CONTENTS

Preface **ix**
Mithran S. Sukumar

Defining N2 Disease in Non–Small Cell Lung Cancer **333**
Edmund S. Kassis and Ara A. Vaporciyan

Simply defined, N2 disease in non–small cell lung cancer (NSCLC) is the presence of ipsilateral mediastinal nodal metastases. This definition does little justice to what is in actuality a heterogeneous and challenging patient population. The presence of ipsilateral mediastinal nodal metastases (N2 disease) in NSCLC is a poor prognostic sign. This article demonstrates that the definition of N2 disease includes many subgroupings with widely disparate effects on prognosis.

Detection of Occult N2 Disease with Molecular Techniques **339**
Loretta Erhunmwunsee and Thomas A. D'Amico

Lymph node involvement is the most important factor affecting the prognosis and treatment of patients with potentially resectable NSCLC. Radiographic imaging is inadequate to ascertain lymph node involvement. Currently, lymph nodes are assessed pathologically using conventional histologic techniques; however, lymph node micrometastases may be missed, leading to inaccurate staging and suboptimal treatment. Assessment of occult involvement using antibody expression improves the sensitivity of lymph node analysis, and more advanced techniques, using molecular biologic methods, may further improve lymph node staging. Optimizing outcomes of patients with lung cancer depends on accurate lymph node staging, and the development of the strategies that improve the assessment of lymph node micrometastases will be beneficial.

Radiographic Staging of Mediastinal Lymph Nodes in Non–Small Cell Lung Cancer Patients **349**
Shawn S. Groth, Bryan A. Whitson, and Michael A. Maddaus

In order for non–small cell lung cancer patients to undergo the most appropriate treatment, accurate clinical staging (including an assessment for mediastinal lymph node metastasis) is essential. Imaging studies play a critical role in this process. To screen for mediastinal lymph node metastasis, the most sensitive and accurate imaging modality is a positron emission tomography/computed tomography scan. Despite improvements in the sensitivity and accuracy of imaging techniques, histologic assessment of the mediastinum is still required.

Minimally Invasive Staging of N2 Disease: Endobronchial Ultrasound/ Transesophageal Endoscopic Ultrasound, Mediastinoscopy, and Thoracoscopy **363**
Paul Schipper and Matt Schoolfield

Multiple methods of minimally invasive evaluation of the N2 lymph nodes have been developed in hope of providing information similar to that obtained by a lymph node dissection, but with less morbidity. This article details four minimally invasive procedures: endobronchial ultrasound and needle biopsy, endoscopic transesophageal ultrasound and needle biopsy, cervical mediastinoscopy and biopsy, and thoracoscopy and biopsy. It discusses the lymph nodes that can be evaluated by these procedures, the limitations of the procedures, additional information the procedures can yield beyond lymph node staging, the procedures' reliability in determining whether cancer is present in the N2 lymph nodes, and, most importantly, the potential cost to the patient in answering that question.

Intraoperative Staging and Surgical Management of Stage IIIA/N2 Non–Small Cell Lung Cancer **381**
Igor Brichkov and Steven M. Keller

Thorough staging of the mediastinum is an integral component of the operative treatment of non–small-cell lung cancer. Systematic sampling and systematic lymph node dissection provide similar and accurate staging information; however, systematic lymph node dissection is more likely to identify multiple levels of N2 disease and may be associated with improved survival. Although every effort should be made to identify N2 disease before surgery, if intraoperative metastases to mediastinal lymph nodes are discovered, the planned operation should proceed. Cisplatin-based adjuvant chemotherapy has moderate but proven survival benefit after resection of N2 disease. The role of postoperative radiotherapy remains uncertain.

Definitive Chemoradiotherapy for Non–Small Cell Lung Cancer with N2 Disease **393**
Shilpen Patel, Rachel E. Sanborn, and Charles R. Thomas, Jr.

Non–small cell lung cancer remains the leading cause of cancer death in men and women, with a significant proportion of patients having locally advanced, unresectable disease at the time of diagnosis. Although significant advances in definitive therapy have been made with the concurrent administration of combination cytotoxic chemotherapy and thoracic irradiation, recurrence rates are still high, and long-term survival rates are suboptimal. The application of more modern radiation techniques and the addition of molecularly targeted systemic agents may add further benefit in survival.

Neoadjuvant Therapy for Resectable Non–Small Cell Lung Cancer with Mediastinal Lymph Node Involvement **403**
Brandon H. Tieu, Rachel E. Sanborn, and Charles R. Thomas, Jr.

Survival outcomes of patients with stage IIIA non–small cell lung cancer (NSCLC) with mediastinal lymph node involvement (N2 disease) have been poor when treated with surgery alone. Numerous studies have investigated induction chemotherapy, radiation, and chemoradiation to attempt to improve outcome in this high-risk population. The appropriate application and sequence of these treatments is still the subject of ongoing study. Surgical resection appears to have the greatest benefit in patients who have decreased mediastinal involvement following induction therapy, although the type of surgical resection (pneumonectomy or lesser resection) impacts morbidity and mortality risks after induction therapy. Molecularly targeted agents are also being studied as a potential induction therapy for use in the treatment of stage IIIA disease.

Restaging After Neo-Adjuvant Chemoradiotherapy for N2 Non–Small Cell Lung Cancer **417**
Robert J. Cerfolio and Ayesha S. Bryant

Recent studies have shown that patients who are down-staged via neoadjuvant therapy and undergo resection have a significant increased 5-year survival rate (as high as 40%–50%) when compared with patients who have residual N2 disease. The identification of patients who are N2 negative after the completion of their neoadjuvant therapy is a critical component of proper patient selection for thoracotomy. Some may even argue that it is a necessary step before resection. In this article we review the best ways to restage patients with N2 disease after they have completed their neoadjuvant therapy.

Adjuvant Therapy for Non–Small Cell Lung Cancer with Mediastinal Nodal Involvement **423**
Rachel E. Sanborn and Brian E. Lally

The presence of ipsilateral mediastinal lymph node involvement (N2 disease) is a marker of poor prognosis in patients with resected non–small-cell lung cancer. The addition of systemic chemotherapy to the adjuvant setting has been shown to improve survival by eliminating occult micrometastatic disease. The administration of adjuvant radiotherapy for resected N2 disease is more controversial, although the data regarding outcomes rest primarily on older modalities of delivering radiotherapy. Other modalities of possibly improving survival for resected non–small-cell lung cancer with N2 disease, such as combined modality chemoradiation, prophylactic cranial irradiation, or the addition of molecularly targeted agents, remain to be proven.

Management Algorithms for Stage IIIA Non–Small Cell Lung Cancer with N2 Node Involvement **437**
Frank Detterbeck and Mithran S. Sukumar

Stage IIIA non–small cell lung cancer (NSCLC) with N2 node involvement (IIIA[N2]) is a complex area characterized by much confusion and controversy, because data derived from a particular subgroup of IIIA(N2) often are inappropriately applied to another subgroup. The problem is not so much that stage IIIA(N2) encompasses a spectrum of disease, which is true in each stage of NSCLC. Rather, our ability to describe a patient cohort has been limited, and it is therefore often difficult to determine how and when to apply data from published studies. A simple, pragmatic approach is taken in this article to define algorithms for the management of these patients.

Index **443**