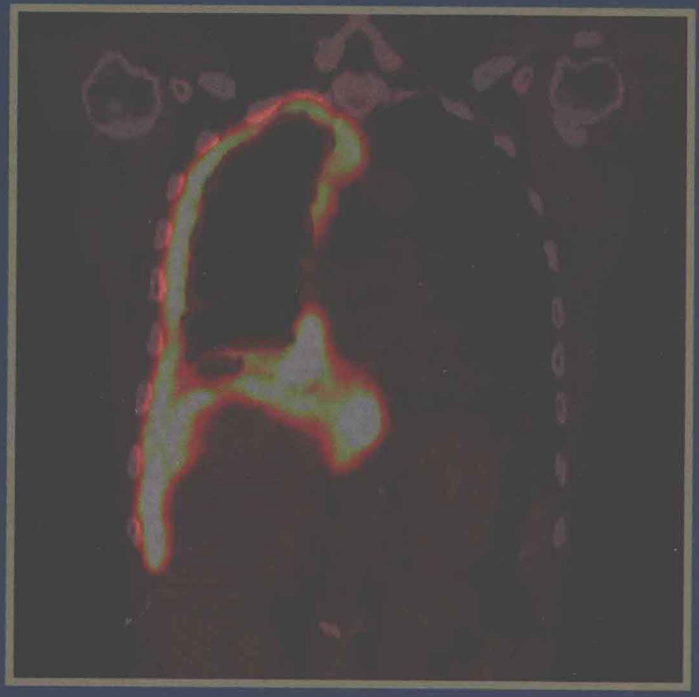
Lung Cancer

Prevention, Management, and Emerging Therapies

David J. Stewart
Editor



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This book is dedicated to Lesley, Megan, Adam, Andrew, Jenika, Grayson and Cameron whose love gives purpose to my life and work, and whose support, understanding and patience make all things possible.

Preface

Defining the Lung Cancer Problem

Lung cancer is the leading cause of cancer death in the world.[1] It kills almost as many Americans as cancers of the breast, prostate, colon, rectum, pancreas, and kidney combined, and accounts for 28.6% of all US cancer deaths.[2] With an increase in the 5-year relative survival rate from 13% to only 16% in the more than 30 years from 1974 to the present,[2] it will take us another 840 years to eradicate lung cancer deaths if we do not improve the current rate of progress.

As discussed in this text, lung cancer prevention has received substantial attention. The decrease in smoking in recent decades has helped, but smoking is not the only problem. Lung cancer in people who have never smoked is currently the 5th leading cause of cancer death in the United States.[3]

Several factors contribute to the lethality of lung cancer, including the rapidity of tumor growth, advanced stage at diagnosis (due to nonspecificity of early symptoms and the uncertain efficacy of screening), early development of metastases, and resistance to therapy. Several chapters in this book discuss new molecular targets that may be potentially exploitable in the future, as well as discussing our track record to date in exploiting them.

Over the last few decades, we have made several errors that have slowed our pace in the war against lung cancer. For example, until recently, most nonsmall cell lung cancers were treated more or less as if they were the same disease. It has been postulated that common cancers are both common and resistant to therapy since many different mutations may give rise to them, and that each underlying mutation may require a different treatment approach.[4] Hence, there may never be one silver bullet for lung cancer. We may need instead 20 or 30 different agents, each targeting a molecularly distinct subpopulation of patients. Large randomized trials ignore this possibility and try to overpower biological realities by using the statistical power of large patient numbers to achieve a significant p value. Hence, we have ended up with a variety of therapies that achieve statistical significance, but with survival gains of mere weeks.[5]

There are two major problems with this. The first is that if the p value is not significant, a drug may be abandoned despite being of marked benefit in a small

subpopulation of patients, as happened with gefitinib. The other side of the problem is that with $p<0.05$, the drug may be accepted as being "effective", and the drug may be applied widely at high cost and potential toxicity, despite being of value in only a small subpopulation of patients. We feel that progress against lung cancer and other malignancies has been slowed by our placing the efficacy bar too low, using large randomized trials to eke out small gains.[5] We would argue that we need small trials looking for large gains, not large trials looking for small gains. We need to molecularly characterize the tumors of *all* patients from the earliest phase I trials onward and use the results of this molecular profiling to identify those most and least likely to benefit from the therapy.[5]

If we do randomized trials without fully characterizing patients, we may well be misled. For example, simulations suggest to us that if a new therapy quintuples survival in a 10% subpopulation of patients whose tumors express a particular target, this will be missed unless around 2,000 patients are included in the trial. If the new agent only doubles survival in this 10% subpopulation, then more than 5,000 patients may be needed to detect the benefit. As discussed earlier, at the end of the study, we will either conclude that the therapeutic approach is "effective" and inappropriately apply it widely, or we will conclude that it is "ineffective" and inappropriately discard it. If, however, one correctly identifies the required target, then one may get the correct answer (that the agent is effective in the subpopulation with the target) with fewer than 20 patients if survival is quintupled and with fewer than 100 patients if survival is only doubled. At $26,000 per patient (the amount that it currently costs per patient on a phase III trial[6]), the money saved by reducing phase III trial sizes would pay for very extensive molecular profiling of every patient to ever participate in phase I and II trials of the agent, and correlating these profiles with % tumor shrinkage or with some other measure of tumor cell kill would go a long way toward defining the population that should subsequently be targeted in phase III trials.

There are also other problems with randomized trials in unselected patients. The study may indicate that the agent was not helpful when in fact benefit in one subpopulation was balanced by harm in another, as may be the case with EGFR inhibitors in patients with EGFR vs. Kras mutations.[7] Furthermore, if an agent hitting a target present in 5% of the population is compared to another hitting a target present in 40% of the population, the agent hitting the more common target will win and will be the new "standard of care". It will be incorrectly concluded that this agent is the "better" agent when in fact it is not: it just hits a more common target. If there is no exploitable target that is present in >40% of patients, progress will plateau and we would make no further gains. In addition, an agent which increases the survival of all patients by 30% (equivalent to increasing median survival from 6 months to 7.8 months) may consistently beat an agent which increases survival 5-fold in a 10% subpopulation, but we would argue that the latter agent is the more important one. Contrary to this, some newer statistical approaches such as randomized discontinuation strategies[8] are specifically designed to try to identify small advances, and in our opinion contribute to the problem. Overall, as stated above, we feel that it is of paramount importance to molecularly characterize all

patients on study, and then to aim for large gains in appropriate subpopulations rather than using unselected patients to aim for small gains in large studies.[5]

In addition to the efficacy bar being set too low, we feel that the safety bar has been set too high for fatal, incurable diseases like cancer.[5] We recently calculated that increasingly stringent research regulations might have decreased toxic death rates by 0.3% for patients on study. However, with the cost of complying with these regulations running at an estimated $8,000 per patient studied and an estimated life expectancy for patients on study of 1 year, this translates into $2.7 million per year of life gained - an amount far higher than either other preventive measures or the figure of $50,000–$100,000 per year of life gained that is regarded as being acceptable for therapies.[9] In addition, if 5,000–10,000 patients need to be treated on studies to make a small advance (eg., a new therapy that increases cure rate of lung cancer by 1% through improved adjuvant therapy and that increases survival of incurable patients by a median of 3 months), the regulations would have led to a savings of 15–30 life-years (5,000–10,000 × 0.3% × 1 year), but if the regulations slow the advance by a conservatively estimated 5 years, the regulation-induced delays will have cost 285,000 life-years in the United States and almost 2 million life-years worldwide, seriously challenging equipoise. We feel that the regulations governing cancer research need to change.[5]

Overall, lung cancer remains a formidable foe. While we have made some progress, much remains to be done. In this book, we give a brief description of where we stand today, as well as offering a glimpse of the path forward.

Houston, TX David J. Stewart, MD, FRCPC

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Lung Cancer

Contents

Molecular Pathology of Lung Cancer

Alejandro Corvalan and Ignacio I. Wistuba

Abstract In contrast to most other organs, the lungs demonstrate a very wide range of epithelial tumors that vary in their location and histology. These tumors show varying degrees of relationship to smoke exposure, with the central carcinomas showing the greatest relationship. The molecular lesions found in the tumors share certain common elements and have characteristic changes. Their precursor lesions also differ, with some being well defined, whereas others are poorly understood because of the difficulty in identifying them before surgical resection of an existing tumor. Thus, their natural history is also poorly understood. The advent of newer molecular genetic methods to examine lung tumor and preneoplastic lesion tissue specimens will help delineate all the significant molecular abnormalities responsible for lung cancer development and progression. Gene-specific and copy-number alteration approaches have identified mutations that have proven to be unique in lung cancer. Simultaneously, molecular profiling studies at DNA, RNA, and protein levels have provided a molecular classification of lung cancer while also improving the ability to predict prognosis and response to treatment. The integration of these different platforms might overcome the overtraining and instability of the identified signatures. Combining clinical covariates with molecular profiling approaches may be the optimal approach for building new models for lung cancer. The ultimate goal is to be able to identify all molecular changes present in any one patient's tumor and to use this information for early molecular detection, prediction of biological/clinical behavior and prognosis, and selection or rational development of therapeutics.

Keywords Molecular pathology • Lung cancer • Oncogenes • Tumor suppressor genes • Preneoplasia • Pathogenesis

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Introduction

Accurate pathological classification of lung cancer is essential for patients to receive appropriate therapy. From a histopathological and biological perspective, lung cancer is a highly complex neoplasm (1, 2). There are several histological types, with the most frequent being small cell lung carcinoma (SCLC, 15%) and the non-small cell lung carcinoma (NSCLC) variants such as squamous cell carcinoma (30%), adenocarcinoma (45%), and large cell carcinoma (9%) (3).

Advances in molecular technologies have provided insight into the biological processes involved in the pathogenesis of lung cancer. Recent findings have indicated that clinically evident lung cancers are the result of the accumulation of numerous genetic and epigenetic changes, including abnormalities in the inactivation of tumor suppressor genes and the activation of oncogenes (1, 2). All of these molecular abnormalities involve the "hallmarks of cancer," including abnormalities in the self-sufficiency of growth signals, insensitivity to antigrowth signals, sustained angiogenesis, evasion of apoptosis, limitless replicative potential, and tissue invasion and metastasis (4, 5). Recent molecular advances have provided unique opportunities to develop rational targeted therapies for lung cancer. These advances have led to an emerging and exciting new area of therapy that takes advantage of cancer-specific molecular defects which render the cancer cells more likely to respond to specific agents (6, 7). In this setting, the analysis of molecular abnormalities of lung cancers is becoming increasingly important, and the adequate integration of routine pathological and molecular examinations into the diagnosis, classification, and choice of therapy options presents an interesting challenge.

Although many molecular abnormalities have been described in clinically evident lung cancers, relatively little is known about the molecular events preceding the development of lung carcinomas and about the underlying genetic basis of lung carcinogenesis (2, 8, 9). In the past decade, several studies have provided information regarding the molecular characterization of the preneoplastic changes involved in the pathogenesis of lung cancer, especially squamous cell carcinoma and adenocarcinoma (8, 10).

In this chapter, we will describe the most relevant molecular abnormalities observed in lung cancer with regard to their pathological and clinical characteristics. In addition, we will review the current understanding of this cancer's early pathogenesis and progression.

Molecular Pathology of Lung Cancer

It has been shown that multiple genetic changes are found in clinically evident lung cancers and involve several dominant oncogenes as well as known and putative recessive oncogenes (tumor suppressor genes) (1, 2). Many growth factors or regulatory peptides and their receptors are overexpressed by cancer cells and adjacent normal-appearing cells in the lung and thus provide a series of autocrine and paracrine