of local control or survival. The analysis of local effects is extremely complex due to the simultaneous delivery of chemotherapy, external beam radiation



Number of Prognostic factors	Prognostic group	% Local control 2 y	5 y	10 y	MST (CI 95%)
0	Very low risk	100	100	100	not reached
1	Low risk70	70	70not reached		
2	High risk	21	13	8	14 (11-17)
3	Very high risk	10	0	0	9 (7-11)

Fig. 3.2.4.9. Local control depending on prognostic groups ($p<0.001$) (Aristu 2000) (see also Table 3.2.4.7)

therapy, and surgery, which must contaminate the potential contribution of IOERT as a local treatment within a multidisciplinary program (Aristu et al. 1999; Fisher et al. 1994b, 1998; Rodriguez et al. 1998).

The clinical analysis reported from the University Clinic of Navarra is the largest experience encountered in the literature on the use of IOERT in non-small cell lung cancer. Phase I–II trials confront the data derived from experimental animal studies and suggest that 20 Gy is the threshold dose for IOERT over mediastinal structures. When IOERT is combined with external beam radiation therapy, the dose should be restricted to 10–15 Gy. From the logistic point of view the previously mentioned reports confirm that IOERT can be integrated in a safe way within multidisciplinary programs. The RTOG (Byhardt et al. 1998) has recently reported the patterns of failure of 461 patients with medically inoperable NSCLC stage II, IIIA, and IIIB. Relapse within the radiation field was observed in 56% of the patients treated with induction chemotherapy and radiation, in 71% of the patients treated with induction chemotherapy followed by concomitant chemoradiation and in 55% of the patients treated with concomitant chemotherapy and hyperfractionated radiotherapy. The local relapse rate observed in our series was 45% and the relapse within the IOERT field was 36%. In view of these results we suggest that the use of IOERT may increase local control in a percentage of patients ranging from 10% to 15% compared with programs combining chemotherapy and definitive radiation without surgery. However, one must take into account that the interpretation of the patterns of failure data is complex due to the diversity of stage III patients and also due to the inclusion of some cases of stage II patients in these studies.

The analysis of the patients with stage IIIB tumors shows that local control is very poor. The 5-year local control for these patients is only 21% and this raises the concern of increased morbidity without therapeutic gain in this group of patients. The 5-year and 10-year overall survival was 11% and 3%, respectively. These results are comparable with those obtained with induction chemotherapy and definitive radiation. The use of adjuvant surgery after neoadjuvant therapy has mainly included patients with stage IIIAN2. Although the patterns of failure have not been systematically studied in these trials, the overall local relapse rates is 40% for patients who undergo surgical resection and 20% for those patients undergoing complete resections (Kumar et al. 1996; Elias et al. 1994; Weiden and Piantadosi 1991). In CALGB study (Kumar et al. 1996) 74% of patients stage IIIAN2 were treated with two cycles of neoadjuvant chemotherapy with cisplatin and vinblastine, surgery, and postoperative radiation. Of the patients who entered the trial, 49% developed local relapse. In the present study, eight out of 28 patients staged as IIIAN2 (29%) presented local relapse within the IOERT field. Only in one patient the chest relapse was marginally located to the IOERT field. Local intensification with IOERT over the primary tumor areas seems reasonable in this group of patients to increase local control, especially in those patients with metastatic mediastinal nodes.

Standard therapy yields local control rates around 90% in clinical stage II patients and 80% in pathological stage II patients (Baldini et al. 1999; Martini et al. 1983; Gradishar et al. 1992). In our study 18 patients (100%) stage IIB were locally controlled at 5 and 10 years.

Overall survival at 2 and 5 years for all series was 37% and 20% with a median survival time of 15 months. Taking into account that more than 50% of the patients included in the study were stage IIIB (56%) it seems that the present study compares favorably with other studies that include stage IIIB patients treated with a combination of chemotherapy, radiotherapy, and surgery. Most published reports include a much lower percentage of stage IIIB patients and report 2-year survival rates ranging from 20% to 30% (Weiden and Piantadosi 1991).

Multivariate analysis has identified two clinical factors (stage and nodal disease) and one surgical factor (type of resection) with a statistically significant impact on local control. The presence of these factors stratifies the local control probability for each individual patient. Patients without risk factors have a local control of 100% at 5 and 10 years and correspond to stage IIB and IIIA (N1) tumors after complete surgical resection. On the other hand, patients who present three risk factors have a poor local control (0%) and correspond to those patients with stage IIIB and N2–N3 disease who did not undergo complete resection. Patients who present two risk factors have local control rates at 5 and 10 years of 13% and 8%, respectively. In the light of these results it is not justified to include patients with two or three risk factors in programs that include surgical resection and IOERT. Patients with one risk factor have a local control at 5 and 10 years of 70% which is considered acceptable taking into account that these patients have tumors stage IIIA (N2) and IIB (N0, N1) tumors with complete resection and patients with IIB and IIIA (N0, N1) tumors with incomplete resection. The rela-

tionship between intrathoracic control in NSCLC and irradiation dose have been reported since the 1980 when the RTOG published the preliminary results of a randomized study that compared radiation doses of 40, 50, or 60 Gy for the treatment of 378 patients with unresectable non-small cell lung cancer (Perez et al. 1980). Local control was superior in those patients treated with 50 or 60 Gy with a trend towards improved survival. These results were subsequently confirmed with longer follow-up showing slight improvement in 3-year survival for those patients treated with 60 Gy. This improvement disappeared at a longer follow-up (Perez et al. 1987). Patients who presented intrathoracic control had better survival in spite of the very high risk of development of metastatic disease (Perez et al. 1986).

In our experience local relapse is related to decreased overall survival when groups are adjusted by stage, location of the tumor, pathological response, and type of resection. This relationship is close to statistical significance. The 5-year overall survival for those patients with local control is 41% versus 2% for those patients who presented local relapse (Aristu 2000). Local control is, therefore, a mandatory objective in therapeutic strategies research for non-small cell lung cancer. The delivery of radiation doses beyond 60 Gy using conventional radiation techniques did not increase local control due to the concerns of increased toxicity. IOERT must be considered a highly sophisticated radiation technique that may increase the therapeutic window in the thoracic oncology.

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3.2.5 Intraluminal Radiotherapy

Ron Stout, Paul Burt, and Philip Barber

CONTENTS

3.2.5.1 Introduction

Approximately 75% of patients with non-small cell lung cancer present with locally advanced or metastatic disease which renders them inoperable and virtually incurable. The aim of treatment is often palliative and radiotherapy can give considerable relief of troublesome symptoms, thereby improving the quality of remaining life. A number of patients present with thoracic symptoms which are predominantly due to the endobronchial component of their disease such as cough, hemoptysis, breathlessness and those of obstructive pneumonitis. Endobronchial radiotherapy in such circumstances has its attractions because any adverse effects on normal tissues are confined to those within the immediate vicinity of the bronchus. Endobronchial brachytherapy holds out the prospect of similar levels of palliation with less morbidity than external irradiation. If a more radical approach to treatment is considered appropriate, brachytherapy may then be combined with external beam radiotherapy to boost the dose to the primary tumour, since the trachea and the main airways are relatively resistant to radiation injury being composed largely of fully developed cartilage, a post mitotic cellular system. For the same reason, brachytherapy may be given to patients who require further palliation having relapsed after previous external beam irradiation which was given to tolerance for the lung parenchyma, oesophagus or spinal cord.

Endobronchial brachytherapy was used for the first time more than 80 years ago (Yankauer 1922). Radon seeds were implanted through a rigid bronchoscope directly into a tumour in 1921. Iodine-125 and gold-198 have also been used for permanent interstitial transbronchial implantation. The early techniques, which were difficult to perform and very demanding of physicians' time, never gained widespread acceptance because of the additional risks of severe haemorrhage and oedema and the problems of poor source distribution and source displacement. In due course, after-loading techniques were developed to facilitate intraluminal brachytherapy using caesium-137, cobalt-60 or iridium-192. Although this led to the more frequent use of this treatment, it was still of limited application because of the large size and low activity of the radioactive sources, prolonged treatment times because of the low dose-rate and the exposure of staff to significant radiation doses. In addition, both permanent interstitial implantation and temporary intraluminal brachytherapy required general anaesthesia for insertion of the sources or their carrying applicators. Technological advances in the mid 1980s led to the development of a miniature, high activity, iridium-192 source which could be used in a remote after-loading system and this overcame many of the problems previously associated with endobronchial brachytherapy. The introduction of high dose-rate intraluminal radiotherapy, now an outpatient procedure using local anaesthesia and flexible bronchoscopy, offered a practical and safe treatment alternative which was well tolerated by patients. Several studies have since shown that high dose-rate is just as effective and safe as low dose-rate brachytherapy (Mehta et al. 1992; Lo et al. 1995).

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3.2.5.2 The Technical Aspects and Practical Application of Endobronchial Brachytherapy

The miniature iridium source (typically 1.1 mm diameter and 3.5 mm long) can be accommodated in a closed-end 2 mm diameter catheter which can access upper lobe and segmental bronchi previously beyond the scope of brachytherapy using larger sources. The small source size also permits the use of multiple catheters to enlarge the treatment volume and encompass bulkier tumours involving more than one of the bronchi. Various attempts have been made to ensure that the treatment applicator lies centrally within the bronchial lumen, so as to obtain a better dose distribution and avoid localised areas of high dose on the normal mucosa (Huber et al. 1997; Marsiglia et al. 2000; Nomoto et al. 1997). None of these methods have gained widespread acceptance.

The system is extremely flexible. The single iridium source can be programmed to dwell in up to 48 different positions within each catheter. If the distance between each position is 5 mm, then lengths of up to 24 cm of the bronchi may be treated anywhere within the last 28 cm of the closed-end catheter. The time that the source dwells in any one position can also be varied so that different isodose distributions can be obtained if so desired, e.g. cylindrical, dumb-bell or pear-shaped. The high activity of the source (nominal activity 10 Ci or 370 GBq) enables treatment delivery at high dose-rate resulting in short treatment times of approximately 15 min which significantly improves patient compliance and acceptability. Further details of the actual technique are described by Stout (1993).

In order to facilitate the comparison of results from different treatment regimes, it is generally accepted that the intraluminal dose should be specified at a depth of 1 cm from the source axis. Typical prescriptions in previously untreated patients include: (a) radical intent: 64 Gy in 2 Gy fractions external plus 3 fractions of 5 Gy internal during weeks 1, 3 and 5; (b) palliative intent: 37.5 Gy in 2.5 Gy fractions external plus 3 fractions of 5 Gy internal; (c) palliative intent using brachytherapy alone: 3 fractions of 7.5 Gy at weekly intervals or a single fraction of 10–15 Gy. For recurrent tumours in patients who have previously received full dose radiotherapy, 5 Gy in 1–4 fractions of endobronchial brachytherapy is most commonly used.

3.2.5.3 The Efficacy of Endobronchial Brachytherapy

The patients most likely to benefit from endobronchial brachytherapy are those with central tumours which are visible endoscopically in the trachea and main stem or lobar bronchi. The results of treatment with high dose-rate endobronchial brachytherapy in more than 4500 patients world-wide have been published since the mid 1980s. Numerous studies, mostly non-randomised but also supported by some phase 3 clinical trials, have documented good symptomatic, endoscopic, radiological and physiological responses for a range of doses given in one, or as many as six, weekly treatments per patient.

Response rates can vary considerably with patient selection, intention to treat (curative, palliative or relapse re-treatment) and the addition or otherwise of external beam radiotherapy. The assessment of palliation in lung cancer is further confounded by three other factors: (1) the imprecise nature of some of the symptom end points, e.g. it is easier to assign a symptom score for hemoptysis which is more likely to be accurate than it is for cough or breathlessness; (2) some of the tumour related symptoms under consideration are also produced by pre-existing chronic obstructive pulmonary disease which may undergo acute exacerbations from time to time; and (3) the same symptoms may occur after treatment as a consequence of the early or late side-effects of brachytherapy. These problems were highlighted and addressed by Stephens et al. (1999) in a publication from the Medical Research Council cancer trials office. They proposed that the palliation of any symptom could be described using a four point scoring system and be expressed in terms of: (a) improvement (a reduction in moderate or severe symptoms to nil or mild), (b) control (no deterioration in mild symptoms) and (c) prevention (no deterioration in those with no symptoms), see Table 3.2.5.1.

The accurate assessment of symptomatic response to a particular treatment may also require the use of patients' self-ratings in a validated 'quality of life' analysis tool (Stephens et al. 1997). The disparities that can arise between clinician and patient assessments are illustrated in Table 3.2.5.2, taken from the first UK trial of endobronchial brachytherapy (Stout et al. 2000).

In spite of these difficulties of assessment, individual symptom responses have been observed and reported in numerous publications with response rates consistently in the range of 50%–90%. Hemoptysis, breathlessness and the symptoms of ob-

Table 3.2.5.1. The definition of 'positive' and 'negative' endpoints for palliation

Baseline symptom	8-Week assessment	Category	Comment
None	None	Positive	Prevention
None	Mild, moderate, severe	Negative	
Mild	None or mild	Positive	Control
Mild	Moderate or severe	Negative	
Moderate or severe	None or mild	Positive	Improvement
Moderate or severe	Moderate or severe	Negative	
Any	Death	Negative	

Table 3.2.5.2. Palliation expressed as the percentage of positive symptom endpoints (see Table 3.2.5.1) for each treatment as recorded by clinicians at 8 weeks to assess response and by patients at 8 weeks for comparison

	Clinician Assessments		Patient Assessments	
	8 Weeks		8 Weeks	
	EBT	XRT	EBT	XRT
The number of completed assessments	46	46	40	43
Cough (%)	50	67	45	65
Hemoptysis	78	89	71	90
Breathlessness	59	78	38	49
Chest pain	61	80	43	77
Dysphagia	80	87	71	86
Anorexia	63	78	43	77
Tiredness	57	74	30	65
Nausea	83	87	58	81
Hoarseness	70	91	70	79

EBT, endobronchial brachytherapy; XRT, external beam radiotherapy.

structive pneumonitis are generally better relieved than cough. Resolution of endobronchial tumour has been confirmed endoscopically on many occasions with response rates (partial and complete) in the range of 55%–100%. Those reported by Spicer and Spratling (1993a) are typical. Complete resolution is also supported by the reports of patients with small localised tumours who have survived long-term following brachytherapy as the sole treatment (Sutedja et al. 1994; Tredaniel et al. 1994; Gollins et al. 1996a; Perol et al. 1997; Marsiglia et al. 2000). Improvements in chest X-ray appearances following brachytherapy are usually noted in 40%–90% of patients depending upon the series. Significant physiological as well as subjective, bronchoscopic and radiological benefit has been well documented in a small but carefully investigated group of patients by Goldman et al. (1993).

3.2.5.4 The Side-Effects of Endobronchial Brachytherapy

The commonest early side-effect which can be attributed to intraluminal radiotherapy is a transient exacerbation of cough which has usually settled within 2–3 weeks of treatment. When endobronchial brachytherapy is used as the sole treatment, there is usually no significant radiation esophagitis. This results in less overall morbidity, an obvious gain in

favour of endobronchial brachytherapy when the aim of treatment is palliation. The later effects of radiation bronchitis and stenosis, elegantly described by Spicer and Spratling (1993b), and massive fatal hemoptysis, give rise to more concern.

The grading system for radiation bronchitis and stenosis as described by Spicer and Spratling is a useful tool to document what is seen at bronchoscopy at various time intervals following treatment. During the first 3 months following treatment the reactions on the mucosa are predominantly inflammatory. A fibrotic reaction with associated stenosis is more prevalent beyond 6 months. The incidence of radiation bronchitis reported by them is highest in the patients receiving potentially curative radiotherapy using a combined approach of brachytherapy and external beam radiotherapy but the only significant factor predicting for the severity of late response was length of follow-up. In our own series in Manchester, Gollins et al. (1996b) where the majority of patients were treated with a single exposure of brachytherapy as the sole treatment, a dose response relationship was identified.

Massive hemoptysis is usually a fatal event which occurs in lung cancer whether or not radiotherapy has been given. Its exact incidence in untreated patients or in those who have received external beam radiotherapy and or chemotherapy is unknown but has been variously reported in the range of 5%–20%. Its occurrence following brachytherapy with or without external beam radiotherapy has been documented in the range 0%–50%. In the large retrospective series of 406 patients reported by Gollins et al. (1996b), massive fatal hemoptysis was 8% (32 patients). The review included 322 new cases of inoperable non-small cell lung cancer who were treated with a single fraction of high dose-rate brachytherapy to a total dose of 15–20 Gy. Massive hemoptysis leading to death usually occurred between 9 and 12 months after treatment whereas deaths from other causes occurred between 3 and 6 months. Associated treatment factors increasing the likelihood of massive fatal hemoptysis were a brachytherapy dose greater than 15 Gy, prior laser treatment, a second or third brachytherapy treatment at the same site and concurrent external beam radiotherapy. However, in 25 of the 32 patients whose deaths were assessable, there was evidence of recurrent and or residual tumour in 20. The UK randomised trial reported by Stout et al. (2000) where brachytherapy (15 Gy) as a sole primary treatment was compared directly with a palliative course of fractionated external radiotherapy (30 Gy in 8 fractions), the incidence of massive fatal hemoptysis was the same in both arms of the trial, occurring in only seven out of 99 patients overall.

3.2.5.5 The Role of Endobronchial Brachytherapy

No evidence has yet been found from large retrospective series or a limited number of prospective randomised trials, that the addition of endobronchial brachytherapy to external beam radiotherapy (radical or palliative) has produced any significant improvement in survival.

A trial by Huber et al. (1997) compared a planned dose of 60 Gy external radiotherapy with an additional boost of high dose-rate brachytherapy of 4.8 Gy immediately before and after external irradiation. There was an improvement in local control in the combined arm and a trend towards improved survival which did not reach statistical significance. There was no significant difference in the incidence of fatal hemoptysis between the two groups.

A similar trial by Langendijk et al. (2001) included patients who were being treated with palliative as well as radical intent. No survival benefit was found in patients receiving external and internal treatment, although the trial was not designed to investigate survival. The addition of brachytherapy did provide higher rates of re-expansion of collapsed lung resulting in a transient improvement in breathlessness. The beneficial effect was only observed among patients with obstructing tumours in the main bronchus. The investigators concluded that the results did not support the addition of endobronchial brachytherapy to external radiotherapy as a standard approach but combined treatment could be considered in patients with severe breathlessness due to an endobronchial tumour obstructing the main bronchus.

Two Manchester trials of palliative radiotherapy in 200 patients have compared a fractionated course of external radiotherapy, 30 Gy in 8 fractions, with the same treatment plus a boost of brachytherapy of 15 Gy in 1 session. A detailed analysis of palliation is being carried out in preparation for publication, but neither trial has demonstrated a survival gain in favour of the combined treatment.

In some patients it may be useful to re-expand a collapsed lobe or lung before embarking on a course of radical external beam radiotherapy. Re-expansion of the collapsed lung may lead to a better defi-

nition of the gross tumour volume, a more accurate radiotherapy treatment plan and a reduced risk of a geographical miss. Theoretically, this could result in better local control and improved survival for more localised tumours.

Although endobronchial brachytherapy can provide good symptom relief, if the aim of treatment is palliation, then external irradiation as the initial sole treatment would seem preferable to brachytherapy alone. That at least was the conclusion of the investigators in the first UK trial, Stout et al. (2000), who found that external radiotherapy gave better overall and more sustained palliation with fewer re-treatments, a modest gain in median survival of 287 versus 250 days and a better 1-year survival of 38% versus 22%. Brachytherapy alone clearly has a useful role where external irradiation is contra-indicated.

Endobronchial brachytherapy may also offer further palliation in patients who have symptomatic endobronchial relapse following previous external beam radiotherapy. In all, 60%–70% of these patients will obtain worthwhile symptom relief although the incidence of fatal hemoptysis and bronchial fistulae may be high (Sutedja et al. 1992; Macha et al. 1995). Care should be taken where external irradiation has been given to tolerance and where laser treatment has been used to clear the airway before brachytherapy. Doses less than 10 Gy, e.g. 5 or 7.5 Gy, should be used and a single treatment is often sufficient.

3.2.5.6 Conclusion

Endobronchial brachytherapy can undoubtedly provide good palliation of hemoptysis, breathlessness, cough and obstructive pneumonitis when used alone or with external irradiation as described above. The optimal dose and number of fractions to provide the best symptom relief for the least morbidity still have to be defined. Individual practitioners will have their own preferences based on their experience and the evidence currently available in the literature. Where a more radical approach is required, it would seem that brachytherapy can improve local control without making a significant impact on survival. As developments in chemo-radiotherapy lead to better tumour control outside the airways, the role of brachytherapy as an intraluminal boost may become more important. Careful assessment in clinical trials will be required to document the potential benefits and identify any excess morbidity when multi-modality treatment is employed.

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Treatment of Small-Cell Lung Cancer

4.1 Limited-Disease of Small Cell Lung Cancer

Branislav Jeremić

CONTENTS

4.1.1 Introduction

Small cell lung cancer (SCLC) is a highly aggressive carcinoma and represents approximately 20% of all lung cancer cases (Grenlee et al. 2000). It is an entity of lung cancer that is biologically and clinically different from non-small cell lung cancer. The World Health Organization classification of 1988 and 1999 and the International Association for the Study of Lung Cancer panel divide SCLC into three subtypes: classic small cell carcinoma (combined oat-cell and intermediate-cell), mixed small cell/large cell carcinoma (components of small cell and large cell carcinoma), and combined small cell carcinoma (small cell with a component of squamous or adenocarcinoma cells) (Zakowski 2003). The mainstay of the diagnosis is still light microscopy, either cytologic or histologic. The addition of immunostaining and common molecular and genetic abnormalities implicated in the pathogenesis of SCLC – amplification of ***c-myc*** oncogene, allelic loss on the short arm of chromosome 3, deletion and phosphorylation, altered protein expression of retinoblastoma (Rb) gene and frequent mutations in ***p53***, located at chromosome 17p13.1 – have increased our understanding of these lesions, but have not yet replaced the use of routine microscopy (Zakowski 2003).

Cigarette smoking has long been known to be the primary risk factor for small cell lung cancer, accounting for >90% cases (Mulshine et al. 1993; Ihde et al. 1993). The most frequent clinical signs and symptoms include cough, hemoptysis, dyspnea, hoarseness, and dysphagia. Contrary to non-small cell lung cancer, the common paraneoplastic syndromes occur frequently in a variety of presentations, including the syndrome of inappropriate antidiuretic hormone (SIADH), ectopic Cushing's syndrome, Lambert-Eaton myasthenic syndrome (LEMS), and rare neurologic syndromes, such as subacute spinal or peripheral neuropathy, cerebellar ataxia, limbic encephalopathy and retinal degeneration (Curran 2001).

The Veterans Administration Lung Group proposed a two-stage system dividing all small cell lung cancer cases into "limited disease" and "extensive disease" 35 years ago (Green et al. 1969) and the system is still used today. The vast majority of patients (approximately two-thirds) fall into the extensive disease category while limited disease occurs in approximately one-third of all small cell lung cancer cases. Limited-disease small cell lung cancer is defined as disease confined to the hemithorax of origin along with the involved regional lymph nodes (hilar and mediastinal), with or without ipsilateral supraclavicular lymph nodes. It can also be considered as a disease which can be incorporated within a single, tolerable radiotherapy treatment field, and may include patients with contralateral mediastinal or hilar lymph nodes. Almost 15 years ago, the International Association for the Study of Lung Cancer recommended that limited-disease small cell lung cancer include patients with ipsilateral hilar nodes, ipsilateral and contralateral mediastinal and supraclavicular nodes, and ipsilateral pleural effusion (Stahel et al. 1989), which would correspond to stages I–IIIB.

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4.1.2 Treatment

Due to extreme chemosensitivity and a propensity for early spread beyond the thorax, chemotherapy was the mainstay of treatment several decades ago, although chemotherapy alone led to intrathoracic failure in up to 80% of cases, leading to a median survival of 10–14 months (Cohen et al. 1979). Since a number of studies showed that radiation therapy has great potential in decreasing locoregional failures it was increasingly practised in the 1970s and 1980s, but radiation therapy was introduced as a necessary part of the combined modality approach owing to the results of two meta-analyses that appeared a decade ago (Pignon et al. 1992; Warde and Payne 1992). They both showed a small but significant improvement in 2-year and 3-year survival, averaging 5%–7% and an improvement in local control rates in 25% of cases with the addition of thoracic radiation therapy. With the widespread use of the cisplatin/etoposide regimen, and its lower toxicity (lower than that observed with the cyclophosphamide, doxorubicin, vincristine) when combined with thoracic radiation therapy, concurrent thoracic radiation therapy and platinum-based chemotherapy is now considered as the standard treatment in limited-disease small cell lung cancer. Recent meta-analysis (Auperin et al. 1999) confirmed the necessity for prophylactic cranial irradiation, but its timing, dose and fractionation require further investigation.

There are, however, a number of questions which warrant further studies into this disease such as optimisation of both chemotherapy (choice of drugs and its schedule/timing/dosing) and thoracic radiation therapy (timing of thoracic radiation therapy and dose/volume/fractionation). Some of these questions will be addressed in the following sections.

4.1.2.1 Chemotherapy

A number of chemotherapeutic agents with response rates of ≥30% in small cell lung cancer include cisplatin, carboplatin, etoposide, cyclophosphamide, doxorubicin, methotrexate and vincristine (Sandler 2003). Cyclophosphamide/doxorubicin/vincristine regimen was mostly used in earlier studies, while studies carried out in the 1980s frequently employed cisplatin/etoposide, the latter being not only less toxic, but also very active (Einhorn et al. 1988). The results of Einhorn et al. (1988) were subsequently reconfirmed by Fukuoka et al. (1991) in a trial with alternating cyclophosphamide/doxorubicin/vincristine and cisplatin/etoposide being superior to either cisplatin/etoposide or cyclophosphamide/doxorubicin/vincristine alone (median survival: 16.8 vs. 11.7 vs. 12.4 months). Since it was shown that cisplatin/etoposide had less cardiac and lung toxicity, compared with cyclophosphamide/doxorubicin/vincristine, it was preferentially used with thoracic radiation therapy, providing 2-year survival rates of ≥40% (Turrisi et al. 1999; Takada et al. 2002). While cisplatin/etoposide and thoracic radiation therapy is the mainstay of concurrent treatment today, carboplatin was sometimes used instead of cisplatin (Kosmidis et al. 1994; Jeremic et al. 1997), in combination with etoposide (i.e. carboplatin/etoposide) due to a similar response and survival as with cisplatin/etoposide but with less nephro- and ototoxicity than cisplatin/etoposide (Kosmidis et al. 1994; Jeremic et al. 1997). Attempts were also made to incorporate other drugs in the treatment plan (Woo et al. 2000; Hanna et al. 2002).

One of the frequently practised approaches in the past was to treat patients for the duration of their life. Of several randomised trials to test this hypothesis, frequently including both stages, only one study could demonstrate a survival advantage for limited-disease small cell cancer patients (Maurer et al. 1980), which is in sharp contrast to numerous studies showing either no advantage at all (Woods and Levi 1984; Cullen et al. 1986; Bleehan et al. 1989; Lebeau et al. 1992; Giaccone et al. 1993; Beith et al. 1996; Sculier et al. 1996) or showing even detrimental effects of continuous chemotherapy (Byrne et al. 1989). Given the lack of survival improvement and increased toxicity in maintained treatment, this approach has no role in the treatment of limited-disease small cell lung cancer patients nowadays. Some studies focused on the question of an optimal number of induction chemotherapy cycles. If the option of a second line chemotherapy was offered, no survival benefit was seen for eight cycles of cyclophosphamide/etoposide/vincristine compared to four cycles (Spiro et al. 1989). Indirectly, this was confirmed in as early as 1996 by results of an Intergroup 0096 study which produced convincing results with only four cycles of cisplatin/etoposide and thoracic radiation therapy (Johnson et al. 1996). It seems, therefore, that the current standard chemotherapy protocol is four (to six) cycles of a platinum-based regimen.

The dismally high recurrence rate was the impetus for investigating other approaches like rapid alternation or dose intensification, or testing the intro-

duction of "third" generation drugs like irinotecan, topotecan and paclitaxel. The mathematical model of Goldie and Coldman (1984) indicated that rapid alteration of non-cross-resistant chemotherapy should improve survival in SCLC. It was tested (Einhorn et al. 1988) and confirmed in practice (Fukuoka et al. 1991), to demonstrate an improvement in survival by adding cyclophosphamide/doxorubicin/vincristine and cisplatin/etoposide in a sequential protocol.

Dose intensification was tested in randomised trials including either doxorubicin or alkylating-based chemotherapy in limited-disease small cell lung cancer in the 1970s and 1980s (Cohen et al. 1977; Mehta et al. 1982; Figueredo et al. 1985), or cisplatin-based chemotherapy in the 1990s (Arriagada et al. 1993), including granulocyte colony-stimulating factor support (Ardizzoni et al. 2002). Improved survival was noted in the dose-intensive arm in three studies, with two trials showing significant improvement, but this was accompanied with more severe toxicity, with the result that the dose intensification did not become standard treatment approach. An attempt to rectify the issue of increased dose intensity is made by reducing the interval between cycles of chemotherapy. Two trials demonstrated an improvement in survival (Steward et al. 1998; Thatcher et al. 2000) but again, however, due to increased toxicity it could not be considered as standard treatment.

Of the third generation drugs, irinotecan was combined with cisplatin and compared to cisplatin/etoposide in a Japan Clinical Oncology Group phase III study in extensive-disease small cell lung cancer only (Noda et al. 2002). A significant survival advantage for the irinotecan/cisplatin arm was observed (the median survival time, 390 versus 287 days; 1-year survival, 58% versus 38%; p=0.002). Overall responses were also significantly higher in the irinotecan/cisplatin arm (83% versus 63%). High-grade diarrhoea was seen only in the irinotecan/cisplatin arm, while high-grade haematological toxicity was seen more frequently in the cisplatin/etoposide arm. Topotecan was initially shown to be effective in relapsed small cell lung cancer patients. This led to its evaluation as maintenance after initial cisplatin/etoposide in chemonaive extensive-disease small cell lung cancer patients compared to no maintenance therapy. With the addition of topotecan, progression-free survival was improved but no impact on survival (8.7 months versus 9.0 months, p=0.71) was observed (Schiller et al. 2001). Although taxanes have also been increasingly used in small cell lung cancer, only paclitaxel was tested in a phase III studies. Two recently published studies compared cisplatin/etoposide with cisplatin/etoposide/paclitaxel. Mavroudis et al. (2001) found no difference in response rates, median and overall survival, but observed more treatment-related deaths in the cisplatin/etoposide/paclitaxel regimen (p=0.001). Niell et al. (2002) also observed no significant difference in the median survival time (10.3 vs. 9.8 months, p=0.33) while toxicity was increased in the cisplatin/etoposide/paclitaxel arm (neutropenia: 63% vs. 44%; thrombopenia 21% vs. 11%; grade 5 toxicities: 6.4% vs. 2.7%). Gatzmeier et al. (2000) showed no difference in toxicity between paclitaxel, carboplatin and etoposide versus carboplatin, etoposide and vincristine in limited-disease and extensive-disease small cell lung cancer. Finally, a preliminary analysis of another study (Birch et al. 2000) showed only modest improvements in the overall response rate with a trend toward improvement in survival for paclitaxel, carboplatin and etoposide when compared to carboplatin and etoposide in patients with extensive-disease small cell lung cancer. Data from four phase II trials in small cell lung cancer showed only moderate success with concurrent cisplatin/etoposide/paclitaxel and thoracic radiation therapy (Levitan et al. 2000; Ettinger et al. 2000; Sandler et al. 2000; Bremnes et al. 2001), with complete response rates of 13%–81% and median survival times of about 22 months. Finally, recent analysis of the Southwest Oncology group phase II study 9713 provided another set of data on the use of paclitaxel in 87 patients with limited-disease small cell lung cancer (Edelman et al. 2004). Concurrent cisplatin/etoposide/radiation therapy as part of the combined modality program was followed by three cycles of consolidation paclitaxel/carboplatin. While the response rate was 86%, the median survival time was 17 months and the 2-year survival rate was 33%, while the progression-free survival at 2 years was only 21%. This prompted authors to conclude that paclitaxel is inactive against small cell lung cancer and suggested it's further investigation be abandoned. These results confirmed previously disappointing results of the Eastern Cooperative Oncology Group in a similar study (Sandler et al. 2000). Contrary to these results, the European Organization for research and treatment of Cancer (Reck et al. 2003) found an advantage in the paclitaxel-containing arm in patients with small cell lung cancer, including limited-disease small cell lung cancer patients who achieved the median survival time of 17.6 months in that study. It must, however, be clearly stated that this result is quite similar to that of the Southwest Oncology group study cited above, as well as those achieved during the Intergroup study (Turrisi et al. 1999), and somewhat

lower than achieved in other prospective randomised studies which used only a cisplatin/etoposide combination (Jeremic et al. 1997; Takada et al. 2002).

To summarise the preceding part on chemotherapy in limited-disease small cell lung cancer, there is no firm basis to recommend either dose intensification or the integration of new drugs into actual regimens, due to the risk of severe toxicity and the lack of clearly demonstrated improvement in overall survival, and particularly due to a lack of data on chemotherapy combined with thoracic radiation therapy. It has already become policy, however, in the testing of new drugs and combinations in this disease and the long-term data from the completed studies, as well as those still underway, will help identify those drugs/regimens which may be useful in further clinical testing for cisplatin/etoposide and thoracic radiation therapy to treat this disease.

4.1.2.2 Radiation Therapy

Thoracic radiation therapy issues have mainly focused on timing, dose and fractionation and treatment volumes. In relation to timing, a combination of thoracic radiation therapy and chemotherapy can be defined as either concurrent, sequential or alternating. Regarding concurrent thoracic radiation therapy and chemotherapy, earlier studies used non-platinum regimens, or mixed regimens with cisplatin/etoposide, while newer ones used exclusively platinum-based regimens. Some studies (Perry et al. 1987; Schultz et al. 1988; Work et al. 1997) suggested that thoracic radiation therapy delayed until the fourth cycle of chemotherapy (Perry et al. 1987) or until day 120 (Schultz et al. 1988) may be superior to initial radiation therapy or suggested no difference when compared to early thoracic radiation therapy and chemotherapy (Work et al. 1997). One possible explanation lies in the marked reduction of chemotherapy dose in the Cancer and Leukemia Group B (Perry et al. 1987) and the Danish trial when thoracic radiation therapy was applied early. Also, the Danish trial (Work et al. 1997) can not really be considered as a concurrent thoracic radiation therapy and chemotherapy study because sequential radiation therapy was used before and after chemotherapy. Newer studies using cisplatin/etoposide or cisplatin/etoposide alternating with cyclophosphamide/doxorubicin/vincristine (Murray et al. 1993; Jeremic et al. 1997; Takada et al. 2002) showed clear superiority for early (cycle one or two of chemotherapy) administration of thoracic radiation therapy. These studies have also reconfirmed in clinical practice an original Goldie and Coldman (1979) theoretical consideration that early administration of both treatment modalities leads to the best outcome on both a local and distant level (Table 4.1.1), with only early concurrent thoracic radiation therapy and cisplatin/etoposide being capable of achieving 5-year survival of >20%, whilst late delayed thoracic radiation therapy usually obtained only about 10%. Therefore, it became common practice to offer thoracic radiation therapy with curative doses worldwide (cycle one or two of chemotherapy) as early as possible. Others have also proved this in an institutional setting. Kamath et al. (1998) showed in a small study of 48 patients that early concurrent thoracic radiation therapy/cisplatin/etoposide offers an advantage over sequential chemotherapy and thoracic radiation therapy in terms of overall survival and decreased distant metastasis in patients with limited-disease small cell lung cancer. Most recently, Fried et al. (2003) performed a meta-analysis evaluating the timing of thoracic radiation therapy in combined modality therapy for limited stage small cell lung cancer. Seven trials with a total of 1524 patients met inclusion criteria. A significantly higher 2-year survival was observed in the early group and there was a suggestion of a similar trend at 3 and 5 years. This advantage was a consequence of significantly better outcome for studies employing hyperfractionated radiation therapy and platinum-based chemotherapy. Contrary to that, once-daily regimens and doxorubicin-based chemotherapy brought no improvement for early regimens.

With regard to *thoracic radiation therapy dose and fractionation,* the doses used for small cell lung cancer were usually about 50 Gy, standard fractionation. Even in the era of concurrent thoracic radiation therapy and chemotherapy one major site of recurrence continues to be in-field (about 30% pure and 20% combined with systemic progression). The majority of studies evaluating this issue are retrospective, with one study (Choi and Carey 1989) observing a better local control for doses of 40–50 Gy than with doses <40 Gy (>50% versus 30%). Another study indicated excellent local control after 60 Gy, being 97% (Papac et al. 1987). Recently, however, Choi et al. (1998) from the Cancer and Leukemia Group B identified at least 70 Gy using standard fractionation as the maximum tolerated dose for combination with chemotherapy. More recently, the Cancer and Leukemia Group B (Bogart et al. 2002) reported on the preliminary analysis of their phase II trial in which 70 Gy thoracic

Table 4.1.1. Prospective randomised trials investigating optimal timing of concurrent thoracic radiation therapy and chemotherapy in limited-disease small cell lung cancer

Author	CHT	RT	RT timing	Survival (5-year)	Outcome
Perry et al. (1987)	6 × CEV + CEV/CAV	50 Gy/24 fx (once daily)	Cycle 1 Cycle 4	7% 13%	Trend for improved survival for late RT (p=0.08)
Murray et al. (1993)	6 × CAV/PE	40 Gy/15 fx (once daily)	Week 3 Week 15	20% 11%	Improved survival for early RT (p=0.008)
Work et al. (1997)	3 × PE + 6 × CAV	40–45 Gy/22 fx (once daily)	Week 1 Week 18	11% 12%	No difference (p=0.4)
Jeremic et al. (1997)	CpE with RT + 4 × PE	54 Gy/36 fx (twice-daily)	Week 1 Week 6	30% 15%	Improved survival for early RT (p=0.052)
Takada et al. (2002)	4 × PE	45 Gy/30 fx (twice-daily)	Cycle 1 Cycle 4	24% 18%	Trend for improved survival for early RT (p=0.097)

CHT, chemotherapy; CEV, cyclophosphamide, etoposide, vincristine; CAV, cyclophosphamide, doxorubicin, vincristine; PE, cisplatin, etoposide; CpE, carboplatin, etoposide; fx, fraction; RT, radiation therapy.

radiation therapy was shown to be feasible and effective when given concurrently with an initial three cycles of carboplatin and etoposide, following an induction with two cycles of paclitaxel and topotecan. Median failure-free survival was 12.9 months and the median overall survival was 19.8 months with a 1-year survival rate of 70%. Only one treatment-related death occurred during this study. Good tolerability of higher thoracic radiation therapy doses was recently confirmed by Miller et al. (2003) who retrospectively evaluated the data from 65 patients from the Duke University in which 58–66 Gy standard fractionation was used with either concurrent (n=32) or sequential (n=33) chemotherapy. The somewhat lower (30%) 2-year survival rate was explained by the fact that less than one-half of patients received concurrent thoracic radiation therapy and chemotherapy and only 26% received prophylactic cranial irradiation. The toxicity was low. Similarly, in a cohort of limited-disease small cell lung cancer treated between 1987 and 2000 with ≥50 Gy, Roof et al. (2003) observed that overall survival, local control and disease-free survival compared favourably with the historic controls. More recently, Komaki et al. (2003) reported on the Radiation Therapy Oncology Group 9712 study which was a phase I dose-escalation study of thoracic radiation therapy with concurrent cisplatin/etoposide in limited-disease small cell lung cancer. Thoracic radiation therapy was given in the form of 1.8 Gy daily to 36 Gy followed by small boost fields encompassing only the gross disease delivered with escalations of 1.8 Gy b.i.d. during the final days to establish the maximum tolerated dose. Escalations of twice-daily thoracic radiation therapy during the last 5, 7, 9 and 11 days permitted doses of 54 Gy, 57.6 Gy, 61.2 Gy and 64.8 Gy. The maximum tolerated dose was determined to be 61.2 Gy in 34 fractions of 1.8 Gy when given concurrently with two cycles of cisplatin/etoposide and followed by two additional cycles of cisplatin/etoposide.

While earlier studies mostly employed conventional fractionation (once a day, five times a week), a few of them used somewhat hypofractionated radiation therapy regimens, thought to cause more damage to small cell lung cancer cells. A recent study showed that shifting from hypofractionated to conventionally fractionated thoracic radiotherapy in a single institution's 10-year experience in limited stage small cell lung cancer did not alter outcomes because the survival, thoracic control and toxicity rates were statistically similar (Videtic et al. 2003). With more pronounced interest for the altered fractionated regimens, however, accelerated hyperfractionation seemed the logical choice due to the high sensitivity of small cell lung cancer to radiation therapy, the sparing effect of twice-daily fractionation and the possible effect of dose acceleration to combat rapid proliferation thought to occur in small cell lung cancer. In the Intergroup study (Johnson et al. 1996; Turrisi et al. 1999), 45 Gy given in 30 fractions in 3 weeks (1.5 Gy b.i.d. fractionation) was compared with the same dose given once daily. With

survival significantly better in the b.i.d. arm (5-year, 26% versus 19%). This, however, was achieved with a somewhat higher incidence of acute toxicity. Another study investigating this issue was a North Central Cancer Treatment Group study which compared concurrent two cycles of cisplatin/etoposide and either b.i.d., split-course thoracic radiation therapy (48 Gy in a total of 5.5 weeks) or once-daily thoracic radiation therapy (50.4 Gy), both given after three cycles of cisplatin/etoposide (Bonner et al. 1999). There was no difference in a 3-year overall and locoregional control. After 5 years (Schild et al. 2003), the median and 5-year survival were 20.4 months and 22% for b.i.d. versus 20.5 months and 21% for once-daily thoracic radiation therapy, respectively (p=0.7). Having these two studies together, a possible explanation may lie either in the inferiority of the split-course regimen (which undermined the effect of hyperfractionation) or the effects of acceleration outweighing those of hyperfractionation. Extending the overall treatment time, therefore, which allows tumour cell regeneration, may have been the reason for this finding due to a delay in thoracic radiation therapy either by long lasting induction chemotherapy or by split-course protocol for thoracic radiation therapy. A quality-adjusted reanalysis of a phase III trial comparing once-daily thoracic radiation vs. twice-daily thoracic radiation in patients with limited stage small cell lung cancer using 'quality time without symptoms or toxicity' methodology showed no difference in survival after adjusting for toxicity and progression (Sloan et al. 2002).

A number of groups and institutions world-wide accepted the policy of accelerated hyperfractionated thoracic radiation therapy, and the accumulated data show different outcomes (Johnson et al. 1996; Ali et al. 1998; Mennecier et al. 2000; Segawa et al. 2003) and toxicity profiles. The future studies directly comparing b.i.d. to once-daily fractionation will bring definitive answers about optimal total dose and fractionation regimen preferentially used. While this task is already underway, the "third" generation of drugs eagerly awaits its place and time in this disease and the data are slowly emerging (Sandler et al. 2000).

With the change of practice from sequential to concurrent thoracic radiation therapy and chemotherapy, the issue of *thoracic radiation therapy volumes* became particularly important in the latter case, while it is of no importance if one use early (cycle one) concurrent thoracic radiation therapy and chemotherapy. Several questions provide an interesting framework for further investigation, such as whether one should treat pre-chemotherapy or post-chemotherapy visible volumes, and what should be the safety margin around the visible tumour and which, if any, elective nodal coverage should be used. There is no consensus to date, although common policy is to include the original tumour with 1.5–2.0 cm safety margin. One prospective study showed no difference between large field thoracic radiation therapy and limited field thoracic radiation therapy (Kies et al. 1987), but others showed the opposite (Perez et al. 1981; White et al. 1982). Larger thoracic radiation therapy volumes will inevitably lead to more toxicity, but this must be carefully balanced against the increased risk of high incidence of local recurrence. Any appropriate solution of this question must take the dose/fractionation regimen used into account. It is also expected that newer diagnostic tools such as positron emission tomography and newer, more powerful, computer-driven radiation therapy technologies may help solve the problem of optimal thoracic radiation therapy volumes.

To further extend this, three-dimensional treatment planning and delivery using conformal techniques are increasingly used. Intensity-modulated radiation therapy and stereotactic fractionated radiation therapy are expected to fully bloom in the near future. It is reasonable to expect that they will be introduced in clinical practice to treat limited-disease small cell lung cancer, as a tool for both tumour dose increase and the dose normal tissue receives. This is an important issue since toxicity during concurrent thoracic radiation therapy and chemotherapy may lead to poor compliance and may necessitate treatment interruptions to palliate existing symptoms. As recently shown they result in poorer local control and decreased survival (Videtic et al. 2001).

4.1.3 Conclusions

The standard treatment for the majority of patients with limited-disease small cell lung cancer is a combination of thoracic radiation therapy and cisplatin/etoposide, given concurrently, with thoracic radiation therapy being started early. While the majority of institutions world-wide use four cycles of cisplatin/etoposide, numerous thoracic radiation therapy and chemotherapy issues remain unsolved. Ongoing studies will help clear up these important issues in optimising the treatment approach and outcome in this disease. The lessons we have learned from optimisation of the treatment approach in limited-dis-

ease small cell lung cancer also served as an attempt to optimise the treatment in extensive-disease small cell lung cancer. As we have recently shown in a prospective randomised trial, thoracic radiation therapy can play an important role in extensive-disease small cell lung cancer, provided that suitable patients are identified (Jeremic et al. 1999). We have focused on those patients who have the most favourable prognosis after induction chemotherapy, i.e. those achieving complete response at distant sites accompanied with either complete response or partial response intrathoracically. They were chosen as a subject of our study because they most closely resembled limited-disease small cell lung cancer patients. In these patients, after three initial cycles of cisplatin/etoposide, accelerated hyperfractionated thoracic radiation therapy offered a survival advantage over that achieved with chemotherapy alone (the median survival time: 17 vs. 11 months; 5-year survival rates: 9.1% vs. 3.7%, respectively; p=0.041) due to an improvement in the local recurrence-free survival (p=0.062). Patients treated with thoracic radiation therapy achieved better results than those treated with chemotherapy only regarding both median time to first relapse (13 vs. 9 months, respectively) and 1-5 year first relapse-free survival (p=0.045). Interestingly, after initial 3 cycles of cisplatin/etoposide, thoracic radiation therapy offered higher response rate than additional cisplatin/etoposide. When further response was evaluated, additional cisplatin/etoposide (in both groups) offered nothing but a few percent of additional response, an indirect evidence of the necessity of limiting of the number of chemotherapy cycles to 4–6. Results of this study await further verification, an important task for the future endeavours in small cell lung cancer.

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4.2 Prophylactic Cranial Irradiation in Small Cell Lung Cancer

Cécile Le Péchoux

CONTENTS

4.2.1 Introduction

Small cell lung cancer (SCLC) has several features that distinguish it from other tumor types, such as an early propensity to disseminate and most particularly in the brain. Chemotherapy is therefore the cornerstone treatment in both limited and extensive disease. Radiotherapy also has a role in the therapeutic strategy used for certain patients and two meta-analyses have contributed to establishing "the standard treatment": thoracic radiotherapy should be combined with chemotherapy in limited disease and prophylactic cranial irradiation (PCI) should also be part of treatment among complete responders (Pignon et al. 1992; Aupérin et al. 1999). Both systemic and local control have been improved in the past 20 years so that about two-thirds of these patients, mainly those with limited disease, will be put in complete remission. However, there is a high risk of relapse, and brain failures have become a significant cause of relapse as the risk of developing brain metastases increases with length of survival to a cumulative risk that can be as high as 80% (Komaki et al. 1981; Nugent et al. 1979). At the time of initial diagnosis, up to 24% of patients may be found to have brain metastases if MRI is used as part of the initial work-up (Nugent et al. 1979; Hansen 1973; Hochstenbag et al. 2000). Even in patients who achieve a complete response, the incidence of cerebral metastasis as the sole site of initial relapse varies between 14% and 45% at 2 years (Arriagada et al. 1995; Ball and Matthews 1995). Historically, chemotherapeutic agents have had a limited role in the treatment of cerebral metastases because of the inability of cytostatic drugs to cross the blood–brain barrier. However more recent studies have reported efficacy of chemotherapy alone, with response rates in brain metastases ranging from 40% to 76% (Postmus et al. 1989; Kristjansen et al. 1992, 1993; Lee et al. 1989), results equivalent to those obtained with radiation therapy (Nugent et al. 1979; Baglan and Marks 1981; Cox et al. 1980; Carmichael et al. 1988; Hagerdorn et al. 1993). Chemotherapy administered post-radiation could also be more effective (van Vulpen et al. 2002). However, even if the symptomatic relief is of some benefit, quality of life is poor and overall survival after development of brain metastases is low, with median survival times ranging from 1.5 to 4.5 months (Arriagada et al. 1995; Cox et al. 1980; Hagerdorn et al. 1993; van Hazel et al. 1983; Feletti et al. 1985).

PCI has thus been developed as a strategy to prevent dissemination to the uninvolved brain, as we know systemic agents do not cross the blood–brain barrier effectively (Hansen 1973). However, even if several retrospective and prospective studies have shown that PCI significantly reduced the incidence of a CNS relapse compared with patients who did not receive PCI, the utility of PCI has been a controversial issue for several years due to the lack of

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improvement in survival in individual trials and a possible risk of neurotoxicity and cognitive deficits in long-term survivors (Einhorn 1995; Wagner 1997; Turrisi 1990). PCI is now less controversial because of the results of the meta-analysis on PCI in SCLC complete responders, showing the benefit of PCI not only in terms of brain control but also in terms of survival (Aupérin et al. 1999).

4.2.2 Studies Evaluating Prophylactic Cranial Irradiation

4.2.2.1 First Generation of Randomized Trials

PCI has been used routinely in the past 20 years, since it was generally accepted that PCI would delay the appearance of symptomatic cerebral metastases and that it would reduce the life-time risk of CNS relapse by 30%–50% (Komaki et al. 1981; Nugent et al. 1979). Several randomized trials listed on Table 4.2.1 have been published showing a significant two- to three-fold decrease in brain metastases incidence in the PCI arm compared to the control arm (Aroney et al. 1983; Beiler et al. 1979; Cox et al. 1978; Eagan et al. 1981; Hansen et al. 1980; Jackson et al. 1983; Maurer et al. 1980; Niiranen et al. 1989; Perez et al. 1981; Seydel et al. 1985). However, they included a very heterogeneous patient population. There were trials that included patients who were in complete remission, others that included patients who failed to achieve a complete remission, patients with limited and extensive disease, as well as patients who had concomitant chemotherapy and different PCI doses and fractionations. None of these randomized studies could show an impact on the survival rate. However, in 1983 Rosen et al. were the first ones to report than PCI could have an impact on survival in a sub-group of patients and, since then, several retrospective studies have suggested that PCI could not only reduce brain failure rates, but also improve survival in complete responders to induction treatment (Rosen et al. 1983; Rosenstein et al. 1992; Rubenstein et al. 1995).

Table 4.2.1. Older randomized trials evaluating PCI in small cell lung cancer patients

Study	Number of patients	PCI dose Gy/fraction Timing of PCI	Brain metastases rate (%)		p Value	Median survival or survival at X years	
			PCI (+)	PCI (–)		PCI (+)	PCI (–)
Beiler et al. (1979)	54	24/8 3rd week	0%	16%	<0.05	>104 weeks LD	58 weeks LD
Cox et al. (1978)	45	20/10 D1	17%	24%	NS	40 weeks	
Eagan et al. (1981)	30	36/10 20th week	13%	73%	<0.05	13.6 months	12.9 months
Hansen et al. (1980)	110	40/20 12th week	9%	13%	NS	9.2 months	10.2 months
Jackson et al. (1983)	29	30/10 D1	0%	27%	<0.05	9.8 months	7.2 months
Maurer et al. (1980)	163	30/10 9th week	4%	18%	<0.01	8.4 months	8.8 months
Niiranen et al. (1989)	51	40/20 4th week	0%	26%	<0.05	13 months	10 months
Seydel et al. (1985)	217	30/10 D1	5%	21%	<0.005	53 weeks	52 weeks

CR, PCI given when patients are in complete remission; D1, PCI given on the first day of induction treatment; NR, not reported; LD, limited disease.

4.2.2.2 Second Generation of Randomized Trials: PCI in Complete Responders

In more recent randomized trials listed in Table 4.2.2, that have included only patients considered in complete remission, the rates of brain failure seem higher than in older trials probably because they are reported as actuarial and not as crude brain metastasis rates (Arriagada et al. 1995; Gregor et al. 1997; Laplanche et al. 1998; Ohonoshi et al. 1993; Wagner et al. 1996). The overall 2-year actuarial brain failure rates are 40% and 67%, respectively, in the trial reported by Arriagada and colleagues (1995), and 30% and 54% in the trial reported by Gregor and colleagues (1997). Even if there was a trend in favor of PCI, none of these more recent randomized trials were large enough to confirm statistically the survival benefit suggested in retrospective studies (Rosen et al. 1983; Rosenstein et al. 1992; Rubenstein et al. 1995; Work et al. 1996). A study reporting later results of the two French trials involving 505 patients did not show any difference in terms of survival either (Arriagada et al. 2002). Only the meta-analysis which will be discussed later could help clarify this issue.

4.2.2.3 Optimal Treatment Schedule for PCI

4.2.2.3.1 Dose–Response Relationship

Although the dose–response relationships for PCI in small cell lung cancer are fundamental to predicting the optimal treatment schedule, they have not been well established and there are no adequate prospective studies to evaluate the effects of total dose and/or fraction size in PCI. In most studies, the prescribed PCI dose is about 24–30 Gy with fraction sizes varying between 2 and 3 Gy. Only one randomized trial has directly addressed the issue of PCI dose (Gregor et al. 1997). The first part of the UKCCR-EORTC trial was a three-arm comparison, with two PCI dosages (24 Gy and 36 Gy) being compared to no PCI, and the higher dose was more effective in reducing the risk of brain metastasis. A trend for a dose–response relationship was also observed in the study of Work et al. (1996) which did not address the question of PCI dose directly.

Most importantly, a marked trend for a dose–response relationship was observed in the meta-analysis by Aupérin et al. (1999). The effect of PCI on

Table 4.2.2. Randomized trials evaluating PCI in small cell lung cancer complete responders included in the meta-analysis and results of the meta-analysis

Study	Number of patients	PCI dose Gy/fraction Timing of PCI	Brain metastases rate (%)		p Value	Median survival or survival at X years	
			PCI (+)	PCI (–)		PCI (+)	PCI (–)
Aroney et al. (1983)	29[a]	30/3	0%	36%	0.02	NR	NR
Arriagada et al. (1995)	300	24/8 CR	2-Year rate 40%	2-Year rate 67%	$<10^{-13}$	2-Year SR 29%	2-Year SR 21.5%
Gregor et al. (1997)	314	Various CR	2-Year rate 30%	2-Year rate 54%	0.00004	3-year SR 21%	3-year SR 11%
Laplanche et al. (1998)	211	24/8-30/10 CR	4-Year rate 44%	4-Year rate 51%	0.14	4-year SR 22%	4-year SR 16%
Ohonoshi et al. (1993)	46	40/20 CR	22%	52%	<0.05	21m	15m
Wagner et al. (1996)	31	25/10 CR	20%	50%	NS	15.3m	8.8m
Meta-analysis Aupérin et al. (1999)	987	Various	3-Year rate 33.3%	3-Year rate 58.6%	<0.001	3-Year SR 20.7%	3-Year SR 15.3%

CR, PCI given when patients are in complete remission; SR, survival rate; D1, PCI given on the first day of induction treatment; NR, not reported.

[a] Out of 172 patients evaluated and analyzed, only 29 patients achieving CR were randomized.

brain metastases increased with the total PCI dose when four dose groups (8 Gy, 24–25 Gy, 30 Gy, 36–40 Gy) were analyzed (trend $p = 0.02$). Hence the relative risk of developing brain metastasis as compared to the control group was respectively 24% in the 8 Gy group, 48% in the 24–25 Gy group, 68% in the 30 Gy group and 73% in the 36–40 Gy group, but the effect on survival did not differ significantly according to the dose. A dose–response relationship was also found in a review that collected data from 12 non-randomized studies and 12 randomized studies comparing brain relapse rates with and without PCI (Suwinski et al. 1998). The dose–response curve was almost linear within the dose range of 20–35 Gy.

If we have studies that have evaluated total dose effect, we also know from retrospective evaluations that the dose per fraction should be less than 3 Gy because of late radiation effects. The use of twice-daily treatments with a smaller dose per fraction and an interval between fractions of at least 6 h, could decrease the risk of late toxicity. A phase II trial has suggested recently that hyperfractionated PCI (30–36 Gy given in twice-daily 1.5-Gy fractions) was a well tolerated and effective PCI schedule (Wolfson et al. 2001). This dose schedule is being tested in a phase II/III randomized study led by the Radiation Therapy Oncology group (RTOG 0212).

4.2.2.3.2 Optimal Timing for PCI

The optimal timing for PCI in limited stage small cell lung cancer has also not been clearly determined. Even if PCI should be administered relatively early in order to avoid re-seeding of the brain, it has been recommended that it should be administered following documentation of complete remission, after 2–4 months but before 6 months from the start of chemotherapy (Lee et al. 1987). In the study of Lee et al. (1987), the overall incidence of brain metastasis was higher in patients who received PCI after five or six cycles of chemotherapy than in patients who received it after two or three courses of induction and maintenance chemotherapy. Only one small and rather old trial has directly addressed the issue of PCI optimal timing but was not conclusive (Perez et al. 1981). The incidence of brain metastases was 7% whether PCI was administered during the first week (early PCI group), or during the seventh week (late PCI group) .

The meta-analysis addressed the question of optimal timing in a subgroup analysis, and there was a trend (p=0.01) toward a greater effect of PCI on the incidence of brain metastasis in patients randomized within 4 months after start of induction treatment than in those randomized later (Aupérin et al. 1999). The recent study by Suwinski et al. (1998) has also made an interesting analysis of PCI dose response according to its timing. They showed that the delay between initiation of induction treatment and the start of PCI introduces a 20-Gy threshold in the dose–response curve which seems to be linear otherwise. Considering only studies where PCI was initiated less than 60 days after the first day of induction treatment, there was nearly a linear relationship between the given dose in 2-Gy fractions equivalent and the percentage reduction in total brain relapse rates within the range of 8–30 Gy. In the studies where PCI was initiated later, it looked as if higher doses were necessary to obtain the same prophylactic effect. Thus by increasing the delay between induction treatment and PCI, one possibly increases the burden of metastatic disease to the brain.

4.2.3 Meta-analyses of Prophylactic Cranial Irradiation

A meta-analysis collecting individual data from seven trials including a total of 987 patients randomized from 1977 to 1995, comparing PCI to no PCI in patients with small cell lung cancer in complete remission was consecutively performed, the primary endpoint being overall survival (Aupérin et al. 1999). The results showed that PCI led to a 5.4% increase in the 3-year survival rate (from 15.3% observed in the control group to 20.7%). Therefore PCI not only decreases, significantly, the risk of developing brain metastases (from 58.6% to 33.3% at 3 years) as proven in other individual trials, but also improves overall survival and disease-free survival.

Meert et al. (2001) recently published a systematic review of the literature with meta-analysis, including 12 published trials (1547 patients) which randomly assigned patients to receive PCI or not. Whereas the meta-analysis of Auperin et al. (1999) included only trials addressing the question of PCI in complete responders, out the 12 selected trials by Meert et al. (2001), five included exclusively complete responders, five included patients where PCI was eventually administered at initiation of chemotherapy, and two included patients given PCI as consolidation treatment whatever the response status. As expected, PCI significantly decreases brain metastases incidence

when all studies are considered with a hazard ratio of 0.48 (95% CI, 0.87–1.02). However, in the Meert et al. (2001) study, PCI improved survival significantly only among complete responders; the hazard ratio being then 0.82 (95% CI, 0.71–0.96). When all studies were considered, the hazard ratio was 0.94. The authors conclude that PCI can only be recommended in complete responders documented by a work-up including brain CT scan.

4.2.4 Neurotoxicity of Prophylactic Cranial Irradiation

4.2.4.1 Retrospective Studies

The meta-analysis by Aupérin et al. (1999) showed that PCI influences long-term survival of patients who achieve a complete response to therapy. However, several studies have reported neurologic and intellectual impairment and abnormalities on brain CT scan potentially related to PCI that could be of concern to clinicians (Catane et al. 1981; Craig et al. 1984; Crossen et al. 1994; Frytak et al. 1989; Johnson et al. 1985, 1990; Laukkanen et al. 1988; Lee et al. 1986; Lishner et al. 1990; Twinjstra et al. 1987). Neurological evaluation is difficult and some research suggests that neuropsychologic impairment in this subset of patients may be attributable to the disease process itself rather than treatment exclusively; furthermore, age, effects of chronic cigarette abuse, possible paraneoplastic syndromes, and micrometastases may also contribute to neurotoxicity (Erlington et al. 1991; Hill 1989; Komaki et al. 1995; van Oosterhout et al. 1996a). Baseline evaluations are lacking in most of these retrospective studies. Thus, PCI is probably only in part responsible for the leukoencephalopathy that can be observed and neurotoxicity seems dependent on total dose, dose per fraction, timing of chemotherapy (concomitant with PCI), and type of chemotherapy.

This contributed largely to the controversial issue of PCI, neurotoxicity being the major argument against PCI, especially in the absence of demonstrable improvement in survival before the meta-analysis results. Most data on late neurotoxicity are based on small retrospective studies with variable protocols of PCI and chemotherapy regimens: ataxia, seizures, and even dementia have been reported (Catane et al. 1981; Craig et al. 1984; Crossen et al. 1994; Frytak et al. 1989; Johnson et al. 1985, 1990; Laukkanen et al. 1988; Lishner et al. 1990; Twinjstra et al. 1987). Brain CT scan abnormalities are common: cerebral atrophy, ventricular dilatation, periventricular and subcortical white matter changes, which may progress after treatment is finished (Johnson et al. 1985, 1990). However these abnormalities do not always correspond with altered neuropsychological functioning. The abnormalities observed affect indeed white matter and it is not certain if the underlying white matter disease is caused by a primary demyelination, an endarteritis of the microcirculation, or both (Crossen et al. 1994). As suggested by Johnson et al. (1985, 1990), patients who were given chemotherapy during the time of cranial irradiation or large radiotherapy fractions (more than 3 Gy) were more likely to have abnormal neuropsychologic tests and have abnormal mental status examinations.

Difficulty in analyzing these retrospective studies derives from the fact that PCI has often been delivered with chemotherapeutic agents with a potential to contribute to neurotoxicity either by synergism with PCI or by independent mechanisms. Several studies have reported that the combined combination of PCI and concomitant CT has a negative impact on neuropsychologic functioning. Van Oosterhout et al. (1996b) reported neurological sequelae in a series of 51 long-term SCLC survivors who were treated with chemotherapy alone (group 1), with sequential PCI (group 2) or with concurrent chemotherapy and PCI (group 3). They concluded that there was no statistical evidence for additional neurotoxicity of PCI. However, they could observe marked neuropsychometric differences between patients and matched controls, so that cognitive impairment may be partly related to disease, but also to deteriorated physical condition and emotional distress (van Oosterhout et al. 1996b). In a smaller retrospective study, Komaki et al. (1995) evaluated thoroughly the magnitude of neuropsychologic deficits in 30 patients with small cell lung cancer who had PCI, pointing out the importance of baseline evaluations. Almost all patients with favorable responses to combination chemotherapy had specific cognitive deficits before receiving PCI (29 out of 30 patients). A recent study by Cull et al. (1994), also reported neurological and cognitive impairment in 64 long-term survivors ($\geq$2 years). By using validated scales of toxicity and performance status, they reported that 75% of these patients had no significant deterioration of neurocognitive functions, 11% had cognitive deficits, and 16% had ataxia that could be attributed to PCI . These data contrast with those reported in older studies where up to

85% of patients were found to have clinically detectable neurological problems (Johnson et al. 1985). Neurological evaluation is difficult in this subset of patients and there may be a wide variety of conclusions as to the possible morbidity of PCI in all of these retrospective studies or very small prospective evaluations. In some studies patients with brain metastases would be analyzed with patients having PCI, in others PCI would be given concomitantly to chemotherapy; furthermore, patients often present symptoms of depression or anxiety that may interfere with neuropsychological evaluations; age, effects of chronic cigarette abuse, possible paraneoplastic syndromes, and micrometastases may also contribute to neurotoxicity (Erlington et al. 1991; Hill 1989; Komaki et al. 1995; van Oosterhout et al. 1996a).

4.2.4.2 Prospective Evaluation of Neurological Functions

We know from the results of all these studies the importance of pretherapeutic assessment and that the use of PCI alone, without concomitant chemotherapy and lower fractionation schedules (<3 Gy), does not seem to cause significant long-term neurotoxicity. This is confirmed by the results of two recent prospective trials that have included a neurological assessment in their study (Arriagada et al. 1995; Gregor et al. 1997). Several patients had an initial neuropsychological examination (before PCI would possibly be administered) that was abnormal (40%–60%). The results within the first years of follow-up did not show any significant difference in neuropsychological modifications between treated and untreated patients in both studies. These results have been confirmed with longer follow-up; however, there is a non-significant memory deterioration in the PCI group (Le Péchoux et al. 2003). The only prospective study that showed significant neurocognitive deterioration was the CALGB study that used concurrent chemotherapy and brain irradiation. This study recently evaluated the psychologic and neuropsychologic functioning of 347 patients with limited disease who were randomized to intensive chemotherapy, thoracic radiation, and PCI with or without warfarin (Ahles et al. 1998). All patients had PCI given concomitantly with chemotherapy. Emotional distress was measured by the POMS (profile of mood states) and cognitive functioning was assessed using the Trail Making B Test at baseline before any treatment, after completion of intensive chemotherapy, and after the completion a different regimen of chemotherapy administered concomitantly to PCI. POMS scores remained stable over the course of treatment but there was a significant change of neurocognitive functions over the course of treatment suggesting that the combination of chemotherapy and PCI had a negative impact on cognitive functioning. Therefore, the use of PCI without concomitant chemotherapy and lower fractionation schedules (<3 Gy) should be considered for all patients in complete remission.

4.2.5 Conclusion

Several studies in the past 20 years have reported a lower incidence of brain metastases with PCI, thereby reducing the risk of the associated morbidity and social consequences of brain failure. If recent trials have shown that brain metastases really could be prevented and not just delayed with PCI in complete responders, the meta-analysis has now demonstrated that PCI leads to a 5.4% increase in the 3-year survival rate (from 15.3% observed in the control group to 20.7%). This benefit on overall survival can be added up to the effect of thoracic radiotherapy which has about the same value.

The selection of an optimal dose for PCI that would lead to a further decrease in brain metastasis incidence with minimal toxicity is one of the challenges raised by the meta-analysis as well the ideal timing of PCI. There is an ongoing international trial addressing the question of dose effect for the prevention of metastases in patients with limited disease who achieved a complete response. It compares a standard dose of 25 Gy in 10 fractions to a higher dose of 36 Gy (36 Gy/18 fractions or 36 Gy in 24 twice-daily fractions) (Le Péchoux et al. 2000). In order to evaluate whether dose escalation results in higher cerebral control rates and to evaluate its impact on neurological functions, all patients have a baseline radiological evaluation as well as a quality of life and clinical evaluation at baseline before PCI, 6 months after PCI, and then yearly. A phase II/III RTOG trial has also recently been activated comparing conventional fractionation (36 Gy in 18 fractions) to hyperfractionated accelerated radiotherapy (36 Gy in 24 twice-daily fractions). All patients will have a neurocognitive assessment in their follow-up.

Even if there are questions left concerning the optimal dose and fractionation of PCI as well as the optimal timing, there is level 1 evidence that prophy-

lactic cranial irradiation is effective. It should now be considered as part of the standard treatment of patients with small cell lung cancer in complete remission.

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5 Radiation Therapy for Recurrent Lung Cancer

Branislav Jeremić and Michael Bamberg

CONTENTS

5.1 Introduction

The treatment of choice for early stages non-small cell lung cancer (NSCLC) is surgery (Mountain 1986, 1997; Naruke et al. 1988). This treatment modality may also be successfully applied in selected patients with stage IIIA (Mountain 1986, 1997; Naruke et al. 1988). While there is an increasing possibility of detecting early stage tumours with the use of positron emission tomography, there is also an increasing possibility of using induction (neoadjuvant) chemotherapy and surgery in selected cases of locally advanced NSCLC (Pass et al. 1992; Rossell et al. 1994; Roth et al. 1994). It is anticipated, therefore, that not only will more patients be undergoing surgery alone or combined with chemotherapy in the future than before, but that these patients will be more likely to have the stage of the disease defined during pretreatment investigation. Also, a number of patients with non-metastatic lung cancer are offered either radiation therapy alone or a combination with chemotherapy. They also experience disease recurrence in high percentage of cases.

Locoregional recurrence is a well-documented event in the history of lung cancer. As the first site of failure, it was documented in surgical series in as low as 3%–9 %, but also as high as 32% or even 38% (Holmes et al. 1986; Immerman et al. 1981; Ishida et al. 1990; Kaiser et al. 1989; Ludwig Lung Cancer Study Group 1987; Matthew et al. 1973; Spjut and Mateo 1965; Thomas and Rubinstein 1990). When, however, more intensive follow-up procedures after an initial operation are carried out, this rate may go as high as 52% as in one series (Westeel et al. 2000). It is, therefore, not surprising that after curative resection, 5-year survival can be as high as 54%–83% for stage I squamous-cell carcinoma but as low as 10%–21% for stage IIIA adenocarcinoma (Holmes 1988; McGovern et al. 1988). Also in non-surgical studies, radical radiation therapy alone or combined with chemotherapy achieved only about 15% local control, as assessed by bronchoscopy (Arriagada et al. 1991).

Thus recurrence is still a dominating and bitter event after the treatment of lung cancer, irrespective of histology (non-small cell versus small cell), stage (early versus locally advanced versus metastatic), or initial treatment (surgery, radiation therapy, chemotherapy or any combination of these). While some failures are reported to appear soon after the initial treatment, some manifest years later. All recurrences can be broadly divided into local (e.g. bronchial stump recurrences only or thoracic wall), regional (e.g. mediastinal lymph node), and distant (brain, liver, bones or contralateral lung). Again, any combination of these may occur in a patient.

Since some recurrences may appear in lung parenchyma (ipsilateral or contralateral lung), it is important to recognise the distinct features of the second primary metachronous primary lung cancer as opposed to lung parenchyma recurrence occurring after the initial treatment. A second primary metachronous lung cancer appears after an initial treatment of the primary lung cancer and a particular set of criteria is

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considered necessary to differentiate second primary lung cancer from recurrent or metastatic lung cancer (Martini and Melamed 1975). A tumour was considered a second primary if it: (1) had different histology, or (2) had the same histology as the initial lung cancer but if: (a) the disease-free interval between the occurrence of cancers was at least 2 years, (b) the second cancer originated from a carcinoma in situ, or (c) the second cancer was in a different lobe or lung, but neither cancer was in lymphatics common to both cancers, nor extrapulmonary metastases were found at the time of diagnosis. This entity will not be discussed in this chapter.

As recurrence may appear after any of the treatment modalities used in lung cancer (surgery, radiation therapy, chemotherapy) or any combination of these, recurrences can also be treated by any of these. Patients with isolated intrathoracic recurrence have been treated with different approaches, including a more aggressive surgical approach (Gabler and Liebig 1980; Matthew et al. 1973) or endobronchial irradiation (Hilaris et al. 1979). Photodynamic therapy was shown to be ineffective in this patient population, especially those with bronchial stump recurrence. In a series by Lam (1994), as many as 75% of patients with bronchial stump recurrence re-recurred after photodynamic therapy, despite achieving an initial response. When several large surgical series are taken into account together (Gabler and Liebig 1980; Dartevelle and Khalif 1985; Watanabe et al. 1992; Voltolini et al. 2000), it can be observed that in more than 6000 patients recurring locally, re-operation with curative intent was managed in 1%–1.7% of patients. Results with re-operation were mostly discouraging such as 23% with 2-year survival (Pairolero et al. 1984). The median survival times (MST) ranged from 7–26 months (Becker et al. 1990; Lesser et al. 1997; Voltolini et al. 2000; Westeel et al. 2000). More recent studies reported more promising results such as 15.5% 5-year survival obtained, however, in a smaller patient population (n=12) (Voltolini et al. 2000). In early stages of recurrent lung carcinoma even higher local control and overall survival rates can be achieved by completion pneumonectomy, with 5-year survival of about 50% in stage I and 40% in stage II carcinoma (Regnard et al. 1999), although patient cohorts included those with second primary lung cancer. The poor results of some studies clearly warrant newer strategies, which may include more intensive follow-up procedures, as well as alternative treatment approaches.

There are also reports (Curran et al. 1992; Emami et al. 1997; Green and Kern 1978; Jeremic et al. 1999b; Kagami et al. 1998; Kono et al. 1998; Kopelson and Choi 1980; Law et al. 1982; Leung et al. 1995) indicating the effectiveness of radiation therapy when given as a sole treatment. Since these reports covered long periods of time during which great variance in the diagnostic and radiotherapeutic approaches occurred, including a number of different recurrent tumour locations, these reports, unfortunately, suffer from a mixture of potentially different entities frequently treated with a wide range of doses and different fractionation patterns. Radiation therapy was sometimes also combined with chemotherapy (Itoh et al. 2002) or brachytherapy. All of these factors contributed to a confusing picture of the use of external beam radiation therapy in this disease, in spite of the fact that some reports clearly indicated the effectiveness of external beam radiation therapy with results showing at least similar effectiveness to those obtained with surgery.

In this chapter, we will focus on the use of radiation therapy in the treatment of locoregionally recurrent lung cancer.

5.2 External Beam Radiation Therapy for Locoregional Post-Surgical Recurrences of Non-Small Cell Lung Cancer

In contrast to surgery, which has been exclusively used to treat post-surgical recurrences, radiation therapy has been used to treat both those recurrences occurring after initial surgery and after previous radiation therapy. When used for post-surgical recurrences, the aim of radiation therapy was to treat local/regional recurrences located at various intrathoracic sites. These were usually divided into chest wall/pleural, parenchymal, bronchial stump, and mediastinal lymph node recurrences, but could include any combination of these.

It seems that the history of radiation therapy in treating *locoregional post-surgical recurrences of non-small cell lung cancer* starts with the first report by Green and Kern (1978) on 46 patients with local recurrence without documented metastasis. Low doses were those which ranged from 2500–3999 cGy and while high doses were those which ranged between 4000 and 6500 cGy. Subjective improvement was observed in about 2/3 of patients, improvement being dose-related. The median survival time was 11 months with a 4-year survival rate of 4%. The median survival time for patients in the high dose group

responding to radiation therapy was 19 months, which was in sharp contrast to those radically treated with radiation therapy and having no response (8 months), or those treated with the low dose radiation therapy (4 months). The impact of response to radiation therapy on treatment outcome was also documented by Yano et al. (1994). In their study, high local control rates and higher overall survival were achieved if the tumour responded to radiation treatment (the median survival time, 27 months vs. 6 months for responders and non-responders, respectively).

Also, several other reports indicated effectiveness of radiation therapy alone in treating locoregionally recurrent lung cancer. Kopelson and Choi (1980) reported on 24 patients with a median survival time of 12 months and 5-year survival of 10%. Shaw et al. (1992) reported on a series of 37 patients, the majority of whom were treated with 40 Gy in 10 fractions using the split-course technique. The median survival time was 13.7 months and 5-year survival was 4%. It is likely that somewhat lower local control rates and lower 5-year survival in that study resulted from the inclusion of patients with hilar, mediastinal and even supraclavicular lymph node recurrence (57% of the patients had stage IIIA and 22% had stage IIIB disease at the time of recurrence). In the study of Curran et al. (1992), who reported on 37 patients treated with external beam RT to a median dose of 56 Gy, the median survival time was 12 months and 2-year survival was 22%. Also, Leung et al. (1995) reported on 45 patients who achieved the median survival time of 10 months and 2-year survival of 27%. The radiation dose played an important role: there was a significant difference between patients treated curatively (n=17) and those treated with palliative intent (n=28) (median survival time: 15.6 vs 4.0 months, respectively; p=0.02). Patients whose recurrence was confined to the bronchial stump had a better median survival time than those with other sites of relapse (15 months vs. 9 months), and patients treated with radical intent (total dose >50 Gy) did well with an estimated 2-year survival of 41%. A similar effect of higher radiation disease was also observed in the study of Emami et al. (1997) who reported on 52 patients treated with radiation therapy doses that ranged from 16 Gy to 75 Gy with 15 (29%) patients receiving >60 Gy. The 5-year survival was 4%, with the median survival time of 8.5 months, when all patients were considered, with a significantly better response obtained with increased dose of radiation therapy (p=0.02). More recently, Kagami et al. (1998) reported on 32 patients treated within a hypofractionated schedule of a daily dose of 2.5 Gy, four times per week with total radiation therapy doses that ranged from 47.5 Gy to 65 Gy. There were 25 patients who received ≥60 Gy. The median survival time was 14 months, and 5-year survival was 12.5%. More recently, Jeremic et al. (1999b) observed a 5-year survival rate of 14% with the median survival time of 18 months in a group of patients harbouring a variety of post-surgical locoregional recurrences of non-small cell lung carcinoma.

Of all locoregional recurrent tumour locations, high-dose radiation therapy proved to be particularly effective in patients with bronchial stump recurrences. In the study by Law et al. (1982), the investigators reported on their experience with post-surgical bronchial stump recurrence only. A total of 14 patients were irradiated, three by bronchoscopic implantation of radioactive gold grains and 11 by external beam radiation therapy. Three patients were not irradiated (two with extension to tracheal wall and one with extension into the contralateral main bronchus) and they survived for 4, 8, and 10 months, respectively. Of irradiated patients, those confined to stump alone reported 5-year local control of 100%, overall survival of 50%, and cause-specific survival of 83%. In contrast, in cases of more extensive tumours (n=8) survival ranged from 11 to 46 months.

Curran et al. (1992) treated a total of 37 patients with post-surgical recurrences with external beam radiation therapy. There were 25 nodal recurrences, four in the chest wall/pleura, while eight patients had isolated bronchial stump recurrence. The treatment field encompassed all known disease, without chemotherapy or radiation sensitisers. When analysed according to the site of recurrence, patients with bronchial stump recurrence did better than those with either nodal or chest wall recurrences (median survival time: 36 vs 9 vs 7 months, respectively; 2-year survival: 50% vs 18% vs 0%, respectively). Of the eight patients with bronchial stump recurrence, four experienced no further evidence of lung cancer. In contrast, no patient with chest wall recurrence survived 2 years. In patients with bronchial stump recurrences locoregional recurrence was found in 75%, while distant metastasis was found in the remaining 25%.

In the study of Leung et al. (1995), for ten patients with bronchial stump recurrences the median survival time was only 15 months and 3-year survival was 20%. This was not significantly different from the results obtained in patients with recurrences elsewhere (median survival time: 9 months), which the authors attributed to the fact that 8 (80%) of the 10 patients with local recurrence confined to the bronchial stump were treated with radical intent

compared with 9 (26%) of the 34 patients with local recurrence elsewhere (p=0.007).

In the study of Kagami et al. (1998) the treatment fields covered the clinical gross tumour with adequate margins. Ten patients had bronchial stump recurrence alone, 14 bronchial stump with mediastinal and/or supraclavicular lymph node recurrence, while eight patients had nodal recurrence only. When bronchial stump recurrences only were considered separately, the median survival time was 15 months and 3- and 5-year survival were both 30%. This was significantly better than results achieved in those with combined stump and node recurrences (median survival time: 8 months), with patients with node recurrence only having a prognosis similar to that of stump recurrences only (median survival time: 14 months)(Cox-Mantel test, p<0.05).

Kono et al. (1998) reported on 46 patients with post-surgical intrathoracic recurrences which included 18 cases of bronchial stump recurrences. Of the latter, five patients had bronchial stump recurrence only, while 13 patients had combined bronchial stump and mediastinal lymph node recurrences. The delivered dose ranged from 45 to 80 Gy and 19 patients also underwent chemotherapy. All patients with bronchial stump recurrence received doses of ≥60 Gy. For five patients with bronchial stump recurrence only, radiation therapy fields covered the recurrent mass and mediastinum, including the ipsilateral hilum and subcarinal area as well as the superior mediastinum, but excluding the supraclavicular fossa and contralateral hilum. Overall 2- and 5-year survival rates were 17% and 11%, respectively, with the median survival time being 10 months for the whole group. For the group with bronchial stump recurrence alone, median survival time was 20.9 months and 3-year survival was 20%, which was very similar to the results achieved in the stump plus node group of patients (3-year survival: 15.9%). There was no difference between the groups of patients treated with 45–60 Gy and those treated with >60 Gy, probably due to a small patient number treated with high dose external beam radiation therapy. Analysis of patterns of failure in five patients with bronchial stump recurrence only revealed that only one patient failed within the radiation therapy field (accompanied by distant failure), another failed only distantly, while two patients died of other causes. One patient was alive and disease-free at the time of the report. No impact of chemotherapy was observed in this study (p=0.5695).

In the study by Jeremic et al. (1999b) patients with this location had the median survival time of 38 months, and 5-year survival of 33%. Contrary to that, only one out of 27 patients with nodal recurrence remains alive with no evidence of the disease for >5 years post-radiation therapy (p=0.0004). Patients with combined stump and nodal recurrences (p=0.0020) and those with chest wall/pleura (p=0.0054) did particularly poorly, all of them dying by the second year post-radiation therapy, confirming previous observations about their incurability (Ludwig Lung Cancer Study Group 1987; McGovern et al. 1988).

When we pooled the data on bronchial stump available in the literature (Jeremic and Bamberg 2002), in 54 documented cases with no other intrathoracic component, the median survival time was estimated to be approximately 28.5 months and the 5-year survival to be about 31.5%, results which clearly establish external beam radiation therapy as a treatment of choice in this patient population (Table 5.1). Two studies, however, showed somewhat inferior results for patients with recurrences located at bronchial stump only. In the study by Leung et al. (1995), the median survival time of 15 months is likely to be the effect of the fact that two out of ten such patients were treated with 30 Gy in 10 daily fractions, with an accompanied finding that in the whole cohort of patients in that study, radically treated patients achieved significantly better survival than those treated palliatively (p=0.02). Similarly, in the study of Kagami et al. (1998), besides a wide range of doses used (47.5–65 Gy), a total of seven out of 32 patients received less than 60 Gy. This was an important finding in the study which observed significantly better response on increasing the radiation therapy dose. Also in another study (Kono et al. 1998), this may have well been the reason for overall poorer survival for the whole group of patients with locoregional recurrences (1997) where doses of ≤50 Gy were used in one-third of patients. Unfortunately, it is very difficult to draw firm conclusions about the effect of dose because in some studies (Jeremic et al. 1999b; Kagami et al. 1998; Leung et al. 1995) lower doses of radiation therapy have been used because of tumour volume or poor performance status, both of which might well determine the outcome.

Further evidence of the effectiveness of external beam radiation therapy in this patient population relates to a small (n=7) subset of "early" (i.e. stage I: /T2N0) bronchial stump recurrences in the study of Jeremic et al. (1999b) which achieved excellent survival (5-year: 57%) with high-dose external beam radiation therapy (≥60 Gy). Indeed, in a very small and highly selected patient population, these results

Table 5.1. Outcome of patients with bronchial stump recurrence treated with external beam radiation therapy

Author	Location	*n*	RT Total dose (cGy)/*n* of fx	MST (months)	Survival (%)				
					1-year	2-year	3-year	4-year	5-year
Law et al. (1982)[a]	Stump only	6	5000–6100/25–35	>60	83	83	83	83	50
	Stump/extension[b]	8[c]	5000–6100/25–35	19	75	37.5	12.5	0	0
Curran et al. (1992)	Stump only	8	5600 Gy[d]/25–31	36		50			
Leung et al. (1995)	Stump only	10	3000–6000[e]	15	60	40	20	10	10
Kagami et al. (1998)	Stump only	10	4750–6500/19–24	14	80	30	30	30	30
	Stump/mediastinal nodes	14	4750–6500/19–24	8	36	21	7	7	0
Kono et al. (1998)[f]	Stump only	5	≥6000	21		60	40	20	
	Stump/mediastinal nodes	13	4500–8000	5.5		32	16	16	
Jeremic et al. (1999b)[g]	Stump only	15	5500–6000/26–30	38	93	73	60	33	33
	Stump/lymph-nodes	5	5500–6000/26–30	16	80	0	0	0	0
Pooled data	Stump only	54		28.5	81.5%	55%	40%	30%[h]	31.5%[h]

RT, radiation therapy; MST, median survival time; fx, fractions.
[a] Includes three patients not irradiated and three patients who received bronchoscopic implantation of radioactive gold grains.
[b] Extensions into main bronchus, lateral tracheal wall or contralateral principal bronchus.
[c] Three additional patients not irradiated.
[d] Median delivered dose.
[e] Two patients treated with 30 Gy in 10 daily fractions.
[f] All patients with stump recurrences treated with ≥60 Gy.
[g] Data for patients treated with 55–60 Gy.
[h] Due to small patient numbers.

are approaching those obtainable with surgery alone in newly diagnosed non-small cell lung cancer of the same stage (Mountain 1986; Naruke et al. 1988). An interesting and still unexplained fact is that their survival seems much better than that of patients with newly diagnosed non-small cell lung cancer of a similar stage when treated with high-dose standard or hyperfractionated radiation therapy (Ono et al. 1991; Morita et al. 1997; Jeremic et al. 1997, 1999a; Sibley et al. 1998; Hayakawa et al. 1999).

The findings of the study by Law et al. (1982) who also provided the data on such patients having a "more extensive" bronchial or tracheal component of the disease further support the effectiveness of external beam radiation therapy in bronchial stump recurrence. These patients achieved the median survival time of 19 months and 1- and 3-year survival rates of 75% and 12.5%, respectively, showing that more extensive, but still localised (no nodes present) disease may also benefit from radiation therapy. On the other hand, three patients with "more extensive" bronchial stump recurrence not treated with external beam radiation therapy survived for only 4, 8, and 10 months, respectively. When stump recurrence was accompanied with other sites, such as nodes, inferior survival was clearly documented (Curran et al. 1992; Jeremic et al. 1999b; Kagami et al. 1998; Kono et al. 1998). Taken together, these data indicate high efficacy of external beam radiation therapy which seems to be limited to a very selected population of patients with small recurrence, and no accompanying lesions in the thorax and other extrathoracic sites.

There seems to be a dose-response effect in bronchial stump only recurrences as well as probably in the whole group of patients with locoregional post-surgical recurrences. While some did not enable such evaluation (Curran et al. 1992; Kopelson and Choi 1980), the majority of studies unequivocally showed that higher doses enable better response (Kagami et al. 1998; Law et al. 1982; Leung et al. 1995) and better local control (Jeremic et al. 1999b), leading to better survival (Jeremic et al. 1999b; Leung et al. 1995). However, the "optimal" dose level for bronchial stump recurrence remains imprecisely

defined. Available evidence in non-small cell lung cancer seems to suggest that the dose necessary for tumour control should be at least 60 Gy, and preferably 65–70 Gy with standard fractionation. Some of the studies reported herein, however, also used 55 Gy, described as "high" dose level, which may not be high enough for permanent tumour control, regardless of recurrent tumour stage. This particular dose may actually be one of the reasons for the inferiority of the overall results in studies which grouped patients receiving it with those receiving 60 Gy or more. In the study of Jeremic et al.(1999b) patients treated with 55 Gy tended to have worse survival than those treated with 60 Gy (median survival time: 20 vs. 13 months; 5-year survival: 16% vs. 0%; p=0.31), which would probably have reached significance if more than only four patients treated with 55 Gy would have been encountered. Additionally, patients with larger tumours are usually administered palliative therapy, whereas those with less advanced disease are approached with higher doses. The dose-effect could, therefore, be, at least in part, a consequence of tumour size and not just of the dose itself.

It is interesting to observe a similar incidence of local failure after external beam radiation therapy in the majority of these studies, when all patients with post-surgical recurrences are considered. While Kopelson and Choi (1980) observed local failure in 48%, both Shaw et al. (1992) and Leung et al. (1995) in 64% and Kagami et al. (1998) in 66%, Curran et al. (1992) observed it in 57% patients, an identical finding to that of Jeremic et al. (1999b), showing that the primary pattern of failure in this patient population remains local. Another consistent finding was that there was no difference between the various locations of locoregional recurrences (e.g. stump vs. other). It is unknown which (if any) particular biological property leads bronchial stump and other post-surgical locoregional recurrent tumours to recur locoregionally. This finding remains to be investigated in future studies because, together with the results obtained with external beam radiation therapy to doses ≥60 Gy (especially in stump recurrences), it may indicate a possibility for dose escalation which should nowadays be easier to achieve by using three-dimensional treatment planning and conformal RT. To further extend this, some (Yano et al. 1994) noted that the subsequent appearance of metastatic disease did not affect the survival time after local recurrence, implying the crucial importance of locoregional spread of the disease and its control, even if temporary.

Another issue not well defined is the "optimal" treatment field. Owing to the long time periods, it frequently varied not just between institutions, but also intra-institutionally, ranging from local fields with wide margins to prophylactic inclusion of nodal areas thought to be at risk. Due to the lack of knowledge of precise biological behaviour of these recurrent tumours and treatment inconsistencies, suggesting one approach or another regarding the treatment fields remains purely speculative. However, the "local" nature of these recurrences, both post-surgery and post-radiation therapy, could favour the use of more "localized" radiation therapy fields, the precise definition of which remains to be investigated in the future.

A number of potential factors influencing survival were examined. Unfortunately, the results are conflicting and multivariate analysis which could have helped to indicate if any of these factors may be considered are lacking. Some of these factors such as the time from initial surgery to documented recurrence or histology may indicate different biological behaviour of these tumours, while others such as age, performance status, weight loss, stage or presenting symptoms may indicate that there is a need for a different approach or modification of the intent of administered radiation therapy.

While in the vast majority of studies chemotherapy was not used (Curran et al. 1992; Emami et al. 1997; Jeremic et al. 1999b; Kagami et al. 1998; Kopelson and Choi 1980; Law et al. 1982; Leung et al. 1995), in some it was given (Green and Kern 1978; Kono et al. 1998; Yano et al. 1994) and in none was it shown that it contributes to the overall effect of radiation therapy alone. Its role, at present, remains outside the major focus of interests, except perhaps if given as a radioenhancing agent (e.g. low-dose, protracted administration during the radiation therapy course).

Curative, high-dose (≥60 Gy) radiation therapy can be recommended as an effective treatment in patients with isolated locoregional recurrent non-small cell lung cancer, particularly if located at the bronchial stump after curative resection. In the latter cases, it can produce the median survival time of approximately 30 months and 5-year survival of approximately 30%. However, further studies with high-dose external beam radiation therapy which may help clearly define a subset of patients most likely to benefit from this approach, similar to newly diagnosed non-small cell lung cancer, are warranted. It is necessary to distinguish between these as well as to address numerous questions in both patients with bronchial stump and other post-surgical recur-

rences after complete resection in non-small cell lung cancer. Then, patients not suitable for a curative approach, mostly those with other than stump or stump plus other intrathoracic recurrence may appropriately be treated with a palliative approach. Although prospective studies will be difficult to perform given the small number of eligible cases, they are urgently needed.

5.3 External Beam Radiation Therapy for Local/Regional Intrathoracic Recurrences After Previous Radiation Therapy

External beam radiation therapy was also used to treat *local/regional intrathoracic recurrences after previous radiation therapy* for lung cancer, mostly non-small cell histology. Feasibility and efficacy of re-irradiation was clearly documented in several reports on treatment of recurrent lung cancer (Green and Melbye 1982; Jackson and Ball 1987; Montebello et al. 1993; Gressen et al. 2000; Okamoto et al. 2002). These studies were retrospective in nature with inherent bias including patients with post-surgical relapses, postoperatively irradiated patients, those with metastasis and those with second primary lung cancer. Doses of the initial course of radiation therapy ranged from 25 Gy to 80 Gy, while those administered at the time of recurrence ranged from 6 Gy to 70 Gy. Therefore, cumulative doses ranged from 43 Gy to 150 Gy. Few patients underwent even a third course of radiation therapy (second re-irradiation). Contrary to radiation therapy treatment portals used during the initial course of radiation therapy, which usually included more or less uninvolved (prophylactic) nodal regions, those used at the time of re-irradiation were obviously limited, in general only including visible recurrence with a safety margin of 1–2 cm (Green and Melbye 1982; Jackson and Ball 1987; Montebello et al. 1993; Gressen et al. 2000; Okamoto et al. 2003). Fear of excessive toxicity, primarily that which may have occurred in lung and spinal cord, clearly governed the choice of both total dose and treatment field used during the re-irradiation. Symptom relief was the main goal of re-irradiation. In a comprehensive review from the year 2000 (Gressen et al. 2000), clinical data from original articles were summarised, indicating a control of hemoptysis in 83%, cough in 65%, dyspnea in 60% and pain in 64% of cases. Re-irradiation seemed to be less hazardous than anticipated with a mere 5% complication rate (Green and Melbye 1982; Jackson and Ball 1987; Montebello et al. 1993; Gressen et al. 2000; Okamoto et al. 2003). The most frequent event was radiation pneumonitis appearing in 3% of cases, with radiation myelopathy and rib fracture being a rare event. Although a higher incidence of radiation pneumonitis was noted in the recent study (Okamoto et al. 2002), described as grade 2 (moderate) and occurring after cumulative RT doses of 12–150 Gy, in that study (Okamoto et al. 2002), a somewhat different policy was instituted resulting not only in symptomatic, but also asymptomatic patients being re-irradiated. This has given the authors an opportunity to use higher radiation therapy doses. Patients received a median radiation therapy dose of 45 Gy. While symptomatic response in earlier studies ranged from 48% to 72% with an average cumulative dose of 30 Gy (Green and Melbye 1982; Jackson and Ball 1987; Montebello et al. 1993; Gressen et al. 2000), in that study (Okamoto et al. 2002), palliation was achieved in 75%. Again, this may indicate that higher doses may lead to a higher palliation rate at no cost of increased high-grade ($\geq$3) radiation pneumonitis. Indeed, whereas earlier reports achieved the median survival time of approximately 5 months (Green and Melbye 1982; Jackson and Ball 1987; Gressen et al. 2000), this study (Okamoto et al. 2002), reported on the median survival time of 8 months and a 2-year survival of 27%, being as high as 15 months and 51%, respectively, for patients treated with curative intent and higher radiation therapy doses. Of additional importance was the fact that no difference in the treatment outcome between patients <70 years and those $\geq$70 years was observed (Gressen et al. 2000), indicating greater applicability of external beam radiation therapy in this disease, in particular when palliative intention is pursued and when severe late effects become less important. Finally, the most recent study of Kramer et al. (2004) confirmed this observation, using 2 fractions of 8 Gy given with a 1-week split, a practical and comfortable regimen for both patients and hospitals. The median survival time was 5.6 months and 71% of patients had partial or complete relief of one or more of their symptoms. Relief of dyspnea, hemoptysis, and cough was observed in 35%, 100% and 67%, respectively. The Karnofsky performance status score improved in 45% patients. The overall median duration of symptom relief was 4 months.

A recent study by Wu et al. (2003) was the first ever to address the issue of re-irradiation of locoregionally recurrent lung cancer after previous external

beam radiation therapy through a prospective phase I–II study. Of a total of 23 patients in that study (age range, 43–79 years; median age, 68 years), there were nine patients with squamous cell carcinoma, seven with adenocarcinoma and seven patients with small-cell carcinoma. Initial tumour staging included stage II in seven and stage III in 16 patients. The interval between the first course of RT and recurrence varied from 6 to 42 months (median, 13 months). While the median dose of the first course of RT was 66 Gy (range, 30–78 Gy), re-irradiation was carried using a 3D-CRT to deliver a median dose of 51 Gy (range, 46–60 Gy), using standard fractionation, to a radiographically visible recurrent lesion. After re-irradiation, the median survival time was 14 months and the 2-year survival rate was 21%, while 2-year locoregional progression-free survival was 42%. Grade 1–2 esophagitis occurred in 9% of patients and grade 1–2 pneumonitis in 225 of patients. No grade $\geq$3 toxicity was reported during the follow-up (median 15 months after the end of re-irradiation). A total of 17 (74%) patients had either grade 0 or 1 late toxicity. Of six (26%) patients with pulmonary fibrosis on CT scan, two patients were observed to be symptomatic (grade 3). This pioneering study on the use of novel and widely available technology, holds promise for further use in this disease, targeting a huge number of patients experiencing a locoregional recurrence regardless of the initial treatment, although longer follow-up (at least for late toxicity) is necessary for definitive conclusions.

In cases of small cell lung cancer, radiation therapy was not frequently used to treat locoregional recurrence. This was especially true in cases of limited disease previously treated with a combined radiochemotherapy approach, because of the fear that it may add only toxicity without clear benefit for patients. For extensive disease, radiation therapy at the time of recurrence after initial chemotherapy can also be considered, but this was mostly related to a symptomatic patient. Retrospective studies (Ihde et al. 1979; Ochs et al. 1983; Salazar et al. 1991) used the doses ranging 21–60 Gy in patients harbouring recurrences from both limited and extensive disease small cell lung cancer. Although a response rate observed within the radiation therapy field was seen in 52%–77% of patients, the median survival times ranged only between 3 and 4 months, which is also likely to have been the cause of early systemic progression. Nevertheless, the wide range of doses used gave the authors an opportunity to speculate about higher doses ($\geq$40 Gy) producing better palliation, an important issue in patients with limited remaining lifetime.

5.4 Endobronchial (Endoluminal) Brachytherapy for Locoregional Recurrent Lung Cancer

Besides external beam radiation therapy, endobronchial brachytherapy was used to treat recurrent bronchogenic carcinoma, particularly when previous external beam radiation therapy had been given. Here as well, the vast majority of reports included the mixture of histologies with only a minority of patients having small cell histology. Some reports even included patients with primary lung carcinomas. First reports more than 20 years ago provided different aspects of endobronchial radiation therapy with different sources such as 137-CS 198-Au, or 192-Ir combined with low-dose external beam radiation therapy to treat recurrent bronchogenic carcinoma (Mendiondo et al. 1983) with satisfactory palliative results. These two decades witnessed studies with endoluminal brachytherapy using different dose rates in this disease. The vast majority of reports included the use of high dose rate brachytherapy (Seagren et al. 1985; Mehta et al. 1989; Bedwinek et al. 1991; Sutedja et al. 1992; Gauwitz et al. 1992; Gustafson et al. 1995; Delclos et al. 1996; Hatlevoll et al. 1999; Kelly et al. 2000). In the majority of reports previous external beam radiation therapy was used with median doses mostly ranging between 54 and 58 Gy (Bedwinek et al. 1991; Sutedja et al. 1992; Gauwitz et al. 1992; Gustafson et al. 1995). Only a few studies reported on the use of a single fraction of endobronchial irradiation of either 10 Gy (Seagren et al. 1985; Hatlevoll et al. 1999) or 20–30 Gy (Mehta et al. 1989), the majority of other reports using 2–3 fractions given in weekly intervals. The dose per fraction/session ranged from 6 to 15 Gy. Subjective response to treatment was observed in 66%–94%. Objective response measured during bronchoscopy was observed in 72%–100% patients, while radiologic documentation of re-aeration was observed in 64%–88% patients. Duration of response ranged between 4.5 and 6.5 months. Survival was rarely reported, being approximately 25% at 1 year (Bedwinek et al. 1991). The median survival time ranged from 5 to 8 months (Bedwinek et al. 1991; Gauwitz et al. 1992; Delclos et al. 1996) with two studies reporting identical finding of the median survival time of 7 months for responders (Sutedja et al. 1992; Kelly et al. 2000). Although a number of different treatment-related complications have been observed, the most feared was fatal bleeding. Whilst initial reports (Seagren et al. 1985; Bedwinek et al. 1991; Sutedja et al. 1992) stated an incidence

of severe pulmonary bleeding of 25%–32%, those reported in the last decade (Gauwitz et al. 1992; Gustafson et al. 1995; Delclos et al. 1996; Kelly et al. 2000) reported on significantly lower incidence of this complication ranging from 0% to 7%. A number of factors were investigated in relation to their influence on the incidence of fatal bleeding. No firm conclusion could be drawn due to the varying nature of reporting (crude versus actuarial), and due to frequently lacking pre-treatment patient and tumour characteristics. Regardless of these shortcomings, endobronchial brachytherapy remains one of the cornerstones of successful palliative approaches in patients with symptomatic endobronchial recurrences of lung cancer.

5.5 Conclusions

Recurrence is a frequent observation during the course of lung cancer, regardless of its initial treatment. While the recurrences occurring after chemotherapy for metastatic disease are instantly incurable, there is still some hope for patients recurring locoregionally after initial treatment for either early or locally advanced non-small cell lung cancer; small cell lung cancer has only sporadically being investigated regarding this issue, mostly in cases of extensive disease when radiation therapy had been given to control locoregional recurrences.

It is for this reason that the search for better (earlier) recognition and more successful treatment of locoregional recurrence must start as soon as initial treatment has been completed. This means close follow-up, which has been shown to be rewarding in diagnosing early post-treatment recurrences and also in detecting early metachronous second primary lung cancer. When done properly, it results in more early stages of recurrent/metachronous lung cancer which are more easily locally controlled, a prerequisite for treatment success. But even before the intensive follow-up starts, mostly occurring during prospective clinical studies, information can be gathered to identify patients more likely to experience regional intrathoracic recurrence. In such an attempt, Sawyer et al. (1999) used the findings of preoperative bronchoscopy, tumour size, grade and histology from 346 patients undergoing complete resection of early clinical stage (I/II) NSCLC to create risk groups for N1/N2/local/regional recurrence. The risk of subclinical nodal involvement was ≥15.6% in the low risk subgroup, while all other patients had ≥35% risk. Increasing risk correlated with increasing size and grade of tumour, accompanied with positive findings of bronchoscopy. Thus, groups with different risk could be identified and different (risk-adapted) follow-up strategies implemented. Hopefully, this could result in better (earlier) detection of recurrences (or second metachronous primary lung cancer) in earlier stages, being more suitable for curative intervention. This must be one of the major goals of future studies, in particular those dealing with the treatment of early stages of non-small cell lung cancer.

Also, novel technologies, such as three-dimensional treatment planning and delivery could enable successful dose escalation and provide the necessary tools for treating those recurrences which are presumably "more local" (e.g. bronchial stump) and, therefore, need only radiation therapy. It is also not unrealistic to expect that other technological advances in radiation therapy, such as intensity modulated radiation therapy or stereotactic fractionated radiation therapy become indispensable tools in treating these patients with more success. In contrast, it became clear that other-than-stump recurrences may require a different approach, including possible administration of chemotherapy concurrently with radiation therapy or chemotherapy preceding concurrent radiation therapy and concurrent chemotherapy, due to poor results obtained with radiation therapy alone.

Finally, as became clear in other tumour entities, the best way to ask interesting questions and get answers which may be used in a clinical setting, is to perform prospective clinical studies. This is particularly the case for tumour entities which have previously been largely denied an adequate diagnostic and treatment approach, a fate which should no longer fall to locoregionally recurrent lung cancer.

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6 Radiotherapy for Lung Cancer in Elderly Patient

Branislav Jeremić and Michael Molls

CONTENTS

Introduction

The Western world is rapidly ageing. The fastest-growing segment of the population being that composed of individuals over the age of 65 years. By the year 2030, they will constitute approximately 20% of the total population of the United States. The number of persons of more than 75 years old will triple by 2030, while the number of those aged more than 85 years will double in the same period (Yancik 1997). There is, however, no widely accepted and exact definition of an elderly person. Cut-off age thresholds vary between 60 and 80 years and many studies use cut-offs between 65 and 75 years of age. In contrast to fixed thresholds to define elderly persons, geriatric oncology has often been defined operationally as "when the health status of a patient population begins to interfere with the oncological decision making guidelines" (Extermann 2000). Therefore, biological age should be defined individually by performance status and co-morbidities, which will influence the decision-making, rather than an arbitrarily established age limit.

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Among many consequences, increasing age has a particular one: it is directly associated with increasing cancer occurrence rates; there is an 11-fold increase in the cancer incidence in persons more than 65 years of age when compared with their younger counterparts, indicating that elderly population may well become one of the major targets in oncology in the future, requiring specific managements for various cancers (Yancik 1997).

Lung cancer is a typical disease of the elderly patient. It is the most lethal of the cancers in both sexes. Treatment approaches with curative intention are feasible in patients with localized disease, but the evidence is based on studies which are usually performed with selected patients, the elderly patients being underrepresented in clinical trials. A frequent observation in daily practice is that elderly patients are less likely to be vigorously screened and staged, and frequently their cancers receive less-aggressive treatment (Nugent et al. 1997).

However, when evaluated for specific features, they did not seem to have different characteristics at presentation, particularly related to stage of disease, performance status and histology, when compared with their non-elderly counterparts, although other characteristics such as type and number of co-morbidities and organ function differ in the two groups (Montela et al. 2002). Furthermore, although not clinically overt and therefore undetected in many "healthy" elderly persons, there may be a reduction in functional organ capacity. With increasing age, not only the kidneys, but also the lungs and heart and even the immune system show a reduced function (Balducci and Extermann 2000).

A common practice in oncology is to base patient selection on clinical judgement with performance status and organ function parameters. This, however, may not be adequate when one considers elderly patients, since it seems that there is a need for a more comprehensive tool of pre-treatment assessment which would take into account potential hazards in treating elderly patients the same way as their non-elderly counterparts. This may help in

predicting and avoiding such hazards (Monfardini et al. 1995). To do so, a comprehensive geriatric assessment as an adjunct to general and cancer-specific diagnostic procedures is developed and defined as a multidimensional, interdisciplinary diagnostic process to determine the medical, psychological and functional capabilities of a frail elderly person in order to develop a coordinated and integrated plan for treatment and long-term follow-up (Rubenstein 1995; Osterweil et al. 2000; Bernabei et al. 2000). Assessment is mandatory for adequate patient selection for radiation therapy, too. This assessment includes the medical assessment, assessment of functioning, psychological assessment, social assessment and environmental assessment (Balducci and Extermann 2000).

This chapter addresses important issues in radiation therapy of lung cancer in elderly patients. Widely accepted clinical designation of non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) as two separate entities will here serve also to enable a suitable framework for addressing these issues in elderly patients.

6.2 Non-Small Cell Lung Cancer

Non-small cell lung cancer accounts for approximately 80% of all lung cancer cases, with more than 50% of all patients with non-small cell lung cancer being older than 65 years and about one-third of all patients being more than 70 years old at the time of diagnosis. While curative approaches are feasible in patients with early stage (I/II) disease and in a proportion of patients with locally advanced disease (stage IIIA/IIIB), palliation is the goal for the remainder of locally advanced and all metastatic (stage IV) non-small cell lung cancer patients. This general concept should also prove to be feasible in elderly with non-small cell lung cancer. Surgery is the treatment of choice for patients in early stage (I/II) non-small cell lung cancer, whereas the standard treatment for locally advanced non-small cell lung cancer is not well defined. Although stage IIIA non-small cell lung cancer patients can be treated with surgery alone if completely resectable or in combination with radiotherapy or chemotherapy, the majority of patients with locally advanced non-small cell lung cancer are unresectable, and, with increasing tumour stage, the outcome is inevitably limited by the distance spread.

6.2.1 Early Stage Non-Small Cell Lung Cancer

Besides their advanced age, elderly patients frequently are not undergoing surgery owing to existing co-morbidity and, only occasionally, owing to refusal. In these cases, radiation therapy has been used and has been shown to be effective. It seems that Aristizabal and Caldwell (1976) were first to show that elderly patients (70 years old or more) have significantly better 2-year survival than non-elderly patients (49-69 years; 35.7% versus 13.1%, p=0.044). This is explained by high local control (70%) and a lower incidence of distant metastasis. Coy and Kennelly (1980) and Newaishy and Kerr (1989) have observed a significant trend towards better survival in older patients with non-small cell lung cancer treated with radiation therapy alone. Noordijk et al. (1988) have found no difference in the outcome of elderly patients treated with radiation therapy alone or surgery. Furthermore, when only patients treated with radiation therapy alone are considered, elderly patients have a similar outcome to non-elderly patients. Also, Sandler et al. (1990) and Rosenthal et al. (1992) have found no significant difference in overall survival, disease-specific survival or local, progression-free survival in elderly versus non-elderly patients. Wurschmidt et al. (1994) have used multivariate analyses also, as have Kaskowitz et al. (1993), to show no difference between elderly and non-elderly patients. The same observation has been made by Slotman et al. (1994), Gauden et al. (1995) and Krol et al. (1996). In the two of studies of Jeremić et al. (1997, 1999), no difference has been observed between patients less than 60 years old and those 60 years old or more with stage I and II non-small cell lung cancer, respectively, treated with hyperfractionated radiation therapy alone, with a total dose of 69.6 Gy using 1.2 Gy b.i.d. fractionation, in either survival or relapse-free survival. Multivariate analyses using both survival and relapse-free survival confirms that age plays no important role in this setting.

Hayakawa et al. (1999) treated 97 patients of 75 years old or more (elderly) and 206 patients less than 75 years old (non-elderly), with radiation therapy doses of 60 Gy or more (up to 80 Gy) for inoperable non-small cell lung cancer. Elderly patients were classified into two subgroups: A, 75–79 years; and B, 80 years or older. No difference was found between the three age groups (5-year survival : 12% versus 13% versus 4% for non-elderly, elderly A and elderly B, respectively), but a multivariate analysis disclosed

a detrimental effect of the oldest age, due to 14% treatment-related deaths in patients receiving 80 Gy. Unfortunately, no multivariate analysis has been done using disease-specific survival as endpoint to give better insight into this finding.

Most recently, Gauden and Tripcony (2001) have investigated the effect of age (less than 70 years versus 70 years or older) on treatment outcome in patients with stage I non-small cell lung cancer. The median survival times (22 versus 26 months) and a 5-year survival (22% and 34%), respectively, for non-elderly and elderly patients were observed. The same held true for recurrence-free survival. Finally, when the study group was divided into the 5-year subgroups, both overall survival and recurrence-free survival remained similar regarding the age groups. The multivariate analysis excluded age as an important prognostic factor in predicting either of these two endpoints.

In contrast, Morita et al. (1997) have found a survival advantage for patients less than 80 years old when compared with those 80 years old or more (5-year survival rate: 25.2% versus 7.7%). Similarly, Sibley et al. (1998) have documented superior outcome in younger (less than 60 years) patients with stage I compared with older patients; this is unconfirmed, however, when local progression is used as an endpoint ($p = 0.10$).

Although numerous studies have attempted evaluation of toxicity, in none of these series is it specified that these toxic events happen in elderly patients. When specifically addressing elderly patients with early stage non-small cell lung cancer, no significant radiation therapy-related complications are found, and the incidence of both acute and late high-grade toxicity is similar among all age groups (Gauden and Tripcony 2001). When radiation therapy-related deaths occur, again, there is no difference between elderly patients (5%) treated with the highest dose levels (80 Gy) and their non-elderly counterparts (4%) treated the same way (Hayakawa et al. 2001).

Taken together, the data from the literature show that conventionally planned, external beam radiation therapy is capable of producing the median survival times of 20–27 months and 5-year survivals of 15–34% in patients of more than 70 years, and event better results are obtained when the cut-off of 60 years is used.

Recent years have also brought attempts to address prospectively the issue of the use of sophisticated treatment planning and delivery in this population. Niibe et al. (2003) have treated 22 elderly patients who have tumours up to 5 cm with fraction size of 3–4 Gy, 5 fractions per week, to a mean total dose of 65.3 Gy. Local control rates at 1–3 years were 92%, 83% and 83%, respectively, while overall survival rates at 1–3 years were 100%, 83% and 56%, respectively. No patients experienced grade 2 or greater toxicity. These results show that this tool, now widely available worldwide, is feasible and effective in elderly patients. The results hold promise for future studies in elderly patients with small-sized tumours.

Most recently, however, there has appeared an initial study which compares surgery with continuous hyperfractionated accelerated radiation therapy in elderly patients with stage I non-small cell lung cancer (Ghosh et al. 2003). One-hundred and forty-nine patients underwent lobectomy, 47 had wedge resection, while 19 had radiation therapy alone. Non-lobectomy patients have significantly lower pulmonary function. Survival at 1 and 5 years was 97% and 68% versus 98% and 74% versus 80% and 39%, respectively ($p = 0.0484$), but this was associated with a 2.7%, 30–day operative mortality in the lobectomy group.. The frequency of loco-regional recurrence is similar between the groups. This study shows again that radiation therapy alone is a reasonable treatment option for those who are not suitable candidates for surgery.

6.2.2 Locally Advanced Non-Small-Cell Lung Cancer

Some of the studies discussed in the previous section include also a proportion of patients with stage III, while some do not specify outcome regarding age. Nevertheless, due to poor results, early studies prompted some to advocate prohibition of radiation therapy in patients over 70 years of age (Aristizabal et al. 1976; Patterson et al. 1998). Similarly, Nakano et al. (1999) have undertaken a retrospective study of elderly patients with stage III non-small cell lung cancer who had been treated with radiation therapy alone. It resulted in a median survival time (MST) of 11.5 months in the younger group and 6.3 months in the elderly group ($p = 0.0043$). In multivariate analysis, good performance status (age less than 75 years) and good response are significant, favourable independent predictors of survival. In the elderly group of patients, there were more frequent deaths from respiratory infections and there were lower prognostic nutritional indexes before and after radiation therapy. Hayakawa et al. also reports an inferior survival for the subgroup of elderly patients with stage III disease, but only in patients more than 80 years of

age (2001). Contrary to that, Kusumoto et al. (1986) have investigated this effect in stage III/IV non-small cell lung cancer. Patients less than 70 years old (n=64) and those 70 years and older (n = 36) achieve a MST of 7 and 6 months, respectively, the difference being insignificant.

Others, however, have provided data on the effectiveness of radiation therapy in elderly patients. Zachariah et al. (1997) have reported on radiation therapy in lung cancer in octogenarians treated with 59.40–66 Gy using standard fractionation. Response was observed in 43% patients, while only 24% had progressive disease. Evaluation of the data on 1,208 patients enrolled on several trials conducted by the European Organization for Research and Treatment of Cancer (Pignon et al. 1998) has given the opportunity to investigate the influence of age on treatment outcome as well as acute and late toxicity of curative thoracic radiotherapy. Survival adjusted for the primary location of the tumour is comparable in each group. The difference in distribution over age is not significant for acute nausea, dyspnoea, oesophagitis, weakness and the World Health Organization performance status alteration. The minimal time to complication is similar in all age groups. There is no difference between age groups regarding the patients experiencing no complications at post-treatment year 4. Among various toxicities, only grade 2 late oesophagitis demonstrates a significant trend to be more frequent in older patients (p=0.01), but this difference disappears after adjustment to the study (p = 0.32). The Italian Geriatric Radiation Oncology Group (Gava 1999) has reported on outcome of radiation therapy alone in stage III non-small cell lung cancer in 38 elderly patients. The 1-year survival rate approaches 44%. Another Italian study has confirmed the effectiveness of radiation therapy in 48 patients of 75 years or older with locally advanced non-small cell lung cancer (Lonardi et al. 2000). Radiation therapy alone was used to give a median dose of 50 Gy. Overall survival was 10% at 24 months. Elderly patients treated with 50 Gy or more achieved significantly better survival than those treated with less than 50 Gy (the MST, 8 versus 4 months; 2-year survival, 20% versus 4%, respectively; p = 0.03). Tombolini et al. (2000) have also analysed patients 70 years and older in stage III treated by radiation therapy alone with 50–60 Gy (and a 10-Gy boost to the gross tumour volume) in 1.8- to 2-Gy fractions. Two-year overall and disease-free survival was 27% and 14.6%, respectively. Most recently, Pergolizzi et al. (2002) have reported on curative radiation therapy alone in 40 elderly patients with stage IIIA. Radiation therapy was directed towards gross tumour burden with a median of 60 Gy, conventionally fractionated. No treatment-related mortality was observed and no clinically significant acute morbidity was scored. The MST was 19 months and 5-year survival was 12%.

Since radiochemotherapy is a widely used approach for non-small cell lung cancer patients with locally advanced, non-resectable non-small cell lung cancer and good performance status, one may wonder whether this is also true for elderly patients with locally advanced non-small cell lung cancer. Some studies provide retrospective subgroup (age) analyses of patients enrolled into radiochemotherapy trials but do not identify age as negative prognostic factor in multivariate analyses (Schaake-Koning et al. 1992; Jeremić et al. 1998; Clamon et al. 1999; Furuse et al. 1999). However, the Radiation Therapy Oncology Group has reported on a study which included 1,999 patients treated with radiation therapy with or without chemotherapy in several prospective studies. Using a recursive partitioning and amalgamation analysis they have found a negative influence of older age on survival (Werner-Wasik et al. 2000). These results confirm earlier results from another analysis by the Radiation Therapy Oncology Group (Movsas et al. 1999), where a quality-adjusted survival was used to examine six prospective Radiation Therapy Oncology Group trials, including 979 patients with inoperable stage II/IIIB non-small cell lung cancer patients treated with radiation therapy with or without chemotherapy. Elderly patients had the best quality-adjusted survival with radiation therapy alone, which was in sharp contrast to their younger counterparts, who benefited mostly from more aggressive, combined approaches. Although these two large analyses stand unified against the more intensive treatment approach in elderly patients, it must, however, be clearly emphasized that they are difficult to interpret, because the compilation of patients treated on separate study protocols implies a comparison between patients with a variety of entry criteria used to define eligibility and different treatment regimens administered, including a single-modality radiation therapy in many of these studies. Contrasting these, Rocha Lima et al. (2002) have analysed older patients from a randomized cancer and leukaemia Group B trial of induction chemotherapy followed by either radiation therapy alone or concurrent radiochemotherapy for locally advanced non-small cell lung cancer. They have shown that patients older than 70 years complete treatment to the same extent as younger patients and attain similar response and survival, but at the expense of in-

creased toxicity, especially high-grade (greater than 3) nephrotoxicity and neutropenia. Furthermore, in a retrospective analysis of the data from the Radiation Therapy Oncology Group 94-10 study, Langer et al. (2001) have investigated the influence of age on treatment outcome. Patients older than 70 years (n = 104) were compared with those younger than 70 years (n = 491) and it was shown that elderly patients benefit from concurrent as compared to sequential radiochemotherapy in a similar way to their younger counterparts. As with the study of Rocha Lima et al. (2002), they suffer from an increase in toxicity, especially severe oesophagitis. Most recently, Schild et al. (2003) have performed a secondary analysis of the North Central Cancer Treatment Group study, which evaluated split-course versus standard fraction radiotherapy and cisplatin/etoposide in stage III non-small cell lung cancer. When restricted to age, the 2- and 5-year survival rates are similar between the two age groups(less than 70 versus 70 years and older), but grade 4+ toxicity occurred in 62% patients less than 70 years of age compared with 81% in those 70 years and older (p=0.007). Both grade 4+ haematological toxicity and grade 4+ pneumonitis are significantly more frequent in the elderly group.

Besides these, some studies have provided data on prospective approaches addressing this issue. Between January 1988 and June 1993, Jeremić et al. (1999) enrolled a total of 58 patients, who entered a phase II study. Carboplatin (400 mg/m^2) was given intravenously on days 1 and 29, and etoposide (50 mg/m^2) was given orally on days 1–21 and 29–42. Accelerated hyperfractionated radiotherapy was administered starting on day 1, with a total dose of 51 Gy in 34 fractions over 3.5 weeks. In 55 evaluable patients, the complete response rate was 27% and the overall response rate was 65%. For the 55 patients, the MST was 10 months, and the 1-, 2-, and 5-year survival rates were 45%, 24% and 9.1%, respectively. The median time until relapse was 8 months, and the 1-, 2- and 5-year relapse-free survival rates were 45%, 20% and 9.1%, respectively. The median time to local recurrence was 14 months and the 5-year local control rate was 13%; while the median time to distant metastasis was 18 months and the 5-year distant metastasis-free rate was 15%. Haematological, oesophageal and bronchopulmonary acute grade 3 or 4 toxicities were observed in 22%, 7% and 4% of the patients, respectively. There was no grade-5 toxicity or late grade-3 toxicity. Jeremić et al. have concluded that concurrent accelerated hyperfractionated radiotherapy and carboplatin/oral etoposide produce relatively low and acceptable toxicity. The survival results appear to be comparable with those obtained in non-elderly patients with stage III non-small cell lung cancer treated by full-dose radiation.

During a phase II study, Atagi et al. (2000) used standard fraction radiation therapy with 50–60 Gy and concurrent, low-dose daily carboplatin (30 mg/m^2) in 38 patients with locally advanced non-small cell lung cancer, 26 of whom were stage III. The MST was 15.1 months and 2-year survival was 20.5%. Finally, Nakano et al. (2003) have reported on a pilot study in which low-dose cisplatin (6 mg/m^2; days 1–5, 8–12, 29–33 and 36–40) was added to conventionally fractionated radical radiation therapy (60 Gy in 20-Gy daily fractions) in elderly patients with locally advanced, unresectable non-small cell lung cancer. Of 12 registered patients, 11 were eligible for this analysis, 91% of whom were stage III. The overall response rate was 82% and the median overall survival was 23 months. The 2-year survival rate was 53%. The most common grade 3 toxicities included grade 3 leucopenia and thrombocytopenia, occurring in 20% and 9%, respectively. No other high-grade toxicity was observed during this study.

In an interesting attempt to selectively target tumour cells with cisplatin and to decrease the toxicity that concurrent radiochemotherapy can bring, Karasawa et al. (2002) have used bronchial arterial infusion of cisplatin and concurrent radiation therapy (dose, 50.4–73.2 Gy; median, 60.8 Gy) in 31 elderly, stage III non-small-cell lung cancer patients. The results were compared with those obtained in 30 elderly patients receiving no cisplatin. Response rate was 90% in the cisplatin group and 83% in the non-cisplatin group. Two-year, local control MST and 5-year survival were all improved in the cisplatin group (81.0%, 33.4 months and 38.3% versus 38.1%, 9.8 months and 4.2%, respectively; local control, p<0.01; survival, p <0.00). Multivariate analysis shows that addition of bronchial infusion cisplatin is the strongest predictor of improved survival achieved with no increase in life-threatening toxicity.

In most of these studies, the toxicity of the combined treatment is tolerable (Jeremić et al. 1999; Lonardi et al. 2000), with both acute and late high-grade toxicity not different from that observed with similar approaches in non-elderly patients. Contrary to that, Atagi et al. (2000) have observed high-grade haematological toxicity in 34.2%–71.1% of patients. Non-haematological toxicity was mild, with no patient developing grade 3 oesophagitis or higher, although two (5%) grade 4 pulmonary toxicities occurred.

6.2.3 Metastatic Non-Small-Cell Lung Cancer

Although radiation therapy is frequently used to treat intrathoracic or distant spread in stage IV (metastatic) non-small cell lung cancer, there are virtually no data on the feasibility and effectiveness of radiation therapy in this setting. In order to define the "optimal" treatment approach in these patients, Jeremić et al. (1999) have designed and performed a phase II study evaluating concurrent short-term chemotherapy and palliative radiotherapy. Between January 1988 and June 1993, a total of 502 patients entered into a study that used 2 cycles of carboplatin, 300 mg/m^2, on days 1 and 29, and oral etoposide, 50 mg/m^2, on days 1–21 and 29–42. Radiation therapy was administered with a dose of 14 Gy, in two fractions, given with a 1-week split, days 1 and 8. From 47 patients evaluable for the response, there were 3 (6%) complete responses and 10 (21%) partial responses, making an overall response rate of 13 (28%). Response duration was 2–8 months (median, 5 months; mean, 5 months). MST for all 50 patients was 7 months, and 1- to 3-year survival rates were 31%, 4.1% and 2%, respectively. Only 9 (19%) patients experienced haematological grade 3 toxicity, all other chemotherapy-induced toxicity being grade 1 or 2. Of radiation therapy-induced high-grade toxicity (according to the Radiation Therapy Oncology Group), grade 3 oesophageal toxicity was observed in 9 (19%) patients, while only 4 (9%) patients experienced grade 3 bronchopulmonary toxicity. No grade 4 or 5 toxicity occurred during this study. Short-course chemotherapy and palliative radiation therapy in elderly patients with stage IV non-small cell lung cancer was well tolerated, with mild to moderate toxicity. Together with other results obtained this way, these findings warrant further studies evaluating the effectiveness of this approach and possible chemotherapy and/or radiation therapy dose escalation in elderly patients with stage IV (metastatic) non-small cell lung cancer.

6.3 Small-Cell Lung Cancer

Small-cell lung cancer represents 20–25% of all lung cancers cases. Its chemosensitivity and great metastatic potential make it a good candidate for chemotherapy. However, with chemotherapy alone, the outcome of small cell lung cancer is poor. Although the initial response rates are high, only 5% of patients achieve long-term survival at 3 years. Of all small cell lung cancer cases, only approximately 20–30% of all patients present with a tumour confined to the hemithorax of origin, the mediastinum or the supraclavicular lymph nodes, designated as having limited-disease small cell lung cancer. All other patients present with disseminated, extended disease. Since they have a dismal prognosis and are, therefore treated mostly with palliative intention, this section focuses on limited-disease small cell lung cancer in elderly.

Standard treatment for limited-disease small cell lung cancer is combined radiation therapy and chemotherapy, a practice widely accepted after the survival benefit of thoracic radiation therapy has been confirmed by two meta-analyses published in 1992 (Pignon et al. 1992; Warde and Payne 1992). The most widely used approach in limited-disease small cell lung cancer consists of 4 cycles of cisplatin/etoposide and thoracic radiation therapy. This is nowadays routinely followed by prophylactic cranial irradiation in cases of complete remission, owing to findings of a meta-analysis demonstrated that prophylactic cranial irradiation improves survival for limited-disease small cell lung cancer patients in complete remission after radiochemotherapy (Auperin et al. 1999).

For the vast majority of elderly patients with limited-disease small cell lung cancer, the evidence for the standard treatment must be derived from phase III trials in which elderly patients are largely underrepresented. It remains unclear to what extent these results are biased by eligibility criteria of the trials, which restrict the entry of elderly patients, since one of meta-analyses shows that the survival benefit from thoracic radiation therapy is restricted to younger patients (Warde and Payne 1992), possibly because of toxicity. Therefore careful selection of elderly patients suitable for a full dose of radiation therapy and chemotherapy is an important issue.

Randomised phase III studies investigating various issues of radiation therapy and chemotherapy in elderly patients with limited-disease small cell lung cancer are lacking, and the prognostic significance of age in small cell lung cancer is not well defined. While Southwest Oncology Group and Cancer and Leukaemia Group B have demonstrated an influence of age in limited-disease small cell lung cancer (Spiegelman et al. 1989; Albain et al. 1990), others do not confirm this observation (Osterlind and Anderson 1986; Sagman et al. 1991). Among the studies investigating the relationship between the age and toxicity and outcome among elderly patients

treated with combined thoracic radiation therapy and chemotherapy in small cell lung cancer, Findlay et al. (1991) have observed significantly more toxicity in the intensively treated group (cyclophosphamide, doxorubicin, vincristine) than in the less-intensive group of small cell lung cancer patients (single agents, planned dose reductions, or radiation therapy alone), which was accompanied by a higher response rate in that group. However, in the limited-disease small cell lung cancer patients, intensive treatment did not lead to an improvement in overall survival.

The 1990s also brought a number of studies investigating the influence of various prognostic factors in small cell lung cancer, including age (Table 6.1) (Siu et al. 1996; Dajczman et al. 1996; Nou 1996; Jara et al. 1999; Yuen et al. 2000). Conflicting results were observed, probably owing to various cut-off values used with regard to age as prognostic factor. Regardless, in all of the studies frequent dose emissions/reduced number of chemotherapy cycles (Siu et al. 1996; Dajczman et al. 1996; Nou 1996; Yuen et al. 2000) or dose reductions/less intensive (Jara et al. 1999) or less frequent use of radiation therapy made the elderly patients the group not only receiving less-intensive treatment, but also less likely to be included in clinical trials as well. The situation remains the same. In a retrospective analysis of 174 patients with limited-disease small cell lung cancer, Ludbrok et al. (2003) have recently reconfirmed that, during the 1990s, elderly patients continued to be underdiagnosed and undertreated, resulting in lower median and overall survival rates; although toxicity and pattern of failure show no difference when compared with their non-elderly counterparts. When, however, multivariate analysis was done, age was not shown to be an independent prognosticator of treatment outcome. It is more than interesting, however, to observe that none of the studies observed a significantly inferior response rate, overall survival or event-free survival for elderly. If therapy is administered, therefore, the outcome in elderly patients is the same as that in younger patients. For example, Siu et al. (1996) have observed that age influences survival in the univariate analysis, but not in a multivariate analysis. It may well be that factors frequently associated with age, such as co-morbidity, performance status or less-intensive treatment seem to influence prognosis, rather than age itself.

Numerous studies have investigated the influence of age on toxicity. Some have observed fewer elderly patients with high-grade toxicity (p=0.0001), and a similar incidence of treatment-related deaths due to less-intensive treatment (Dajczman et al. 1996). Others have reported on similar toxicities in both age groups. When a higher rate of haematological toxicity and fatal toxicities occur in the elderly group, other toxicities are similar compared with younger patients (Nou 1996; Jara et al. 1999; Yuen et al. 2000).

In addition to retrospective studies, there are also prospective studies specifically addressing the issue of optimising the treatment approach in elderly patients with limited-disease small cell lung cancer. Jeremić et al. (1998) have tailored the combined treatment in elderly with limited-disease small cell lung cancer by administering concurrently only two courses of carboplatin (400 mg/m^2, days 1 and 29) and oral etoposide (50 mg/m^2, days 1–21 and 29–49) with accelerated hyperfractionated radiation therapy (45 Gy in 30 fractions in 15 treatment days, using 1.5 Gy b.i.d. fractionation) in 75 patients of 70 years or older with a Karnofsky performance status score of greater than 60% and without major concomitant diseases. The MST was 15 months and 5-year survival was 13%. Good pre-treatment characteristics led to high compliance (83% received therapy on an outpatient basis) and low toxicity. Grade 4 thrombocytopenia occurred in 1.4% of all patients, thrombocytopenia grade 3 in 11%, grade 3 leucopenia in 8.3%, grade 3 anaemia in 2.8%, infection in 4.2%, and nausea and vomiting in 4.2% of all patients. No high-grade bronchopulmonary toxicity was observed and grade 3 oesophagitis occurred in only 2.8% of the patients. An additional advantage of this approach was its short duration, resulting in more time spent at home and, therefore, a good quality of life. Murray et al. (1998) have also used only 2 cycles of chemotherapy (cyclophosphamide/doxorubicin/vincristine and platinum/etoposide) and radiation therapy (20 Gy in 5 fractions or 30 Gy in 10 fractions) specifically tailored for elderly, infirm or non-compliant patients. Toxicity was low, except in the cases of three treatment-related deaths, two of which were caused by cardiac toxicity, with likely ischemic cause. The median time to progression was 40 weeks and 2-year PFS was 25%. The MST was 54 weeks and 5-year survival rate was 18%. The MST and 5-year survival were similar for 18 patients younger than 70 years and for the 37 patients 70 years or older.

Most recently, Matsui et al. (1998) have reported on 16 patients of more than 70 years of age with limited-disease small cell lung cancer for whom 4 cycles of carboplatin and oral etoposide (40 mg/m^2, days 1–14) were followed by chest radiation therapy (45 Gy). The MST was 15.1 months and a 2-year survival rate was 21.8%. For patients 75 years or older, the MST was 10.3 months and 2-year survival rate was 11.3%.

Table 6.1. Retrospective studies in patients with limited-disease small cell lung cancer treated with radiation therapy and chemotherapy

Author	Year	Age (years)/*n*	RR (%)	Survival	Toxicity	Comments
Siu et al.	1996	<70 (*n*=580) ≥70 (*n*=88)	78%; n.s. 82%; n.s.	5-year OS: 8%; n.s. 5-year OS: 11%; n.s.	Only cardiac grade 3/4 toxicity increase in ≥70)	All LD; CAV/PE + TI + PCI (if CR) Age not a prognostic factor in multivariate analysis
Dajczman et al.	1996	<60 (LD *n*=45, ED *n*=55) 60-60 (*n*=LD *n*=48, ED *n*=73) ≥70 (LD *n*=43, ED *n*=57)	49%; n.s. 52%; n.s. 51%: n.s.	2 year OS: 45 2-year OS: 48 2-year OS: 43	Fewer high-grade toxicity and the mean number of toxicities in elderly patients	*n*=123 LD, *n*=89 ED; CAV or PE + TI; No separate analysis for LD + ED >70: only 23% received optimal treatment (compared with 43%/50% in the younger groups)
Nou	1996	≤70 (*n*=243) >70 (*n*=110)	All: 72% (n.s.)	5-yearOS: 5%; n.s. 5-yearOS: 1.3%; n.s.	No difference between ≤70 and >70	50% LD 50% ED; (85% of LD and 15% of ED treated with CHT (various) + TI
Jara et al.	1999	<70 (*n*=25) ≥70 (*n*=12)	46%; n.s.* 50%; n.s.*	MST: 12.3 months MST: 14.9 months	No difference between ≤70 and >70	only LD evaluated; PE or cPE +TI
Yuen et al.	2000	<70 (*n*=271) ≥70 (*n*=50)	80%; n.s. 88%; n.s.	5-year EFS: 19%; n.s.* 5-year EFS: 16%; n.s.*	Grade III/IV haematological toxicity higher in the elderly group; all other adverse effects: no difference	All LD, except* (data for LD; *n*=37) + ED (*n*=57)
Ludbrok et al.	2003	<65 (*n*=55) 65-74 (*n*=76) ≥ 75 (*n*=43)	91% 79% 74%	MST: 17 months 2-year OS: 37% MST: 12 months 2-year OS: 22% MST: 7 months 2-year OS: 19% *P*=0.003	No difference in the incidence of acute or late grade 3/4 toxicity	Age not significant prognosticator in multivariate analysis since elderly patients less frequently treated with RT/CHT, intensive CHT and PCI

RR, response rates; n.s., not significant; *LD*, limited disease; *CAV*, cyclophosphamide, doxorubicin, vincristine; *PE*, cisplatin, etoposide; *TI*, thoracic irradiation; *PCI*, prophylactic cranial irradiation; *CR*, complete response; *OS*, overall survival; *ED*,

Grade 3 and 4 leucopenia occurred in 36% and 14% of patients, respectively, and grade 3 and 4 thrombocytopenia occurred in 39% and 14% of the patients, respectively. Grade 3/4 anaemia occurred in 50% of patients. Non-haematological toxicity was rare. What these three prospective studies have shown is that well-tailored treatment approaches, carefully balanced between "optimal" thoracic radiation therapy and chemotherapy elderly patients can tolerate and avoid unnecessary toxicity, may lead to high treatment success and a toxicity profile not very different to that usually observed in younger patients.

Retrospective and prospective studies have also shown, despite elderly patients frequently receiving less-intensive chemotherapy and/or thoracic radiation therapy, a similar outcome of elderly and non-elderly patients with limited-disease small cell lung cancer. Furthermore, despite less compliance in elderly patients, no difference in either response rates or survival has been detected between them and their non-elderly counterparts (Kelly et al. 1991; Siu et al. 1996; Dajczman et al. 1996; Tebbutt et al. 1997; Yuen et al. 2000). While the reason for this phenomenon is still unclear, a possible explanation may lie in a different metabolism of drugs, which may lead to a need for lower doses of various drugs in elderly patients (Montamat et al. 1989; McKenna 1994; Joss et al. 1995), since different biological behaviours of tumours in elderly patients is not a very likely cause of this observation (Matsui et al. 1998). As Yuen et al. (2000) point out; there may be a threshold above which a significant benefit can be realized. The modest dose reductions still may result in the delivery of "adequate enough" treatment to achieve a posi-

tive effect. This threshold will be hard to document and/or specify, but it seems that studies of Jeremić et al. (1998) and Murray et al. (1998) support this statement: Although chemotherapy was limited to only 2 cycles given concurrently with thoracic radiation therapy, it was possible to obtain results which are not substantially inferior to those obtained with more intensive approaches. However, every caution should be taken with this patient population, particularly regarding haematological toxicity.

In extensive-disease small cell lung cancer, standard treatment for patients with extensive-disease small cell lung cancer is chemotherapy. The addition of thoracic radiation therapy has not improved survival in the past, and thoracic radiation therapy was applied only for palliation of local symptoms when chemotherapy alone was not efficient (Livingston et al. 1984). However, a recent prospective randomized trial by Jeremić et al. (1999) has shown an advantage for 3 cycles of platinum-etoposide chemotherapy followed by accelerated hyperfractionated thoracic radiation therapy given concurrently with low-dose, daily carboplatin/etoposide over chemotherapy with platinum/etoposide (5 cycles) alone. During that study, survival advantage was observed for patients more than 60 years old, a finding confirmed by the multivariate analysis, identifying the age as an independent prognosticator of survival in patients with extensive-disease small cell lung cancer (unpublished observations; drawn from Jeremić et al. 1999).

6.4 Conclusions

Accumulated evidence identifies radiation therapy as an important treatment modality in elderly patients with lung cancer. This is so irrespective of the consideration of cut-off age, histology or stage, as this applies to combined radiation therapy and chemotherapy. Encouraging results have been obtained in both non-small cell lung cancer and small cell lung cancer, although prospective studies are lacking.

Current evidence, unfortunately, also points out that age alone is an uncertain prognostic criterion when outcome is considered together with toxicity. More important than chronological age seems to be the biological age of each individual elderly patient, which therefore requires a specific geriatric assessment of each individual patient, including detection of co-morbidities and the functional capacity for performing activities of daily living, and the cognitive and nutritional status of the patient. The decision-making of radiation therapy alone or in combination with chemotherapy in elderly patients with lung cancer should be based on both disease- and patient-specific criteria. Age itself is not a contraindication for applying the standard treatment, but the individualized management of the elderly patient must reflect the results of a comprehensive geriatric assessment.

However, a major issue in this field is the lack of prospective clinical studies investigating "optimal" treatments in this setting. This is especially so since accumulated evidence clearly shows that "fit" elderly patients may tolerate the treatments, regardless of its intensity, considerably well. They could serve as the starting point for inclusion of more elderly patients in clinical studies. However, every caution should be undertaken in order not to overemphasize the results of recent studies, which are, unfortunately, mostly retrospective. That said, inherent biases and underlying problems, unsolved so far, may hamper future endeavours having the same goal: enabling elderly patients with lung cancer equal diagnostic and treatment approaches to their younger counterparts, on or off the protocol. While this should be a continuous reminder to all working in this field, we need more clinical studies in elderly patients with lung cancer and we need them now.

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7 Advances in Supportive and Palliative Care for Lung Cancer Patients

Michael J. Simoff and Paul A. Kvale

CONTENTS

7.1 Introduction

The majority of patients with lung cancer will experience some symptoms (dyspnea, cough, and/or hemoptysis) during the course of their disease. These symptoms can greatly affect, not only the quality of life of these patients, but may also influence the therapeutic modalities that their physician may want to employ to deliver further therapy.

Most physicians would define palliation as the relief or soothing of symptoms of a disease, but not affecting cure. Current thinking is that palliative techniques are only for the relief of symptoms. In this chapter a broader view of palliation will be considered, for instance interventional pulmonology techniques, as adjuncts to more standard therapeutic interventions for lung cancer. Although "cure" may not be effected, many palliative techniques can increase survival of patients as well as their quality of life. In the study by Brutinel et al. (1987) in a patient population affected by airways obstruction, 84%–92% of their patients had symptomatic palliation of symptoms solely with laser resection of the endobronchial tumor. Survival at 7 months was better in the laser bronchoscopy group (60%, n=71) than in the control group (0%, n=25).

While these modalities and techniques are often considered of only palliative benefit, they may also effect an occasional "cure." By employing some "palliative techniques" for symptom relief, a more aggressive therapeutic program sometimes can be used potentially allowing a "sicker" population of patients the opportunity to undergo additional therapeutic options. This idea is an expansion on the traditional view of palliation; with more modern tools and techniques, this broader view should be a part of all treating physicians' thinking.

Symptoms patients with lung cancer may experience include: dyspnea, cough, and hemoptysis. Many different manifestations of lung cancer (local invasion, metastasis, or paraneoplastic syndromes) may be responsible for any or all of these. The goal of this chapter will be to expand the treating physician's awareness of a variety of these etiologies and a variety of possible therapeutic interventions.

7.2 Dyspnea

Dyspnea will affect 65% of all patients with lung cancer during some time in their disease course (Jacox et al. 1994; WHO 1990). The etiologies of dyspnea can vary (Hoegler 1997). This section will discuss components of the system, which may commonly manifest as dyspnea in lung cancer patients: endobronchial disease, pleural disease, tracheoesophageal fistula, with a brief look at others.

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If the etiology for the dyspnea can be identified and managed successfully with some type of palliation treatment, the patient may have a much greater tolerance for further therapy (whether it be radiation, chemo-, or surgical), which may be considered appropriate but was not used due to the patient's limitations.

7.2.1 Hypoxia

Hypoxia is a common complication in patients with lung cancer. Some patients will have hypoxia at rest and are more easily identified by checking their pulse oximetry readings of $\leq$88%. Other patients will maintain adequate oxygenation while resting, but quickly desaturate with activity developing dyspnea. Supplemental oxygen is a very common intervention to help relieve dyspnea in patients with hypoxia both at rest and with exertion (Escalante et al. 1996). The use of oxygen, particularly with activity and sleep will often help relieve some of the patients' symptoms of dyspnea.

7.2.2 Chronic Obstructive Pulmonary Disease

Patients with lung cancer often have: chronic obstructive pulmonary disease (COPD). Beta-2 agonists, antibiotics, and sometimes steroids often improve the tracheobronchitis and/or bronchospasm. By the use of aggressive treatment regimens, of the shortness of breath patients experience can be abated.

7.2.3 Endobronchial Disease

Most new cases of lung cancer in the United States will be in an advanced stage (American Cancer Society 2001). More than 50% of these patients will have some involvement of the central airways (Luomanen and Watson 1968). This can be in the form of bulky endobronchial disease, endobronchial extension, or extrinsic compression of the airways by the tumor or by lymphadenopathy. These patients may have respiratory symptoms: shortness of breath, hemoptysis, and cough. Some of these patients may benefit from endobronchial intervention as part of the management of their disease (American Cancer Society 2001).

Not all endobronchial disease causes complete obstruction of the airways. Sometimes patients have partial obstruction, and symptoms may be less severe. When these patients begin therapy, their "limited" endobronchial disease can become more complicated. Therefore, endobronchial techniques should not only be considered in the beginning or more commonly at the end of the management of lung cancer patients, but throughout (Cortese and Edell 1993).

Lastly, when all management options have been used, end-stage patients can develop compromise of their airways as the cancer continues to progress. In these situations, endobronchial techniques may benefit the patient in its more traditional role. Endobronchial management options may help to relieve some of their symptoms, allowing the patient freedom from shortness of breath in conjunction with hospice or other palliative therapies (Cortese and Edell 1993; Sutedja et al. 1995).

Most endobronchial techniques are performed in the United States on an outpatient basis. Unless a patient presents with respiratory failure, many of the procedures performed provide immediate relief of symptoms. This rapid symptomatic improvement allows patients to remain ambulatory with an improved quality of life. It may also prepare them to continue additional anti–cancer treatment. Although interventional procedures are not definitive therapies, they often provide partial to total relief of the severe dyspnea produced by nearly complete airway occlusion.

Interventional pulmonary programs that include endobronchial procedures should include an armamentarium of therapeutic modalities rather than a single invasive approach to manage patients with complicated lung cancer. As each patient's anatomy differs, the manner in which the patient's cancer leads to symptoms varies. Several procedures used in conjunction (i.e., laser and stenting) may be necessary to provide the most effective treatment. Offering different modalities allows the best selection of approaches for the patient (Cortese and Edell 1993).

The following sections discuss a variety of techniques and tools available to the interventionalist. In many cases, no one technique is better than the others, and some combination of these techniques often offers the greatest benefit to the patient.

7.2.3.1 Bronchoscopy

Since the inception of flexible fiberoptic bronchoscopy in the late 1960s in Japan and in 1970 in the United States, the flexible bronchoscope has become

the most widespread tool for evaluating and diagnosing diseases of the airways and lungs (Ikeda 1970). The rigid bronchoscope, the flexible bronchoscope's predecessor, was in many regards forgotten as a tool until interventional pulmonology evolved in the 1980s. Interventional pulmonologists reevaluated this tool and found its properties advantageous to the procedures that are currently performed. A survey in 1991 by the American College of Chest Physicians reported that only 8% of responding pulmonologists used a rigid bronchoscope (Prakash and Stubbs 1991).

Overall, both the flexible bronchoscope and the rigid bronchoscope are necessary for the practice of interventional pulmonology. The rigid bronchoscope offers many advantages to the interventional pulmonologist, one of which is superior control of the airway. Ventilation is performed through the rigid bronchoscope itself rather than around the flexible bronchoscope. The larger-bore rigid bronchoscopes allow optical systems, large caliber suction catheters, and ablative instruments to pass through the scope simultaneously. Large biopsy forceps are used through the rigid bronchoscope, which can provide more significant tissue biopsies as well as assist in mechanical debulking of lesions.

The rigid bronchoscope itself can be used to debulk tumor from the airway lumen. The distal end of the bronchoscope has a beveled end. This edge can be used to shear large sections of endobronchial tumor away from the airway wall in a technique often referred to as apple-coring. In a report on 56 patients with endobronchial obstruction from the trachea to the distal main stem bronchi, Mathisen and Grillo (1989) described improvement in 90% of their patients. Only three of the 56 patients had more than minor bleeding with this procedure. Apple-coring combined with the use of larger biopsy forceps allows tumor to be quickly resected from the obstructed airway.

More and more can currently be performed via the flexible bronchoscope. It is an excellent tool for some airways procedures. The rigid bronchoscope is a more difficult instrument to use than a flexible bronchoscope, and the rigid bronchoscope requires additional training beyond the typical fellowship. Rigid bronchoscopy is most commonly performed in the operating room with general anesthesia, limiting its availability to some pulmonary physicians.

7.2.3.2 Laser Therapy

Lasers have many medical uses, including the endobronchial ablation of lung cancer. Several types of lasers are currently used within the bronchi: neodymium:yttrium-aluminum-garnet (Nd:YAG), potassium-titanyl-phosphate (KTP), and carbon dioxide (CO_2). The most common laser used endoscopically is the Nd:YAG, which delivers energy at a wavelength of 1064 nm. The laser energy can be conducted via a quartz monofilament and thus can be easily used with either the rigid or flexible bronchoscope. Normally, Nd:YAG is used at 30–60 W, but it has a wide range of power outputs, up to 100 W. Depending on the energy level used, the laser can penetrate tissue several millimeters in depth. The KTP laser has many of the same properties as the Nd:YAG with a delivered wavelength of 532 nm. The CO_2 laser can be used only through a rigid bronchoscope or suspension laryngoscope, so it is not often used with endobronchial lesions below the proximal trachea. Moreover, the CO_2 laser is not a good photocoagulation device, in contrast to Nd:YAG and KTP wavelengths.

The predominant tissue effects of Nd:YAG lasers are thermal necrosis and photocoagulation. Thermal necrosis uses higher energy levels to destroy tissue, causing the formation of eschar. The problem with this approach is the significant vascularity of most lung cancers. In destroying tissue with laser energy, large blood vessels can be perforated with the tissue destruction, leading to significant hemorrhage. This is less likely to occur if lower power settings are used. Photocoagulation, using lower energy levels, causes the tumor to shrink and diminishes the blood flow to that region. By devascularizing the tumor, more rapid mechanical debulking can be performed with improved control of bleeding.

Laser therapy can be performed via either flexible or rigid bronchoscopy. Many interventionalists prefer rigid bronchoscopy for laser procedures when possible. Nd:YAG laser fibers can be passed through the working channel of most flexible bronchoscopes. An advantage of using the flexible bronchoscope is that laser energy can be delivered to areas that cannot be reached with a rigid bronchoscope (Brutinel et al. 1987; Mathisen and Grillo 1989; Hetzel et al. 1983; Mehta et al. 1985; McDougall and Corese 1983; Toty et al. 1981; Dumon et al. 1982; Arabian and Spagnolo 1984; Beamis et al. 1991; Sonett et al. 1995; Macha et al. 1994; Desai et al. 1988; Stanopoulos et al. 1993; Cavaliere et al. 1994; Ross et al. 1990). For this reason, a fiberoptic bronchoscope can be inserted through the rigid bronchoscope whenever necessary.

The reported success rate of symptom palliation using laser energy in the endobronchial management of lung cancer is high. Reports of clinical im-

provement rates range from 84% to 92% following laser bronchoscopy (Dumon et al. 1982; Beamis et al. 1991; Cavaliere et al. 1988; Kvale et al. 1985; Eichenhorn et al. 1986). Other studies demonstrate improved survival in patients treated with laser bronchoscopy (Brutinel et al. 1987; Desai et al. 1988; Stanopoulos et al. 1993; Petrovich et al. 1981).

7.2.3.3 Endobronchial Prosthesis

Endobronchial prosthesis involves the use of stents, which can be placed in response to several clinical situations: intrinsic, extrinsic, or mixed endobronchial obstruction. Stents work well in conjunction with other modalities such as laser and mechanical debulking of tumors. Currently, stents are composed of Silastic rubber and metal alloys, or hybrids. Advantages and disadvantages of each are given in Tables 7.1 and 7.2.

7.2.3.3.1 Silastic Stents

Many of the Silastic stents now in use evolved from the Montgomery T–tube, which was first used in the early 1960s. This T-shaped stent supports the entire trachea with an arm that extends through a permanent tracheostomy. In patients with a patent tracheostomy, the Montgomery T-tube remains an excellent tool for the management of endotracheal disease (Colt and Dumon 1993; Cooper et al. 1989; Montgomery 1965).

In 1990, Dumon reported the use of what is now referred to as the Dumon stent (Novatech, Plan de Grasse, France). Developed in 1987, it is a Silastic stent with evenly spaced studs along its outside walls (Fig. 7.1). The studs are intended to minimize migration of the stent in the airway. The studs also allow the clearance of secretions around the walls of the stent.

Dumon stents are effective in maintaining their structural integrity when placed endobronchially. The solid walls of the stent prevent tumor growth from re-obstructing airways. In the situation of a newly diagnosed lung cancer with airways obstruction, the endobronchial tumor can be debulked and

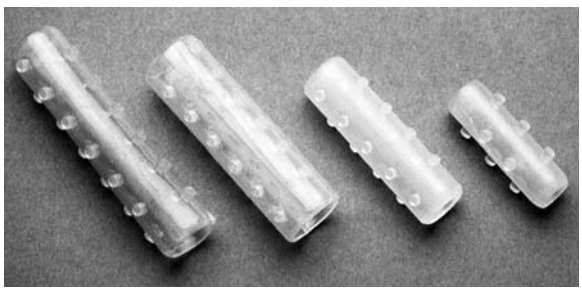

Fig. 7.1. The Dumon Silastic stent

Table 7.1. Advantages/disadvantages of Silastic stents

Advantages:	Disadvantages:
• Removable and replaceable	• Potential for migration/dislodgment
• No growth through stent	• Rigid bronchoscopy needed for placement
• Low cost	• Possible secretion adherence
• Low likelihood of granulation tissue formation	

Table 7.2. Advantages/disadvantages of metal stents

Advantages:	Disadvantages
• Easy to place	• Permanent
• Good wall/internal diameter relationship	• Tumor regrowth (non-covered)
• Powerful radial force	• Possible migration of covered stents
• Excellent conformity for irregular tracheal or bronchial walls	• Significant granulation tissue stimulation
• Good epithelialization	• Epithelialization adversely affecting wall mechanics and secretion clearance
	• Radial force causing necrosis of bronchial wall, erosion, fistulas, perforation

then a stent placed prior to the initiation of radiotherapy, chemotherapy, or both. Both external beam radiotherapy and brachytherapy can be used with a Dumon stent in place.

Another advantage of the Dumon stent is the ease of its removal. This can be important when endobronchial procedures are used early in the management of cancer patients. After definitive therapies have been used (radiation, chemotherapy), re-evaluation of the airway can be performed, at which time the stent can be left in place, removed (if deemed of no further clinical advantage), or replaced with a larger stent that would further improve the caliber and stability of the airway. The disadvantages of the Dumon stent are the potential for migration and the need for a rigid bronchoscope for placement. Migration occurs less often when an experienced interventional endoscopist places the stent (Colt and Dumon 1993; Dumon 1990; Tojo et al. 1996; Dumon et al. 1996; Diaz-Jimenez et al. 1994; Freitag et al. 1995; Clarke et al. 1994).

Another Silastic stent is the Hood stent (Hood Laboratories, Decatur, Georgia). The Hood stent is similar to the Dumon stent in design and use. The Hood stent is placed in the same manner as the Dumon stent, using a rigid bronchoscope (Fig. 7.2). (Gaer et al. 1992) The Rüsch-Y stent (Rüsch, Duluth, Georgia) is a Silastic stent with stainless steel c-rings that artificially represent the cartilage (Fig. 7.3). The posterior wall of the stent is made of a thinner Silastic plastic to make it more functional, similar to the membranous trachea. The three available sizes of this stent are designed to traverse the entire length of the trachea with branches into the right and left main stem bronchi. The Rüsch-Y stent requires rigid bronchoscopy and is difficult to place, remaining uncommon in clinical practice. Despite this, the Rüsch-Y stent offers excellent results when placed in the appropriate. The Polyflex stent (Boston Scientific, Boston, Massachusetts) is a woven polymer stent made of silicon with a complete coating of the same material. Due to its design, like the other Silastic stents, it also does not allow growth through its wall (Fig. 7.4).

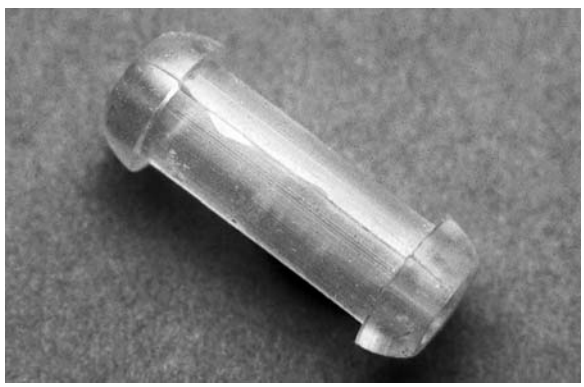

Fig. 7.2. The Hood bronchial stent

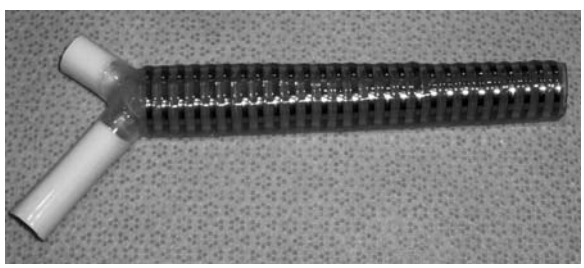

Fig. 7.3. The Rüsch-Y Hybrid stent

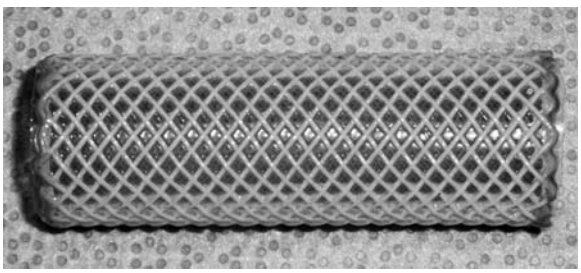

Fig. 7.4. The Polyflex stent

7.2.3.3.2 Metal Stents

Metal stents, such as the Gianturco (Cook, Bloomington, Indiana), the Palmaz (Johnson & Johnson Interventional Systems, Warren, New Jersey), the Wallstent (Schneider, Minneapolis, Minnesota), and the Ultraflex (Boston Scientific, Boston, Massachusetts) have been used in the endobronchial management of lung cancer. The advantage of metal stents is the relative ease for placement via a flexible bronchoscope with fluoroscopic assistance. This ease of placement has led some bronchoscopists to use these stents as their only method to manage endobronchial disease. Such a practice limits the options to patients that may otherwise be available if all interventional modalities were offered. The wire mesh design of many of the original metal stents did not prevent the tumor from growing through the stent. The Wallstent and Ultraflex stents are now available in covered versions. A wrap is applied to the outside of the wire mesh to prevent tumor invasion through the stent. Data that support the use of both of these stents for the endobronchial management

of lung cancer are available (Colt and Dumon 1991, 1993; Tojo et al. 1996; Boliger et al. 1993; Gelb et al. 1992).

Wallstents are made of woven stainless steel wires with exposed proximal and distal ends (Fig. 7.5). These exposed ends imbed in the endobronchial mucosa to fix the stent into place. Significant stimulation of granulation tissue development at both the proximal and distal ends of the exposed Wallstent is a concern for long-term endobronchial management. Studies using this stent demonstrate excellent initial outcomes, particularly with the release of the covered version (Tojo et al. 1996; Tsang et al. 1992).

Ultraflex stents are made of nitinol, a titanium and nickel alloy, which has little bioreactivity. This stent has excellent inner to outer diameter and conforms well to various airway shapes, maintaining an equal pressure along the entire length of the stent. Ultraflex stents are available in a variety of lengths and diameters. Overall the covered version of this stent is excellent for use in palliation of airway obstruction (Fig. 7.6).

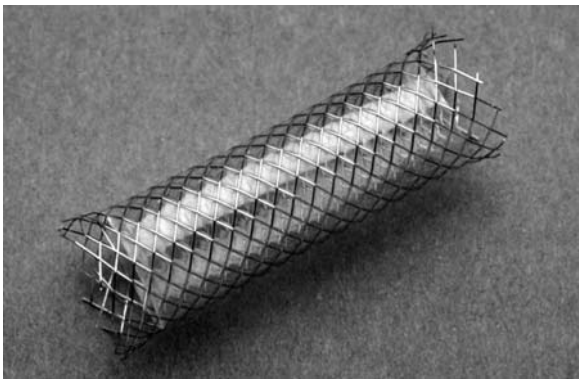

Fig. 7.5. The Wallstent – covered

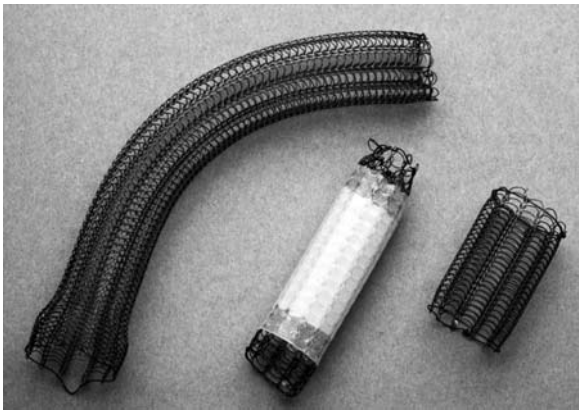

Fig. 7.6. The Ultraflex stent – covered and uncovered

Alveolus stents (Alveolus Charlotte, North Carolina) are another metal stent that will soon be available for clinical use (Fig. 7.7). They have all of the advantage of Ultraflex stents, with the added benefit of removability. After further studies have been completed, this may become the stent of choice in the future, merging the positive aspects of both metallic and Silastic stent technology.

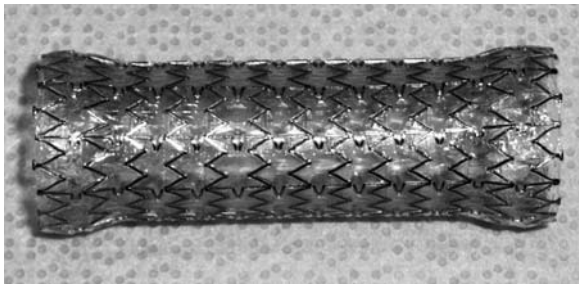

Fig. 7.7. The Alveolus stent

The uncovered portions of metal stents epithelialize as they remain in the airways, thereby becoming incorporated into the wall of the bronchus. This epithelialization changes the mechanics of the airways with time by making them stiffer, which may lead to further airway complications (Freitag et al. 1995; Gelb et al. 1992). This may not be a concern in situations of palliation of late stage disease, but must be considered if long-term survival is expected. Another consideration with metal stents is that once they are inserted, their removal can be difficult and often impossible. Although uncommon, another risk with the use of metal stents is the erosion that can occur through bronchial/tracheal walls. This was more of a concern with the older Gianturco stents than with newer metallic stents.

Stents are effective tools for the endobronchial management of lung cancer. Stents should be chosen carefully, weighing advantages and disadvantages of each.

7.2.3.4 Photodynamic Therapy

Photodynamic therapy (PDT) is an important adjunctive modality to the management of endobronchial disease, but it does not replace Nd:YAG lasers, stents, and rigid bronchoscopy. PDT also can be used with bulky disease, but most interventionalists feel that it is of limited benefit in this role (Lam 1994; Sutedja et al. 1994). The most suitable lesions for PDT are in situ carcinomas or those limited to 4–5 mm of microinvasion (Furuse et al. 1993).

A photosensitizing drug is intravenously administered to the patient 48–72 h prior to the procedure. Porfimer sodium (Photofrin, Axcan Pharma, Birmingham, Alabama) is the most common agent used. This photosensitizer penetrates all cells systemically. It is not cleared as quickly from cancer cells as in most other cells of the body and is therefore found in higher concentrations in cancer cells as opposed to the endothelium surrounding the tumor at the time of treatment (Furuse et al. 1993; Hayata et al. 1993). An argon dye laser is then used to provide the 632-nm wavelength light energy required to activate the intracellular porfimer sodium. The laser energy is transmitted via a flexible quartz fiber, which can be used through either a flexible or rigid bronchoscope. The fiber tip can be placed in close proximity to the tumor mass, or it can be imbedded into the tumor to provide the energy needed to start the intracellular activation of the porfimer sodium. This reaction leads to cellular destruction by a variety of mechanisms. Tissue necrosis ensues as the cancer cells die (Furuse et al. 1993; Hayata et al. 1993; Moghissi et al. 1999).

As the neoplastic tissue becomes necrotic, it must be removed. This requires repeated bronchoscopies. Flexible bronchoscopy is commonly performed daily or every other day for up to 1 week to remove the necrotic tissue produced. The necrosis of bulky tumor can be dangerous to the patient if the necrotic tissue separates from the bronchial wall and occludes the airway. In some programs that use only PDT, patients remain intubated following the procedure for 1–2 days because of this concern. If necrotic tissue is removed over the first 24–48 h, a second laser application to the cancer can be performed, thus improving the cancer tissue destruction.

PDT is an excellent therapeutic modality for patients with early-stage cancers. It destroys neoplastic tissue effectively and is an outstanding therapeutic modality in carcinoma in situ and microinvasive cancers. Further discussion of this is beyond the scope of this chapter. PDT is a necessary tool in the armamentarium of endobronchial treatments, but the time delays and multiple steps of management make it a more cumbersome therapy for the management of late-stage endobronchial lung cancer (Moghissi et al. 1999).

7.2.3.5 Cryotherapy

Cryotherapy is another method to destroy malignant tissue that obstructs the tracheobronchial tree. Tissue is frozen and then thawed to destroy it, instead of the heat used in laser-based technologies. A probe is placed onto or into an obstructing tumor mass. Liquid nitrogen (–196°C) or nitrous oxide (–80°C) cools the probe tip when performing cryotherapy. The tissue freezing induced by cryotherapy leads to the destruction of all cells in an area of approximately 1 cm in diameter from the probe tip. Vascular thrombosis occurs with the super-cooling of tissue, minimizing the bleeding during resection of the tumor.

The limiting factor to using cryotherapy is that the tissues destroyed with the freezing procedure take time to die and necrose. This requires returning to the lesion to remove the necrosed tissue and, in some cases, repeating treatments. Although cryotherapy is effective at tumor destruction and management, the necessity of repeated procedures makes this a more time-consuming technique to perform, limiting its usefulness in the management of bulky endobronchial disease causing severe dyspnea (Maiwand and Homasson 1995). Another advantage of cryotherapy is that it can be used at any level of oxygen (FiO_2) a patient may require to correct hypoxia. Laser, electrocautery, and argon plasma coagulation all must be used in an environment with an $FiO_2 \leq 40\%$. If the FiO_2 is greater than 40%, the risk of an airway fire become very high and places the patient at significant risk.

7.2.3.6 Electrocautery/Argon Plasma Coagulation

Electrocautery devices or the argon plasma coagulation (APC) catheters can be introduced through a flexible bronchoscope (one that is grounded and designed for this therapy) and can then be used to debulk endobronchial disease. With both devices electrical energy is used to cauterize tissue, thus minimizing the bleeding that occurs with tumor resection. Endobronchial electrocautery treatment can be used similar to laser therapy and/or cryotherapy for managing advanced endobronchial lung cancer (Gerasin and Shafirovsky 1988).

Electrocautery uses unipolar electrodes to deliver electric current to the tissue. The delivered energy affects the tissue in three ways: an electrolytic effect (altering chemical bonding), a capacitance effect (affecting the electrical potential of local structures), and a thermal effect (due to the resistance of the tissue to he flow of electrical current). Of these, the thermal effect is clinically that, which is most desired.

Argon plasma coagulation, instead of using a unipolar contact delivery mechanism for electrical

energy, uses ionized argon gas as the conductance medium between the electrode and tissue. This noncontact tool allows a "painting" of the desired area with, in essence, a gaseous form of electrical energy causing a similar thermal effect as electrocautery. This delivery of energy allows large areas to be treated relatively quickly and can be an ideal tool when significant bleeding is encountered. On the other hand, the more defined area of contact with the electrocautery delivery devices allows a higher energy to be delivered point specific to the tissue, creating an excellent tool for cutting as well as coagulating.

7.2.3.7 Balloon Dilatation

Balloons used for intravascular procedures can be used to manage endobronchial stenosis secondary to both malignant and benign disease. At our institution, we are currently using the Guidant vascular balloon (Guidant, Santa Clara, California) for endobronchial narrowings. The Guidant balloon comes in a variety of diameters and lengths to help dilate areas of bronchial compromise. Occasionally, strictures are dilated prior to the placement of a stent or even used to fully expand a stent already in place.

The balloon is passed endobronchially via either a rigid or flexible bronchoscope. The appropriate diameter and length of the balloon are chosen for the particular lesion. Ideally, 5–20 mm of balloon should extend beyond the lesion both proximally and distally. The treatment should be performed as a series of dilatations with gradual increase in the balloon diameter to minimize the risk of tracheobronchial rupture. The balloon is inflated with a fluid, usually saline. The use of fluid provides a more even distribution of pressure across the entire balloon rather than the unequal pressures seen when air is used to inflate the balloon. Once inflated to the prescribed pressure, the dilatation pressure should be maintained for 1–2 min; 2 min is preferable if the patient can tolerate this without discomfort or hypoxia.

Balloon dilatation is an adjunctive therapy to bronchoscopy, laser, and/or stenting. When used alone, its effects are most often temporary and lead to symptom recurrence.

7.2.4 Pleural Disease

Malignant pleural effusions occur in 7%–15% of lung cancer patients (Cohen and Hossain 1966; Emerson et al. 1959; Johnston 1985; Le Roux 1968), greater than half of whom develop dyspnea (Chernow and Sahn 1977). The mechanism of dyspnea with pleural effusions is unclear. Mechanical factors influencing the chest wall, mediastinum, pleural space, and lung itself may all contribute to the sensation of dyspnea in the patient with a pleural effusion.

Pleural effusions in the setting of lung cancer may be malignant or benign. Three primary techniques are used to diagnose malignant pleural effusions: thoracentesis, closed needle pleural biopsy, and pleuroscopy or medical thoracoscopy.

Thoracentesis is the most common technique used in the initial evaluation of pleural effusion. Cytologic processing of pleural fluid obtained by thoracentesis yields malignant cells in 62%–90% of true malignant pleural effusions (Johnston 1985; Hsu 1987; van de Molengraft and Vooijs 1988; Starr and Sherman 1991; Loddenkemper et al. 1983). Closed needle pleural biopsies remain an option for the evaluation of a malignant pleural effusion. Pleural biopsy historically has a lower diagnostic yield than cytology from thoracentesis, 40%–75% (Starr and Sherman 1991; Loddenkemper et al. 1983; Prakash and Reiman 1985; Poe et al. 1984; Escudero Bueno et al. 1990). There is a 7%–12% additive yield from closed needle biopsy over cytology alone (Starr and Sherman 1991; Loddenkemper et al. 1983; Prakash and Reiman 1985). Perhaps because of this small, added benefit, the practice of closed needle pleural biopsies has diminished in most clinical practices.

Medical thoracoscopy is a procedure more commonly being used by non-surgeons for the diagnosis and treatment of pleural effusions. This technique has excellent results in the diagnosis and treatment of malignant pleural effusions in appropriate populations. In a study of patients being evaluated for malignant effusion, all enrolled patients had cytologic assessment by thoracentesis, closed needle pleural biopsies, followed by thoracoscopy. This representative study demonstrated diagnostic yields of 62% for thoracentesis, 44% for closed needle pleural biopsy, with a combined sensitivity of 74%, and a diagnostic yield for medical thoracoscopy of 95% (Loddenkemper 1998). Other studies have demonstrated similar results (Boutin et al. 1981; Oldenburg and Newhouse 1979; Menzies and Charbonneau 1991; Canto et al. 1977). After medical thoracoscopy had been performed less than 10% of effusions remain undiagnosed (Boutin et al. 1981; Canto et al. 1977; Loddenkemper 1981; Martensson et al. 1985), while after thoracentesis for cytology and closed needle pleural biopsy are performed greater than 20%

of effusions remain undiagnosed (Storey et al. 1976; Hirsch et al. 1979; Lamy et al. 1980).

The major indication for treating a pleural effusion is for the relief of dyspnea. Once the diagnosis has been made, a therapeutic plan needs to be established; remembering that the etiology of the dyspnea is more complex than the amount of fluid identified in the pleural space (Estenne et al. 1983; Light et al. 1986; Agusti et al. 1997; Karetzky et al. 1978; Brown et al. 1978; Krell and Rodarte 1985), and may be related to problems with the lung itself (lymphangitic spread of tumor, atelectasis, direct tumor invasion, etc.). Trapped lung due to parenchymal or pleural disease will minimize the relief of dyspnea by the evacuation of pleural fluid and/or pleurodesis. Therefore initially, a therapeutic thoracentesis should be performed to assess the effects upon breathlessness by fluid removal and the ability of the lung to re-expand, as well as the rate and degree of re-accumulation.

Chest radiographs should be used to assess as to whether or not the pleural fluid is free flowing or loculated, as well as the mediastinal position in respect to the volume of the pleural effusion. Contralateral shift of the mediastinum with large effusions suggests that evacuation of the effusion should provide relief of dyspnea to the patient. Expert opinion would suggest that no greater than 1–1.5 l of effusion be removed at each thoracentesis, stopping earlier should the patient experience dyspnea, chest pain, or coughing. The coughing and/or pain experienced by a patient is considered to be due to the expansion of the lung. It is suggested that this subpopulation of patients (those that have pain, etc.) may benefit from immediate chest tube placement with pleural evacuation or medical thoracoscopy with pleurodesis due to the common belief that the patient's lung is re-expanding (ATS Guidelines 2000).

Ipsilateral or at least no contralateral mediastinal shift identified on chest radiographs suggests trapped lung or endobronchial obstruction, potentially limiting the relief of dyspnea a patient may experience with evacuation of pleural fluid. Limited removal of fluid ($\leq$300 ml) by thoracentesis is suggested in this sub-population to minimize reducing the pleural pressure rapidly and increasing the risk of re-expansion pulmonary edema in these patients (ATS Guidelines 2000).

Pleural pressure monitoring can be performed before, during, and after thoracentesis to determine the amount of fluid that can be removed in a physiologic manner. The use of this technique may minimize the risk of re-expansion pulmonary edema and help assess for the presence of a trapped lung at the time of the diagnostic/therapeutic thoracentesis (Rodriguez-Panadero and Lopez-Mejias 1989; Light et al. 1980; Lan et al. 1997). Pleural pressure monitoring may be a more objective assessment for trapped lung than chest radiograph assessment but is complex and not regularly practiced.

Therapeutic modalities for managing malignant pleural effusions include repeated therapeutic thoracentesis, chemical pleurodesis via chest tube or medical thoracoscopy, pleuroperitoneal shunting, pleural drainage catheters, and systemic therapy. Repeated therapeutic thoracocenteses are a viable option for those patients with poor performance status or with advanced disease. There are no studies upon which to base repeated thoracentesis. If the malignant pleural effusion continues to accumulate, a more definitive procedure can be considered. A variety of new and old agents can and are being used for pleurodesis.

Chemical pleurodesis has a reported complete response rate of 64%. A comprehensive review of pleurodesis further discussed response; fibrosing agents as a group had a 75% complete response, with talc specifically, 93%. Antineoplastic agents had a reported complete response at initial pleurodesis of 44% (Walker-Renard et al. 1994).

Talc is currently the sclerotic agent of choice for pleurodesis and can be used either via chest tube placement with pleural evacuation and talc slurry instillation, or during medical thoracoscopy or video-assisted thoracic surgery, with talc poudrage. Poudrage and slurry pleurodesis methods demonstrated clinical success rates of 91% with no significance difference in recurrence rates of effusions (Hartman et al. 1993; Hamed et al. 1989; Fentiman et al. 1986; Kennedy et al. 1994; Todd et al. 1980; Fentiman et al. 1983). The greatest concern with the use of talc is the one percent risk of developing fatal acute respiratory distress syndrome (ARDS) and the 4% risk of non-fatal ARDS reported in the literature (Milanez Campos et al. 1997; Rehse et al. 1996). Despite these reported risks, talc is the most commonly used pleurodesis agent.

Other pleurodesis agents used include doxycycline, which when compared to historical controls had a similar clinical success rate as previous studies with tetracycline, 80%–85% (Patz et al. 1998; Heffner et al. 1994; Pulsiripunya et al. 1996). Bleomycin has been used and compared in randomized format to tetracycline, and found to have similar complete response rates also (Hartman et al. 1993; Moffett and Ruckdeschel 1992; Martinez-Moragon et al. 1997). Doxycycline when compared directly with

bleomycin had a 79% complete response to bleomycin's 72% (Hayata et al. 1993). When bleomycin was compared to talc, talc demonstrated superior complete response rates in all studies (Walker-Renard et al. 1994; Hamed et al. 1989; Zimmer et al. 1997).

The use of pleuroperitoneal shunting has been reported for the management of malignant and other intractable pleural effusions. All of these studies are case series rather than randomized in any fashion. Initial data looks promising, but it has not been evaluated in head-to-head studies with more conventional treatment methods (i.e. chest tube drainage with chemical pleurodesis) (Ponn et al. 1991; Schulze et al. 2001; Reich et al. 1993; Petrou et al. 1995).

Another technique, tunneled long-term catheter drainage of the pleural space is also found in several studies in case series formats. These studies suggest good results for the relief of dyspnea over extended time in patients with malignant effusions. Although encouraging, many of these studies are retrospective in assessment with no comparison to other treatment modalities (Chen et al. 2000; Pien et al. 2001; Pollak et al. 2001). One device, the Pleurx catheter (Denver Biomedical, Golden, Colorado) shows significant promise. This device when placed into the pleural space, allows the patient to drain a portion of their pleural effusion on a daily basis, thereby controlling the build-up of fluid and in doing so, limiting the dyspnea patients experience due to this complication. When used daily, one study (Putnam et al. 1999) suggests that approximately 50% of these patients will experience pleurodesis without the use of sclerotic agents in a median of 25 days. Such techniques should be explored further to fully understand their possible palliative implications.

For malignant effusions due to small cell lung cancer lung cancer the therapy of choice is systemic chemotherapy. Often these patients will respond with resolution of pleural effusions and dyspnea (Livingston et al. 1982).

7.2.5 Tracheoesophageal Fistula

Tracheoesophageal fistulas are serious complications of lung and esophageal cancer. The life expectancy after the development of a tracheoesophageal fistula with no therapy is estimated at 1–7 weeks. Patients have repeated aspiration of food, gastric contents, and saliva. This persistent aspiration leads to patient distress due to coughing and shortness of breath. Patients can develop recurrent pneumonia with persistent inflammation of the airways. Patients frequently lose weight and become dehydrated secondary to their intolerance of taking anything by mouth. Even with abstinence from eating and drinking most patients continue to have symptoms due to lack of control of their own secretions and reflux of gastric contents.

Curative resection of the involved tracheal-bronchial and/or esophageal segments in face of a malignancy should not be considered, as most of these patients are at the end-stage of their lung cancer and palliative management should be emphasized. Esophageal bypass procedures should also not be considered, as they have very high morbidity.

The goals of therapy for tracheoesophageal fistula are to restore patency of the trachea, bronchi, and/or esophagus, to prevent spillage of further material into the lung, and ensure the patient receives nutrition and fluid. By addressing all of these issues, the most debilitating symptoms of this condition, the dyspnea and coughing, are also corrected.

Double stenting of the tracheo-bronchial tree and the esophagus appears to be the procedure that yields the best overall results for symptomatic relief in patients with this condition. Clinical series have attempted either esophageal or tracheo-bronchial stenting individually with mixed results. Most series with higher success rates use a double-stenting technique. With limited published information, our clinical experience has been most successful with initial bronchial stenting followed in close succession with esophageal stenting (Freitag et al. 1996; Colt et al. 1992; Alexiou et al. 1998; Koeda et al. 1997; Spivak et al. 1996; Cook and Dehn 1996).

Placement of a percutaneous entero-gastric (PEG) or percutaneous entero-jejunal (PEJ) tubes can ensure proper nutrition and fluid management in patients with tracheoesophageal fistulas. Patients may be able to eat once the double stenting is performed, but maintaining adequacy of fluid status and nutrition is often difficult.

7.3 Cough

Cough can be a debilitating symptom for some patients with lung cancer. As with dyspnea, the etiology of the cough should be identified to best treat a patient. Cough can be a manifestation of endobronchial disease, pleural disease, or tracheoesophageal fistula as discussed above. Cough can also originate from

something as uncommon as endobronchial irritation status post-resection, when the staples migrate endobronchially and become foreign bodies in the airways. Or cough may be a manifestation of something more common, such as the patients underlying COPD with or without a tracheobronchitis. Again, the most useful management remains that specifically suited to the patient's individual problem.

Sometimes, however, the etiology of the cough is never identified. It is in these situations where cough suppressants like benzonate (Donna and Walsh 1998) or opiates (particularly codeine) can be used. Occasionally beta-2 agonists are prescribed with identified underlying COPD but are only occasionally of significant benefit (Kvale et al. 2003).

7.4 Hemoptysis

Hemoptysis will be the presenting symptom in 7%–10% of lung cancer patients. About 20% will have hemoptysis some time during their clinical course, with 3% having terminal massive hemoptysis (Miller and McGregor 1980; Chute et al. 1985; Hyde and Hyde 1974; Grippi 1990; Frost et al. 1984). Massive hemoptysis, that which most commonly requires intervention, has a broad definition as expectoration of from 100 to 600 ml of blood in 24 h. Blood clot formation obstructing airways is suggested as the most common cause of respiratory insufficiency from massive hemoptysis.

Initial evaluation of patients with known lung cancer in a specific location is somewhat different from that of those patients without a known diagnosis. Massive hemoptysis due to lung cancer has a much poorer prognosis than hemoptysis of other etiologies. One retrospective review defined the mortality of massive hemoptysis as 59% in patients with bronchogenic carcinoma (Corey and Hla 1987). In many of these patients surgery, a more definitive therapeutic modality is not on the algorithm for intervention in that many of these patients are already non-surgical candidates from their primary disease.

The initial priority in managing a patient with massive hemoptysis should be, maintaining adequate airway protection (Cahill and Ingbar 1994; Jean-Baptiste 2000). This may require endotracheal intubation to maintain good control. It is suggested that use of a single lumen endotracheal tube is of greater benefit than double-lumen endotracheal tubes (Strange 1991).

Standard endotracheal intubation should use the largest tube possible. Occasionally selective right or left main stem intubations are performed to protect the non-bleeding lung. This technique can be beneficial in protecting the good lung, but the fact that when a right sided intubation is performed, it often occludes the right upper lobe and the difficulty of selective left sided intubations need to be considered prior to attempting this.

Optimization of oxygenation needs to then be undertaken to clinically stabilize the patient with massive hemoptysis. Next, assessment and management of cardiovascular/hemodynamic status has to take place for proper management of the patient with hemoptysis (Cahill and Ingbar 1994; Jean-Baptiste 2000). Reversal of any coagulation disorders should to be considered at the time of hemodynamic management. If the bleeding site is known, the bleeding lung should be placed in the dependent position to help protect the non-bleeding lung. Cough suppression with a narcotic (particularly codeine) can be used to help minimize further endobronchial bleeding in non-intubated patients.

Bronchoscopy is often used to identify the source of bleeding. Early bronchoscopy to assess the site of bleeding is recommended. Studies have demonstrated identification of the bleeding site 91% of the time when performed early versus 50% when delayed (Credle et al. 1974). A more recent retrospective study had much less supportive results, with the limitation of early being defined as less than 48 h. Despite this, there results suggest early bronchoscopy is indicated (Gong and Salvatierra 1981). The goal of early bronchoscopy should be first to lateralize the bleeding side, secondly localization of the specific site to a lesion, lobe or segment, and lastly identify the lesion that is bleeding whenever possible.

In the patient with hemoptysis, several studies have looked at the use of early high-resolution computed tomography (HRCT). In those patients without a diagnosis, this technique appears to have benefits. The use of HRCT may help diagnose: bronchiectasis, an aspergilloma, and possibly identify a previously undiagnosed lung cancer (Set et al. 1993; McGuiness et al. 1994; Muller 1994; Hirschberg et al. 1997). In the patient with the known diagnosis of lung cancer, this technique will be of limited value, particularly in those patients that have had previous radiation therapy.

The first therapeutic approach, which should be considered for the management of hemoptysis, particularly massive hemoptysis, in the patient with lung cancer is external beam radiation (Hoegter 1997).

Prior to initiation of this therapy, sometime other procedures are necessary to temporize the patient.

Endobronchial management of hemoptysis should be subdivided into identified location of bleed (i.e. bleeding from the anterior segment of the left upper lobe) versus bleeding from an identified source (i.e. bleeding from an endobronchial tumor). When the location of the bleed is identified, but no direct source is found, endobronchial management includes: bronchoscopic tamponade of the segment, usually recommended with continuous suctioning to collapse the segment (Zavala 1976). The use of vasoactive drugs (i.e., 1:10,000 epinephrine solution) is suggested, although this is most useful on visualized lesions (Magee and Williams 1982; Worth et al. 1987). Ice saline lavage is discussed as a temporizing technique for control of hemoptysis (Sahebjami 1976; Conlan and Hurwitz 1983). Balloon tamponade techniques, using a variety of different balloons, can control hemoptysis and minimized risk of further aspiration of blood. It is suggested that balloons remain in place for 24–48 h to allow tamponade of hemoptysis (Schlehe et al. 1984; Tsukamoto et al. 1989; Bense 1990).

When an endobronchial source of bleeding is identified, attempts with vasoactive drugs can be used, but often this type of bleeding requires a more aggressive mode of management. Use of Nd:YAG photocoagulation is an efficient tool for the management of bleeding endobronchial lesions with a reported response rate of 60% (Hetzel and Smith 1991; Jain et al. 1985; Clarke et al. 1994). Use of electrocautery is also suggested in the literature but support other than anecdotal reporting is limited for the management of hemoptysis. Use of argon plasma coagulation in one study demonstrated resolution of hemoptysis in 100% of patients with a 3-month follow-up (Morice et al. 2001).

Bronchial artery embolization appears to be a semi-definitive therapy for hemoptysis. Embolization stops bleeding in greater than 85% of all patients that it is used. This excellent success rate should be tempered with the fact that 10%–20% of these patients have rebleeding in the next 6–12 months (Mal et al. 1999; White 1999; Osaki et al. 2000; Eurvilaichit et al. 2000). The management and long term follow-up of bronchial artery embolization is limited by the few cases of lung cancer managed in almost all studies. Much of the information used must be extrapolated to the lung cancer population.

Surgery would appear to be the most definitive therapeutic modality available. Retrospective studies demonstrate good long-term results with surgical resection of the source of bleeding (Knott-Craig et al. 1993; Bobrowitz et al. 1983). This route should be cautioned in that limited information regarding surgical resection of a bleeding source due to lung cancer is available. If a lung cancer was previously diagnosed, surgical resection should have been considered had the patient been a surgical candidate and the tumor amenable to surgical resection. If a tumor was previously not amenable to surgical treatment, the addition of hemoptysis to this scenario should not give cause to surgical intervention at the time of this complication. In the case where a cancer is newly diagnosed at the time of management of hemoptysis, controlling the hemoptysis with other techniques to allow full assessment/staging prior to acute surgical management should be performed. Rarely, in a life-threatening situation, surgical intervention for both the hemoptysis and the lung cancer may be effective.

7.5 Conclusion

There are many symptoms associated with lung cancer that can be palliated, to allow patients the opportunity to maximize other more definitive treatments of their lung cancer. Consultation with a team of experts at your facility will allow the quickest assessment of a patients' complaints and the most rapid institution of palliative measures.

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Treatment-Related Toxicity

8.1 Hematologic Toxicity in Lung Cancer

Francesc Casas and Núria Viñolas

CONTENTS

8.1.1 Introduction

Hematologic toxicity in non-surgical treatment of lung cancer generally depends on the type of treatment administered, whether chemo- and/or radiotherapy. This chapter will describe the normal physiology of bone marrow followed by a synthesis of the current knowledge of the toxicity of these two treatments either alone or in combination. Lastly, support treatments and the management of these secondary effects is proposed.

The toxicity of tumor cells after chemo- and radiotherapy, administered either alone or in combination is dose-dependent. Aggression to the bone marrow, which is expressed by a reduction in circulating blood cells, is often the main dose-limiting toxicity because of the risks of anemia, bleeding and infection. Strategies aimed at protecting the hematopoietic cells or the stroma of the bone marrow from death induced by the treatment, the acceleration of hematopoiesis after treatment, may theoretically allow more intensive treatments in lung cancer without the above mentioned associated risks. To know the true impact of individual or combined, sequential or concurrent treatment to thereby act accordingly, it is necessary to know the structure and function of the bone marrow as an organ. Thus, the pluripotent stem cells replicate and differentiate in lymphoid or myeloid lines through a complex process regulated by a network of hematopoietic growth factors as well as by cellular interactions. The cascade through myeloid differentiation leads to the erythrocytes, platelets, granulocytes and macrophages, while the lymphoid differentiation leads to T and B cells. Families of growth factors (or cytokines) which control these processes of replication and differentiation have been identified. The hematopoietic progenitor cells and their daughter cells are enveloped in a stroma of endothelial cells, adventitial cells, fibroblasts, macrophages and fat cells in the sinus of the bone marrow. This microscopic medium is a physical support and director of the development of the replication process. In addition, the geographic distribution of the bone marrow is particularly relevant to know the possible local effects of radiotherapy in the treatment of lung cancer. The most functional and important localizations are the pelvis, the vertebrae (these two represent 60% of the total of the bone marrow), as well as the ribs, the sternum, the cranium, the scapula and the proximal portions of the femur and humeral bones. It should also be remembered that hematopoietic stem cells are also found in the spleen and circulate in the blood.

Bone marrow dysfunction in neoplastic processes may be due to different etiologies:

1 Depletion or direct lesions of the hematopoietic stem cells
2 Functional or structural damage of the stroma or the microcirculation
3 Lesion of other collaborator cells which have a regulator function or hemostasis

The consequences of the aggression of cytotoxic and radiotherapeutic treatment to the bone marrow should, therefore, be understood within the context of the previously described mechanisms. Nonetheless, it may be difficult to elucidate the most important variables due to the limitations in the evaluation of both the structure and bone marrow function. The peripheral determination of the blood cells fails to demon-

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strate the true extension of bone marrow suppression or its capacity to tolerate additional cytotoxic therapy mainly because of the capacity of the bone marrow to transitorily compensate the aggression. To evaluate several quantitative and functional aspects of the bone marrow cultures of progenitor cells, histopathologic studies (bone marrow aspirate and biopsy), and determined radioisotopes or stromal cell cultures may be used, although to a limited extent.

8.1.2 Toxicity in Chemotherapy

The myelosuppression directly caused by chemotherapy depends not only on the agent used but also on patient-dependent factors, such as age and general status. Important factors in relation to the type of chemotherapy administered are the doses, the interval of the doses, the route of administration or the use of a single or several antitumoral agents. On the other hand, the site of action of the antineoplastic drug within the cellular cycle also appears to influence myelosuppression (Howard and Pelc 1951).

It is known that the S phase represents DNA synthesis and M the period of mitosis. G1 and G2, respectively, represent the gaps between mitosis and the beginning of DNA replication and between the end of replication and the beginning of mitosis. Some cells have very prolonged G1 periods and may be considered as resting cells which are said to be in the G0 phase.

Most of the cells maturing in the bone marrow are actively dividing. This means that cytostatic drugs which act in a specific phase of the cycle, for example in the S phase of synthesis, cause a rapid, early and reversible reduction in the number of granulocytes. Thus, for agents which act on the cell cycle and which are phase-specific, the length of exposure determines the toxicity in relation to the greater number of cells exposed during continuous infusion compared to bolus administration. Other classes of agents, mainly the cell-cycle agents that are not specifically phase-selective (such as anthracyclines and certain alkylators, i.e. busulfan) may cause slightly more delayed suppression of bone marrow and longer recovery than phase-specific agents.

On the other hand, many hematopoietic stem cells are not in a cycle and may only be altered by agents which act in the G0 phase. These chemotherapeutic agents act on the DNA bridges provoking cell death. If a particular agent predominantly affects the stem cells rather than cells in specific phases of the cell cycle, then all the cell lines are suppressed. Very few cytostatics selectively depress the stem cell (i.e. nitrosoureas, streptozotocin) and none are used at present in the treatment of lung cancer.

The damage results from a depletion in the total number of stem cells (the stem cell pool) with a late myelosuppression pattern which takes place when the peripheral blood cells die and cannot be replaced. That is to say that myelotoxicity by chemotherapy agents produces a decrease in the production of blood cells more than an immediate elimination of the peripheral cells (Ratain et al. 1990).

Because of differences in the peripheral blood half life, drugs that induce myelosuppression first result in leukopenia followed by thrombocytopenia with the former generally being more severe than the latter. Thus, the nadir for neutrophils and platelets is normally between 7 and 15 days after drug administration. For most of the compounds, neutropenia and thrombocytopenia are reversible and not accumulative. In addition to the direct cytotoxicity at the level of the progenitor cells, at an erythrocytic level, blood cells with a more prolonged half life, the mechanisms involved may be direct hemolysis of the red blood cells after the administration of, for example, mitomycin (Vervey et al. 1987) or a decrease in the production of endogenous erythropoietin due to chronic renal insufficiency by cisplatin (Pivot et al. 2000). The pluripotent stem cells are protected from the toxic effects of chemotherapy because of their slow proliferation.

The biological differences among different patients affects the degree of bone marrow damage for a determined chemotherapy agent, although they may also reflect differences in bone marrow cellularity before treatment. Advanced age is associated with a reduction in bone marrow cellularity and a lower tolerance to chemotherapy which may be related to pharmacokinetic alterations of drugs in the elderly in whom drug clearing may be decreased. The nutritional status may also be an important factor in patients with a negative balance of nitrogen and weight loss is also associated since it has been found that it provokes lower tolerance to chemotherapy (Dewys et al. 1980). It is also known that anything which interferes with the route of activation, metabolism or excretion of a chemotherapy drug may exacerbate myelosuppression. Other possible causes include effects in cell regulation (that is, an alteration in growth factor secretion) or cell interaction. For example, it appears that chemotherapy may affect the response of endogenous erythropoietin to anemia causing a dysregulation in the normal control of red blood

cells (Miller et al. 1990). One of the main factors of toxicity for a given chemotherapy agent is the pharmacodynamic interaction between the drug and the combination of other anticancer drugs. Thus, one of the general principles for combining different drugs is that they should have a different limiting toxicity, although a sum of these effects is normally produced in relation to myelotoxicity. There is, however, an exception to this rule in the case of the combination of paclitaxel-carboplatin: paclitaxel decreases the platelet toxicity of carboplatin in relation to a non-pharmacokinetic mechanism (Calvert et al. 1999).

Patients who have undergone previous chemotherapy present a greater susceptibility of hematologic toxicity with new treatment. This observation has even led to the consideration of different doses of carboplatin in patients who have been previously treated (Albers and Dorr 1998). Previous irradiation may also decrease the tolerance to chemotherapy agents and vice versa. Finally, circadian variations have been reported in the pharmacokinetics of some drugs. Since cell division of hematopoietic cells has a circadian variation, the time of administration may influence hematologic toxicity (Kerr et al. 1990).

Chemotherapy is the standard treatment in patients with stage IIIB non-small cell lung cancer (NSCLC) with pleural effusion and stage IV. The aim of this treatment is palliative and attempts to improve the quality of life and prolong survival. It has also been demonstrated to have a role in stage III NSCLC as neoadjuvant therapy to surgery in stage IIIA with or without radiotherapy and in combination with the latter in patients with stage IIIB and good performance status. The role of chemotherapy in early stages as a neoadjuvant or complementary therapy to surgery is still under study.

The most frequent schedules of chemotherapy currently used in NSCLC include combinations of cisplatin or carboplatin with some of the new drugs (gemcitabine, vinorelbine, paclitaxel, docetaxel). All have been shown to be similar in regard to efficacy in stage IV although the toxicities observed, including hematologic toxicity, differs (Schiller et al. 2002). These combinations of chemotherapy cause grade 3 and 4 neutropenia which varies from 40% to 70% with febrile neutropenia in less than 10%. Some of the randomized studies comparing these different schedules have shown that the combination of cisplatin and vinorelbine causes grade 3 and 4 neutropenia in a greater percentage of patients, although in the study by Fosella et al. (2003), which compared this schedule with docetaxel in addition to platin drugs, did not find differences in regard to neutropenia. Grade 3 and 4 platelet toxicity was observed in 1%–55% of the patients, with a schedule combining cisplatin and gemcitabine showing a greater percentage of thrombocytopenias (Cardenal et al. 1999). No serious hemorrhagic events were reported with these different schemes. In the study by Scagliotti et al. (2002) in which patients were randomized to receive three different chemotherapy schedules (cisplatin-gemcitabine, carboplatin-paclitaxel and cisplatin-vinorelbine) the percentages of patients who received platelet transfusions for each arm was 8%, 2% and 8%, respectively, and were not consistent with the respective percentages reported for grade 3/4 thrombocytopenia. In regard to anemia, the percentages varied from 10% to 30%, with the schedules based on cisplatin and gemcitabine or vinorelbine being those producing the greater percentage of patients with anemia (Kelly et al. 2001; Schiller 2002).

Continuous infusion of paclitaxel leads to an increase in neutropenia without greater efficacy, thus, this drug is currently administered in shorter infusions of 1 or 3 h. The sequence of administration is also very important since an increase in myelotoxicity has been observed when cisplatin is administered before paclitaxel. Platelet toxicity is not of note in schemes including paclitaxel combined with carboplatin suggesting that paclitaxel protects against the thrombopenia associated with carboplatin.

To improve the effectiveness and/or reduce the toxicity of chemotherapy schedules based on cisplatin, different randomized studies have been carried out with schemes based on cisplatin and combination therapy without this drug. In a randomized study by Georgoulias et al. (2001), patients with advanced NSCLC received treatment with cisplatin and docetaxel versus gemcitabine-docetaxel and although no differences were observed in the effectiveness of both schedules, a better toxicity profile was found with the latter scheme including less neutropenia.

With respect to small-cell lung cancer (SCLC) the most commonly used schedules which show greater effectiveness are those based on cyclophosphamide and adriamycin combined with vincristine (CAV) or etoposide (CAE) or those based on a combination of platin and etoposide derivatives. The combination of cisplatin and etoposide produces less neutropenia than the CAV and CAE schemes although with more anemia (Fukuoka et al. 1991). The profile of hematologic toxicity with the combination of etoposide and carboplatin is similar to that found with the schedule of cisplatin except with a greater percentage of thrombocytopenia (Ettinger 1988).

The benefits of palliative treatment with chemotherapy in advanced lung cancer are basically achieved in patients with a good functional status. It was traditionally believed that patients with performance status 2 (PS 2) presented greater toxicity with chemotherapy, thereby reducing the possible beneficial effect. Retrospective analysis of prospective studies in patients with NSCLC receiving treatment based on cisplatin demonstrated that the subgroup of patients with PS 2 presented a much lower median survival than patients with a better general status. In this way the group of ECOG (Sweeney et al. 2001) has recently published the results of a subgroup of patients receiving chemotherapy with cisplatin and paclitaxel versus three experimental arms (cisplatin and gemcitabine, cisplatin and docetaxel and carboplatin and docetaxel). This study confirmed that patients with PS 2 have a greater incidence of grades 3 and 4 hematologic toxicity. Nonetheless, analysis of the cause of death during treatment demonstrated that most of the deaths were associated with the disease and that the poor survival was due to the disease more than to treatment-associated toxicity.

It is difficult to know whether this subgroup of patients with a short survival and greater possibilities of treatment-associated toxicity benefits from chemotherapy treatment. The study of Billingham and Cullen (Billingham 2001) suggested that PS 2 patients had no survival benefit from chemotherapy but in contrast these patients experienced the gratest improvement in quality of life during the first cycle of chemotherapy. Subgroup analysis from several randomised trials seems to demonstrate that several new generation cytotoxic drugs are superior to supportive care alone in patients with PS 2 (Elvis 1999; Ransom 2000). In the analysis of PS 2 patients in CALGB 9739 study comparing pladitaxel plus carboplatin versus pladitaxel, median survival in the combination chemotherapy was significantly longer than with pladitaxel alone although it should be noted that combination produced a statistically significant higher incidence of several hematological and non hematological toxicities. (Lilenbaum 2002). The preliminary results of a randomized, prospective study comparing carboplatin plus paclitaxel versus cisplatin plus gemcitabine in patients with PS 2 showed greater response for patients in the latter group but with greater thrombopenia (Langer et al. 2003). Chemotherapy appears justified to patients with advanced NSCLC and PS 2 although it is not clear the best regimen taking into account the efficacy and toxicity.

In elderly patients or those with concomitant diseases, trials with monotherapy or combined therapy without cisplatin have demonstrated to be active and well tolerated. One clinical trial compared monotherapy with vinorelbine versus the best support treatment in patients over 70 years of age, 25% of whom had PS 2. Greater palliation, time to progression, survival and quality of life were observed in the patients treated with vinorelbine (ELVIS 1999). In a similar population of patients (Frasci et al. 2000) combined treatment with gemcitabine plus vinorelbine was compared with monotherapy with vinorelbine and found better survival and quality of life with the combined treatment without differences in toxicity. These results disagree with those by Gridelli et al. (2003) who did not find better results and observed greater toxicity in the patients receiving combined therapy. The combination produced a greater percentage of anemia and neutropenia in relation to gemcitabine and platelet toxicity related to vinorelbine.

Isolated administration of gemcitabine has confirmed its activity as well as its tolerable toxicity profile in elderly patients with NSCLC, although with a greater proportion of patients with grades 3 and 4 anemia (Shepherd et al. 1997).

The administration of combinations with cisplatin and the new cytostatic drugs have not shown notable differences between patients older or younger than 70 years of age, with a tolerable toxicity profile and the main toxicity being hematologic (Booton et al. 2003).

Elderly patients with advanced stage NSCLC presenting an acceptable general status should receive chemotherapy treatment (Langer et al. 2002).

To date two randomized studied have compared standard endovenous treatment with doses at the lower limit with oral treatment with etoposide alone in fragile, elderly patients with SCLC. Both studies showed that combination therapy was superior in regard to response to treatment and survival than monotherapy and had less hematologic toxicity (Souhami et al. 1997; Thatcher 1996).

8.1.3 Toxicity in Radiotherapy

In the case of irradiation in lung cancer, acute toxicity of the bone marrow depends on the volume irradiated, the doses of radiation and its rate. Although the compensatory mechanisms are mainly relevant for the knowledge of long term effects, some effects are acute. Thus when volumes limited to the bone mar-

row are irradiated, such as, for example 10%–15%, the remaining bone marrow responds by increasing the population of progenitor cells. This is why the bone marrow, as an organ as a whole, is able to regenerate the previously irradiated zone by a compensatory process to satisfy the needs of hematopoiesis and acute toxicity is not observed. This compensatory phenomenon may be observed by factors (CSFs) from the cell stroma suggesting the implication of a humoral mechanism (Croizat et al. 1976).

It has been shown that there is a extensive communication and compensation network in the bone marrow after aggression with radiation and this may be summarized as follows:

1 Regeneration within the field of irradiation
2 Hyperactivity in non-irradiated regions
3 Extension of the function of bone marrow production in previously dormant zones (Tubiana et al. 1979)

This reparation or compensatory capacity of the bone marrow makes the bone marrow toxicity secondary to exclusive radiotherapy treatment in lung cancer difficult to observe clinically. Nonetheless, this exclusive irradiation using standard fractionation leads to subclinical, but quantifiable, hematologic toxicity which we will describe more in depth later when we go into combined treatment (chemo- and radiotherapy) and compare the resulting myelotoxicity using references from randomized studies related to radiotherapy alone.

8.1.4 Hematologic Toxicity After Combined Chemo- and Radiotherapy

The combined effects of chemotherapy and radiotherapy on the bone marrow are complex (Kovacs et al. 1988). The selective action of the chemotherapy agents for different populations of hematopoietic cells determine the temporary consequences of the tolerance of the bone marrow to radiation after chemotherapy. In addition, when wide fields are used, before chemotherapy, the tolerance expected is poor. This may be due not only to the suppression or ablation of determined segments or portions of the bone marrow, but also because of the increase in the sensitivity of non exposed zones of the bone marrow which, at that time, are in a period of hyperactivity. This is produced in the case of sequential treatments further complicating the question when referring to combined treatments of radio- and chemotherapy. In the case of SCLC, the study by Abrams et al. (1985) is of note. These authors randomized 42 patients to receive either chemotherapy alone or in combination with thoracic irradiation. In the group receiving combined treatment an increase was observed in both hematopoietic toxicity and the circulating number of progenitor cells suggesting that the toxicity of concurrent treatment is additive. It was found that:

1 The combination of chemotherapy and thoracic radiotherapy produces somewhat more hematologic toxicity than when chemotherapy is administered alone.
2 This increase may be explained by a generally subclinical, although measurable, toxicity of the thoracic radiotherapy when administered alone.
3 The potential of hematopoietic toxicity by irradiation by itself may vary in relation to the timing, the volume of treatment, to the region irradiated and the treatment fields used. That is, that the greater the volume treated and the greater the quantity of the cardiac circuit and bone marrow involved in the irradiated fields, the greater the toxicity.

The third point of this study introduces the concepts that not only irradiation of the bone marrow may cause hematologic toxicity but blood irradiation within the cardiac circuit may also play a role that should be taken into account in this toxicity. Turrisi et al. (1993) have also shown this in the sense that the great vessels are in the irradiated fields, the cardiac output is probably irradiated twice– once from the pulmonary circuit and then again in the systemic circuit.

In recent years the contribution of not only the importance of the timing of the administration (early or late) in concurrent combined treatment, but also the alterations of the fractionation (accelerated hyperfractionation versus standard fractionation) in patients with SCLC conditioned changes in hematologic toxicity. Thus, Murray et al. (1993) randomized a group of patients into two arms of early concurrent irradiation (in the third week) versus late (in the fifteenth week) and found that although the differences between neutropenia and thrombocytopenia greater than or equal to grade 3 were not statistically significant for either of the treatment arms, they were so in relation to grade 3 anemia which was greater in the late administration ($p<0.03$).

In a study by Jeremic et al. (1997), 107 patients were randomized to receive either chemotherapy plus early hyperfractionated radiotherapy (weeks 1–4) with concurrent chemotherapy versus late administration (weeks 6–9) and did not find statisti-

cally significant differences in hematologic toxicity. In the same year the group of the EORTC (Gregor et al. 1997) published another randomized study in patients with limited stage SCLC comparing sequential chemoradiotherapy versus alternating treatment and reported that the latter schedule was as effective as the sequential administration but caused greater grades 3 and 4 hematologic toxicity.

Turrisi et al. (1999) carried out a randomized study comparing concurrent chemotherapy with hyperfractionated radiotherapy versus the same chemotherapy with standard fractionated radiotherapy and found greater toxicity in the treatment with hyperfractionated radiotherapy. Lastly, Takada et al. (2002) randomized concurrent versus sequential chemoradiotherapy and observed greater hematologic toxicity in the first treatment arm (Table 8.1.1).

At the beginning of the 1990s a series of randomized studies in NSCLC were performed which evaluated both the effectiveness and the toxicity of concurrent or sequential chemoradiotherapy versus irradiation alone (Table 8.1.2). Firstly, the study by Le Chevalier et al. (1991) was of note. In this study 353 patients were randomized to receive 65 Gy of irradiation alone versus the same irradiation preceded by three cycles of vindesine, lomustine, cisplatin and cyclophosphamide. The group receiving irradiation alone showed three-fold less hematologic toxicity than the group administered combined therapy. In 1990, Dillman et al. (1990) randomized 155 patients to receive two cycles of cisplatin and vinblastine followed by 60 Gy of irradiation versus radiotherapy alone at the same doses. Although the hematologic toxicity in this study was not correctly explained, it was of note that neutropenic infection was more prevalent in the patients receiving chemotherapy with double the number of admissions due to severe infections versus the patients administered irradiation alone.

In a study by Trovó et al. (1992) 173 stage III patients were randomized to receive 45 Gy versus the same irradiation administered concurrently with a daily dose of 6 mg/m2 of cisplatin. The hematologic toxicity of the combined treatment was only slightly superior to that of radiotherapy alone. Schaake-Koning et al. (1992) randomized 331 patients to receive 56 Gy administered by split-course or the same radiotherapy plus 30 mg/m2 of cisplatin administered each week of irradiation versus the same total doses of irradiation administered continuously with a daily doses of 6 mg/m2 of cisplatin during irradiation. It was found that grades 3–4 hematologic toxicity was four-fold greater in the group with concurrent administration with weekly cisplatin compared to radiotherapy alone and was double in the concurrent treatment with daily versus weekly chemotherapy.

In 1995, Sause et al. (1995) published a randomized study on whether patients receiving chemotherapy followed by irradiation showed longer survival than hyperfractionated radiotherapy or irradiation

Table 8.1.1. Hematologic toxicity in randomized concurrent hyperfractionated arms on SCLC

	Leukopenia		Thrombocytopenia		Anemia	
	Grade	%	Grade	%	Grade	%
Jeremic et al. (1995)	3	21	3	25	3	11
	4	11	4	13	4	2
Turrisi et al. (1999)	3	38	3	13	3	23
	4	44	4	8	4	5
Takada et al. (2002)	3	51	3	23	3	54
	4	38	4	5	4	–

Table 8.1.2. Hematologic toxicity in randomized trials on NSCLC

	Hematologic toxic effect	RT Group	CH + RT Group (monthly CH)	CH + RT Group (daily CH)
Le Chevalier et al. (1991) (sequential)	Grade 2–5	1.4%	4.2%	–
Trovo et al. (1992) (concurrent)	Hemoglobin (grade 1–2)	1.7%	–	2.3%
	Leukopenia	1.1%	–	1.7%
Schaake-Koning et al. (1992) (concurrent)	Leukopenia (grade 3–4)	3.3%	6.6% (weekly CH)	14.5%
	Thrombopenia (grade 3–4)	0.6%	0.9% (weekly CH)	1.8%
Dillman et al. (1990) (sequential)	Neutropenia (infection)	3%	7%	–

with standard fractionation in patients with stage III NSCLC. Hematologic toxicity greater than grade 3 in the white cells was presented in 50% of the patients with combined treatment and was null in the other two treatment arms. Jeremic et al. (1995) randomized 169 patients to receive hyperfractionated radiotherapy at 1.2 Gy/twice per day up to a total dose of 64.8 Gy versus the same doses of irradiation plus 100 mg of carboplatin on days 1 and 2 and 100 mg of etoposide days 1 and 3 of each week of irradiation versus a third group in which the same radiotherapy was administered plus 200 mg of carboplatin administered days 1 and 2 and 100 mg of VP-16 on days 1 and 5 of the first, third and fifth week of irradiation. Likewise, the toxicity was greater in the combined treatment, especially in the second group.

On demonstration of the greater effectiveness, but with more hematologic toxicity, of sequential treatment versus exclusive irradiation, the next step was to demonstrate that concurrent administration was better than sequential. This was corroborated by Furuse et al. (1999) in a study in which 320 stage III NSCLC patients were randomized to receive concurrent treatment with cisplatin, vindesine and mitomycin and 56 Gy administered by split-course versus the same chemotherapy and one continuous dose of 56 Gy. Greater immunosuppression was also observed in the concurrent treatment arm. Another study which demonstrated greater survival with concurrent treatment was that by RTOG 9410 published only in abstract form and thus, the toxicity cannot by completely presented.

A new combination of treatment has been investigated. In a randomized phase II study the effectiveness and tolerance of two cycles of induction chemotherapy (with the so-called new chemotherapy drugs) followed by two additional cycles of the same chemotherapy plus concurrent radiotherapy have been studied. The chemotherapy used was doublets of cisplatin with gemcitabine, vinorelbine and paclitaxel (Vokes et al. 2002) and in this study hematologic toxicity was presented separately in the induction and also in the concurrent treatment (Table 8.1.3). In the first part grade 3–4 granulocytopenia was of note in 50% of the patients in the three treatment arms presented, and in the arm with gemcitabine 25% of the patients also presented grades 3 and 4 thrombocytopenia. In regard to the toxicity observed with concurrent treatment it was of note that notable differences were found in the three treatment arms of the study. Thus, while in the groups treated with gemcitabine and paclitaxel grades 3 and 4 granulocytopenia were observed in 51% and 53%, respectively, in the group receiving vinorelbine this hematologic toxicity was seen in 27% of the patients. Platelet toxicity was also found to be greater (50%) in the group with concurrent treatment with gemcitabine.

Finally, a new strategy used in inoperable stage III patients is of note in which initial plus consolidation chemotherapy was administered (Gandara et al. 2000). This strategy is also part of a phase III study published only in abstract form (Choy et al. 2002) which evaluates induction chemotherapy followed by irradiation alone, induction chemotherapy followed by concomitant chemoradiotherapy and lastly, concomitant chemoradiotherapy followed by consolidation. Definitive publication of these studies, together with other ongoing studies such as the randomized trial of CALGB 3981 and the Hoosier Oncology Group will aid in determining whether complete doses of chemotherapy before or after chemoradiotherapy increase survival and with what toxicity.

8.1.5 Preventive or Support Treatment of Hematologic Toxicity in Lung Cancer

In the last 20 years the knowledge of the physiology of hematopoiesis has been broadened and has led to

Table 8.1.3. Hematologic toxicity of Vokes's scheme on induction chemotherapy and concurrent chemoradiotherapy on NSCLC

	Hematologic toxic effect	Gemcitabine/cisplatin		Paclitaxel/cisplatin		Vinorelbine/cisplatin	
		Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Vokes et al. (2002) induction	Platelets	18%	7%	0%	0%	0%	2%
	Granulocytes	23%	25%	25%	23%	32%	23%
	Lymphocytes	26%	5%	27%	12%	14%	7%
Vokes et al. (2002) concurrent	Platelets	33%	23%	2%	4%	0%	2%
	Hemoglobin	30%	2%	4%	0%	19%	0%
	Granulocytes	33%	18%	29%	24%	19%	8%
	Lymphocytes	17%	62%	12%	67%	21%	44%

the use of the so-called hematopoietic growth factors in the treatment of bone marrow toxicity. These factors are glycoproteins which stimulate the myeloid progenitor cells and produce mature myeloid elements. Their objective is to reduce the length and intensity of neutropenia associated with chemotherapy, allow the administration of this treatment at the doses initially planned, increase the doses of chemotherapy and/or reduce the time interval between each treatment cycle. A systematic review of the literature of 12 randomized studies including 2107 patients evaluated the effectiveness of the colony stimulating factors (of granulocytes or G-CSF and granulocytes-macrophages or GM-CSF), in the treatment of SCLC with regard to survival, the rate of response, toxicity and frequency of infection or neutropenic fever. This review concluded that the administration of G-CSF or GM-CSF to maintain or increase the dose intensity of planned chemotherapy has not been demonstrated to be effective in terms of a greater rate of response and survival. Moreover, a harmful effect has been observed with the use of this cytokine in patients with an intrathoracic stage who had been treated concomitantly with chemo- and radiotherapy, as well as in extrathoracic stages treated with high dose chemotherapy (Berghmans et al. 2002). Other studies along the same line have coincided in that more studies on the use of CSF as a support treatment or as primary or secondary prophylaxis in patients with SCLC are required (Adams et al. 2002). In 1996, the American Society of Clinical Oncology (ASCO) recommended that the use of CSF should be avoided in patients who had received concomitant chemo-radiotherapy, and 4 years later specified that its use should be avoided in patients with radiochemotherapy if the mediastinum had been irradiated (Ozer et al. 2000) as in the case of lung cancer.

In relation to the preventive use of antibiotics to reduce the febrile leukopenia observed in patients with lung cancer, a randomized study of the EORTC on the prophylactic use of ciprofloxacin and roxithromycin during chemotherapy administration is of note (Tjan-Heijnen et al. 2001). These antibiotics reduced the incidence of leukopenic fever, the number of infections, and the use of antibiotics and hospitalizations due to this fever by 50%, as well as death caused by infection.

The clinical studies do not advise the routine use of CSF as a treatment added to antibiotics in the treatment of patients with uncomplicated febrile neutropenia.

The efficacy of most of the antibiotic regimens, the good results obtained even with wide spectrum antibiotics in patients who may present rapid neutrophil recovery without the administration of CSF makes its routine use in all patients with neutropenic fever inadvisable. Nonetheless, in certain high risk patients with clear predictive factors of worse outcome (for example in sepsis, pneumonia, fungal infections, etc.) the use of CSF together with antibiotics may be justified (Bennet et al. 1999).

In relation to anemia, another known effect of bone marrow toxicity, it should be remembered that its etiology is multifactorial and includes an inappropriate production of erythropoietin in response to the alteration of the normal hemoglobin levels (Miller et al. 1990). This abnormality in the production of erythropoietin is also exacerbated by chemotherapy (Schapira et al. 1990). On the other hand, recombinant human erythropoietin (r-Hu-EPO) has been used to improve the anemia observed in patients with cancer with an increase being observed in the number of erythroid progenitors in both the bone marrow and peripheral blood (Ludwig et al. 1990). One of the first studies on the possibility of achieving the prevention or reduction of anemia by the administration of r-Hu-EPO in patients with lung cancer was by de Campos et al. (1995). Later studies have shown that the use of r-Hu-EPO in lung cancer not only does not produce adverse effects, but also decreases both the degree of anemia as well as the blood transfusion needs in patients who have been treated with schemes including cisplatin (Zaragoulidis et al. 1997; Thatcher et al. 1999). On the other hand, in addition to studying anemia within the context of bone marrow toxicity, it has also been correlated with the probability of tumoral control and survival in some types of cancer (Henke et al. 1999). To this effect, a metaanalysis by Caro et al. (2000) should be pointed out. The aim of these authors was to determine whether anemia was an independent prognostic factor of survival in patients with different neoplasms. In relation to anemic patients with lung cancer it was concluded that the relative risk of death increased by a factor of 1.9.

A study by Casas et al. (2003) also studied the impact of the use of r-Hu-EPO in the maintenance of Karnofsky and the hemoglobin levels in patients with lung cancer receiving concurrent treatment of chemoradiotherapy after induction therapy (11 limited small cell and 40 non-small cell lung cancers). In addition to finding a beneficial and significant impact of the administration of r-Hu-EPO at the level of general status and hemoglobin levels, it was also found to be a significant prognostic factor of survival on multivariate analysis, together with classical factors such as weight loss and final improvement in hemoglobin,

the histology of SCLC and finally, hemoglobin levels greater than 10 g/dl prior to concurrent chemoradiotherapy. MacRae et al. (2002) analyzed the impact of the hemoglobin levels of groups of patients with lung cancer treated with different protocol of the RTOG and also described a relationship between hemoglobin levels and survival. Lastly, a study by Robnett et al. (2002) showed a significant relation between hemoglobin levels in patients who had received concurrent treatments of induction chemoradiotherapy and histologic response with regard to the pathological tissue.

The ASCO has made recommendations with an evidence level of II concerning the treatment of this anemia with r-Hu-EPO (Rizzo et al. 2002) in treatment with chemotherapy and anemia with hemoglobin concentrations close to 10 g/dl. It has also made recommendations with the same level of evidence II for patients with baseline hemoglobin levels between 10 and 12 g/dl based on the clinical judgment or the premise that patients with specific comorbidity have a greater absolute probability of anemia or a greater risk of adverse effects related to this grade of anemia than other patients with the same hemoglobin concentrations. As an example the ASCO has indicated patients who may be considered for the use of r-Hu-EPO in levels close to 12 g/dl, among others, including elderly individuals with limited cardiopulmonary reserves or patients with symptomatic coronary disease and angina. These recommendations have been made because although the patients over the age of 70 years present similar rates of response and survival than younger patients to combined treatments for lung cancer, they show a greater grade of hematologic toxicity, and thus, elderly patients with a good general status should probably be selected (Yuen et al. 2000). This greater hematologic toxicity may be due to the fact that the concentration of pluripotent hematopoietic stem cells seems to reduce with age, since a reduction has been observed in this concentration in the bone marrow of subjects with anemia over the age of 65 years. Other clinical findings such as an increase in the incidence and prevalence of anemia with age, a reduction in reticulocyte response in elderly anemic patients, an increase in death due to infection and a reduction in hematopoietic tissue concentration with age, indicate a decrease in the reserves of pluripotent hematopoietic stem cells (Baraldi-Junkins et al. 2000). On the other hand, as reported by Balducci and Hardy (1998), anemia is considered to be an important parameter since it is associated with a decrease in the quality of life and the levels of energy in the patient. These levels appear to be optimum with hemoglobin concentrations from 11 to 13 g/dl since they allow greater autonomy for elderly patients. This is why the use of growth factors is recommended to prevent the early mortality observed in elderly patients who are treated with schedules with a doses toxicity similar to CHOP and also to maintain the hemoglobin levels at approximately 12 g/dl with the aim of preventing the complications of anemia and finally, to carry out the adjustment of the doses of the cytostatic drugs for the renal excretion of these patients (Balducci et al. 2000).

From our point of view, objective clinical data which patients with lung cancer present such as smoking-related diseases and comorbid pulmonary and cardiac disease, and concurrent or sequential chemotherapy or chemoradiotherapy should also make up part of the group of patients in whom the use of r-Hu-EPO with hemoglobin levels of 12 g/dl should be considered similar to what has been recommended by ASCO.

In relation to thrombopenia, thrombopoietin, the synthesized factor for the stimulation of this series based on preventing hemorrhagic problems after myelosuppressive chemotherapy is still under evaluation and clinical implementation (Vadhan-Raj 2001).

In addition to the development of specific cytokines for the production and secretion of different hematologic cells, trials with medications such as glutation are currently ongoing on different methods of prevention of bone marrow toxicity. Glutation has been shown to be an effective chemoprotector against toxicity induced by cisplatin. Although the main experience is in ovarian cancer, randomized studies in other types of tumors such as the lung and the head and neck have demonstrated lower hematologic toxicity in patients receiving glutation compared with the control group (Schmidinger et al. 2000). Other drugs such as amifostine, have also shown a significant reduction in hematologic toxicity in randomized studies including patients with lung cancer undergoing concurrent chemoradiotherapy (Antonadou et al. 2003; Komaki et al. 2002).

There is a new pathway to reduce bone marrow toxicity secondary to radiotherapy alone or associated with chemotherapy. Radiotherapy modulated by doses intensity (IMRT) in different locations have been demonstrated to be useful to significantly reduce the doses of radiotherapy in critical tissues. Studies in gynecologic tumors have shown that this type of irradiation reduces the volume of bone

marrow in the pelvis irradiated compared with conformed radiotherapy, with a probable secondary decrease in hematologic toxicity although prospective studies are necessary to know the true clinical impact of this partial bone marrow protection at a hematologic level (Lujan et al. 2003).

With IMRT planning it may be possible to reduce both bone marrow volume at a thoracic level and cardiac circulation thereby avoiding blood cells to be irradiated with radiotherapy alone or in combination. Prospective studies aimed at achieving a reduction in hematologic toxicity by this way should be undertaken.

Finally, it is currently possible to prospectively monitor or even predict bone marrow toxicity after chemotherapy (Lyman et al. 1995) or radiotherapy. A recent article demonstrated that the variations of the cytokine called Glt-3 ligand in plasma directly reflect the damage induced by radiotherapy in the bone marrow during fractionated radiotherapy, even when this damage is maintained at subclinical levels (Huchet et al. 2003). This may be very useful for the preventive monitoring of hematologic toxicity in determined groups of patients with lung cancer receiving chemo- or radiotherapy.

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8.2 Radiation-Induced Lung and Heart Toxicity

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CONTENTS

For many patients with lung cancer, thoracic radiation therapy (TRT) is an integral part of their treatment. The effect of TRT on normal structures is an important consideration when optimizing treatment plans for patients. This chapter will review radiation therapy (RT)-induced lung and heart injury, including both the clinical and biological mechanisms for these toxicities. It will also analyze the variety of predictors of RT-induced lung and heart damage, as well as methods to prevent and treat these toxicities.

8.2.1 Pulmonary Effects of Thoracic Radiation Therapy

8.2.1.1 Clinical RT-Induced Lung Toxicity

8.2.1.1.1 Introduction

Radiation-induced lung toxicity is a common occurrence in patients treated with curative intent for lung cancer. Approximately 5–20% of patients treated with RT for lung cancer have been reported to develop RT-induced lung injury (Table 8.2.1). Clinical symptoms range from mild shortness of breath to chronic pulmonary dysfunction requiring oxygen therapy and potentially leading to death. The wide range in incidence of reported toxicity is secondary to the different methods used to measure pulmonary dysfunction. While most patients have radiographic changes, fewer have changes in functional endpoints and even fewer have severe clinical symptoms (Table 8.2.1).

Clinical endpoints for RT-induced lung injury are biphasic and have traditionally been divided into acute (early) and chronic (late) toxicity. Acute pneumonitis typically occurs 1–6 months after TRT. Chronic lung fibrosis usually evolves 6 months to several years after treatment.

8.2.1.1.2 Early Toxicity

Patients with RT-induced pneumonitis often present with shortness of breath, cough and congestion, and some may have a low-grade fever. For patients with chronic obstructive pulmonary disease (COPD), it may be difficult to distinguish COPD from acute pneumonitis. In general, the severity of the symptoms is related to the amount of normal lung irradiated. Pneumonitis usually responds well to steroids; 40–60mg of prednisone each day for several weeks, followed by a slow taper, provides relief for most patients. It is important to consider the possibility of infection, which can be worsened by the use of steroids. In situations where either infection or pneumonitis appear likely, an initial trial of empiric antibiotics, followed by steroids if there is no response to antibiotics, may be indicated. In patients with an unsatisfactory response to either treatment, tumor progression and/or lymphangitic tumor should be considered. Severe RT-induced pneumonitis can result in serious respiratory distress, requiring hospitalization and intubation, and it can be fatal.

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Table 8.2.1. Incidence of RT-induced clinical and radiologic lung injury

Reference	Number of patients	Symptom rate (%)				Incidence of radiologic changes (%)	Follow-up duration (months)
		Grade 1	Grade 2	Grade 3	Grade 4		
Favaretto et al. 1996	39	13%					64–90
Segawa et al. 1997	89	*38%	5.6%	8.9%	5.6%	58%	–
Fu et al. 1997	60	–	*17%	8%	–		23
Monson et al. 1998	83	8%	2%		7%	34%	≥4
Yamada et al. 1998	60	–	*13.3%	11.6%	3.4%	85%	≥6
Nyman et al. 1998	90	–	–	*8%	–		22 (minimum)
Van den Brande et al. 1998	23	–	–	*11%	–		>24
Makimoto et al. 1998	111	15%					<6
Graham et al. 1999	99	–	*14%–20%				24 (median)
Robnett et al. 2000	144	–	–	*8.3%			11.5 (median)
Sunyach et al. 2000	54	–	29% (Lent–Soma scale)			37%	≥6
Inoue et al. 2000	191	*36%		13%			≥12
Hernando et al. 2002	201	–	13%	4%	–		≥6
Oetzel et al. 1995	46	20%					>3
Perry et al. 1987	391	7%					17.3 (median)
Gross 1977	_	5%–15%				65%	_
Simpson et al. 1985	316	3%					36
Kwon et al. 2000	47	–	*8.5%	–	–		2–33
Perez et al. 1980	365	4%					60
Martel et al. 1994	42	21.4%					>7

*RTOG criteria

Thoracic radiation therapy can also cause acute irritation of the pleura, with secondary pleuritic pain, and this can be treated with anti-inflammatory and/or narcotic pain relief medicines. Irritation of the trachea and bronchial airways, which can lead to a cough, may also occur and can be treated with cough suppressant medicines.

8.2.1.1.3 Late Toxicity

The most prominent late consequence of TRT is pulmonary fibrosis. Radiological changes consistent with fibrosis are seen in most patients. Symptomatic patients present with progressive chronic dyspnea and this can occur months to years after TRT (Perez et al. 1980; Martel et al. 1994; McDonald et al. 1995; Morgan et al. 1995; Abid et al. 2001; Gross 1977). Relief of symptoms is the goal of treatment, given that the reversal of the fibrosis is highly unlikely. Treatment includes anti-inflammatory agents such as corticosteroids, and, in some cases, supplemental oxygen. Similar to acute pneumonitis, tumor progression, infection and COPD must be ruled out as exacerbating factors for symptomatic fibrosis and treated appropriately. As noted earlier, radiographic evidence of regional lung scarring is seen in almost all patients, including those without clinical symptoms. There does not appear to be an association between the presence of an abnormality on CT scan and the development of symptoms, but this has not been extensively studied (Garipagaoglu et al. 1999). After high doses of TRT there have been rare reports of pulmonary complications, such as bronchial stenosis, bronchomalacia and mediastinal fibrosis with secondary recurrent laryngeal nerve injury (Maguire et al. 2001; Dechambre et al. 1998).

8.2.1.1.4 Radiographic Changes

Radiographic findings are common in patients following TRT, even among those who do not have symptoms of RT-induced lung injury. The ability to detect these changes depends on the type of radiographic assessment performed. Chest x-rays (CXR), performed after TRT, can reveal a diffuse infiltrate, corresponding to the radiation field. There can also be an associated volume loss of the affected portion of the lung, and, in late toxicity, there can be an ex-

tension of the findings outside the treated area and deviation of the trachea towards the irradiated area.

Computed tomography (CT) scans are more sensitive than CXR and can detect abnormalities in more than 50% of patients (Mah et al. 1987). Computed tomography scans are very sensitive to slight changes in lung densities and are therefore the favored diagnostic procedure for the detection of RT-induced lung injury (Mah et al. 1987; Libshitz and Shuman et al. 1984). There is a well-defined dose/response relationship for the patterns seen on CT scans after TRT. These include: a homogeneous, slight increase in lung density; patchy consolidation; discrete consolidation and solid consolidation (Libshitz and Shuman et al. 1984; Mah et al. 1986). Chronic changes in the thorax that can be seen on the CT scan following TRT include lung contraction, pleural thickening, tenting of the diaphragm and deviation of the mediastinal structures toward the treated area. These can appear months to years after radiotherapy.

Lung perfusion and ventilation can be abnormal following TRT (Gross 1977; Prato et al. 1997). Single Photon Emission Computed Tomography (SPECT) perfusion and ventilation scans are more frequently abnormal than are planar images, similar to CT's advantage over chest x-rays (CXR) (Gross 1977; Prato et al. 1997). Perfusion appears to be more sensitive than ventilation in the evaluation of RT-induced lung injury, and both are more sensitive than CXR or CT (Bell 1988; Shapiro et al. 1990). This is most apparent at modest doses, 15–40Gy, where often there is no change seen in tissue density, yet clear reductions in both ventilation and perfusion. Perfusion and ventilation abnormalities have been seen in 53–95% and 35–45% of irradiated patients, respectively. The inconsistencies between changes in ventilation and perfusion support the idea that, following TRT, some areas remain ventilated, but not adequately perfused (Bell 1988; Marks et al. 1993).

Some of the studies that have reported both clinical pneumonitis and radiographic abnormalities following TRT are summarized in Table 8.2.1. As shown, radiographic changes occur far more frequently than clinical symptoms.

8.2.1.1.5 Functional Endpoints

In general, abnormalities in pulmonary function tests (PFTs) do not occur during the first weeks following TRT. After this period, however, changes in PFTs can occur, along with the signs and symptoms of pneumonitis and/or fibrosis. Pulmonary function tests measure the transfer of large volumes of air through the conducting airways and the transfer of gases through the alveolar surfaces. Spirometry assesses the rate of gas movement; the most commonly measured parameter is the forced expiratory volume in one second (FEV1). The FEV1 is a measurement of air movement. It can be normalized to the forced vital capacity (FVC), a measurement of "useful" lung volume or FEV1% (FEV1/FVC). While the response of the tumor to TRT may lead to an increase in the FEV1, the FVC may decrease secondary to restrictive disease (fibrosis) and thus the FEV1% (FEV1/FVC) may increase. Reductions in FEV1 following TRT range from 0–30%, but there is a wide variety of confounding variables that limit meaningful interpretation of this data.

A variety of PFTs measure lung volume, including the total lung capacity (TLC), vital capacity (VC), (FVC), and residual volume (RV). The volume of air in the lung can increase following TRT if there is an expansion of lung volume, or it can decrease secondary to fibrosis. Reports in the literature describe both and the range varies from –20% to +9.5% (Table 8.2.2).

Table 8.2.2. Percent reduction in pulmonary function parameters after thoracic radiation therapy

Reference	FEV1	DLCO	FVC	TLC	VC
Sunyach et al. 2000	+0.1	4.3		6.5	
Mattson et al. 1987		27			16
Van den Brande et al. 1998	10	25			15
Choi et al. 1985	18	28	22	10	20
Rubenstein et al 1988	11				
Brady et al. 1965		14			
Bonnet et al. 2001	8	11.5	5.5	+6	

Gas exchange in the lungs is measured via the carbon monoxide (CO) diffusion capacity (DLCO), which quantifies the transfer of CO from inspired gas into pulmonary capillary blood. Many complex factors besides gas diffusion contribute to the DLCO, including ventilation/perfusion characteristics of alveolar units, capillary blood volume, hemoglobin concentration and the reaction rates between CO and hemoglobin. In addition, other clinical factors such as diurnal variation, menstrual cycle, ethanol ingestion and cigarette smoking can affect DLCO (Garipagaoglu et al. 1999). The DLCO is frequently corrected for anemia but the other factors known to affect the DLCO are difficult to control (Garipagaoglu et al. 1999). The DLCO, which can be reduced from 5 to 35% following TRT, tends to be affected to a greater degree than

other variables involved (Table 8.2.2). It is difficult to generalize changes in PFTs, given the wide variety of pre-treatment values and the diverse amounts of lung irradiated in each patient. Other standard measurements of pulmonary function, such as the six-minute walk test or exercise stress tests, have not been routinely used to measure RT-induced lung injury.

8.2.1.2 Biology of Radiation-Induced Lung Injury

Radiation-induced lung injury is characterized by progressive histological changes, linked with the clinical syndromes and radiological findings of pulmonary dysfunction. Acute exudative and organizing phases are related to RT-induced pneumonitis; and the chronic fibrotic phase is associated with RT-induced lung fibrosis (Gross 1977; Katzenstein and Askin 1990).

Injury to both type II pneumocytes and vascular endothelial cells has been implicated in acute pneumonitis. The initial latent period following TRT may reflect the inherent turnover time of these cells (Gross 1977; travis et al. 1977; travis 1990). RT-induced pneumonitis is typified by an exudate of proteinaceous material into the alveoli, desquamation of epithelial cells from the alveolar lining, alveolar edema and an infiltration of inflammatory cells. This leads to thickening of the alveolar septa, reduced lung compliance and eventually impairment of gas exchange. Radiation causes the early release of surfactant by type II pneumocytes and this results in alterations in alveolar surface tension and low lung compliance. (Rubin et al. 1980; Rubin et al. 1983).

Damage to vascular endothelial cells results in changes in perfusion and permeability of capillaries (Gross 1977). The endothelial cells become pleomorphic, vacuolated, producing areas of denuded basement membrane and occlusion of the capillary lumen by debris and thrombi (gross 1980). Many of these findings are apparent well before RT-induced pneumonitis develops and they persist throughout the course of the illness and beyond.

Following the acute phase of damage, there is progressive fibrosis of alveolar septa that become thickened with bundles of elastic fibers, while small vessel walls become filled with collagen deposits (Gross 1977; Katzenstein and Askin 1990; roswit and White 1977). The alveoli eventually collapse and become obliterated by connective tissue. This usually occurs 4–6 months following TRT. The mechanism of RT-induced pulmonary fibrosis is poorly understood, and while it is likely to be related to effects on vasculature endothelium and stromal cells of the lung, it has been suggested that a cascade of proinflammatory and profibrotic cytokines produced immediately after irradiation prompts collagen genes to be activated (roswit and White 1977; Rosiello and Merrill 1990; Rubin et al. 1995).

Exposure to ionizing radiation rapidly triggers a cascade of genetic and molecular events that proceed in multiple cells within the lungs Rubin et al. 1995; Hong et al. 1995; Hong et al. 1997). These events occur during a period of clinically normal lung function, but are thought to lead to lung injury that is manifest at a later time. This is an active process and there is evidence that it may be genetically determined (Haston et al. 2002). Irradiation can lead to the induction of several transcription factors that activate genes for cytokines that are linked to RT-induced lung injury (Brach et al. 1991; Hallahan et al. 1994; Hallahan et al. 1991). Elevated levels of the cytokines IL-1, TNF-α, PDGF and TGF-β have been reported after the exposure of tissue to irradiation (Rubin et al. 1995; Finkelstein et al. 1994; Franko et al. 1997; Epperly et al. 1999; Hallahan et al. 1990). In addition, the expression of the adhesion molecules, ICAM-1 and E-selectin, have been shown to increase in mice pulmonary endothelium following irradiation (Hallahan and virudachalam 1997). Several recent studies have also shown that these cytokines and cell adhesion molecules play an important role in RT-induced lung injury (Rubin et al. 1995; Hallahan and virudachalam 1997; Johnston et al. 1995)

Radiation-induced lung fibrosis has recently been associated with the persistent expression of chemokines and their receptors following irradiation (Johnston et al. 2002). The chronic presence of the chemokines is thought to activate a cellular immune response that may contribute to the progression of RT-induced lung fibrosis (Johnston et al. 2002).

The traditional concept of RT-induced lung toxicity asserts that the injury of critical target cells within the lungs, and their eventual depletion, leads to the sequence of early and late pulmonary injury. The prolonged latent period preceding development of sequelae has been attributed to the long cell cycle time of target cells (Rubin and Casarett 1968). This concept is questionable, however, in view of recent findings that radiation can trigger a succession of genetic and molecular events, and that these events occur during a period of clinically silent lung injury, which, in due course, leads to functional lung injury (Rubin et al. 1995).

8.2.1.3 Predictors of RT-Induced Lung Injury

Given the pitfalls of diagnosing and describing the continuum of clinical and radiological RT-induced lung damage, predicting its occurrence is complicated and fraught with deficiencies. The quality of the predictions is related to the endpoint chosen and the method used to calculate the risk.

Several studies have tried to relate changes in PFTs to the percent of functional lung irradiated (Rubenstein et al. 1988; choi et al. 1985; Abratt et al. 1990; Curran et al. 1992). In these investigations, the percent of lung at risk was approximated from planar ventilation and perfusion scans. The observed decline in PFTs was typically less than the models predicted (Rubenstein et al. 1988; choi et al. 1985; Abratt et al. 1990; Curran et al. 1992). Consequently, investigators have used newer 3D planning software and related local RT doses to lung SPECT perfusion/ventilation-defined regional lung injury (Woel et al. 2002; Seppenwoolde et al. 2000; Mah et al. 1994). Clear dose–response relationships for radiographic lung injury have been found. However, predictions of PFT changes and clinical symptoms based on regional dose–response data have been inconsistent (Fan et al. 2001; Theuws et al. 1999).

Patients with lung cancer are typically treated with multiple beams that enter the lungs from different directions and result in a complicated 3-dimensional (3D) dose distribution. Attempts to predict RT-induced lung injury from field size and dose are made difficult by an incomplete understanding of complex dose and volume parameters. While both higher dose/fraction and total dose were found to be correlated with symptomatic lung injury, less consistent results have been found with 2-dimensional (2D) field size (Roach et al. 1995; Robnett et al. 2000; Byhardt et al. 1993). The use of 3D treatment planning has provided investigators with the tools to better evaluate the risk of RT-induced lung injury. Traditionally, 3D dose distributions are recalculated into a 2D dose–volume histogram (DVH), which is easier to interpret. The percent of lung volume receiving equal to or greater than a specific dose can be found from a DVH. Typically a "single value of merit" is derived from the DVH, such as the percent of lung receiving at least 20 (V20) or 30 (V30) Gy. Many studies have demonstrated the usefulness of these dosimetric parameters in predicting the likelihood of RT-induced lung injury (Graham et al. 1999; Hernando et al. 2001; Oetzel et al. 1995; Martel et al. 1994; Lind et al. 2002). Another dosimetric parameter extracted from the 3D dose distribution is the mean lung dose, and this has also been associated with RT-induced lung injury. While these parameters have individually been correlated with clinically significant lung injury, they are highly related to each other and none has been shown to be superior. Rather than providing an absolute risk assessment, these data may contribute more to providing a means of comparing treatment plans for their relative risks.

It is clear from the wide variety of results that the volume of irradiated lung may not be sufficient to accurately predict RT-induced lung toxicity. The data derived from DVHs disregard all spatial information. It is known, however, that some regions of the lung have greater functional importance. In patients with healthy lungs, the ventilation perfusion ratio reveals that gas exchange is better at the lung bases than at the apices. For lung cancer patients with COPD, emphysema preferentially affects the apical lung and therefore the lung bases may be even more important for respiration. Finally, tumor-related lung dysfunction is also related to lung anatomy and is not accounted for in DVHs. Taken together, these data suggest that the usefulness of traditional DVHs in predicting RT-induced lung injury may be suboptimal. Some recent studies of RT-induced lung injury have utilized anatomic information and report that treatment to the lower portion of the lung may be more toxic than treatment of the upper lung; however, this has not been confirmed (Graham et al. 1999; Yorke et al. 2002; Tsujino et al. 2003). A SPECT-perfusion scan is able to define functional areas of the lung and therefore dose–function (i.e. perfusion) data extracted from this test may be more predictive for RT-induced lung injury than is the traditional DVH (Woel et al. 2002; Lind et al. 2002; Seppenwoolde et al. 2000).

Many studies have addressed the role of potential biologic predictors of RT-induced lung injury. These are markers found in the blood prior to or during TRT that reflect a predisposition for RT-induced lung injury. TGF-β is a multifunctional regulator of cell growth and differentiation that stimulates connective tissue formation and decreases collagen degradation, which can result in fibrosis. In a series of patients receiving TRT, it was found that elevated TGF-β levels at the completion of TRT was associated with a significantly higher incidence of clinical pneumonitis (Anscher et al. 1994). The dosimetric predictor, V30, combined with the TGF-β plasma concentration, has been shown to improve the accuracy of predicting pneumonitis (Fu et al. 2001). In patients with a V30 < 30% and stable TGF-β during RT, the incidence of symptomatic RT-induced lung injury was 6.9%.

Patients with a V30 $\geq$ 30% *or* a TGF-β increasing during RT (but not both) had an incidence of RT-induced lung injury of 22.8%. With a rising TGF-β *and* V30 $\geq$ 30%, the incidence was 42.9% (p = 0.02). Other cytokines have also been implicated in RT-induced lung injury. Elevated plasma levels of the pro-inflammatory cytokines IL-1α and IL-6 are associated with the development of pneumonitis (Chen et al. 2002). These studies suggest that biologic markers may be useful in identifying patients at risk for RT-induced lung injury.

Many commonly used chemotherapeutic drugs are associated with lung toxicity when used alone (Abid et al. 2001). The use of combinations of chemotherapy with RT, either concurrently or sequentially, raises the concern of added toxicity. While there is evidence for an increased risk of pulmonary toxicity with concurrent RT and doxorubicin, mitomycin-C, cyclophosphamide and bleomycin, these drugs are not commonly used in lung cancer patients (McDonald et al. 1995). Recent trials using platinum-based regimens have not shown increased RT-induced lung toxicity. In a study comparing induction chemotherapy with cisplatin and vinblastine, followed by thoracic RT at the same dose as RT alone, the frequency of severe lung toxicity was reported to be only 1 percent in each treatment group (Dllman et al. 1990). A comparison of sequential cisplatin, vindesine and mitomycin with RT versus concurrent treatment with the same agents revealed a rate of grade 2 or higher pulmonary toxicity in 2.6% and 1.9% of the concurrent and sequential treatment arms, respectively (p=0.86) (Furuse et al. 1999). It does not appear that the current standard of platinum-based concurrent chemotherapy increases the risk for RT-induced lung injury and, therefore, its use is not typically part of the risk assessment for lung injury.

Tumor location may be a valuable component for assessing the probability of RT-induced lung injury. Reduction in the size of an obstructing tumor may improve respiratory status, even if some lung is injured. As a result, the prediction of post-RT lung function can be complicated by anatomy. It has been shown that patients with central obstructing tumors that result in a shift of ventilation or perfusion away from the area to be treated are more likely to have an improvement of lung function following TRT (Marks et al. 2000; Choi and Kanarek et al. 1994). Among patients with a V/Q shift of >10% to the uninvolved side of the lung by a central cancer, pulmonary function improved in 60% of patients after RT, 20% remained essentially stable and only 20% had the reduction in PFTs that was predicted by the volume of lung irradiated (Choi and Kanarek 1994)). A separate study demonstrated that, in patients with central lung tumors, 8/20 (40%) with adjacent SPECT hypoperfusion had improvements in DLCO following radiation, while only 3/17 (18%) of patients without hypoperfusion had improvement (p=0.10). (Marks et al. 2000). Patients with central tumors appear to be at greater risk for bronchial injury following high-dose RT (e.g. >73Gy) than patients with more peripherally placed lesions (Miller et al. 2004).

While it is reasonable to associate cigarette smoking with an increased risk of RT-induced lung toxicity, the data are somewhat confounding. Chronic lung disease caused by a long history of smoking make patients more susceptible to lung injury; however, some data suggests that active smoking may have a protective effect (Johnston et al. 1995; Johnston et al. 2002; Rubin and Casarett 1968). A retrospective review of patients with RT-induced symptomatic pneumonitis following treatment of esophageal and breast cancer found a lower incidence of lung injury in smokers (Johnston et al. 1995). A study of CT density after RT to the thorax for lymphoma and breast cancer found that smokers had significantly smaller changes (p = 0.002); however, there were no significant ventilation or perfusion differences (Johnston et al. 2002). A multivariate analysis evaluated SPECT-generated dose response curves and found an increase in radiation sensitivity in the dose range >40Gy for nonsmokers vs. smokers (Rubin and Casarett 1968). There has been some speculation that this protective effect may be due to a cytokine effect. These observations are no reason for patients to continue smoking while undergoing TRT; however, they could help researchers develop useful pharmacological interventions.

While many of the methods presented have some utility in predicting RT-induced lung injury, it is likely that a combination of data from several different clinical, biological and dosimetric functions will ultimately provide the most valuable risk assessment. For example, as the cytokine cascade in the pathogenesis of RT-induced lung injury becomes better understood, biologic data will be combined with dosimetric information and patient-specific lung function, which hopefully will lead to improved prognostication of RT-induced lung injury.

8.2.1.4 Modifiers of RT-Induced Lung Injury

A variety of strategies have been attempted to decrease RT-induced lung toxicity, including dosimet-

ric variations, pharmacologic agents and altering dose using patient-specific biological information. There have been several randomized trials of the cytoprotector amifostine (WR-2721) in patients receiving TRT. Amifostine (WR-2721) is a phosphorylated amino thiol that demonstrates cytoprotection of normal tissues when combined with RT (Wasserman 1999). Cytoprotection is believed to result from elimination of free radicals produced by the interaction of ionizing RT and water molecules (Capizzi 1999). There is conflicting evidence that amifostine can offer a pneumoprotective benefit in patients receiving TRT. In a randomized trial of patients with advanced stage lung cancer who received TRT with or without amifostine, dyspnea with minimal exertion was observed during the first month after TRT in 27% of the control patients but only 12% of the patients treated with amifostine ($p = 0.058$) (Antonadou et al. 2002). After three months, the incidence of > grade 2 pneumonitis was 52% in the control arm compared to 12% in the amifostine arm ($p < 0.001$). At six months, significantly more patients in the control arm were found to have fibrosis on chest CT scan (53% vs. 28%, $p < 0.005$). Of equal importance, there was no noticeable difference in tumor response (Antonadou et al. 2002).

A separate trial at M.D. Anderson Cancer Center randomized patients receiving concurrent chemotherapy and hyperfractionated TRT to amifostine or no amifostine (Komaki et al. 2002). In this trial, acute pneumonitis was significantly reduced in patients treated with amifostine (31% vs. 7.4%, $p = 0.03$). There was no difference in median survival time (Komaki et al. 1992).

The Radiation Therapy Oncology Group (RTOG 98-01) recently completed a randomized trial looking at the addition of amifostine to induction carboplatin and paclitaxel (C/P), followed by concurrent hyperfractionated TRT and C/P with or without amifostine. In contrast to the earlier studies, this trial demonstrated no difference in pneumonitis rates with or without amifostine (Werner-Wasik et al. 2003). However, patients received TRT twice a day, but amifostine only once a day, resulting in potential protection for just half of the treatments. There was also a high patient dropout rate in the treatment arm, and, when the results were analyzed by intent to treat, a large portion did not receive amifostine. Because of these caveats, a new trial with once-a-day radiation and subcutaneous amifostine (to decrease toxicity) is being initiated. At the present time it is unclear whether the use of amifostine in patients treated with TRT will be of significant benefit in reducing RT-induced lung injury.

Assessing changes in biological markers during the course of TRT and changing treatment plans according to risk categories could potentially lead to a decrease in RT-induced lung toxicity. This has been undertaken in a series of patients treated twice daily with TRT and, based on TGF-β levels during the course of therapy, escalated RT dose (Anscher et al. 2001). Fourteen patients whose TGF-β levels were normal after 73.6Gy were escalated to 80Gy (n=8) and 86.4Gy (n=6). Overall, the rate of significant lung toxicity was low in patients with stable or declining TGF-β levels, indicating that there is the potential to individualize TRT according to patient-specific biological factors.

In general, patients with lung cancer are simulated for treatment using chest CT scans and standard 3D planning systems. Fields are arranged to treat the tumor, involved lymph nodes and elective mediastinal (as well as, sometimes, supraclavicular) lymph nodes. Variations of these methods could lead to a decrease in RT-induced lung injury. For example, limiting radiation to only areas with known tumor would exclude elective nodal treatment and potentially spare normal lung tissue (Rosenzweig et al. 2001). Treating only positron emission tomography (PET) positive nodal disease has been attempted with no apparent change in tumor control and low pneumonitis rates (Belberbos et al. 2003). Limiting elective nodal radiation is a simple method to decrease the potential for RT-induced lung injury and should become a more widespread technique in patients receiving TRT.

Using the information from ventilation/perfusion scans to decrease the dose to the most functional portion of the lung has the potential of reducing RT-induced lung injury. While most treatment plans are developed with this intention, it is difficult to accomplish with present day technology. Perfusion-weighted optimization using perfusion dose–functional histograms (DFHs) has been attempted and the results appear promising (Seppenwoolde et al. 2002). Moreover, as more sophisticated treatment planning systems are developed, better tailoring of dose using radiological/physiologic data is expected to reduce RT-induced lung injury.

Several methods have been used in an attempt to eliminate the need for larger treatment volumes to compensate for respiratory motion. Respiratory gating is the timing of TRT with the respiratory cycle. The deep inspiration breath–hold technique maintains the GTV in the same position during treatment (Ford et al. 2002; Yorke et al. 2002). Gating, possibly together with intensity modulated RT (IMRT), may help reduce the potential risks of

treatment. Further evaluations of these techniques are necessary.

The use of intensity-modulated radiation therapy (IMRT), which is becoming more widespread, has also been used in TRT. However, the longstanding question of whether a small dose to a large volume of normal lung is better than a high dose to a smaller volume of lung has not been answered. In an analysis of this issue, a recent study compared varying doses to the normal lung during TRT with the incidence of pneumonitis (Willner et al. 2003). When each lung was analyzed separately, the incidence of pneumonitis was highly correlated to the volume of ipsilateral lung receiving > 40Gy. In contrast, the incidence of pneumonitis decreased as the volume of lung receiving less than 10Gy increased. These results indicate that it is reasonable to spread low doses of RT outside the target area. In this study, at any rate, reducing the volume of lung receiving >40Gy and increasing the volume receiving <10Gy appeared to lead to less RT-induced lung injury (Willner et al. 2003). These data could be the basis for DVH constraints in IMRT (Willner et al. 2003). A separate study compared dose escalation strategies using either 3D treatment planning or IMRT using the same dose constraint of MLD <24Gy (Marnitz et al. 2002). It was possible to give higher doses to the target volume while keeping within the MLD restriction using IMRT (Marnitz et al. 2002). A similar study compared IMRT to 3D treatment planning, as well as to traditional treatment planning with elective nodal irradiation (Grills et al. 2003). When meeting all of the standard "normal tissue" constraints, IMRT delivered a 25–35% higher dose to the target, compared with 3D, and a >100% higher dose than standard treatment planning, including elective nodal irradiation (Grills et al. 2003). In the near future, it is likely that a significant amount of prospective data will be available for assessing the possible benefit of IMRT planning in reducing RT-induced lung injury.

8.2.2 Cardiotoxic Effects of Thoracic Radiation Therapy

Heart injury is an inherent risk in the treatment of lung cancer arising from the use of TRT, either alone or in combination with cardiotoxic chemotherapeutic agents. At least a portion of the heart is typically exposed to a relatively high dose of radiation when the mediastinum and/or primary lung tumors are targeted. However, cardiac injury is not commonly reported in patients who receive TRT for lung cancer. There are two primary reasons for this. First, the life expectancy of most patients treated with TRT for unresectable lung cancer is short. Second, patients treated for lung cancer typically have pre-existing cardiopulmonary disease, and subsequent functional deterioration is typically ascribed to pre-existing disease, RT-induced lung dysfunction and/or tumor progression, rather than to cardiotoxicity. As our ability to successfully treat lung cancer and concurrent pulmonary disease/injury improves, minimizing cardiotoxicity will become an important goal of the thoracic radiation oncologist.

Cardiac injury in irradiated lung cancer patients has not been well studied for the reasons described above. However, the late effects of radiotherapy on the heart have been extensively studied in survivors of Hodgkin's disease and breast cancer. While the radiotherapy fields and doses used in the treatment of Hodgkin's disease and breast cancer differ markedly from those used to treat lung cancer, these studies illustrate fundamental principles of radiation-induced cardiotoxicity, which may be applicable to patients with lung cancer.

Incidental cardiac irradiation has been strongly associated with the development of pericarditis and premature coronary artery disease, and weak associations also exist for a wide range of clinical syndromes, including cardiomyopathy, valvular disease, conduction system abnormalities and autonomic dysfunction. When they occur following treatment of children or adolescents, these syndromes are distinguished by their early age of onset. When older patients are irradiated, the resultant cardiac syndromes are generally indistinguishable on clinical grounds from the more usual forms of the disease. Although changes in the structure and function of the intrathoracic viscera after TRT should be considered, the manifestations of TRT-induced heart disease are essentially treated the same as the more usual forms of heart disease (Adams et al. 2003a+b).

An increased risk of death from acute myocardial infarction (AMI) has been observed in long-term survivors of Hodgkin's disease treated with radiotherapy fields that encompassed at least part of the heart. Mediastinal radiation fields typically used for Hodgkin's disease deliver 20–40Gy to the medial aspect of the heart and, thus, include the ostium of the coronary arteries. Occasionally, the remainder of the heart may receive a lesser dose. In adult patients, the relative risk of death from AMI ranged from 2.6 to 14.9, compared with age and gender-matched con-

trols (Boivin and Hutchison 1982; Boivin et al. 1982; Brierley et al. 1998; Gustavsson et al. 1990; Hancock et al. 1993a+b; Hancock and Hoppe 1996; Henry-Amar et al. 1990; NG et al. 2002; Pohjola-Sintonen et al. 1987). The RR of death from AMI for juvenile patients was even higher (41.5), reflecting the increased sensitivity of children to the cardiotoxic effects of radiation and/or the low baseline risk of AMI in the general population below age 50 (Hancock and Hoppe 1993). Pericarditis has also been reported following mediastinal irradiation for Hodgkin's disease, and its incidence is strongly related to the volume of the heart irradiated (Carmel and Kaplan 1976). The results of these studies have had a significant impact on the management of Hodgkin's disease today. Many of the patients in these studies were treated with radiotherapy alone to doses in excess of 40Gy. Current treatment approaches emphasize combination chemotherapy followed by low-dose consolidative RT, in part to reduce the expected long-term cardiac toxicity resulting from treatment.

An increased risk of cardiac death, in particular AMI, can also been seen in older trials of post-mastectomy RT, particularly for left-sided breast cancer (Gyenes 1998; Cuzick et al. 1994; Rutqvist and Johansson 1990; Rutqvist et al. 1992; Early Breast Cancer Trialists' collaborative Group 1990; Early Breast Cancer Trialists' collaborative Group 1995; Early Breast Cancer Trialists' collaborative Group 2000; Host and Brennhovd 1986; Jones and Ribeiro 1989; Paszat et al. 1998; Cuzick et al. 1987). These older trials used RT techniques that resulted in a larger volume of heart in the RT field than is typically seen with modern treatment approaches. As a result, reductions in breast cancer death in these trials were offset by increases in cardiac death. As a result, post-mastectomy RT had a detrimental effect on overall survival. With modern RT techniques, cardiac toxicity appears to be reduced, resulting in an net mortality benefit following post-mastectomy RT (Overgaard et al. 1997; Overgaard et al. 1999; Ragaz et al. 1997; Whelan et al. 2000). Even with modern RT approaches, however, cardiac toxicity may result. Modern techniques typically incorporate tangential fields that incidentally include the anterior myocardium. Furthermore, some patients are treated with beams that are directed from the anterior direction towards the medial breast/chest wall and internal mammary lymph nodes. Typical doses are 45–50Gy. The incidence of cardiac dysfunction following radiation for breast cancer is related to the volume of heart irradiated (Rutqvist et al. 1992; Gyenes et al. 1998). Pericarditis has also been reported in these patients.

Subclinical cardiac injury is very common. Non-lethal symptomatic cardiac injury is reported to occur in up to 50% of patients receiving incidental cardiac irradiation during treatment for Hodgkin's disease or carcinoma of the breast, lung, esophagus or medulloblastoma (Pohjola-Sintonen et al. 1987, Carmel and Kaplan 1976; Cosset et al. 1988; Cosset et al. 1991; Applefeld and Wiernik 1983; Jakacki et al. 1993; Yu et al. 2003). Among asymptomatic patients, subclinical damage can be detected by electrocardiogram (EKG), echocardiogram (ECHO) or other radiological studies in approximately 67% of all reported cases (Carmel and Kaplan, 1976; Strender et al. 1986; costine et al. 1997; Gomez et al. 1983; Gottdiener et al. 1983; Lagrange et al. 1992; van Rijswijk et al. 1987; Hardenbergh et al. 2001; Makinen et al. 1990; Watchie et al. 1995).

We, as well as others, have used SPECT cardiac perfusion imaging as a means of detecting microvascular injury in the myocardium. In patients irradiated for left-sided breast cancer, approximately 50–75% will develop new perfusion defects if ≥5% of the left ventricle is included within the radiation field (Marks et al. 2003;). These defects appear to be associated with corresponding abnormalities in wall motion and possibly subtle reductions in ejection fraction.

The reported incidence of RT-induced cardiac toxicity varies widely depending on the endpoint used. The reported frequency of cardiac morbidity also depends on the population of patients considered. Studies that report on a group of patients seen by cardiologists tend to overestimate the incidence, since asymptomatic patients are often not included. Conversely, retrospective studies of patients evaluated years following RT tend to underestimate the incidence since only the survivors are included. Nevertheless, a preponderance of the data suggests that RT-induced cardiac damage, either clinical or subclinical, is common.

The experience with Hodgkin's disease and breast cancer demonstrates the potential impact of TRT on cardiac function in patients irradiated for lung cancer. As outlined above, the generally poor survival rates and concurrent illnesses in patients irradiated for lung cancer probably account for the low reported incidence of radiation-associated cardiac events in these patients. Nevertheless, there are some data that demonstrate that this may be an important clinical problem. In a meta-analysis, post-operative RT was associated with a 6% increased rate of mortality in

cases where the cause of death was not specified (Port Meta-analysis Trialists Group 1998). In a randomized clinical trial assessing the utility of post-operative TRT, the addition of RT increased the rate of cardiac mortality threefold, compared with non-irradiated controls. Five percent of the irradiated patients died of cardiac disease; non-lethal morbidity was not addressed (Dautzenberg et al. 1999). Cardiac toxicity has not been reported in patients treated definitively for lung cancer, but it has been reported in the post-operative setting, where survival rates are higher (Dautzenberg et al. 1999). This observation supports the concept that such cardiac events may be under-reported in long-term survivors of lung cancer.

The concern for RT-induced cardiotoxicity is heightened by the widespread use of potentially cardiotoxic systemic therapy and the high prevalence of cardiac risk factors in the lung cancer patient population. Paclitaxel, a widely used agent in the treatment of lung cancer, is potentially cardiotoxic (Vogt et al. 1996; Kelly et al. 1997). A variety of clinical factors (age, male gender, tobacco use, obesity, diabetes mellitus, family history, hypercholesterolemia and hypertension) have been associated with an increased incidence of ischemic cardiac disease. Many of these same factors, hypertension (Lauk and Trott 1988), a lack of exercise (Geist et al. 1990) and a high cholesterol/fat diet (Artom et al. 1965; Amromin et al. 1964), may increase the risk of RT-induced cardiac injury.

A clinical study from the Memorial Sloan Kettering Cancer Center suggests that the dose to the inferior lung is more predictive of radiation pneumonitis than is the dose delivered to the superior aspect of the lung (Yorke et al. 2002). A similar finding has been reported in mice (Tucker et al. 1997; Travis et al. 1997). It is possible that irradiation of the inferior lung may be a barometer for incidental cardiac irradiation, as the heart is located in the inferior chest in both mice and humans. Interestingly, in rats (where the heart is located in the superior left hemi-thorax), irradiation of the superior or left lung resulted in more "lung" toxicity than did similar treatment to the right or inferior lung (Jiresova et al. 2002). In concert, these data suggest that incidental cardiac irradiation may result in subclinical injury that masquerades as, or interacts with, "lung" toxicity.

In light of these issues, we recommend that care be taken to minimize incidental cardiac irradiation during TRT for lung cancer. To this end, we often use non-axial beams to minimize incidental cardiac irradiation. This is most useful in patients with lower lobe tumors and hilar/mediastinal nodes. In these cases, one is often able to shadow the primary tumor with the nodal disease, resulting in a beam aperture that can actually be smaller with non-axial beams than with axial beams. For example, a primary tumor in the left lower lobe, with metastases to the left hilum and pre-carinal area, can often be treated with oblique fields oriented from right anterior-superior and opposed left posterior-inferior directions, resulting in irradiation of a smaller cardiac volume.

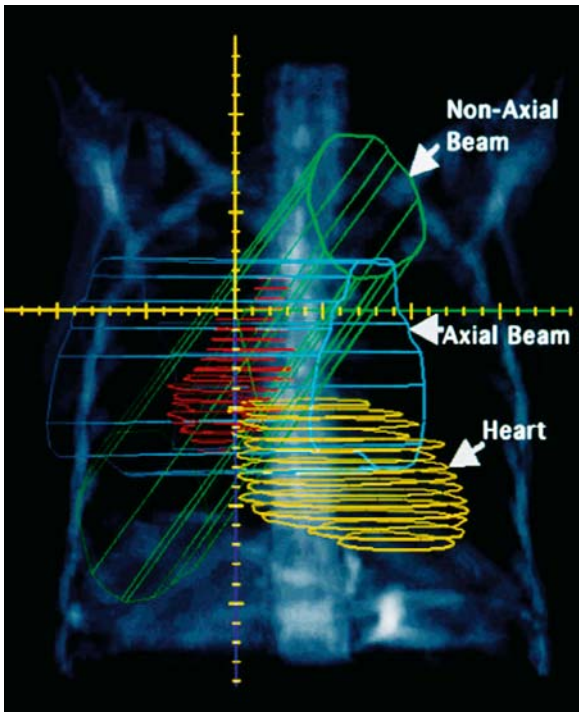

Fig 8.2.1. Non-axial beams to limit cardiac dose

It is important to remember that incidental cardiac irradiation is a concern for tumors in both the left and right thorax. Off-cord oblique axial boost fields for right lung tumors usually include the anterior heart.

Given the degree of cardiac injury observed in patients irradiated for breast cancer, Hodgkin's disease and other mediastinal neoplasms, it is extremely likely that similar events are occurring in patients irradiated for lung cancer. To date, this has not been recognized as an important clinical problem, due primarily to competing morbidity/mortality. The possibility of RT-associated cardiac dysfunction should be considered in patients who have been irradiated for lung cancer. Additional investigations are needed to better understand the clinical importance of such injury.

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8.3 Spinal Cord

Timothy E. Schultheiss

CONTENTS

8.3.1 Introduction

Radiation myelopathy is one of the most dramatic complications of radiation therapy. Consequently, many clinical reports of this injury appeared in the literature during the 1970s and 1980s. This period saw a transition from the use of cobalt-60 to linear accelerators. This was also a period when spilt course treatments with large doses per fraction were used. It is primarily from these reports that our current understanding of clinical radiation myelopathy is gleaned. However, we are also guided by many experimental studies of radiation injury to the spinal cord in mice, rats, guinea pigs, dogs, pigs and monkeys. Nonetheless, there are many unanswered questions regarding the radiation response of the spinal cord.

8.3.2 Histopathology

Late radiation damage to a tissue or organ can be diffusely distributed over a volume closely corresponding to the irradiated volume, as in late fibrosis. Conversely, it can be focal and occur at unpredictable locations within a uniformly irradiated organ. The latter is the case for radiation myelopathy. The initial lesion occurs exclusively within the white matter of the spinal cord, but its pathogenesis is complex and multifactorial. In its simplest form, the pathogenesis has one of two origins – either (relatively) direct damage to white matter parenchyma, ultimately leading to a necrotic lesion via a complicated pathway, or a lesion in the white matter that is secondary to microvascular damage. (The white matter parenchyma is understood to include glial cells in this case.) Lesions can appear adjacent to areas that show no evidence of radiation damage but were identically irradiated. Reviews of the pathology and pathogenesis of radiation myelopathy can be found in the works from the laboratories of van der Kogel [van der Kogel and Barendsen (1974), van der Kogel (1986)], Stephens [Schultheiss et al. (1988), Stephens et al. (1989)] and Hopewell (1979).

It seems clear that in most animals, including humans, there is a vascular-based lesion and a parenchymal-based lesion. Zeman was the first to articulate the dual hypothesis of radiation injury of the spinal cord [Zeman (1961)], but van der Kogel definitively verified this hypothesis and explored it in detail in rats [van der Kogel (1979), van der Kogel (1980)]. In his studies, the white matter lesion occurred earlier and at higher doses. Clearly, if the later lesion occurs at higher doses, it will never be seen. This may explain why only the parenchymal-based lesion is seen in some strains.

These same general observations have been made in humans [Schultheiss et al. (1984), Schultheiss et al. (1988)]. However, the data are much more difficult to interpret since autopsy reports often reflect the status of the lesions months or years after the onset of symptoms.

In humans, latencies as short as 4 months have been observed, but these are very rare. Typically, the onset of symptoms occurs 9 to 48 months after the

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completion of treatment. There is no difference between latency in the cervical and thoracic levels of the cord. The latency in children is shorter than in the adult, but there does not seem to be much difference in tolerance. Nonetheless, it is customary to respect a lower tolerance in the child.

8.3.3 Symptoms and Treatment

The progression of symptoms for thoracic radiation myelopathy consists of generally altered sensation in the lower extremities, including numbness, tingling and reduced sensitivity to temperature. A sensory level is sometimes seen corresponding to the irradiated spinal segment. Pain is sometimes reported, more often associated with tingling. This progresses to weakness, which can be manifest as changes in gait or foot drop. Paresis, rectal and bladder incontinence, and complete paralysis may develop. Symptoms can progress rapidly, with patients sometimes presenting with paralysis. Recovery from sensory losses may occur over time, but motor deficits are rarely recovered. Although thoracic myelopathy does not have the morbidity associated with cervical myelopathy, it can still become life threatening as a result of the secondary effects of incontinence and paralysis [Schultheiss et al. (1986)]. No treatment has shown long-term effectiveness [Ang et al (1994)].

8.3.4 Dose Response

The most widely used dose limit for the spinal cord is 45-Gy at 1.8 to 2-Gy per fraction. Some clinicians routinely respect an even lower dose for the spinal cord. This policy cannot be challenged as long as the tumor is adequately irradiated. However, it would be imprudent to compromise the tumor dose in order to limit the spinal cord to a dose lower than 45-Gy in patients for whom there is no evidence of increased radiation sensitivity.

It has been reported that the dose producing a 5% rate of radiation myelopathy is between 57 and 61-Gy in conventional dose fractions [Schultheiss (1994)]. According to Wong et al., no case of radiation myelopathy has been found at Princess Margaret Hospital after 50-Gy in 25 fractions [Wong et al. (1994)], although there are literature reports of myelopathies at this dose. Although it may be an unusual circumstance, 50-Gy (or higher) in 2-Gy fractions should be considered if the tumor would otherwise be underdosed. However, it is imperative that the patient be properly informed of the risk.

Factors other than the dose schedule that affect the spinal cord tolerance, either clinically or experimentally, include irradiated volume, chemotherapeutic agents, age, oxygenation, vascular disease, concurrent disease processes and congenital abnormalities.

There have been numerous studies of the effect of chemotherapy on the tolerance of the spinal cord, but the clinical data are mostly anecdotal [Ang et al. (1986), Bloss et al. (1991), Schultheiss (1994), van der Kogel and Sissingh (1983), van der Kogel and Sissingh (1985)]. With the possible exception of chemotherapeutic agents that are known to be neurotoxic, one cannot state unequivocally that chemotherapy reduces the radiation tolerance of the spinal cord. This is especially true for those agents causing peripheral neuropathy, but not central neuropathy [St Clair et al. (2003)].

8.3.5 Hyperfractionation

The effect of hyperfractionation on the response of the spinal cord is not fully understood. Although the spinal cord has a high capacity for long-term repair of radiation damage, as will be discussed later, its interfraction repair is slower than many other tissues [Ang et al (1992)]. Although there have not been any published reports of unexpected myelopathies occurring after two fractions per day, unanticipated myelopathies have occurred after regimens of three and four fractions per day [Dische and Saunders (1989), Wong et al. (1991)]. In two separate publications, Jeremic has shown that 50.6-Gy in 1.1 or 50.4-Gy in 1.2Gy fractions produced no myelopathies in either the cervical or thoracic cord, respectively [Jeremic et al. (1998), Jeremic et al. (2001)]. In the adult rat, Ang et al. found that the repair was described better by a bi-exponential function than by a mono-exponential function [Ang et al. (1992)]. However, Ruifrok et al. found no evidence of this biexponential repair in the newborn rat [Ruifrok et al. (1992)]. In the rhesus monkey, no difference was observed in the response at 98.4-Gy at 1.2-Gy per fraction, compared with 84-Gy – the data were 8/15 versus 6/11, respectively (unpublished data).

8.3.6 Anatomic Level

There is little evidence that any section of the spinal cord differs in intrinsic radiosensitivity from any other segment. However, there may be extrinsic factors affecting spinal cord radiosensitivity that apply more frequently to one section of the cord than another. The thoracic cord's apparent radiosensitivity may be slightly lower (higher tolerance) simply because there is a smaller volume of white matter in the cervical cord. However, the spinal cord's dose response is not very sensitive to changes in volume, and this effect is unlikely to appreciably alter the incidence of radiation myelopathy.

Dische et al. (1986) have observed a dramatic effect of hemoglobin on the tolerance of the spinal cord. Furthermore, data from van den Brenk et al. [van den Brenk et al. (1968)] and Coy and Dolman (1971) indicate that the spinal cord is sensitive to extrinsic oxygen tension. Publications that report the incidence of thoracic radiation myelopathy come almost exclusively from studies of lung cancer. One may reasonably infer that these patients have seriously impaired oxygenation of the spinal cord, owing to a smoking history and to lung cancer. Therefore it is possible that their spinal cord tolerance is increased owing to a decrease in the oxygenation of the white matter.

It is difficult to compare the clinical response of the cervical cord to that of the thoracic level. The radiation regimens from which crude estimates of the incidence of radiation myelopathy can be made generally employed high doses per fraction, but the regimens for cervical myelopathy and thoracic myelopathy are too dissimilar to compare directly. Furthermore, the survival of the cohort is generally much shorter in patients with thoracic myelopathy. As a result, the number of patient-years of exposure is very different from what it is in cervical myelopathy.

8.3.7 Retreatment

The spinal cord appears to have a substantial capacity for long-term recovery from subclinical radiation damage. In animals, this recovery appears to be dependent on the initial dose or level of damage and the time between the initial course of treatment and the second course of treatment. In cancer patients, the level of recovery is probably more variable and possibly dependent on intervening therapies as well.

Retreatment dose-response studies in rats have been performed by a number of authors. Generally, it appears that following a treatment of approximately 50% of the D_{50} for an untreated rat, 75% of the dose is recovered in 20 weeks, and close to 100% is recovered in a year. In guinea pigs, Knowles found the D_{50} for one-year old animals who received 10-Gy one day after birth was only 5% less than one-year old unirradiated animals [Knowles (1983)]. Both van der Kogel (1991), as well as Wong and Hao [Wong et al. (1997)], have shown the dependence of the retreatment tolerance on the initial dose and the interval between treatments. The relative steepness of the retreatment dose/response function, compared with the de novo dose-response function is not certain.

Ang et al. have performed retreatment experiments on rhesus monkeys [Ang et al. (1993), Ang et al. (2001)]. Their findings indicate that about 75% of 44-Gy in 20 fractions is recovered after 1 year and nearly 100% is recovered after 3 years. Forty-four Gy represents 57% of the initial D_{50} in these animals. Thus, the primate data is in reasonable agreement with the rodent data.

The largest number of clinical cases of radiation myelopathy following retreatment was reported by Wong et al. In their report on 11 cases, all but two had equivalent doses in 2-Gy fractions of 52-Gy or more (using an α/β=0.87 [Schultheiss and Hanks (1999)]). In those two cases, the break between courses was only 2 months, and little or no repair would be expected. Thus, in all of their reported cases, either the spinal cord tolerance could have been exceeded by one of the treatment courses alone, or there was insufficient time for repair between courses. The average latency following the second course of treatment was 11 months, with a range of 4 to 25 months.

It is clear that the spinal cord can tolerate a significant retreatment dose. The clinical decision to retreat part of the spinal cord must be based on the availability of alternative treatments, the consequences of not treating, the initial cord dose and the interval since the initial treatment. As always, a specific and detailed informed consent is mandatory. For palliation or for treatment of cord compression, 30-Gy in 15 fractions should be given consideration if the initial treatment did not exceed 45-Gy to the cord and was given at least 9 months prior to the potential second course. Care should be taken to minimize the spinal cord volume, but radiation myelopathy is still a possibility.

8.3.8 Volume

The conventional radiation volume effect on the spinal cord is understood as a decrease in the tolerance dose as the length of irradiated cord increases. In rats, there is a striking volume effect at field sizes below 1cm, but very little effect as the length of irradiated cord is increased beyond 1cm [van der Kogel (1991)]. This volume behavior may result from the fact that the size of the lesion is not negligible compared to 1cm. In rhesus monkeys, the volume effect is consistent with the probability model [Schultheiss et al. (1983)], which has been inappropriately called the "critical element model." This model is derived using simple probability theory, where the probability of not producing a lesion in the irradiated volume is simply the product of the probabilities of not producing lesions in all subvolumes. A consequence of the model is that for steep dose/response functions, there is very little volume effect. This can explain why there is no volume effect in rats at field sizes above 1cm.

No unequivocal volume effect for the spinal cord has been observed in humans. The reason for this, perhaps, is that, for a specific dose regimen or clinical trial reported to result in radiation myelopathy (for example, in a clinical trial for lung cancer), the variation in field size is not large and the sample size is too small to see any field size effect. In anecdotal radiation myelopathy reports, field size effects cannot be demonstrated because controls (patients without myelopathy) are never included. Nonetheless, it is reasonable to assume that a field size effect is operational in the radiation response of the human spinal cord. However, the increase in risk that accompanies an increase in field length is not likely to be very significant if one is operating within the limits of the conventional standard-of-care for cancer patients. The risk of radiation myelopathy in patients receiving conventional doses to the spinal cord is so low that no volume effect will be seen clinically at these doses.

Of more immediate concern is the risk of radiation myelopathy in patients for whom the dose varies significantly across the spinal cord. With the advent of IMRT, small portions of the cord can be irradiated to doses that would be intolerably high for the whole cord, while the remainder of the cord receives much lower doses. The only study that addresses this issue is a paper by Debus et al., where patients undergoing proton radiation therapy for base-of-skull lesions had part of their brainstems irradiated to high doses [Debus et al. (1997)]. Debus et al. found a relative risk of 11.4 for patients in whom more than 0.9cm^3 of the brainstem had received 60-Gy or higher (photon equivalent). Also of significant risk on multivariate analysis were patients having two or more base-of-skull surgical procedures and a diagnosis of diabetes. The maximum dose to the brainstem was not significant ($p \sim 0.09$) in this study of 348 patients.

Based on the study discussed above, one could reasonably infer that a sharp dose gradient across the spinal cord can be tolerated if the maximum dose is less than 60-Gy. However, it is likely that one cannot achieve as sharp a gradient with photons as with protons. Moreover, these patients were meticulously immobilized and imaged prior to treatment. In routine practice, some dose smearing will occur as a result of setup variations. With IMRT, this smearing should be less problematic because of the care that should be taken in the positioning of patients. Beyond stating that the spinal cord should be able to tolerate a higher maximum dose, provided there is a dose gradient across the cord, it is not currently possible to give quantitative guidance related to the tolerance associated with small hot spots on the spinal cord.

8.3.9 Other Observations

There are species-specific responses of the spinal cord that deserve mention. In the pig, the pathology and radiation dose response is similar to that which is observed in other animals. The difference in the pig response is that the latent period is far shorter than is seen in other models [Hopewel and van den Aardweg (1992), van den Aardweg et al. (1995)]. In the dog, there are reactions in the meninges and the dorsal root ganglia not seen in other animals [Powers et al (1992)]. Furthermore, the role of the vascular response is relatively greater in the dog [Schultheiss et al. (1992)]. In the rhesus monkey, and in some rat strains, a primarily vascular lesion is infrequently seen. The reason for this in the monkey may be that this type of lesion occurs after the time during which these animals are typically held (24 months). In some rat strains, the reason is probably the same, with the addition that the animals' life expectancy may be of similar duration to the latency for a vascular lesion.

8.3.10 Conclusions

There is no indication that the thoracic and cervical levels of the spinal cord have different intrinsic responses. Extrinsic conditions may result in apparent differences. Differences in the survival of the cohort population may result in fewer thoracic myelopathies being observed. The morbidity of thoracic radiation myelopathy is generally lower than that for cervical myelopathy. Administration of common chemotherapeutic agents for lung cancer may reduce the radiation tolerance of the spinal cord, but no quantitative studies have demonstrated this for cisplatin, vinblastine or gemcitabine – the most commonly used chemotherapeutic agents in lung cancer.

In this era of intensity modulated radiation therapy, techniques for concurrent boosts of the tumor will be developed, making a cone down no longer necessary. This will result in a lower dose per fraction to normal tissues outside the target. The effect of this decrease in the dose per fraction will be more significant in tissues such as the spinal cord, whose late effects are dose-limiting.

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8.4 Radiation Therapy-Related Toxicity: Esophagus

Maria Werner-Wasik

CONTENTS

Acknowledgement: Part of this work will be published in the *Hematology and Oncology Clinics of North America,* 2004.

8.4.1 Pathophysiology and Clinical Picture of Esophagitis

The esophagus is lined with a convoluted squamous epithelium, a basal cell layer, submucosa and a layer of striated muscle fibers underneath, without surrounding serosa. In mice irradiated with a single radiation therapy (RT) fraction to the thorax (Phillips and Ross 1974), evidence of damage to the esophagus was observed at 20.0 Gy, three days after RT. This included vacuolization of the basal cell layer, absence of mitosis and submucosal edema. Some regeneration was evident by 1–2 weeks after RT, including proliferating basal cells, regenerating epithelium and scattered areas of complete esophageal denudation. At three weeks, the regeneration of the esophageal lining was complete, and after 4 weeks the appearance of the irradiated esophagus was normal. For fractionated RT doses, the $LD_{50/28}$ (or RT dose causing death in 50% of the animals over 28 days) was estimated as 57.45 Gy (in 10 fractions).

Radiologic findings of esophageal injury were described in 30 symptomatic patients who received thoracic RT to 45–60 Gy (Goldstein et al. 1975). The most common findings consisted of esophageal dysmotility, such as failure to complete primary peristaltic waves, nonperistaltic or tertiary contractions and failure of distal esophageal sphincter relaxation. Smooth esophageal strictures were demonstrated in some patients, and one frank ulceration of the irradiated site was observed.

Abnormal esophageal motility was noted to occur within 4–12 weeks from RT alone and as early as one week from concurrent chemotherapy and RT (Lepke and Libshitz 1983). Strictures generally developed at 6–8 months but were seen as early as 4 months.

The first symptoms of acute esophagitis start usually in the second or third week of thoracic radiation therapy, commonly at the dose of 18.0–21.0 Gy of standard fractionated RT, and include a sensation of difficult swallowing (dysphagia). This may progress to painful swallowing of food and saliva (odynophagia) and later to constant pain not necessarily related to swallowing. In severe cases, patients may not be able to swallow at all and may require intravenous hydration, feeding through the gastric tube and, in extremely rare cases, parenteral nutrition. In patients receiving concurrent chemotherapy and thoracic RT, acute esophagitis symptoms peak within 30 days from start of RT in 23% of patients and within 60 days in 36% (Werner-Wasik et al. 2002). Symptoms of acute esophagitis commonly persist for 1–3 weeks after completion of RT. Esophageal damage may develop at 3–8 months from completion of RT and manifests most often as dysphagia to solids, caused by a permanent narrowing of the esophagus (stricture). The presence of stricture requires periodic surgical dilation of the esophagus, usually with excellent results.

Acute esophagitis may be very severe and disabling, resulting in hospitalization, placement of a feeding

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tube in the stomach or intravenous feedings for a period of time. Additionally, the course of RT may need to be halted temporarily in order to allow for healing of the esophageal lining. Treatment breaks in turn have been unequivocally demonstrated to decrease survival of patients with unresectable lung cancer (Cox et al. 1993). Therefore, a proper diagnosis, treatment and prevention of esophagitis as a dose-limiting toxicity of chemoradiotherapy may have a direct impact on tumor control and the patient's chance of survival.

Patients with esophagitis symptoms require steady supportive care, starting with a low-acid and bland diet when the first sensation of a difficulty in swallowing is reported (grade 1). Patients should be instructed to avoid coffee, hot beverages, spicy foods, citrus fruit and juices, tomato products, alcohol and tobacco. In addition, a mixture of a local anesthetic (2% viscous lidocaine), coating substance (Benadryl elixir) and saline/baking soda ("Magic Mouthwash") is frequently prescribed and should be taken liberally before meals to facilitate swallowing. Once symptoms progress with more severe pain and only a soft diet is feasible (grade 2), stronger oral analgesic agents should be prescribed (hydrocodone with acetaminophen; liquid morphine; prolonged action opiate preparations etc.) to control pain and allow good nutrition. High-calorie liquid oral nutritional supplements are very helpful in maintaining a satisfactory caloric intake and minimizing weight loss and anemia. If an adequate oral intake of fluids is impaired (as determined by the dietary interview, positional changes in blood pressure and low urinary output), intravenous fluids should be promptly initiated in order to break the vicious cycle of dehydration–poor oral intake–further dehydration. A simple initial step is to give fluids intravenously on an outpatient basis for a day or two, while continuing thoracic RT (grade 2 in the new version 3 CTC scale; grade 3 in the older scales). When the patient is unable to swallow despite optimal oral analgesics, hospitalization is indicated for intravenous hydration and intravenous pain control (grade 3). In extreme cases, placement of a gastric tube or parenteral nutrition may be necessary (grade 4).

The speed of recovery from acute esophagitis seems related to the recovery from neutropenia induced by concurrent delivery of chemotherapy. Prolonged neutropenia does not allow sufficient healing of the esophageal mucosa. This situation is a classic indication for a temporary suspension of RT, which allows the administration of granulocyte-stimulating factor preparation to shorten the neutropenic period. Otherwise, thoracic RT should be continued as dictated by clinical judgment, since RT breaks are strongly associated with decreased chances of tumor control.

8.4.2 Evaluation of Esophagitis

Historically, various criteria have been used to grade acute esophagitis (Tables 8.4.1, 8.4.2). Radiation Therapy Oncology Group (RTOG) criteria and version 2.0 of National Cancer Institute's (NCI) Common Toxicity Criteria (CTC) were based on the clinical assessment of patient symptoms, need to change diet, analgesic requirements, weight loss and need for intervention (such as intravenous fluids and/or feeding tube or parenteral nutrition). However, in order to diagnose grade 4 esophagitis, endoscopic or radiographic tests may be necessary (see Table 8.4.1a). The next version of CTC – on the NCI's Common Terminology Criteria for Adverse Events, v3.0, CTCAE scale, introduced in October 2003 (http://ctep.info.nih.gov/reporting/ctc.html) – removed the need for analgesics and weight loss as evaluation criteria, for both "Dysphagia" and "Esophagitis," and is based nearly entirely on symptoms, altered diet and the need for intervention. An exception exists in the case of the asymptomatic patient who is found to have endoscopic or radiographic findings and, consequently, assigned a grade 1 esophagitis (Table 8.4.1b).

Hirota et al. (Hirota et al. 2001) were successful in their attempt to correlate acute esophagitis, assessed with endoscopy, with the RTOG grade in patients treated with RT +/– chemotherapy. With a Spearman coefficient 0.428 ($p<0.0001$), the result of their work gives validity to the currently used clinical grading of esophagitis.

The grade of esophagitis describes toxicity at one point in time, but it does not provide information about the length of time during which the patient experiences the symptoms of esophagitis

The Esophagitis Index (Fig. 8.4.1) (Werner-Wasik et al. 2001, 2002) is a novel measure of toxicity and may be applied to any irradiated organ. The Index is obtained by plotting the esophagitis grade over time measured in weeks, and it is presented as a single numerical value, based on calculation of the area under the curve (AUC) (Rowland and Tozer 1995). It may be a more comprehensive measure of normal tissue toxicity than maximum grade alone. Its calculation requires the accumulation of prospective data points

Table 8.4.1a. NCI CTC v2.0 Scale

0	1	2	3	4
None	Mild dysphagia, but caneat regular diet	Dysphagia, requiring predominantly pureed, soft or liquid diet	Dysphagia, requiring feeding tube, IV hydration or hyperalimentation	Complete obstruction (cannot swallow saliva); ulceration with bleeding, not induced by minor trauma

Table 8.4.1b. NCI CTCAE v3.0 Scale: Acute esophagitis (dysphagia-esophageal, related to radiation)

	Grade				
	1	2	3	4	5
Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing (e.g.altered dietary habits, oral supplements); iv fluids, indicated <24 hrs	Symptomatic and severely altered eating/swallowing (e.g. inadequate oral caloric or fluid intake); iv fluids, tube feedings .or TPN indicated ≥24 hrs	Life-threatening consequences (e.g. obstruction, perforation)	Death
Remark: Dysphagia requiring dilation is graded as stricture/stenosis					
Esophagitis	Asymptomatic Pathologic, radiographic or endoscopic Findings only	symptomatic; altered eating/swallowing (e.g. altered dietary habits, oral supplements); iv fluids indicated <24 hrs	Same as above	Same as above	Death

Table 8.4.2. RTOG/EORTC Late Esophagitis Criteria

	Grade				
	0	1	2	3	4
ESOPHAGUS	No symptoms	Mild fibrosis; slight difficulty in swallowing solids; no pain on swallowing	Unable to take solid food normally; swallowing semi-solid food; dilatation may be indicated	Severe fibrosis; able to swallow only liquids; may have pain on swallowing; dilatation required	Necrosis/Perforation Fistula

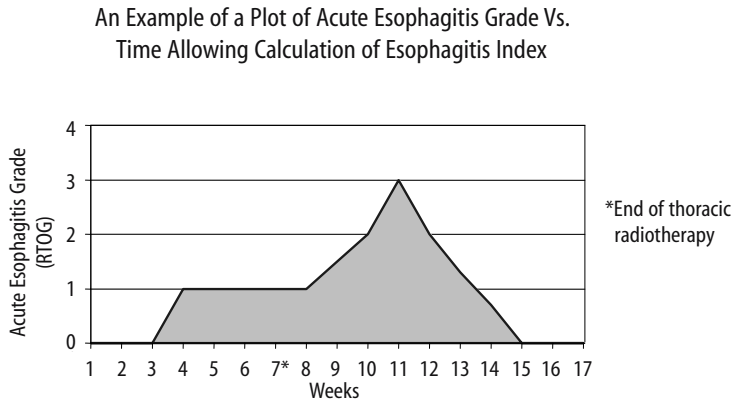

Fig. 8.4.1. Calculation of Esophagitis Index.

of toxicity over time and, therefore, its applicability may be limited to investigational pursuits. However, a broader application of the Esophagitis Index may allow a more precise definition of normal tissue toxicity, facilitate toxicity comparisons between various treatment regimens and be a useful tool in investigations of the quality of life.

In a recently completed study performed by the Radiation Therapy Oncology Group (RTOG) 98–01 (Movsas et al. 2003), other measures of esophagitis were implemented, based on physician assessment (weekly Physician Dysphagia Log), as well as on daily patient assessments of difficulty swallowing (Patient Swallowing Diary). These measures allowed a direct comparison of healthcare worker-based vs. patient-based esophagitis endpoints.

8.4.3 Incidence of Esophagitis and Predisposing Factors

The evolution of therapeutic approaches for lung cancer illustrates the trend for treatment intensification, with hopes that dose-intense chemotherapy regimens and/or higher RT doses, or novel fractionation schemes, will result in the prolongation of survival. To date, the best cooperative group results of intense chemoradiotherapy for LA–NSCLC report median survival times (MST) as high as 26.0 months (Gandara et al. 2003).

In the RTOG trial (94–10)(Curran et al. 2000), 610 patients were randomized to receive induction chemotherapy (vinblastine and cisplatin), followed in sequence by standard thoracic radiotherapy, or the same chemotherapy delivered concurrently with standard RT or the same chemotherapy given concurrently with hyperfractionated RT. The results support the superiority of the concurrent approach over the sequential approach, with best median survival time of 17.1 months (standard RT) and 15.6 months (hyperfractionated RT) observed in both concurrent arms of the trial, vs. 14.6 months in the sequential arm (p=0.038). Based on these data and another phase III randomized trial from Japan (Furuse et al. 1999), the paradigm for the nonoperative treatment of lung cancer is clearly no longer the previously-accepted standard of sequential treatment but, instead, the use of concurrent regimens.

The incidence of severe, acute esophagitis (grade 3 or higher) in patients treated for lung cancer with standard (once daily) radiation therapy alone is 1.3%. Induction chemotherapy increases the risk of severe acute esophagitis slightly, compared with standard radiotherapy alone (Werner-Wasik et al. 2000; Byhardt et al. 1998). In contrast, the strong radiosensitizing effect of chemotherapy given concurrently with standard thoracic RT is evident from the incidence of severe esophagitis of 6–14% (Byhardt et al. 1998), as well as from values on the Esophagitis Index that are more than twice as high for the concurrent chemotherapy/standard RT group as for the RT-alone group (Werner-Wasik **et al.** 1999, 2000). It had been reported in the literature that agents such as Adriamycin (Boal et al. 1979; Umsawasdi et al. 1985) cause severe primary or recall esophagitis at RT doses as low as 20.0 Gy. Vokes et al. (Vokes et al. 2002) described an incidence of 49% of acute grade 3 or higher esophagitis with concurrent gemcitabine and thoracic RT. Whether the degree of esophagitis is related to the type or scheduling of chemotherapy used (daily vs. weekly, or every three weeks) is uncertain.

Aggressive types of RT fractionation have also been reported to be associated with a worsening of the esophagitis grade and the duration of the condition. This is evident in the report of 100 patients treated in Australia (Ball et al. 1995) in a four-arm, randomized study, as well as in our analysis (Werner-Wassik et al. 2000). The duration of symptomatic esophagitis was 1.4 months (mo) in the conventional RT arm, 1.6 mo in the conventional RT arm with concurrent carboplatin, 3.2 mo in the accelerated arm and 2.4 mo in the accelerated RT plus carboplatin arm (Ball et al. 1995). In fact, in the Ball et al. multivariate analysis (Ball et al. 1995), accelerated radiotherapy (defined as fractions of 2.0 Gy delivered twice daily) was the only significant factor influencing the duration of esophagitis. In our study (Werner-Wasik et al. 2002), a similar pattern was observed, with hyperfractionated radiotherapy predicting very strongly for both the Esophagitis Index and the worst esophagitis grade, as well as longest time of suffering from esophagitis. Hyperfractionated RT to a total dose of 69.6 Gy was associated with a 24–34% incidence of severe esophagitis (Byhardt et al. 1998). During the most intense thoracic RT ever reported (used without CT for locally advanced non-small cell lung cancer), CHART regimen (Continuous Hyperfractionated Accelerated Radiation Therapy) resulted in 19% of patients having severe esophagitis (Saunders et al. 1996). In addition to the studies cited above, concomitant boost technique with concurrent chemotherapy (Dubrai et al. 1995) resulted in a dose-limiting incidence of esophagitis of 33%.

Current chemotherapy – and the RT-intense regimens – should not be intensified further without addressing the dose-limiting toxicities, such as esophagitis. It is important to understand factors predisposing patients to esophagitis, so that strategies to minimize its severity can be implemented.

8.4.4 Dosimetric Factors Associated with Esophagitis

It is commonly assumed in radiation oncology clinics that the longer the length of the esophagus segment included in the radiotherapy field, the higher the probability of esophageal toxicity, despite that fact that, in the literature, different opinions have been expressed on this topic (Werner-Wasik et al. 2000; Ball et al. 1995; Choy et al. 1999; Langer 1999). This assumption is based on murine observations that doubling the length of the irradiated portion of the esophagus leads to a decrease in the LD_{50} dose, i.e. in the dose causing death in 50% of irradiated animals (Michalowski and Hornsey 1986). The classic fields recommended for use in radiotherapy of lung cancer include the primary lesion, ipsilateral hilum, bilateral mediastinum and, often, the ipsilateral supraclavicular region, establishing elective nodal irradiation as a standard approach. The current trend is for smaller, tighter fields, frequently encompassing only the grossly visible tumor with a margin (such an approach is used in the RTOG phase II studies of RT dose escalation for non-small cell lung cancer). The benefits include less irradiated lung volume and a shorter length of irradiated esophagus. However, the evidence that esophageal toxicity is minimized with shorter esophageal length irradiated is inconsistent.

In two studies providing a multivariate analysis of various treatment-related factors, the length of the esophagus was not related to either the severity or the duration of esophagitis. In Ball et al.'s analysis (Ball et al. 1995), 100 patients were divided into three groups based on the length of the treatment field (<14.0cm, 14.0–15.9cm and >16.0cm), which presumably correlates with the length of the esophagus. No relationship was observed between esophageal length and the severity of esophagitis. In Choy's analysis of 120 patients (Choy et al. 1999), there was no correlation between the esophagitis grade and the length of esophagus in either the primary ($p = 0.4$) or boost ($p = 0.1$) radiation fields. In contrast, after analyzing 15 patients treated with chemoradiotherapy, Langer (Langer 1999) observed that grade 1 esophagitis occurred in five of six patients with esophageal exposure less than 16cm, and that grade 2 or greater esophagitis occurred in eight of nine patients in whom esophageal exposure exceeded 16cm.

We studied 105 patients with lung cancer receiving concurrent chemo-radiotherapy or RT alone. These patients had precise data on esophageal length as it relates to the fields used for irradiation. In a multivariate analysis of acute esophagitis scored prospectively in a uniform fashion, we found two factors to be significantly associated with an increasing maximum esophagitis grade: concurrent chemotherapy with once daily RT and concurrent chemotherapy with twice daily RT ($p < 0.001$, considered jointly) (Werner-Wasik et al. 2002). The duration of acute esophagitis was longest in the concurrent chemotherapy/twice daily radiotherapy group. An increased length of esophagus in the radiation field did not predict for the severity of acute esophagitis.

Recent advances in three-dimensional conformal radiation therapy provide a unique opportunity for gathering direct volumetric data pertaining to organ damage. These data are far more meaningful than the data from previous studies, obtained through estimates based on organ length (e.g. of the esophagus) or organ portion (e.g. of the lung or spinal cord).

The tolerance of the normal esophagus to RT has been studied in both animals and humans. The tolerance doses (TD) for esophageal clinical stricture or perforation in 5% of irradiated patients at 5 years ($TD_{5/5}$) are 60 Gy for the entire esophagus, 58 Gy for two thirds of the organ and 55 Gy for one third of the esophagus (Emami 1991).

Many primary lung tumors or involved mediastinal lymph nodes are centrally located and lie in close proximity to the esophagus. Therefore, exclusion of the entire esophageal length/volume from the high dose radiation region is extremely difficult. However, partial exclusion and lowering the radiation dose delivered to the entire circumference of the esophagus may be feasible. A dosimetric study by MaGuire et al. (Maguire et al. 1999) established a relationship between irradiation of the entire circumference using high doses to the risk of esophagitis. In a detailed multivariate analysis of 91 patients treated using a median corrected dose of 78.8 Gy, MaGuire et al. found that the percent of esophageal volume treated by >50.0 Gy and the maximum percent of esophageal circumference treated by >80.0 Gy were significant predictors of late (but, interestingly, not of acute) esophagitis. Overall, a total of 12/91 (18%) patients

developed late esophageal toxicity in their patient population. A novel concept emerging from the data described above is the importance of sparing a portion of the esophageal circumference to prevent or decrease the incidence of late damage to the esophagus. A potential explanation for the benefit of such sparing may be that epithelial healing in the portion of the esophageal circumference receiving a subcritical RT dose will be sufficient to maintain organ function even though the remainder of the wall circumference is irradiated using doses causing irreversible late damage.

Another analysis of the three-dimensional RT dose distributions of 26 patients with lung cancer who received 50–60 Gy of thoracic RT concurrently with carboplatin/paclitaxel chemotherapy (Hirota et al. 2001) concluded that the length of the esophagus (total circumference) treated using ≥45 Gy (>9.5 cm), as well as the percentage of esophageal volume receiving ≥45 Gy (>40%), were predictive of severe radiation esophagitis.

Predictors of radiation-induced esophageal toxicity in 207 patients with non-small cell lung cancer treated with three-dimensional conformal radiotherapy (26% with concurrent chemotherapy) were studied by Singh et al (Singh et al. 2003). Concurrent chemotherapy and a maximal esophageal point dose >58.0 Gy were associated in the multivariate analysis with a high risk of grade≥3 esophagitis. In addition, all assessable patients who developed grade 3–5 esophageal toxicity had a mean dose to the entire esophagus >34.0 Gy, but this dose was not predictive on multivariate analysis.

Because RT doses of 90.0–100.0 Gy are commonly believed necessary to achieve a local control of lung tumors measuring >3cm (Fletcher 1973), several dose escalation trials were initiated both in the US and in Europe. The maximum RT dose levels in these trials were 102.9 Gy (Hayman et al. 2001) or 90.3 Gy (Bradley et al.). The RTOG study evaluated the feasibility of dose escalation for patients with LA–NSCLC treated with three-dimensional (3D) conformal RT to the gross tumor only, without elective nodal irradiation. Maximum doses of 77.4 –90.3 Gy were prescribed, depending on the percentage of the total lung receiving more than 20.0 Gy.

Given that such doses differ significantly from those used in current clinical practice (60.0–64.0 Gy), restraints had to be placed on the doses to be delivered to the dose-limiting normal organs in the chest, such as lung, esophagus and spinal cord. With non-coplanar beams and 3D planning, allowing improvement of the target volume definition, doses to critical structures can often be reduced and esophageal toxicity less pronounced, compared with standard RT.

The RTOG 93–11 trial of thoracic RT-alone escalated the dose to the tumor for group 1 to 90.3 Gy (<25% of both lungs receiving ≥20 Gy), for group 2 to 83.8 Gy (25–37% of lungs receiving ≥20 Gy) and for group 3 to 77.4 Gy (>37% of lung receiving ≥20 Gy). The maximum dose allowed to 1/3 of esophageal volume was 65 Gy; to 2/3 of the volume, 58 Gy; and to the whole esophagus, 55 Gy. The clinical endpoint for this $TD_{5/5}$ is a stricture or perforation. No severe acute esophagitis was observed even with the highest RT dose. However, late esophageal toxicity was manifested in 8%, 0%, 4% and 11% of group 1 and in 0% and 10% of group 2 (Bradley et al. 2003), suggesting a dose–response relationship.

In the current ongoing RTOG trial (L-0117) of thoracic 3D RT dose escalation with concurrent paclitaxel and carboplatin chemotherapy, a mean esophageal dose of ≤32 Gy and esophageal V55 of ≤28% is mandated. "V55" is defined as the percentage of esophageal volume exceeding 55.0 Gy. If the esophageal dose exceeds the constraint of 28%, the patient cannot be treated in this RT dose escalation and chemotherapy trial. The constraint was derived based on data from a study of acute severe esophageal complications in patients previously treated with 3D RT at Washington University, MO (graham et al. 1994). Table 8.4.3 summarizes the data (RTOG, personal communication).

In the University of Michigan trial (Hayman et al. 2001), one-third of the esophagus was allowed to receive 80.0 Gy (Veff, or effective volume of <0.33). Only one patient (out of 63 evaluable) experienced acute grade 4 esophagitis, having received a prescription dose of 63.0 Gy, and six patients experienced acute grade 3 esophagitis. The report did not comment on any late cases of esophagitis.

Table 8.4.3. Acute Severe Esophageal Complications

Mean Dose (Gy)	% Volume >55 Gy (V55)(%)			
	<14	14-27	28-41	>41
<19	0/12	0/1	---	---
20-31	2/18	0/2	0/2	---
32-40.5	4/17	4/7	3/22	---
>40.5	0/2	0/3	6/11	5/12

8.4.5 Intensity-Modulated Radiation Therapy as a Tool of Lowering RT Dose to Esophagus

Up to now, standard RT techniques, even those utilizing 3D RT, have not been able to lower the maximum RT doses to the esophagus significantly. Intensity-modulated radiation therapy (IMRT) seems well suited for such a purpose, with its ability to deliver concave-shaped RT dose distributions around organs at risk, such as the esophagus.

Work performed in European institutions (DeGersem et al. 2000; Derycke et al. 1998) involved a comparison of 3D conventional thoracic radiation therapy vs. noncoplanar intensity-modulated beams (BIM) in 10 patients with Stage III non-small cell lung cancer. Within each group, normal vs. optimized plans were compared. In optimized BIM plans vs. optimized 3D plans, the volumes of the esophagus that was irradiated at high doses (60, 70 or 80 Gy) were reduced by the optimization (3D: $p = 0.01$ at 60 Gy; $p = 0.01$ at 70 Gy; $p = 0.4$ at 80 Gy; and BIM: $p = 0.14$ at 60 Gy; $p = 0.2$ at 70 Gy, $p=0.1$ at 80 Gy; where p is the statistical significance index). Therefore, it appears that for doses at least up to 80 Gy, a significant lowering of the dose to the esophagus can be accomplished with the optimization of the standard 3D plans, and that IMRT plans, in general, are even better than the best optimized 3D plans.

Figure 8.4.2 illustrates the concept of the conformal avoidance of a portion of esophageal circumference with IMRT, while at the same time allowing the delivery of high-dose RT to the neighboring lung tumor (Xiao et al. 2002). "Bending" of high-dose isodose lines with a relative sparing of part of the organ is evident. For now, the use of IMRT for such purposes is experimental and more work is needed before it can be applied widely in the clinic.

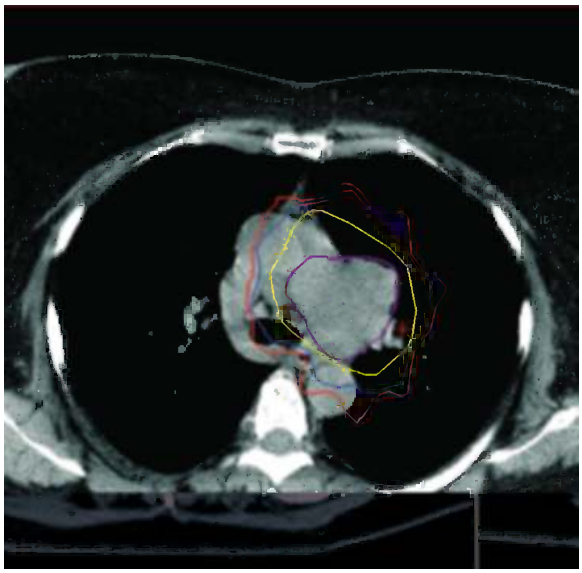

Fig. 8.4.2 IMRT conformal avoidance of the portion of esophageal circumference. Esophagus is outlined with a *blue-green line*. *Purple line*, gross tumor volume; *yellow line*, isodose line = 60.0 Gy; *blue line*, isodose line = 45.0 Gy; *red line*, isodose line = 40.0 Gy

8.4.6 Strategies Used to Prevent or Treat Esophagitis

The complete exclusion of the esophagus from the standard RT field designed to treat a locally advanced lung cancer is most often not feasible due to the central position of the esophagus in the mediastinum (Emami et al. 1996). Therefore, the main strategies in controlling esophagitis evolve around identifying an effective radioprotecting agent. One such agent is amifostine, an organic thiophosphate that is dephosphorylated to its active metabolite (WR-1065) by alkaline phosphatase. Once inside the cell, WR-1065, the free thiol, acts as a potent scavenger of the oxygen free radicals induced by ionizing radiation. It also provides an alternative target to DNA and RNA for the reactive molecules of alkylating or platinum agents. In a phase III randomized trial, amifostine was demonstrated to have a role in xerostomia prevention in irradiated patients with head and neck cancer, which served as the basis of the drug's FDA approval in 1999 as the first ever radioprotector (Brizel et al. 2000).

In the animal model of thoracic RT, amifostine administered to mice (400mg/kg intraperitoneally 30 minutes before irradiation) has been demonstrated to increase mean lethal doses (LD_{50}) of RT from approximately 38.0 Gy to 60.0 Gy, achieving an overall protection factor (PF) of 1.5–1.6 for both acute and chronic esophageal damage (Ito et al. 1986).

Encouraging results of improved esophagitis with amifostine have been reported in phase II (Werner-Wasik et al. 2001, 2002; Koukourakis et al. 1996; Antonadou et al. 2002) and III randomized trials performed in Greece (Antonadou et al. 2001; Antonadou et al. 2002) in patients with non-small cell lung cancer receiving thoracic RT, with or without concurrent chemotherapy. In the first trial (Antonadou et al. 2001), 146 patients with lung can-

cer treated with thoracic RT received daily infusion of amifostine (340 mg/m^2) or no amifostine. Grade 2 or higher acute esophagitis occurred in 32/72 RT patients vs. 6/72 in amifostine/RT patients ($p<0.001$). Acute pneumonitis was decreased as well ($p<0.001$). In a subsequent study of chemoradiotherapy for lung cancer (Antonadou 2002), a similar significant decrease in esophagitis or pneumonitis was observed (88% vs. 47% and 59% vs. 21%, respectively).

The team from MD Anderson Cancer Center (Komaki et al. 2002) recently reported a significant attenuation of acute esophagitis (31% vs. 7.4%; $p=0.03$) and pneumonitis (23% vs. 3.7%; $p=0.03$) in 60 patients receiving amifostine vs. no amifostine during a combined modality therapy course for lung cancer.

A large cooperative group phase III randomized study of amifostine for esophagitis prevention has been completed by the RTOG (98-01) (Movsas et al. 2003; Werner-Wasik et al. 2003). A total of 243 patients with locally advanced non-small cell lung cancer received two courses of induction chemotherapy (carboplatin and paclitaxel), followed by concurrent twice-daily thoracic RT and weekly low-dose carboplatin and paclitaxel. Patients were randomized to receive amifostine (500mg iv four times weekly, preceding the afternoon dose of RT) vs. no amifostine. In contrast to other studies, the NCI CTC assessment criteria and weekly physician dysphagia logs showed that amifostine did not reduce severe esophagitis (the rate was 30% with amifostine vs. 34% without). However, based on patient diaries, the swallowing dysfunction measured over time (equivalent Esophagitis Index) was significantly lower with amifostine ($p=0.03$). Given that only 40% of all RT fractions were "protected" by amifostine infusion in the study, and that only 29% of patients received the medication according to the protocol, further investigation of this agent is justified, possibly with subcutaneous administration to increase compliance and higher dose intensity.

So far, the search for other clinically important esophageal radioprotectants has been unsuccessful. Oral sucralfate, although applied commonly in the clinic, turned out not to have value in decreasing acute esophagitis in a double-blind phase III randomized trial of 97 patients receiving thoracic RT (McGinnis et al. 1997).

An interesting approach using plasmid/liposome delivery by the human manganese superoxide dismutase transgene has been reported successful in the prevention of radiation esophagitis in mice receiving carboplatin, paclitaxel and thoracic RT (Stickle et el. 1999).

In summary, although there has been significant progress in understanding the basis for esophageal injury resulting from thoracic radiation therapy, additional effort is needed to find effective measures for minimizing or eliminating esophagitis.

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8.5 Brain Toxicity

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CONTENTS

8.5.1 Introduction

Despite considerable improvements in local and systemic therapy for lung cancer, the incidence of brain metastases is still very high. Up to 60% of patients with small-cell lung cancer (SCLC) will be diagnosed with brain metastases at some time during the course of the disease. Therefore, prophylactic cranial irradiation (PCI) is often administered in patients with SCLC. The second indication for brain irradiation in lung cancer is palliation of symptoms from brain metastases. Depending on the number of lesions, their size and location and prognostic factors, either whole-brain radiotherapy (WBRT), open resection or stereotactic radiosurgery (SRS) may be the preferred option. Another indication is adjuvant radiotherapy after resection of brain metastases, which is usually administered by means of WBRT. This chapter will therefore cover the normal tissue effects of both partial brain radiotherapy and WBRT to the normal adult brain. The issue of reduced tolerance in the immature brain will not be discussed, due to the fact that it is less relevant in the context of lung cancer.

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The physical and technical developments and refinements over the last two decades in radiation oncology have been impressive. But still, the easiest and most effective way of avoiding side effects to the normal brain is by minimizing its exposure to ionizing radiation. While individually-shaped, highly conformal dose distributions can be created now–for example, for SRS treatment–this does not solve the problem of the presence of normal tissue within the irradiated target volume (the result of diffuse microscopic spread, which escapes current imaging technology). Therefore, many patients will continue to receive WBRT. Where a reduction of the irradiated volume is not feasible, further progress can only be expected from efforts directed at optimizing fractionation or widening the therapeutic window between tumor and normal tissue through modulation of the patient's responses to radiotherapy.

We will discuss the pathogenesis of radiation-induced brain toxicity, the incidence of typical side effects, risk factors, diagnostic aspects and the role of multimodal treatment concepts in the development of side effects. Increasing evidence can be found in the literature about the influence of cytotoxic drugs and the general side effects of cancer treatment, such as anemia, on the normal brain. Finally, pre-clinical and clinical data on the prevention and treatment of side effects will be reviewed.

8.5.2 Pathogenesis of Radiotherapy-Induced Brain Toxicity

Early evaluations of radiotherapy-induced central nervous system (CNS) toxicity date back at least to 70 years ago. It is not the aim of this chapter to discuss these historical data, which have been summarized in previous reviews, for example, by van der Kogel (Van Der Kogel 1986). When appropriate, data from spinal cord radiotherapy will be included in the current chapter because of the similarity of radiation-

induced changes in the brain and the spinal cord. In brief, previous experimental studies have indicated that signs of diffuse demyelination develop in animals 2 weeks after CNS radiotherapy. After approximately 2 months, remyelination processes have been observed. These early changes correspond to clinical symptoms such as Lhermitte's sign and somnolence in humans. After a variable latency period, and dependent on total dose, white matter necrosis may develop. The gray matter is less sensitive. Latency time decreases with increasing radiation dose. The most important determinants of CNS tolerance are the volume of normal tissue exposed, dose per fraction and total dose. Overall treatment time is less important. With multiple fractions per day, incomplete repair needs to be taken into account, especially when the interfraction interval is less than 6 h.

When WBRT is being administered, the complete intracranial vascular system is exposed to ionizing radiation, although at relatively modest doses, in contrast to focal treatment where only limited parts of the blood vessels might receive a significantly higher dose. When high focal doses are combined with lower doses to a large surrounding volume, tolerance decreases, compared with the same focal treatment alone.

Significant long-term recovery has been observed after spinal cord radiotherapy. Although not experimentally tested in the same fashion, it can be assumed that the brain recovers, too. Especially with larger intervals of at least 1–2 years and when the first treatment course was not too close to tolerance, re-irradiation is now considered as a realistic option. After an initial course of 40–60% of $ED_{50,}$ the tolerance of rodent cervical spinal cord increases by a factor of 1.3–1.4 after 20–28 weeks, compared with a single treatment course. Thus, 50–66% of occult initial damage has been "forgotten" by this time. Experimental data from fractionated radiotherapy of rhesus monkeys suggest a recovery of up to 75% of the initial damage within 2–3 years (Ang et al. 2001).

The past few years have witnessed a significant improvement as far as techniques are concerned in cellular and molecular biology, resulting, for example, in a description of more and more radiobiologically-relevant cellular pathways. Better methods for the identification of stem and progenitor cells have been developed. This progress has led to a better understanding of tissue responses to ionizing radiation. Obviously, radiation-induced reactions of the CNS are not limited to reproductive or mitotic cell death in mature parenchymal and vascular cell populations. Apoptosis, induced by sphingomyelinase-mediated release of ceramide, has been described as an early reaction in endothelial cells within the irradiated CNS (Pena et al. 2000), as well as in oligodendrocytes (Larocca et al. 1997). Besides cell death, a large number of alterations in gene expression, transcription factor activation and functional changes in basically every cell type examined may develop (Raju et al. 2000). Current models of radiotherapy-induced brain alterations include a cascade of complex and dynamic interactions between parenchymal cells (oligodendrocytes, astrocytes, microglia), stem and progenitor cells and vascular endothelial cells (Tofilon and Fike 2000). The latent time preceding the clinical manifestation of damage is viewed as an active phase, where cytokines and growth factors play important roles in intra- and intercellular communication. Clinically recognized phenomena, such as intellectual decline, memory loss, lethargy, dysphoria, dementia and ataxia, also suggest the possible involvement of neurons in radiotherapy-induced CNS reactions. EEG data derived from animal studies have shown that neurons can react to clinically applied doses of radiation (Pellmar and Lepinski 1993). In vitro studies have demonstrated that neurons may undergo apoptosis after radiotherapy (Gobbel et al.1998). Fractionated brain irradiation inhibited the formation of new neurons in the dentate gyrus of the hippocampus in rats (Madsen et al. 2003). Animals with blocked neurogenesis performed poorer in short-term memory tests that are related to hippocampal function. The deficit in neurogenesis is based on both the reduced proliferative capacity of progenitor cells and alterations in the microenvironment that regulates progenitor cell fate (disruption of the microvascular angiogenesis, activation of microglia) (Monje et al. 2002).

CNS radiotherapy induces the production of inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1), by microglia and astrocytes (Chiang and Mc Bride 1991, Hayakawa et al. 1997). IL-1 release leads, via autocrine mechanisms, to further activation and proliferation of these glia cells. As shown in vivo, this cascade results in the development of astrogliosis (Chiang et al. 1993). Already 2 h after single-fraction radiotherapy to the midbrain of mice (25 Gy), TNF-α and IL-1 mRNA levels have been shown to increase (Hong et al. 1995). After 24 h, the levels start returning to normal. Experimental rat brain irradiation has also been shown to induce apoptosis, which, in turn, appears to result in an increase in the number of microglial cells participating in phagocytotic reactions. Besides the cytotoxic effects of TNF-α on oligodendrocytes, for example, through induction of caspase-mediated apoptosis (Hisahara

et al. 1997, Akassoglou et al. 1998, Gu et al. 1999), the cytokine in vitro prevents the differentiation of O-2A progenitor cells into oligodendrocytes. Thus, compensation for radiation-induced cell loss can be impaired. TNF-α is also known to damage endothelial cells, leading to increased vascular permeability. TNF-α and IL-1 induce the expression of intercellular adhesion molecule-1 (ICAM-1) in oligodendrocytes and microvascular endothelial cells (Satoh et al. 1991, Wong et al. 1992). Increased levels of ICAM-1 mRNA were detectable after midbrain irradiation with 2 Gy (Hong et al. 1995). Recent results of localized single-fraction treatment with 20 Gy confirm the presence of an early inflammatory response, an increased numbers of leukocytes, increased vascular permeability, altered integrity of endothelial tight junctions and increased cell adhesion (Yuan et al. 2003). Injection of an anti-ICAM-1 monoclonal antibody significantly reduced leukocyte adhesion and permeability in this model. The exact role of such cytokines and mediators after radiotherapy with conventional fraction sizes is not well understood yet; clearly, the cellular and molecular events during the latent phase require further research. The role of TNF, for example, may be more complex than initially thought. In some models, this cytokine mediates antioxidant defense mechanisms and is able to induce antiapoptotic proteins, such as Bcl-2. Furthermore, TNF receptor-p75 knockout mice were more sensitive against radiation-induced brain damage than control mice and TNF receptor-p55 knockouts (Daigle et al. 2001).

Studies of boron neutron capture therapy (BNCT) support the view that vascular damage is one of the crucial components of radiotherapy-induced CNS toxicity. The choice of boron compounds that are unable to cross the blood-brain barrier allows a largely-selective irradiation of the vessel walls with BNCT. Nevertheless, as with conventional non-selective radiotherapy methods, spinal cord lesions (with a similar histological appearance) have been induced. Latency time also is comparable between damage induced by BNCT and conventional radiotherapy (Morris et al. 1996). Additional evidence has been provided by histological examinations of rat brains after radiotherapy with 22.5 Gy or 25 Gy, resulting in reduced numbers of blood vessels and endothelial cells before manifestation of necrosis (Calvo et al. 1988). Theses changes are accompanied by hyperpermeability, resulting in perivascular edema and consecutive ischemic damage (Hopewell et al. 1999). Microvascular networks, consisting of arterioles, capillaries and venoles, which impact the delivery of oxygen and nutrients to tissues and organs, are the most radiosensitive parts of the vascular system (Roth et al. 1999). Common therapeutic doses of ionizing radiation lead to functional and, later, to structural vascular damage, such as increased permeability and changes in shape and diameter, as well as in fibrous proliferation, ultimately resulting in reduced perfusion. Theses changes develop earlier in small versus large vessels. After lower doses, structural changes are hardly ever seen. After WBRT in rats (5 fractions of 4 Gy) alterations in vessel configuration, either density or diameter, were not detected (Mildenberger et al. 1990). Interestingly, a localized significant increase of microglia was found after 6 months, possibly as a result of the loss of axons in the striatal white matter. The pattern was suggestive of vascular insufficiency in this region, which was being perfused by only few small vessels. Electron microscopy in rats 15 days after the end of conventional fractionated WBRT (40 Gy) showed increased vascular permeability without structural changes of the blood-brain barrier or astrocytes (Cicciarello et al. 1996). A follow-up examination after 90 days revealed ultrastructural changes of the microvasculature and the neuropil, as well as astrocytes with perivascular edema.

Another study (partial brain irradiation with 40 Gy or 60 Gy, or WBRT with 25 Gy in rats) showed a 15% reduction in the number of endothelial cells 24 h to 4 weeks after radiotherapy. A further reduction was seen with even longer intervals (Ljubimova et al. 1991). Depending on dose, a progressive atrophy of smooth muscle cells develops with increasing time after radiotherapy (Hopewell et al. 1989). This could explain the development of telangiectasia after an initial functional reduction of the vessel diameter.

Kamiryo et al. showed how the latency to development of vascular damage after SRS to the parietal cortex of rat brain with a 4mm collimator decreases from 12 months to 3 weeks with an increase in radiation dose from 50–75 Gy or 120 Gy (Kamiryo et al. 1996). The amount of vessel dilation, increased permeability, thickening of the vessel wall, vessel occlusion and necrosis also increased with dose. In a different model of rat brain irradiation, time and dose-dependent vascular alterations were also seen (dilation, wall thickening, reactive hypertrophy of neighboring astrocytes) before the development of white matter necrosis (Hopewell et al. 1989). Rubin et al. performed comprehensive magnetic resonance imaging (MRI) and histological examinations of rat brains after 2–24 weeks following high dose, single-fraction irradiation with 60 Gy (Rubin et al. 1994). After 2 weeks, a significant increase in blood–brain permeability was observed. Partial recovery occurred after 8–12 weeks,

followed by pronounced deterioration after 24 weeks, when the first sites of necrosis developed. Spinal cord data suggest an increase in the release of vascular endothelial growth factor (VEGF) as a result of impaired perfusion and hypoxia signaling. Obviously, the clinically observed latent phase is characterized by persistent and increasing oxidative stress and active responses to this factor. The extreme sensitivity of the myelin membrane to oxidative damage explains the preference of radiotherapy-induced lesions for white matter.

8.5.3 Acute and Subacute Radiotherapy-Induced Brain Toxicity

As stated in the previous paragraph, acute and subacute radiotherapy-induced brain toxicity can develop within hours from the start of treatment even if low doses are given. It is usually characterized by increased vascular permeability, edema and demyelination manifesting as headache, nausea, somnolence or lethargy. However, it has been characterized as a temporary, self-limiting reaction, which responds to corticosteroid treatment (Schultheiss et al. 1995). Subacute reactions may develop 2–6 months after WBRT, resulting, for example, in lethargy and reduced vigilance. Most likely, such symptoms are related to a second phase of transient demyelination and blood–brain barrier disturbance. Treatment with corticosteroids again is likely to improve the patient's condition. With SRS, acute reactions are rare. They include symptomatic edema, seizures and nausea and vomiting, especially when doses >3.75 Gy are given to the area postrema. Antiemetics, corticosteroids and anticonvulsant drugs may be used to treat these symptoms. Temporary blood–brain disturbance may result in increased contrast enhancement in computed tomography (CT) during the first few months after SRS. These changes should not be misinterpreted as tumor progression. Usually they resolve with longer follow-up.

8.5.4 Delayed or Chronic Radiotherapy-Induced Brain Toxicity

Sustaining toxicity that may impair the patient's lifestyle significantly can be observed several years after radiotherapy in the form of radionecrosis and cognitive dysfunction associated with leukoencephalopathy. Several scoring systems are available for recording and reporting late toxicity (RTOG/EORTC, LENT/SOMA). Necrosis develops for the most part after 1–3 years (Keime-Guibert et al. 1998). Symptoms of radionecrosis depend on localization and are comparable to tumor-related symptoms before treatment (focal neurologic deficits and seizures, speech disturbance, signs of increased intracranial pressure). CT and MRI are unable to firmly discriminate between hypometabolic necrosis and tumor relapse (Fig. 8.51). Dynamic susceptibility contrast-enhanced MRI, magnetic resonance spectroscopy (MRS) and functional imaging by means of [^{18}F]-fluorodeoxyglucose(FDG)–positron emission tomography (PET) and ^{201}Tl–single photon emis-

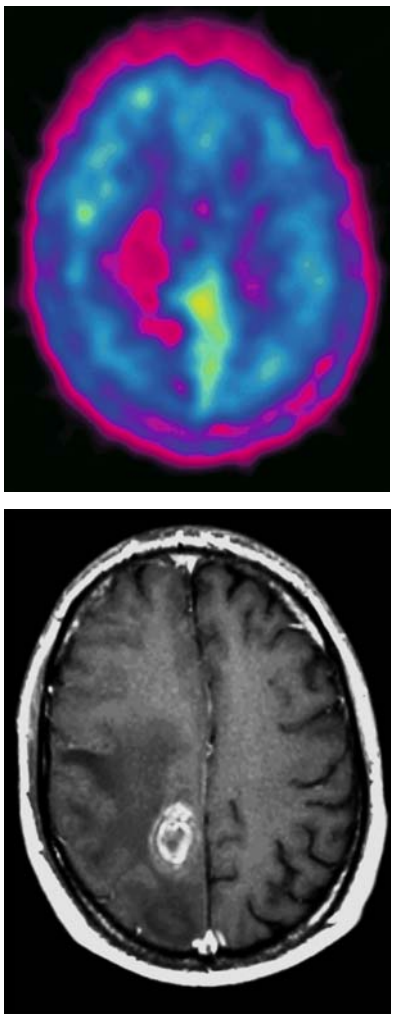

Fig.8.5.1 Radionecrosis with extensive surrounding edema after radiosurgery for solitary brain metastasis with a prescribed dose of 20 Gy: Gd contrast-enhanced T1-weighted MRI (*bottom*) and ^{11}C-methionine PET (*top*; unlike in active tumor tissue, no uptake can be seen)

sion computed tomography (SPECT) can provide useful additional information (Munley et al. 2001). Eventually, in many cases, only histopathological examination of resection specimens can establish the diagnosis. The typical finding is coagulation necrosis in the white matter, with a largely normal appearance of the cortex. Fibrinoid necrosis and hyalinous wall thickening of blood vessels are commonly observed. The risk of radionecrosis amounts to approximately 5% within 5 years ($ED_{5/5}$) after conventional fractionated partial brain radiotherapy (one third of the brain) with 60 Gy or WBRT with 45 Gy. The dose–response curves are quite steep. Thus the risk increases to 10% within 5 years when a partial brain dose of 65 Gy is applied (according to data from the randomized U.S. intergroup low-grade glioma trial) and 50% when 75 Gy is given. Irradiated volume, dose per fraction and total dose are the most important risk factors. Recent series reported radionecrosis after SRS of brain metastases in 1–6% of cases, probably dependent on brain region and vascular supply (Grosu et al. 2001). Commonly prescribed doses are in the range of 15–20 Gy, depending on volume, technique of SRS and use of additional WBRT. The risk increases when more than 10 cm^3 of the normal brain receives more than 10 Gy. The optic apparatus should not receive more than 8 Gy (Tishler et al. 1993). Varlotto et al. reported the results of SRS in 137 patients with brain metastases who had a minimum follow-up of 1 year after SRS (Varlotto et al. 2003). The median marginal tumor dose was 16 Gy. NSCLC was the underlying primary tumor in 77 patients. Eleven patients developed serious side effects, such as visual loss, hemorrhage and persistent steroid-dependent edema or necrosis necessitating surgical intervention. The actuarial incidence of such adverse events was 4% after 5 years for patients with brain metastases ≤2 cm^3 and 16% for those with larger lesions. Age and additional use of WBRT did not influence the complication rate. Therapeutic intervention with corticosteroids or anticoagulants is sometimes successful (Glantz et al. 1994). Often, surgical resection is the only way to effectively improve the symptoms.

Diffuse white matter changes are frequently observed in imaging studies. Fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted MRI may improve visualization of white matter abnormalities. These abnormalities are not necessarily associated with clinical symptoms but often present after fractionated doses of ≥30 Gy. ^{99m}Tc hexamethyl propyleneamine oxime (HMPAO) SPECT has also been used in monitoring radiation-induced brain alterations (Dadparvar et al. 2000). Perfusion abnormalities appear to be more readily detected with this method than with anatomical studies. Concordance with neurocognitive testing was approximately 80%. Neuropsychological sequelae typically manifest within 4 years of radiotherapy. Psychometric findings suggest greater vulnerability of white matter and subcortical structures, resulting in reduced processing speed, heightened distractibility and memory impairment. Within the temporal lobe, the hippocampal formation plays a central role in short-term memory and learning. These functions are related to the activity of neural stem cells. The hippocampal granule cell layer undergoes continuous renewal and restructuring. Radiotherapy can affect this sensitive cell layer leading to impaired function without overt pathological changes. Our own retrospective data from 49 patients who had received WBRT with a median dose of 30 Gy showed that 33% of patients develop mild to moderate clinical symptoms of brain toxicity (in one case, RTOG/EORTC grade III, median follow-up 10 months, median dose per fraction 3 Gy) (Nieder et al.1999). This resulted in a Karnofsky-performance status decline in 10 patients (20%). None of the PCI patients belonged to this subgroup. Risk factors included a biologically effective dose (BED, α/β value 1 Gy) >120 Gy_1 and medication with the anticonvulsant carbamazepine during and after radiotherapy. Most likely, the side effects of carbamazepine are similar to those of radiotherapy. CT showed increasing brain atrophy and bilateral periventricular hypodensity in most patients. The actuarial risk of brain atrophy was 84% after 2 years. Median time to development of this side effect was 11 months. Patients with pre-existing brain atrophy had a higher risk of further shrinkage of the brain parenchyma than those with normal baseline status. White matter changes were observed in 85% of surviving patients. Nonetheless, the incidence of these changes was significantly higher when the BED was >120 Gy_1. Radiologic abnormalities did not correlate with the rate of clinical symptoms. Previous studies described such correlations for patients treated with PCI and chemotherapy for SCLC (Laukkanen et al. 1988, Johnson et al. 1990). Whether or not clinical symptoms and radiologic abnormalities correlate might depend on variables such as length of follow-up, methods of assessment and severity of clinical symptoms.

When evaluating radiotherapy-induced cognitive impairment, it is important to consider reference values from the normal population. A Canadian Study of Health and Aging with 9.008 randomly selected

men and women 65 years or older showed cognitive impairment 5 years after baseline examination in 9% and dementia in an additional 6% (Laurin et al. 2001). Decline was significantly associated with reduced physical activity. There is increasing evidence that partial brain radiotherapy alone rarely causes significant neurocognitive decline (Torres et al. 2003, Duchstein et al. 2003). One of the largest comparative studies in low-grade glioma showed poorer cognitive function in irradiated patients (KLEIN et al. 2002). However, cognitive disability was associated to fraction doses exceeding 2 Gy. In addition, anti-epileptic drug use was strongly associated with disability in attentional and executive function. This finding supports the results of our own group in WBRT patients (Nieder et al. 1999)

After WBRT, neuropsychological tests in 29 patients showed no significant decrease (Penitzka et al. 2002). In this study, patients with SCLC were significantly below average before PCI, but did not deteriorate further. Patients with fewer cycles of preceding chemotherapy performed better before PCI. These results are in accordance with earlier prospective findings where 97% of patients with SCLC had cognitive dysfunction prior to PCI (Komaki et al. 1995). Six to 20 months later, no further deterioration was identified. Another group of 51 long-term survivors of SCLC showed marked neuropsychometric differences compared to matched controls regardless of treatment with chemotherapy only, sequential PCI or concurrent or sandwiched PCI (Van Oosterhout et al. 1996). However, white matter abnormalities were more frequent after concurrent or sandwiched PCI in this study. Obviously, cognitive impairment is at least in part related to emotional distress, anemia and deteriorated physical condition after treatment of SCLC. PCI (15 fractions of 2 Gy) after combined chemotherapy, radiochemotherapy and surgery in NSCLC patients led to white matter abnormalities in T2-weighted MRI (Stuschke et al. 1999). However, some impairment in attention and visual memory in long-term survivors was detected in both PCI and non-PCI patients. Additional prospective data from 12 patients also failed to demonstrate significant short-term neurotoxicity from PCI with 10 fractions of 3 Gy (Parageorgiou et al. 2000). Whether use of this fraction size might cause long-term impairment is controversial. Some authors found indications for increased toxicity when fraction size exceeded 2 Gy (Herskovic and Orton 1986, Twijnstra et al. 1987, De Angelis et al. 1989). The risk of toxicity might also increase with age (Asai et al. 1989). In patients with manifest brain metastases, the 10x3 Gy schedule led to a slight drop of 0.5–0.6 in Mini Mental Status Examination (MMSE) score in patients with controlled brain metastases after 2 and 3 months, respectively. Certainly, additional prospective studies of neurocognitive function and quality of life are warranted.

Neurocognitive dysfunction was reported to stabilize spontaneously (Van De Pol et al.1997, Armstrong et al. 2002) or to progress over time (Johnson et al. 1990). In extreme cases, subcortical dementia may result which often is associated with gait disturbance and incontinence. Due to the lack of effective treatment, most patients with this severe complication die after several months or a few years. Histopathologic findings include diffuse spongiosis and demyelination, as well as disseminated miliary necrosis.

Further late complications in terms of stenosis of blood vessels and moyamoya syndrome (multiple, diffuse, progressive infarctions due to occlusion of the anterior and medial cerebral arteries) have occasionally been described, mostly in patients irradiated at a younger age. Endocrine dysfunction resulting from damage to the pituitary gland or the hypothalamic region can result in hypothyroidism, amenorrhea, etc. Hearing loss is very uncommon after doses typically prescribed for lung cancer metastases.

Importantly, all types of iatrogenic neurotoxicity can only be diagnosed after comprehensive evaluation excluding other causes, for example brain metastases, leptomeningeal spread, infections, cerebral infarction and hemorrhage. In addition, systemic metabolic disorders (hypercalcaemia, hepatic failure, diabetes, changes in osmolality etc.), alcoholic cerebellar degeneration, Wernicke-Korsakoff syndrome and paraneoplastic disorders (for example, limbic encephalitis, chorea, cerebellar degeneration and Lambert-Eaton myasthenic syndrome in SCLC) must be considered. Besides physical and neurologic examination, blood tests, EEG and cerebrospinal fluid diagnostic are indicated. In addition to imaging studies – for example, myelography, CT, MRI and functional imaging – factors such as time interval between radiotherapy and diagnosis, dose per fraction, number of fractions per day, total dose and location of the treatment fields need to be considered. In the era of multimodal treatment regimens, injury should not be attributed solely to one modality. Therefore, interdisciplinary evaluation integrating the radiobiological knowledge of radiation oncologists is mandatory when radiotherapy-induced neurotoxicity is being considered.

8.5.5 Toxicity Prevention Strategies

At present, pharmacologic or biologic prevention is not clinically available despite intriguing data from a non-randomized trial of SRS of arteriovenous malformations, where patients treated with gamma linolenic [omega-6] acid had less permanent complications than those who did not receive this medication (Sims and Plowman 2001). Therefore, the most effective way of toxicity prevention is a reduction of fraction size and normal tissue volume, the latter, for example, by means of SRS and other techniques. However, several rational experimental interventions based on the pathogenetic models reviewed in 8.5.2 have been studied or are currently under investigation. The clinical effectiveness of these putative prevention strategies has yet to be established. The prophylactic use of dexamethasone 24 h and 1 h before radiation exposure reduced the expression of TNF-α, IL-1 and ICAM-1 (Hong et al. 1995). In vitro, corticosteroids influence the function of microglial cells and inhibit their proliferation (Tanaka et al. 1997). A less pronounced effect, which was limited to TNF-α and IL-1, was found when pentoxifylline was given prophylactically (Hong et al. 1995). The hyperpermeability of blood vessels could be reduced at all time points after irradiation by application of rh-MnSOD (manganese superoxide dismutase), suggesting that free oxygen radicals could be involved in the dysfunction of microvessels. Various other compounds are also able to interact with free radicals, for example, glutathione. N-Acetyl-L-Cysteine (NAC), a non-toxic substance increasing the intracellular cysteine levels which are necessary to produce glutathione, protects oligodendrocytes against TNF-α induced cell death (Noble et al. 1996). Ciliary neurotrophic factor (CNTF) is also protective against TNF-α toxicity (Louis et al. 1993). Older literature reports of normal brain protection by application of barbiturate in rodents (Oldfield et al. 1990) also failed to result in clinical strategies. In a single-fraction WBRT model, intraperitoneal injection of the radioprotective compound Gammaphos, [S-2-(3-amino-propylamino) ethylphosphorothioate, which is comparable to WR-2721 or amifostine] immediately before application of 25 Gy (ED_{50}) led to a significant reduction of late vascular changes and radionecrosis in rats (Plotnikova et al. 1988). Fike et al. reported that i.v. injection of α-difluoromethylornithine (DMFO), a polyamine synthesis inhibitor, starting 2 days before and continuing for 14 days after ^{125}I brachytherapy reduced the volume of radionecrosis in irradiated dog brain (Fike et al. 1994). Kondziolka et al. irradiated rats with implanted cerebral C6 glioma by SRS, either with or without i.v. administration of U-74389G, a 21-aminosteroid which is largely selective for endothelium (Kondziolka et al. 1999). The compound reduced the development of peritumoral edema and radiation-induced vascular changes in the parts of the brain that were within the region of the steep dose gradient outside the target volume. No tumor protection was observed. In general, normal tissue selectivity of prevention approaches is an important issue. Protecting tumor cells against the effects of radiation can counteract the effort of improving the therapeutic ratio.

More recent data suggest the possible role of certain growth factors with antiapoptotic effects that also influence the proliferation of stem cells, neurogenesis and angiogenesis. Pena et al. showed that i.v. injections of basic fibroblast growth factor (FGF-2) 5 min before, immediately after and 1 h after total body irradiation in mice (1–20 Gy or 50 Gy) significantly reduced the number of apoptotic vascular and glial cells in the CNS (Pena et al. 2000). Spinal cord experiments suggest that other growth factors, such as platelet-derived growth factor (PDGF) can increase the long-term radiation tolerance by approximately 10% (two fractions of 16–20 Gy 24 h apart, PDGF given for 4 days starting 24 h before the first fraction of radiation) (Nieder et al. 2003). Whether these effects result primarily from protection of the vascular system or from more widespread action is presently not known. The experiments, however, demonstrate that delayed toxicity can be prevented by early intervention at the time of radiation treatment, and they offer new strategies of toxicity prevention.

Transplantation of stem cells or stimulation of the endogenous stem cell compartment by growth factor application might also offer exciting prospects. In principle, mature functional cells can be generated by proliferation and differentiation from stem and progenitor cells or by recovery and repair of damage in already existing cells, which then continue to survive. Immature cells are able to migrate within the CNS for a limited distance, possibly leading to remyelination of small lesions from the surrounding healthy tissue (Chari and Blakemore 2002). Different experimental CNS damage models suggest that insulin-like growth factor-1 (IGF-1) causes an increase in oligodendrocyte numbers in previously damaged areas of the rat spinal cord (Yao et al. 1995). IGF-1 reduces the permeability of the blood-brain barrier and has been found to influence the restoration of neurogenesis in the adult and aging hippocampus (Lichtenwalner et al. 2001). It has also been shown in preliminary experiments to influence the radiation tolerance of rat spinal cord against high doses per fraction (Nieder et al. 2002a and b). Finally,

erythropoietin is beneficial in different models of CNS damage and could well be explored in conjunction with radiotherapy (Senzer 2002).

8.5.6 Treatment of Radiotherapy-Induced Brain Toxicity

Despite improvements in radiobiologic and neurobiologic understanding of CNS reactions, treatment options unfortunately are still limited and not yet based sufficiently on specific interventions targeting the cells and pathways which have now been identified as major players in the development of toxicity. Probably, preventing serious complications will remain preferable to trying to reverse or ameliorate them. It is of course important to exclude other causes of CNS dysfunction, to correct any metabolic abnormality and to optimize the treatment of endocrinological dysfunction, depression and other comorbid conditions. A few case reports have described successful treatment of late CNS toxicity by hyperbaric oxygen treatment (HBO). For example, one out of seven patients with cognitive impairment at least 1.5 years after radiotherapy improved after 30 sessions of HBO (Hulshof et al. 2002). In contrast, HBO during radiotherapy can cause radiosensitization. Patients with leukencephalopathy and moderate hydrocephalus (diagnosed by intracranial pressure monitoring) may profit from ventriculoperitoneal shunt insertion (Perrini et al. 2002). Quality of life can be improved by supportive measures (cognitive training, rehabilitation, special education etc.) and possibly by methylphenidate medication (Meyers et al. 1998). For radionecrosis, therapeutic intervention with corticosteroids or anticoagulants is sometimes successful (Glantz et al. 1994). They should be administered early before the stage of cystic liquefaction. Often, surgical resection is the only way to effectively improve the symptoms.

8.5.7 Aspects of Chemotherapy-Induced Brain Toxicity

Chemotherapy can cause a variety of brain injuries. Most of these changes are temporary and reversible. Sometimes the symptoms are secondary to hyponatremia or hypomagnesemia. Posterior reversible encephalopathy syndrome can develop after systemic administration of cytotoxic drugs, including gemcitabine, cisplatin, 5-fluorouracil (5-FU), methotrexate and paclitaxel. White matter hyperintensity from vasogenic edema can clinically result in headache, somnolence and seizures. Symptoms can be reversed when the drugs are discontinued. Cerebellar toxicity of 5-FU is rare and mostly found in patients with a deficiency of dihydropyrimidine dehydrogenase. Cisplatin is able to induce cerebral edema and cortical blindness, as reviewed by (Sloan et al. 2003). Mild to moderate neurocognitive impairment can develop after systemic chemotherapy, for example with paclitaxel (Ahles and Saykin 2001, Herbst et al. 2002). Chronic encephalopathy also can result from chemo- or radiochemotherapy (Keime-Guibert et al. 1998).

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9 Quality of Life in Radiation Oncology of Lung Cancer

Hans Langendijk and Neil Aaronson

CONTENTS

9.1 Introduction

In the last decade, there has been a growing interest in the evaluation of the quality of life (QoL) of patients suffering from lung cancer. Traditionally, the primary goal of treatment in lung cancer patients is to achieve prolonged survival, long-term local-regional tumor control and/or tumor regression. However, taking into account the relatively poor prognosis in the majority of cases, researchers and clinicians, as well as patients, are increasingly concerned about the impact of standard and novel treatment approaches not only on these traditional endpoints, but also on QoL. There are a number of reasons for this increasing interest in QoL issues. First, more and more patients will be treated with combined modality strategies (e.g., chemotherapy and radiation therapy). Most of these novel approaches are associated with increased morbidity that sometimes lasts for several months, especially when the treatments are given concomitantly. Conversely, advances in radiotherapy (e.g., intensity-modulated radiotherapy), and the availability of more adequate staging techniques (e.g., PET), enable radiation-oncologists to administer a high dose to the tumor and to high-risk areas, while reducing significantly the impact on surrounding at-risk organs. This results in a lower probability of early and late radiation-induced morbidity. Despite the improvements achieved with these newer approaches, the gain in terms of life expectancy remains relatively small. The result is that, for many patients, QoL is an important consideration when selecting among the available treatment options. This is especially the case in very advanced and metastatic disease where QoL issues are particularly salient since treatment does not offer cure and may have a significant impact on the patient's daily functioning and sense of well-being. In the subset of patients where cure is possible, QoL considerations also remain important. Most patients are willing to undergo very aggressive forms of therapies, in order to be cured of their disease (Jansen et al. 2001). Even in the absence of alternative treatment approaches, assessment of QoL in these circumstances may yield unexpected and important information for the development of future therapeutic directions. Finally, QoL information may help in identifying the residual psychosocial problems of long-term survivors of lung cancer, which can be of use in the planning and development of appropriate rehabilitation programs.

The Oncology Division of the Food and Drug Administration (FDA) has advocated the inclusion of QoL outcomes as part of the drug approval process (Johnson and Temple 1985, Beitz et al. 1996). Similarly, organizations involved in cancer clinical research such as the European Organization for Research and Treatment of Cancer (EORTC), the U.K. Medical Research Council (MRC), and the National Cancer Institute (NCI) of Canada have incorporated QoL assessments in many of their clinical trials. The

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American Society of Clinical Oncology (ASCO) has also recommended inclusion of QoL outcomes in technology assessment and in developing treatment guidelines in oncology.

Given this growing interest in QoL assessment in oncology, we believe that it is both timely and appropriate to examine the role of such measures in the field of lung cancer research. In this chapter, we first discuss a range of methodological issues surrounding the assessment of QoL. We then go on to review the QoL results and implications of clinical studies in which radiotherapy was part of the treatment.

9.2.1 Defining Quality of Life

Although many of us will have some intuitive sense of what QoL means, a precise definition remains elusive. Often, QoL is used synonymously with the term subjective or general well-being. Some authors have suggested that QoL can be defined in simple, global terms, and thus can be assessed by just one question: "How would you rate your quality of life today?" (Gough et al. 1983). Gough and colleagues supported this global approach to QoL assessment with the finding that this single question correlated relatively strongly with scores derived from an extensive battery of questionnaires. Yet, this global approach may have only limited usefulness in that it provides the clinician-researcher with no information about the specific types of problems with which their patients are confronted. Moreover, more recent work has shown that not all local symptoms or changes in local symptoms are correlated with overall QoL ratings. More specifically, among lung cancer patients, most respiratory symptoms (with the exception of dyspnea) have not been found to correlate highly with more general dimensions of QoL (Langendijk et al. 2000b). In many situations, and particularly in palliative treatment, there may be trade-offs between relief of tumor-related symptoms and inducement of treatment-related side effects.

For these reasons, there is now widespread advocacy of a multidimensional approach to QoL that includes, at a minimum, measures of patients' physical functioning and physical symptom experience, psychological well-being, and social functioning (Aaronson 1991). More recently, and particularly in the field of palliative care, there have been calls for the inclusion of more existential and spiritual issues in the assessment of patients' QoL. A major advantage of such a multidimensional approach is that it facilitates disentangling the positive and negative effects of a given treatment (e.g., reduced pain, but increased fatigue and cognitive complaints), and also allows one to track changes in specific QoL domains over time (Aaronson and Fayers 2002).

9.2.2 How Does One Measure Quality of Life?

Early on, performance status was often used as a measure of QoL. In 1949, Karnofsky introduced the Karnofsky Performance Status (KPS) scale as a simple but systematic approach to assessing the physical functioning and well-being of lung cancer patients undergoing chemotherapy (Karnofsky 1949). The Eastern Cooperative Oncology Group (ECOG) and the World Health Organization (WHO) performance status scales represent comparable tools. The KPS and related performance status measures have proven their usefulness in clinical trials in oncology. Yet, they are limited in that they do not address issues that may be very relevant to assessing the health and well-being of patients with cancer, including specific symptoms such as pain or fatigue, psychological and cognitive functioning, and the ability to function in daily work and social settings. Moreover, performance status measures rely on the judgment of physicians and other health care providers, rather than on the reports of the patients themselves. Unfortunately, performance status measures not only yield less than optimal interrater reliability, but they also have been found to correlate poorly with patients' self-reports (Hutschinson 1979; Slevin et al. 1988; Presant 1984; Langendijk et al. 2000b). For these reasons, it is today widely accepted that the patient should be the primary source of information about his or her QoL, and that QoL should be assessed by means of multidimensional questionnaires to be completed by the patients themselves.

9.2.2.1 Quality-of-Life Questionnaires

QoL questionnaires can be organized into several categories depending on their focus and intended target population. At the broadest level, there are the so-called generic questionnaires that are designed to be used in the general population and among patients with a wide range of diagnoses. Examples of generic QoL measures include the Sickness Impact Profile (SIP) (Bergner et al. 1976), the Nottingham Health Profile (NHP) (Hunt et al. 1981), the Dartmouth

COOP Function Charts (Nelson et al. 1987), the EuroQoL (EuroQol Group 1990), and the Medical Outcomes Study 36-Item Short Form Health Survey (MOS SF-36) (Ware and Shelbourne 1992). The major advantage of such generic QoL measures is that they facilitate comparison of results across studies, and often allow one to interpret patients' QoL levels in light of age- and gender-specific normative data from the general population. The major disadvantage of this type of QoL measure is that it may fail to address specific issues of particular importance to a given population of patients.

The second category of QoL instruments includes the so-called condition-specific measures that have been developed for use among patients with a specific health condition or disease (cancer, diabetes, heart disease, etc.). Within oncology, examples of such condition-specific questionnaires include the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (the EORTC QLQ-C30) (Aaronson et al. 1993), the Cancer Rehabilitation Evaluation System (CARES) (Ganz et al. 1992), the Rotterdam Symptom Checklist (RSCL) (De Haes et al. 1990), the Functional Living Index–Cancer (FLIC) (Schipper et al. 1984), and the Functional Assessment of Cancer Therapy–General Scale (FACT-G) (Cella et al. 1993).

The third category of QoL questionnaires includes the so-called site- or treatment-specific measures. Several such measures are currently available for use among patients with lung cancer, including the Lung Cancer Symptom Scale (LCSS), the EORTC QLQ-LC13, and the FACT-L (Table 9.1). All three of these questionnaires are widely used and are available in a large number of languages.

The LCSS

The Lung Cancer Symptom Scale (LCSS) consists of two parts (Hollen et al. 1993, 1994a, b). The first part is designed as a patient self-report questionnaire, while the second part, which is optional, is

Table 9.1. Attributes of the three lung cancer–specific questionnaires. EORTC combination of the EORTC QLQ-C30 and the EORTC QLQ-C13

Characteristics and psychometric properties	LCSS	FACT-L	EORTC
Modules	Site-specific	Disease + site–specific	Disease + site–specific
Self-report	Yes (+ optional observer scale)	Yes	Yes
Number of items	9 items (+ 6 items in an optional observer scale)	34 items in the core questionnaire + 7 items in the lung cancer module	30 items in the core questionnaire + 13 items in the lung cancer module
Local symptoms	Cough, dyspnea, hemoptysis, and pain	Dyspnea, cough, and chest pain	Cough, hemoptysis, dyspnea, chest pain, and pain in the arm/shoulder
General symptoms	Appetite loss and fatigue	Weight loss and appetite loss	Fatigue, appetite loss, pain in other parts of the body
Treatment-related symptoms	None	Nausea and hair loss	Nausea and vomiting, sore throat and mouth, dysphagia, tingling hands and feets, and hair loss
Other quality-of-life dimensions	Very limited	Yes	Yes
Reliability			
Internal consistency	Acceptable	Acceptable	Acceptable
Test-retest	Acceptable	Acceptable	Acceptable
Validity			
Content validity	Yes	Yes	Yes
Construct validity	Yes	Yes	Yes
Clinical validity	Yes	Yes	Yes
Responsiveness	Yes	Yes	Yes

intended to be completed by health care professionals. The patient self-report questionnaire focuses on physical and functional dimensions of health. It contains nine items, six of which are major symptoms of lung cancer (appetite loss, fatigue, cough, dyspnea, hemoptysis, and pain), and three of which address more general issues of overall symptom distress, activity level, and QoL. The observer version of the LCSS addresses the same six symptoms included in the patient version.

Both the patient and observer versions of the LCSS have been shown to be reliable and valid measures (Hollen 1993). However, the LCSS has been criticized for not addressing a broader range of QoL issues (e.g., including psychological and social functioning) and for failing to assess important treatment-related symptoms such as emesis, alopecia, and/or dysphagia (Hollen and Gralla 1996). This latter issue limits the usefulness of the LCSS in comparing treatment modalities with differing toxicity profiles.

The FACT-L

The Functional Assessment of Cancer Therapy–Lung (FACT-L) (Cella et al. 1995) is a self-report questionnaire consisting of two parts. The first part contains 27 items measuring general health-related dimensions including physical well-being, social/family well-being, emotional well-being, and functional well-being. The second part is specifically designed for lung cancer patients and contains 9 items concerning frequently reported symptoms in lung cancer patients (i.e., dyspnea, weight loss, cough, appetite loss, chest pain, and hair loss) and an item concerning smoking. Although hemoptysis is an important symptom of lung cancer, it is not assessed with the FACT-L. Another potential limitation of this questionnaire is that – in particular in studies involving radiotherapy and/or chemotherapy – important treatment-related symptoms such as dysphagia are not assessed. The FACT-L has exhibited good reliability and validity, and is one of the most widely used lung cancer–specific QoL questionnaires, particularly in the United States. It has subsequently been translated into a large number of languages.

The EORTC QLQ-C30 and EORTC QLQ-LC13

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) (Aaronson et al. 1993) is a cancer-specific core questionnaire addressing various aspects of QoL. It contains five functional scales (physical, role, emotional, cognitive, and social), a global health/quality-of-life scale, three multi-item symptom scales (pain, fatigue, and emesis), and a number of additional single items addressing various symptoms and perceived financial impact. The EORTC QLQ-LC13 (Bergman et al. 1994) is a supplemental QoL questionnaire module for lung cancer designed specifically to be used in conjunction with the QLQ-C30. It contains 13 items addressing the most frequently reported pulmonary symptoms (i.e., cough, hemoptysis, dyspnea, pain in the chest, pain in the arm/shoulder, and pain in other parts of the body) and a number of treatment-related symptoms (sore mouth or throat, dysphagia, tingling hands or feet, and hair loss). Although there were some problems with patients' compliance with the first versions, high compliance rates have been reported with later versions (Sadura 1992). The reliability, validity, and responsiveness of these questionnaires have been confirmed in international studies (Aaronson et al. 1993; Bergman et al. 1994). One of the advantages of the EORTC instrument is that it contains a number of questions relevant to investigations of new treatment modalities in lung cancer. Additionally, the QLQ-C30 and QLQ-LC13 were originally designed for use in international research settings, and have been translated into a wide range of languages and validated in international studies.

Other Frequently Used QoL Instruments in Lung Cancer Studies

Although not lung cancer–specific, there are two other cancer-specific QoL instruments that have been widely used in lung cancer studies: the Rotterdam Symptom Checklist (RSCL) and the Daily Diary Card (DDC). The RSCL is a 38-item questionnaire assessing physical symptoms, physical activity level, psychological symptoms, and social functioning (De Haes et al. 1990). It yields two summary scores for physical and psychological functioning. For many years, the RSCL was the primary QoL questionnaire used in lung cancer clinical trials conducted by the UK Medical Research Council. The DDC consists of two parts: a patient self-report questionnaire containing five items (overall condition, physical activity, vomiting, mood and anxiety), and a two-item questionnaire (overall condition and physical activity) to be completed by a health professional (Fayers et al. 1991). The brevity of the DDC has facilitated its use in assessing the symptoms and condition of patients on a daily basis. In the past, it was used frequently by the UK Medical Research Council, often in combination with the RSCL.

How Does One Select the "Best" QoL Instrument?

In general, the use of a lung cancer–specific instrument is preferable because it is likely to be better able to detect differences in QoL between treatment groups and/or within-group changes in QoL over time than are generic questionnaires. Table 9.1 summarizes the most important attributes and psychometric properties of the three lung-cancer specific questionnaires. In particular, in reviewing the literature on these three questionnaires, we were concerned with evidence regarding their reliability, validity, and responsiveness to change over time.

Reliability refers to the extent to which an instrument is free from random error. Two types of reliability often assessed with QoL questionnaires are internal consistency and test-retest. In general, reliability estimates of 0.70 or higher are considered acceptable for questionnaires that are intended to be used at the level of group comparisons (as is the case in clinical trials) (Nunnaly and Bernstein 1994).

Content validity refers to whether a questionnaire assesses the full range of relevant issues or, conversely, whether important issues have not been addressed. It is typically examined in qualitative terms, by eliciting feedback from patients and health care professionals alike.

Construct validity refers to the ability of an instrument to measure what it is intended to measure. It is typically evaluated by examining the direction and strength of correlations between scales that are hypothesized to be relatively strongly related (e.g., physical functioning and role functioning) or, conversely, are expected to be only weakly related (e.g., physical and emotional functioning).

Clinical validity refers to the ability of a questionnaire to discriminate between patient groups that are known to differ on some key sociodemographic or clinical variables (e.g., age, gender, stage of disease, treatment status, etc.).

Responsiveness refers to the ability of an instrument to detect (i.e., be sensitive to) changes in patients' health over time. For example, if, over time, a given patient's disease progresses, then this should be reflected in their self-reported QoL (e.g., increased pain and dyspnea, problems in carrying out daily activities, etc.). As can be seen in Table 9.1, three QoL questionnaires exhibit very similar psychometric properties. Thus the question arises as to how one can determine which questionnaire is best suited for a given clinical study. Such choices can often be made on relatively nontechnical grounds by examining the specific content and wording of the questionnaire items. For example, the LCSS, QLQ-C30, and FACT-L differ with regard to the range of generic health issues, lung cancer–specific symptoms, and treatment-specific side effects that they assess. The LCSS is the briefest of the three questionnaires, but this may result in the loss of information captured by the QLQ-C30 and the FACT-L. In comparing the QLQ-C30 and the FACT-L, there are clear differences in the relative emphasis placed on disease- and treatment-related symptoms, with the former questionnaire containing more such items. Ultimately, the investigator needs to decide which questionnaire is most relevant and appropriate for use in a clinical trial. Such decisions should be based on a careful review of the specific content of candidate questionnaires, the amount of patient burden involved in their completion, their availability in requisite languages, and other relatively nontechnical, but important issues.

9.2.3 Compliance

One of the most important and challenging problems in many clinical trials in which QoL is assessed is low compliance. In the past, it was not uncommon that large amounts of QoL data were missing (upwards of 50%). This obviously raises serious concerns regarding the integrity of the QoL component of a trial, the possibility of results being biased, and the generalizability of results to the larger population of patients in which one is interested. Low compliance rates may be due to a number of causes, including frank refusal by patients or their inability to complete questionnaires due to deteriorating health, lack of enthusiasm on the part of the participating clinicians, and insufficient infrastructure and logistical support for collecting patient-based information (Aaronson and Fayers 2002; Ganz et al. 1989; Langendijk et al. 2000a). Of particular concern are missing data due to the patients' poor or deteriorating health status (so-called informative censoring). Failure to be aware of and adequately address the missing data problem may lead to a serious underestimation of patients' functional limitations and symptom burden, and an overestimation of the patients' QoL. Such problems can arise in nonrandomized and randomized studies alike. In randomized studies, differences between

treatment arms in selective dropout from QoL assessments due to tumor progression or death are of particular concern. Although there are a number of statistical methods that have been proposed to deal with missing data, none of these (post hoc) methods provides a completely satisfying solution to the problem. As is so often the case, "an ounce of prevention is worth a pound of cure." Clinical investigators should anticipate problems in QoL data collection, and should ensure that adequate financial and organizational assets are available to yield relatively high (e.g., 70% or higher) compliance rates. Steps that can be taken to improve compliance include providing patients and participating health care providers (physicians and nurses) with sufficient information about the purpose and nature of the QoL assessments. Most patients are willing to complete the QoL questionnaire when they are assured that the data will be useful for medical research and will benefit future patients. Many patients mistakenly believe that there is less interest in their situation as their condition deteriorates. Thus it is particularly important that patients receiving palliative treatment understand that it is important that we continue to obtain their self-reported QoL ratings as their condition deteriorates. Of course, it is up to the responsible physician (and ultimately the patient himself or herself) to determine the point at which completion of questionnaires is no longer feasible or acceptable.

It is important to note that compliance varies widely between institutions and between physicians. An effective strategy for improving compliance is to ensure that there is at least one individual within each participating hospital who carries the primary responsibility for ensuring that the QoL data are collected in a timely manner. Often this will be someone other than the treating physician (e.g., a nurse or data manager). In some cases, the QoL data collection can be centralized and carried out by mail and/or by telephone. Studies that have employed these kinds of strategies for QoL data collection have reported very high compliance rates, varying from 90% to 95% (Sadura et al. 1992), even among patients with a poor prognosis (Langendijk et al. 2000a).

9.2.4 Analysis of Quality-of-Life Studies

Patients participating in clinical studies that include QoL assessments are usually asked to complete questionnaires prior to randomization or before the start of treatment, at several time points during the scheduled treatment period, and then periodically during follow-up (i.e., after completion of treatment). The focus of the data analyses is to determine if there are statistically significant differences between groups and/or within groups over time in self-reported QoL.

9.2.4.1 Group-Based Analysis

In most studies, the statistical analysis involves a comparison of group changes over time in the mean QoL scores (per QoL domain and or total scores). A commonly used statistic for determining the significance of (group) changes in QoL over time is repeated measures analysis of variance (ANOVA). Although this is a robust statistical technique, one of its major disadvantages is that it requires the use of complete cases only (i.e., cases where all questionnaires have been completed). As has already been discussed, missing data are common in QoL studies and are sometimes unavoidable (i.e., due to severe illness or death). This is particularly the case in clinical trials of palliative treatment where the survival time is relatively short. In such situations, the proportion of patients who do not complete the requisite QoL assessments is often high, and thus relatively few patients are available for a "complete cases" ANOVA. Not only does this compromise the statistical power of the study, but it can also yield misleading results based on that subset of patients who survive the longest. A number of advanced statistical methods have been proposed to overcome the problem of missing data, including simple and multiple imputation, pattern mixture models, and random effects models (Hahn et al. 1998; Qian et al. 2000; Ribaudo and Thompson 2002; Fairclough et al. 1998; Zee 1998; Matthews 1993). It is beyond the scope of this chapter to discuss the pros and cons of these various statistical techniques. Suffice it to say that the analysis of longitudinal QoL data is complex and challenging, and necessitates the input of experienced statisticians.

9.2.4.2 Which Differences in QoL Scores Are Clinically Relevant?

When sufficiently large groups of patient are investigated, small differences or changes in QoL scores may be statistically significant. The question arises as to whether (and to what extent) such small differences are clinically meaningful. Osoba and co-

workers investigated the significance for patients of changes in physical, emotional and social functioning, and global QoL as assessed by the EORTC QLQ-C30 (Osoba et al. 1998). The perceived changes in functioning and global QoL were assessed with the Subjective Significance Questionnaire (SSQ). In the SSQ, patients could rate their perception of change using a seven-category scale ranging from "much worse" through "no change" to "much better." For patients who indicated "no change," the mean change in score was not significantly different from zero. In those who indicated "a little," the mean change in scores varied between 5 and 10, for those who indicated "moderate" between 10 and 20, and for those who indicated "very much" change, greater than 20.

Cella and co-workers (Cella et al. 2002) investigated clinically meaningful change (CMC) on the FACT-L questionnaire among patients with NSCLC who were entered in a prospective randomized study comparing three chemotherapy regimens. In this study, a two- to three-point change over time for the Lung Cancer Subscale was determined to be clinically meaningful. For the Trial Outcome Index, in which the scores range from 0 to 84, a change of 5 to 7 points was clinically meaningful. The results of these types of studies are useful in identifying the magnitude of change in well-known QoL scale mean scores that can be interpreted as being meaningful from the perspective of patients.

9.2.4.3 Subject-Based Analysis with Response Rates

One of the disadvantages of analyses based on changes of mean scores is that physicians and patients may have difficulty in interpreting and translating such group level data for use at the level of the individual patient. For both physicians and patients, it is particularly important to know the probability of achieving relief for a given complaint. For instance, for a patient with severe pain referred for radiotherapy, knowing that there is an approximately 60% likelihood that the treatment will achieve significant pain relief is more easily interpretable and meaningful than being informed that, on average, one can expect a decrease of approximately 20 points on a zero to 100 scale. Therefore, an alternative (or supplementary) method for analyzing and reporting QoL changes is to perform a subject-based analysis whereby a priori decision rules are applied to classify individual patients as being QoL responders (or nonresponders), analogous to the type of classifications used when evaluating the effect of a treatment on tumor status.

The simplest method of conducting such a QoL-response analysis is to determine if a patient's symptoms (e.g., pain or dyspnea) have improved by a predefined degree from baseline to a given point in time (e.g., 2 months posttreatment). This basic method can, by definition, only be applied to those patients who are symptomatic at baseline, and who are alive and able to complete a posttreatment questionnaire. As suggested earlier, this can be problematic, particularly in palliative treatment trials, where there is poor survival expectancy or where one of the goals of treatment is to prevent the onset of symptoms. Another disadvantage of this basic approach is that it only provides information regarding symptom relief at a single point in time. This latter limitation can be overcome by defining response as a decrease of symptoms at two or more consecutive assessments following treatment (Bleehen et al. 1991, 1992), by providing response rates for each posttreatment assessment point separately (Speiser and Spratling 1993), by reporting the duration of response (e.g., pain relief) as a proportion of survival time, or with the use of Kaplan-Meier plots to estimate the frequency of palliation of individual symptoms by specified time points (Muers and Round 1993; Medical Research Council Lung Cancer Working Party 1996a, b).

Stephens and co-workers have proposed that symptom palliation can be defined in terms of "improvement," "control," or "prevention" (Stephens et al. 1999). They define "improvement" as a positive shift of at least one response category on a self-report symptom measure (e.g., from moderate to mild pain). For those patients with mild symptoms at baseline, no change in symptom severity over time would be classified as "control." Finally, for those patients who are without symptoms at baseline and who do not develop symptoms during the follow-up period, the term "prevention" could be applied. A major advantage of this approach is that a larger percentage of patients can be retained in the analysis (i.e., irrespective of the presence of symptoms at baseline).

Langendijk and colleagues have applied a modified version of this classification scheme, using both single-item (Table 9.2) and multi-item QoL scales (Table 9.3) from the EORTC QLQ-C30 and QLQ-LC13, in two longitudinal studies of NSCLC patients treated with radiotherapy (Langendijk et al. 2000b, 2001).

Table 9.2 Response criteria for general and respiratory symptoms

Follow-up	Baseline score		
	Moderate or severe	Mild	Nil
Moderate or worse on two consecutive assessments	No response	Worse	Worse
Mild on two consecutive assessments	Improvement	Control	Worse
Nil on two consecutive assessments	Improvement	Improvement	Prevention
Dead before first assessment	Dead without palliation	Dead without palliation	Not evaluable
Dead before second assessment with mild on first assessment	Not evaluable	Dead without palliation	Dead without palliation
Dead before second assessment with nil on first assessment	Not evaluable	Not evaluable	Not evaluable

Note 1: patients were classified as responders in case of improvement, prevention, or control
Note 2: patients were classified as nonresponders in case of no response or dead without palliation

Table 9.3 Response criteria for functioning scales and global quality of life

Follow-up	Baseline score		
	0–59	60–79	80–100
Increase of at least 5 points on two consecutive assessments to a minimal value of 40	Improvement	Improvement	Improvement
Decrease of at least 5 points on two consecutive assessments	Worse	Worse	Worse
No change (i.e., < 5 points) on two consecutive assessments	No change	Control	Prevention
Dead before first assessment	Dead without palliation	Dead without palliation	Dead without palliation
Dead before second assessment without an increase of at least 5 points to a minimal value of 40 on first assessment	Dead without palliation	Dead without palliation	Dead without palliation
Dead before second assessment with an increase of at least 5 points to a minimal value of 40 on first assessment	Not evaluable	Not evaluable	Not evaluable

Note 1: patients were classified as responders in case of improvement, prevention, or control
Note 2: patients were classified as nonresponders in case of no change or dead without palliation

9.2.5 Quality-of-Life Assessment in Clinical Studies

Although some have argued that QoL should be assessed in most if not all clinical trials, we believe that it is particularly relevant in the following types of clinical radiotherapy trials: (1) in studies investigating treatment strategies in which the most important goal is to palliate symptoms and/or to improve QoL. In such studies, QoL may be the primary endpoint; (2) in studies investigating new fractionation schedules or multimodality treatments (e.g., concomitant radiotherapy and chemotherapy) where survival benefit is expected to be only limited and there is the risk of significant treatment toxicity; and (3) in "equivalence" studies investigating new radiotherapy strategies that are less toxic but are not expected to result in improved survival (e.g., short hypofractionation schedules in poor prognosis patients). In all these settings, QoL assessments can yield important information that may have a significant impact on the choice of (standard) treatments.

9.2.6 Summary of Studies of the QoL of Lung Cancer Patients Treated with Radiotherapy

The number of studies addressing QoL issues in the radiation treatment of patients with SCLC and NSCLC is surprisingly low (Table 9.4), particularly given the relatively poor prognosis of these patients and the palliative intent of much of the treatment. To date, the majority of randomized studies that have incorporated QoL assessment have made use of the Rotterdam Symptom Checklist (RSCL) and/or the Daily Diary Card (DDC), often in combination with the Hospital Anxiety and Depression Scale (HADS). This reflects the fact that many of these trials were run by the UK Medical Research Council, which, in the past, employed these questionnaires in almost all of their QoL investigations in lung cancer. The EORTC QLQ-C30 and QLQ-LC13 and the FACT-L have also been used in a number of longitudinal studies.

What is the added value of these clinical trial–based QoL studies? Do they contribute meaningfully to the conclusions that are made regarding treatment effectiveness and risks?

A summary of the results of all studies that incorporated QoL in their analysis is listed in Table 9.4. In this review, only studies addressing radiotherapy questions were included.

Gregor and co-workers (Gregor et al. 1997) reported on a prospective randomized study in which patients with limited disease SCLC in complete response after induction chemotherapy were randomly assigned to prophylactic cranial irradiation (PCI) or no PCI. This study showed a significant reduction of brain metastases with PCI, but no difference in the overall survival. Overall, patients reported significant declines in cognitive functioning and global QoL over time, but this was no more pronounced in the PCI than in the non-PCI group. The authors concluded that patients with a complete response to induction therapy should be offered PCI.

The Medical Research Council (MRC) performed a number of randomized trials searching for the optimal fractionation schedules for palliatively irradiated patients (Bleehen et al. 1991, 1992; Medical Research Council Lung Cancer Working Party 1996a,b). In these studies, QoL issues, as assessed with either the RSCL or the DDC, played an important role in guiding the design of consecutive trials. In the first of these trials (Bleehen et al. 1991), conventional fractionation consisting of 30 Gy in ten fractions or 27 Gy in six fractions was compared with a two-fraction regimen, consisting of two fractions of 8.5 Gy with a 1-week interval. Patients with inoperable NSCLC were eligible for the trial if their disease was judged to be too advanced for curative or radical treatment. No significant differences were observed between the two treatment arms in survival, palliation of pulmonary symptoms, or QoL. Based on these results, the regimen of two fractions of 8.5 Gy given 1 week (F2 regimen) apart was recommended.

In the second study (Bleehen et al. 1992), the F2 regimen from the initial study was compared with a regimen consisting of a single fraction of 10 Gy (F1 regimen). The eligibility criteria were similar to those of the initial study, with the addition that patients had to have had a poor performance prior to radiation (WHO performance status of 2 to 4) and that the major symptoms were related to the primary intrathoracic tumor. The QoL assessments were similar to those of the initial study. Overall survival and the rate and duration of palliation were similar in the two groups. However, patients treated with the F2 regimen experienced significantly more dysphagia than those treated with the F1 regimen. Based on these results, the investigators recommended a single fraction of 10 Gy for patients with inoperable NSCLC with a poor performance status.

The third study (Macbeth et al. 1996) randomized patients with good performance between the F2 regimen of the initial MRC study and a regimen of 39 Gy in 13 fractions (F13 regimen). Although the F2 regimen resulted in more rapid palliation and less dysphagia than the F13 regimen, the overall survival was significantly better with the F13 regimen. Based on these results, the investigators recommended the F13 regimen for patients with inoperable NSCLC with good performance status.

In another study performed by the MRC (Falk et al. 2002), immediate versus delayed palliative radiotherapy were compared among patients with inoperable NSCLC and minimal thoracic symptoms. In the delayed treatment group, 56% of the patients died without receiving any radiotherapy. There was no difference in overall survival. Furthermore, no evidence of a difference was noted in terms of level of anxiety assessed from the Hospital Anxiety and Depression Scale (HADS). Similarly, the median RSCL psychological distress scores were similar in both treatment groups, while adverse effects were more common in the immediate group. The authors concluded that in minimally symptomatic patients, palliative radiotherapy can be prevented in the majority of cases without compromising survival and/or QoL.

Bailey and co-workers (Bailey et al. 1998) reported on the QoL of patients with inoperable NSCLC

Table 9.4 Overview of clinical studies in radiation oncology that incorporated QoL as primary or secondary endpoint

Author	Number	QoL instrument	Study design	Outcome	QoL outcome
Small cell lung cancer					
Gregor (1997)	314	RSCL* + HADS**	Phase III study: prophylactic cranial irradiation (PCI) vs no PCI	Significant reduction in brain metastases with PCI. No significant improvement of survival	Significant impairment of cognitive functioning and global QoL after PCI but no difference with no PCI
Non–small cell lung cancer					
Kaasa (1988a)	95	Questionnaire ****	Phase III study: external irradiation (XRT) (30 Gy or 27 Gy) vs hypofractionated XRT (2 x 8.5 Gy)	No difference in overall survival	Similar results regarding palliation of pulmonary symptoms and QoL
Bleehen (1991)	369	DDC***	Phase III study: external irradiation (XRT) (30 Gy or 27 Gy) vs hypofractionated XRT (2 x 8.5 Gy)	No difference in overall survival	Similar results regarding palliation of pulmonary symptoms and QoL
Bleehen (1992)	233	DDC***	Phase III study: hypofractionated XRT (2 x 8.5 Gy) vs hypofractionated XRT (1 x 10 Gy)	No difference in overall survival	Similar results regarding palliation of pulmonary symptoms and QoL; significantly more dysphagia with 2 x 8.5 Gy
MacBeth (1996)	509	RSCL*	Phase III study: hypofractionated XRT (F2) (2 x 8.5 Gy) vs extensive XRT (F13) (13 x 3 Gy)	Median survival F2 (7 months) vs F13 (8 months) ($p<0.05$)	The F2 regimen gave a more rapid palliation of symptoms and dysphagia was more pronounced with the F13 regimen
Bailey (1998)	356	RSCL* + HADS**	Phase III study: conventional radiotherapy (60 Gy) vs CHART	Significant improvement of the overall survival with CHART (2 years); OS, 29% vs 20%	Little difference between the two regimens, except for more transient pain on swallowing and heartburn with CHART
Stout (2000)	99	RSCL* + HADS**	Phase III study: external irradiation (XRT) (30 Gy) vs endobronchial brachytherapy (EBB) (1 x 15 Gy)	No difference in overall survival. Significantly more retreatment after EBB	Better palliation of pulmonary symptoms with XRT at the cost of more dysphagia and general symptoms
Schaafsma (2000)	42	EORTC QLQ-C30	Longitudinal study: high-dose palliative radiotherapy (30 Gy in 10 fractions to 52.5 Gy in 20 fractions)	Median survival 266 days	Improvement of global QoL over the first 86 days; about one third of the quality-of-life adjusted years can be attributed to radiotherapy
Langendijk (2001b)	95	EORTC QLQ-C30 + QLQ-LC13	Phase III study: external irradiation (XRT) vs XRT plus endobronchial brachytherapy (EBB) (2 x 7.5 Gy)	No difference in overall survival	Lower mean scores for dyspnea up to 3 months in favor of XRT + EBB
Langendijk (2000a)	65	EORTC QLQ-C30 + QLQ-LC13	Longitudinal study: palliative radiotherapy (30 Gy in 10 fractions)	Median survival 4.1 months	Excellent response rate for hemoptysis; good for chest wall pain, pain arm/shoulder, and cough; moderate for dyspnea and minimal for fatigue and appetite loss. 35–50% response rate for functioning and global QoL. Tendency for better scores in case of tumor response

Table 9.4 (continued) Overview of clinical studies in radiation oncology that incorporated QoL as primary or secondary endpoint

Author	Number	QoL instrument	Study design	Outcome	QoL outcome
Auchter (2001)	30	FACT-L	Longitudinal study: accelerated radiotherapy (57.6 Gy in 36 fractions in 15 days)	Not mentioned	Decrement of physical and functional QoL during radiation that returned to baseline 4 weeks after treatment.
Langendijk (2001a)	164	EORTC QLQ-C30 + QLQ-LC13	Longitudinal study: radical radiotherapy (60 Gy in 24 fractions)	Median survival 8.5 months	Excellent response rates for hemotysis; good for chest pain, pain arm/shoulder, and appetite loss; poor for dyspnea, cough amd fatigue. 35–55% response rates for functioning and global QoL
Bezjak (2002)	230	EORTC QLQ-C30 + DDC*** + LCSS	Phase III study: XRT F5 (5 x 4 Gy) versus XRT F1 (1 x 10 Gy)	Survival in F5 significantly better than in F1 (p=0.03)	No difference in QoL during the 1st month according to the DDC. Better palliation with the F5 regimen as assessed with the LCSS and EORTC QLQ-C30. No difference in treatment-related toxicity
Langendijk (2002)	46	EORTC QLQ-C30 + QLQ-LC13	Longitudinal study: curative radiotherapy (70 Gy in 35 fractions)	Median survival 19.0 months	Gradual increase in dyspnea, fatigue, and appetite loss over time. Gradual increase of functioning and global QoL. Less dysphagia in case of local radiotherapy vs locoregional radiotherapy
Falk (2002)	230	RSCL* + HADS**	Phase III study: immediate vs delayed palliative radiotherapy	No difference in overall survival	No differences in palliation and QoL

* RSCL = Rotterdam Symptom Checklist
** HADS = Hospital Anxiety and Depression Scale
*** DDC = Daily Diary Card

randomly assigned to receive conventional fractionation radiotherapy versus continuous hyperfractionated accelerated radiotherapy (CHART). The overall survival in the CHART group was significantly better than that achieved with conventional fractionation, although it resulted in more transient pain on swallowing and heartburn. No significant differences were observed between the two treatment arms in any of the other QoL domains assessed. The conclusion drawn from this trial was that CHART yielded an important overall survival benefit without any enduring negative QoL effects. More recently, in a prospective phase II trial of hyperfractionated accelerated radiotherapy in NSCLC showed a decrement in physical and functional QoL during treatment that returned to baseline level at 4 weeks after completion of treatment (Auchter et al. 2001). In this study, the FACT-L was used.

Langendijk and colleagues reported on the QoL of inoperable NSCLC patients treated with palliative (30 Gy), radical (60 Gy), or curative (70 Gy) radiotherapy (Langendijk et al. 2000a, 2001, 2002). Selection of the different fractionation schedules was based on WHO performance status, weight loss, and disease stage. These prospective longitudinal studies were the first to describe the course of QoL using the EORTC QLQ-C30 and QLQ-LC13 among patients with inoperable NSCLC treated with radiation for a period of 2 years. The fact that more than 90% of the patients referred for radiation were included in these studies supports the generalizability of the findings to the large population of lung cancer patients referred for radiation. The baseline QoL profiles of these patients are reported in Table 9.5. For purposes of comparison, mean values on these measures for a large general population sample are also presented. As expected,

patients treated with palliative intent reported more local and general symptoms and significantly lower scores for the functioning scales and the global QoL scale than did those patients treated with radical of curative radiotherapy. The mean baseline QoL scores of the patient samples were significantly worse than those of the general population, with the exception of emotional, cognitive, and social functioning in the curative group. In these studies, QoL changes over time were evaluated by means of the response classification system described previously. After palliative radiotherapy, the QoL response rates were excellent for hemoptysis (79%); good for arm/shoulder pain (56%), chest wall pain (53%), and cough (49%); moderate for dyspnea (39%); and minimal for the general symptoms of fatigue (22%) and appetite loss (11%). The QoL response rates for the functioning scales of the QLQ-C30 varied from 35% for role functioning to 57% for emotional functioning. Global QoL improved in 37% of the cases (Langendijk et al. 2000). In general, there was a tendency for better palliation of symptoms and improvement of functioning and global QoL among those patients with objective tumor response. Similar results were observed after radical radiotherapy (Langendijk et al. 2001b). After curative radiotherapy, a significant, gradual increase over time was observed for dyspnea, fatigue, and appetite loss. A significant, gradual deterioration was also observed for role functioning. No significant changes were noted for the other symptoms or the functioning scales of the QLQ-C30.

Two prospective, randomized studies have investigated the role of endobronchial brachytherapy in the treatment of lung cancer. Langendijk and co-workers (Langendijk et al. 2000) compared external irradiation plus endobronchial brachytherapy versus

Table 9.5 Baseline scores of symptom and functioning scales assessed with the EORTC QLQ-C30 and QLQ-LC13 among 275 patients with inoperable NSCLC referred for primary radiotherapy alone

Symptom and functioning scales	Mean scores			Mean scores in normal population*	Proportion of patients with symptom (%)		
	Palliative n=65	Radical n=164	Curative n=46		Palliative n=65	Radical n=164	Curative n=46
Local symptoms							
Cough	51.3	48.9	41.3	–	89	91	89
Dyspnea	46.3	34.6	32.8	16.4	88	78	87
Chest pain	34.9	17.1	9.4	–	62	38	22
Pain arm/shoulder	28.2	21.3	13.8	–	43	36	26
Hemoptysis	21.5	9.2	9.4	–	46	22	20
Dysphagia	14.4	8.7	8.7	–	25	18	17
General symptoms							
Fatigue	54.4	39.9	32.2	23.4	94	84	80
Insomnia	35.4	33.7	23.9	20.3	57	56	44
Pain	42.3	22.0	18.5	20.6	86	53	44
Appetite loss	47.7	27.2	8.0	5.0	71	44	20
Nausea and vomiting	13.8	7.3	2.1	3.7	34	24	9
Constipation	17.4	8.7	9.4	6.8	31	18	24
Functioning scales and global QoL							
Physical functioning	43.6	61.8	56.6	88.0	–	–	–
Role functioning	50.0	62.5	71.7	86.0	–	–	–
Emotional functioning	56.7	64.9	72.3	78.3	–	–	–
Cognitive functioning	73.1	83.8	85.1	88.5	–	–	–
Social functioning	69.7	80.4	88.0	90.4	–	–	–
Global QoL	40.1	56.7	60.7	74.7	–	–	–

* Health-related QoL measured by the EORTC QLQ-C30 in a large sample of the Swedish population [Michelson et al. 1999]

external irradiation only. The primary endpoint of this study was self-reported dyspnea, as assessed by the EORTC questionnaires. The combined treatment resulted in significantly less dyspnea in the immediate 3-month posttreatment period. No statistically significant differences between treatment arms were noted for any of the other endpoints, including QoL.

Stout and co-workers (Stout et al. 2000) reported on a phase III study in which patients were randomly assigned to external irradiation or endobronchial brachytherapy only. QoL assessment in this study showed better palliation of pulmonary symptoms with external irradiation, but at the cost of more dysphagia, fatigue, and appetite loss.

9.2.7 Conclusions and Future Directions

Despite advances in diagnostics and treatment, lung cancer remains one of the most common and deadly of malignant diseases. In evaluating the effectiveness of new treatment strategies in lung cancer, it is essential to assess not only the classical outcomes of tumor response and survival, but also the impact of the disease and its treatment on the symptoms experienced, functional health, and well-being of patients.

In the past several decades, major advances have been made in the field of QoL assessment. We currently have at our disposal a number of reliable and valid questionnaires for assessing the QoL of cancer patients in general and of lung cancer patients in particular. These methodological advances have facilitated the standardized assessment of patients' QoL in both clinical trials and longitudinal, observational studies.

There are a number of steps that need to be taken to refine the methodology of QoL assessment and to increase the usefulness of such measures in both clinical research and clinical practice. First, because there are a number of questionnaires available for assessing the QoL of patients with lung cancer, we need to develop a better understanding of their relative strengths and weaknesses from a psychometric perspective and, perhaps more importantly, to develop methods for comparing directly the scores derived from these different measures (i.e., calibrating scores).

Second, QoL questionnaires for use in lung cancer may well require modification in the future as new treatments become available that carry with them different side-effects profiles. Input is required from medical specialists in reviewing the content of the currently available QoL measures and developing additional questionnaire items were necessary.

Third, we need to develop a much better understanding of the clinical significance of QoL scores. One way of doing so would be to generate normative or reference data for groups of patients with different diagnoses, stages of disease, and treatment experiences. Further refinements in defining "QoL response," will increase the likelihood that such data are well understood and will be used by clinicians and patients alike in making treatment decisions.

Fourth, further effort is needed to ensure high levels of compliance with QoL data collection in prospective clinical studies. The decision to include QoL as an endpoint in a clinical study requires the commitment of additional resources, both financial and human, to ensure that patients complete questionnaires at the scheduled points in time. However, even when an optimal research infrastructure is available, it is likely, if not inevitable (e.g., in palliative treatment settings), that there will be some missing data. One of the ongoing statistical challenges is to develop methods that are able to deal with such informative censoring mechanisms in the data analysis.

Finally, an exciting challenge is to develop QoL measures and data collection methods that will facilitate monitoring the QoL of individual patients in daily clinical practice. Recent studies have demonstrated the feasibility of using computer touch screen technology for administering QoL questionnaires in outpatient clinic settings (Buxton et al. 1998; Wright et al. 2003) and have documented the effectiveness of routine QoL assessments in facilitating doctor-patient communication, increasing physicians' awareness of their patients' symptoms and functional limitations, contributing to patient management, and ultimately in improving the QoL of patients over time (Detmar et al. 2002; Velikova et al. 2004).

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10 Prognostic Factors in Lung Cancer

Frank B. Zimmermann

CONTENTS

10.1 Introduction

Lung cancer is a heterogeneous clinical entity, including small cell and non–small cell cancer. Both groups share molecular and cellular origins, but have distinct clinical behaviors and prognoses, even within their particular pathologic subgroups. This chapter documents the heterogeneous nature of the disease and explains why it is difficult therefore to determine the prognosis for an individual patient – in part because of the clinical heterogeneity of patients within subgroups, too.

The afflicted patients present a diverse constellation of clinical symptoms and biochemical values, in part caused by different manifestations of the primary tumor, distinct distribution of metastatic sites involved, and the varied extent of paraneoplastic syndromes, and even comorbidities. In spite of the remarkable predictability of population survival outcomes, this knowledge is of limited value to clinicians for treatment decisions in a single patient, due to the marked heterogeneity of the clinical course in the individual patient (Brundage et al. 2002). In this situation, prognostic factors may play a critical role in explaining the different outcomes of the patients, and might support treatment decisions, research design and analysis, and health policy development (Brundage et al. 2001; Mackillop 2001). This explains why clinical and basic science research on prognostic factors has been increased, including clinical characteristics of the tumor and of the patient, numerous clinical laboratory tests, and, most recently, investigations of the cellular and molecular biology of lung cancer and the environment (Table 10.1) (Buccheri and Ferrigno 2004; Feld et al. 1994; Brundage et al. 2002).

More than 900 articles have been published including a lot of reviews and describing more than 150 different prognostic factors (Table 10.2). And, besides the large amount of literature, it must be considered that the literature is markedly heterogeneous, with interstudy variations, patient selection bias, low numbers of patients in most trials, and poor statistical power (Brundage et al. 2002). Therefore, the main purpose of the following overview is to offer a view of the most important and significant prognostic factors and a basis for treatment decisions in clinical practice concerning patients with small cell and non–small cell lung cancer.

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Table 10.1 Prognostic factors in non-small cell and small cell lung cancer

Non-small cell lung cancer			Small cell lung cancer		
Tumor-related	Patient-related	Treatment-related	Tumor-related	Patient-related	Treatment-related
Tumor stage	Performance status	Clinically resectable disease	Tumor stage	Performance status	
Histology	Gender and age	Locally advanced disease	Histologic subtypes	Gender and age	
Serologic factors (tumor markers)	Laboratory, hematologic and immunologic factors	Metastatic disease	Serologic factors (tumor markers)	Laboratory, hematologic and immunologic factors	
Biological and genetic factors			Biological and genetic factors		

10.2 Non–Small Cell Lung Cancer

10.2.1 Tumor-Related Factors

10.2.1.1 Tumor Stage

The definition of major clinical subgroups on the basis of tumor stage (TNM staging system) (Mountain 1997) has been consistently shown to be the strongest determinant of outcome of NSCLC patients overall. Within this system each single parameter describing the anatomic burden of disease (T = local extent of tumor; N = site of nodal metastases; M = number and location of distant metastases) reflects prognosis (Buccheri and Ferrigno, 2004). Revisions to the TNM system were made in 1997 to provide greater specificity for patient subgroups, recognizing the prognostically relevant difference between pT1 and pT2, the importance of tumor-related factors (e.g., cN2 or cT4 disease) that estimate the likelihood of definitive resectability within stage III, and of the presence of intrapulmonary ipsilateral satellite tumor metastases (T4). Several reviews highlight the role of prognostic factors such as local tumor invasion with neurologic and vertebral body involvement in cT3 N0 M0 disease located in the superior pulmonary sulcus (i.e., Pancoast tumor) (Detterbeck 1997). Besides T category, it is known that tumor size is the powerful predictor of survival in patients who have disease that is amenable to resection but who are inoperable due to medical reasons and will undergo definite radiotherapy (Wigren et al. 1997).

In summary, the TNM system is the most accurate and reliable way to estimate a patient's prognosis. However, it can not precisely predict the 5-year survival rate even in fictitious homogeneous early stage tumors (mean value 67%) (Mountain 1997; Kwiatkowski et al. 1998). This indicates that the TNM system, based as it is on clinical, radiologic, and even histopathologic results, is far from sufficient. This might be explained by problems in staging procedures, but also by other prognostic factors, in part tumor-related. One of those factors might be major blood vessel or lymphatic infiltration. Both were explored in clinical studies and proven significant in univariate and multivariate analysis (Kessler et al. 1996; Brechot et al. 1996). Also neoangiogenesis as a major basis for tumor growth and metastasis has been evaluated in surgical specimens. Microvessel optical count was carried out in patients with stage I to IIIA disease, and found to be a powerful independent prognostic factor (Fontanini et al. 1998). The statistical significance of the results of this procedure was confirmed by a large review of several thousands of patient records by the European Lung Cancer Working Party in 2002 (Meert et al. 2002).

10.2.1.2 Histology

The prognostic significance of tumor cell type (e.g., large cell undifferentiated, adenocarcinoma, or squamous cell) has been studied extensively. It has been concluded from several studies that adenocarcinoma has an independent negative impact on survival prognosis. Other studies of comparable design have not shown cell type to have independent prognostic value, and in summary, the histologic subtype does not provide additional independent prognostic information in resectable NSCLC (Quejada and Albain 2004).

Table 10.2 Prognostic factors in non-small cell and small cell lung cancer (modified from Iyengar and Tsao 2002; Vansteenkiste et al. 2002; Brundage et al. 2002; Bremnes et al. 2003; Buccheri and Ferrigno 2004; Paesmans 2004)

	Non–small cell lung cancer		Small cell lung cancer	
	Tumor-related	Patient-related	Tumor-related	Patient-related
Essential and proven factors (at least in several large or randomized trials)	Tumor stage (TNM) including intra-pulmonary metastasis and pleural effusion	Performance status	Disease extent	Performance status
	Complete resection	Quality of life	Number of metastatic sites	Serum LDH
	Pathologic response to neoadjuvant treatment	Weight loss	Bone marrow infiltration	
	Cytokeratin markers (Cyfra 21-1)	Pretreatment serum LDH	Simultaneous radiochemotherapy	Serum NSE
	p53 tumor suppressor gene	Serum albumin		
		Pretreatment hemoglobin value		
Additional but not yet evident factors (divergent results and/or proven in smaller or retrospective trials only)	Tumor size or volume	Depression	Pleural effusion	Age
	Location of primary (central vs peripheral)	Age and comorbidities	Superior vena cava syndrome	Gender
	Distribution of involved lymph nodes	Gender		Smoking history
	Number of metastastic sites	Hemoglobin value		Neutrophilia
	CEA	Leukocyte counts		Hemoglobinemia
	NSE	Neutrophil counts		Uremia
	CA 125	Thrombocyte counts		Serum alkaline phosphatase
	Density of tumor vessels	Hypercalcemia		Serum albumin
	Vessel invasion	Total serum protein		
		Alkaline phosphatase		
		Ferritin		
		D-dimer		
		ESR		

10.2.1.3 Serological Factors (Tumor Markers)

The value of standard tumor markers as a predictive parameter has been tested in several clinical trials. Cytokeratin 19 fragments (Cyfra 21-1), tissue polypeptide antigen (TPA), cancer antigen 125, and carcinoembryonic antigen (CEA) have been evaluated as prospective prognostic determinants, with cytokeratin fragments almost certain to be significant. Unfortunately, the prognostic capability of CEA was rather weak (Buccheri and Ferrigno 2004). Cyfra 21-1 has been evaluated in a multivariate analysis, and was proven to have a higher sensitivity to predetermine the treatment outcome than CEA and NSE (Picardo et al. 1996). Therefore, it is the best marker to control the therapeutic efficacy of chemotherapy or radiochemotherapy, but

it cannot be used for treatment decisions before initiating therapy.

10.2.1.4 Biological and Genetic Factors

Biological and genetic tumor factors have been evaluated mostly in resected specimens, therefore data on patients with advanced disease are rare. Nevertheless, some of those factors have been shown to have independent prognostic significance. These include histologic features, markers of tumor proliferation, markers of cellular adhesion, and other molecular biological markers, which are rarely assessed in clinical routine practice. The last group includes regulators of cellular growth (e.g., ras oncogene or protein, retinoblastoma, epidermal growth factor receptor, erb-b2, motility-related protein-1, and hepatocyte growth factor), regulators of the metastatic cascade (e.g., tissue polypeptide antigen [TPA], cyclin D-1, and cathepsin), and regulators of apoptosis (p53 and bcl-2). The potential clinical application of the factors is discussed below. Markers of angiogenesis, p21 status, status of the serum assay for detection of the cytokeratin 19 fragment, status of the argyrophilic nucleolar organizer region, and p185 status have been significantly associated with prognosis in about 80% of the studies, whereas Ki-67 status, vascular endothelial growth factor status, and vessel invasion were positively correlated in only 50–60%. Data on mutation of the p53 suppressor gene is also conflicting, but three systematic reviews have confirmed its prognostic impact at least in adenocarcinoma. Unfortunately, only a few reports are based on prospectively designed studies thus decreasing their value (Buccheri and Ferrigno 2004; Fontanini et al 1997; Mori et al. 1997). And so far none of these factors can really be used for treatment decisions.

10.2.2 Patient-Related Factors

10.2.2.1 Performance Status (Karnofsky and Weight Loss)

Numerous studies have investigated patient characteristics as predictors of survival after surgical resection, definite radiotherapy or radiochemotherapy in non–small cell lung cancer. Due to the fact that most patients with early stage disease are asymptomatic, only a few studies have systematically evaluated the prognosis of patients as it is related to clinical symptoms in stage I cancer. They have been found to be less powerful predictors of outcome, particularly in stage I disease, than in the advanced disease setting, and therefore these factors are not generally considered to be important for clinical decision making. Nevertheless, hemoptysis, coughing, and thoracic pain were identified as risk factors for tumor recurrence and poor survival (Harpole et al. 1995).

In locally advanced and unresectable cancer as well as functional inoperable patients, an increasing amount of research has addressed the use of patient-reported parameters. The majority of those patients will show significant symptoms or other general manifestations of illness such as weight loss or poor performance status.

The Karnofsky Performance Status (KPS) and Eastern Cooperative Oncology Group Performance Status (ECOG PS) scales have been examined in large trials, and ahead of 50 other factors, KPS and weight loss within the previous 6 months were the most important, aside from extent of disease (Stanley 1980). Large clinical studies or reviews confirmed KPS as well as ECOG PS as one of the two most important prognostic factors, with ECOG PS being the more reliable and useful (Buccheri and Ferrigno 2004). In more recent trials, the role of cancer-related symptoms, quality-of-life scores, and/or anxiety and depression measures have been investigated more in depth. Those studies reported the importance of quality of life as a stronger determinant than pure performance status (Langendijk et al. 2000, Buccheri and Ferrigno 2004). Quality-of-life scores and anxiety and depression assessments may reflect the extent of disease and also the patients' inherent characteristics or degree of emotional support, which may better predict disease outcomes, possibly through psychophysiologic mechanisms.

Weight loss within the last 6 months before diagnosis has an important impact on survival, with total proportional weight loss being the most significant factor (Buccheri and Ferrigno 2004).

10.2.2.2 Gender and Age

In several former studies, male sex was discussed as an adverse prognostic factor. Unfortunately, the literature is quite varied in the conclusions drawn about the prognostic value of gender and age, and the strength of the association with survival outcomes. Though results of age in multivariate analysis have been inconsistent, younger age might carry a better prognosis (Quejada and Albain 2004). Albain and colleagues identified good performance status,

female sex, and age below 70 years as the most important factors that were predictive of favorable survival rates overall. In 1994, a review described significant evidence in 7 out of 19 studies with univariate analysis, and in 9 of 23 studies with multivariate analysis, in favor of female sex (Buccheri and Ferrigno 1994). These data were confirmed by an evaluation in a tumor register population. Median survival was significantly better for women than for men, and together with extent of tumor and weight loss, gender was the strongest independent predictor even in multivariate analysis (Palomares et al. 1996).

10.2.2.3 Laboratory, Hematologic, and Immunologic Factors

Hematologic or biochemical markers might be associated with disease extent, and were therefore evaluated in numerous trials. In a large study of 2,531 patients who were enrolled in a variety of clinical trials, four prognostic factors for patients receiving cisplatin chemotherapy were identified that had significantly distinct survival implications: performance status, age, and hemoglobin and serum LDH levels. Other studies employing secondary analysis of clinical trial information or after retrospective evaluation of patient data outside of clinical protocols have reached similar conclusions (Paesmans et al. 1995; Hespanhol et al. 1995; Takigawa et al. 1996). In general, LDH is certainly the strongest prognostic factor, whether considered alone or in combination with weight loss, performance status, or tumor stage (Buccheri and Ferrigno 1994). Further independent laboratory tests are albumin, plasmatic level of hemoglobin, and white blood cell counts, with decreased values indicating poor prognosis. Thrombocytosis with a platelet count above 400,000/µl, tested in a specifically designed study, showed a strong correlation with advanced disease and decreased survival even after adjustment for stage and histologic type of tumor, and sex and age of the patient (Pedersen and Milman 1996).

10.2.3 Treatment-Related Factors

10.2.3.1 Clinically Resectable Disease

No modern studies exist comparing resection with other single or combined modality treatments, since surgery is considered to be the standard management of patients who are medically fit for thoracotomy, producing the best results both in terms of local disease control and overall survival rates (Sabiston and Spencer 1995). In this situation, complete resection is essential, and lobectomy or pneumonectomy are standard approaches, with wedge resection being reserved for patients in poor condition, due to inferior results possibly caused by close resection margins or limited lymph node dissection (Sabiston and Spencer 1995; Lee et al. 1999). Tumor wedge resection, segmental or atypical resection increases the risk of local recurrence threefold to fivefold with a reduced 5-year survival rate, but not in very early stage NSCLC (pT1–2 N0) where it gives the same results as lobectomy (Graziano 1997; Jazieh et al. 2000).

Of fatal prognostic significance is an incomplete resection, either with gross disease remaining or with positive microscopic resection margins, even when additional postoperative therapy (radiotherapy or chemoradiotherapy) is provided (Ginsberg et al. 1999), suggesting the poor biological characteristics of the tumor being associated with both locoregional extension that causes microscopic residual disease and early systemic spread as well. Perioperative blood transfusions, required mainly in extensive dissections, is postulated to decrease overall survival by mediated immunosuppression favoring proliferation, distant spread, and migration of tumor cells. Published data are incongruous, with shortening time to recurrence, decreasing overall and recurrence-free survival by 30% in some publications, and no significant influence in others (Quejada and Albain 2004).

Primary radiotherapy with curative intent is only recommended for patients who can not undergo resection with curative intention, although no modern randomized trials have directly compared surgery with radiotherapy (Ginsberg et al. 1999; Zimmermann et al. 2003b). In this situation, it is well known that treatment results depend on total dose and fractionation schedule, with acceleration and hyperfractionation to biologically effective doses of more than 70 Gy producing superior outcomes (Sause 2001; Jeremic et al. 2002, Saunders et al. 1999; Willner et al. 2002; Choi et al. 2001; Zimmermann et al. 2003b).

10.2.3.2 Locally Advanced Disease

Patients without clinical symptoms or without radiologic signs of systemic manifestations but unresectable disease have been shown in a number of clinical trials to have higher survival rates when they receive induction chemotherapy followed by radiotherapy

or, even better, concurrent chemoradiotherapy, compared with radiotherapy alone (Stewart and Pignon 1995). The same subgroup of patients has been shown to experience higher survival rates when treated with continuous hyperfractionated and accelerated radiotherapy compared with conventional fractionation, and when treated with higher doses of conventional radiation compared with lower doses (Saunders et al. 1999; Willner et al. 2002; Choi et al. 2001; Emami and Perez 1993). The role of surgery in relation to induction chemotherapy and radiotherapy is still being investigated, as is the role of combination chemoradiotherapy in more symptomatic patients (Ginsberg et al. 1999).

10.2.3.3 Metastatic Disease

For patients without substantial systemic manifestations of illness and in good condition (Karnofsky scale value >60), chemotherapy is known to improve median survival time when compared with the best supportive care alone (Stewart and Pignon 1995). This has not been documented for patients with poor performance status, where best supportive care is recommended in general.

10.3 Small-Cell Lung Cancer

10.3.1 Tumor-Related Factors

10.3.1.1 Tumor Stage

In contrast to NSCLC, small cell lung cancer is generally classified into a two-stage system – limited and extensive disease – with limited disease (defined as tumor confined to one hemithorax, by the Veterans Administration Lung Study Group [VALG], or as without distant metastases, by the International Association for the Study of Lung Cancer [IASLC]) being tested as a definite and the most powerful prognostic factor in most of the published series using the IASLC definition (Micke et al. 2002; Paesmans et al. 2000; Jorgensen et al. 1996). The median survival is around 15 months in limited stage disease, in contrast to about 10 months in extensive stage disease patients (Yip and Harper 2000), and this has major implications for treatment decisions.

Besides this two-class system, a lot of other prognostic factors that describe the extent of tumor and the number or location of metastatic sites involved have been evaluated (vena cava syndrome, pleural effusion or nodal involvement, and involvement of different organs like the liver, brain, or bone) (Albain et al. 1990; Würschmidt et al. 1995; Tamura et al. 1998; Bremnes et al. 2003). Mediastinal involvement and the infiltration of several organs might worsen the prognosis of the patient, but data are not consistent. Therefore, these factors are not generally used as a basis for treatment decisions.

10.3.1.2 Histologic Subtypes

Small cell lung cancer can carry a mixture of different tumor cells in up to 20% of cases, large cell carcinoma being the most commonly combined cell type. This led the pathologic committee of the IASLC to adopt three new subtypes of small cell lung cancer: small cell, mixed large and small cell, and combined small cell carcinomas (Hirsch et al. 1988). Unfortunately, several studies that followed this new classification could not document a different clinical outcome for these three subgroups, and the actual WHO classification abandoned the idea of different subgroups (Brambilla et al. 2001). Nevertheless, the high percentage of patients with various combinations of small cell and non–small cell lung cancer might explain the divergent responses to chemotherapy, and support the idea of salvage resection for locally poorly responding cancer (Sheperd et al. 1991).

10.3.1.3 Serologic Factors (Tumor Markers)

Besides the tumor extent, simple laboratory parameters like biochemical tests and serum tumor markers have their predictive value.

Serologic factors (tumor markers) produced by tumor cells and released into the bloodstream, have been evaluated in a lot of different studies. Due to their low tumor specificity, only a few of them have unquestionable prognostic value: neuron-specific enolase (NSE) and cytokeratin 19 fragments (Cyfra 21-1).

NSE has been tested in several large trials, and a significant correlation was found between elevated NSE levels and poor prognosis both in univariate and multivariate analyses, making it one of the most powerful prognostic factors (Bremnes et al. 2003; Jorgensen et al. 1996). Using NSE in a simple

algorithm together with performance status of the patient and tumor extent produces a clearly defined prognostic classification that can be used for treatment decisions (Jorgensen et al. 1996).

Cyfra 21-1 has been the most commonly studied cytokeratin, and besides extensive disease and increased levels of LDH and NSE, elevated levels to more than 3.6 ng/ml significantly indicated a poor outcome for the patient (Pujol et al. 2003).

Among the many other serologic markers tested, only serum carcinoembryonic antigen (CEA) deserves to be mentioned: in univariate analyses its value has been confirmed, whereas chromogranin A (CgA), pro-gastrin-releasing peptide (ProGRP), and creatine kinase-BB (CPK-BB) have not yet been confirmed to be significant (Ferrigno et al. 1994; Lamy et al. 2000; Sunaga et al. 1999).

10.3.1.4 Biological and Genetic Factors

The genetic deletion of a number of chromosomes is discussed as the major impetus to the development of human lung cancer, stimulating the activation of proto-oncogenes and the loss of tumor suppressor genes. In small cell lung cancer, the activation of genes of the myc family (c-myc, L-myc, N-myc) seems to be notable (Rygaard et al. 1993). Their expression depends on tissue type, and corresponds to the maturity and development of different cell lines. The c-myc oncogene may play an important role for the differentiation of the cell in many cellular processes (proliferation, differentiation, apoptosis). It is highly amplified in SCLC cell lines in vivo, indicating its relation to tumor progression and aggressiveness of the tumor (Bergh 1990). In clinical studies, a high amplification of c-myc strongly correlates with tumor progression and a poor outcome of the patient (Salgia and Skarin 1998).

The value of p53 antibody has been evaluated in several clinical trials. It seems possible that the presence of a high titer of p53 antibody (titer ratio >5) is correlated with a survival advantage. Unfortunately, in contrast to the prognostic value of p53 antibodies in NSCLC, the results from several clinical trials are contradictory, so that its value as a prognosticator in small cell lung cancer has not been proven with any certainty (Jassem et al. 2001; Murray et al. 2000).

Further genetic abnormalities connected to the pathogenesis of small cell lung cancer are under investigation, but none has been established as a trustworthy marker for the prognosis of a patient with small cell lung cancer.

10.3.2 Patient-Related Factors

10.3.2.1 Performance Status (Karnofsky and Weight Loss)

The performance status describes the patient's ability regarding self-care and the performance of normal activities including participation in social life. There are two different schedules in use: the Karnofsky Performance Status scale (KPS; with 11 levels from 0 to 100) and the Eastern Cooperative Oncology Group Performance Status scale (ECOG PS; with 5 levels). The value of both schedules has been tested, with the ECOG PS being easier to apply and of better discriminatory value for patient prognosis (Buccheri et al. 1996). In numerous clinical trials, performance status—independent of the schedule used—has been confirmed as a significant prognostic cofactor (Paesmans et al. 2000; Buccheri and Ferrigno 1994).

Besides tumor extent and performance status, weight loss has been identified as an important prognostic factor in small cell lung cancer, too (Stanley 1980; Tamura et al. 1998; Bremnes et al. 2003).

A more complex determinant predicting the survival of patients with small cell lung cancer is quality of life, a multifactorial concept considering all aspects of the physical, psychological, social, and functional status of the patient. Quality-of-life tests have been shown to be valid in several clinical studies, but are more difficult to establish in clinical practice and are therefore rarely used outside clinical trials (Naughton et al. 2002; Montazeri et al. 2001; Buccheri 1998).

10.3.2.2 Gender and Age

Gender was documented to be a discriminating factor of SCLC outcome, with the combination of female sex and younger age (below 60 years) carrying the best prognosis regarding response rates, median survival, and 2-year survival rate. This observation was independent of any other relevant prognostic variable (Buccheri and Ferrigno 1994; Wolf et al. 1991).

10.3.2.3 Laboratory, Hematologic, and Immunologic Factors

There is a long list of laboratory tests which have been evaluated as indicators of possible prognostic factors in small cell lung cancer: lactate dehydrogenase (LDH), hemoglobin serum concentration (Hb), al-

bumin, alkaline phosphatase (AP), sodium, calcium, creatininemia, bicarbonates, bilirubinemia, erythrocytes, leukocytes, neutrophilia, and thrombocytes.

Elevated LDH, tested in 10 of 13 multivariate and 3 large trials with more than 500 patients each, is the strongest hematologic prognostic factor, with high accuracy in predicting poor outcomes. It seems to be even more important than tumor markers (NSE), and is recommended by different groups as the cheapest and most significant marker for small cell lung cancer as a stratification criterion for clinical trials (Quoix et al. 2000; Rawson and Peto 1990). Of all the other factors mentioned above, the results are more or less inhomogeneous: low serum albumin concentration, decreased plasmatic level of hemoglobin, leukocytosis, increased alkaline phosphatase and serum bicarbonate were shown to be significant in only some of the trials in which they were evaluated, and can not be integrated into clinical routine as a basis for treatment decisions (Bremnes et al. 2003; Quoix et al. 2000; Rawson and Peto 1990).

10.3.2.4 Treatment-Related Factors

The response to treatment has been found to be a highly significant indicator for survival of patients treated with chemotherapy and radiochemotherapy. Complete responders had better survival rates than partial responders, who in turn had superior outcomes to nonresponders (Lebeau et al. 1995; Ray et al. 1998; Paesmans et al. 2000).

In several randomized trials it has been documented that simultaneous radiochemotherapy, with radiotherapy being administered early in the treatment schedule, will improve the outcome in patients in good condition compared with chemotherapy or radiotherapy alone, and that altered fractionation of irradiation might further enhance the results (Warde and Payne, 1992; Murray et al. 1993; Jeremic et al. 1997; Work et al. 1997; Lebeau et al. 1999; Turrisi et al. 1999; Takada et al. 2002; Zimmermann et al. 2003a). The value and the optimal timing of resection of persistent tumor at the end of chemotherapy in sequential protocols, or after simultaneous radiochemotherapy, has not yet been evaluated in randomized trials, but can be recommended for patients in good condition. It might increase local control and recurrence-free survival as well (Lad et al. 1994). In extensive disease, radiotherapy should not be omitted in treatment responders, because local tumor control and median survival can be improved by additional irradiation (Jeremic et al. 1999).

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Future Strategies in Lung Cancer

11.1 Intensity-Modulated Radiation Therapy for Lung Cancer

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CONTENTS

Acknowledgement: The project "Conformal Radiotherapy Ghent University Hospital" is supported by the Belgische Federatie tegen Kanker and by grants from the Fonds voor Wetenschappelijk Onderzoek Vlaanderen (grants FWO G.0049.98, G.0039.97), the Ghent University (GOA 12050401, BOF 01112300, 011V0497, 011B3300), and the Centrum voor Studie en Behandeling van Gezwelziekten.

11.1.1. Introduction

In the 1980s, Brahme (1982) demonstrated the unique potential of intensity-modulated (IM) beams to create homogeneous concave dose distributions. Inside IM beams, the radiation fluence (intensity) was not equal at all sites inside the beam i.e. the beam was not flat (unmodulated) but had a value that was function of its location across the field (Lax and Brahme 1982). Brahme (1988) also proposed the concept of inverse planning as a possible strategy to make the design of IM beams feasible. Intensity-modulated radiation therapy (IMRT) remained a research topic in physics laboratories until 1993, when Carol et al. (1996) proposed a novel planning and delivery system (NOMOS MiMiC) as a comprehensive solution for clinical IM tomotherapy. Since 1993, the three major vendors of linear accelerators have developed multileaf collimator (MLC) technology capable of delivering IMRT, and smaller companies have developed micro-MLCs with IMRT capability. IMRT research is intense, and clinical results have been published for various tumour sites, including the prostate, head and neck, and base of the skull. A PubMed search on 25 March 2004 using "intensity modulated lung cancer" as keywords yielded 45 publications, most of which were on physics issues. None reported on the clinical outcome of IMRT in lung cancer.

Against this background, a chapter on the use of IMRT in lung cancer remains largely speculative. Our aims are to formulate the clinical objectives of IMRT to treat lung cancer; to discuss the anatomical challenges of IMRT, the choice of beam directions, and the potential of intensity-modulated beams to spare lung, oesophagus, and spinal cord; to describe the potential clinical benefit of biological image-guided IMRT optimisation; to discuss specific planning issues, including the problem of heterogeneities in tissue density for IMRT optimisation; and finally to discuss the implementation and quality assurance problems that have delayed clinical trials.

11.1.2 Clinical Objectives

In limited-disease (LD) small cell lung cancer (SCLC), randomised trials comparing early versus late accelerated radiation therapy concurrent with chemotherapy showed a significant increase in 5-year survival from 13-20% for the late arm to 22-30% for the early arm (Jeremic et al. 1997; Takada et al. 2002; Murray et al. 1993). A large difference in survival between early and late thoracic radiation as well as survival

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rates above 20% were seen in randomised trials using a dose intensity of about 15 Gy/week (Perry et al. 1998; Work et al. 1997) instead of the standard of 9-10 Gy/week. Using early thoracic radiation, a randomised trial (Turrisi et al. 1999) comparing 45 Gy in 3 weeks (group 1) with 45 Gy in 5 weeks (group 2) confirmed the advantage of a high dose intensity, with a 26% 5-year survival rate for group 1 and 16% for group 2 (p=0.04). A 50-66% local control rate that was achieved with the best schedules (Knoos et al. 1995; Murray et al. 1993; Turrisi et al. 1999) using 40-54 Gy in 3-3.5 weeks indicates the existence of a window for improvement with more efficient local treatment. A phase I dose and dose-intensity escalation study showed that the maximum tolerated radiation dose intensity is limited by acute oesophageal toxicity at 45 Gy in 30 fractions over 3 weeks (Choi et al. 1998). An analysis of patients with LD-SCLC treated with doses ≥ 50 Gy suggests further increase of dose response above 50 Gy (Roof et al. 2003). These results direct us to a design of IMRT studies with further dose and dose-intensity escalation at the tumour, respecting isotoxicity at the oesophagus by selective underdosage. The hypothesis that such use of IMRT can improve the therapeutic result should be tested.

In patients with locally advanced (LA) non-small cell lung cancer (NSCLC), combined treatment with radiotherapy and second-generation chemotherapy drugs was extensively studied over the past 20 years, and it became the standard over radiotherapy alone in patients with good performance status. Cisplatin seems the drug of choice but results in significant increase of oesophageal toxicity. In LA-NSCLC, the maximum dose of radiotherapy with or without concurrent chemotherapy is most often restricted by pulmonary toxicity (radiation pneumonitis). For further improvement in survival, the two components of the treatment need to be improved. An effective treatment of micrometastatic disease through full-dose delivery of cytotoxic drugs could be obtained by adding at least one more active drug in conjunction with cisplatin. To further improve loco-regional control of the disease, radiotherapy dose escalation seems a logical strategy. Clinical data regarding the magnitude of dose escalation that can be achieved by IMRT are inexistent. In planning studies, the Rotterdam Oncological Study Group (Van Sornsen de Koste et al. 2001) showed a reduction of 20.3% in the mean lung dose using three-dimensional (3D) missing tissue compensators, as well as a reduction in the total lung volume exceeding 20 Gy (V20). Derycke et al. (1997) compared a three- or four-beams conventional 3D technique (3D-CRT) and two techniques involving, respectively, seven and five non-coplanar beam incidences with intensity modulation and showed an improvement both in tumour control probability (TCP) and lung normal tissue complication probability (NTCP) for the IMRT plans, with a window for 20-30% dose escalation. Marnitz et al. (2002) showed a reduction of the irradiated lung volume using non-coplanar IMRT fields.

Randomised trials have shown an improved outcome of combined radiation therapy and chemotherapy over radiotherapy alone, with the concurrent radio-chemotherapy schedules being the most efficient (Lara et al. 2002). Accelerated radiotherapy schedules were shown to be superior to schedules using conventional fractionation (Saunders et al. 1996). The design objectives of IMRT for LA-NSCLC seem very similar to those of IMRT for LD-SCLC, namely to obtain an accelerated radiation treatment that can be delivered simultaneously with chemotherapy. For both pathologies, IMRT needs to address at least three objectives: limiting oesophageal toxicity, limiting the risk of radiation pneumonitis, and increasing dose and dose intensity selectively to the tumour. Dose intensity escalation seems to be more important than physical dose escalation for LD-SCLC, whereas both types of dose escalation seem important for LA-NSCLC. As a result of improved survival and enhanced local control, most of the present radiochemotherapy studies show a significant increase in the incidence of brain metastases (Reboul 2004). Addressing the question of prophylactic cranial irradiation might be a 4th objective in future IMRT trials.

11.1.3 Challenges Related to Anatomy and Preservation of Organ Function

Safe delivery of high doses to lung tumours is prohibited most often by risk of toxicity to lung, spinal cord, and oesophagus. Lung can be considered as an organ that consists of functional units organised in a parallel architecture. The probability of life-threatening radiation pneumonitis can be estimated from the percentage volume of lung irradiated above a critical dose – for example, 20 Gy (V20) (Graham et al. 1999) – or from the mean (biological) lung dose (MLD) (Kwa et al. 1998; Seppenwoolde et al. 2003). With a fixed constraint on V20 or MLD, the maximum prescription dose decreases for larger planning target volumes (PTVs) and is dependent on the location of the PTV. For equal PTV size and doses above 50 Gy

in 2-Gy fractions, often used as the maximum dose that can be safely delivered to the spinal cord, a PTV with a more peripheral or more cranial location can be planned to higher doses than can a PTV with a more central or caudal location. The MLD was shown to be a strong predictor of the risk of life-threatening radiation pneumonitis. Mathematically, MLD = 1/V.∫D.dV where V is the total lung volume and D the biologically normalised dose at the volume element dV. By synchronising irradiation with deep inspiration breath hold, V is increased (Rosenzweig et al. 2000) and the MLD decreases. Breathing control is discussed elsewhere in this book.

The second term, ∫D.dV, is the lung integral (biological) dose that can be lowered by decreasing beam aperture and by applying beams with a shorter path length through lung. Brugmans et al. (1999) and Dirkx et al. (1997) have shown that a specific form of intensity modulation involving the creation of sharp intensity peaks near the beam edges allows the application of smaller beam apertures. The influence of beam energy on the integral dose to lung is controversial. Some authors advocate the use of beams of less than 10 MV (Brugmans et al. 1999). Liu et al. (2004) compared IMRT plans using 6 MV and 18 MV beams. The use of 18 MV beams showed no noticeable difference in the quality of the IMRT plans. In our experience, replacement of 18 MV beams with 6 MV beams often decreases the quality of the plans (De Gersem, unpublished).

11.1.4 Selection of Beam Directions

For most lung tumours, the PTV prescription dose is limited by lung, spinal cord, and oesophagus. Because lung tumours have a poor prognosis and cardiac toxicity is a late event, larger volumes of heart irradiated at high doses are usually allowed in these patients than in patients with breast cancer or lymphomas. When lung tumours are located close to the diaphragm, the dose-volume integral of radiation to liver and kidneys may be of concern, especially when set-ups with nontransverse plane beams are used. The use of appropriate beam directions is as important in IMRT as in conventional radiation techniques, and beam directions should be optimised. However, optimisation of the number of beams and their orientations in three dimensions is still a research challenge and is not routinely available in IMRT planning systems. In daily practice, beam directions are imposed by a class solution or are chosen by the planner.

The basic principles of choosing beam directions are very similar for photon IMRT as for flat-beam conformal treatments. First, the best beam directions are those that feature the smallest aperture, which is especially important if the beam trajectory passes through organs of parallel functional unit architecture, such as lung. Second, the location and magnitude of the intended dose gradients determine the choice of beam directions. Where the PTV extends close to organs at risk with serial functional unit architecture, such as spinal cord or oesophagus, steep dose gradients are needed. The steepness of dose gradients is limited by the penumbra width achieved by the beam collimating system. Beam directions orthogonal to the desired gradient vector yield the steepest dose gradients. The choice of beam directions is, however, limited by physical constraints imposed by the gantry in relation to the table couch and patient, and by concerns on dosimetric uncertainty (beam entrance through the patients' arms).

For the centrally (close to the midsagittal plane) located tumour shown in Fig. 11.1.1a, beam 1 seems the best choice to spare lung, for two reasons: 1) it exhibits the smallest aperture, and 2) the beam axis is aligned with the long axis of the tumour. Beam 1 irradiates the smallest area of lung, but its beam weight and thus its contribution to the PTV prescription dose will be limited by the spinal cord tolerance. Other beam directions will be needed to increase the minimum PTV dose above the spinal cord tolerance, irrespective of the use of intensity modulation. Two candidate beams (beams 2 and 3 in Fig. 11.1.1a) have equal angular separations to beam 1 and have the same aperture, and both can create the required dose difference. However, beam 2 is a better choice than beam 3 because the former irradiates less lung volume. Fig. 11.1.1a illustrates the benefits of using parasagittal beams (i.e. beams that make small angles with the sagittal plane) for the treatment of centrally located tumours. Parasagittal beams can be used to deposit entrance- and exit-dose in the mediastinum rather than in lung. More lateral beams with gantry angles around 90° or 270° are obviously poor choices to spare lung.

For peripherally located tumours, tangential beams can be used to limit the irradiated lung volume (Fig. 11.1.1b).

A centrally located PTV with its largest axis in the laterolateral direction forms one of the biggest planning challenges (Fig. 11.1.1c). The advantages of

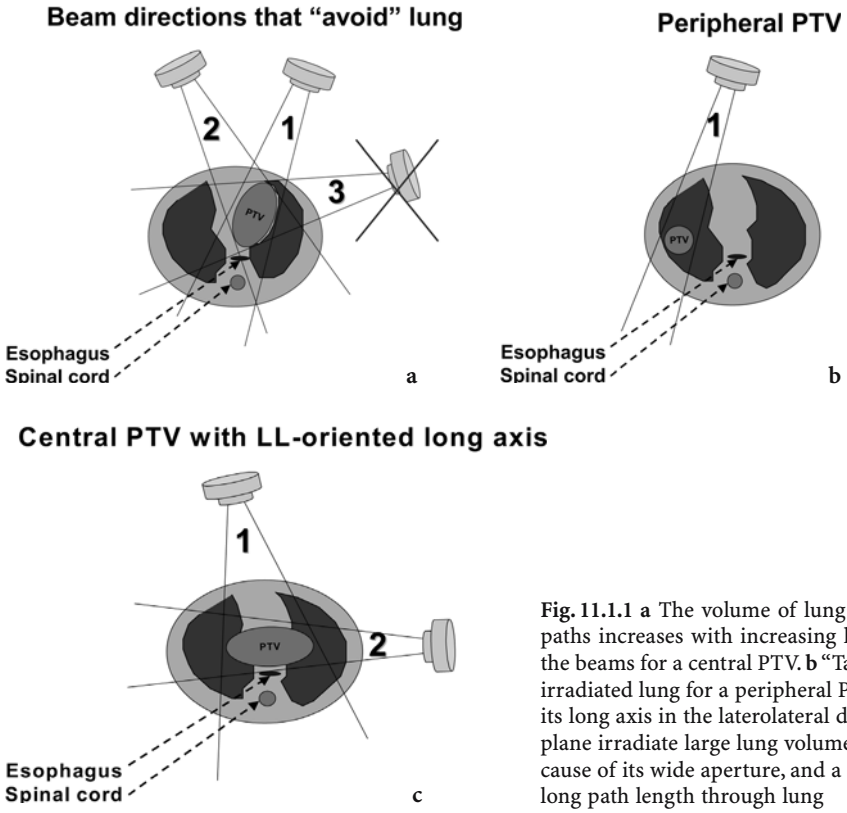


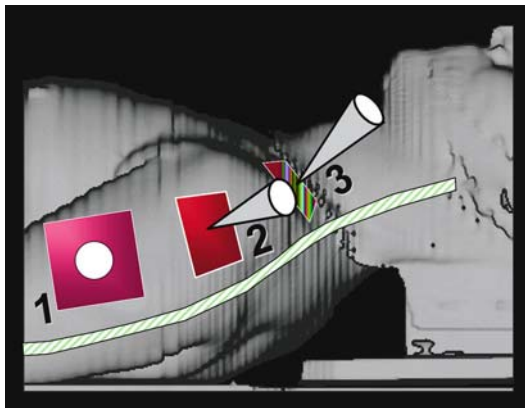
Fig. 11.1.1 a The volume of lung irradiated by the entrance and exit paths increases with increasing hinge angles to the sagittal plane of the beams for a central PTV. **b** "Tangential" beams limit the volume of irradiated lung for a peripheral PTV. **c** Centrally located tumour with its long axis in the laterolateral direction. All beams in the transverse plane irradiate large lung volumes: a parasagittal beam (beam 1) because of its wide aperture, and a lateral beam (beam 2) because of its long path length through lung

parasagittal beams are reduced because these beams also expose a large lung volume because of their wide beam apertures that are needed to cover the PTV. Lateral beams use smaller apertures and are needed to create a dose gradient between PTV and spinal cord or oesophagus, but they feature long trajectories through lung.

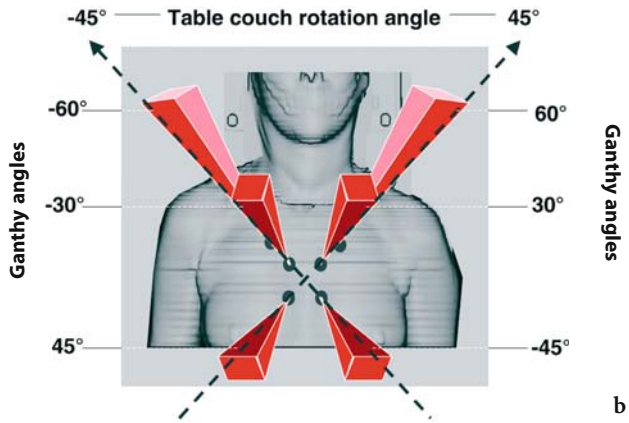
Nontransverse beams may provide additional possibilities for creating dose gradients between the PTV and spinal cord or oesophagus, as illustrated by Fig. 11.1.2a. The beam set-up shown in Fig. 11.1.2b also enables beam entrance above the heart for PTV locations at the bottom of the lungs.

Fig. 11.1.3 shows a dose distribution of a clinical IMRT plan for lung cancer in a transverse slice. The PTV volume was 1,101 cc. The optimisation of segment weights and leaf positions was performed using a biophysical objective function. All beams used 18 MV photons. This slice demonstrates the possibilities of a non-coplanar beam set-up to deposit exit doses in the mediastinum instead of inside the lungs. The largest part of the exit dose is deposited outside the slice shown in the figure. With a coplanar beam setup, it is not feasible to spare the homolateral as well as the contralateral lung in this slice to this amount. In this planning, 75% of the lung volume receives less than 20 Gy. The figure also displays the avoidance of high doses to the spinal cord. The treatment was well tolerated, and tumour regression was visible on portal images taken for patient setup.

Fig. 11.1.4 shows a dose distribution in a coronal slice of a clinical IMRT planning for a treatment with two dose levels (70/50 Gy) administered in one phase. The close conformity of isodose lines to the PTV in a coronal view is typical for a parasagittal beam setup. The PTV volume for this patient was 810 cc, and the volume of the dose grid inside the patient was 54,049 cc. The planning for this patient was complex due to the patient's obesity and to the extent of the PTV and its location close to the spinal cord and extending over almost the whole craniocaudal range of the lungs. In order to respect the clinically applied dose constraint to the lungs (V20<30%), the leaf position optimisation eroded the dose distribution at the edge of the PTV. The figure also shows the possibility of using a beam with a long path through the PTV with entrance through the patient's left shoulder (at the right side on the figure and tilted anteriorly with regard to the coronal slice).



a



b

Fig. 11.1.2 a A lateral beam (1) allows the creation of a steep dose gradient in the anteroposterior direction of the patient; for example, between the PTV and oesophagus or spinal cord at the expense of a long trajectory through lung. By isocentric rotation of the couch (beam 2), the trajectory through lung can be shortened because the beam's exit path tends to leave the thorax through the mediastinum with or without a shorter path through the heterolateral lung. With further couch rotation (beam 3), lung sparing improves as an increasingly large volume of the exit as well as the entrance trajectories of the beam traverse the mediastinum instead of lung, but the risk of collision between the collimator and the patient's head increases. By changing the gantry angle, collision can be avoided at the expense of a decreased steepness of the dose gradient in the anteroposterior direction. A compromise between lung sparing and the steepness of the anteroposterior dose gradient can be made using beams that enter the patient through the shoulders. To use such beams, a patient position with the arms alongside the body is suitable. A couch design with an Ω-shaped head-end allows anterior as well as posterior beam entrance through the shoulders. **b** The anterior part of the beam set that is used as a class solution at Ghent University Hospital. Planning is now started with a set of nine beam directions using three couch isocentre rotation angles. Six of the seven anterior-side beams are shown. At couch rotation angles of 45° and −45°, the set consists of beams with gantry angles of 60°, 30°, and −45° and −60°, −30°, and 45°, respectively. Not shown are the beams at couch rotation angle of 0°, namely the anterior-side beam at gantry 0° and the two posterior-side beams with gantry angles of 155° and −155°

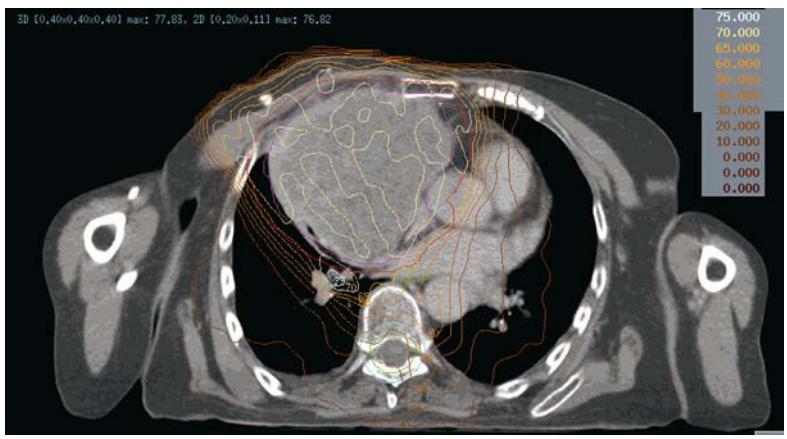


Fig. 11.1.3 Dose distribution of an IMRT planning for lung cancer in a transverse slice. The clinical target volume (CTV) is drawn in purple, the PTV (5-mm expansion of the CTV) in red, the 5-mm expansion of spinal cord in green, a 10-mm expansion of the spinal cord in light blue, and the oesophagus in green

11.1.5 Increasing Dose and/or Dose Intensity Selectively to Tumour

At the risk of oversimplification, we could state that larger tumours need higher doses for cure (Bradley et al. 2002). Especially in many patients with LA-NSCLC, the volumes are too large for a strategy of dose escalation when the aim is a homogeneously irradiated PTV. Dose escalation focused to small subvolumes of the PTV may be the option. The potential of inhomogeneous dose distributions for dose escalation has been demonstrated previously (De Gersem et al. 1999). The safety of substantial dose escalation to small volumes is illustrated by studies conducted at the University of Michigan (Hayman et al. 2001). In their study design, the maximum prescription dose was limited by the predicted risk of severe radiation

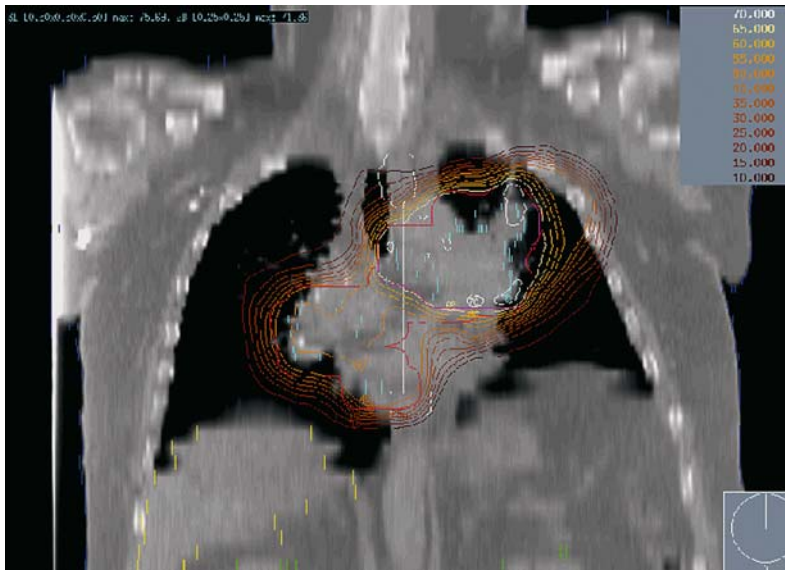


Fig. 11.1.4 Coronal view of the dose distribution of an IMRT planning for lung cancer. The PTV (CTV + 5 mm) is red, and the purple contour delineates the part of the PTV with a prescription dose of 70 Gy

pneumonitis. Doses over 100 Gy could be delivered to small PTV volumes. The maximum tolerated dose to the structural elements of lung (bronchi, blood vessels) had not been reached. For larger tumours, the unwanted dose to lung becomes too large, and such high doses could not be attempted because of an unacceptably high risk of severe radiation pneumonitis. Considering the size of the PTV in most patients with LA-NSCLC, it seems unlikely that escalation to doses around 100 Gy will be possible by IMRT. Therefore, it may be preferable to direct the foci of dose escalation to the regions inside the tumour that are supposed to be the most radiation-resistant. Novel biological imaging techniques, mostly based on positron-emission computed tomography (PET), magnetic resonance imaging (MRI), and magnetic resonance spectroscopy (MRS), may have the potential to construct 3D maps of radiobiologically relevant parameters (Bentzen et al. 2002; Van De Wiele et al. 2003). These maps can be fused with high-resolution computed tomography (CT) and MRI for treatment design and optimisation with a strategy of small-volume focused dose escalation. At Ghent University Hospital, the strategy for clinical trials of focused dose escalation involves the flow of procedures given in Fig. 11.1.5. Anatomical (CT) information on CT (Fig. 11.1.5a) remains the basis for conventional PTV definition. Biological (PET) imaging (Fig. 11.1.5b) provides radiobiological information as signal intensities (SI) to voxels, related to radiobiological parameters such as hypoxia, proliferation, and intrinsic radiation sensitivity. Fusing provides an image (Fig. 11.1.5c) in which each voxel has a Hounsfield value for computation of absorbed dose and an SI for intratumour guidance of the dose distribution. Bioimage-guided-IMRT optimisation requires the development of a transformation engine (Fig. 11.1.5c and Fig. 11.1.5d) that secures a spatial dose variation in the anatomical PTV (Fig. 11.1.5e) as a function of SI in the PET imaging. For the design of early clinical implementation studies, we refer to Fig. 11.1.5d and Fig. 11.1.5e. The D-base in Fig. 11.1.5d means a conventionally applied dose level that encompasses the anatomical PTV. Dose escalation (D+, D++, Dmax) is limited to intra-PTV regions as a function of SI values.

11.1.6 Dose Computation for IMRT Planning

The low density of lung tissue (typically 0.3 g/cm^3) considerably complicates the computation of the dose distribution in the human thorax and deteriorates the accuracy of all conventional computation algorithms. Especially when the beams cross inhomogeneities as air cavities (trachea, bronchi) and tumour tissue in lung, dose planning system calculations using analytical approximations are inadequate (Knoos et al. 1995; Mohan and Antolak 2001).

The lower attenuation of radiation in lung gives rise to a higher dose in the tissues downstream from the lung volume. This effect is adequately taken into account by most dose planning systems. Three counteracting effects, however, are not well modelled in conventional dose calculation algorithms. They are all due to a loss of electron equilibrium: absorbed electrons are not balanced in number by the produced (leaving)

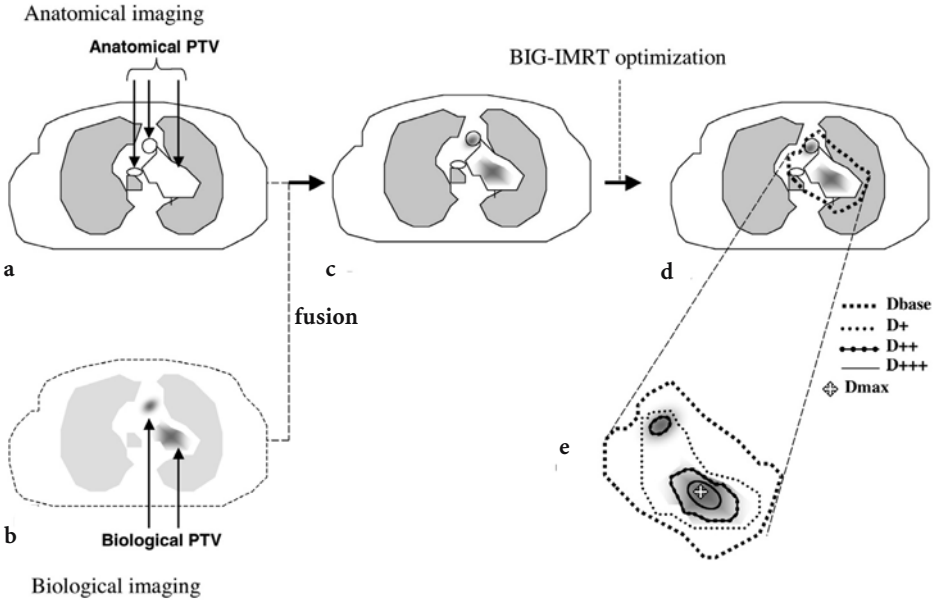


Fig. 11.1.5 Biological image guided intensity modulated radiation therapy (BIG-IMRT). **a** CT scanning provides the anatomical information, resulting in the anatomical PTV. **b** Biological images (e.g. PET) provide information on radiobiological parameters. **c** Image fusion is performed to position the biological on the anatomical information. **d** IMRT is used to irradiate the anatomical PTV to a minimal dose level (Dbase), and to increase the dose selectively within the PTV, dependant on the signal intensities of the biological images (panel **e**).

electrons. In addition, the secondary electrons after single and multiple scattering can deposit their energy at a relatively large distance, i.e. their path lengths are longer in low-density tissues such as lung (Fig. 11.1.6a). The three particular effects are the following:

1. A local dose decrease in regions where the beam reenters the soft tissue (rebuild-up). This rebuild-up is caused by the higher production of secondary electrons in tissue outside the lungs and can be important for beams that traverse lung tissue before hitting the (soft-tissue equivalent) tumour (Fig. 11.1.6b). In the case of small beam width, the underdosage in the rebuild-up region is deepened by the loss of secondary electrons outside the beam's boundaries (Martens et al. 2002).

2. Lateral dose spread in lung tissue beyond the geometrically expected beam boundaries (Fig. 11.1.6c). The reason is that even for modest photon energies, the electron path length in lung tissue is in the order of centimetres. This implies that the beam edges become dosimetrically blurred and that larger volumes of lung are exposed to significant doses (Dirkx et al. 1997; Miller et al. 1998).

3. Underdosage in regions where the tumour flanks air-like tissue at the beam edges because more electrons leave the tumour interface zone than arrive from the air-like tissues (Fig. 11.1.6d) (Dirkx et al. 1997; Miller et al. 1998).

The conventional dose computation algorithms lead to deviations larger than 10% from measurements at lung tissue or bone tissue interfaces and in build-up regions behind air cavities (Mijnheer et al. 1988; Werner et al. 1987). More recent convolution/superposition methods using point spread functions or kernels may provide more accurate dose distributions, dependent on the specific implementation of tissue inhomogeneity corrections (path length corrections and adaptations of point spread functions or kernels in regions with high electron density inhomogeneities).

In most IMRT planning systems, conventional computation algorithms are used during the optimisation process. Inaccuracies in dose computation may lead to erroneous adaptations of beamlet intensities during inverse planning optimisation. The term *convergence error* (Jeraj and Keall 2000) has been used to describe the error in the result of an optimisation algorithm that was misled by inaccurate dose computation. Computer performance limits the possibility to incorporate more accurate dose computation based on convolution-superposition or Monte Carlo algorithms in the optimisation process. Inaccuracies in dose computation and the subsequent convergence error in optimisation have hampered the clinical implementation of IMRT for lung tumours. Two interesting approaches to reduce the convergence er-

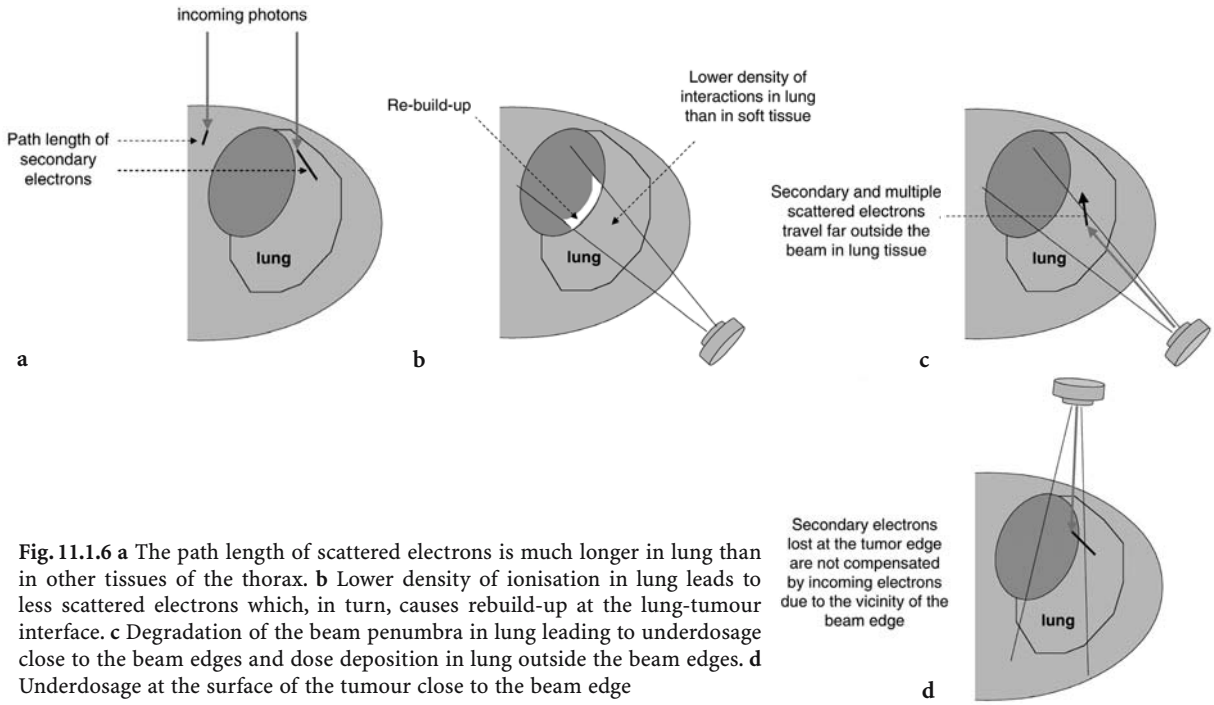


Fig. 11.1.6 a The path length of scattered electrons is much longer in lung than in other tissues of the thorax. **b** Lower density of ionisation in lung leads to less scattered electrons which, in turn, causes rebuild-up at the lung-tumour interface. **c** Degradation of the beam penumbra in lung leading to underdosage close to the beam edges and dose deposition in lung outside the beam edges. **d** Underdosage at the surface of the tumour close to the beam edge

ror have been presented, one by Hong et al. (2002), applicable to fluence optimisation-based inverse planning, and the other by De Gersem et al. (2001b), applicable to direct segment outline (aperture) and weight optimisation.

The method described by Hong et al. (2002) was devised to take into account the scattered dose component during fluence optimisation for the large fields used for whole abdominal irradiation. The iterative process they used (only) included scatter from within a 2-mm radius of a pencil beam kernel. At the end of each optimisation cycle, the dose distribution was recomputed with full scatter contributions. The difference between the accurately computed dose distribution and the dose distribution computed with restricted scatter contribution was used as a correction in the next optimisation cycle, and the process was iterated until further improvement became minimal. The principle the authors described could be used to account for loss of electron equilibrium during optimisation of lung tumours. After each optimisation cycle, leaf sequencing should be performed and the dose distribution recomputed with an appropriate dose algorithm such as convolution/superposition or Monte Carlo.

The method of De Gersem et al. to incorporate accurate dose computation in direct segment outline and weight optimisation is shown in Fig. 11.1.7.

For each chosen incidence, an anatomy-based segmentation tool (ABST) created segments (De Gersem et al. 2001a). By the use of ABST, a starting set of segments is created. For each segment, a 0.4×0.4×0.4-cm^3 dose grid is computed. A starting set of weights is obtained using SWOT, a segment weight optimisation tool previously described (De Gersem et al. 1999). Subsequently, the method of direct segment aperture and weight optimisation (SOWAT, segment outline and weight adapting tool), was applied to optimise the plans (De Gersem et al. 2001b). SOWAT is built to use dose grids computed by an external dose computation engine, as shown in Fig. 11.1.7. The Philips-Pinnacle (Philips Medical Systems, Eindhoven, The Netherlands) convolution-superposition algorithm was used as the external engine. This algorithm allows relatively accurate computing of the dose delivered to lung tissue. Both the penumbra broadening in lung and rebuild-up downstream from lung are well reproduced (Ahnesjo and Aspradakis 1999; Martens et al. 2002). Inside SOWAT, a predefined set of MLC leaf repositioning values is tested according to the algorithm drawn in Fig. 11.1.7. The default set of repositioning values spanned a range of ±1–8-mm (positive values indicate an opening leaf position change; negative values indicate leaf closing). After each leaf position adaptation cycle, monitor units are optimised, and a new repositioning value is set

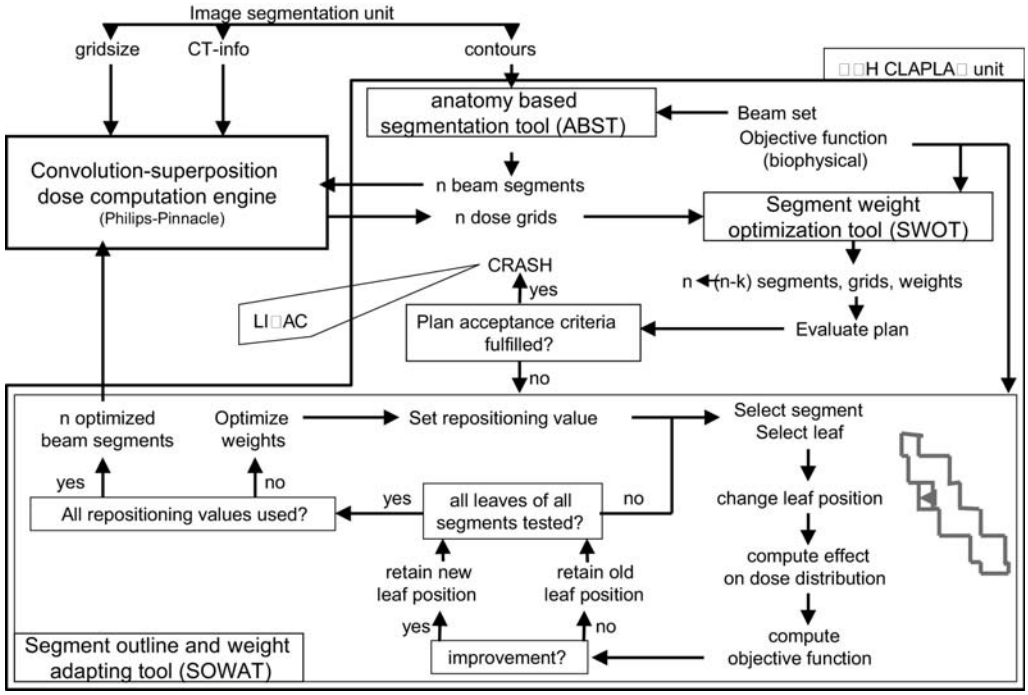


Fig. 11.1.7 Use of a convolution-superposition dose algorithm in IMRT optimisation. Description of the algorithm can be found in the text section 11.1.6 on dose computation for IMRT planning

to execute the next cycle. When all repositioning values have been tested, SOWAT sends beam segments with optimised apertures and weights to the external dose engine to compute the dose grids.

As shown in Fig. 11.1.7, the cycle with passage through SOWAT and the external dose engine is to be reiterated until the plan acceptance criteria are fulfilled. Then, segment sequencing by the CRASH (combine, reorder and step and shoot) tool results in a prescription file for the linear accelerator (De Neve et al. 1999).

11.1.7 Quality Assurance for Clinical Trials

Many of the difficulties regarding the implementation of IMRT in lung cancer clinical trials are being solved. Solutions exist for accurate dose computation in lung and across interfaces between lung and other tissues during optimisation. Respiratory gating techniques become feasible for clinical practice. Accurate delineation of critical organs and pretreatment analysis of toxicity-predicting factors allow for safer application of high-dose schedules. Considering the complexity of the chain of procedures that involves imaging, planning, and optimisation and that finally leads to the instruction files for the linear accelerator, a test system to evaluate whether the execution of the instruction files leads to the calculated dose distribution would be welcome. Polymer gel dosimetry has been used for this purpose (Vergote et al. 2003) and has the advantage of providing 3D quantitative information. However, the cost of gel dosimetry is prohibitive for testing each individual IMRT plan before it is delivered to the patient. More economical systems need to be developed. In a future European Organization for Research and Treatment of Cancer (EORTC) trial, a multipurpose phantom that allows for studying the effects of tissue inhomogeneities on dose deposition will be used (Swinnen et al. 2002). This phantom allows studying key discrepancies between calculations and measurements for each individual intensity-modulated beam. Considering the large variability in IMRT techniques and procedures, practical validation systems of patient-individual treatments will be required for clinical trials of IMRT in lung cancer patients, especially in a multicentre setting.

11.1.8 Conclusions

IMRT may become an important element of future strategies to improve local control and survival in lung cancer. For LD-SCLC as well as for LA-NSCLC, concurrent dose-intensive radiation and chemotherapy seem to be the paradigm. In such schedules, safe delivery of radiation will involve multiple technical improvements including (1) a decrease of the internal margin of the PTV by breathing control techniques, (2) a decrease of the external margin of the PTV by online imaging and correction, (3) use of dose computation algorithms during IMRT optimisation that accurately model electron nonequilibrium, (4) a decrease of the beam aperture by a rind-boost technique, (5) a focused dose escalation to subvolumes, determined by biological imaging, inside the PTV, (6) a better dose prescription and constraint definition to decrease ambiguity in clinical protocols, (7) the development of class solutions for routine clinical implementation, and (8) the development of quality assurance for clinical trials of IMRT in lung cancer.

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11.2 Stereotactic Radiotherapy and Gated Therapy

Hiroki Shirato, Rikiya Onimaru, Masaharu Fujino, Hiroshi Onishi

CONTENTS

11.2.1. Overview

Some patients with early-stage non-small cell lung cancer (NSCLC) have technically operable but medically inoperable tumors, and radiation alone is the treatment of choice for achieving a median survival of 30 months and a 5-year survival of up to 42% for these patients (Zimmermann et al. 2003). However, the local failure rate is still high with conventional local irradiation. Stereotactic irradiation for lung cancers has emerged as an expatiation of stereotactic irradiation for small intracranial metastasis from lung cancers; the technique has achieved a local control rate as good as that achieved with surgical removal (Lax et al. 1994; Blomgren et al. 1995). Extracranial stereotactic irradiation is a technique in which a high dose is focused on an extracranial target using many convergent small beams, with specific devices to constrain the error due to set-up of the patients and internal organ motion. Many of the stereotactic irradiation devices for body disease are using noninvasive localization systems and a variety of methods to reduce the uncertainty due to organ motion. The target volume parameters should be determined by the precise measurement of systematic error and random error for set-up and internal organ motion (Hurkmans et al. 2001), but obtaining these values has not usually been possible in the case of lung tumors because of the large intrafractional organ motion. In practice, a 5-mm planning target volume (PTV) margin in the lateral and anterodorsal direction and a 10-mm margin in the craniocaudal direction for clinical target volume (CTV) are used in many institutions [Lohr et al. 1999; Wulf et al. 2000; Uematsu et al. 2000; Nakagawa et al. 2000; Nagata et al. 2002; Onimaru et al. 2003; Hof et al. 2003; Timmerman et al. 2003).

Even though the margin seems to be large enough in population-based studies, it is usually difficult to verify the accuracy in each treatment in each patient. In fact, the accuracy of stereotactic irradiation of lung tumors may not have been so different from conventional three-dimensional (3D) conformal radiotherapy with the proper set-up (Halperin et al. 1999). If one uses advanced imaging tools, the set-up accuracy may be better than that of irradiation with a rigid body frame. Therefore, there are still many objections to the use of the term "stereotactic irradiation" for radiotherapy with only a rigid body frame in the era of advanced image-guided radiotherapy.

Meanwhile, the promise of the concept of body stereotactic irradiation has persuaded investigators to develop new precision radiotherapy techniques to reduce the uncertainty in localizing soft and moving tumors. Imaging tools and insertion techniques of fiducial markers have made it possible to reduce interfractional set-up error for body tumors (Uematsu et al. 2000; Takai et al. 2001; Uematsu et al. 2001; Onishi et al. 2003; Whyte et al. 2003; Shirato et al. 1999). Respiration-gated radiotherapy has emerged as the tool to reduce intrafractional uncertainty. The localization of lung tumors has moved from

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3D accuracy to four-dimensional (4D) accuracy to account for interfractional and intrafractional temporal changes of anatomy (Shirato et al. 2000a). Real-time tracking of the internal marker with pattern recognition technology and radiotherapy gated to the motion of the marker have made it possible to irradiate the moving lung tumor within a few millimeters of uncertainty (Shirato et al. 2000b; Shimizu et al. 2001; Seppenwoolde et al. 2002; Shirato et al. 2003). Four-dimensional stereotactic irradiation is now possible with real-time tracking radiotherapy (RTRT), with an accuracy of ±1.0 mm and 0.03 sec in the frame of time and space. Focusing the irradiation to a lung tumor in motion, as in the case of treating static brain diseases, is now feasible because of conceptual and technological breakthroughs.

11.2.2 Technical Advances

11.2.2.1 Stereotactic Localization

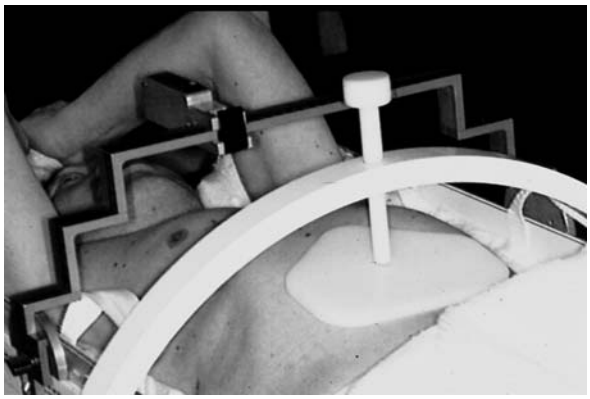
The idea of using a frame with a coordinate for extracranial stereotactic irradiation to treat static brain diseases was proposed by investigators in Karolinska Hospital in the mid-1990s (Lax et al. 1994; Blomgren et al. 1995), and that system became commercially available and has been used clinically (Fig. 11.2.1a). Wulf et al. (2000), Nagata et al. (2002), and Timmerman et al. (2003) have published their results using the fixation device for treating lung tumors. Investigators in Heidelberg, Germany, have also made a stereotactic fixation device and used it for stereotactic single-dose radiotherapy (Lohr et al. 1999; Hof et al. 2003). Negoro et al. (2001) have shown that these devices achieve ± 5 mm set-up accuracy for 75% of patients without radiographic verification, but 25% of patients required correction.

Image-guided localization has been tested with single or hypofractionated high-dose irradiation of lung tumors. Arimoto et al.(1998) have used two orthogonal high-voltage portal images to correct the manual set-up of patients after computed tomography (CT) simulation. Vertebral bony structures can be used as the landmark for patient set-up if they are visible. Round peripheral tumors may be visible, but small tumors with a ground-glass appearance cannot be visualized. Takai et al. (2001) have used implantation of fiducial markers in invisible tumors for this reason. Nagata et al. (2002) have used portal verification with the stereotactic body frame. Nakagawa et al. (2000) have proposed using CT scans with direct therapeutic megavoltage x-rays to verify tumor location. Uematsu et al. (2000) have used diagnostic CT in the treatment room for correcting manual set-up of patients. Slow CT scanning without a breath hold for one slice makes it possible to verify that the tumor is grossly within the PTV. Onishi et al. (2003) have also used the diagnostic CT scan in the treatment room without needing to rotate the table (Fig. 11.2.1b). Using CT scans in the treatment room is increasing worldwide for precise patient set-up (Fung et al. 2003).

11.2.2.2 Gross Tumor Volume and Clinical Target Volume

Timmerman et al. (2003) have adapted the typical method for determining gross tumor volume (GTV) and CTV in their prospective clinical trial of stereotactic irradiation. Using 2- to 5-mm slice CT images in the pulmonary window, both solid tumor areas and those with ground-glass density were targeted. The CTV was identical to the GTV, as no prophylactic treatment was allowed (Onimaru et al. 2003). The PTV, which included set-up uncertainty, was designated from the GTV by enlarging the volume 0.5 cm in the axial plane and 1.0 cm in the craniocaudal plane. The beam apertures were drawn to just encompass the PTV with no margin. Ninety-five percent of the PTV was covered by the 80% prescription isodose volume. Dose constraint to the spinal cord was 18 Gy in three fractions. Hof et al. (2003) used the maximum dose of 5 Gy for the spinal cord and 8 Gy to the esophagus as the dose constraint in single-fraction irradiation. A conventional 3D treatment planning system cannot calculate the precise dose distribution in lung tissue, so the dose is usually prescribed at the isocenter, where the algorism does not influence the calculated results as much.

Determination of GTV and CTV for NSCLC has been improved by a recent rigorous work by Giraud et al. (2000). They have examined the relationship between radiologic and pathologic findings in NSCLC. Using thin slice CT images at the lung setting (level at –700 and window 1,000, personal communication) for peripheral tumors and the soft-tissue setting (level at 40 and window at 400) for central tumors, they found that 95% of the microscopic extension of the tumor is included if one uses an 8-mm CTV margin for adenocarcinoma and a 6-mm margin for squamous cell carcinoma.



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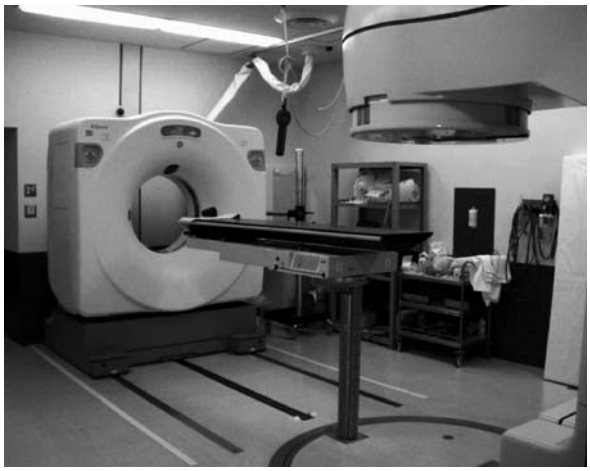

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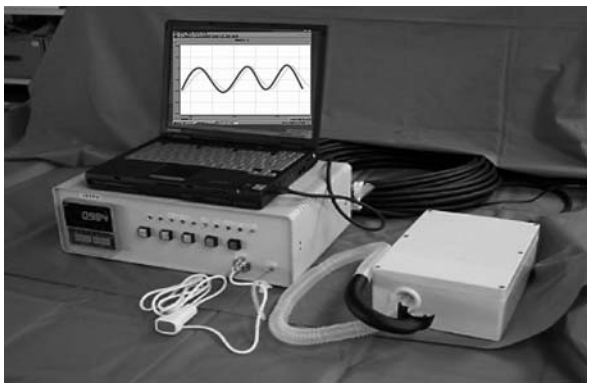

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Fig. 11.2.1a–c Stereotactic and respiratory-gating devices. **a** Stereotactic body frame. **b** CT scanner on the rail in the treatment room. **c** Respiratory-gating device

External beams from a linear accelerator are multiple static beams or dynamic arcs. A total of seven to ten noncoplanar, nonopposing beams are used to deliver a dose to the PTV. Xu (1998) has shown that 7–10 noncoplanar beams are equivalent to multiple arc therapy in small-field stereotactic irradiation of lung tumors.

11.2.2.3 4D Radiotherapy

Because the position of the lung tumor can differ between planning and irradiation, localization of lung tumors should take care of temporal changes in the anatomy. The 4th dimension of accuracy, time, is now often investigated in addition to 3D accuracy in space. Four-dimensional stereotactic irradiation for moving tumors can be characterized by the following four components: (1) 4D treatment planning, (2) 4D set-up, (3) 4D treatment delivery, and (4) 4D treatment verification. Stereotactic irradiation uses some sort of 4D treatment planning. Respiration-gated radiotherapy is an approach for adding 4D set-up and 4D delivery to 4D planning (Fig. 11.2.1c). Real-time tumor-tracking radiotherapy also adds 4D verification (Fig. 11.2.2).

11.2.2.3.1 4D Treatment Planning

There are several approaches for incorporating temporal change of CTV in 4D treatment planning: (1) slow CT scanning that takes longer than one respiratory cycle, (2) gated CT scanning at a respiratory phase, (3) reconstruction of images at a respiratory phase, and (4) breath-hold CT scanning at a respiratory phase. Slow CT scanning is useful for irradiation with normal breathing (Uematsu et al. 2001; Arimoto et al. 1998; van Sornsen de Koste et al. 2003). The gated CT can reduce intra- and interfraction variability of anatomy that is due to respiratory motion, but systematic displacements are observed in some cases between the location of an anatomic feature at simulation and its location during treatment due to delay between signal generation and imaging (Ford et al. 2003). A CT image at a respiratory phase can be reconstructed from a spiral CT to reduce the residual uncertainty in the gated CT scan (Vedam et al. 2003). For real-time tumor-tracking radiotherapy, breath-hold CT scanning or the CT scan reconstructed at a respiratory phase is useful providing that an internal fiducial marker is inserted before the planning CT (Shirato et al. 2000a).

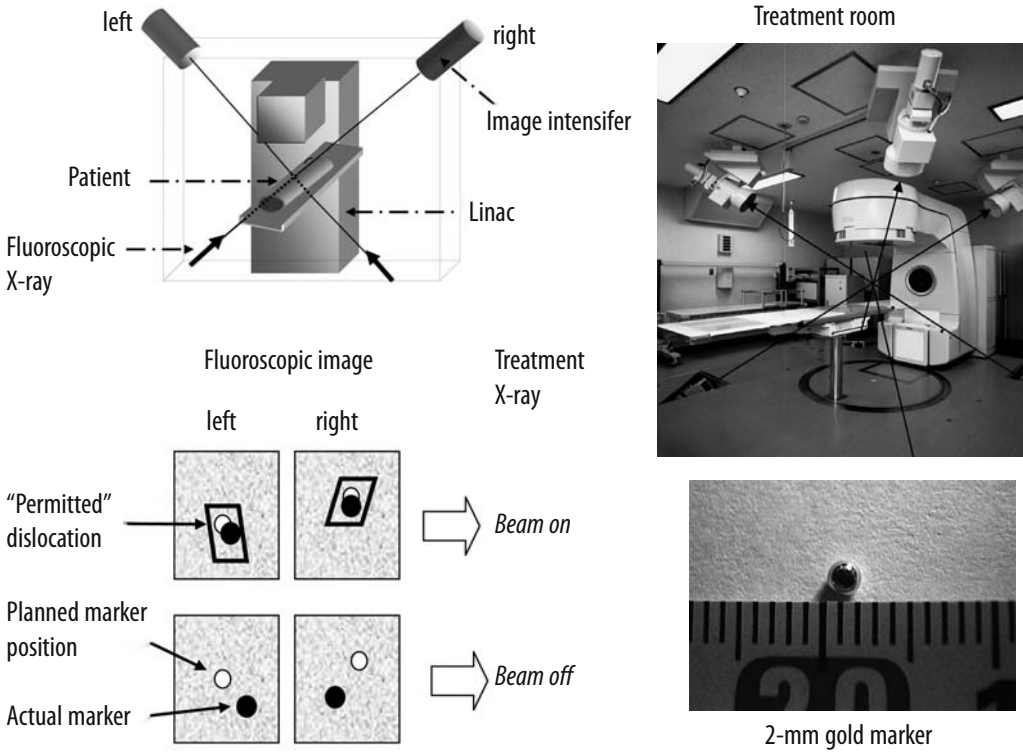

Fig. 11.2.2 Real-time tumor-tracking radiotherapy system. *Left upper* configuration of the RTRT system, right upper the prototype RTRT system, *left lower* concept of the RTRT, *right lower* a 2-mm gold internal fiducial marker

11.2.2.3.2 4D Set-up of Patients

Recent advances in patient set-up have been achieved based on investigations of lung tumor motion. Seppenwoolde et al. (2002) have shown that the trajectory of the tumor motion is unique to each tumor and that the amplitude and hysteresis of the movement differ from one another (Fig. 11.2.3). The baseline of the tumor position relative to the bony structure can change every day and every second due to the patient's emotion, abdominal fullness, and other, unknown factors. The potential for change is understandable because the lung tissue is soft and vulnerable to the position of the diaphragm and the tone of the intercostal muscles, both of which can change voluntarily and involuntarily (Shirato et al. 2004). Real-time tumor-tracking makes it possible to set up the table position at the proper phase of the tumor motion by seeing the tumor trajectory before each treatment (Fig. 11.2.4). Fig. 11.2.4 shows that the trajectory of the same marker near a lung tumor changes day by day.

11.2.2.3.3 4D Delivery

There are several ways to detect one-dimensional or two-dimensional external monitors of respiratory motion (Ohara et al. 1989; Inada et al. 1992; Minohara et al. 2000; Tada et al. 1998; Kubo et al. 2000; Mageras et al. 2001; Zhang et al. 2003). Following the pioneering work of Ohara et al. (1989) on photon therapy, respiration-gated irradiation has been used in Japan in particle therapies (Inada et al. 1992; Minohara et al. 2000). A proton accelerator in Tsukuba was gated by the signals generated by a strain gauge (Inada et al. 1992). This sensor is taped on the patient's flank near the umbilicus for irradiation in the supine position. The heavy ion beam accelerator in Chiba was gated by using a light emitting diode taped to the patient in a manner similar to that used at Tsukuba (Minohara et al. 2000). A position-sensitive detector (PSD) rigidly mounted on the couch tracks the position of a light-emitting diode. Mageras et al. (2001) investigated the efficiency of the PSD and found that the average patient diaphragm excursion was reduced from 1.4 cm (range

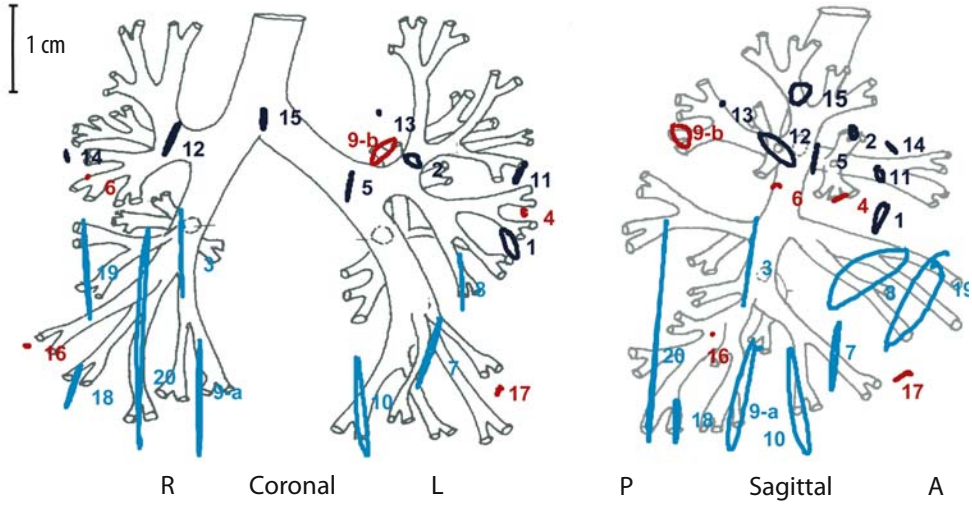

Fig. 11.2.3 Relationship between the tumor position and the trajectory of the tumor. Tumors in the lower lobe (blue) showed a large amplitude, whereas tumors in the upper lobe (black) showed less amplitude. Hysteresis was obvious for tumors near the anterior chest wall. Tumors attatched to some structure did not move so much (red)

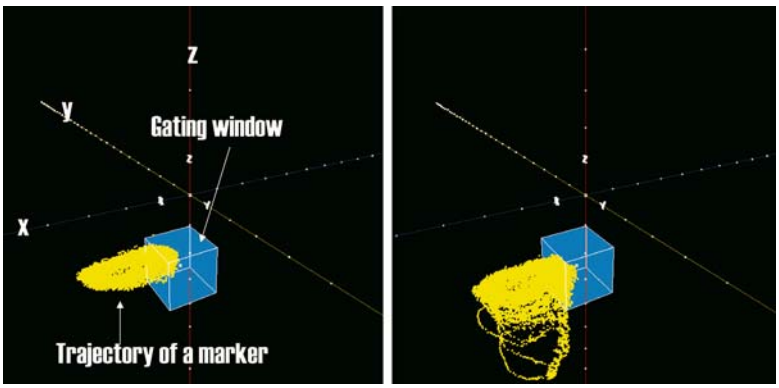

Fig. 11.2.4 Three-dimensional trajectory of the internal gold marker near a lung tumor in the same patient on day 1 and day 2 of radiotherapy, detected by the RTRT system (*dots*). The trajectory varied day by day. The box is the 3D gating window of which coordinates are fixed to the isocenter of the linear accelerator in RTRT

0.7–2.1 cm) without gating and without breathing instruction and to 0.3 cm (range 0.2–0.5 cm) with both gating and breathing instruction. However, they suggest the importance of checking with fluoroscopy for possible time delays in patients with impaired lung function. A physiological monitor such as a spirometer should be used with careful attention to the long-term drift of the baseline during breathing (Zhang et al. 2003).

The shortcoming of respiration-gated radiotherapy is that the internal motion of the tumor may be different from the motion of signals such as those of skin and diaphragm motion. Registration of the internal fiducial marker and motion of the skin surface take place before irradiation, and the motion of the skin surface was used as the gating signal in several studies (Whyte et al. 2003; Kubo et al. 2000; Mageras et al. 2001). This solution requires attention to the fact that the internal motion of lung tumors is not always consistent with the motion of the skin surface in terms of both amplitude and phase.

Harada et al. (2002) have developed a method to insert internal fiducial markers with a diameter of 1.5–2.0 mm in or near a lung tumor through fiberoptic bronchoscopy. Using real-time pattern recognition technology, two sets of fluoroscopy in the RTRT system can detect the 3D position of the markers relative to the isocenter of the linac 30 times a second (Shimizu et al. 2001). A therapeutic beam is gated to irradiate the target only when the marker is located within a permitted dislocation (usually ±1–3 mm) from its planned position. The treatment beam can

be delivered to the tumor with a delay of 0.05 seconds after detecting the tumor position. The tumor can be irradiated at the same phase of respiration in the treatment planning (Seppenwoolde et al. 2002). The system reduces the fundamental uncertainty about temporal changes in the lung tumor's position during irradiation, although there remains uncertainty about the relationship between the tumor and the internal fiducial markers. Three markers are now inserted to reduce the uncertainty about the migration and deformation.

Intensity modulated radiation therapy (IMRT) for lung tumors using the gated radiotherapy technique is attractive for treating relatively large lung tumors that are not treatable with stereotactic irradiation (Hugo et al. 2003). Dynamic IMRT (Neicu et al. 2003) or robotic dynamic chasing irradiation (Kim et al. 2001) has been proposed as a possible approach. These techniques need to overcome the problem of the intra- and interfractional variation of the amplitude and the phase of the respiratory movement before clinical application. Real-time tumor-tracking radiotherapy is now combined with IMRT technology in a treatment known as intensity synchronized radiotherapy (ISRT). With this technique it is possible to irradiate stage III lung cancer with a smaller margin than that included in conventional IMRT. ISRT has been used for the irradiation of a larger lung tumor with ipsilateral hilar and mediastinal involvement, giving 66 Gy in 33 fractions successfully. A prediction model of the respiratory motion is going to be installed in the ISRT system to reduce the amount of fluoroscopic dose in the longer treatment time of ISRT compared with that of RTRT.

11.2.2.3.4 4D Verification

Because inter- and intrafractional changes of amplitude, phase, and baseline of the lung tumor movement are not always predicable, the internal position of the tumor during irradiation delivery should be carefully monitored. Internal fiducial markers and diagnostic x-ray imaging are useful for detecting the difference in the actual position of the internal fiducial marker from its planned position. The real-time tumor-tracking radiotherapy system can detect and record the actual position of internal fiducial markers with the gating parameters 30 times a second during the irradiation. This system enabled us to verify the efficiency of gated irradiation in time and space (Fig. 11.2.5). Intrafractional 4D verification is a key issue in performing adaptive irradiation for tumors in motion with a small PTV margin and dose escalation.

11.2.3 Clinical Results

11.2.3.1 Stereotactic Irradiation

Stereotactic irradiation for lung tumors with a modest number of patients (110 lung tumors in 85 patients) was reported in 1998 by a Japanese research group (Sakamoto and Arimoto 1998). The study consisted of 40 lesions treated with 60 Gy (isocen-

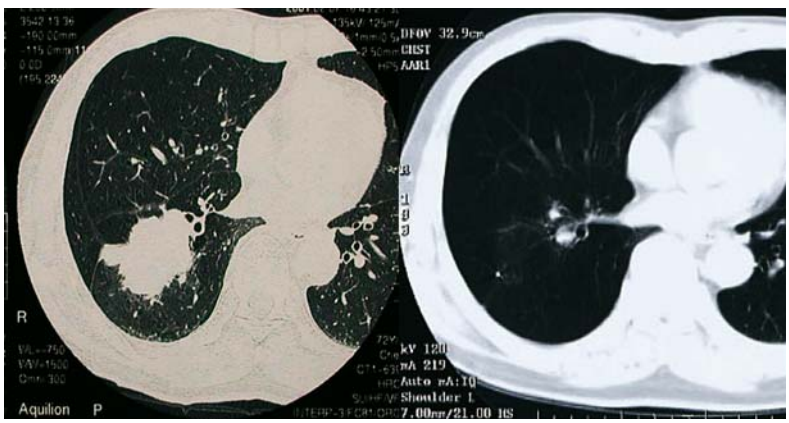

Fig. 11.2.5 Non-small cell lung cancer treated with RTRT giving 48 Gy in four fractions at the isocenter and 90% dose at the periphery of the gross tumor volume. *Left* before radiotherapy, *right* 23 months after treatment

ter) in eight fractions in 35 patients from Kitami Red Cross General Hospital and 70 lesions treated with 50–60 Gy in five to six fractions in 50 patients from Defense Medical College. The former hospital used orthogonal megavoltage portal images, and the latter used a CT scanner in the treatment room for the set-up. Field size was less than 5.5 cm in all patients. There were 48 NSCLC and 62 metastatic lesions. The 1-year local control rate was 93% (56/60) in 60 patients who were followed more than 1 year. Eight patients survived without relapse for more than 3 years. No patients experienced symptomatic radiation adverse effects, although CT scan detected localized pneumonitis in 70% of the lesions at 4.2 months on average. The localized pneumonitis occurred at the 75% isodose volume of the isocenter dose. Pulmonary perfusion scanning was useful for detecting low-perfusion areas in 7/9 patients who did not develop CT-detectable pneumonitis. The study's authors concluded that stereotactic irradiation was safe for lung tumors up to 4.5 cm in the maximum diameter by using 5×5-cm noncoplanar multiple arcs.

Other published data in the literature are shown in Table 11.2.1. Uematsu et al. (2001) have published their results of 50 patients treated with T1-2N0M0 NSCLC at the Defense Medical College. With a median follow-up period of 36 months (range 22–66), the 3-year overall survival rate was 66% in all 50 patients and 86% in the 29 medically operable patients (Fig. 11.2.6a). The 5-year survival rate using stereotactic irradiation reached 72% in the operable patients. No definite adverse reaction was noted except for two patients with minor bone fractures and six patients with temporary pleural pain. Nagata et al. (2002) have reported that the 2-year overall survival rate was 79% for T1N0M0 using a stereotactic body frame giving 48 Gy/4 fractions/5–13 days. No local relapse or symptomatic complications were noted. Timmerman et al. (2003) have reported that the maximum tolerated dose for T1 and T2 (<7 cm) N0M0 NSCLC has been higher than 60 Gy in three fractions from their phase I study in 37 patients. A patient with a T1 tumor and a patient with a T2 tumor experienced grade 3 hypoxia requiring oxygen after 48 Gy/3 Fr and 42 Gy/3 Fr, respectively, and they did not experience grade 3 hypoxia following treatment. A single patient experienced grade 3 radiation dermatitis with skin redness, peeling, and discomfort along the entrance trajectory of each treatment beam. Hof et al. (2003) at the German Cancer Research Center reported that 8/10 patients with stage I NSCLC were locally controlled with a median follow-up period of 15 months. They used 19–26 Gy at the isocenter with an 80% isodose surrounding the PTV tightly in a single fraction.

Several Japanese institutions began using stereotactic irradiation for stage I NSCLC in the late 1990s. Although the fractionation schedule has not been standardized, the investigators noticed that the difference in the techniques and schedule, in fact, might not be so important as long as the treated volume is restricted. Recently, they retrospectively studied their experience with stage I NSCLC in a multi-institutional survey (Onishi et al. 2003) that included 245 patients from 13 institutions. There were 110 squamous cell carcinomas, 109 adenocarcinomas, and 26 tumors of other pathology for a total of 155 stage IA (T1N0M0) and 90 stage IB (T2N0M) diseases. Age was distributed from 35 to 92 (median 76) years old. Performance status was 0 in 94, 1 in 104, and 2 in 47 patients. One hundred and forty-nine patients suffered from pulmonary diseases such as emphysema, and 158 tumors were judged inoperable. Tumor diameter was 7–58 (median 28) mm. Vacuum pillows were used in five institutions, a body frame was used in four institutions, and an image-guided localization system with-

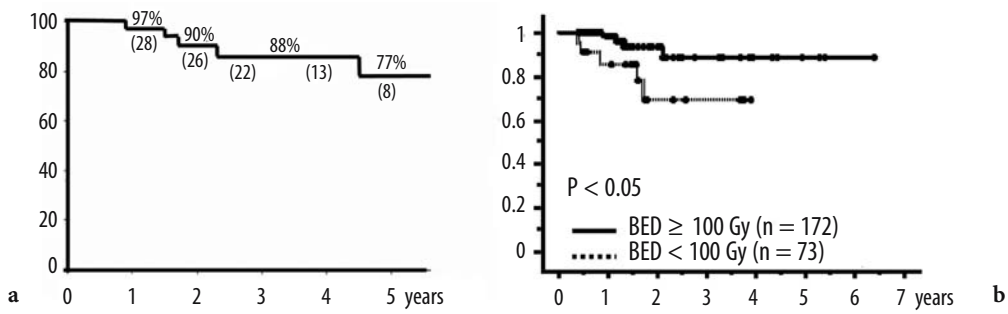

Fig. 11.2.6a,b Clinical outcome of patients with T1N0M0 non-small cell lung cancers treated with stereotactic irradiation in Japan. **a** Actuarial overall survival of 29 operable patients treated by stereotactic irradiation (from Uematsu et al. 2001). **b** The overall survival of 64 operable patients treated with biological effective dose (BED) ≥100 Gy and 23 patients treated with BED <100 Gy. (from Onishi et al. 2003).

Table 11.2.1.

Author (ref)	No of lesions (patients)	Dose / fractionation / days	Prescription	Tumor diameter (cm)	Follow-up period (range, median)	Crude local control (All lesions)	Crude local control (NSCLC)	Actuarial 3-year survival (NSCLC)	Adverse events (NCI-CTC equivalent)
Arimoto et al. (25)	40 (35)	60 Gy / 8 / 11	isocenter	<4.5	6–54	31/33 (94%)	–	60.4% (includes metastasis)	No grade 3 or more
Blomgren et al. (3)	17 (13)	23–68 Gy / 1–3	65%-isodeose	1.8–7.2 (3)	4–25, 8	16/17 (94%)	3/3 (100%)	–	Grade 3; Chronic cough (6%)
Uematsu et al. (51)	66 (45)	30–76 Gy / 5–15 / 5–20	80%-isodose	0.8–4.8 (2.5)	3–31,11	64/66 (97%)	22/23 (96%)	–	No grade 3 or more
Nakagawa et al. (7)	22 (15)	18–25 Gy /1/1	"periferal dose"	<1.1cm	0.8–82, 8	21/22 (100%)	21/22 (100%)	–	No grade 3 or more
Uematsu et al. (15)	50 (50)	50–60 Gy / 5–10 / 5–11	80%-isodose	0.8–5.0 (3.2)	22–66,36	–	47/50 (96%)	66% in T1-2N0M0 (86% in operable patients)	minor rib fracture (4%), temporal chest pain (12%)
Wulf et al. (52)	27 (27)	30Gy / 3 / 4–8	65%-isocenter	<8.0	2–33, 8	23/27 (85%)	7/8(88%)	–	Grade 3: esophageal ulcer (4%) Grade 5: bleeding from pulmonary artery (4%)
Nagata et al. (8)	43 (40)	40–48 Gy / 4 / 5–13	isocenter	<4.0	4–37,19	31/33 (94%)	16/16 (100%)	79% at 2-year (T1N0M0)	No grade 3 or more
Hara et al. (53)	23 (19)	20–30 Gy / 1 / 1	Min dose to GVT	<4.0	3–24,13	19/23 (83%)	5/5 (100%)	–	Grade 3: hypoxia requiring oxygen (4%)
Whyte et al. (17)	23 (23)	15 Gy / 1 / 1	80%-isodose	1-5	1–26,7	21/23 (91%)	–	–	Pneumothorax due to marker insertion (13%)
Onimaru et al. (9)	57 (45)	48–60 Gy / 8 / 11	isocenter	0.6–6.0 (2.6)	2–44,18	50/57 (88%)	20/25 (80%)	85% at 2-year (T1-2N0M0)	Grade 5: esophageal ulcer (2%)
Hof et al. (10)	10 (10)	19–26 Gy / 1 / 1	isocenter	<1.6	8–30,15	–	8/10 (80%)	–	No grade 2 or more
Lee et al. (54)	34 (28)	30–40 Gy / 3–4 / 3–4	90%-isodose	0.7-7.4(4.2)	7–35,18	31/34 (91%)	8/9 (89%)	–	No grade 2 or more
Timmerman et al. (11)	37 (37)	24–60 Gy / 3 / 8–16	80%-isodoe	<7.0	2–30,15	–	31/37 (84%)	–	Grade 3 dermatitis (3%), Grade 3 hypoxia (5%)

out immobilization devices was used in four institutions. Devices to reduce respiratory motion by breath hold, abdominal pressure, or gating technique were used in seven institutions. Multiple static ports were used in seven institutions, and a dynamic arc using megavoltage x-ray beams was used in six institutions. Single irradiation was used in two institutions, and hypofractionation was used in 11 institutions. Many fractionation schedules were used in each institution, and their biological effective dose ranged from 57 to 180 (median 108) Gy. Conventional irradiation of 30–44 Gy/15–20 fractions was used additionally in 27 (11%) patients. During the follow-up of 7–78 (median 24) months, pulmonary complications greater

than NCI-CTC criteria grade 2 were noted in only six (2.4%) patients. The local progression occurred in 33 (14.5%) patients, and a lower local recurrence rate was observed (8.1% vs. 26.4%, p=0.04) when the biological effective dose (BED) was ≥100 Gy compared with BED <100 Gy. The 3-year overall survival rate of medically operable patients was 88.4% vs. 69.4% (p<0.05) when BED was ≥100 Gy vs. <100 Gy (Fig. 11.2.6b), respectively. The 88% 3-year overall survival rate in operable patients treated with BED ≥100 Gy was consistent with the single institutional results, 88% in the 29 operable patients, by the Medical Defense College, whose patients were not included in this multi-institutional survey. Based on these clinical results, the Japanese Clinical Oncology Group has prompted a multi-institutional prospective single-arm phase II study of the use of 48 Gy/4 Fr STI for T1N0M0 NSCLC.

Most of the studies examined the treatment of peripheral lung tumors. In the early Japanese study group reported in 1998, 10 patients with centrally located lung tumors showed no radiation injury within the maximum follow-up period of 36 months (Sakamoto and Arimoto 1998). However, Wulf et al. (2001) reported that two patients with a central lung tumor experienced serious late morbidity. One patient showed chronic ulcerous esophagitis 4 months later, occurring in the lower esophagus adjacent to the tumor, after 28 Gy in four fractions at 65% isodose. Another patient had fatal bleeding from the right pulmonary artery after 30 Gy (65% isodose) in three fractions for a relapsed tumor that had already received 63 Gy. Onimaru et al. (2003) reported a fatal bleeding from an esophageal ulcer 5 months after stereotactic irradiation of 48 Gy in eight fractions to the 3.0-cm central lung tumor, with the dose given to 1 cc of the esophagus at 42.5 Gy in eight fractions. These findings are consistent with the report from Hayakawa et al. (1996), who reported that 80 Gy in 40 fractions or more caused the development of severe stenosis of the proximal bronchus in 42% (5/12) of patients. At present, it is not certain whether high-dose stereotactic irradiation with a small PTV is safe enough for central lung tumors.

11.2.3.2 Gated Radiotherapy

Although there have been many technical publications about gated radiotherapy, clinical reports of gated x-ray radiotherapy for lung cancers are still sparse. Hara et al. (2002) have used laser monitoring of the chest wall for gating in 23 malignant lung tumors <40 mm in diameter. Using a stereotactic set-up, they obtained a local progression-free state in 7/10 patients treated with <30 Gy minimum GTV dose in a single fraction and in 12/13 patients treated with 30 Gy, with a follow-up of 3–24 months (median 13).

Harada et al. (2002) have reported their early experiences using RTRT for 12 lung tumors, showing the feasibility of bronchofiberscopic insertion of the fiducial markers. Shirato et al. (2003) have reported that the marker was successfully inserted and used for RTRT in 38/41 peripheral lung tumors without any serious complications related to marker insertion. Fujino et al. (2003) have reported on 42 lesions in 37 patients with lung tumors who were entered into an RTRT feasibility study in 1999 and 2002 with 40 NSCLC and two metastatic adenoid-cystic carcinomas. Giving 35 Gy (eight patients) or 40 Gy (23 patients) in four fractions with a very tight PTV margin (1–5 mm) without consideration for CTV margin for GTV, eight local or marginal relapses were noted in the 31 patients within a median follow-up of 16 months (range 4–35). The rate of marginal/local relapse was higher than that in the experience with non-gated stereotactic irradiation (Onimaru et al. 2003; Fukumoto et al. 2002). However, in recent results of RTRT with a CTV margin of 8 mm for adenocarcinoma and 6 mm for squamous cell carcinoma, there were no relapses during the median follow-up of 8 months (range 6–16) after RTRT (Fujino et al. 2003). Those results suggest that precisely gated irradiation using an RTRT system requires serious attention to the subclinical extension of the tumor that overlaps the margin for organ motion in non-gated radiotherapy. More careful dose-finding investigation of RTRT is now underway in the other eight Japanese hospitals that have installed the same system.

In conclusion, the benefit of gated radiotherapy and RTRT is not yet certain compared with that of using non-gated stereotactic irradiation for small peripheral tumors. The real benefit of gated radiotherapy will probably be apparent for treating larger tumors that are not candidates for non-gated stereotactic irradiation. Careful clinical studies are certainly required to estimate the benefit of this exciting technique to justify the cost and the effort. However, because the nature of the radiotherapy is to be more precise in time and space, 4D radiotherapy may eventually become one of the standard treatments. It is the same as the case with 3D radiotherapy, which has been improved without statistical confirmation

of its superiority to conventional radiotherapy (Suit 2002). Four-dimensional radiotherapy is now challenging clinicians, who must determine how to use it properly.

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11.3 Novel Substances in the Treatment of Lung Cancer for the Radiation Oncologist

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CONTENTS

11.3.1 Introduction

Radiotherapy has been a major treatment modality for regionally confined lung cancers. The rate of treatment failure is still high, particularly for large tumors or advanced disease, which lowers the overall tumor response rate to radiotherapy and the patient survival. Improvements in radiotherapy have been made both in technological innovations, allowing delivery of higher radiation doses to the tumor or lower doses to normal tissues, and in the implementation of strategies that modulate the biological response of tumors or normal tissues to radiation. The latter strategies include altered fractionation of radiotherapy, combined modality therapy using systemic chemotherapy or biological agents, and, more recently, targeting of molecular processes and signaling pathways that have become dysregulated in cancer cells.

The combination of chemotherapeutic drugs with radiation has had a significant impact on current radiotherapy practice for non-small cell lung cancer (NSCLC). This combination has been used for many years but has now become a common treatment option for lung cancer patients. This is particularly true for concurrent chemoradiotherapy, which in many recent clinical trials has been shown to be superior to radiotherapy alone in controlling local-regional disease and in improving patient survival. Combining chemotherapeutic drugs with radiotherapy has a strong biologic rationale. Such chemotherapeutic agents reduce the number of tumor cells undergoing radiotherapy by their independent cytotoxicity and often render tumor cells more susceptible to killing by ionizing radiation. An additional benefit of combined treatment is that chemotherapeutic drugs, by virtue of their systemic activity, may also act on subclinical metastatic disease. Most chemotherapeutic drugs have been chosen for combination with radiotherapy based on their known effectiveness in lung cancer. Alternatively, agents that are effective in overcoming resistance mechanisms associated with radiotherapy could be chosen. There have been improvements in clinical outcome with concurrent chemoradiotherapy using traditional drugs, such as cisplatin, and these studies have led to extensive research on exploring newer chemotherapeutic agents for their interactions with radiation. A number of new potent chemotherapeutic agents, including taxanes, nucleoside analogs, and topoisomerase inhibitors, have entered clinical trials or practice. Preclinical testing has shown that they are potent enhancers of radiation response and thus might improve the therapeutic outcome of chemoradiotherapy. Also, rapidly emerging molecular targeting strategies are aimed at improving the efficacy of chemoradiotherapy.

This chapter reviews the biologic rationale and principles fundamental to the use of radiotherapy

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with systemic therapy, the knowledge of which is essential in developing the optimal treatment strategies. It also overviews novel biologic therapy combined with radiotherapy in the treatment of NSCLC.

11.3.2 Current Strategies in Chemoradiotherapy

The goals of combining chemotherapy with radiotherapy in the management of lung cancer are to increase patient survival by improving local-regional tumor control and by reducing distant metastases. Combined modality treatment can further improve positive therapeutic outcome of individual treatments through a number of specific strategies, which Steel and Peckham (1979) classified into four groups: "spatial cooperation," independent toxicity, enhancement of tumor response, and protection of normal tissues.

"Spatial cooperation" was the initial rationale for combining chemotherapy with radiotherapy, where the action of radiation and chemotherapeutic drugs is directed towards different anatomical sites. Localized tumors would be the domain of radiotherapy, as large doses of radiation can be given. On the other hand, chemotherapeutic drugs are likely to be more effective in eliminating disseminated micrometastases. Thus, the cooperation between radiation and chemotherapy is achieved through the independent action of two modalities. The concept of "spatial cooperation" is also applied in the treatment of hematological malignancies that have spread to "sanctuary" sites such as the brain. These sites are poorly accessible to chemotherapeutic agents, and thus they are more appropriately treated with radiotherapy.

Independent toxicity is another important strategy for increasing the therapeutic ratio of chemoradiotherapy. Normal tissue toxicity is the main dose-limiting factor for both chemotherapy and radiotherapy. Therefore, combinations of radiation and chemotherapy would be better tolerated if drugs were selected such that toxicities do not overlap with, or minimally add to, radiation-induced toxicities. This strategy requires a thorough knowledge of chemotherapy toxicity, underlying mechanisms, and drug pharmacokinetics. Careful drug selection based on these mechanisms may minimize normal tissue damage while retaining tumoricidal efficacy when combined with radiotherapy.

Another strategy in chemoradiotherapy is to exploit the ability of chemotherapeutic agents to enhance tumor response to radiotherapy. The enhancement denotes the existence of interaction between chemotherapeutic drugs and radiation at the molecular, cellular, or metabolic level, resulting in an antitumor effect greater than would be expected on the basis of additive actions of chemotherapy and radiotherapy. The enhancement must be selective or preferential to tumors compared to critical normal tissues in order to achieve therapeutic gain. The ability of chemotherapeutic agents to enhance tumor radioresponse by counteracting factors associated with tumor radioresistance is a major rationale for concurrent radiotherapy.

An additional strategy is to protect normal tissues in order to deliver higher doses of radiation to the tumor. This protection can be achieved through technical improvements in radiation delivery or administration of drugs that exert increased protection of normal tissues against the damage by radiation or drugs.

11.3.3 Drug-Radiation Interactions

11.3.3.1 Radiation-Induced Damage

Radiation induces many different effects on DNA, which is the critical target for radiation damage. The effect may include single-strand breaks, double-strand breaks (DSBs), base damage, and DNA-DNA and DNA-protein cross-links. DSBs and chromosome aberrations that occur in association with or as a consequence of DSBs are generally considered to be the principal damage that ultimately results in cell death (Radford 1986). Any agent that makes DNA more susceptible to radiation damage may enhance cell killing. Certain drugs, such as halogenated pyrimidines, incorporate into DNA and make it more susceptible to radiation damage (Kinsella et al. 1987).

11.3.4 Inhibition of Cellular Radiation Injury Repair

Both sublethal (SLDR) (Elkind and Sutton 1959) and potentially lethal (PLDR) (Little et al. 1973) damages caused by radiation can be repaired. SLDR is rapid, with a half-time of about 1 hour, and is usually complete within 6 hours after irradiation. This

time between two radiation fractions allows radiation-induced DSBs in DNA to rejoin and repair. SLDR is expressed as the restitution of the shoulder on the cell survival curve for the second dose. PLDR occurs when environmental conditions prevent cells from dividing. Preventing cells from division allows completion of repair of DNA lesions that would have been lethal had DNA undergone replication shortly after irradiation. PLDR is considered to be a major determinant responsible for radioresistance in some tumor types, such as melanomas.

Many chemotherapeutic agents used in chemoradiotherapy interact with cellular repair mechanisms and inhibit repair, and hence may enhance cell or tissue response to radiation. For example, halogenated pyrimidines enhance cell radiosensitivity not only through increasing initial radiation damage but also by inhibiting cellular repair (Kinsella 1987; Wang et al. 1994). Nucleoside analogs, such as gemcitabine, are a potent in inhibitor of the repair of radiation-induced DNA and chromosome damage (Plunkett et al. 1995; Lawrence et al. 1997; Gregoire et al. 1999; Milas et al. 1999a).

11.3.5 Cell Cycle Redistribution

Both chemotherapeutic agents and radiation are more effective against proliferating than nonproliferating cells. Their cytotoxicity further depends on the position of cells in the cell cycle. Terasima and Tolmach (1963) reported that radiosensitivity of cells varied widely depending on which phase of the cell cycle the cells were in at the time of irradiation. Cells in the G_2 and M cell cycle phases were about three times more sensitive than cells in the S phase. The exact mechanism for this variability is still unknown.

The influence of cytotoxic agents on the cell cycle can be therapeutically exploited in chemoradiotherapy by using cell cycle redistribution strategies. For example, some chemotherapeutic drugs, such as taxanes, can block transition of cells through mitosis. This results in accumulation of cells in the radiosensitive G_2 and M phases of the cell cycle. The enhanced radioresponse of cells can be demonstrated in vitro (Tishler et al. 1992; Choy et al. 1993) and of tumors in vivo (Milas et al. 1995, 1999b). However, this cell-cycle mechanism of taxane-induced enhancement of tumor radioresponse is dominant only in tumors that are resistant to paclitaxel or docetaxel as a single treatment. Although the drug does not substantially affect tumor growth in taxane-resistant tumors, tumors do exhibit significant transient accumulation of cells in mitosis 6–12 hours after the treatment (Milas et al. 1999b).

Elimination of the radioresistant S phase cells by the chemotherapeutic agents may be another cell-cycle redistribution strategy in chemoradiotherapy. Nucleoside analogs, such as fludarabine or gemcitabine, are good examples of the agents that become incorporated into S phase cells and eliminate them by inducing apoptosis (Gregoire et al. 1999; Milas et al. 1999a). In addition to purging S-phase cells, the analogs induce the surviving cells to undergo parasynchronous movement to accumulate in G_2 and M phases of the cell cycle between 1 and 2 days after drug administration, a time when the highest enhancement of tumor radioresponse is observed (Milas et al. 1999a).

Tumors with a high cell growth fraction are likely to respond better to the cell-cycle redistribution strategy in chemoradiotherapy than tumors with a low cell growth fraction.

11.3.5.1 Tumor Hypoxia and Radioresistance

Solid malignant tumors often display abnormal vascularization, both in the number of blood vessels and vessel function. The blood supply to tumor cells may be inadequate, and multiple tumor microregions may be hypoxic, acidic, and eventually necrotic. Hypoxia occurs at distances from blood vessels >100–150 ìm. The hypoxic cell content in tumors varies widely and can be more than 50%. The presence of hypoxia may induce aggressive and virulent tumor cell variants and stimulate metastatic spread (Brizel et al. 1996; Brown and Giaccia 1998). Hypoxic cells are 2.5–3 times more resistant to radiation than well-oxygenated cells. The fact that hypoxia may be a critical factor in radiotherapy is suggested by the findings that reduced hemoglobin levels (Bush et al. 1978) and low tumor pO_2 (Hockel et al. 1993; Nordsmark et al. 1996) are associated with higher treatment failure rates in some tumors. Also, there are reports showing that local tumor control by radiotherapy can be improved by the use of hypoxic cell radiosensitizers (Dische 1988) or hyperbaric oxygen (Henk and Smith 1977). With respect to the effects of chemotherapy, hypoxic regions are less accessible to chemotherapeutic drugs; in addition, hypoxic tumor cells are either nonproliferating or proliferate poorly and as such do not respond well to chemotherapy.

Combining chemotherapeutic agents with radiotherapy can reduce or eliminate hypoxia or its negative influence on tumor radioresponse. Most chemotherapeutic drugs preferentially kill proliferating cells, which are primarily found in well-oxygenated regions of the tumor. Because these regions are located at a close proximity to blood vessels, they are easily accessible to chemotherapeutic agents. Destruction of tumor cells in these areas will lead to an increased oxygen supply to hypoxic regions and hence reoxygenate hypoxic tumor cells. Massive loss of cells after chemotherapy lowers the interstitial pressure, which then allows reopening of previously closed capillaries and reestablishment of blood supply. It also causes tumor shrinkage so that previously hypoxic areas are closer to capillaries and thus accessible to oxygen. Finally, by eliminating oxygenated cells, more oxygen becomes available to cells that survived chemotherapy. It was recently shown that tumor reoxygenation is a major mechanism underlying the enhancement of tumor radioresponse induced by taxanes in tumors sensitive to these drugs (Milas et al. 1995).

Another approach to counteract the negative impact of hypoxia is selective killing of hypoxic cells through bioreductive drugs, such as tirapazamine (Brown and Giaccia 1998), which undergo reductive activation in a hypoxic milieu, rendering them cytotoxic. A related possibility is exploiting the acidic state (low pH) of tumors – which develops as a result of hypoxia-driven anaerobic metabolism that produces lactic acid (Vaupel et al. 1989) – through the use of drugs that selectively accumulate in acidic environments or become activated by low pH (Tannock and Rotin 1989).

One of the newer agents to counteract tumor hypoxia is RSR13. RSR13 (efaproxiral) is a synthetic small molecule that enhances the diffusion of oxygen to hypoxic tumor tissues from hemoglobin. It allows the partial pressure of oxygen to increase in tumor tissues to enhance the efficacy of radiation therapy and certain chemotherapeutic drugs. Preclinical studies have demonstrated that RSR13 increases normal tissue oxygenation, reduces tumor hypoxia, and improves the efficacy of radiation therapy. Preliminary clinical results using RSR13 have been reported for locally advanced inoperable stage IIIA-IIIB NSCLC (Hak Choy et al. 2001). All patients received two cycles of induction chemotherapy that consisted of paclitaxel 225 mg/m^2 and carboplatin AUC 6, followed by thoracic radiation therapy at a total dose of 64 Gy delivered in 32 fractions with concurrent daily infusion of RSR13 at a dose of 50–100 mg/kg. The overall response rate was 88.6%, with a 1-year survival of 64.7 %. There is currently a phase III randomized trial testing the role of RSR13 in stage III NSCLC.

11.3.5.2 Inhibition of Tumor Cell Repopulation

The constant balance between cell production and cell loss maintains the integrity of normal tissues. When this balance is disturbed by cytotoxic action of chemotherapeutic drugs or radiation, the integrity of tissues is reestablished by an increased rate of cell production. The cell loss after each fraction of radiation during radiotherapy induces compensatory cell repopulation, the extent of which determines tissue tolerance to radiotherapy. In contrast to normal tissues, malignant tumors are characterized by imbalance between cell production and cell loss in favor of cell production. And, as with normal tissues, tumors also respond to radiation- or drug-induced cell loss with a compensatory regenerative response. Preclinical studies have provided evidence demonstrating that the rate of cell proliferation in tumors treated by radiation or chemotherapeutic drugs is higher than that in untreated tumors (Hermens and Barendsen 1978; Stephens and Steel 1980; Milas et al. 1994). This increased rate of treatment-induced cell proliferation is commonly termed accelerated repopulation. Accelerated repopulation of tumor clonogens has been shown to occur during clinical radiotherapy as well. Withers et al. (1988) showed that the total dose of radiation needed to control 50% of head and neck carcinomas progressively increased with time whenever radiotherapy treatment was prolonged beyond 1 month. This increase in radiation dose required to achieve tumor control was greater than what would be anticipated based on the pretreatment tumor volume doubling time of about 60 days for head and neck tumors. The increase was attributed to accelerated repopulation, and it was estimated to average about 0.6 Gy/day (Withers et al. 1988) but may be as high as 1 Gy/day (Taylor et al. 1990).

Although accelerated cell proliferation is beneficial for normal tissues because it spares them from radiation damage, it has an adverse impact on tumor control by radiotherapy or chemotherapy. Therefore, any approach that reduces or eliminates accelerated clonogen repopulation in tumors would improve radiotherapy. Chemotherapeutic drugs, because of their cytotoxic or cytostatic activity, can reduce the rate of proliferation when given concurrently with radio-

therapy, and hence increase the treatment's effectiveness. Caution must be taken to select drugs that preferentially affect rapidly proliferating cells and that preferentially localize in malignant tumors. However, the main limitation of concurrent chemoradiotherapy is the enhanced toxicity of rapidly dividing normal tissues because most available chemotherapeutic agents show poor tumor selectivity. Experimental evidence suggests that drug-induced accelerated cell repopulation can actually make the tumor more difficult to control with radiation (Stephens and Steel 1980; Milas et al. 1994).

11.3.5.3 Emerging Strategies for Improvement in Chemoradiotherapy

Despite increasing therapeutic achievements of chemoradiotherapy for patients with NSCLC, the use of this form of therapy is still very much restricted by its narrow therapeutic index. The available agents are either insufficiently effective on their own or in combination with radiation against tumors, or normal tissue toxicity prevents the use of effective doses of drugs or radiation. Significant preclinical and clinical research has been undertaken to improve chemoradiotherapy, and includes the development of more selective and more effective chemotherapeutic agents. In addition, drugs that either protect normal tissues from injury by drugs or radiation or that selectively target molecular processes responsible for tumor radio- or chemoresistance have been developed.

11.3.5.4 Timing of Therapy

Induction chemotherapy has resulted in therapeutic improvement in a number of clinical trials when compared to radiotherapy, but in general the therapeutic benefits are below expectations. A number of factors could account for this, including accelerated repopulation of tumor cell clonogens and selection or induction of drug-resistant cells that are cross-resistant to radiation. The preclinical findings provide solid evidence for the existence of accelerated repopulation in tumors treated with chemotherapeutic agents. Although development of drug resistance is a significant problem in chemotherapy, a similar degree of evidence that cells that acquire chemotherapy resistance are also resistant to radiation is lacking.

Concurrent chemoradiotherapy consists of administering chemotherapeutic agents during a course of radiotherapy. Concurrent treatment is intended to treat both the metastatic foci and the primary tumor. In addition, it incorporates the advantage of drug-radiation interactions to maximize tumor radioresponse. The drug scheduling in relation to radiation fractions is important. The selection of optimal timing of drug administration must be based on multiple factors, including mechanisms of tumor radioenhancement by a given drug, the drug's normal tissue toxicity, and conditions under which the highest enhancement is achieved. The data from preclinical studies contribute to the selection of the most optimal schedules. For example, it has been demonstrated that murine tumors sensitive to taxanes show enhanced radioresponse when the drug treatment precedes radiation by 1–3 days (Milas et al. 1999b). A major mechanism for tumor radioenhancement was reoxygenation of hypoxic cells. Based on this preclinical information, one would anticipate that in clinical protocols such tumors would best respond to a bolus of a taxane given once or twice weekly during radiotherapy. In contrast, tumors resistant to taxanes may benefit from daily administration of a taxane, since they show accumulation of radiosensitive G2 and M cells 6–12 hours after drug administration. If the objective is to counteract rapid repopulation of tumor cell clonogens induced by radiation, then administration of cell-cycle-specific chemotherapeutic agents during the second half of radiotherapy might be more effective. Optimal scheduling is essential in concurrent chemotherapy, not only to maximize tumor radioresponse but also to minimize toxicity to critical normal tissues. The enhancement in normal tissue complications remains the major limitation of concurrent chemoradiotherapy. Nevertheless, concurrent chemoradiotherapy has provided better clinical results both in terms of local tumor control and patient survival than have other modes of chemoradiotherapy combinations (Munro 1995; Morris et al. 1999). (See Table 11.3.1.)

11.3.5.5 Increasing Antitumor Efficacy of Existing Chemotherapeutic Drugs

A number of chemotherapeutic agents are effective against lung cancer and are potent radiosensitizers. Among these are taxanes, nucleoside analogs, and topoisomerase inhibitors. However, normal tissue toxicity is still a major limitation for the effective use

Table 11.3.1 Advantages and disadvantages of different chemoradiation sequencing strategies

Strategy	Advantages	Disadvantages
Sequential chemoradiation	• Least toxic • Maximize systemic therapy • Smaller radiation fields if induction shrinks tumor	• Increased treatment time • Lack of local synergy
Concurrent Chemoradiation	• Shorter treatment time • Radiation enhancement	• Compromised systemic therapy • Increased toxicity • No cytoreduction of tumor
Concurrent chemoradiation and posterior chemotherapy	• Maximize systemic therapy • Radiation enhancement • Both local and distant therapy delivered upfront	• Increased toxicity • Increased treatment time • Difficult to complete chemotherapy after chemoradiation

of these agents. One approach to make currently existing chemotherapeutic drugs more effective against tumors and less toxic to normal tissues is to conjugate them with water-soluble polymeric drugs, such as polyglutamic acid. These conjugates accumulate in tumors and release the active drug into the tumor in high concentrations and for a longer time. This effect is thought to be due to the increased permeability and retention effect of macromolecular compounds in solid tumors (Maeda et al. 1992; Li et al. 2000a). The abnormal vasculature in tumors is porous to macromolecules, but high concentrations of drug can build up in tumors because of inadequate lymphatic drainage, whereas polymer-drug conjugates are confined to the bloodstream in normal tissue (Maeda et al. 1992). A recently developed polyglutamic acid-paclitaxel conjugate (CT-2103) may be less toxic and more effective against tumors in preclinical studies than unconjugated paclitaxel (Li et al. 2000a, 2000b). It is undergoing phase III clinical trials in the U.S. (Phase III Randomized Study of Polyglutamate Paclitaxel).

Another example is oxaliplatin, which is a third-generation cisplatin compound. Platinum chemotherapy has been used widely in managing advanced NSCLC. Oxaliplatin is a new diamonicyclohexane that has a different toxicity profile than that of other platinum compounds such as cisplatin and carboplatin. Oxaliplatin has almost no nephrotoxicity, produces mild nausea and vomiting, and has a mild to moderate hematologic toxicity. The dose-limiting toxicity of oxaliplatin includes dose-dependent and reversible peripheral neuropathy. Based on the favorable toxicity profile of oxaliplatin as well as the potential for even higher activity against NSCLC, a combined modality therapy of oxaliplatin and thoracic radiotherapy will likely be started soon. Several studies have reported the use of oxaliplatin in NSCLC, but none has incorporated radiotherapy (Monnet et al. 1998, 2001, 2002; Faivre et al. 2002; Kakolyris et al. 2002; Vittorio et al. 2003; Kourousis et al. 2003)

The use of oxaliplatin has the potential advantage of reducing cisplatin- or carboplatin-associated toxicity as well as potentiating the effects of radiation.

11.3.6 Incorporation of Molecular Targeting

Recent advances in molecular biology have identified a number of molecular determinants that may be responsible for resistance of cancer cells to radiation or other cytotoxic agents. Among these determinants are epidermal growth factor receptor (EGFR), cyclooxygenase-2 (COX-2) enzyme, mutated *ras*, angiogenic molecules, and various other molecules that are involved in signal transduction pathways (Mason et al. 2001).

11.3.6.1 Epidermal Growth Factor Receptor

EGFR is a transmembrane glycoprotein with a tyrosine kinase activity. There are in fact four transmembrane receptor tyrosine kinases in the epidermal growth factor receptor class: EGFR, HER2, HER3, and HER4. On binding to a ligand, such as epidermal growth factor (EGF) or transforming growth factor-α (TGF-α), EGFR undergoes autophosphorylation and initiates transduction signals regulating cell division, proliferation, differentiation, and death (see Fig. 11.3.1). EGFR plays an impor-

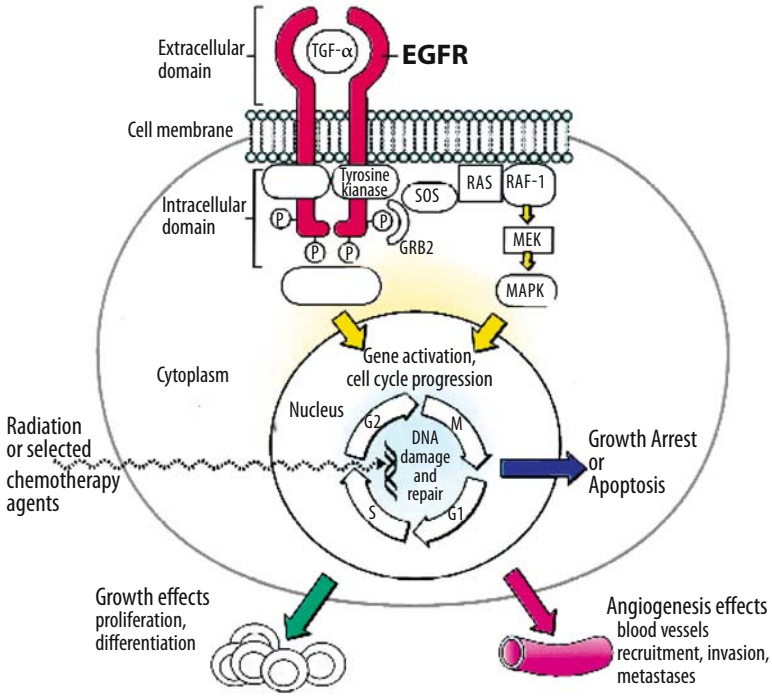

Fig. 11.3.1 Potential benefits of blocking the EGFR. Modified from Harari and Huang (2000) Copyright American Association for Cancer Research

tant role in tumor growth and tumor response to cytotoxic agents, including ionizing radiation. The receptor is frequently expressed in many types of cancers. It is often associated with aggressive tumors, poor patient prognosis, and tumor resistance to treatment with cytotoxic agents (Mendelsohn and Fan 1997; Schmidt-Ullrich et al. 2000). In vitro studies have provided evidence linking EGFR with drug resistance. While incorporation of EGFR into tumor cells increases their drug resistance (Dickstein et al. 1995), the blockade of the EGFR-mediated pathway with antibodies to EGFR enhances the sensitivity of tumor cells to chemotherapy (Mendelsohn and Fan 1997) and radiotherapy (Huang et al. 1999). In vivo studies have shown that blockade of EGFR with anti-EGFR monoclonal antibody, such as with C225, or interference with its signaling processes can improve tumor treatment with chemotherapy and radiotherapy (Milas et al. 2000; Huang and Harari 2000). C225 (Cetuximab; Erbitux, Imclone, NJ, USA) is a highly specific monoclonal antibody that binds to EGFR and blocks its activation. Synergistic effects with radiotherapy have been seen in NSCLC cell lines that expressed EGFR (Salek et al. 1999; Raben et al. 2002).

A phase I study of C225 and radiotherapy combination in advanced head and neck cancer was generally well tolerated by the patients. The C225-related morbidity included fever, nausea, hepatic transaminase elevation, and skin reaction. Thirteen of 15 evaluable patients achieved complete response (Robert et al. 2001). A study found that EGFR levels were inversely correlated with radiation-induced apoptosis (Akimoto et al. 1999). There are also data to suggest that EGFR expression may be increased as a defense mechanism against the harmful effects of ionizing radiotherapy (Schmidt-Ullrich et al. 1997). In addition, EGFR inhibition induces cell-cycle arrest at theG_0/G_1 phase of the cell cycle, which reduces the proportion of cells in the S phase, which are more resistant to the effects of radiation. ZD 1839 (Iressa) is an example of an orally active inhibitor of EGFR-tyrosine kinase (EGFR-TK). Administration of ZD 1839 enhanced apoptosis, reduced tumor cell growth, and was synergistic with radiation (Solomon et al. 2002; Huang et al. 2002). The optimal combination of ZD 1839 and radiotherapy is unknown, but ongoing studies including the Southwest Oncology Group (SWOG) 0023 trial administer ZD 1839 as a maintenance therapy for locally advanced NSCLC after chemoradiotherapy. The Cancer and Leukemia Group B (CALGB) is also studying the role of ZD 1839 in the management of stage III NSCLC. The CALGB study administers

ZD 1839 concurrently with chemoradiotherapy, followed by additional administration of ZD 1839. (See Table 11.3.2.)

Table 11.3.2. Ongoing trials of ZD 1839 and radiotherapy in NSCLC

ZD 1839 regimen	Eligibility	Study group
Maintenance	Unresectable stage III	SWOG
Concurrent	Unresectable stage III	CALGB

11.3.6.2 Cyclooxygenase-2

COX-2 relates to prostaglandins (PGs). PGs are metabolites of arachidonic acid that possess diverse biologic activities, including vasoconstriction, vasodilatation, platelet aggregation, and immunomodulation. They are also implicated in the development and growth of malignant tumors as well as in the response of tumor and normal tissues to cytotoxic agents, including radiation (Milas and Hanson 1995; Milas 2001; Koki et al. 1999). Two cyclooxygenase enzymes, COX-1 and COX-2, mediate production of PGs. Whereas COX-1 is ubiquitous and has physiological roles in maintaining homeostasis, such as the integrity of gastric mucosa, normal platelet function, and regulation of renal blood flow, COX-2 is nonphysiological but induced by diverse inflammatory stimuli, mitogens, and carcinogens. Increasing evidence shows that COX-2 expression is upregulated in many human tumors. This selective or preferential expression of COX-2 in tumors makes this enzyme a potential target for cancer therapy. Selective inhibitors of COX-2 have recently been developed for use as anti-inflammatory and analgesic agents, but the availability of these inhibitors has provided a tool for evaluating the role of COX-2 in cancer. Selective COX-2 inhibitors are reported to enhance tumor response to chemotherapeutic drugs or radiation (Milas 2001; Koki et al. 1999; Milas et al. 1999c). One of the effects of COX-2 overexpression in malignant cells is inhibition of apoptosis. Several preclinical studies have shown that inhibition of COX-2 results in restoration of apoptosis and increased cell death. The mechanisms of the enhancement seem to be multiple, including increases in intrinsic cell radiosensitivity and inhibition of tumor neoangiogenesis. For example, Kishi et al reported that inhibition of COX-2 resulted in enhancement of radioresponse of murine sarcoma with little effect on COX-2 protein expression (2000). COX-2 is observed within human tumor neovasculature, suggesting that COX-2-derived prostaglandins contribute to formation of new tumor blood vessels. Indeed, Celecoxib, a COX-2 inhibitor, is a potent inhibitor of angiogenesis and has been shown to inhibit neoplastic cells.

11.3.6.3 Tumor Angiogenesis Inhibitor

Inhibitors of tumor angiogenesis have been investigated extensively for possible tumor treatment. The formation of tumor vasculature, which is a prerequisite for tumor growth, is initiated and sustained by angiogenic mediators secreted by tumor cells and cells from the surrounding tissues. Many different angiogenic factors have been identified, including vascular endothelial growth factor/vascular permeability factor (VEGF/VPF), members of the fibroblast growth factor (FGF) family, platelet-derived growth factor (PDGF), interleukin-8, and PGs. In addition to angiogenic factors, tumors secrete substances that inhibit angiogenesis, such as angiostatin, endostatin, thrombospondin-1, and interferons. The final outcome of angiogenesis depends on the balance between proangiogenic and antiangiogenic activities. Radiotherapy may induce angiogenesis by increasing the levels of angiogenesis stimulator, transforming growth factor β1(TGF β-1). Increased levels of both VEGF and TGF β-1 have been observed after radiotherapy (Canney and Dean 1990; Gorski et al. 1999). There are also data supporting an antiangiogenesis effect of radiotherapy, which implies a dual effect of radiotherapy (Hartford et al. 2000). Thus angiogenesis is a complex interaction of multiple factors, including VEGF, TGF β-1, ionizing radiation, and others. Angiogenesis inhibitors are undergoing extensive testing for tumor therapy purposes, used alone or in combination with chemotherapy or radiotherapy. Angiogenesis inhibitors, such as angiostatin, inhibit the growth or even cause temporary regression of established murine tumors or human tumor xenografts in mice (O'Reilly et al. 1996). Angiostatin selectively inhibits proliferation of endothelial cells and indirectly induces tumor cell loss through apoptosis. Angiostatin has been shown to potentiate the effects of radiotherapy in lung cancer xenograft if given concurrently, but not when given after radiotherapy. However, other inhibitors of angiogenesis such as SU5416 and SU 6668 exhibited no difference in response according to the sequence of administration (Ning et al. 2002).

Because antiangiogenesis therapy inhibits formation of new blood vessels, such therapy may not result in rapid tumoricidal response. A number of antiangiogenic agents have been shown to improve the antitumor efficacy of chemotherapeutic drugs or radiation, either by additive or synergistic effect (Teicher et al. 1995; Mauceri et al. 1998). The mechanisms of action include direct effect on tumor cells, rendering them more sensitive to killing by radiation or drugs, and indirect effect through the damage of tumor vasculature.

Antiangiogenic agents, such as TNP-470, may enhance tumor radioresponse by increasing tumor oxygenation (Teicher et al. 1995). It has been suggested that this increase in oxygenation could result from decreased oxygen consumption as a result of the reduced number of endothelial cells. In addition, decreased tight junctions between endothelial cells may allow more oxygen to diffuse to tumor cells more distantly located from vasculature.

Ongoing clinical studies will investigate the role of angiogenesis inhibitors in NSCLC. The University of Texas M.D. Anderson Cancer Center will lead an investigation into the role of AE-941 (Neovastat) in stage III NSCLC patients (MD Anderson Cancer Center). The Eastern Cooperative Oncology Group (ECOG) has an ongoing trial investigating the role of thalidomide in patients with stage III NSCLC. In addition, the Radiation Therapy Oncology Group (RTOG) will study the role of celecoxib in patients with locally advanced NSCLC. (See Table 11.3.3.)

Table 11.3.3. Ongoing trials of angiogenesis inhibitors and radiotherapy in NSCLC

Angiogenesis inhibitor	Eligibility	Study group
Thalidomide	Stage III	ECOG
AE 941(Neovastat)	Stage III	MD Anderson
Celecoxib	Stage III	RTOG

11.3.6.4 RAS Farnesylation Inhibitors

The *ras* nucleotide binding proteins relay signals from growth factor receptors such as EGFR and regulate transcription of genes required for proliferation (Radiation Therapy Oncology Group; Grunicke and Maly 1993). The *ras* oncogenes (H, K, and N) are often mutated in many types of human cancer, including pancreatic, lung, and head and neck carcinomas. This mutation often causes persistent activation of *ras* oncogenes, alters tumor cell growth, and makes cells resistant to radiation (Bernhard et al. 2000). Therefore, blocking mutated *ras* oncogenes may also improve chemoradiotherapy. Because *ras* proteins must be farnesylated by farnesyltransferase in order to be active, inhibition of farnesylation could counteract the negative impact of mutated *ras* oncogene. A number of farnesyl transferase inhibitors have been developed and shown to increase tumor cell radiosensitivity in vitro and increase tumor radioresponse in vivo (Bernhard et al. 1998; Cohen-Jonathan et al. 2001). These compounds selectively affect tumors because the *ras* genes in normal tissues are not mutated and may result in an improved therapeutic index.

11.3.6.5 Promoters of Apoptosis

Complex interactions of molecular events determine the proliferation and death of tumor cells. Bcl-2 is an important modulator of apoptosis. It functions to inhibit apoptosis, and studies have shown that overexpression of Bcl-2, for instance by loss of p53, results in suppression of apoptosis induced by cytotoxic agents (Rafi et al. 2000; Eliopoulos et al. 1995). An example of manipulation of bcl-2 is the use of G3139, which is an antisense oligonucleotide preventing the expression of Bcl-2. It has been used to treat low-grade non-Hodgkin's lymphomas, with overexpressed Bcl-2. Hematologic toxicity was not seen, but the effect on the tumor volume was also not significant (Kuss and Cotter 1997). Whether an initial modulation of Bcl-2 can lead to increased response to subsequent cytotoxic therapy, including radiotherapy, remains to be determined. The development of an effective pro-apoptosis regimen in combination with radiotherapy will require better definition of a preclinical model of the synergy between an apoptosis promoter and ionizing irradiation.

11.3.6.6 Normal Tissue Protection

Normal tissue toxicity represents a major limitation of concurrent chemoradiotherapy. Preventing or minimizing normal tissue complications is an important strategy. This could be achieved through

incorporating radio- or chemoprotective agents into the treatment or through improving radiation delivery. A number of chemical and biological compounds are available that in preclinical in vivo testing exhibited either selective or preferential protection of normal tissues (Milas and Hanson 1995; Yuhas and Storer 1969; Hahn et al. 1994). The most commonly tested radioprotectors are thiol compounds, such as WR2721 (amifostine). The principal mechanisms of protection by these agents include scavenging of free radicals generated by ionizing radiation and some chemotherapy agents, such as alkylating agents, and donating hydrogen atoms to facilitate direct chemical repair of DNA damage. WR-2721 must be converted in vivo into its active metabolite WR-1065. The protector is taken up preferentially by normal tissues, where the entry into cells is accomplished by active transport. In contrast, the cytotoxic drugs diffuse passively into tumors, where its availability is further reduced by deficient tumor vasculature. Amifostine has been shown to reduce normal tissue toxicity in a number of clinical settings, including protection of salivary glands in head and neck radiotherapy (Brizel et al. 1999) and of the esophagus in chemoradiotherapy of lung cancer (Komaki et al. 2000), without adversely affecting tumor response to treatment. Technical improvements in radiotherapy, such as three-dimensional treatment planning, conformational radiotherapy, or use of protons, are other approaches likely to minimize the toxicity, and consequently enhance the effectiveness, of chemoradiation. The use of either radioprotective compounds or implementation of technical advances may enable administration of higher doses of radiation, chemotherapeutic drugs, or both, which may result in superior treatment outcome.

11.3.6.7 Topoisomerase I Inhibitors

The camptothecins are potent radiation sensitizers that are increasingly incorporated in clinical studies. Camptothecin is a plant alkaloid obtained from the tree *Camptotheca acuminata*. Its initial clinical evaluation in the 1960s and 1970s was abandoned because of severe and unpredictable hemorrhagic cystitis (Moertel et al. 1972; Muggia et al. 1972). Camptothecin and its derivatives (irinotecan, topotecan, 9-aminocamptothecin, SN-38, etc.) target DNA topoisomerase I (Hsiang et al. 1985; Hsiang and Liu 1988; Andoh et al. 1987). This enzyme relaxes both positively and negatively supercoiled DNA and allows processes such as replication and transcription to proceed. In the presence of camptothecin, a camptothecin-topoisomerase I-DNA complex becomes stabilized with the 5'-phosphoryl terminus of the enzyme-catalyzed DNA single-strand break bound covalently to a tyrosine residue of topoisomerase I. These stabilized cleavable complexes interact with the advancing replication fork during S phase or during unscheduled DNA replication after genomic stress and cause the conversion of single-strand breaks into irreversible DNA double -strand breaks, resulting in cell death (Iliakis 1988).

Several investigators have reported that camptothecin enhances the cytotoxic effect of radiation in vitro and in vivo (Omura et al. 1997; Chen et al. 1997). Chen et al. (1997) showed that cells exposed to 20(S)-10,11 methylenedioxycamptothecin before or during radiation had sensitization ratios of 1.6, whereas those treated with the drug after radiation had substantially less enhancement of radiation-induced DNA damage. There are several hypotheses regarding the mechanism of interaction between radiation and irinotecan, which is perhaps the best studied of the camptothecin derivatives. The first hypothesis suggests that inhibition of topoisomerase I by irinotecan leads to inhibition of repair of radiation-induced DNA strand breaks. The second hypothesis suggests that irinotecan causes redistribution of cells into the more radiosensitive G2 phase of the cell cycle. The third hypothesis is that topoisomerase I-DNA adducts are trapped by irinotecan at the sites of radiation-induced single-strand breaks, leading to their conversion into double-strand breaks (Amorino et al. 2000). The primary mechanism involved with radiosensitization may depend on which camptothecin derivative is being used; there is currently insufficient evidence to identify the underlying mechanism with certainty. Data from in vivo experiments demonstrate that the 9-aminocamptothecin (9-AC) and irradiation is more effective when fractionated compared with single doses (Kirichenko and Rich 1999). The integration of this group of drugs into clinical treatments with radiation is ongoing. Much of the current experience with irinotecan has been accumulated in NSCLC (Takeda et al. 1999; Choy and MacRae 2001), whereas much of the experience with topotecan has occurred in brain tumors (Fisher et al. 2001; Grabenbauer et al. 1999).

11.3.7 Conclusion

The combination of chemotherapy and radiation has become a common strategic practice in the therapy of locally advanced cancers, with recent emphasis on the concurrent delivery of both modalities. Improvements in treatment outcome both in terms of local control and patient survival have been achieved with traditional chemotherapeutic agents such as cisplatin and 5-fluorouracil. Nonetheless, the cure rates of the majority of solid tumors remain poor, and the addition of combined treatments is frequently associated with increased normal tissue toxicity. Therefore, there is considerable room for improvement of the combined treatment strategies. However, selection of the most effective drug or the optimal treatment approach remains a significant challenge.

Newer chemotherapies, such as the taxanes, nucleoside analogs, and topoisomerase inhibitors, which interfere with one or more tumor radioresistance mechanisms, are becoming increasingly available. These agents have high potential for increasing the therapeutic effectiveness of radiotherapy; therefore, their evaluation in combination with radiotherapy, both in the laboratory and in the clinic, is essential for improving cancer treatment. Preclinical studies provide not only a biologic rationale for the use of a given drug with radiation but are able to generate information critical to the design of effective treatment schedules in clinical settings. Studies of the mechanisms of chemotherapy-radiotherapy interaction at the genetic-molecular, cellular, and tumor (or normal tissue) microenvironmental levels are essential for obtaining clear insight into the radiomodulating potential of chemotherapeutic agents and their ability to increase radiotherapeutic effects.

Significant progress has been made in our understanding of the basic mechanisms of radiation injury as well as the injury inflicted by chemotherapeutic agents and cellular processing of these injuries in both normal and malignant cells. Recent advances in molecular biology have exposed many potential targets for augmentation of radioresponse or chemoresponse, including EGFR, cox-2, angiogenic molecules, and various components of the signal transduction pathways that these molecules initiate. It has become possible to intervene actively in some molecular pathways in order to improve the therapeutic ratio, and the incorporation of molecular targeting strategies into chemoradiotherapy is becoming increasingly used for therapeutic intervention in many types of human cancer.

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11.4 PET Scanning in Staging and Evaluation of Response to Treatment in Lung Cancer

Michael P. MacManus and Rodney J. Hicks

CONTENTS

11.4.1 Introduction

Positron emission tomography (PET) represents the most significant advance in lung cancer imaging since the introduction of computed tomography (CT) (Stroobants et al. 2003) and is having an increasing impact on the management of lung cancer patients who are candidates for radiotherapy (Hicks and MacManus 2003). Modern PET scanners can produce three-dimensional images of the distribution of the positron emitting isotopes in humans and animals with a resolution previously unseen in nuclear medicine. These images allow direct qualitative and quantitative analyses of a range of metabolic processes in tumours and normal tissues, depending on the positron emitting isotope chosen and the molecule (if any) to which it is attached. Coregistration and image fusion techniques allow for powerful combinations of functional images from PET and structural images, usually from CT, which can give precise information on the anatomic location of structures seen on PET (Hutton et al. 2002). Fused CT/PET images are proving to be superior to separate CT or PET images in cancer staging (Townsend and Beyer 2002). PET scanning is becoming an essential tool for planning radical radiotherapy for lung cancer, which should ideally be based on the most accurate available estimate of the true extent of gross disease. PET has the potential to exclude patients from radical radiotherapy who cannot benefit from it because they have metastatic disease. Evidence supports the use of PET in radiotherapy treatment planning (Erdi et al. 2002; Kiffer et al. 1998; Mah et al. 2002). By more accurately conforming the planning target volume to gross tumour volume, the risk of a geographic miss can be minimised, and in some cases the unnecessary irradiation of normal tissues can be reduced (Mah et al. 2002; Schmucking et al. 2003). Preliminary data indicate that the new combined PET/CT scanner may provide the most efficient and accurate means of integrating structural and molecular information into the treatment planning paradigm (Ciernik et al. 2003).

Most published studies of PET in lung cancer have focused on the use of ^{18}F-fluorodeoxyglucose (FDG), a glucose analogue that is taken up and trapped by tumour cells in most non-small cell lung cancers (NSCLC). The positrons emitted by the ^{18}F atom travel a short distance before they encounter an electron and undergo annihilation with the emission of a pair of photons in opposite directions. When the annihilations of millions of positrons are detected in a PET scanner, a detailed three-dimensional image of the distribution of FDG in normal and tumour tissue can be produced. Although limited data are available for small cell lung cancer that is well-imaged by FDG-PET (Pandit et al. 2003), the bulk of the literature on the value of PET scanning in lung cancer relates to NSCLC. The role of PET in evaluating patients with known or suspected lung cancer will be reviewed in this chapter, with particular emphasis on information of value for managing patients who are planned to receive radical radiotherapy.

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11.4.2. PET in the Diagnosis of Lung Cancer

PET is significantly more accurate than structural imaging methods such as CT scanning for determining whether pulmonary nodules are benign or malignant (Gould et al. 2001), and it has been shown to be superior to CT in all published studies. High levels of FDG uptake are strongly correlated with malignancy, although false positive results may rarely be seen with conditions such as histoplasmosis (Croft et al. 2002) and tuberculosis (Goo et al. 2000). Conversely, lesions with low FDG uptake are benign in the great majority of cases (Abou-Zied et al. 2000). PET is highly accurate in characterising pulmonary mass lesions that are either unsuitable for, or that have failed, histopathological characterisation (Pitman et al. 2001). In malignant lung tumours, uptake of FDG is strongly associated with proliferation as assessed by immunohistochemistry for Ki-67 (Vesselle et al. 2000). False negative PET scans may occur when lesions are too small to be accurately imaged (<1 cm) (Pitman et al. 2002) or that are of low-grade malignancy such as bronchioloalveolar carcinoma, although many bronchioloalveolar carcinomas can still be imaged by PET. There is evidence that tumours with low FDG avidity have an indolent natural history and that an observation period does not lead to adverse prognosis in these cases. In the rare instance when lung cancer is suspected on the basis of conventional imaging but histologic confirmation is impossible to obtain without surgery, but surgery is contraindicated because of severe comorbidities, a positive PET scan may be sufficient evidence to proceed to treatment with radiotherapy without histology.

11.4.3. Preoperative PET Staging in Potentially Resectable NSCLC

Intrathoracic Lymph Node Evaluation

CT scanning has long been the most commonly used non-invasive method for detecting intrathoracic lymph node metastasis in NSCLC. Lymph node size is the only significant parameter used, and an arbitrary cut-off point is used to distinguish positive from negative nodes; a short axis diameter of 1 cm or more commonly indicates malignancy. Because reactive lymphadenopathy is common and because tumour is often present in nodes smaller than 1 cm, CT has low sensitivity and specificity for detecting lymph nodes involved by tumour (Toloza et al. 2003). Although increasing the diameter required for diagnosis of malignancy to greater than 1.5 cm improves CT's specificity, the sensitivity becomes unacceptably low. The accuracy of FDG-PET in staging the intrathoracic lymph nodes has been directly estimated in numerous clinicopathological studies. In all of these studies (Bury et al. 1996; Farrell et al. 2000; Poncelet et al. 2001; Vansteenkiste et al. 1997), including a meta-analysis (Dwamena et al. 1999), PET has been shown to be more accurate than CT for staging the mediastinum. The best non-invasive results have been obtained by correlating the results of both PET and CT images (Hicks and MacManus 2003; Wahl et al. 1994). The results of these clinicopathological staging studies are of great importance for radiation oncologists. They conclusively prove that when PET is used in addition to CT to evaluate intrathoracic nodes for malignancy, the accuracy of the assessment is significantly greater than for CT alone.

Survival in NSCLC is powerfully correlated with lymph node staging, and it drops precipitously when mediastinal nodes contain tumour (Mountain et al. 1987). Dunagan and colleagues (2001) reported that survival was more strongly correlated with PET stage than CT-based stage in a large group of patients who were mostly surgical candidates.

Evaluation for Distant Metastasis

PET can typically detect unsuspected distant metastasis in 5–10% of patients with potentially-resectable stage I–II disease. PET is capable of detecting disease in adrenal glands (Yun et al. 2001), liver (Timms 2000), and other organs that may appear normal on CT (Marom et al. 1999; Valk et al. 1995). PET is also more specific than radionuclide bone scanning for detecting bone metastasis in lung cancer (Bury et al. 1998), but it may not be as sensitive (Gayed et al. 2003) and therefore should not necessarily replace bone scans. The limited axial extent of PET scans previously performed for the staging of lung cancer that often included only the thorax and upper abdomen may account for some of the apparently lower sensitivity. Accordingly, this statement may not necessarily be true of newer instrumentation that allows more rapid scanning, making more comprehensive body surveys practical. Few data exist on the prognostic significance of PET-detected distant metastasis in patients who would otherwise have been considered to have potentially curable disease. In a study from Peter MacCallum

Cancer Institute of 42 patients with PET-detected distant metastasis before planned surgery (n=7) or radical radiotherapy (RT)/chemoradiotherapy (n=35) for NSCLC, survival was investigated as the principal endpoint (MacManus et al. 2003a). The influence of metastasis number and other prognostic factors was investigated using Cox regression analysis. All but four patients had died by the last follow-up. Median survival was 9 months overall, 12 months for 27 patients with single PET-detected metastasis, and 5 months for 15 patients with more than one metastasis (p=0.009). ECOG performance status (p=0.027) but not pre-PET stage, weight loss, or metastasis site correlated with survival. PET-detected metastatic tumour burden appeared to influence survival and should be evaluated further as a potential prognostic factor in NSCLC. It is clear that PET evidence of distant metastasis, even if unsupported by other evidence, is powerfully associated with subsequent progression of metastatic disease and death. In a recent study, the use of dual modality PET/CT staging was shown to be more accurate for detecting distant metastasis in NSCLC than either PET or CT as single modalities (Antoch et al. 2003). Accurate localisation of FDG-avid regions on fused CT/PET images reduces the risk of false positive interpretations of physiologic phenomena such as uptake in bowel (Vesselle and Miraldi 1998) or metabolically active brown fat (Hany et al. 2002).

Impact of PET on Overall Patient Management

Early detection by PET of disease that is too advanced for surgery or other radical treatments has been shown to profoundly influence patient management in a prospective trial (Kalff et al. 2001). In the Dutch randomised trial of PET-assisted staging versus conventional staging in patients undergoing evaluation for surgery for lung cancer, PET was associated with a significant reduction in the "futile thoracotomy rate" (Van Tinteren et al. 2002). Patients with advanced intrathoracic disease, distant metastasis, or without lung cancer were less likely to receive an unnecessary thoracotomy if PET was part of the staging workup. Consequently, those patients with truly localised NSCLC formed a higher proportion of those subjected to surgical resection in the PET group compared with the non-PET group. In addition, PET appeared to be highly cost-effective in the health care environment in which the study was performed (Verboom et al. 2003).

11.4.4 Role of PET in Selecting Patients for Radiotherapy/Chemoradiotherapy in NSCLC

Radical radiotherapy or chemoradiotherapy is offered predominantly to suitable patients who have stage IIIA or IIIB disease. Patients with stage I–II disease who cannot undergo resection because of significant comorbidity may also be treated with radical radiotherapy. The factors that make these patients unsuitable for surgery (advanced disease or significant comorbidities) militate against confirmation of their intrathoracic lymph node status at thoracotomy and therefore necessitate accurate non-invasive methods of staging. The PET literature has focused on staging prior to surgery in cohorts of patients with predominantly stage I–II disease. However, there is no reason to suppose that PET is any less reliable in stage III disease, and as the most reliable non-invasive staging test, FDG-PET should certainly be used in the staging of patients who are candidates for radical radiotherapy.

Results of a staging investigation should correlate with outcome. The better the staging test, the stronger the correlation between survival and apparent disease extent should be. At Peter MacCallum Cancer Centre, a prospective study was instituted in 1996 in which 153 consecutive patients with NSCLC who were candidates for radical radiotherapy – in most cases given with concurrent chemotherapy – underwent both conventional staging and FDG-PET prior to therapy (MacManus et al. 2001a). Patients were eligible for radical treatment on the basis of their pre-PET stage and included those patients with stage IIIA and IIIB disease with disease that could be encompassed within an acceptable radiation target volume, as well as a smaller number of medically inoperable patients with stage I–II disease. Each patient was assigned a conventional stage based on the results of non-PET investigations, including CT and radionuclear bone scans and a "PET-stage" based on conventional imaging plus PET. Early in the study, unsupported PET findings of extensive disease were not judged to be sufficient reason to deny a patient an attempt at radical therapy, but it soon became clear that early progression occurred at all untreated metastatic sites detected by PET. Accordingly, unsupported PET evidence of advanced disease was subsequently considered sufficient to change therapy from radical to palliative. After PET, 30% of patients were denied radical radiotherapy because of unexpected distant metastasis (Fig. 11.4.1) or because of PET-detected intrathoracic disease that was too extensive for

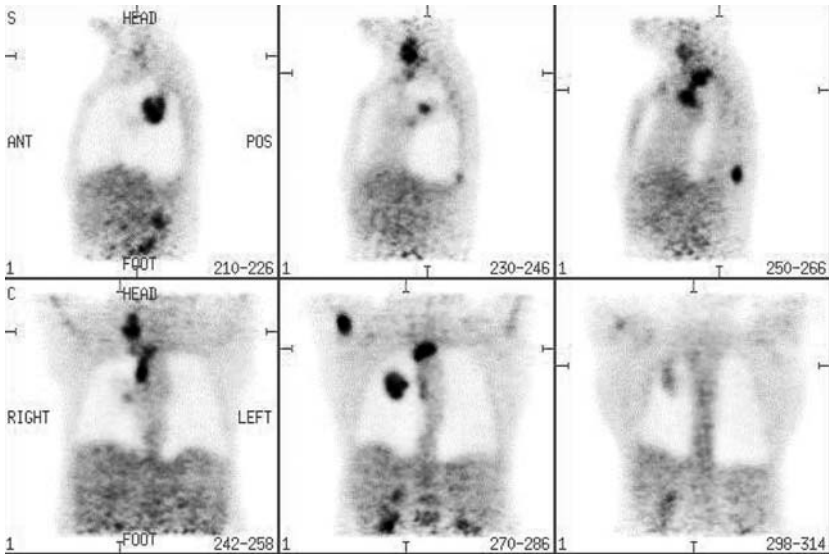

Fig. 11.4.1 PET in staging. Staging PET scan for radical radiotherapy candidate thought to have stage IIIA NSCLC of the right upper lobe. PET showed disease in the right supraclavicular lymph node, shoulder girdle, and thoracic spine. He received palliative therapy only

safe radical irradiation. In five patients who became candidates for surgery after PET showed less extensive disease than suspected, complete resections were performed. Patients who were denied radical therapy on the basis of PET findings had very poor survival compared with those who proceeded to radical therapies, confirming that PET-based selection for radical treatment had been appropriate.

After PET, 107 patients actually underwent radical therapies. In these patients, PET stage correlated powerfully with survival (p=0.0041), whereas conventional stage correlated rather poorly with survival (p=0.19). The major effect of PET was to appropriately allocate N and M stages. In a separate study from Peter MacCallum Cancer Centre, it was reported that conventional T and N stage assessment in patients treated with radical radiotherapy is a relatively poor predictor of outcome in contrast to the situation of surgically-treated patients who are well served by the current staging system (Ball et al. 2002).

The high rate of detection of unexpected distant metastasis by PET (18%) in this group of radiotherapy candidates, many with stage III disease, led to an investigation of the effect of pre-PET clinical stage on the probability that PET would upstage a patient to stage IV (MacManus et al. 2001b). In a cohort of 167 patients, the rate of PET-detected metastasis increased significantly (p=0.016) with increasing pre-PET stage from I (7.5%) through II (18%) to III (24%), and, in particular was significantly higher in stage III (p=0.039) than in I–II. A similarly high rate of detection of distant metastases in apparent stage III disease was reported by Eschmann and colleagues (2002).

The effect of PET selection on survival of patients treated with radical radiotherapy was illustrated by a further study from Peter MacCallum Cancer Centre in which two prospective cohorts were compared. Cohort 1 consisted of all participants from 1989 to 1995 in an Australian randomised trial from our centre given 60 Gy conventionally fractionated radical radiotherapy with or without concurrent carboplatin. Eligible patients had stage I–III, Eastern Cooperative Oncology Group status 0 or 1, <10% weight loss, and had not undergone PET. Cohort 2 included all radical radiotherapy candidates between November 1996 and April 1999 who received RRT after PET staging and fulfilled the same criteria for stage, Eastern Cooperative Oncology Group status, and weight loss. Eighty and 77 eligible patients comprised the PET and non-PET groups, respectively. The median survival was 31 months for PET patients and 16 months for non-PET patients. Mortality from NSCLC and other causes in the first year was 17% and 8% for PET patients and 32% and 4% for non-PET patients, respectively. The hazard ratio for NSCLC mortality for PET vs. non-PET patients was 0.49 (p=0.0016) on unifactorial analysis and was 0.55 (p=0.0075) after adjusting for chemotherapy, which significantly improved survival. This study suggests that, by using PET to exclude unsuitable patients with advanced disease and by integrating it within the radiotherapy treatment planning process, previously unattainable survival results can be obtained. These results also confirm the value of radiotherapy as a highly active treatment modality in appropriately selected patients.

11.4.5 Role of PET in Restaging After Definitive Radical Radiotherapy/Chemoradiotherapy for NSCLC

Response to therapy could potentially determine the further management of patients with lung cancer, including consideration for salvage or consolidation therapies in incomplete or complete responders. Three-dimensional structural imaging modalities, such as CT and MRI, have long been the most important investigations for assessing response to nonsurgical therapies such as radiation therapy or chemotherapy. World Health Organization or RECIST criteria are applied to measurements of tumour dimensions made before and after therapy, and responses are categorised as complete response (CR), partial response (PR), no response (NR), or progressive disease (Green and Weiss 1992). However, CT and MRI scanning have significant limitations in the assessment of tumour response in solid tumours in general and in NSCLC in particular. Tumours may be obscured by atelectasis before or after therapy and may be obscured by radiation pneumonitis or fibrosis in the post-treatment period (Lever et al. 1984). As discussed above, lymph node size measured on CT is an unreliable measure of lymph node involvement by tumour. Tumours often regress gradually over several months, mandating serial measurements to assess response (Werner-Wasik et al. 2001). Lesions may never regress radiologically despite having been controlled by treatment. FDG-PET may facilitate more accurate early assessment of response to treatment of NSCLC than structural imaging. There is accumulating evidence that PET scanning may be useful after radiation therapy (Bury et al. 1999; Erdi et al. 2000), and it is probably superior to CT for detecting both the presence and the extent of recurrent disease (Hicks et al. 2001).

Prospective data from Peter MacCallum Cancer Institute (MacManus et al. 2003b) show that a visually-read PET response is much more powerfully correlated with survival than response measured by CT scanning. Seventy-three patients with NSCLC underwent PET and CT scans before and after radical radiotherapy (n=10) or chemoradiotherapy (n=63). Follow-up PET scans were performed at a median of 70 days post-radiotherapy. Each patient had prospective determinations of response to therapy made with PET and CT. In this study a visual assessment was made to determine PET-response, while WHO criteria were used for CT response. PET response categories were defined as follows:

1. CR (or CMR, complete metabolic response): No abnormal tumour FDG uptake; activity in the tumour absent or similar to mediastinum
2. PR (or PMR, partial metabolic response): Any appreciable reduction in intensity of tumour FDG uptake or tumour volume. No disease progression at other sites
3. SD (or SMR, stable metabolic disease): No appreciable change in intensity of tumour FDG uptake or tumour volume; no new sites of disease
4. PD (or PMD, progressive metabolic disease): Appreciable increase in tumour FDG uptake or volume of known tumour sites and/or evidence of disease progression at other intrathoracic or distant metastatic sites

Responses were correlated with subsequent survival. Median survival after follow-up PET was 24 months. There was poor agreement between PET and CT responses (weighted kappa =0.35), which were identical in only 40% of patients. An example of discordant CT and PET responses is shown in Fig. 11.4.2. There were significantly more complete responders on PET (n=34) than CT (n=10), while fewer patients were judged to be non-responders (12 vs. 20) or non-evaluable (0 vs. 6) by PET. Both CT and PET responses were individually significantly associated with survival duration, but on multifactor analysis, including the known prognostic factors of CT response, performance status, weight loss, and stage, only PET metabolic response was significantly associated with survival duration (p<0.0001).

The best method for response assessment after therapy has not yet been determined, whether visual, as used at Peter MacCallum Cancer Centre, or semiquantitative, using standardised uptake values (SUV) or similar approaches (Hoekstra et al. 2002). Changes in SUV have been shown to have prognostic significance after neoadjuvant chemotherapy prior to surgery (Vansteenkiste et al. 1998) and after palliative chemotherapy for incurable NSCLC (Weber et al. 2003). Use of SUV-based assessment following radiotherapy may be compromised by a number of factors, including the commonly observed and sometimes intense inflammatory reaction to radiotherapy in normal tissues. These changes may have a measured value of FDG uptake in the «malignant» range. This is not a significant problem with the visual assessment method, which takes account of the distribution of normal tissue reactions. Post-radiotherapy changes conform to the volume of aerated lung in the radiation treatment volume, are of a geographic rather than segmental or anatomical distribution, and are

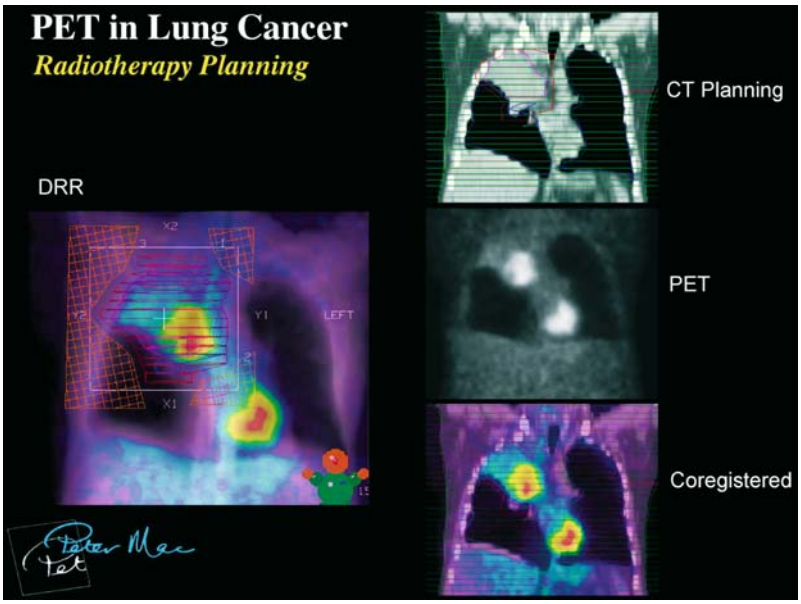

Fig. 11.4.2 PET in radiotherapy planning. These images are all from a single patient with NSCLC planned for radical radiotherapy. *left* PET scan superimposed on digitally reconstructed radiograph, *right upper* planning CT scan with target volume marked, *right middle* PET scan, *right lower* coregistered PET and planning CT scans

non-congruent with the biodistribution of uptake in tumoral sites on baseline scanning. Residual disease, on the other hand, conforms to the position of initial tumour allowing for anatomical distortion relating to further collapse or re-expansion of lung parenchyma and tends to maintain a lobular shape. Similarly, tumoral uptake tends to respect and follow natural tissue barriers such as the pleura of the oblique fissure, whereas radiation changes are not influenced by such boundaries. Although there is scientific appeal in the absolute evaluation of glucose metabolic rate in tumours, fully quantitative approaches using arterial blood analysis are probably too invasive and complex for routine clinical use.

Thus, PET appears to be far superior to CT scanning for predicting survival after radical radiation therapy. The powerful prognostic information available from post-treatment PET may encourage the development of investigational «response-adapted» therapeutic approaches. It is possible that patients with localised residual disease could benefit from surgery or further conformal radiotherapy.

11.4.6 Use of PET in Restaging After Induction Therapy Prior to Surgery

Several groups have investigated the use of PET scanning after induction therapy prior to surgery (Vansteenkiste et al. 1998; Akhurst et al. 2002). These studies have most often used quantitative or semiquantitative methods rather than direct visual methods to assess response. Choi and colleagues found that the residual metabolic rate of glucose (MRglc) as measured using FDG-PET was strongly correlated with response to preoperative chemoradiotherapy in locally advanced NSCLC as assessed by pathological examination of tumour obtained at thoracotomy (Choi et al. 2002). Vansteenkiste and colleagues investigated the use of FDG-PET scans after induction chemotherapy in surgically staged IIIa–N2 NSCLC. They reported that survival was significantly better in patients with mediastinal clearance (p=0.01) or with a greater than 50% decrease in the SUV of the primary tumour (p=0.03).

11.4.7 The Future of PET in NSCLC

Use of PET Tracers Other Than FDG in Staging and Treatment Response Assessment in Lung Cancer

One of the theoretical limitations of FDG as a tracer for evaluating lung cancer is the presence of false positives related to inflammatory conditions. The excellent clinical performance of FDG-PET suggests that this is not a major practical limitation. The combination of the intensity and pattern of uptake, combined with consideration of the pre-test probability of disease, enables many potential false posi-

tive results based on the intensity of uptake (SUV) to be prospectively identified, and most conditions that cause false positive results benefit from diagnosis and specific therapy. Nevertheless, there has been interest in developing alternative tracers for tumour imaging that may be less prone to uptake in inflammatory diseases. Comparison has been made between FDG PET and ^{201}Tl, a tumour imaging agent commonly used in conventional nuclear medicine. The hope that ^{201}Tl SPECT might prove more specific than FDG has not been realised (Higashi et al. 2001; MacManus 2001c). The lower spatial and contrast resolution generally achieved with SPECT limits its ability to detect disease in non-enlarged mediastinal nodes and beyond the thorax, which, as shown above, accounts for the major incremental value of FDG-PET compared with CT and for much of its clinical impact.

Recognising the instrumentation advantages of PET, comparison with other PET tracers is probably more important. One of the first PET agents to be compared was the amino acid tracer, 11C-methionine. In a small series from Sweden, all primary tumours were equally well visualised by both tracers, and because there were no false positive FDG results, the possibility that amino acid imaging may have a lower propensity for false positive results could not be evaluated (Nettelbladt et al. 1998). A larger study from Japan found that the performance of both tracers was similar, with a marginally higher specificity and accuracy with ^{11}C-methionine, but did not reach statistical significance of the lung (Sasaki et al. 2001). In the restaging setting, in which inflammatory changes may pose difficulties in determining the nature of increased FDG activity, the MD Anderson Cancer Center group found that ^{11}C-methionine and FDG had similar diagnostic performance although FDG yielded significantly higher SUVs than ^{11}C-methionine. In a study looking at the accuracy of ^{11}C-methionine for mediastinal nodal staging, superior accuracy compared with CT was demonstrated using histopathological validation, with results comparable to those reported using FDG-PET (Yasukawa et al. 2000). However, this study did not directly compare the ^{11}C-methionine results with those from FDG-PET.

Enhanced production of cell membranes in cancer cells requires uptake of choline to form phosphatidylcholine. Accordingly, radiolabeled choline analogues have been investigated as potential cancer imaging agents. Initial studies focussed on ^{11}C-choline and involved comparison with FDG-PET in 29 patients with biopsy-proven NSCLC (Hara et al. 2000). This study demonstrated superior sensitivity of ^{11}C-choline for detecting mediastinal nodes. These results were not, however, confirmed by a subsequent study from The Netherlands (Pieterman et al. 2002). Fluorinated choline analogues have recently been described (DeGrado et al. 2002), but these have not yet been validated as tracers in lung cancer.

Another potential imaging target of lung cancer cells is their high proliferation. Proliferative rate may also provide insights into the biological activity and prognosis of lung cancers. Although there does appear to be a relationship between FDG uptake and proliferation in NSCLC (Higashi et al. 2000), there are factors other than proliferation that potentially drive FDG uptake in cancer cells. One of these factors is hypoxia, which increases expression of glucose transporters and glycolytic enzymes but decreases cell proliferation. Hence, tracers that more directly reflect cell proliferation, such as tracers of DNA synthesis, are attractive. Thymidine analogues have been developed for PET imaging. These include ^{11}C-thymidine (Mankoff et al. 1999) and, more recently, the fluorinated analogue FLT (Shields et al. 1998). Studies in lung tumours have demonstrated the feasibility of FLT for evaluating cell proliferation (Buck et al. 2003), but demonstration that this tracer will be superior to staging or therapeutic monitoring are not yet available.

Use of Hybrid CT/PET Images in Staging

As a surrogate for survival, characterisation of tumour, nodal, and metastatic (TNM) stage has become a major focus of the pretreatment evaluation of lung cancer patients. T-stage is generally related to characteristics of tumour size and penetration of tissue boundaries. Neither of these parameters is easily or necessarily precisely determined from PET images. However, peripheral lung collapse can make definition of tumour boundaries difficult on CT. The limitations of CT for defining N-stage and M-stage have been detailed above. Nevertheless, despite the higher sensitivity of PET than CT for detecting occult disease, knowledge of the precise location of nodal and systemic metastases may be crucial for therapeutic decision-making, including the modality and intent of treatment; therefore, CT or other anatomical techniques remain essential for treatment planning.

Recognition of the complementary strengths and limitations of structural and functional imaging has underpinned the concept of correlative imaging. The traditional method for performing correlative imaging has been to visually compare the qualitative appearances of the structural and functional imaging

result. This cognitive integration of information by direct visual comparison is an inexpensive and useful technique that benefits from the great facility of the human brain to conceptualise three-dimensional space. Alternative methods have been developed to integrate the different data volumes into a matrix common to both. These approaches generally involve image-processing software that allows translation, scaling, and, sometimes, warping of one imaging data set to match the other. This process can be based on mutual information points, i.e. structures that are visualised well within both data sets, or by providing reference fiducial markers that can be located independently on each study (Ackerly et al. 2002). These software fusion algorithms can work very well, but many are labour-intensive and require particular attention to patient positioning to minimise the effects of posture on structural relations of organs that are deformable. Even this does not overcome the issue of structures that are independently mobile, such as the large bowel, and that, therefore, may move in relationship to other structures over time. An elegant approach to these difficulties was the development of hybrid imaging devices that allow "hardware" fusion to occur. By contemporaneously acquiring both data sets in a known geometry with the patient positioned identically for both studies, the data sets can be merged with minimal and fixed software manipulation. Coregistration of the CT and PET images (Hutton et al. 2002) enables physiological uptake to be more confidently assigned to normal structures and enables pathological uptake to be both recognised and localised (Bar-Shalom et al. 2003). Examples of the coregistered CT and PET images used in radiotherapy treatment planning are given in Fig. 11.4.3.

Once patients have been shown by PET staging to be suitable candidates for radical radiation therapy, targeting of this therapy can also be improved by more accurate determination of the gross tumour volume by PET. Preliminary studies have suggested that PET/CT is an ideal technique for this purpose (Ciernik et al. 2003).

Respiratory Gating of PET Data

The acquisition of the emission data used to reconstruct PET images occurs over several minutes and therefore integrates the effect of respiratory movement. This has the effect of increasing the apparent supero-inferior size of lesions near the base of the lungs that move predominantly in the coronal plane during respiration, as well as the anteroposterior dimensions of lesions in the anterior aspect of the lungs that move mainly in the axial plane. In both circumstances, apparent activity is slightly reduced by this movement due to partial volume effects. CT scanning, however, is acquired very rapidly, and multislice scanners can acquire images sufficiently fast to effectively "freeze" respiratory motion. Alternatively, CT scan images can be acquired during breath holding at a given phase of respiration. As derived from instanta-

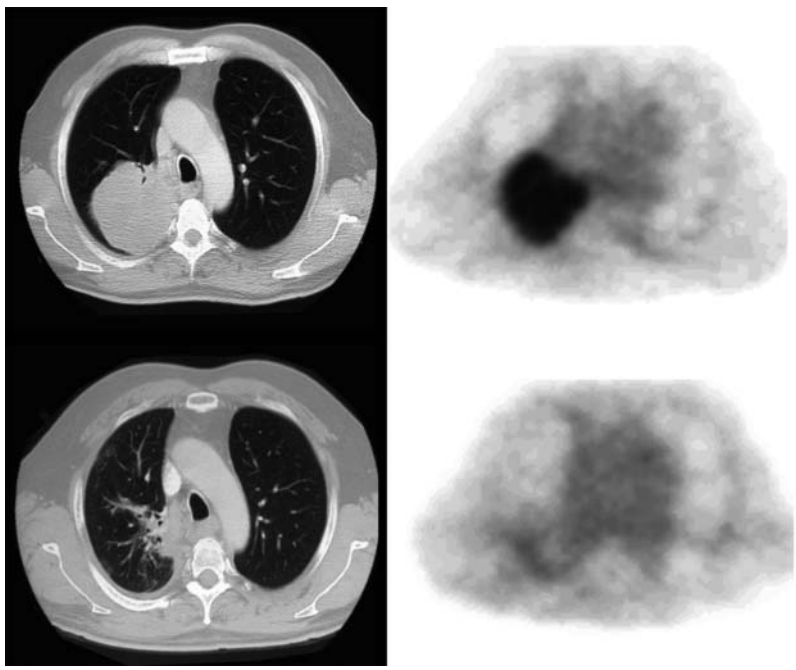

Fig. 11.4.3 PET in restaging after chemoradiation. Upper panels show pretreatment CT and PET scans. Lower panels show post-treatment scans. Post-treatment PET shows CR. Post-treatment CT shows PR. Patient is free from progression after more than 3 years. Reprinted with permission from the American Society of Clinical Oncology

neous images of the relative position of organs, the location of lesions on CT planning images does not necessarily correspond to the averaged or integrated position of lesions detected by emission scanning. It is clear that respiratory movement can lead to misregistration of PET and CT lesions on fused PET and CT images, whether acquired on stand-alone or combined devices. Although this is not a particularly frequent diagnostic problem, it may pose difficulties when determining the GTV and PTV for radiotherapy. The approach at Peter MacCallum Cancer Centre has been to assume that, since the PET data represent the integrated position throughout the respiratory cycle, PET should be used to plan the GTV. This is because radiotherapy is generally delivered during normal breathing. An alternative approach would be to perform respiratory gating of both the PET, CT and radiotherapy delivery. This is an extremely complex undertaking. Efforts to develop methodology for respiratory gated PET have been reported (Nehmeh et al. 2003) and offer the potential for highly sophisticated treatment planning and delivery. Whether the resource implications of such an approach make it practical and affordable for routine clinical application remains to be seen, but for patients in whom lung function is marginal for radical therapy, these highly targeted approaches may be critical to outcome.

11.4.8 Conclusions

PET scanning is vastly superior to conventional methods used in staging and restaging lung cancer. It provides more accurate information on the extent of NSCLC and can give an early assessment of response to treatment that correlates more powerfully with survival than do assessments made using other non-invasive imaging studies. The use of PET to exclude patients with incurable extensive disease from potentially toxic radical radiotherapy will significantly improve the overall results of treatment with this modality, and early diagnosis of limited recurrent disease could potentially facilitate salvage therapies. Furthermore, by decreasing futile attempts at curative treatment, expensive radical radiotherapy resources can be more effectively used.

However, despite the clear benefits of PET, the uniformly positive PET literature should be interpreted with caution. Most reports describe large series of patients managed at centres with extensive experience in PET imaging and treating lung cancer. The best results are obtained when scans are read by an experienced nuclear medicine physician with all available clinical information and with close liaison with the treating physician. There has been a rapid proliferation of smaller PET centres, and it is possible that not all of these will have the experience or expertise to produce the best possible images and interpret them appropriately. The learning curve is steep, so PET scans should be viewed with considerable caution until both the PET physician and the treating oncologist have experience and expertise in their use.

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11.5 Heavy Particles in Lung Cancer

David A. Bush

CONTENTS

11.5.1 Introduction

Lung cancer remains a major medical problem worldwide, with a clear need for more effective treatments. Unfortunately, the inadequacies in lung cancer treatment are well seen by reviewing the history of lung cancer treatment with radiation therapy. In patients with unresectable lung cancer, radiation therapy is the main modality used to attempt to eradicate gross disease from within the thorax. Early work in lung cancer used chest radiography to evaluate local tumor control and led to a conclusion that local disease control was reasonably good while systemic failure was responsible for excessive mortality. With advances in imaging techniques and use of more aggressive follow-up evaluations, it is clear that local tumor control is not as good as initially thought. Local failure rates following radical thoracic radiotherapy have been reported to be as high as 60–80%. Clearly, if radiation therapy is going to play a significant role in improving cure rates in lung cancer patients, local disease eradication within the chest will need to be substantially increased. Virtually all local relapses following radiation therapy can be traced back to either poor targeting of the primary tumor site and/or delivery of an inadequate dose of radiation treatment. It would seem reasonable that simply increasing the dose delivered would confer an increased incidence of tumor control; however, serious treatment-related side effects such as pneumonitis and esophagitis would likely also increase. Thus, there appears to be a need to deliver accurate, high-dose radiation treatment without excessive doses given to sensitive normal tissues for patients with lung cancer.

Before discussing the role of heavy particles in treating lung cancer, it is important to understand some definitions and basic physical and biological differences of this treatment compared with X-ray (photon) treatment. As the name implies, particles have size and mass; hence, they are subject to the laws of momentum, in contrast to electromagnetic radiation (photons). Particles may be charged (protons and heavy ions) or uncharged (neutrons), which has a profound effect on how they deposit energy (dose) in tissues. The term "heavy" implies that these particles are heavier than electrons; however, there is a large variation in the size (i.e., atomic weight) of particles used for therapy, which dictates the biological effect of these beams. Particle beams differ from photon beams in two important ways: dose distribution and biological effectiveness.

11.5.2 Dose Distribution

It is first important to understand how photons deposit their energy in human tissues. As a photon beam enters tissues of the body, the deposited dose quickly builds up and reaches a maximum only a few centimeters below the skin's surface. From there, the dose declines exponentially as it traverses through the body until the beam exits. Most lung tumors lie deep within the body, generally within a range of 5–20 cm from the skin's surface. Thus, when a photon beam reaches the depth within the body where the tumor lies, it generally is delivering approximately 60–80% of the maximum dose administered. Once

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the photon beam traverses the tumor's full thickness, it continues to deliver radiation treatment to tissues distal to the targeted region until the beam exits the body.

Charged particles deposit their energy in tissues with a distinctly different distribution when compared with X-rays. Charged particles have a finite range in tissue and deposit most of their energy just before stopping. This is known as the Bragg peak effect. For a collimated proton beam of a given energy, the dose delivered upon entering the body proximal to the intended target is approximately 50–60% of the maximum dose delivered. By varying the beam energy, the high dose or Bragg peak region can be made to cover the full thickness of the intended target region, thus delivering the maximal dose of each beam to the intended target instead of just the below the skin, as X-rays do. Once a charged particle beam has reached the distal edge of the targeted region, the beam stops, and no further dose is delivered to distal tissues. Thus, when charged particle beams are compared with X-ray beams, it can be easily shown that a higher proportion of the dose is delivered to the intended target while minimizing the dose delivered outside the targeted region, reducing normal tissue exposure. While avoiding a larger portion of normal tissue, charged particle beams may safely deliver higher doses to targets within the thorax than is possible with conventional X-ray beams. A graphic representation of the dose delivered per depth in tissue for photons and charged particles (i.e., protons) is shown in Fig. 11.5.1.

Neutrons are also considered heavy particles; however, they differ from other particles in that they possess no charge. This lack of charge has a significant effect in the way neutrons deposit their dose in tissues. In fact, dose distributions for collimated neutron beams are very similar to those of low-energy X-ray beams (Raju 1980). Thus, neutrons do not possess the normal tissue-sparing properties described above for charged particle beams.

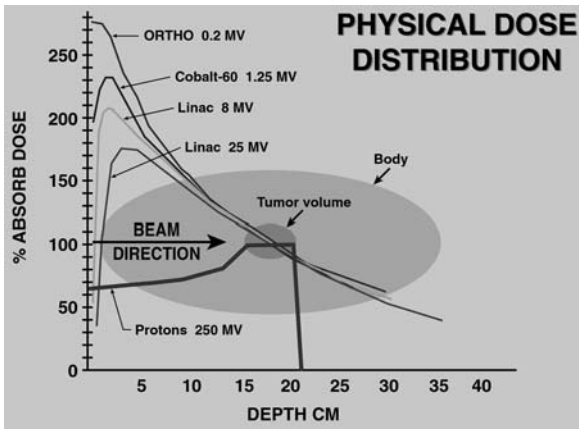


Fig. 11.5.1 Percent dose deposited per depth in tissue for photon and charged particle beams

11.5.3 Biological Effects

Throughout the history of radiation therapy, the vast majority of clinical outcomes have been generated through the use of X-rays or photons. This information was gathered clinically over many years of radiotherapy practice. Through this trial-and-error process, normal tissue tolerance levels have been established for vital organs such as the spinal cord and bowel. This information is vital to the safe application of radiotherapy to patients with various malignancies. These guidelines, however, cannot be applied to all radiation types. Photons are known to be a sparsely ionizing type of radiation treatment. Some heavy particles, though, are known as densely ionizing radiation. This means that many more ionizations will occur per path length for a heavy particle as compared with an X-ray; therefore, certain heavy particle radiation beams can produce different biological responses even if the physical dose is the same.

This has led to the concept known as relative biological equivalents (RBE). The RBE for a particular type of radiation is a factor that is determined experimentally or clinically and that, when multiplied by the physical dose, results in an equivalent biological effect when compared to the same dose given with photons from a cobalt-60 source (Hall 2000). For example, if a type of radiation was found to have an RBE of 2 for spinal cord injury, a dose of 25 Gy of that type of radiation would be expected to cause the same injury to the spinal cord as would 50 Gy of cobalt-60 photons.

RBE, however, has proven to be a difficult parameter to measure. Even for a given radiation type, a number of factors can alter the RBE, such as radiation dose, the number of fractions, and dose rate, as well as the tissue and endpoint being studied. Thus, there may not be a single RBE value that is appropriate for a radiation type in all situations. Densely ionizing heavy particle beams that have clinically significant associated RBEs are neutrons and heavy charged ions such as carbon and iron. These radiation types may have considerable uncertainties as to the appropriate dose to administer for tumor eradication, as well as

for normal tissue complications. Hence, a need exists to collect a large body of clinical data to determine the safe and effective radiation doses when administering these types of radiations. Protons, however, have a linear energy transfer (LET) and RBE that differ little from that of cobalt-60 X-rays. Thus, it is easier to extrapolate safe and effective dose levels from the long history of X-ray therapy to help guide treatment plans when proton beams are used.

11.5.4 Clinical Results

Neutron Therapy

Non-small cell lung cancer (NSCLC) frequently presents with large volume disease within the chest. Large tumors generally have areas of hypoxia that are relatively radioresistant. Because the biological effect of neutron therapy is less dependent on oxygenation than is X-ray therapy, neutrons were thought to be valuable in treating patients with large lung tumors.

In the 1970s, Eichorn (1982) began using neutron therapy in patients with lung cancer. He treated patients with various combinations of photon and neutron therapy and used autopsy information to assess the results in terms of local tumor eradication. He found that complete pathologic tumor response with photon treatment was 33%, compared with 48–51% in patients receiving various proportions of neutron therapy. This was felt to be a strongly positive result and led to a number of prospective trials.

Based on these early encouraging results, the Radiation Therapy Oncology Group initiated the first of two randomized trials evaluating neutron therapy in lung cancer (Laramore et al. 1986). The first trial began in 1979 and enrolled 113 patients with unresectable NSCLC. Subjects were randomized to three treatment arms. The control arm received 60 Gy in 30 fractions over 6–7 weeks with conventional X-ray therapy. There were two experimental arms, with one receiving neutron radiation alone to a total dose of 18 neutron Gy in 12–24 fractions over 6–7 weeks. The second arm received "mixed beam" irradiation in which patients received two neutron treatments and three photon treatments per week. The study was designed so that the biological effective dose was essentially equivalent in all three treatment arms. The overall local control and long-term survival rates showed no differences in the three treatments, but a higher number of life-threatening and fatal side effects were noted in patients treated with increasing neutron dosages. These toxicities mainly consisted of pulmonary complications, subcutaneous fibrosis, and myelitis. The severe toxicity rate was 5% in the photon arm, 14% in the mixed-beam arm, and 31% in the neutron-alone arm. Five complications were fatal, occurring only in the neutron-treated patients and related to pulmonary complications and myelitis. Reasons given for this increased complication rate include low-energy neutron generators, poor beam shaping and port verification techniques, and inadequate understanding of the RBE values used in dose calculations.

In the mid-1980s, modern neutron treatment facilities became available in the United States. These facilities were equipped with hospital-based cyclotrons that could produce high-energy neutron beams with isocentric beam delivery systems. Prospective trials were developed to determine the optimal neutron dose for lung cancer, and it was determined that 20 Gy in 12 fractions over 4 weeks would be used in a subsequent randomized trial. In 1986, the Neutron Therapy Collaborative Working Group 85–24 was initiated. A total of 200 patients were enrolled and were randomized to receive definitive thoracic irradiation with either photons or neutrons (Koh et al. 1983). Patients receiving photon treatment completed 66 Gy in 33 fractions over 7 weeks. Patients randomized to receive neutron therapy received a total of 20.4 neutron Gy in 12 fractions over 4 weeks, with spinal cord being limited to 10 neutron Gy. All patients were required to undergo treatment simulation, CT-based treatment planning, and port film verification. Statistical analysis revealed no observed difference in overall survival, with a median survival in neutron-treated patients of 9.7 months. A subset analysis was performed, which revealed that patients with squamous carcinoma had improved 2-year survival of 16% vs. 3% in the photon arm (p=0.02). Treatment toxicities were described as similar in both treatment groups; however, three treatment-related deaths occurred in the neutron arm.

In 1987, Livingston et al. (1987) reported on a prospective trial combining chemotherapy and neutron therapy in patients with advanced lung cancer. Seventy-three patients were enrolled in this trial and received induction chemotherapy with vinblastine, mitomycin C, and cisplatin. Patients then received neutron therapy to areas of gross disease within the chest of 17–22 neutron Gy in 12 fractions over 4 weeks. During neutron therapy, patients also received elective brain radiation of 36 Gy. Following neutron therapy, chemotherapy was again given to

complete a total of four cycles. Survival at 2 years of all patients treated in this trial was approximately 12%. Twelve (16%) patients died of treatment-related causes. It was believed that at least some of the deaths were in part due to the use of physics-based neutron generators with limited treatment delivery systems.

In light of these clinical results, it is difficult to foresee a significant role for neutron therapy in the future NSCLC treatment. Because of the poor dose distribution characteristics of neutron beams combined with an increased RBE, treatment-related toxicities seem to be increased compared with the current literature reports on conformal photon therapy. Many neutron facilities are no longer clinically active, and little clinical research is currently being conducted on the use of neutron therapy in lung cancer.

Proton Beam Therapy

Proton therapy differs from neutron therapy in two important ways. First, the RBE of proton beams is quite similar to that of photon beams, so knowledge of normal tissue tolerance is more accurately known. Proton beams also have a favorable dose distribution profile because of the Bragg peak effect of charged particle beams. Proton therapy has been in clinical use since the late 1950s at the Harvard Cyclotron Laboratory and at the Lawrence Livermore Laboratory in Berkeley, California. Although initial work in proton therapy established a clinical role for this treatment in patients with tumors in the eye and the base of the skull, little work was done in lung cancer.

In 1991, the first hospital-based proton treatment center became operational at Loma Linda University Medical Center (LLUMC), with a goal of applying this form of treatment to tumors in other parts of the body (Slater 1992). It was believed that patients with localized NSCLC could benefit from the normal tissue-sparing effects of proton beam therapy by allowing the safe application of significant dose escalation. The potential gain with dose escalation with proton beams is well described in a publication by Fowler (2003), who predicted significant gains in local tumor control by using this modality.

The first clinical trial in patients with NSCLC initiated at LLUMC targeted patients with stage I, medically inoperable lung cancer. Eligible patients were staged with a contrast-enhanced CT scan, with the addition of PET scanning when it became available. The region targeted for treatment included the gross tumor volume within the lung, with added margin for respiratory motion. No treatment was given to hilar or mediastinal lymph nodes. Initially, the dose delivered was 51 CGE in 10 equally divided fractions. Once the safety profile of this treatment was established, the dose was increased to 60 CGE in 10 fractions. This fractionation schedule is approximately equivalent to 80 Gy given in standard fraction sizes.

A recent analysis of 68 patients treated in this trial has been performed. The median patient age was 72 years, with an average primary tumor size of 3.3 cm. Most patients were medically inoperable because of smoking-induced chronic obstructive pulmonary disease that was reflected by an average pretreatment FEV1 of 1.15 liters. There were no enrollment restrictions based on tumor size, performance status, or pulmonary function. Median follow-up time was 30 months. Acute or subacute pulmonary toxicity was not observed in this group of patients. No cases of symptomatic radiation pneumonitis occurred. Likewise, no esophageal or cardiac toxicity was identified. All patients completed the prescribed treatment without difficulty. The 3-year local control rate was found to be 74%, and the disease-specific survival was 72% (Fig. 11.5.2). The majority of deaths seen in this cohort were from intercurrent disease. There was a significant improvement in local control for tumors <3 cm compared with tumors that were larger (87% vs. 49%), with a trend towards improved survival. Proton treatment and radiographic outcome for one patient in this trial are shown in Fig. 11.5.3 and Fig. 11.5.4.

Pulmonary toxicities were closely monitored in this trial. Initially, all patients underwent high-resolution CT scans to access radiographic lung injury. It was found that when local field proton beam therapy was used, considerably less lung injury was identified when compared with a similar group of patients treated with a combination of protons and X-ray ther-

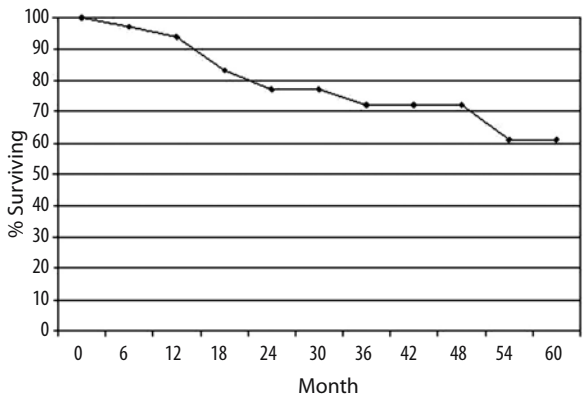
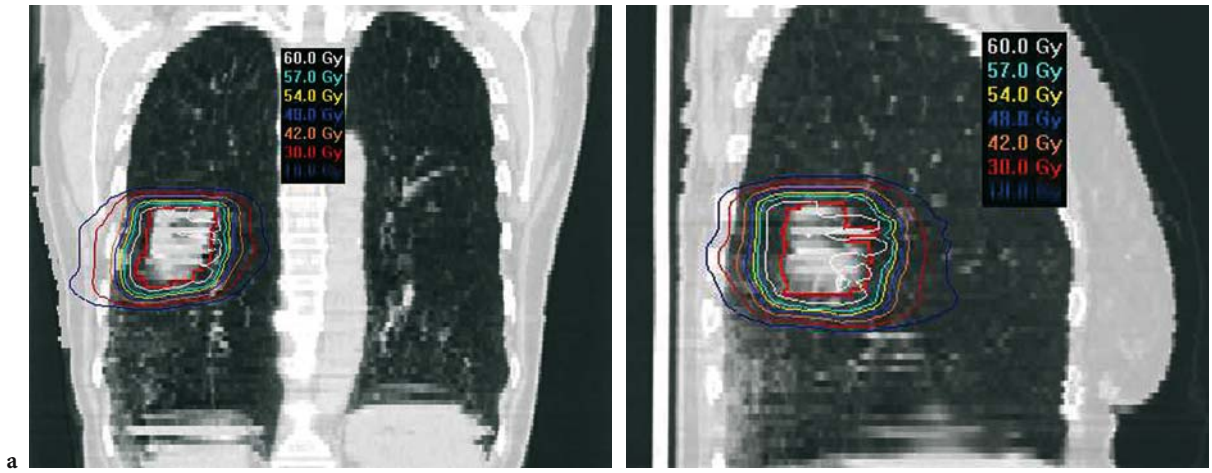


Fig. 11.5.2 Disease-specific survival of stage I lung cancer patients treated with proton beam



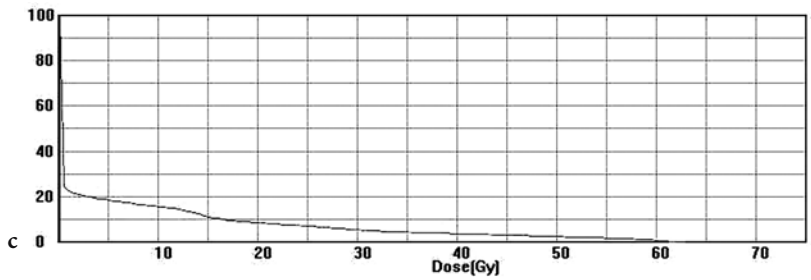


Fig. 11.5.3 a, b Isodose plan for stage I lung cancer patient treated with proton beam. **c** Dose-volume histogram showing the percentage of total lung volume receiving a given dose

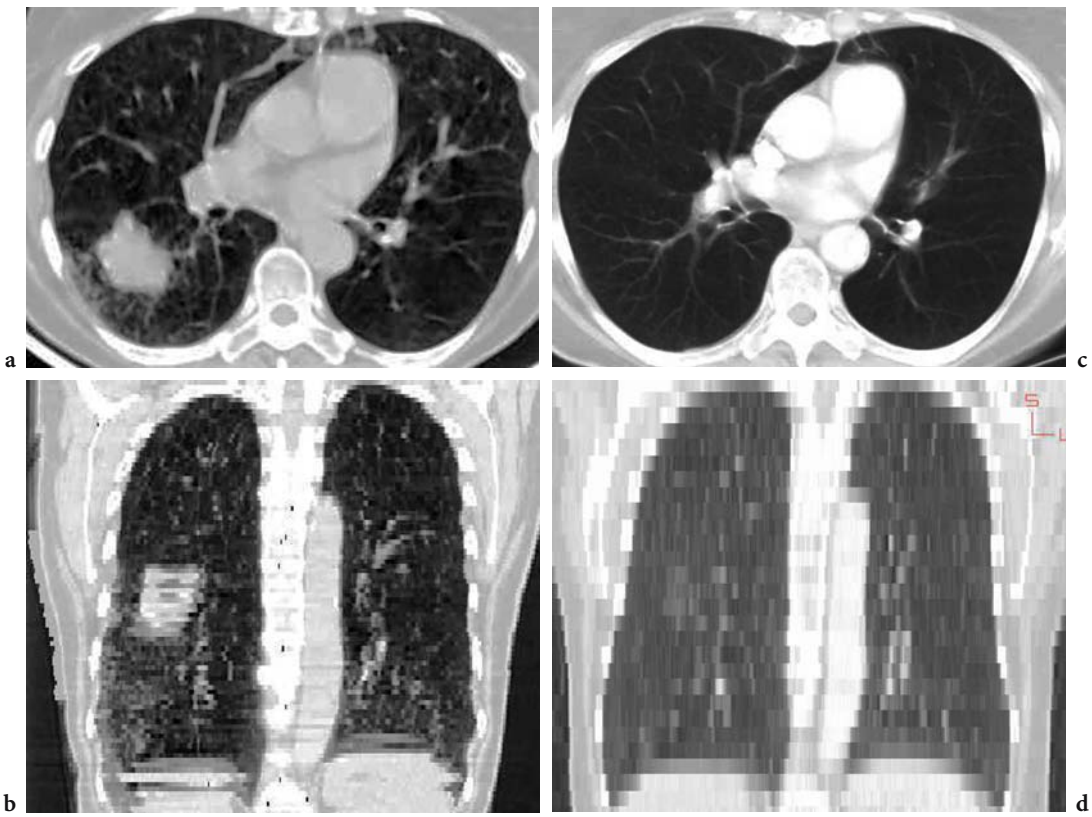


Fig. 11.5.4a–d CT images showing lung tumor before and after treatment. **a, b** Pretreatment. **c, d** Six months after proton therapy

apy to a larger volume (Bush et al. 1999). This finding underscores the close correlation between volume of lung irradiated and the degree of pulmonary injury observed. Pulmonary function both before and after treatment was also evaluated. An assessment of these results demonstrated no decrement in pulmonary function following treatment (Bonnet et al. 2001). Based on the lack of observed morbidity or pulmonary toxicity, and increased in-field failure in patients with larger tumors, a dose escalation is planned.

After this initial work in early-stage lung cancer, a new study was initiated for patients with locally advanced NSCLC that also incorporated chemotherapy. The concept in this trial, which continues to enroll patients, is to implement treatment modalities that have demonstrated improved outcomes in this group of patients. This trial incorporates treatment paradigms such as induction chemotherapy, concurrent chemoradiotherapy, and high dose radiation delivered in an accelerated fractionation schedule. Each of these concepts has been shown to improve outcomes in lung cancer patients in prior randomized trials. Patients enrolled in this trial have stage II-IIIB NSCLC without evidence of systemic disease. Subjects receive two cycles of induction chemotherapy with Taxol and carboplatin. Proton beam therapy is administered to include the mediastinum and primary lung tumor. A proton beam boost is delivered to the region of gross disease as a second daily fraction in a twice-daily fashion. The total dose delivered to subclinical disease is 46 Gy in 23 fractions, whereas gross disease receives a total of 76 Gy in 38 fractions over 5 weeks. Weekly chemotherapy with Taxol and carboplatin is given during proton treatment. Fifteen patients have completed this treatment with follow-up adequate to assess acute side effects. No severe hematologic complications or esophageal or pulmonary injuries have occurred.

Proton beam therapy is also available in Japan at the University of Tsukuba, and Shioyama et al. (2003) have reported their experience in treating lung cancer patients. The report describes 51 patients with NSCLC who were treated with proton beam therapy; however, the majority (28) had clinical stage I disease. A range of doses and fractionation schedules were used, but most patients received a hypofractionated treatment schedule with an average biological equivalent dose of approximately 80 Gy. The results were strikingly similar to those produced at Loma Linda. The overall and cause-specific survival rates were 60% and 66%, respectively, for stage I patients. The overall local control rate was 57% at 5 years. Improved local tumor control and survival were noted for T1 tumors vs. T2 lesions. Observed pulmonary side effects were reported to be minimal. Further study on using hypofractionated proton beam radiotherapy for early-stage lung cancer is being conducted at this institution.

These results seem to indicate a role for proton beam radiotherapy in patients with early-stage lung cancer. Pulmonary complication rates are remarkably low, while local tumor control and disease-specific survival rates seem improved over those reported with conventional radiotherapy techniques. Dose escalations are currently under further evaluation. Clinical trials using proton therapy in conjunction with chemotherapy for locally advanced lung cancer are currently underway.

Heavy Ion Radiotherapy

Heavy ion beams have also been used to treat patients with lung cancer. These beams have dosimetric properties that are virtually identical to those of proton beams. They exhibit a Bragg peak effect wherein the maximal dose deposited is delivered just before the beam stops. Thus, highly conformal dose distributions can be delivered to localize targets within the lung, as with protons. The biological effectiveness of these beams, however, differs substantially from that of protons. The most frequently used heavy ion in clinical use is carbon. The RBE used in most settings for carbon ions is 3, similar to that in neutron therapy. This increased biological effect may be useful in increasing the chance of complete tumor eradication, but it may be harmful if the dose is deposited in normal tissue regions. It would be expected that heavy charged particles may produce substantially less normal tissue damage compared with neutron therapy because of the improved physical dose deposition.

A facility capable of delivering high-energy carbon ion radiotherapy has been constructed in Chiba, Japan. Treatment for lung cancer began in 1994 and has been reported on by Miyamoto et al. (2003). As with proton therapy, the researchers elected to begin their studies with early-stage NSCLC patients who are medically inoperable or refused surgery. Their report summarizes outcomes of 81 patients with clinical stage I lung cancer treated with carbon ion therapy using doses ranging from 59.4 to 95.4 Gy equivalence in a dose escalation trial. They reported three cases of grade 3 radiation pneumonitis that resolved after therapy and was not felt to be a dose-limiting factor. Local tumor control was seen in 76% of patients after 5 years. Improved tumor control was

identified in patients with smaller tumors as well as the use of higher doses. Cause-specific survival and overall survival at 5 years was 60% and 42%, respectively. A significant correlation between tumor size and survival was found, similar to that reported with proton therapy.

Kadono et al. (2002) reported on the pulmonary function following heavy ion treatment in this group of patients. They detected the significant decrease in FEV1 and total lung capacity; however, this decrease was relatively small—6% and 4%, respectively. Other parameters such as DLCO and PAO_2 showed no significant changes. The authors concluded that no severe loss of pulmonary function occurred following this form of treatment.

Heavy ion radiotherapy with carbon ions appears to produce a good expectation of local tumor control and disease-specific survival in patients with early-stage lung cancer. The rate of significant pulmonary toxicity appears low. As with proton beam therapy, this may represent an improvement compared with conventional photon therapy. To avoid severe normal tissue complications, as seen with other high RBE beams (neutrons), carbon ion radiation therapy should be used cautiously if it is applied to patients with locally advanced tumors that require mediastinal treatment.

11.5.5 Summary

A strong scientific rationale exists for using heavy particle beams in lung cancer patients. Neutron radiotherapy failed to show a significant advantage compared with X-ray therapy, and normal tissue complications were considerable. A poor understanding of the biological effectiveness of these beams as well as poor quality of treatment delivery probably contributed to this outcome. Emerging evidence from two facilities using proton beam radiotherapy suggests that this type of treatment may provide a significant advantage for patients in early-stage lung cancer. Proton therapy likely represents the most "clinic-ready" particle for treatment because of the superior dose distribution provided by charged particle beams, with a well-established biological effect after years of clinical use. Heavy charged particles such as carbon ions represent an exciting area of research that needs to be pursued; however, the increased biological effect of these beams needs to be carefully evaluated in the clinical setting.

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11.6 Translational Research in Radiation Oncology of Lung Cancer

Yuhchyau Chen

CONTENTS

11.6.1 Introduction

Although radiation is an essential modality for cancer therapy because of its powerful DNA-damaging effects, those same effects unfortunately cause simultaneous injury to patients' normal tissues. Thus the success of radiotherapy relies on the fine balance between eradicating cancer cells and minimizing injury to normal tissues. In lung cancer research and treatment, basic biomedical research and clinical studies have flourished in the past two decades, but lung cancer remains the most deadly cancer of all types. Despite the explosion of discoveries that have elucidated our understanding of the molecular mechanisms and regulatory signals involved in cancer progression, transferring knowledge into practical advances for treating lung cancer and preventing side effects from cytotoxic therapy has been a more deliberate process. The translation of knowledge gained from the laboratory into improving treatment outcomes will serve as the vital bridge between scientific discovery and the welfare of patients and will offer hope for further improvement of lung cancer therapy.

Because the scope of this chapter is limited, it will focus on two areas of translational research in radiation oncology for lung cancer treatment: 1) the attempt to potentiate radiation effects by a unique radiosensitizing strategy that optimally integrates paclitaxel and radiation to enhance radiation's local effects in treating locally advanced non-small cell lung cancer (NSCLC), and 2) the cytokines involved in radiation lung injury that lead to radiation pneumonitis and progressive fibrosis.

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11.6.2 Optimizing Paclitaxel Chemoradiation Sensitizing Strategy in Stage III Non-Small Cell Lung Cancer: A Phase I/II Study Based on Pre-Clinical Research

The treatment of locally advanced, stage III NSCLC remains a challenging task for oncologists because of lack of local disease control and high rates of distant disease failures. Although aggressive combination chemoradiation therapy is now the new standard of treatment for stage III NSCLC, 5-year survival rates are only in the range of 5%–25%, and local failure rates have been as high as 55%–85% (Dillman et

al. 1990; Sause et al. 2000; Schaake-Koning et al. 1992; Arriagada et al. 1991; Morton et al. 1991). In addition, due to aggravated toxicity from therapy, combined modality treatment is offered to a limited population of patients in good clinical performance status only. Both the optimal regimen and sequence of chemoradiation therapy for stage III NSCLC remain unclear.

At least two randomized studies have demonstrated that concurrent chemoradiation is more effective than sequential chemotherapy followed by radiation for the treatment of stage III NSCLC, supporting the radiosensitization mechanism in improving survival of lung cancer patients (Furuse et al. 1999; Curran et al. 2000). The phase III randomized study conducted by the Radiation Therapy Oncology Group (RTOG) for stage III NSCLC represents a good example of the dilemma in trading toxicity for efficacy. RTOG 94–10 compared three arms of chemoradiation treatments: sequential chemoradiation vs. concurrent chemotherapy and once-daily (QD) radiation vs. concurrent chemotherapy and twice-daily (BID) radiation. The combined chemoradiation strategy resulted in a modest survival gain in the concurrent chemoradiation arm, with a median survival of 17 months for the concurrent QD arm vs. 14.6 months for the sequential chemoradiation arm (P=.038), and a median survival of 15.6 months for the concurrent BID arm. Most notable was a dramatic increase in grade 3/4 acute nonhematologic toxicities such as esophagitis, pneumonitis, and others, observed in 48% of the concurrent QD arm, 30% of the sequential arm, and 62% of the concurrent BID arm (Curran et al. 2000). The observed increase in normal tissue toxicity in concurrent chemoradiation treatment supports the notion that while concurrent chemoradiation enhances radiation tumoricidal effects, it simultaneously enhances injuries to normal tissues. As cancer therapy continues to explore newer agents in combination with radiation, balancing the therapeutic effect and treatment-related toxicity will also continue to challenge oncologists.

11.6.2.1 Paclitaxel Chemoradiation for NSCLC

Despite the convincing evidence from randomized studies of stage III NSCLC that chemoradiation is superior to radiation alone, the optimal chemotherapeutic agent(s), dosing schedule, sequence, and timing of chemoradiation to achieve the best therapeutic gain remain unknown. Because of lack of effective therapy for stage III NSCLC, newer agents including the 3rd-generation chemotherapeutic agents have been tested with the intent to improve the efficacy of combination chemoradiation for stage III NSCLC over cisplatin-based chemoradiation (Chen and Okunieff 2004). Among the 3rd-generation chemotherapeutic agents, paclitaxel has been the favorite chemotherapeutic agent investigated in many phase I/II clinical studies due to its putative radiosensitizing effect. Paclitaxel, as a single agent, has demonstrated response rates of 21–24% in the metastatic setting (stage IV) of NSCLC (Murphy et al. 1993). It is theoretically the ideal radiosensitizer due to its cytokinetic stabilization of the spindle microtubule resulting in arresting cells in the G2/M phase of the cell cycle, which is the most radiosensitive phase of the cell cycle (Sinclair and Morton 1966; Schiff and Horwitz 1980; Parness and Horwitz 1981; Manfredi et al. 1982; Kumar 1981; Rowinsky et al. 1988). The cytotoxic effect is attributed to tumor apoptosis after treatment with paclitaxel (Milas et al. 1995, Milross et al. 1996; Jordan et al. 1996; Pukkinen et al. 1996). For the interaction with radiation treatment, in vitro studies have also demonstrated the radiosensitizing effects of paclitaxel in a variety of cancer cell lines, including cervical cancer, ovarian cancer, astrocytoma, melanoma, pancreatic carcinoma, breast cancer, colon cancer, lung cancer, prostate adenocarcinoma, and others (Tishler et al. 1992; Steren et al. 1993; Geard et al. 1993; Rodriguez et al. 1995; Lokeshwar et al. 1995; Elomaa et al. 1995; Choy et al. 1993; Jordan et al. 1996; Pukkinen et al. 1996; Hornback et al. 1994). In addition to cell cycle and apoptotic effects, paclitaxel offers antineoplastic potential through other mechanisms such as enhancing tumor reoxygenation, thereby reducing the resistance of hypoxic cells to radiation and chemotherapy (Milas et al. 1995a). Furthermore, paclitaxel exhibits antiangiogenic effects on tumor vasculature by causing apoptosis of endothelial cells as well (Grant et al. 2003). In the clinical setting, there have been several different dose schedules of paclitaxel-based chemoradiation regimens reported for treating stage III NSCLC (Choy et al. 1994; Lau et al. 1997; Chen et al. 2003; Rathmann et al. 1999; Kirkbride et al. 1999; Brodin et al. 2000; Havemann et al. 1995; Rosenthal et al. 2000), but the optimal dosing schedule in integrating paclitaxel with radiation remains to be defined.

Because paclitaxel is a cell-cycle-specific agent, its effect can theoretically be optimized by timing radiation to allow for radiation injury at the G2/M phase of cancer cells. Because normal tissue and cancer cells have different growth kinetics, minimizing normal tissue injury is also possible if information from pre-

clinical research and pharmacokinetics are taken into consideration in the design of a clinical study. Here a phase I/II clinical study will be presented to illustrate the application of preclinical research on lung cancer cell lines and the pharmacokinetic characteristics of paclitaxel infusions to the design of the clinical study. The hypothesis is that maximum tumor control and minimal normal tissue injury can be achieved by strategically optimizing the timing of daily irradiation and low-dose paclitaxel treatment.

11.6.2.2 Pharmacokinetic Consideration of Paclitaxel for Radiosensitization

Understanding the pharmacokinetics of paclitaxel is essential for optimizing the timing of paclitaxel chemotherapy and radiation treatments to enhance radiation effects and reduce normal tissue side effects. The pharmacokinetics of paclitaxel infusion are unique in that not only does the drug concentration influence the pharmacokinetics of the drug, but also the infusion time significantly influences the pharmacokinetics of plasma concentration. Furthermore, bone marrow toxicity is directly related to the infusion time and drug concentration. Pharmacokinetic studies have reported a nonlinear disposition of paclitaxel in humans. In the reported clinical trials, the infusion time of paclitaxel has varied significantly: 1 h, 3 h, 24 h, or continuous. Gianni et al. (1995) compared the nonlinear disposition of paclitaxel with different drug concentrations and infusion times. As demonstrated in Fig. 11.6.1a, the shorter infusion time of 3 h resulted in a fairly rapid increase to a high peak plasma level at 2–3 h after infusion, which was followed by a rapid decline of plasma concentrations. The longer infusion time of 24 h was associated with a rise in plasma level to a moderately high plateau level for 24 h, followed by a slower decline of the drug concentrations.

As described by the same investigators, the decrease of absolute neutrophil counts from paclitaxel treatment was directly associated with the "duration" of plasma drug concentration above 0.05 μM (Fig. 11.6.1b). Thus, the long plateau of plasma concentration ≥0.05 μM from a 24-h infusion was associated with more myelotoxicity, and the shorter infusion time of 3 h was associated with less myelotoxicity despite the higher initial peak plasma level. In the design of a clinical study when neutropenia is a concern and when radiosensitization is the primary interest, the choice of the shorter infusion time will be the logical one.

11.6.2.3 Paclitaxel Cell Cycle Effect on Human Cancer Cell Lines

The cell cycle effect of paclitaxel on human cancer cell lines was investigated in cell lines A431, A549, and

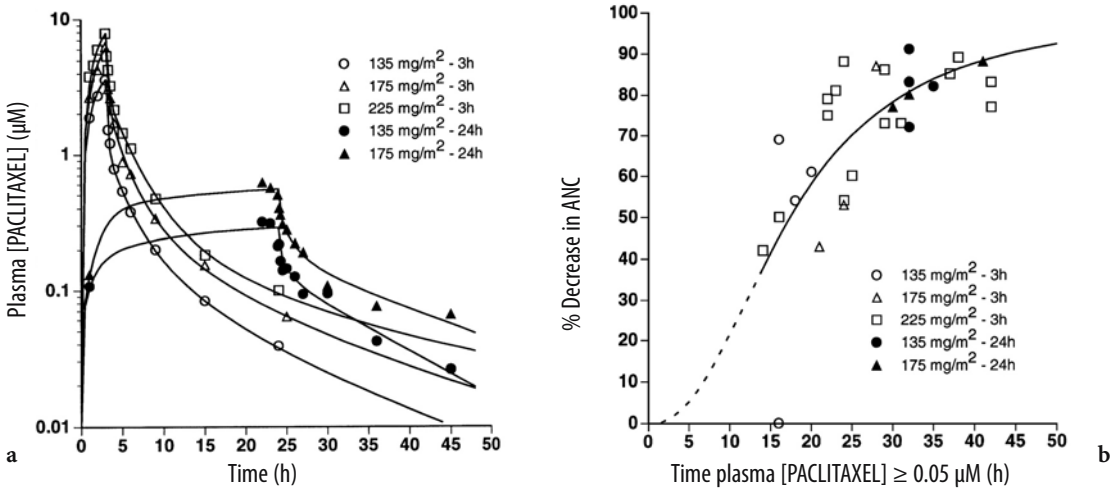


Fig. 11.6.1 a Plasma paclitaxel concentration vs. time profiles of representative patients who received the drug at various indicated doses and infusion durations. Symbols represent actual measured plasma paclitaxel concentrations and lines represent model fit curves. **b** Pharmacokinetic/pharmacodynamic relationship between duration spent at a plasma paclitaxel concentration ≥0.05μM/l and percentage reduction in absolute neutrophil count in the first course of therapy. Symbols represent individuals treated at different doses and schedules. Curve depicts the sigmoid E_{max} model fit to the data. The broken portion of the curve represents that region for which data were not available. Adapted from Gianni et al. (1995). Reprinted with permission from the American Society of Clinical Oncology

NCI-H520. A431 is a human epidermoid cancer cell line; A549 and NCI-H520 are both human lung cancer cell lines. Fig. 11.6.2a demonstrates the cell cycle progression of cell line A431 after a 3 h treatment with 1μM paclitaxel. G2/M accumulation was appreciated at approximately 4 h after drug treatment. Further cell cycle progression to the G2/M phase was observed and was followed by a dynamic redistribution of cell cycle to return to the baseline by 48 h. In an attempt to sustain the G2/M cell cycle arrest for maximal radiosensitizing effect, an in vitro study was conducted by pulsing paclitaxel every 48 h and analyzing the cell cycle effect 24 h later. Fig. 11.6.2b shows that by pulsing paclitaxel on alternate days using one-third of the concentration (0.33 μM), there was sustained cell cycle arrest in the G2/M phase for 6 days. Sustained G2/M cell cycle arrest by pulsing paclitaxel at lower doses was observed in all three cancer cell lines and supported the application of this schedule to the design of a clinical trial (Chen et al. 2003a).

11.6.2.4 Paclitaxel Apoptotic Effect

In the current study, cells were treated with paclitaxel for 3 h and assayed by the Tunnel assay for apoptosis. As shown in Fig. 11.6.3, although the percentage of apoptotic cells varied among these three cell lines, common observations were made in that higher doses (600 nM and 2 μM) of paclitaxel caused more apoptosis than the lowest dose (200 nM). It was also observed that more apoptosis occurred at 48 h after drug treatment than at 24 h. The timing of maximal paclitaxel apoptotic effect also supports pulsing paclitaxel treatment every 48 h (Chen et al. 2003a).

11.6.2.5 Schedule-Dependent Radiosensitizing Effect In Vitro

In preliminary studies, Keng et al. (2000) and Chen et al. (2001) investigated the schedule dependence of paclitaxel interaction with radiation in three lung cancer cell lines. Cells were treated in the culture with either 50 nM or 100 nM of paclitaxel for 3 h. The control received no paclitaxel. Radiation at various doses was delivered either immediately after the 3-h drug treatment (labeled as 3 h) or 21 h after drug treatment (labeled as 24 h). The clonogenic survival was assayed 2 weeks after radiation. The survival curves showed that delaying radiation resulted in fewer survival clones. When other cell lines were tested, it appeared that paclitaxel chemopotentiation of radiation was often through the sub-additive mechanism rather than an addi-

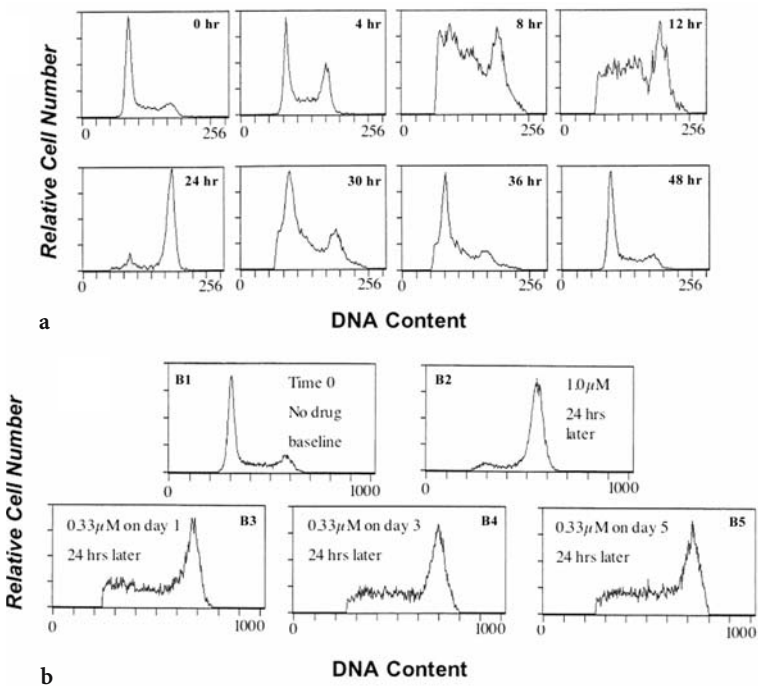


Fig. 11.6.2 a Human epidermoid cell line A431 culture was exposed to 1.0 μM paclitaxel for 3 h. After 3 h the drug-containing medium was removed and replaced with fresh culture medium. At different time intervals, cells were analyzed for cell cycle progression. Data show that treatment with paclitaxel caused G2/M arrest at approximately 4 h posttreatment, maximizing at 24 h. This was followed by a timely reversal of G2/M arrest to the baseline level by 48 h. **b** Cells were treated with paclitaxel for 3 h using pulsed dose schedules: Drug treatment with 0.33 μM on day 1 (B3); or day 1 and day 3 (B4); or day 1, day 3, and day 5 (B5). Drug-containing culture medium was removed after treatment and replaced with fresh maintenance medium. The cells were analyzed for cell cycle distribution at 24 h after drug removal. B1 shows the cell cycle distribution of baseline without drug treatment. B2 shows the maximal arrest of G2/M 24 hours after treatment with 1.0 μM paclitaxel. B3–B5 show that treatment with pulsed paclitaxel three times a week using one-third of the initial dose sustained the G2/M cell cycle effect. Adapted from Chen et al. (2003a), and used with permission

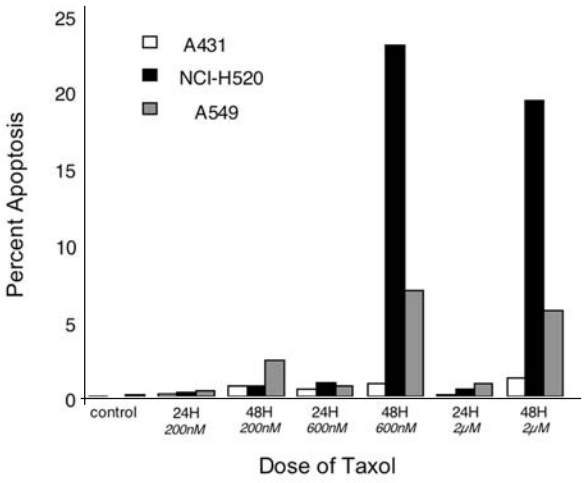


Fig. 11.6.3 Human cancer cell lines A431, A549, and NCI-H520 were treated with paclitaxel at 200 nM, 600 nM, or 2 μM concentrations. Cells were analyzed for apoptosis using Tunnel assay at 24 h as well as 48 h after drug treatment. Data showed that apoptosis was more prominent at a higher drug concentration and was observed primarily at 48 h after drug treatment. Adapted from Chen et al. (2003a), and used with permission

tive or synergistic mechanism. Even in the subadditive situation, delaying radiation resulted in fewer surviving clones than immediate irradiation after drug treatment.

11.6.2.6 Clinical Protocol of Pulsed Paclitaxel and Radiation

A phase I/II clinical study for stage III NSCLC was designed taking into account the pharmacokinetic information, the timing of radiosensitization, and the cell cycle and apoptotic effect of paclitaxel from the preclinical studies. A 1 h infusion time was chosen to allow for a short exposure time to the drug for sensitization, followed by a rapid clearing of plasma drug concentration to avoid sensitizing normal tissues and to allow for less cytotoxicity to bone marrow. The clinical trial design dictated low-dose paclitaxel infusion in the morning on Monday, Wednesday, and Friday. Thoracic radiation (XRT) was given after 4:00 PM on the days when patients received paclitaxel, to allow for a minimum of a 4 h interval for cell cycle progression. On Tuesday and Thursday, when there was no paclitaxel treatment, XRT was given any time after 11:00 AM. For the phase I study, the starting dose of paclitaxel was 15 mg/m^2 with a dose escalation in 5 mg/m^2 increments. The average XRT dose was 60–65 Gy to gross disease and 45–58 Gy to microscopic disease, given at 1.8 Gy daily fractions over 6–7.5 weeks. Forty-one patients were enrolled (23 for the phase I study and 18 for the phase II study), and 33 completed treatment. Eight patients did not complete protocol treatments due to acute allergic reactions in three, distant disease spread during therapy in three, and two intercurrent deaths unrelated to therapy. Stage distribution of patients with NSCLC was two in stage I, one in stage IIB, 15 in stage IIIA, and 22 in stage IIIB. One patient had stage II mesothelioma.

11.6.2.7 Tumor Response, In-Field Tumor Control, and Survival

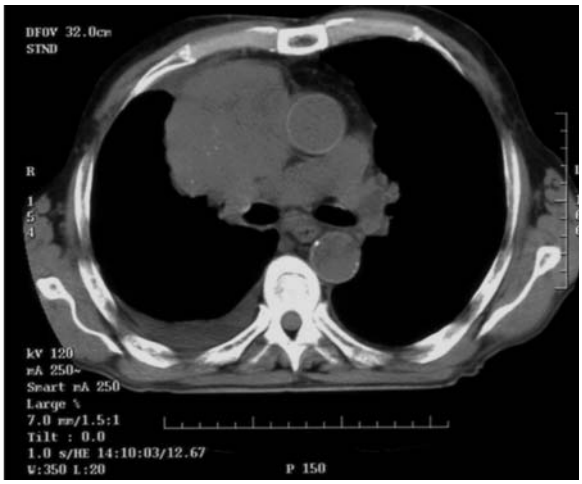
Almost all tumors had a remarkable and durable response to therapy using this regimen. Table 11.6.1 demonstrates the tumor response in the phase I study. Mean tumor shrinkage was 82%±14%, 84%±16%, and 84%±27% for dose levels I, II, and III, respectively, with an average primary tumor shrinkage at 4–6 weeks posttherapy of 83%±7% (95% confidence interval). The overall locoregional tumor response rate in the phase I study was 100% (2/17 [12%] complete response and 15/17 [88%] partial response). Fig. 11.6.4 demonstrates an example of radiographic tumor shrinkage 4 weeks after treatment in a patient with stage III NSCLC. Local control for those patients who completed radiotherapy in both phase I and II was 98%, with a median follow-up of 11 months. For patients who did not complete the 7.5-week protocol treatment, the survival was dismal. For those who completed the protocol treatment, the survival estimate was 52% at 1 year, 40% at 2 years, and 21% at 3 years, and survival for all patients enrolled was 46% at 1 year, 33% at 2 years, and 18 % at 3 years (Table 11.6.2). The in-field local control was durable up to the last day of follow-up for most patients, which has been demonstrated by the PET scans obtained 3 years later in some patients (Chen et al. 2003a).

11.6.2.8 Toxicity

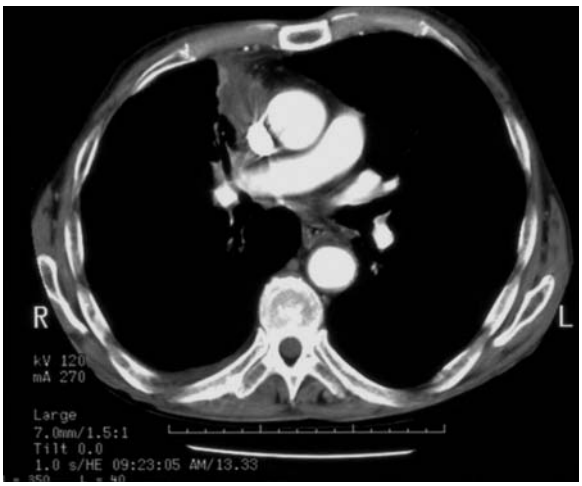
As anticipated, low-dose pulsed paclitaxel chemoradiation was associated with low toxicity. There was no treatment interruption from side effects of

Table 11.6.1 Tumor response 4–6 weeks after pulsed low-dose paclitaxel chemoradiation. Adapted from Chen et al. (2003a) with permission. (CR complete response [disappearance of tumor], PR partial response [>50% volume reduction])

Pulsed paclitaxel dose level	Tumor shrinkage	Response rate	
		CR	PR
I, 15 mg/m^2 (n=6)	82%±14%	2	4
II, 20 mg/m^2 (n=6)	84%±16%	0	6
III, 25 mg/m^2 (n=4)	84%±27%	0	4
Average	83%±7% (95% CI)	14%	86%



pre-treatment



1 month post-treatment

Fig. 11.6.4 Tumor response by CT scans. A large lesion of non-small cell lung cancer presented with superior vena cava compression in the right upper lobe of the lung. The lesion had completely disappeared 4 weeks after pulsed paclitaxel chemoradiation. Adapted from Chen et al. (2003), and used with permission

Table 11.6.2 Survival and local tumor control comparisons for stage III NSCLC treated with combination chemoradiation. Adapted from Chen et al. (2003a) with permission (RT radiotherapy)

Chemoradiation trials	2-year survival	3-year survival	Local control
Chen et al.: Pulsed Taxol and RT			
All patients	33%	18%	N/A
Patients completing therapy	40%	21%	98%
Schaake-Koning et al. (EORTC)			
Chemoradiation arm	26%	16%	30%[a]
RT arm	13%	------	19%
Furuse et al. (Japanese)			
Concurrent chemo arm	35%	22%	------
Sequential chemo arm	27%	15%	------
Dillman et al. (CALGB)			
Chemoradiation arm	26%	23%	------
RT arm	13%	11%	------
Arriagada et al. (French)			
Chemoradiation arm	21%	11%	17%[b]
RT arm	14%	5%	15%
Sause et al. (RTOG8808)			
Chemoradiation arm	32%	17%	------
RT arm	22%	11%	------
Morton et al. (NCCT)			
Chemoradiation arm	21%	------	46%[c]
RT arm	16%	------	45%

[a] Actuarial local control at 2 years
[b] Local control at 1 year
[c] Local control at time of first relapse

therapy. Toxicity was assessed for all patients in the phase I study, including one patient who received only two-thirds of the total radiation dose. There were no patients who experienced grade 3 or 4 neutropenia, thrombocytopenia, neuropathy, or cardiac arrhythmia. Three of 18 patients (17%) experienced grade 3 pneumonitis, and 3/18 (17%) experienced grade 3 esophagitis. No patients experienced grade 4 pneumonitis or esophagitis (Chen et al. 2001).

11.6.2.9 Future Directions in Chemopotentiation of Radiotherapy for Stage III NSCLC

At least eight different dosing schedules for paclitaxel chemoradiation have been employed in clinical trials for treating stage III NSCLC; as a whole, they

have shown both mixed response rates and toxicity profiles. These schedules include concurrent radiation with continuous infusion of paclitaxel, daily paclitaxel, twice-weekly paclitaxel, thrice-weekly paclitaxel, weekly paclitaxel, and once-every-3–4-weeks paclitaxel as a single agent or in combination with a second chemotherapeutic agent. The overall response rates have been in the range of 65–100%, but generally treatment toxicities also have been high, particularly in neutropenia, thrombocytopenia, esophagitis, and pneumonitis (Chen and Okunieff 2004). These effects are attributed to the radiosensitizing effect of paclitaxel on normal tissues as well.

Stage III NSCLC often presents with large tumor volume for the primary and the regional nodal disease. If the primary and regional tumors are not controlled, distant metastasis cannot be prevented. The lack of effective local therapy for inoperable NSCLC has been well recognized. Biopsy of tumors after therapy for locally advanced NSCLC resulted in only 17% local tumor control after chemoradiation therapy and only 15% after radiotherapy alone (Arriagada et al. 1991). Although chemoradiation is the current standard of care for stage III NSCLC, improvements in local disease control and survival have been modest, despite aggressive clinical investigations using numerous chemotherapeutic agents in conjunction with radiation in many phase I/II studies (Chen and Okunieff 2004). Among these dose schedules, the pulsed paclitaxel chemoradiation schedule, which was based on the preclinical research model, yielded superior primary tumor response and ultimate local control. These results support the idea that preclinical studies using cancer cell lines or animal models to address the sequence and timing of treatment modalities may prove more fruitful in gaining favorable clinical outcomes than those regimens built on an empirical basis. The superior local tumor control produced by pulsed paclitaxel chemoradiation for stage III NSCLC has provided new information in the understanding of cancer biology for this tumor stage. This regimen has overcome the local failure of stage III NSCLC for primary chest tumors as large as 10–12 cm at the time of presentation. The differential between the significant gain of local disease control (98% by pulsed paclitaxel vs. historical control of large randomized studies of 46% at best) vs. the modest survival gain (3-year survival of 21% vs. 15% of large studies of historical control) emphasizes that future therapy should aim not only for chemopotentiation for chest disease control, but also for more effective prevention and treatment of distant micrometastasis (Table 11.6.2). Antiangiogenic therapy, molecularly targeted therapy, gene therapy, hypoxic cell-targeted therapy, or other innovative therapeutic approaches may help prevent distant metastasis.

11.6.3 Cytokine Markers for Radiation Pulmonary Injury

11.6.3.1 Radiation Lung Injury

Due to normal tissue constraints, high-dose radiation to the tumoricidal dose for chest tumors has not been feasible using standard external beam radiation therapy. For standard radiation treatment to the chest, radiation dose has been limited to 60–65 Gy in order to avoid serious pneumonitis, esophageal stricture, fistula, or cardiac damage. Indeed, normal tissue injury from combined modality treatment for lung cancer has been the major dose-limiting factor for aggressive chemoradiation treatment. Through clinical experience using chemoradiation combined modality therapy for lung cancer, higher rates of both esophagitis and pneumonitis have been consistently observed (Chen and Okunieff 2004). Although interstitial pneumonitis has been recognized as a distinct clinical complication of cancer therapy, no routine diagnostic testing has been established as a simple way to assess the risk of pneumonitis prior to cancer treatment. Although most interstitial pneumonitis from cancer therapy is self-limiting, serious and potentially lethal incidences have been observed following all treatment modalities, including radiation therapy (Yorke et al. 2002; Jenkins et al. 2003; Ash-Bernal et al. 2002; Reckzeh et al. 1996), chemotherapy (Thomas et al. 2000; Sleijfer 2001; Wang et al. 2001), and even some of the more recently developed molecularly-targeted therapies (Rosado et al. 2003; Burton et al. 2003).

Among all types of interstitial pneumonitis caused by different agents, radiation-induced pneumonitis has been the most widely investigated, both in clinical and in laboratory research. The peak incidence of radiation pneumonitis is between 6 weeks and 3 months after completion of radiation treatments. However, it can also occur unexpectedly, with little or no warning; therefore, many attempts have been made to identify clinical risk factors for its onset. Clinical studies have reported a number of clinical factors, including total radiation dose, irradiated lung volume exceeding 20 Gy, mean lung dose, fractionation,

daily fraction size, performance status, pretreatment pulmonary function, gender, low pretreatment blood oxygen, high C-reactive protein, and others (Roach et al. 1995; Kwa et al. 1998; Graham et al. 1999; Inoue et al. 2001; Segawa et al. 1997; Robnett et al. 2000; Hernando et al. 2001). However, despite the identification of these clinical contributing factors, clinical research has not led to the development of a reliable and simple diagnostic laboratory test that could predict the risk of postradiation pneumonitis and, in particular, one that could be administered before starting therapy. The development of such a test using patient blood specimens or lavage fluid from bronchial washing is highly desirable because of the unpredictable nature of serious adverse events, which occur sporadically and without reliable clinical warning signs; its use prior to or during the early phase of therapy would allow clinicians to customize and modify therapy intensity for those patients at higher risk for serious interstitial pneumonitis.

11.6.3.2 Cytokine and Radiation Lung Injury

Progress made in recent years has increased our understanding of the cellular and molecular mechanisms involved in radiation lung injury. We have come to appreciate the complexity of radiation pneumonitis, now seen as a process involving active interaction among resident cells of the lung parenchyma and circulatory immune and inflammatory cells. There is increasing evidence of immune cells augmenting pneumonitis through complex autocrine, paracrine, and systemic regulatory mechanisms critically orchestrated by cytokines. Early studies suggested that radiation-induced lung injury was characterized by alveolar infiltrates of mononuclear cells, primarily $CD4^+$ T cells and macrophages/monocytes (mononuclear alveolitis), while exhibiting a relative lack of neutrophils (Fryer et al. 1978; Roberts et al. 1993), a common marker for infectious processes. In addition, several studies using bronchoscopy have confirmed this finding in patients with active pneumonitis, demonstrating the presence of mononuclear cells without significant numbers of neutrophils in the lavage fluids (Maasilta et al. 1993; Nakayama et al. 1996). Ultimately, mononuclear alveolitis is followed by progressive fibrosis of the lung as well as the deposition and accumulation of collagen fibers and extracellular matrix. Clinically, a decline in lung volume, compliance, and diffusion capacity is an unavoidable long-term consequence of lung fibrosis.

Animal research has induced multiple humoral factors (cytokines) in the lung by ionizing radiation (Rubin et al. 1995; Johnston et al. 1998; Hallahan et al. 1997, 2002). Rubin et al. (1995) reported a cascade of cytokine induction including interleukin 1α (IL-1α), transforming growth factor ß1 (TGF-ß1), and TGF-ß2 in lung tissue after radiation in animal research models. Because most animal research has been conducted in large single fractions of radiation, the relevance to cancer patients receiving fractionated daily low-dose radiation remains unclear. However, based on data from animal research models, it is hypothesized that when normal lung tissue is exposed to chemotherapy, radiation, oxygen, tumor necrosis factor (TNF-α), or other foreign insult such as lipopolysaccharide, a cascade of cellular and humoral events occurs as a tissue response to injury (Chen et al. 2003). There is interaction among alveolar epithelium (type I and type II pneumocytes), vascular endothelium, fibroblasts, lymphocytes, and macrophages through the humoral factors such as adhesion molecules, chemokines, inflammatory cytokines (TNF-α, IL-6, and IL-1), and fibrotic cytokines (basic fibroblast growth factor [bFGF], TGF-ß, and platelet-derived growth factor [PDGF]). Chemokines and adhesion molecules mediate leukocyte trafficking, extravasation from the vascular compartment, and homing to sites of inflammation (Kaseda et al. 2000; Butcher et al. 1996; Hallahan et al. 1997; Ding et al. 2000). Macrophages and lymphocytes are further recruited from the bone marrow to the chest, causing alveolar infiltrates during the pneumonitic phase.

At least three different classes of cytokines have been reported to correlate with the risk of radiation pneumonitis in patients: the inflammatory cytokines IL-1α and IL-6, the profibrotic cytokine TGF-β1, and intercellular adhesion molecule-1 (ICAM-1). These cytokines will be discussed in further detail.

11.6.3.3 Inflammatory Cytokines IL-1α and IL-6

Radiation pneumonitis can be regarded as an aberrant inflammatory response to radiation injuries. Both IL-1α and IL-6 are cytokines central to regulation of immunity and inflammatory responses. These cytokines are important immunoregulatory moieties and share some common immune functions. Both cytokines are pleiotropic inflammatory cytokines, recognized as "acute phase response" proteins. They are chemotactic for mononuclear cells, and they activate lymphocytes, regulate fevers, and precipitate a

fibrovascular response. While the source of IL-1α is primarily from monocytes and alveolar macrophages (Elias et al. 1985; O'Brien-Lander et al. 1993), IL-6 is synthesized by a variety of cells, including the alveolar macrophages, endothelium, type II pneumocytes, T lymphocytes, and lung fibroblasts (Kelley 1990; Cromwell et al. 1992; Crestani et al. 1994).

In vitro experiments have shown that alveolar macrophages exposed to radiation release increased quantities of IL-1α and IL-1β (O'Brien-Lander et al. 1993). It has also been shown that IL-1α stimulates human lung fibroblasts to produce IL-6 and stabilizes IL-6 messenger RNA production (Elias and Lentz 1990). Others have reported IL-1 induction of IL-6 in a variety of cells, including thymocytes, and have suggested that IL-6 is involved in many of the pleiotropic effects of IL-1 (Helle et al. 1988). Such in vitro work indeed suggests a regulatory relationship between the two inflammatory cytokines. Chen et al. (2001a, 2002) analyzed a panel of cytokines in serial blood samples of cancer patients receiving thoracic radiation. Radiation pneumonitis was diagnosed using the National Cancer Institute common toxicity criteria. Cytokine analysis was assayed for IL-1α, IL-6, MCP-1, E-selectin, L-selectin, P-selectin, TGF-ß1, and basic bFGF, using enzyme linked immunosorbent assay (ELISA). Among all these cytokines analyzed, only the two inflammatory cytokines, IL-6 and IL-1α, were persistently higher in patients who subsequently developed pneumonitis after radiation. Additionally, patients with high pretreatment circulating IL-6 and IL-1α levels had a greater chance of developing subsequent pneumonitis after therapy (Fig. 11.6.5), suggesting the possibility of using pretreatment IL-1α and IL-6 levels to predict patients at risk for radiation pneumonitis.

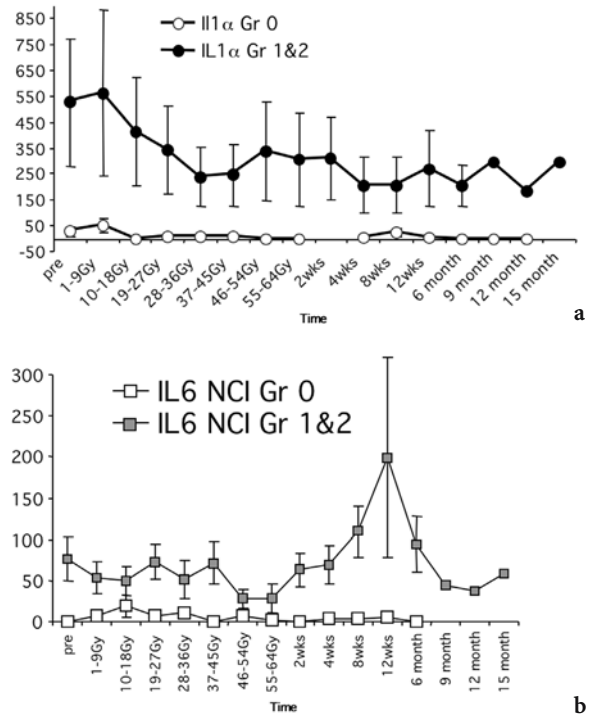


Fig. 11.6.5 a Circulating IL-1α (in pg/ml) before radiation, weekly during radiation, and after completing radiation treatments. **b** Circulating IL-6 (in pg/ml) before radiation, weekly during radiation, and after completing radiation treatments. Adapted from Chen et al. (2001a) and from Chen et al. (2002); used with permission from both publishers

11.6.3.4 Chemokines and Cell Adhesion Molecules

Tissue inflammation requires leukocytes to undergo transendothelial migration and extravasation of the vascular compartment into sites of inflammation. Chemokines and adhesion molecules are key cytokines in facilitating leukocyte recruitment to the site of inflammation (Kaseda et al. 2000; Butcher et al. 1996; Hallahan et al. 1997; Ding et al. 2000). Johnston et al. (1998) investigated a panel of chemokines including monocyte chemotactic protein (MCP)-1, lymphotactin (Ltn), RANTES, eotaxin, macrophage inflammatory protein (MIP-1α, -1ß, and -2), and interferon-inducible protein 10 (IP-10) in fibrosis-prone mice (C57BL/6) and fibrosis-resistant mice (C3H/HeJ). In these studies, local MCP-1 and IP-10 expressions did not increase 8 weeks after lung radiation, but a significantly higher level of expression was found only in the fibrosis-prone mice 26 weeks after lung radiation. Hallahan et al. (1997) investigated the role of adhesion molecules in animal lungs after radiation. They found an increase of ICAM-1 and E-selectin expression in vascular endothelium after radiation. In the animal model, they found that anti-ICAM-1 blocking antibody attenuated the inflammatory cell infiltration to the lungs of mice after radiation exposure. In addition, using ICAM-1 knockout mice, which were deficient in expressing ICAM-1 after radiation, radiation-induced pulmonary inflammatory cell infiltration was abrogated (Hallahan et al. 1997a, 2002). Research in chemokine and adhesion molecules in cancer patients produced some correlated findings. Ishii and Kitamura (1999) reported that patients with an increase of ICAM-1 in circulating cytokine levels during radiation had a higher risk of radiation

pneumonitis. Chen et al. (2002) investigated the role of other chemokine and adhesion molecules in the blood of cancer patients, including MCP-1, E-selectin, L-selectin, and P-selectin, but they found no correlation with the risk of radiation lung injury.

11.6.3.5 Fibrotic Cytokine: Transforming Growth Factor β

TGF-ß is a key modulator in the induction of fibrosis, alterations in collagen metabolism, and increase in extracellular matrix formation following radiation therapy (Burger et al. 1998; Barcelloss-Hoff 1998; Randall and Coggle 1995; Rodemann and Bamberg 1995). TGF-ß has been shown to be a growth factor regulating fibroblast proliferation, differentiation, and matrix production under physiological as well as pathophysiological conditions (Kovacs 1991; Fine and Goldstein 1987; Sigel et al. 1996; Zhang and Jacobberger 1996). It was found to be a primary cytokine for radiation-induced fibrosis (Rodemann and Bamberg 1995). In animal research models, different investigators have found that TGF-ß expression is induced after lung radiation and is the major mediator for postradiation lung fibrosis (Finkelstein et al. 1994; Rubin et al. 1992; Franko et al. 1997). The search for TGF-ß as a marker for radiation lung injury in patients has been complicated by the fact that lung cancers may produce TGF-β. Nonetheless, Anscher et al. (1998) found a correlation between higher risk of radiation lung injury in patients with high circulating levels of TGF-β near the end of radiotherapy. This observation was significant for the patients with normal pretreatment TGF-β levels but not significant for those with higher than normal pretreatment TGF-β levels.

11.6.4 Conclusions

For decades, radiobiologists and radiation oncologists have searched for ways to enhance radiation effects on human solid tumors. Fletcher (1973) reported the clinical dose-response curves of human malignant epithelial tumors based on clinical experiences at M.D. Anderson Cancer Center in Houston. In this report, the volume effect on tumor control probability was explored, and the concept of larger tumors requiring higher radiation doses to effectively control the tumor by radiation was introduced. Oncologists at the University of Florida also reported a similar finding for squamous cell carcinoma of the head and neck region. The dose required to eradicate solid tumors is proportional to the tumor volume: 60–65 Gy for tumors smaller than 1.0 cm in diameter, 65–70 Gy for tumors 1.5–2.0 cm, 70–75 Gy for tumors 2.5–3.0 cm, and 75–80 Gy for tumors 3.5–6.0 cm (Million et al. 1994). If one extrapolates Fletcher's estimate, it would require an 80–100 Gy radiation dose to eradicate large epithelial tumors of stage III NSCLC. Such a high dose to the chest has not been possible in the clinical setting due to potential fatal pneumonitis. Clinical practice in treating stage III NSCLC in general has kept radiation doses below 65 Gy and has therefore produced unsatisfactory local regional disease control for patients in this stage. If gross tumors in the chest cannot be eradicated, distant failures are definite sequelae.

Thus, optimization of chemotherapy and radiation continues to deserve preclinical studies aimed at maximizing the primary tumor control while keeping the toxicity low. For enhancing local tumor control, more frequent but lower doses of drug appear particularly promising in maximizing tumor response and minimizing toxicity. An interesting observation was made in this phase I study of pulsed paclitaxel chemoradiation: The lack of dose response with increasing paclitaxel doses beyond 15 mg/m^2 supports that when low-dose chemotherapy is used as a radiation-sensitizing agent, escalating chemotherapy doses may not further potentiate radiation but rather may increase the toxicity of therapy. The concept of a "minimally effective dose" for radiation potentiation by chemotherapy is contradictory to the traditional strategy of systemic chemotherapy when achieving a maximally tolerated dose is the primary goal. The superior tumor response and the durable tumor control achieved by pulsed low dose paclitaxel chemoradiation are intriguing. This dramatic local tumor effect cannot be explained by cell cycle and apoptotic effects of pulsed paclitaxel alone. More recently, small and frequent dosing of chemotherapeutic agents has been shown to suppress tumor growth through the mechanism of antiangiogenesis in animal tumor models (Boehm et al. 1997; Browder et al. 2000). Other potential mechanisms that may contribute to the effectiveness of the small frequent dosing schedule of paclitaxel and radiation should be further investigated in animals.

Recent discoveries in translational research using specimens from lung cancer patients have allowed a major breakthrough in our understanding of the somatic mutation of epidermal growth factor receptor

(EGFR) in relation to tumor response to treatments by gefitinib (Iressa). Clinically, gefitinib offers an overall 10% response rate for patients with NSCLC. Examinations of the EGFR genes have revealed that mutations at the tyrosine kinase domain not only specifically predicted responders to gefitinib treatments but also showed a striking correlation with patient characteristics: Mutations were more frequent in adenocarcinomas than in other NSCLC, more frequent in women than in men, and more frequent in patients from Japan than in those from the U.S. (Lynch et al. 2004; Paez et al. 2004). Serious lung injury was infrequently observed in large studies of patients treated with gefitinib for NSCLC, and included rare but fatal interstitial pneumonitis occurring with higher incidence in the Japanese patients (1.87%) than in patients outside Japan (0.35%).

Such findings support endeavors in identifying gene and molecular markers, not only for the efficacy of therapy but also for identifying markers for normal tissue injury. Simultaneous measurement of normal tissue consequences in translational research is critical, as the ultimate goal of treatment must include minimizing the acute and long-term toxicity to normal tissues. Cancer therapy has evolved towards a multiagent and multitarget approach, with the inclusion of gene therapy, antiangiogenic therapy, inhibition of epidermal growth factor pathways, inhibition of oncogene pathways, inhibition of other signal transduction pathways, hypoxic cell targeting therapy, and others (Chen et al. 2003). Balancing therapeutic effects versus normal tissue effects will become more complex and more challenging to oncologists in the future.

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12 Pitfalls in the Design, Conduct and Analysis of Randomised Clinical Trials

Richard Stephens

CONTENTS

12.1 Introduction

We are in the era of evidence-based medicine, and the building blocks for this evidence are randomised clinical trials. Therefore the importance of high-quality randomised trials cannot be understated. In theory randomised clinical trials are very simple. Half of the patients receive standard treatment, half receive the new treatment, and the two groups are compared in terms of efficacy. What could go wrong? Well, in practice, many things! The design, conduct and analysis of randomised clinical trials can actually be very complex. This paper aims to highlight some of the common pitfalls, giving examples from recent publications, and to suggest ways of avoiding them.

It is first important to describe what we are trying to do in a randomised trial as without this understanding, the implications of the pitfalls discussed cannot be fully appreciated.

Classically a randomised trial compares a new experimental therapy with the current standard therapy, in an attempt to find out whether the new treatment is better and, if so, to estimate how much better. Usually, in cancer, the primary endpoint of interest is survival, but in addition response, toxicity, quality of life and cost-effectiveness may also be important factors in deciding whether the new treatment is better.

If we had access to every patient with the disease under scrutiny and could randomise them all, we could obtain a fairly accurate measure of whether the new treatment is better than the standard, and if so by how much. However, of course, we don't. We only have access to a sample of these patients, and all the results of our randomised trial can do is give an estimation of the true difference. It stands to reason, therefore, that the larger the number of patients we study, the better the estimation.

The beauty of randomisation is that it ensures that a sample of patients is divided into groups that are as comparable as possible. Given sufficient patients, the groups will not only be automatically matched on obvious characteristics (for example, age and sex), but most importantly, in every other aspect. It is the latter point that makes the act of randomisation so crucial, and the use of historical controls so risky, as we are still unable to predict with any great accuracy which patients will do well, which badly, and what factors influence outcome. Randomisation thus ensures that the only difference between the groups will be the treatment they receive. Nevertheless, it is also important to remember that the sample of patients we are studying may be drawn from anywhere within the full population, and thus groups of patients receiving the same treatment in different trials may have different outcomes.

There are a number of statistical terms that are basically used to describe how close the estimated result from a trial is likely to be to the true result:

The 'power' of a trial relates to the chances of identifying a difference if it exists. Trials that are underpowered (i.e. do not include enough patients to reliably detect the difference) may therefore result in a false-negative result (also referred to as a type II error). Generally trials are powered at 90% but this still

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means that 10 out of every 100 trials so powered will be a false-negative (i.e. although a difference exists between the groups, the trial suggests no difference). Unfortunately, of course, we never know which 'negative' results are false-negatives!

The *p* value indicates how likely it is that an observed difference has been found purely by chance. Thus a *p* value of 0.05 indicates that this result would have occurred by chance 5 times in every 100. It is generally considered that a difference with a *p* value of ≤0.05 is a true and 'positive' result. However, it is vital to remember that this actually means that 5 out of every 100 'positive' results will be false-positives (also referred to as a type I error), found purely by chance. Again, the trouble is we never know which!

Whilst we need to be aware that a proportion of positive trial results may in fact be false-positives (and a proportion of negatives false-negatives), the problem of type I and type II errors also affects analyses within a trial, as the more tests that are performed, the more likely it is that these will be contaminated with false results. To reduce this risk, the number of statistical tests performed in a trial should be limited. A good way of doing this is to consider that within a trial there is only a certain amount of *p* value spending. So, if one test is performed and the result is $p \leq 0.05$, then the result can be considered significant. If two tests are performed then perhaps they should only be considered significant if $p \leq 0.025$ or, as is often used to accommodate interim analyses, the first is only considered significant if $p \leq 0.001$ so that the second can be considered significant if $p \leq 0.049$. Consider, for example, one table relating to the assessment of quality of life in the paper by Sundstrom et al. (2002) where 84 *p* values were calculated, although the authors recognised the problem and indicated that only $p < 0.01$ would be considered significant.

The hazard ratio (HR) is usually used to indicate the overall survival difference, with, conventionally, a value of <1 indicating that the new treatment is better, and >1 indicating that the new treatment is worse. Thus an HR for a survival difference of 0.85 indicates that the new treatment results in a 15% better survival, and an HR of 1.02 indicates that the new treatment is actually 2% worse. A ballpark method of converting the HR into real time is that HR is approximately equal to the median survival of patients on the standard treatment divided by the median survival of patients on the new treatment. In addition the HR is approximately equal to the natural log of the proportion of patients surviving at a particular timepoint on the standard treatment, divided by the natural log of the proportion of patients surviving at the same timepoint on the new treatment. Thus, for example, if the median and 1-year survival of patients on a standard treatment are 9 months and 20% respectively, and the HR from a trial is 0.85, the estimated median and 1-year survival for patients on the new treatment are approximately 10.6 months and 25.5% respectively.

However, probably the most important statistical term is the 95% confidence interval (CI). This indicates the range in which we are 95% sure that the true value lies. Thus, for example, in a survival comparison, an HR of 0.85 with a 95% CI of 0.65-1.05 indicates that our best estimate of the survival difference is that the new treatment is 15% better, but we are 95% confident that it is somewhere between 35% better and 5% worse. This surprisingly wide range, however, is the sort of range commonly obtained from randomised trials with a sample size of about 250 patients. Thousands of patients are required to obtain confidence intervals of only about 5% around the HR. Even in a trial of more than 1,000 patients, comparing surgery with or without adjuvant chemotherapy, Scagliotti et al. (2003) reported an HR of 0.96 with a 95% CI of 0.81-1.31, indicating that compared to the median survival of 48 months with surgery alone, adjuvant chemotherapy could have resulted in a detriment of 5.5 months or a benefit of 11 months.

There are numerous pitfalls that can occur in a randomised trial, although sometimes pitfalls is the wrong word, as trials can, of course, be deliberately designed, or analyses deliberately performed, to weigh the scales in favour of one treatment or another. Nevertheless, the aim of this chapter is to alert readers to the major deficiencies that can occur in trial design and trial reporting which may prevent the trial from being a true and unbiased comparison of the treatments.

12.2 Trial Design

Whilst most randomised trials are designed to test a new treatment against a standard treatment, trials may also be designed to assess whether a new treatment is equivalent to a standard treatment (for example, the new treatment may have preferable attributes, such as being given orally rather than intravenously, or be less costly) or to establish which of two standard treatments is better.

What should guide trial design is equipoise, or the uncertainty principle, which perhaps might be judged by the willingness of clinicians to be enrolled themselves should they develop that condition. Unfortunately, often the trials that are the easiest to accrue to (for example, chemotherapy A vs chemotherapy B) are the ones least likely to change practice, whereas the opposite applies to 'difficult' trials (for example, surgery vs no surgery).

Trials should also always aim to answer only one clear question. Thus a logical trial design in chemotherapy would be to add or replace one drug in the standard treatment combination. Results from trials that change two drugs (or schedules or doses) often leave the question unanswered as to the relative value of each changed factor. For example, Kelly et al. (2001) compared paclitaxel and carboplatin given in 4-weekly cycles with vinorelbine and cisplatin given in 3-weekly cycles, and Souquet et al. (2002) compared vinorelbine 30 mg/m^2 on days 1, 8 and 15 and cisplatin 80 mg/m^2 on day 1 with vinorelbine 25 mg/m^2 on days 1 and 8, cisplatin 75 mg/m^2 on day 1 and ifosfamide 3 g/m^2 on day 1.

It is important that all the decisions regarding design issues are clearly stated and justified in the protocol, and also that a detailed analysis plan is written.

12.3 Choice of Control Therapy

In a randomised trial the choice of control treatment is paramount. Logically it should always be the current best standard treatment for the condition, although often knowing what is acknowledged as 'best' is difficult. Indeed, there may be situations where the local, national and international 'best' are all different because of, for example, differences in facilities, expertise or access to drugs. The choice of control treatment will depend on several factors, including whether the trial result is aimed at affecting local, national or international practice, how pragmatic the trial is (for example, if the question is 'does the addition of drug A to chemotherapy improve survival?', the chemotherapy used may not need to be stated) or how a non-local control treatment will affect accrual. It is not difficult to see that the choice of the control treatment can significantly influence the way the trial result is interpreted, as unfortunately much more attention is paid to trials with a 'positive' result. Thus in order to increase the chances of seeing a 'positive' outcome, trials can be designed to compare the new treatment with a poor or inappropriate control. A common trick is to compare the new treatment alone with the new treatment in combination with a standard treatment. Thus in lung cancer there are examples of trials comparing new drug versus new drug plus cisplatin; for example, Splinter et al. (1996) compared teniposide with or without cisplatin in advanced NSCLC. Cisplatin is a very effective drug and thus the chances are that the combination will appear effective and can be claimed as an effective standard treatment, irrespective of whether the new drug actually has any useful effect or not. Because of the difficulty, due to the huge numbers of patients required, of showing that a new treatment is equivalent to a standard treatment, a course of action sometimes taken is to show that the new treatment is better than a previous standard to the same degree as the current standard. Thus if treatment B is 5% better than treatment A, the options for new treatment C are either to try and show that C is equivalent to B, or that C is also 5% better than treatment A. However, it could be argued that the latter is unethical as patients are not being offered the current standard of care. Nevertheless, this is a commonly used strategy. For example, given that in the NSCLC meta-analysis (Non-small Cell Lung Cancer Collaborative Group 1995) the survival benefit seen with cisplatin-based chemotherapy in the supportive care setting was highly significant ($p<0.0001$), should Anderson et al. (2000) and Roszkowski et al. (2000) have compared gemcitabine and docetaxel respectively against supportive care or cisplatin-based chemotherapy?

12.3.1 Eligibility

The results of trials will influence the way future patients are treated. It is therefore important that the eligibility criteria reflect this population of patients, as it is unlikely that all the eligibility criteria will be remembered and adhered to outwith the trial. Thus, results from trials with strict eligibility criteria are often not reproducible when the treatment in question is adopted in general practice.

12.3.2 Choice of Endpoints

Usually the choice of endpoint will be straightforward, commonly survival, response, toxicity and

quality of life, but the detail of each will be all-important and must be defined.

Survival. Treatments need to be compared on their overall survival as choosing a landmark timepoint, be it median or 1-year survival, may bias the results. For instance, in a trial of surgery versus a non-surgical intervention, the expectation may well be that the surgery group is likely to experience high early postoperative mortality but better longer-term survival. Thus comparing survival at, say, 1 month or 5 years might give an inaccurate picture of the true between-treatment difference. Although the expected median survival or proportion of patients surviving at key timepoints is often quoted in protocols, these are simply snapshots of the likely survivals and the likely survival difference, and are also used to calculate a sample size. For example, the shape of the survival curves seen in the trials reported by Fossella et al. (2000) and Takada et al. (2002) overlap for a considerable time before splitting.

All too often sample sizes are based on what is feasible rather than what is realistic. For instance, we know that, in lung cancer, the addition of a new modality, be it radiotherapy or chemotherapy, to surgery (or supportive care) will probably improve survival by only about 5% (Non-small Cell Lung Cancer Collaborative Group 1995). Therefore it is unrealistic to consider that as a result of tinkering with the drugs, dosages or schedules, we are suddenly going to see advantages of a further 10% or 15%. Yet the vast majority of lung cancer trials are based on seeing differences of about 15%, which will generally require around 400 patients. Some even aim for larger effects. For example, Ranson et al. (2000) powered their trial to look for a 100% improvement (from 20% survival at 1 year with supportive care to 40% with paclitaxel), and Sculier et al. (2001), in a three-arm trial, considered that a 75% increase might be possible with the addition of G-CSF or antibiotics to standard chemotherapy. The sort of target accrual resulting from such over-optimistic expectations is considered feasible, whereas aiming for around 1,500 patients to see a 10% difference, or 4,000 patients to see a 5% difference, which is probably the sort of target most trials should now be aiming at, is simply considered an impossible task. Maybe this explains why progress in lung cancer has been so slow, as we have had to wait for meta-analyses to combine data from a number of trials in order to accumulate the thousands of patients required to confirm these small differences. A question then arises as to whether it is ethical to run any trial of less than perhaps 1,000, patients given the high probability of an inconclusive result. An even greater dilemma occurs with equivalence trials. Taking the same example that the addition of a modality (chemotherapy) improves survival over surgery alone or supportive care by about 5%, what happens when we want to show that a new chemotherapy treatment is as effective as standard? If we compare the new chemotherapy to standard chemotherapy with a trial of 400 patients we may finish up with an HR of around 1.00 but with a 95% CI of about ±15%. So all we could conclude is that the new treatment is somewhere between 15% better and 15% worse than standard and thus could actually be 10% worse than no chemotherapy. Nevertheless, some papers, for example Gatzemeier et al. (2000), claim survival is comparable even though a 20% benefit or detriment cannot be ruled out.

Response. To compare tumour response and/or progression it is of course important that patients in each group undergo the same investigations, undertaken (as far as possible) by the same staff, using the same equipment at baseline and at the same predefined timepoints [in relation to the time from randomisation (the one common timepoint for all patients)] throughout the trial. It is important to choose equivalent follow-up timepoints because if patients in one group are assessed more often, progression will be picked up earlier in that group, and any analysis of progression-free survival will be biased. Complications also arise when patients have non-protocol or second-line treatment. Great care must be taken to define whether response rates reported are purely those related to the protocol treatment or are as a result of the policy of giving a particular regimen.

Toxicity. The same considerations (consistency of investigations and follow-up) need to be applied to the assessment of toxicity. In addition, in cancer the side-effects of treatment can sometimes be very difficult to distinguish from the symptoms of the disease (for example, anorexia and breathlessness). It is perhaps unrealistic, therefore, to ask clinicians to distinguish between these and report just on treatment-related toxicity. Thus it is always preferable to collect information on all symptoms irrespective of the cause and assume that any differences seen will be due to the difference in treatment.

Quality of Life. Numerous issues surround the design of the assessment of quality of life (QL). Few trials actually estimate the number of patients required

for the QL aspects, and consequently many trials include only a small subset of patients. This seldom provides sufficient data. For example, a calculation of the number of patients required to show a 10% difference in, say, shortness of breath at 3 months yields a sample size of about 400 patients. A recent review (Stephens et al. 2004) indicates that only five trials in NSCLC have collected QL data on 200-300 patients at follow-up, and only one more than 300. The solution to many of the QL design issues is to pre-define the primary and secondary QL endpoints. This may involve discussing with doctors and patients how the standard and new treatments are likely to impact on QL and when. Such information will certainly guide the choice of QL questionnaire, the timing of administration and the calculation of sample size, and in addition will focus the analyses. However, very few trials have so far fully embraced this way of working.

12.4 Trial Conduct

12.4.1 Monitoring

To ensure patient safety it is imperative that the accumulating data are reviewed at regular intervals throughout the trial. Whether 'regular' means annually, when accrual reaches certain targets or when certain numbers of events have occurred, will depend on the trial. It is also important that the interim data are reviewed completely independently by clinicians and a statistician not involved with any other aspect of the trial. Rules for when the trial should close early must also be agreed and there are a number of options, from fixed p values to Bayesian statements such as 'the evidence must convince sceptics'. It is important that among the Data Monitoring and Ethics Committee (DMEC) members there is knowledge of the disease and treatments and previous DMEC experience, as often DMECs will be called upon to make very difficult decisions. There are numerous examples where trials have stopped early, but the results have been unconvincing and new trials have had to be set up to clarify the situation. For example, two trials of neo-adjuvant chemotherapy for NSCLC (Rosell et al. 1994; Roth et al. 1994) both stopped early after accruing 60 patients, but subsequently several large trials have been set up to clarify whether any benefit exists.

12.4.2 Follow-up

A major consequence of needing to review the interim data and make important decisions is that the data must always be as up to date as possible as it is vitally important that DMECs make decisions based on all the available data. However, follow-up may be difficult if different modalities are being compared, especially if this requires the patients to be seen at different times by different clinicians (for example, when chemotherapy is being compared to radiotherapy, or surgery to best supportive care). Whenever possible, follow-up should revert to a common time schedule and within each participating centre patients should be assessed by the same clinical team.

To ensure an unbiased comparison of survival, the duration of follow-up in the groups must be similar. If follow-up is different this can subtly affect the Kaplan-Meier curves, as surviving patients are assumed to follow the same survival patterns as those known to have died. A 'reverse' Kaplan-Meier plot, nominating the 'time last seen for those alive' as the event and censoring at the date of death, is a good way of comparing follow-up in the groups, and the resulting p value of the log-rank test can be quoted. Some papers report median follow-up of survivors, although this is rarely split by group, and other papers simply report median follow-up, though it is far from obvious what this latter figure actually represents.

12.5 Trial Analysis

A good policy is to account for every patient in every analysis. Thus including categories such as 'not assessed' or 'died' in tables and reporting the numbers of patients (not just the proportions) makes all analyses completely transparent to the reader.

12.5.1 Patient Population

The easiest and most logical group to analyse is everyone who has been randomised. This is the strict definition of 'intent to treat'. At the time of randomisation all patients should have been considered suitable for the treatments being studied and thus post-trial reflect the population who are likely to be offered

the treatment. Papers often list subgroups of patients who are excluded from analyses, such as those shown to be ineligible by post-randomisation investigations or independent review, those who do not receive any or all of their protocol treatment or those not assessed for an endpoint. However, removing patients for any of the above reasons has the potential to bias the analysis sample. For example, although the primary endpoint of the trial was response, Georgoulias et al. (2001) excluded 35 of the 441 patients randomised and all analyses (which were claimed to be 'intention-to-treat') were then performed on the remaining 406 patients, and Schiller et al. (2002) excluded 52 patients who were found to be ineligible post-randomisation in their trial of four chemotherapy regimens.

12.5.2 Pre-treatment Patient Characteristics

It is, of course, logical to list the pre-treatment characteristics and to highlight balance (or imbalance) between groups. However, it is illogical to apply statistical tests to show balance or imbalance. Statistical tests are used to estimate the likelihood that an observed difference has not occurred by chance. However, differences in pre-treatment characteristics can only have occurred by chance, and it is thus an inappropriate use of a statistical test and a wasteful use of *p* value spending. If imbalances in pre-treatment characteristics are observed, the analysis of the key endpoints should be adjusted accordingly. Recent examples of this unnecessary testing can be found in papers by Tada et al. (2004) and Langendijk et al. (2001).

Survival. Survival should always include all patients randomised, be calculated from the date of randomisation and include all causes of death. It should be measured by constructing Kaplan-Meier curves and comparing them using the log-rank test, and overall survival should be reported using the hazard ratio and 95% confidence interval. Taking the start date as anything other than randomisation (which is the one common timepoint for all patients) will have the potential to bias the result. For example, the date of diagnosis may not be accurate for all patients, the date of start of treatment may include different delays for different groups, and what do you do with patients who don't start treatment?

Although the cause of death may be of interest to the trialists, to indicate how the treatment is working, in a sense this may be much less important to the patient. Thus survival analyses that only report deaths from cancer may be interesting but very misleading. For example, a treatment that causes many early treatment-related deaths may, in a cancer-specific survival analysis, appear to be the better treatment.

Sundstrom et al. (2002) reported the disease-specific survival rates in their trial of chemotherapy regimens, and Shepherd et al. (2002) censored patients who died from causes unrelated to disease or treatment in their analysis of progression-free survival.

Subgroup Analysis. Subgroup analyses are only reliable if they are predefined, which will usually mean they are hypothesis driven, and take account of sample size and multiple statistical testing. Unless the above rules are respected, subgroup analyses should always be considered with caution and treated as only hypothesis generating. All too often when clear overall results are not seen, the data are trawled for interesting subgroup results and, when found, hypotheses built around them. Reporting such findings as definitive results is irresponsible.

It is, of course, often interesting to explore whether any overall survival difference observed is consistent across all subgroups, and analyses stratified for pre-treatment characteristics are therefore useful; whilst Sause et al. (2000) did just that, the subgroup analyses did not appear to have been pre-defined, accounted for in the sample size or considered only as exploratory or hypothesis generating. Whilst exploratory analyses are acceptable, analysis by post-randomisation factors (such as treatment received, or response) are totally unacceptable, as the groups being compared may be defined by the outcome being tested. Thus, for example, comparing the survival of responders versus non-responders is flawed because the responders have to survive long enough to respond. Therefore analyses such as those presented by Fukuoka et al. (2003), comparing survival by responders, and Socinski et al. (2002), showing survival by number of cycles of chemotherapy received, must be viewed with great caution. Prognostic factor analyses are sometimes run to try and identify the factors most related to survival, but usually there are far too few patients in a single trial to draw any firm conclusions. For example, in a trial reported by Pujol et al. (2001) multivariate analyses were performed on 226 patients.

Response. Although the RECIST criteria (Therasse et al. 2000) are now the standard method of assessing response, there are still complications. For example, it is unclear what to do with multiple lesions, disease

present but not measurable, or measurement schedules that are not every 4 weeks. It is important to report the response rate as the proportion of patients who achieve complete or partial response out of the total number of patients in the group. Quoting the response rate as just the proportion of patients who have been assessed at a certain timepoint may mask the fact that patients may have had to stop the treatment due to toxicity or death.

Many papers purport to show differences between treatments in terms of time to progression with the use of a Kaplan-Meier plot, taking progression as the event and censoring those alive (or dead) without progression. This sort of analysis can be very misleading as patients who fail from a competing risk (for example, an early treatment-related death) that precludes the possibility of achieving the event are treated the same as censored patients who still have the potential for progression. Recent examples of this can be found in papers by Sunstrom et al. (2002), Ranson et al. (2000) and Pujol et al. (2001). Progression-free survival, which takes into account deaths without progression, should always be the preferred analysis.

Toxicity. Standard definitions of toxicity, such as the Common Terminology Criteria for Adverse Events developed by the NCI Cancer Therapy Evaluation Programme (2003), should always be used, but there are a number of ways of reporting toxicity. Perhaps the most logical and widely used method is to report the proportion of patients with grade 3 or 4 for each key symptom within a defined time period from randomisation. Such an analysis will inevitably include some noise, as patients will have had symptoms pretreatment and some patients will have toxicity as a result of non-protocol treatment, but understanding and applying the concept of 'intent to treat' is important, as the trial should be trying to record the experiences of a group of patients chosen to receive a certain treatment. If some patients don't actually receive the protocol treatment and have to receive different treatment, perhaps with different side-effects, that is a key message. In virtually all analyses it is much better to report the proportion of patients with a good or bad experience rather than the mean or median score. The mean or median can mask or dilute the fact that a small proportion of patients had good or bad experiences.

Quality of Life. Patient self-assessed quality of life (QL) data are especially difficult to report reliably because the data are multidimensional, longitudinal and inevitably much is missing. There are therefore no agreed methods of presenting QL results, and care must be taken to be conservative in making strong claims. Major problems can arise from starting with inadequate sample sizes, multiple statistical testing, imputing missing data, comparing the treatments at timepoints that favour one group and/or summarising the data inappropriately. Non-standard analyses such as those used by Ranson et al. (2000), estimating separate slopes for dropouts and completers, or Sandler et al. (2000), calculating the change in score from baseline to last observation, should be avoided.

Many of these problems can be mitigated by predefining QL hypotheses which have the effect of guiding the choice of questionnaire, the choice of administration timepoints, the sample size calculation and the analyses to be performed. However, there are few examples of this actually being carried out in practice, and consequently the results from QL aspects of trials are often disregarded and distrusted by clinicians and patients.

Daily diary cards can be very useful to highlight transient changes. Plots of the proportions of patients reporting dyspnoea post radiotherapy, for instance, can be very illuminating, but potentially misleading unless it is made clear how many patients are contributing to the curves at each timepoint.

Interpretation. Trials are rarely islands. Results need to be presented and discussed in the context of the totality of previous work. However, Clarke et al. (1998) reviewed the discussion sections of reports of trials published in five major journals during one month in 1997 and found that only two (of 26) placed their results in the context of an up-to-date systematic review. Repeating this exercise in 2001, they reported no improvement, with only three (of 30) trials being so reported (Clarke et al. 2002). Such findings are disappointing and suggest that there is a general lack of awareness that individual trials are only part of the whole picture. We must never lose sight of the fact that lung cancer is a global problem and without global collaboration progress will continue to be painfully slow.

12.6 Conclusions

There are numerous pitfalls in the design, conduct and analysis of randomised trials. Some are subtle, some less so. What in particular should a trialist try

to ensure, and what should cause a reader to cast doubt on the results in a publication? Here are ten questions to keep in mind:

- What is the control treatment? Is it a widely used standard treatment given in an acceptable schedule?
- Has the trial been designed to answer a clear, unconfounded question?
- Are there pre-defined hypotheses for all key endpoints?
- Do the eligibility criteria cover all the patients who are likely to be treated this way outwith the trial?
- Is the sample size based on information that is sensible and feasible?
- Are the details of the interim analyses and stopping rules clearly laid out?
- Are all randomised patients included and accounted for in all analyses?
- Are the number of statistical tests limited, and if not, have the significance levels been adjusted accordingly?
- Have the hazard ratio and especially the 95% confidence interval of the primary endpoint been given?
- Has the result been put into the context of previous work in the area?

All trials and all trial results are important as they all in some way advance the progress of human knowledge. Our ultimate aim as trialists is to improve the treatment of future patients and it is therefore important that we are as rigorous and honest in our work as we can be.

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13 New Directions in the Evaluation and Presentation of Clinical Research in Lung Cancer

Elinor Thompson and Fergus Macbeth

CONTENTS

13.1 Introduction

Anyone working in oncology is only too familiar with the depressing list of statistics that is inevitably reeled off at the beginning of articles on almost any aspect of lung cancer. Globally lung cancer is the most common cancer in terms of both incidence and mortality, with more than 58% of new cases occurring in developed countries (Parkin et al. 1999). And since time trends in lung cancer reflect past exposure to cigarette smoking, the disease is likely to increase in other parts of the world over the next 20 years as rates of cigarette smoking continue to rise in many countries in the developing world and newly industrialised countries (Stewart and Kleihues 2003).

Equally well recognised is the fact that despite important technological developments in surgery, radiotherapy and chemotherapy over the last 20 years or more and many hundreds of clinical trials, there has been very little overall improvement in survival in people with lung cancer. Population-based 5-year survival rates still range from about 5% to, at best, 15%. But importantly, all too little is known and published about any changes (for either better or worse) in the quality of that survival.

In this chapter we will reflect on what the published research evidence has actually told us and what its limitations are. We will then make some suggestions about how we might improve the quality, reliability and accessibility of that evidence.

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13.2 What the Evidence Does and Does Not Tell Us

There are a few accepted 'truths' in the prevention and treatment of lung cancer. Some of these 'truths' derive from years of accepted clinical practice and some from well-conducted randomised trials. But such is the contestable nature of clinical science and clinical practice that not everyone will agree with even these few 'truths'.

The following are, we believe, more or less firmly accepted in the management of patients with non-small cell lung cancer (NSCLC):

- Radical surgery (lobectomy or pneumonectomy) is an effective, potentially curative treatment for early stage disease.
- A combination of chemotherapy and radiotherapy is effective for patients with unresectable stage III disease, but there is uncertainty about which drugs and radiotherapy regimens are the best.
- Postoperative radiotherapy, using older technologies, is harmful to patients who have had successful surgery. But there is uncertainty whether this also applies to radiotherapy with modern techniques.
- Cisplatin-based chemotherapy has a modest effect on survival in patients with locally advanced and metastatic disease but it is uncertain how much overall benefit there is in terms of quality of life.

And these are the more or less firmly accepted 'truths' in the management of patients with small cell lung cancer (SCLC):

- Combination chemotherapy improves survival in all patients.
- A combination of chemotherapy and thoracic radiotherapy in those with limited stage disease improves survival and results in the cure of a few patients.
- Prophylactic cranial irradiation (PCI) for those with limited disease in complete remission is likely to be beneficial.

But it is very clear that a number of important questions remain, such as:

- Does screening with helical CT scanning reduce mortality in high-risk populations?
- How much benefit do patients with stage III NSCLC derive from neoadjuvant chemotherapy?
- How much more effective is hyperfractionated and/or accelerated radiotherapy than conventional radical radiotherapy?
- Are the newer chemotherapy drugs more effective for both NSCLC and SCLC than the older ones either singly or in combination?
- Does dose intensification improve outcomes from chemotherapy in both SCLC and NSCLC?

More, and more precise, information is also needed on other important issues such as the effects of age, sex, tumour histology, patient genetic profile and co-morbidities on the relative effectiveness and morbidity of interventions. We also need a far better understanding of the effects of patient preferences, perspectives and knowledge on both cure and palliation. And given that so few patients with lung cancer are cured, we must increase our knowledge about some important and difficult end-of-life issues such as the effectiveness and desirability of second-line chemotherapy, when to stop active treatment and how best to palliate important symptoms such as breathlessness.

13.3 A Plethora of Information but Hardly Any Knowledge

There has been a huge and accelerating growth in scientific publications on lung cancer over the last 30 years. Searching Medline, from 1966 to the present, for 'Lung Neoplasms/dt, rt, su, th [Drug Therapy, Radiotherapy, Surgery, Therapy]' gave more than 31,000 hits. A quick search of PubMed using only the search terms 'lung cancer', limited for 'randomised controlled trials', revealed only one trial published in 1970 compared with 89 in 2002 (Fig. 13.1).

A search of the Cochrane Central Register of Controlled Clinical Trials identified around 1,575 trials and a search of PubMed for any clinical trial in lung cancer brought up more than 5,000 study reports. It is therefore surprising that the number of accepted 'facts' listed above is relatively short. There seems to be a lot of information but a shortage of real knowledge.

This inevitably leads both clinician and researcher to pose a number of questions:

- Which trials are of good quality and can be trusted to provide valid and robust information?
- How do I know whether the findings from a small study can be generalised more widely?
- Which trials asked the question that I am interested in?

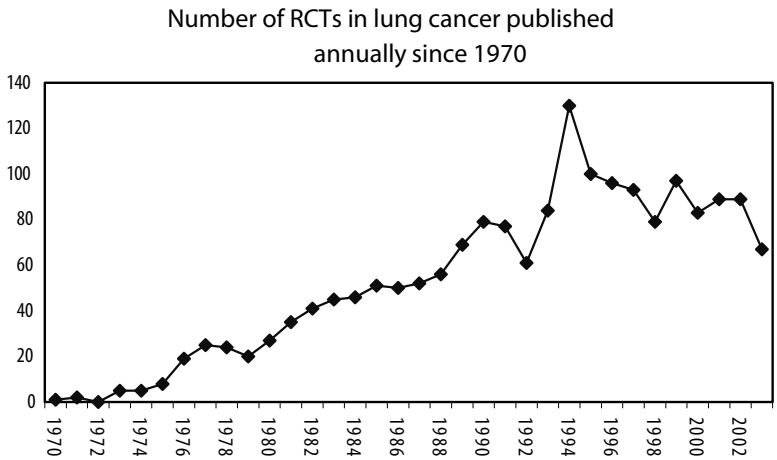

Fig. 13.1. Number of randomised controlled trials in lung cancer published annually since 1970

- Which trials looked at the effects of the treatment I am interested in, in the kinds of patients I treat?
- How do I know whether I have found all the relevant trials on this topic?

In order to be able to answer these questions we need to find better ways of clearing a path through the jungle of papers so that we can find the information we need quickly and easily and then do what we want to do – make better clinical and research decisions.

To be able to find our way to the information we need, every time that we need it, we must develop a very effective and flexible sorting system for managing all the data. A good sorting system of the medical literature needs to be able to do the following:

- Search through all the data quickly, finding everything relevant and *only* the relevant – that is, we need sensitive and specific literature search strategies. Good search strategies will search all the literature, published and unpublished, in all languages and will maximise relevant finds while minimising irrelevant ones.
- Decide which studies are of good quality and which are of lower or poorer quality. Decisions as to study quality need the development and application of a number of valid criteria for assessing the design of a study.
- Undertake sound combinations of data from similar trials so that results (estimates of benefits and harm) from a larger number of people can be evaluated than have been obtained from individual trials alone – these are meta-analyses.
- Repeat the sorts and collations regularly so that the information is up-to-date.

There are two important tools which can help us to construct this sorting system:

- Systematic reviews and meta-analyses
- Specialised trials registers

13.4 Systematic Reviews and Meta-Analyses

Over the past 15 years or so the pitfalls of traditional 'expert' reviews have been clearly identified and well described. They are subject to a variety of biases which are usually not explicit, and the status of the authors may confer a spurious authority and validity to the conclusions. As the problems with these traditional reviews became more widely recognised, the science of systematic reviews, so-called secondary research (research on the research literature) and meta-analyses has developed and achieved widespread recognition and credibility (Mulrow 1994).

Although a literature review may advertise itself as 'systematic', the use of this term does not guarantee either a high-quality or indeed a comprehensive approach to the retrieval of all relevant articles and a systematic assessment of their quality. This may serve to confuse the general reader who is not familiar with the methodology of systematic reviews and therefore may have difficulty distinguishing the good from the bad.

Another area of confusion among general readers is with the term 'meta-analysis'. The term meta-analysis refers to the statistical combination (or pooling) of quantitative data from more than one original study. The reason for doing a meta-analysis is to amalgamate results from a larger sample of patients than was available in any of the individual original studies. A meta-analysis should therefore have greater statistical power to assess the relative risks and benefits of interventions than the individual studies. There are drawbacks associated with pooling data from different studies, which include differences in the populations of patients in the studies, differences in the interventions given and other differences in the studies' designs.

Meta-analyses may be undertaken in one of two ways: either by combining the data as presented in the published reports, or by combining the original data on the individual patients included in each of the original trials – an individual patient data analysis. Most published meta-analyses are reports of pooled data from published reports as these are much quicker and easier to do, although their findings are less robust. An individual patient data (IPD) meta-analysis is a long and time-consuming process which requires contact with the authors of all the original studies to gain access to the original datasets. The data must then be cleaned and re-analysed on all the patients in the included trials – a process which often involves many hundreds if not thousands of patient records. IPD analyses are therefore more robust and reliable than meta-analyses of published data. Three examples of IPD meta-analyses in lung cancer research looked at the role of postoperative radiotherapy for NSCLC (PORT Meta-Analysis Trialists' Group 2003), at chemotherapy for NSCLC (Non-Small Cell Lung Cancer Collaborative Group 2003) and at the effectiveness of prophylactic cranial irradiation for SCLC (The Prophylactic Cranial Irradiation

Overview Collaborative Group 2003). All three of these reviews have been very influential in shaping clinical practice and the research agenda.

A systematic review does not always contain a meta-analysis; in fact many very good systematic reviews do not, because the pooling of quantitative data from studies included in the review would be impossible – as a result of differences in either the data itself or the way that data was collected, analysed and presented. Systematic reviews may be either (a) independent or ad hoc reviews or (b) Cochrane reviews.

13.4.1 Independent Ad Hoc Reviews

Independent research teams may carry out systematic reviews and meta-analyses for a variety of reasons. They are often context dependent and the context may be:

- To inform the development of clinical practice guidelines
- To inform health policy decisions
- To inform research strategy decisions within either public or private research organisations.

Depending on the reason for doing the review, different degrees of precision may be used. The search of the literature may be more or less exhaustive, with date, language or journal restrictions. The assessment of the quality of the source studies and the accuracy of data extraction can be variable. There may be no need for updating, and given the often long timescales for publication, the results may be rendered out of date by significant new papers even before they make it into the public arena. Nevertheless, these reviews usually provide some valuable insights.

13.4.2 Cochrane Reviews

The Cochrane Collaboration was set up in 1993 with the intention of meeting the global need to collect, collate, analyse and disseminate the available scientific evidence in clinical medicine. An international, not-for-profit organisation, the Collaboration consists of a network of researchers, health professionals, consumers and others around the world who work together to prepare, maintain and promote systematic reviews of healthcare interventions. These reviews, all written in a standardised format, each provide recommendations on both research and practice that can be accessed by anyone interested in the topic, be they clinician, health care consumer, manager, health policy maker or researcher. Working together in collaborative topic-focussed Review Groups, of which there are currently 51, Cochrane reviewers use a rigorous methodology for undertaking extensive searches of published and unpublished research, critically appraising abstracts and articles found, and conducting qualitative and quantitative analyses of the findings. Cochrane reviews are published in electronic format (online and on a CD Rom issued quarterly) as part of the Cochrane Library and according to a recently agreed policy of co-publication, versions of reviews may also be published in a peer-reviewed journal (Clarke and Horton 2001).

The main focus of the Collaboration is on conducting reviews of randomised, controlled trials because as the accepted 'gold standard' of scientific investigation (Cochrane 1972), trials designed in this way are more likely to provide reliable therapeutic results than those using other designs (Mulrow and Oxman 1997). But the fact that a trial is randomised and controlled does not guarantee the validity of its results. Cochrane reviewers are careful to apply criteria that assess the likelihood and strength of potential biases, both internal and external, and to make their recommendations with this quality assessment in mind. Weighing up the strength of the evidence for a particular intervention requires detailed and meticulous consideration of several points. Nevertheless, while Cochrane Reviews attempt to present the evidence as objectively as possible, and, where relevant, give data on biological and cultural variation as well as on variations in compliance and baseline risks, the applicability of the recommendations to particular and individual circumstances must be decided by the reader. In other words, Cochrane reviews do not provide recipe-book medicine but rather facilitate a process in which health care decisions can be based on the best available evidence.

Cochrane reviews are based on specific guidelines as set out in the Cochrane handbook, and in general have been found to use higher quality methods than those used by other systematic reviews. A quality assessment of 53 reviews published in the Cochrane library in 1998 (Olsen et al. 2001) showed that although there was a generally high standard, there was still room for improvement, with a tendency for reviewers to over-rate the benefits of new interventions. As a result of this assessment, the Cochrane Collaboration has taken further steps to improve the quality of its reviews. The advantage to the general reader of a Cochrane review is that they know that

the review has followed a pre-set procedure, including the publishing of a peer-reviewed protocol and peer reviewing by experts in both the relevant clinical field and the methodology of systematic reviews.

In addition to the topic-focussed Cochrane Collaborative Review Groups (CRGs) of which the Lung Cancer Collaborative Review Group is one, there are also Methods Working Groups, Fields, the Consumer Network and Cochrane Centres co-ordinated by a steering group (Fig. 13.2).

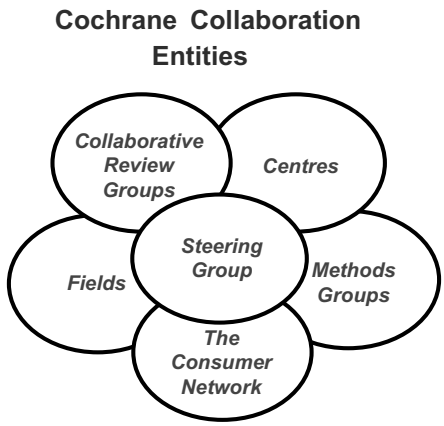

Fig. 13.2. Cochrane collaboration entities

13.4.3 The Cochrane Lung Cancer Collaborative Review Group

The Lung Cancer Group (LCG) was formed in 1997 following an exploratory meeting held in Sabadell (Barcelona), Spain. The organisational structure of the LCG, in common with all other CRGs, includes an international, coordinating editorial team which is supported by reviewers, translators and consumers. The LCG editorial team keeps a list that it has developed in consultation with members of the review group in which are detailed the titles registered for future systematic reviews, published review protocols and completed reviews. A list of the completed systematic reviews and published protocols, as of January 2004, is shown in Table 13.1. A further six titles have also been registered (see http//www.cochrane.es/lcg).

The scope of the LCG covers all aspects of primary and secondary prevention, therapy, supportive care, psychological interventions, biological therapy and complementary therapy for lung cancer, other intrathoracic tumours (if not addressed by other review groups) and metastatic lung disease. Although the remit of the group covers prevention, smoking is not covered because there is a separate Cochrane Review Group addressing tobacco addiction.

Table 13.1. Cochrane Lung Cancer Collaborative Review Group: systematic reviews and protocols published in the Cochrane Library (January 2004)

Topic	Protocol/review
Chemotherapy for malignant pleural mesothelioma	Protocol
Chemotherapy versus best supportive care for extensive SCLC	Protocol
Cranial irradiation for preventing brain metastases of NSCLC in patients at high risk of cerebral metastases	Protocol
Gemcitabine for NSCLC	Protocol
Neo-adjuvant chemotherapy for NSCLC	Protocol
Non-invasive interventions for improving well-being and quality of life in patients with lung cancer	Protocol
Palliative endobronchial brachytherapy for NSCLC	Protocol
Radiotherapy for malignant pleural mesothelioma	Protocol
Synchronous chemoradiotherapy for NSCLC	Protocol
Taxanes for advanced (metastatic and locally advanced) NSCLC	Protocol
Chemotherapy for NSCLC	Review
Cranial irradiation for preventing brain metastases of SCLC in patients in complete remission	Review
Drugs for preventing lung cancer in healthy people	Review
Palliative radiotherapy regimens for NSCLC	Review
Postoperative radiotherapy for NSCLC	Review
Radical radiotherapy for stage I/II NSCLC in patients not sufficiently fit for or declining surgery	Review
Screening for lung cancer	Review
Second-line chemotherapy for NSCLC	Review
Steroids, radiotherapy, chemotherapy and stents for superior vena caval obstruction in carcinoma of the bronchus	Review
Surgical sealant for preventing air leaks after pulmonary resections in patients with lung cancer	Review

As mentioned above, the process of undertaking a Cochrane review is rigorous and structured. First, the title must be registered with the LCG to ensure that no other group is working on the same topic. Then a detailed, peer-reviewed protocol is published in the Cochrane Library in which are outlined the research methods, including the types of study to be reviewed, the outcomes of interest and the strategy for searching the literature and selecting studies. This allows time for others to comment on and improve the protocol. Once the protocol has been published, work starts on the full systematic review. The finished review is then fully peer reviewed before being published in the Cochrane Library with an obligation that it should be updated every 2 years.

The Cochrane Lung Cancer Group has laid the foundation stones and made significant progress in the development of an evidence-based, global information resource in lung cancer care.

13.5 A Specialised Trials Register for Lung Cancer?

13.5.1 What Is a Specialised Trials Register?

Another key resource for both investigators and clinicians who wish to find their way quickly and efficiently through a huge bank of research evidence in a single clinical field is a specialised trials register. A specialised trials register is a database of randomised controlled trials (RCTs) in any particular area of health care. A specialised register can be a useful resource for both clinicians and researchers because it offers a comprehensive and specific source of clinical trials for any one particular health problem.

A general search of any of the major electronic databases (Medline, Embase etc.) to identify trials for lung cancer will turn up a large number of references depending on the search terms used. Searches of the general databases may be highly sensitive, in which case a lot of unnecessary and irrelevant material must be weeded out, or highly specific but run the risk of important references being missed. The aim of a specialised register is to collate the references of all RCTs published, by means of specially designed, exhaustive searches repeated at regular intervals. In addition to searches of the world's major electronic databases (e.g. MEDLINE, EMBASE, CINAHL, LILACS, Current Contents, Biosis and Index to UK Theses), a specialised register includes references to reports of trials (both on-going and completed) that have not been indexed, or that have been published in non-indexed journals, as well as trials found by hand searching of conference proceedings and unpublished trials.

13.5.2 Reference-Based Registers and Study-Based Registers

In its most simple form a specialised register is a reference-based database of citations of RCTs in which any one trial may have several references, one for each article published, whether a primary report, a secondary report, a review article or a letter. A reference-based register is the easiest and least resource-intensive register to assemble. To construct the register, electronic searches are undertaken using specially developed search strategies, and citations and/or abstracts of all references identified are then downloaded and reviewed by an information specialist to ensure that they meet the criteria of the register. For a lung cancer specialised register this would be all study reports of lung cancer trials that are possibly or definitely randomised (or quasi-randomised). All identified references meeting the criteria of the specialised register are then downloaded into the specialised register, which is searchable by author, journal, year and any of the key terms included in the abstract or the key words. In addition to those references found by electronic searching, a complementary hand search of relevant conference proceedings and journals is also undertaken to ensure that relevant references are identified. The electronic searching is repeated at 3-monthly intervals to ensure that it is up-to-date. Within the Cochrane Collaboration, all review groups are expected to develop and maintain their specialised trials register and to download their contents at regular intervals into the Cochrane Central Register of Controlled Clinical Trials (CENTRAL). The specialised register is used by Cochrane review groups as a fundamental resource to support reviewers in the preparation and maintenance of reviews.

A study-based register is a more sophisticated form of register which, though more resource intensive to assemble and update, is inherently more useful than a reference-based register in that it is more flexible and can be developed to support many potential research projects. A study-based register can also be used to provide the essential background data to inform the development of a clinical research strategy. A study-based register uses each individual trial

as the basic record, rather than every reference published. Consequently each trial will have one record, regardless of the number of publications associated with it. The record of each trial holds the same information as a reference-based register, but in this case all the identified associated publications are linked to the main trial record. If a trial has 100 identified publications, these will be linked to the one record relating to the main trial report. Assembling a study-based register requires a more intensive input at the level of the reference identification in that someone must review the abstracts in detail (and sometimes the whole article) to see whether a reference is a primary report and, if not, to identify and link it appropriately to the primary trial report. Depending on the level of sophistication of the register, other types of information about the trial can also be extracted at this stage and entered into separate fields. Extra data might include: precise condition and disease stage, number, age and sex of participants, interventions used (including agents in each arm) and outcome measures assessed. In this way an investigator consulting the register would be able to undertake very precise searches - examples of which might include:

- Trials of chemotherapy in extensive SCLC in which cisplatin was included in one arm
- Trials of people over 75 in whom quality of life was measured

Using a specialised study-based trials register, the investigator could be confident that she or he was consulting the most comprehensive and specific database of randomised trials in the field of lung cancer in the world. A further possible refinement of this kind of register, possibly within the process of undertaking a systematic review, would be to develop specific 'sub-registers' containing particular groups of trials, for example trials of chemotherapy for stage IIIB NSCLC. Such sub-registers could contain highly detailed and specific extracted data such as quality of the randomisation process, presence of follow-up reporting, doses and schedules of agents administered, and study power.

The establishment of a specialised register of lung cancer clinical trials, once fully assembled and with adequate processes established for ensuring its maintenance and regular updating, could be an invaluable global resource for anyone undertaking research in lung cancer. Such a register, if adequately resourced, would only need to be established once, but if adequately updated and maintained could be used by all. Just as is the case with the village 'common', which is owned by no-one but used by all (Hardin 1968), a trials register, once established, could be used by all but belong to no-one. In contrast to physical common resources, however, a common information resource would not be at risk of degradation and eventual loss to all, but would more likely be enriched by overuse!

13.6 What Systematic Reviews and Meta-Analyses Can (and Cannot) Do

Good systematic reviews can identify relevant research studies, classify them by quality, combine the data from them where appropriate and draw reasonable conclusions. These conclusions may have implications for clinical practice – where there are significant findings – but also, importantly implications for new research. One important conclusion from the reviews already published in the Cochrane Library is the need to improve not only the quality of individual trials (their design and reporting) but also the world-wide co-ordination of research in lung cancer so that the important questions outlined at the start of this chapter can be addressed in a more systematic way.

Systematic reviews of the type promoted and published by the Cochrane Collaboration should be an essential tool for clinicians, researchers, research funders, health policy makers and anyone with an interest in lung cancer prevention, treatment and care. They are tools to improve the quality of clinical practice and clinical research, to inform a strategic research agenda and to help streamline a more effective and efficient use of research funding. But systematic reviews are only as good as the original research from which they are derived and they can never compensate for poor quality professional education, poor quality clinical practice, absent research, poor quality research or a disorganised research direction and agenda.

13.7 Conclusion

Both health care professionals and clinical researchers in the field need access to the reliable and up-to-date information on clinical effectiveness that can be provided by systematic reviews and meta-analyses. Researchers would also undoubtedly find a spe-

cialised trial register extremely helpful, especially if it were study based.

Huge challenges must be overcome in clinical research in lung cancer before we are able to solve the many unanswered questions that remain in the prevention, treatment and care of this disease. Resources are increasingly scarce, but innovations in information technology could facilitate a much more organised, strategic and global approach to wider recruitment to soundly designed trials. The means are already at our disposal: if we really want to increase our understanding of the biggest cancer killer of our time, we must have the will to invest in a single common information management resource.

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