unless the patient has medical comorbidities or is of advanced age. Wedge resection may be considered as an alternative to lobectomy, but patients also may be offered local ablative radiation therapy techniques such as stereotactic body radiation therapy (SBRT) or CyberKnife radiosurgery.

Locally Advanced Disease (Stages IIIA and IIIB)

Patients with stage III disease are heterogeneous, and the optimal treatment strategy is unclear. For stage IIIA disease, curative surgery, in combination with neoadjuvant chemotherapy and radiation, may be offered. Most patients with stage IIIB NSCLC are not surgical candidates, and 5-year survival is poor for this group. Concurrent chemotherapy and radiotherapy are preferable to radiotherapy alone.

Advanced Metastatic Disease (Stage IV)

Chemotherapy improves survival and provides palliation for symptoms in stage IV disease. Patients with high performance often receive doublet chemotherapy, combining a platinum agent (cisplatin or carboplatin) and a second agent (e.g., paclitaxel, pemetrexed, gemcitabine). Histology-specific personalized therapy is now becoming possible; for the adenocarcinoma subtype, pemetrexed is used, and for the squamous cell subtype, gemcitabine.

Genomics-Guided Precision Therapy

Mutational analysis and genomic profiling hold promise for "precision therapy" or "personalized targeted therapy." For example, NSCLC, especially adenocarcinoma, can be viewed as having distinct subgroups of mutated oncogenes, some known to be "actionable" or "targetable" with novel treatment (E-Fig. 56-14). In *EGFR*-mutant lung cancer, the EGFR inhibitor gefitinib or erlotinib improved the progression-free survival rate better than chemotherapy treatment did. An era in which "molecular profiling" trumps profiling by clinical parameters has arrived.

Targeted therapy in lung cancer has already made an impact in terms of a treatment paradigm shift and in clinical outcome. The major obstacle in fully unleashing the power of targeted therapy lies in the invariable development of acquired drug resistance, which ultimately leads to disease progression and death of the patient. The predominant mechanism in erlotinib resistance is the emergence of *EGFR* T790M mutation in exon 20, which accounts for about half of all resistant cases. Other novel mechanisms of acquired erlotinib resistance have come to light more recently, including *MET* amplification or the RTK activation, *PIK3CA* mutation, *EGFR* amplification, *AXL* upregulation, and even histologic SCLC transformation. Various mechanisms of resistance against crizotinib in *ALK*-genotype specific targeted therapy are also being uncovered at a rapid pace.

Currently, a number of Clinical Laboratory Improvement Amendments (CLIA)-certified genomics laboratories perform tumor genomic profiling, but what constitutes the best lung cancer genomic profiling method remains uncertain.

PROGNOSIS

The most important prognostic factor in lung cancer is the TNM stage of the disease at the time of presentation. Poor performance status and weight loss are also negative prognostic factors for survival of patients with lung cancer.

For a deeper discussion on this topic, please see Chapter 191, "Lung Cancer and Other Pulmonary Neoplasms," in Goldman-Cecil Medicine, 25th Edition.

SUGGESTED READINGS

Hirsch FR, Jänne PA, Eberhardt WE, et al: Epidermal growth factor receptor inhibition in lung cancer: status 2012, J Thorac Oncol 8:373–384, 2013.

Imielinski M, Berger AH, Hammerman PS, et al: Mapping the hallmarks of lung adenocarcinoma with massively parallel sequencing, Cell 150:1107–1120, 2012.

National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al: Reduced lung-cancer mortality with low-dose computed tomographic screening, N Engl J Med 365:395–409, 2011.

Rosell R, Bivona TG, Karachaliou N: Genetics and biomarkers in personalization of lung cancer treatment, Lancet 382:720–731, 2013.

Sequist LV, Waltman BA, Dias-Santagata D, et al: Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors, Sci Transl Med 3(75):75ra26, 2011.