Advances in Radiation Oncology in Lung Cancer

B. Jeremić
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Editors:
L. W. Brady, Philadelphia
H.-P. Heilmann, Hamburg
M. Molls, Munich
Branislav Jeremić (Ed.)

Advances in Radiation Oncology in Lung Cancer

With Contributions by

N. K. Aaronson · K. S. Albain · M. Anscher · L. Arbea · J. Aristu · M. Bamberg · P. V. Barber
C. P. Belani · A. W. Blackstock · J. A. Bonner · P. A. Burt · D. Bush · F. A. Calvo · F. Casas
M. Chaltin · J. Chang · Y. Chen · L. C. Cho · H. Choy · J. D. Cox · A. Dagović · W. De Gersem
W. De Neve · M. Fujino · S. M. Galbraith · S. P. Gangadharan · Y. Garces · A. L. Grosu
S. M. Hahn · M. Hara · J. C. Haynes · R. J. Hicks · B. Jeremić · M. D. Jeter · R. Komaki · P. A. Kvale
F. J. Lagerwaard · H. Langendijk · C. Le Péchoux · J. Lester · Z. Liao · P. A. Linden
F. R. Macbeth · M. Machtay · M. P. MacManus · L. B. Marks · M. K. Martel · N. E. Martin
K. A. Mason · W. G. McKenna · K. P. McMullen · L. Milas · K. Miller · N. Mirkovic · M. Molls
C. Nieder · R. Onimaru · H. Onishi · R. Prosnitz · S. Ramalingam · T. E. Schultheiss
S. Senan · T. D. Shafman · W. Shi · Y. Shibamoto · H. Shirato · D. W. Siemann · M. J. Simoff
R. Stephens · R. Stout · D. J. Sugarbaker · T. G. Sutedja · E. Thompson · K. Vandecasteele
N. Viñolas · Z. Vujaskovic · M. Werner-Wasik · X. Yu · F. B. Zimmermann

Foreword by

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

With 89 Figures in 133 Separate Illustrations, 50 in Color and 85 Tables
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
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. Christine 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.
# Contents

1 Pretreatment Considerations ........................................ 1

1.1 Molecular Biology and Genetics of Lung Cancer  
*Neil E. Martin, Stephen M. Hahn, and W. Gillies McKenna* .......... 3

1.2 Angiogenesis in Lung Cancer  
*Dietmar W. Siemann, Susan M. Galbraith, and Wenyin Shi* .......... 13

1.3 Contemporary Issues in Staging of Lung Cancer  
*Frank B. Zimmermann* ........................................ 31

2 Basic Treatment Considerations ..................................... 45

2.1 Lung Cancer Surgery  
*Sidhu P. Gangadharan, Philip A. Linden, and David J. Sugarbaker* 47

2.2 Radiation Therapy

2.2.1 Radiobiology of Normal Lung Tissue and Lung Tumours  
*Yuta Shibamoto and Masaki Hara* ................................. 59

2.2.2 Radiation Time, Dose, and Fractionation in the Treatment of Lung Cancer  
*Melenda Jeter, Ritsuko Komaki, and James D. Cox* .......... 67

2.2.3 Treatment Planning and Conformal Radiotherapy  
*Mary K. Martel* ........................................ 77

2.2.4 Target Volumes in Non-Small Cell Lung Cancer  
*Frank J. Lagerwaard and Suresh Senan* ......................... 97

2.2.5 Target Volumes in Small Cell Lung Cancer  
*Yolanda Garces and James A. Bonner* ......................... 111

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* ............................. 123

2.3 Lung Cancer Chemotherapy for Radiation Oncologists  
*Suresh Ramalingam and Chandra P. Belani* ......................... 135

2.4 Radiotherapy and Chemotherapy – Fundamentals and Preclinical Data  
*A. William Blackstock and Kevin P. McMullen* ..................... 155
3 Current Treatment Strategies in Non-Small Cell Lung Cancer ......................... 167

3.1 Early Stage in Non-Small Cell Lung Cancer ............................................. 169

3.1.1 Radiotherapy in Early Stage Non-Small Cell Lung Cancer
BRANISLAV JEREMIĆ ................................................................. 169

3.1.2 Postoperative Radiotherapy for Non-Small Cell Lung Carcinoma
JEFFREY C. HAYNES and MITCHELL MACHTAY ................................. 189

3.1.3 Photodynamic Therapy
TOM G. SUTEDJA ................................................................. 199

3.2 Locally Advanced Non-Small Cell Lung Cancer ................................. 207

3.2.1 Radiochemotherapy in Locally Advanced Non-Small Cell Lung Cancer
BRANISLAV JEREMIĆ and ALEKSANDAR DAGOVIC .............................. 207

3.2.2 Chemotherapy or Chemoradiotherapy Followed by Surgical Resection for Non-Small Cell Lung Cancer
NENA MIRKOVIC and KATHY S. ALBAIN ...................................... 223

3.2.3 Palliative External Beam Thoracic Radiotherapy
JASON LESTER and FERGUS R. MACBETH ....................................... 247

3.2.4 Intraoperative Electron Beam Radiotherapy in Lung Cancer
JAVIER ARISTU, LEIRE ARBEA and FELIPE A. CALVO ......................... 255

3.2.5 Intraluminal Radiotherapy
RON STOUT, PAUL A. BURT, and PHILIP V. BARBER ......................... 269

4 Treatment of Small-Cell Lung Cancer ................................................. 275

4.1 Limited Disease of Small-Cell Lung Cancer
BRANISLAV JEREMIĆ ................................................................. 277

4.2 Prophylactic Cranial Irradiation in Small-Cell Lung Cancer
CÉCILE LE PÉCHOUX ............................................................... 287

5 Radiation Therapy for Recurrent Lung Cancer
BRANISLAV JEREMIĆ and MICHAEL BAMBERG .................................. 297

6 Radiotherapy of Lung Cancer in Elderly Patient
BRANISLAV JEREMIĆ and MICHAEL MOLLS ...................................... 309

7 Advances in Supportive and Palliative Care for Lung Cancer Patients
MICHAEL J. SIMOFF and PAUL A. KVALE ......................................... 321

8 Treatment-Related Toxicity ................................................................. 337

8.1 Hematological Toxicity in Lung Cancer
FRANCESC CASAS and NÚRIA VIÑOLAS .......................................... 339
Pretreatment Considerations
1.1 Molecular Biology and Genetics of Lung Cancer

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

CONTENTS

1.1.1 Introduction 3
1.1.2 Basics of Genetics and Molecular Biology 3
1.1.3 Self-Sufficient Growth Signaling 5
1.1.4 Insensitivity to Antigrowth Signals 6
1.1.5 Evasion of Programmed Cell Death 7
1.1.6 Limitless Replicative Potential 8
1.1.7 Sustained Angiogenesis 8
1.1.8 Tissue Invasion and Metastasis 9
1.1.9 Genetic Alterations in the Progression of Lung Cancer 9
1.1.10 Therapeutic Targets 9
1.1.11 Conclusion 10
References 10

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.

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 (Ronan 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.
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