Lung Cancer

This section will focus on treatment and follow-up of patients with lung cancer. See MKSAP 18 Pulmonary and Critical Care Medicine for discussion of epidemiology, screening, clinical manifestations, diagnosis, and staging of patients with lung cancer. Initial biopsy can distinguish tumors as either non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC). NSCLC can be divided into pathologic subtypes, including large cell, adenocarcinoma, and squamous cell cancer. Although these subtypes have characteristic clinical features, the diagnosis, staging, and therapy for all forms of NSCLC are similar. The staging criteria and treatment of SCLC differ from NSCLC.

Non-Small Cell Lung Cancer

Treatment of NSCLC, like that of most other solid malignancies, is based largely on disease stage. For the purposes of this discussion, it is best to divide NSCLC into early stage, locally advanced, and metastatic categories.

Early-Stage Disease

Early-stage disease refers to lung cancer that is amenable to surgical resection at the time of diagnosis. This typically encompasses stage I and II cancers, though some patients with stage II cancer are not amenable to resection based on location or extent of the primary tumor. Stages I and II are differentiated by hilar nodal metastatic disease (present in some patients with stage II cancer, but not present in stage I) and also by the size and invasiveness of the primary tumor into adjacent structures. As in many other cancers, multidisciplinary evaluation is of vital importance to these patients in order to make the most accurate determination regarding optimal treatment.

Patients deemed potential surgical candidates based on imaging need to have a rigorous functional evaluation to help predict their anticipated pulmonary reserve after surgery. The initial evaluation consists of FEV_1 and DLCO measurement. If both test variables are favorable, then no further evaluation is needed. However, if one or the other variable falls in a range suggesting impaired lung function, then calculation of the predicted postoperative FEV_1 and DLCO should be performed, which is determined by baseline values and assessment of the fractional contribution of the lung to be resected. If the predictive postoperative lung function values indicate mild to moderate impairment, then exercise testing is often used. Based on the results of these assessments, a decision can be made regarding suitability for resection. Patients with pathologic stage I cancer who are undergoing surgical resection have a 60% to 70% survival rate at 5 years and patients with stage II cancer have approximately a 40% survival rate.

For patients who are not surgical candidates, other options are available, including stereotactic body radiation and other ablative treatments that can be used to treat the primary tumor. Such treatments have been shown to have excellent rates of local control, but they are only suitable for patients with relatively small tumors. For larger tumors, conventional radiation is used. There are no data supporting the use of chemotherapy combined with radiation in patients with stage I or II disease. Despite the adverse effect of their comorbid lung disease, patients with localized tumors treated with radiation have a mean survival of greater than 3 years.

Lobectomy is the preferred surgical procedure in early-stage disease. Proximal tumors may be less amenable to lobectomy. In those patients, sleeve resection (resection of the involved lobe and a portion of the main stem bronchus) has fewer postoperative complications and is preferable to pneumonectomy. Sublobar resection is not recommended but can be considered in selected patient populations (such as elderly patients and those with stage I cancer).

Patients treated surgically for stage I or II disease who have positive margins benefit from postoperative radiation therapy and show an improvement in overall survival. This is not the case for patients with negative surgical margins.

Cisplatin-based adjuvant chemotherapy has been shown to improve survival after resection in patients with resected stage II or III lung cancer. The LACE meta-analysis, which used patient data from five different cisplatin-based adjuvant chemotherapy trials, found a 5.4% decrease in the risk of death at 5 years in patients with resected stage II or III disease. Another meta-analysis identified a 4% improvement in survival at 5 years in patients treated with cisplatin-based chemotherapy after surgery and radiation. Approximately 50% of patients who had surgically resected stage I, II, or IIIA cancer survived 5 years. Chemotherapy consists of cisplatin with a second agent and is typically given for four cycles. The most commonly used chemotherapy partners are vinorelbine, pemetrexed, gemcitabine, and docetaxel.

After completion of treatment, patients with early-stage disease remain at risk for both distant and local recurrence. Many patients with smoking histories are also at risk for developing a second primary lung cancer and cancers of the head, neck, and other sites. Current accepted recommendations for surveillance include history, physical examination, and chest CT at least every 6 months for the first 2 years and then annually. Smoking cessation decreases the risk of new primary lung cancers, although the magnitude of benefit is uncertain, ranging from 20% to 90%; the risk steadily declines beginning 5 years after quitting, but it never quite reaches the incidence found in nonsmokers.

KEY POINTS

- Lobectomy is the preferred surgical procedure in early-stage disease.
- Potential surgical candidates with early-stage lung cancer must have FEV_1 and DLCO measurement to predict their anticipated postoperative pulmonary reserve and suitability for resection.

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KEY POINTS *(continued)*

- Patients with early-stage lung cancer who are not surgical candidates can be treated with radiation therapy; stereotactic body radiation is appropriate for small tumors, but conventional radiation is used for large tumors.
- Postoperative radiation therapy is used to treat patients with resected localized lung cancer and positive tumor margins; cisplatin-based adjuvant chemotherapy is standard treatment of all resected stage II and III lung cancer.

Locally Advanced Disease

Locally advanced lung cancer is most commonly defined by the presence of clinically detectable lymphadenopathy in the mediastinum or by a primary tumor that invades into local structures, such as the mediastinum, heart, trachea, esophagus, or great vessels.

Safer, more refined surgical technique, along with more precise preoperative staging that more accurately defines the primary tumor, has expanded the number of patients eligible for surgical resection, although it is unclear whether this has resulted in improved survival outcomes. For example, some patients with T4 tumors showing invasion into adjacent vital structures, with no evidence of mediastinal node involvement, can have surgical resection and their disease treated as stage III disease. Patients with satellite nodules in the same lobe (T3) or in another ipsilateral lobe (T4) were previously considered to have metastatic disease, but can be resected with curative intent. Even patients with an isolated tumor nodule in the contralateral lung, traditionally considered incurable metastatic disease, can now undergo resection to remove all sites of cancer under the assumption that the nodule could represent a second localized primary lung cancer. Finally, patients with limited ipsilateral mediastinal node involvement, a single node station, and nonbulky disease can undergo surgical resection. These patients will all generally receive neoadjuvant or adjuvant chemotherapy or radiation treatment.

Patients who present with bulky or multistation (widespread mediastinal or hilar lymph node involvement) mediastinal lymphadenopathy are treated with combined platinum-based chemotherapy and radiation, which has been found to be superior to sequential treatment. Unfortunately, the risk of recurrence, both locoregional and distant, is very high after chemoradiation treatment (approaching 70% to 90%).

KEY POINT

- Surgical techniques have improved substantially and, along with better preoperative staging, allow surgical therapy with curative intent for various patients who were traditionally considered to have unresectable disease.

Metastatic Disease

Metastatic lung cancer is defined as the spread of disease to distant sites such as liver, bone, or brain. The presence of one or more tumor nodules in the contralateral lung also qualifies as metastatic disease, but as the prognosis for that pattern of metastatic disease is notably better than that of patients with distant disease, it has been reclassified as M1a, with other distant sites given the designation of M1b.

In the past, all patients with metastatic NSCLC were treated with the same chemotherapy regimens. With the recent development of precision medicine, specific molecular and genetic targets have been discovered, resulting in more tailored treatments. Furthermore, it is now understood that patients with different histologic types of lung cancer respond differently to various chemotherapy agents. Immunotherapy has now been shown to have an impact on the treatment of advanced lung cancer. Despite these advances, however, metastatic NSCLC remains incurable. Level 1 evidence supports early palliative care interventions in this patient population. Their quality of life will be improved even as they continue to receive aggressive chemotherapy.

Before deciding the optimal treatment for any given patient, it is essential to define histology, assess for molecular alterations, and determine performance status. For patients with non-squamous histology (particularly adenocarcinoma), testing for molecular alterations is mandatory. At present, it is considered standard care to test for mutation in the epidermal growth factor receptor (*EGFR*) gene and for translocations involving *ALK* or *ROS1*. If an *EGFR* mutation is identified, initial treatment with erlotinib is recommended. If an *ALK* or *ROS1* translocation is identified, initial treatment with crizotinib is recommended. Erlotinib and crizotinib are both small molecule tyrosine kinase inhibitors that are specific for those genetic alterations. Although many other molecular and genetic alterations have been identified in patients with NSCLC, further investigation is required before changes in treatment become evidence-based care.

If a patient has negative findings for the alterations noted above, treatment with chemotherapy is indicated only if the patient has a good performance status. Patients with poor performance status do not benefit from chemotherapy treatment. Front-line chemotherapy is given with a platinum-based doublet regimen. Either cisplatin or carboplatin can be used; cisplatin is slightly more active, but carboplatin is more commonly used because of its more favorable side-effect profile. Histologic assessment can help guide choice of the second agent, as patients with adenocarcinoma have been shown to respond well to pemetrexed, whereas those with squamous cell carcinoma respond better to gemcitabine, based on the results of a phase III clinical trial comparing these two agents. Other commonly used second agents in this setting include paclitaxel, docetaxel, and vinorelbine. Chemotherapy is administered for four to six cycles and can be given in combination with bevacizumab. Bevacizumab is a monoclonal

antibody directed against vascular endothelial growth factor and when given in combination with platinum-based chemotherapy for patients with non-squamous cell forms of NSCLC in the first-line setting, it has been shown to improve both progression-free survival and overall survival, though the degree of benefit is modest. In addition, bevacizumab carries the risk of thrombosis, stroke, myocardial infarction, and hemoptysis in some patients. For patients who respond to front-line chemotherapy, maintenance treatment with docetaxel, pemetrexed, or gemcitabine has been shown to improve progression-free survival, and pemetrexed has also been shown to improve overall survival.

Immunotherapy with agents that act on the programmed cell death ligand 1 (PD-L1) have shown impressive activity in metastatic NSCLC. Pembrolizumab is superior to chemotherapy in the first-line treatment of patients with NSCLC who have PD-L1 expression greater than 50% with a higher response rate, progression-free survival, and overall survival when compared to standard chemotherapy. Pembrolizumab and nivolumab are also both more active than chemotherapy in the second-line setting.

KEY POINTS

- Metastatic non–small cell lung cancer that demonstrates an epidermal growth factor receptor gene mutation should be treated initially with erlotinib; if an *ALK* or *ROS1* translocation is identified, initial treatment should be with crizotinib.
- If metastatic non–small cell lung cancer is negative for gene mutations or translocations, platinum-based doublet chemotherapy in combination with bevacizumab is appropriate for patients with good performance status.

Small Cell Lung Cancer

SCLC, a neuroendocrine neoplasm, has been decreasing in incidence during the past several years, and currently it accounts for approximately 10% of lung cancer cases. SCLC is almost exclusively caused by smoking. In unfortunate contrast to the advances made in the treatment of NSCLC, little has changed in the prognosis or treatment of SCLC patients. Most patients initially present with distant metastatic disease. SCLC is known to be associated with paraneoplastic syndromes, most prominently syndrome of inappropriate antidiuretic hormone secretion and Eaton-Lambert myasthenia. The staging of SCLC is straightforward and defines patients with "limited disease" that can be encompassed by a hemithoracic radiation portal; all others, including those with distant metastases, have "extensive disease." Patients should undergo routine CT scan of the thorax, abdomen, and pelvis, but even those who have no bone or central nervous system symptoms should undergo whole body bone scintigraphy and an MRI of the brain.

Typically, primary SCLC presents with proximal and often large tumors, but occasionally it presents as a solitary pulmonary nodule (see Lung Tumors: Pulmonary Nodule Evaluation) and is often not diagnosed until after surgical resection. After resection, these rare patients can be treated with adjuvant chemotherapy, but radiation therapy can be avoided if surgical margins are negative. Surgery can also be performed for small primary tumors without lymph node spread, although preoperative evaluation in those patients should include endobronchial ultrasonography or, if that procedure is not available, mediastinoscopy to rule out occult nodal involvement. Those patients should also receive adjuvant chemotherapy.

Most patients with SCLC will not meet the criteria for primary surgery. Treatment of limited disease consists of combined cisplatin-based chemotherapy, typically cisplatin plus etoposide, and radiation. Chemotherapy is continued after radiation for up to six cycles; prophylactic cranial irradiation should be used in patients with responsive disease because this treatment decreases the rate of subsequent brain metastases and improves overall survival.

For patients who present with extensive disease, treatment consists of platinum-based chemotherapy without radiation, again for up to six cycles. Patients with limited disease that is responsive to treatment and no evidence of brain metastases should be treated with prophylactic cranial irradiation. Patients with extensive disease who have a favorable response to chemotherapy but persistent involvement in the lung can be treated with additional radiation therapy.

Despite treatment response, recurrences are very common, even in patients with limited disease at the time of diagnosis. For patients who had a disease-free interval of more than 3 months, treatment with the initial platinum-based doublet regimen can be used because the likelihood of response is good. However, for patients who relapsed earlier, treatment options and outcomes are generally poor. As in NSCLC, addressing goals of care and aggressive symptom management are of significant importance in this setting.

KEY POINTS

- Routine staging of patients with small cell lung cancer includes whole body bone scintigraphy and MRI of the brain, even if they have no bone or central nervous system symptoms, along with routine CT scan of the thorax, abdomen, and pelvis.
- Although patients with SCLC typically present at an advanced stage, those with early-stage disease can be considered for resection and adjuvant chemotherapy without radiation if surgical margins are negative.
- Treatment of limited-disease SCLC consists of combined cisplatin-based chemotherapy and radiation to the area of lung involvement; treatment of extensive disease consists of analogous chemotherapy, but additional radiation treatment is not indicated.
- Patients with both limited- and extensive-stage SCLC who respond to chemotherapy should receive prophylactic radiation to the central nervous system.