Small-Cell Lung Cancer, Mesothelioma, and Thymoma

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This management guide covers the symptoms, screening, diagnosis, and treatment of small-cell lung cancer (SCLC), mesothelioma, and thymoma from a surgical, medical, and radiation oncology approach.

Overview

As discussed in the “Non–Small-Cell Lung Cancer” chapter, there are two major subdivisions of lung cancer: small-cell lung cancer (SCLC) and non–small-cell lung cancer (NSCLC). SCLC is decreasing in frequency in the United States, with recent data showing it represents only 14% of lung cancers. This chapter provides information on the staging and prognosis, pathology and pathophysiology, treatment, and follow-up of long-term survivors of SCLC and concludes with brief discussions on mesothelioma and thymoma.

The “Non–Small-Cell Lung Cancer” chapter provides information on the epidemiology, etiology, screening and prevention, and diagnosis of lung cancer in general and covers NSCLC and carcinoid tumors of the lungs.

Small-Cell Lung Cancer

Staging and Prognosis

An international database consisting of 8,088 patients with SCLC was developed by the International Association for the Study of Lung Cancer (IASLC). Their analysis showed that the 7th edition of the American Joint Committee on Cancer (AJCC) TNM staging system is applicable to SCLC. The IASLC recommends that the 7th edition of the AJCC guidelines for staging lung cancer should be applied to both NSCLC and SCLC (see “Non–Small-Cell Lung Cancer” chapter, Table 1). SCLC has previously been described as either limited (M0) or extensive (M1), although these general terms are inadequate when evaluating the role of surgery. Patients with SCLC who have stages I to III disease, excluding those with a malignant pleural effusion, are classified as having limited disease. These patients constitute approximately one-third of all SCLC patients. The remaining SCLC patients fall into the extensive-disease category, which includes any patient with a malignant pleural effusion or any site of distant disease, such as the brain, liver, adrenal gland, bone, and bone marrow.

The staging of lung cancer must be conducted in a methodical and detailed manner to permit appropriate therapeutic recommendations and to allow comparison of treatment results from different institutions.

Stage is commonly reported as either clinical or pathologic. The former is based on noninvasive (or minimally invasive) tests, whereas the latter is based on tissue obtained during surgery (see “Non–Small-Cell Lung Cancer” chapter).

The most important prognostic factor in lung cancer is the stage of disease. Within a given disease stage, the next most important prognostic factors are performance status and recent weight loss. The two scales used to define performance status are the Eastern Cooperative Oncology Group (ECOG) performance status system and the Karnofsky performance index (see Appendix 1). In short, patients who are ambulatory have a significantly longer survival. Those who have lost 5% or more of body weight during the preceding 3 to 6 months have a worse prognosis.

Pathology and Pathophysiology

SCLC tends to present with a large central lung mass and associated extensive hilar and mediastinal lymphadenopathy. Clinically evident distant metastases are present in approximately two-thirds of patients at diagnosis. In addition, data from autopsy examination indicate micrometastatic disease in 63% of patients who died within 30 days of attempted curative resection of SCLC. Thus, it is a
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systemic disease at presentation in the majority of patients. SCLC is a small, blue, round cell tumor that is primitive and undifferentiated at the light microscopic level. Electron microscopy demonstrates its neuroendocrine derivation by the presence of dense core granules. The immunohistochemical evidence of neuroendocrine derivation includes positive staining for chromogranin, synaptophysin, and other proteins. The amine precursor uptake and decarboxylation machinery present in the dense core granule leads to the production of biologically active amines and promotes the synthesis of polypeptide hormones such as antidiuretic hormone (ADH) and adrenocorticotropic hormone (ACTH). Paraneoplastic syndromes develop due to hormone excess. The most common of these syndromes, syndrome of inappropriate antidiuretic hormone secretion (SIADH), occurs in approximately 10% of patients with SCLC. Hypercortisolism and a Cushing-like syndrome are more rare, seen in only 1% to 2% of patients.

Treatment

**Treatment of disease limited to lung parenchyma**

**Surgery.** The majority of patients with SCLC present with advanced-stage disease. In the 5% to 10% of patients whose tumor is limited to the lung parenchyma, very often the diagnosis is established only after the lung mass has been removed. If, however, the histology has been determined by bronchosopic biopsy or fine-needle aspiration and there is no evidence of metastatic disease following extensive scanning, examination of the bone marrow, and biopsy of the mediastinal lymph nodes, then resection should be performed. Adjuvant chemotherapy is recommended because of the high likelihood of development of distant metastases following surgery. The surgical approach in SCLC is similar to that used in NSCLC: A lobectomy or pneumonectomy should be followed by a thorough mediastinal lymph node dissection. In a recent retrospective study by Tashi et al, patients with limited-stage SCLC who underwent surgical resection had improved median survivals across all stages. At this time, however, tumor resection in SCLC should be limited to patients who have no evidence of mediastinal or supraclavicular lymph node metastases. Data suggest that patients with SCLC presenting as a solitary pulmonary nodule and proven pathologically to be stage I have a 5-year survival rate of approximately 70% when treated with resection and adjuvant chemotherapy.

**Treatment of disease limited to the thorax**

Approximately one-third of SCLC patients present with disease that is limited to the thorax and can be encompassed within a tolerable radiation portal. In early studies in which either radiation therapy or surgery alone was used to treat such patients, median survival was only 3 to 4 months, and the 5-year survival rate was in the range of 1% to 2%. The reason for the failure of these therapies was both rapid recurrence of intrathoracic tumor and development of distant metastasis.

**Chemotherapy.** During the 1970s, it became apparent that SCLC was relatively sensitive to chemotherapy. Various combination chemotherapy regimens were used to treat limited SCLC. Although none of the regimens was clearly superior, median survival was approximately 12 months, and the 2-year survival rate was approximately 10% to 15%. It appears that maintenance chemotherapy adds little to survival in patients with limited SCLC.

**Chemotherapy plus thoracic irradiation.** One of the major advances in treating SCLC in the past 15 years is the recognition of the value of early and concurrent thoracic chemoradiation therapy. This advance was clearly facilitated by the increase in therapeutic index when PE (cisplatin [Platinol]/etoposide) chemotherapy is given with thoracic irradiation, as opposed to older anthracycline- or alkylator-based regimens. Although the major impact from this approach is improved locoregional tumor control, there are hints from randomized trials that early control of disease in the chest can also reduce the risk of distant metastasis.

An Intergroup trial directly compared once-daily vs twice-daily fractionation (45 Gy/25 fractions/5 weeks vs 45 Gy/30 fractions/3 weeks) given at the beginning of concurrent chemoradiation therapy with PE. Initial analysis showed excellent overall results, with median survival for all patients of 20 months and a 40% survival rate at 2 years. With a minimum follow-up of 5 years, survival was significantly better in the twice-daily than in the once-daily irradiation group (26% vs 16%). The main difference in toxicity was a temporary increase in grade 3 esophagitis in patients receiving twice-daily radiation therapy.

Outcomes for patients with limited-stage SCLC have improved significantly over the past 20 years. In an analysis of phase III trials during this period, median survival was 12 months in the control arm in 26 phase III studies initiated between 1972 and 1981, compared with 17 months in studies between 1982 and 1992 ($P < .001$). Five studies demonstrated a statistically significant improvement in
survival in the experimental arm compared with the control arm. Interestingly, all five studies involved some aspect of thoracic radiation therapy (three trials compared chemotherapy alone with chemoradiation therapy; one compared early radiation therapy with late radiation therapy; and one compared once-daily with twice-daily thoracic radiation therapy). Similarly, data from the Surveillance, Epidemiology, and End Results (SEER) database demonstrate that the 5-year survival rate has more than doubled from 1973 to 1996 (5.2% vs 12.2%; \( P = .0001 \)).

- **Current recommendations**—Although important questions remain as to the optimal radiation doses, volumes, and timing with regard to chemotherapy, a reasonable standard is to deliver thoracic irradiation concurrently with PE chemotherapy (cisplatin [60 mg/m\(^2\) IV on day 1] and etoposide [120 mg/m\(^2\) IV on days 1 to 3]). An attempt is made to integrate thoracic irradiation as early as possible, during cycle 1 (or 2).

Fried et al performed a meta-analysis evaluating early vs late timing of radiation therapy in limited-stage SCLC. Earlier radiation therapy was defined as that given prior to 9 weeks after initiation of chemotherapy vs late radiation therapy (\( \geq 9 \) weeks). Seven trials (\( N = 1,542 \) patients) were included in the analysis. They reported a small but significant improvement in 2-year overall survival for early vs late radiation therapy (5.2%; \( P = .03 \)). This finding is similar to the benefit of adding radiation therapy or prophylactic cranial irradiation (PCI) to chemotherapy. A greater difference was evident for the subset of patients receiving early rather than late hyperfractionated radiation therapy and platinum-based chemotherapy. Hyperfractionated accelerated fractionation should be considered, given the results of the Intergroup 0096 trial. An Intergroup phase III study is under way to compare twice-daily radiation therapy to 45 Gy, once-daily with radiation therapy to a higher dose (70 Gy), and a modified regimen combining these strategies (Radiation Therapy Oncology Group [RTOG] trial; clinicaltrials.gov ID NCT00632853).

Irradiation can be incorporated sequentially with chemotherapy; however, this approach appears to be inferior to early concurrent therapy and should be reserved for use in patients for whom concurrent approaches are predicted to be excessively toxic.

A randomized trial of concurrent vs sequential thoracic radiotherapy in combination with PE in more than 200 patients with limited-stage SCLC (Takada et al: *J Clin Oncol* 2002) demonstrated a benefit to concurrent therapy, with a median survival of 27 months (30%, concurrent arm) vs 19.7 months (20%, sequential arm; \( P = .097 \)). Thoracic radiation therapy consisted of 45 Gy over 3 weeks, starting either with the first cycle of PE in the concurrent arm or after the fourth cycle in the sequential arm.

Komaki et al have reported both phase I and II data with a “concomitant boost” chemoradiation approach (RTOG 0239). This therapy involved treating the initial large field in daily fractions and boosting the small field to a higher dose (61.2 Gy in 5 weeks), with a second daily fraction on the last 9 days of treatment. The chemotherapy regimen included etoposide and cisplatin. The locoregional tumor control rate at 2 years was 80%, although the 2-year survival rate of 37% was not as promising. Severe grade esophagitis occurred in 18% of patients, which is lower than the rate of 27% observed in the accelerated arm of Intergroup 0096.

Movsas et al reported the results of the first Patterns of Care Study (PCS) for lung cancer in the United States. This study was conducted to determine the national patterns of radiotherapy practice in patients treated for nonmetastatic lung cancer in 1998 and 1999. As supported by clinical trials, patients with limited-stage SCLC received chemotherapy plus radiotherapy more often than radiotherapy alone (92% vs 5%; \( P < .001 \)). However, only 6% of patients received hyperfractionated (twice-daily) radiotherapy. A total of 22% received PCI, with a median dose of 30 Gy in 15 fractions. Of note, in a more recent follow-up PCS/Quality Research in Radiation Oncology study by Komaki et al, the rate of twice-daily radiotherapy increased to about 20% and the rate of PCI use increased to about 50%.

Interestingly, in 2002 Choi et al (*Proc Am Soc Clin Oncol*) reported long-term survival data from their phase I trial assessing chemotherapy with either standard daily radiotherapy or accelerated twice-daily radiotherapy from the Cancer and Leukemia Group B (CALGB) 8837 trial. They previously reported that the maximum tolerated dose was 45 Gy in 30 fractions for twice-daily radiotherapy and more than 70 Gy in 35 fractions for once-daily radiotherapy. The 5-year survival estimated (from this phase I trial) for the twice-daily arm was 20%, vs 36% for the once-daily radiotherapy arm. There is currently a large Intergroup trial testing three chemoradiation regimens for limited-disease SCLC (CALGB 30610/RTOG 0538). This study includes the accelerated regimen from Intergroup 0096, the concomitant boost from RTOG 0239, and the daily conventional fractionation as studied by Choi et al, with etoposide and cisplatin in all three arms.

Kubota et al conducted a randomized phase III study to test the role of three cycles of irinotecan and
cisplatin (IP) vs three cycles of etoposide and cisplatin (EP) following one cycle of EP with concurrent accelerated hyperfractionated radiotherapy (45 Gy/3 weeks) in patients with limited-stage SCLC. No survival advantage was demonstrated by using IP vs EP (with 5-year overall survival rates of 36% and 34%, respectively).

**Surgery.** Although surgical resection is not usually part of the standard therapy for SCLC, the Japanese Clinical Oncology Lung Cancer Study Group (JCOLCSG) reported the results of a phase II trial of postoperative adjuvant PE in patients with completely resected stages I to IIIA SCLC. The 5-year survival rates (in a cohort of 62 patients) for patients with pathologic stages I, II, and IIIA SCLC were 69%, 38%, and 40%, respectively.

The role of surgery for stage II or IIIA SCLC has evolved from a number of phase II trials and retrospective case series to include specific indications. They include resection of tumors with mixed histology (containing both SCLC and NSCLC components), salvage surgery for chemoresistant localized SCLC or local relapse after initial response to chemoradiotherapy, or second primary tumors after cure of initial SCLC. The rate of second primary NSCLC in patients treated for SCLC can be as high as 2% to greater than 10% per year (Johnson: *J Natl Cancer Inst* 1998). Prospective randomized trials are ongoing in Europe and Japan to examine the role of surgery as part of multimodality therapy for patients with stages II and IIIA SCLC.

Recently, gene expression profiling has identified a subset of SCLC patients with good prognosis. A 2014 study by Hamanaka et al reported that low neuroendocrine marker expression, found mainly in SCLC patients who underwent surgical resection, was independently associated with prolonged survival.

**Prophylactic cranial irradiation.** Recognition that patients with SCLC are at high risk for development of brain metastases led to the suggestion that they be given PCI to prevent the clinical manifestation of previously present but occult CNS disease. A meta-analysis of all randomized trials of PCI in patients with SCLC who achieved a complete or near-complete response to induction chemotherapy (alone or combined with thoracic irradiation) showed a statistically significant improvement in survival in patients treated with PCI (20.7% at 3 years vs 15.3% in those not given PCI). The survival improvement with PCI was seen in all patient subgroups, regardless of age, stage of disease, type of induction treatment, or performance status. Approximately 85% of the patients included in the meta-analysis had limited disease, and recommendations for use of PCI have been applied generally to this subgroup. One randomized trial, however, suggests benefit for PCI in patients with responding extensive disease as well. Given the high incidence of symptomatic brain metastases and the relatively short survival following this event in patients with extensive SCLC, the European Organisation for Research and Treatment of Cancer (EORTC) randomized 286 patients after response to chemotherapy to receive PCI or not. Irradiation reduced the risk of symptomatic brain metastases, with a hazard ratio of 0.27 (95% CI, 0.16–0.44; *P* < .001). The cumulative incidence of brain metastases was reduced from 40% in the control group to 15% within 1 year of follow-up. From the time of randomization, patients who were irradiated had an approximate 2-month increase in median survival (6.7 months vs 5.4 months) and double the 1-year survival rate (27% vs 13%); progression-free survival was less affected (14.7 weeks vs 12 weeks). PCI was reasonably well tolerated, with expected acute effects of headache, nausea and vomiting, and fatigue. Irradiated patients were more frequently given chemotherapy at the time of extracranial disease progression (68% vs 45%). Furthermore, only 59% of patients in the control group who developed brain metastases were treated with whole-brain irradiation. These latter factors may have contributed to the observed survival differences. Of note, brain imaging was not required for enrollment in this study.

A randomized trial reported by Le Péchoux et al in 2009 studied the issue of standard-dose vs higher-dose PCI in patients with limited-stage SCLC. Half of 720 patients with limited-stage SCLC in complete remission were randomly assigned to receive a standard-dose PCI regimen (25 Gy in 10 fractions). The other half received a higher PCI total dose (36 Gy) delivered using either conventional (18 daily fractions of 2 Gy) or accelerated hyperfractionated (24 fractions in 16 days of 1.5 Gy) radiation. With a median follow-up of 39 months, there was no significant difference in the 2-year incidence of brain metastases between the arms. The 2-year survival was 42% in the standard-dose group and 37% in the higher-dose group (*P* = .05). The lower overall survival in the higher-dose group was thought to be due to an increase in cancer-related mortality. Overall, this randomized study showed no significant reduction in brain metastases after higher-dose PCI, but there was a significant increase in mortality. Therefore, standard doses of PCI should remain the standard of care in limited-stage SCLC. In reporting on RTOG 0212, Wolfson et al noted that 36 Gy delivered once or twice daily resulted in a greater risk of neurocognitive toxicity than did 25 Gy of PCI. Age greater
than 60 years was significantly predictive for the possibility of this complication. • Current recommendations—Patients should be offered PCI after completion of chemotherapy/chemoradiation therapy if they have clear regression of disease and a retained ECOG performance status of 0 to 2. Optimal integration of PCI should occur within 3 to 5 weeks of the last cycle of chemotherapy.
Radiation doses for PCI should be 25 to 30 Gy, with a daily fraction size of 2.5 to 2 Gy, respectively.

Treatment of extensive disease

As mentioned previously, two-thirds of SCLC patients have extensive disease at diagnosis. Without treatment, median survival in this group of patients is 6 to 8 weeks. Treatment with combination chemotherapy increases the median survival duration to approximately 8 to 10 months.

TABLE 1: Common chemotherapy regimens for SCLC

**Induction chemotherapy.** The combination of cisplatin or carboplatin/etoposide (see Table 1 for common dose ranges) is considered the standard of care in the United States at this time. This standard is primarily based on therapeutic index, because randomized trials have not demonstrated a survival benefit for this combination relative to the older regimen of cyclophosphamide, doxorubicin, and vincristine. The regimen is repeated at 3-week intervals for 4 to 6 courses. In North America, multiple randomized trials of newer cytotoxins replacing etoposide in a doublet with cisplatin, or added to the etoposide/platin base, have not provided a survival benefit. Japanese data that showed a 3.4-month survival advantage for irinotecan, as opposed to etoposide, with cisplatin were not confirmed in a trial in the United States, and the North American patients were less tolerant of the irinotecan.

The role of consolidative extracranial irradiation for patients with one to three sites of extensive SCLC is being studied in a randomized, phase II study (RTOG 0937) currently open to accrual. This research is based on an earlier randomized study (Jeremic et al: *J Clin Oncol* 1999) which indicated that adding consolidative radiation therapy to the treatment of the most favorable subset of patients with extensive SCLC led to improved survival compared with use of chemotherapy alone. Another large North American study, Southwest Oncology Group (SWOG) S0124, and a trial from Germany comparing irinotecan with etoposide, when both are combined with platinating agents, were recently reported. Both showed equivalence in major efficacy outcomes. A Scandinavian trial with a similar design demonstrated a 1.4-month increase in the median survival rate for irinotecan-based treatment. However, these results are suspect because of an imbalance of elderly patients between the arms and a mandated dose reduction for etoposide in the elderly group. Overall, the data suggest that efficacy is equivalent with either approach. Because of problematic severe diarrhea with irinotecan, the therapeutic index may be improved with etoposide-based therapy.

**Treatment of progressive disease**

Progressive SCLC is classified on the basis of response and duration of response to initial induction therapy. Patients whose tumors do not regress or progress up to 60 to 90 days following the last cycle of chemotherapy are considered to have refractory disease. Conversely, patients whose tumors respond and who have an unmaintained progression-free interval longer than 60 to 90 days are deemed to have sensitive relapse. This categorization is based on the probability of objective response to additional cytotoxic therapy, which is uncommon, typically less than 15%, in the case of platin-refractory SCLC.

Topotecan is the only drug approved by the US Food and Drug Administration (FDA) for the treatment of recurrent disease. Its initial indication in 1998 was for patients with sensitive relapse and was based on similar efficacy compared with an older three-drug regimen. A subsequent trial compared IV administration with oral topotecan capsules, documenting similar efficacy and tolerance.

Most recently, a randomized trial compared oral topotecan with best supportive care in 141 patients with an ECOG performance status of 0 to 2. Patients with both refractory and sensitive disease were accrued. Median survival was nearly doubled on the topotecan arm, 26 weeks vs 14 weeks (*P* = .0104), as was 6-month survival, 49% vs 26%. Benefit was seen in all subgroups analyzed, including
patients with refractory cancer and an ECOG performance status of 2. Despite a low rate of response to topotecan of 7% and typical adverse effects, treated patients had slower deterioration of quality of life and improved symptom control. On the basis of these data, in October 2007 the FDA granted topotecan in capsule form a broad indication for treatment of recurrent SCLC. More limited data with irinotecan suggest that its activity is probably similar to that of topotecan; however, it has never been evaluated in a randomized trial in the recurrent setting. Amrubicin, a synthetic anthracycline, has been studied extensively in recurrent SCLC in Japan and has been approved there. Initial data published in abstract form in North American patients suggest promising response rates with amrubicin in patients with refractory disease and a similar survival benefit as observed with topotecan in sensitive relapse. Amrubicin remains investigational in the United States. Other cytotoxins, known more for their efficacy in NSCLC, such as docetaxel and paclitaxel, gemcitabine, and vinorelbine, do not have high single-agent response rates in therapy-naive SCLC and are not recognized as standard in management.

Integration of biologics in therapy. Ongoing clinical research is focused on integration of molecularly targeted therapy in an effort to make progress in treating this stubborn malignancy. At this time, data from completed trials do not indicate an active strategy with a biologic, whether in combination with induction chemotherapy, as maintenance following induction, or as single agents for recurrent disease.

• High-dose chemotherapy plus bone marrow transplant (BMT) —Most phase II trials using high doses of chemotherapy plus BMT appear to show no advantage to the high-dose approach over standard doses of chemotherapy.

• Alternating chemotherapy regimens—These have been used to overcome drug resistance. In randomized trials, alternating chemotherapy regimens have shown a slight improvement in terms of median survival (4 to 6 weeks) when compared with a single chemotherapeutic regimen, but no improvement in long-term survival.

Sidebar: In 2013 the American College of Radiology (ACR) published appropriateness criteria for the role of radiation therapy in SCLC. The ACR Appropriateness Criteria are evidence-based guidelines for specific clinical conditions. They are reviewed every 2 years by a multidisciplinary expert panel. The guideline development includes an extensive analysis of current medical literature and the application of a consensus methodology (modified Delphi) to rate the appropriateness of treatment recommendations by the panel. The SCLC topic provides an evidence-based approach regarding the role, dose, fractionation, technology, volume, and timing of thoracic radiation, as well as PCI in SCLC. The ACR Appropriateness Criteria also include discussions of other topics related to lung cancer and guidelines for patients with other types of cancer (Kong FM et al: Am J Clin Oncol 36:206–213, 2013).

Palliation of local and distant symptoms

Radiation therapy. Many patients with lung cancer have distressing local symptoms at some point in their disease course. These symptoms may arise from airway obstruction by the primary tumor, compression of mediastinal structures by nodal metastases, or metastatic involvement of distant organs. Radiation therapy is effective in palliating most local symptoms as well as symptoms at common metastatic sites, such as in bone and the brain.

In the United States, most radiation oncologists use doses in the vicinity of 30 Gy in 10 fractions for palliative treatment. Data from the United Kingdom suggest that similar efficacy without greater toxicity may be achieved with more abbreviated schedules, such as 17 Gy in two fractions 1 week apart or single fractions of 11 Gy (see “Non–Small-Cell Lung Cancer” chapter, Table 8). Such schedules may facilitate the coordination of irradiation and chemotherapy, and they also may reduce patient travel and hospitalization.

Endobronchial irradiation with cobalt-60 or iridium-192 has been used to palliate symptoms arising from partial airway obstruction, including cough, dyspnea, and hemoptysis. The dosimetric advantage of being able to deliver a high radiation dose to the obstructing endobronchial tumor while sparing adjacent normal structures, such as the lungs, spinal cord, and esophagus, has clear appeal, particularly in the patient whose disease has recurred following prior external beam irradiation. Although good rates of palliation have been reported with endobronchial irradiation, significant complications, including fatal hemoptysis, are seen in 5% to 10% of patients. It remains unclear whether this represents a true treatment complication or symptoms related to the underlying disease.

Other local approaches. Endobronchial irradiation should be considered as only one of several approaches (including laser excision, cryotherapy, and stent placement) in the treatment of patients with symptomatic airway obstruction, and management should be individualized. All of these
approaches are more suitable for partial than for complete airway obstruction. **Chemotherapy.** Several trials have explored the use of chemotherapy to palliate specific symptoms in patients with lung cancer. In general, these trials have found that rates of symptomatic improvement were considerably higher than objective response rates and were not dissimilar to symptomatic response rates with local radiation therapy. Chemotherapy in the patient with newly diagnosed lung cancer is highly palliative for relief of symptoms related to superior vena cava syndrome, obstructive lung disease, and painful bony metastases. In the patient with recurrent disease, irradiation is more commonly associated with symptomatic relief of these localized problems. Radiation therapy remains the standard of care even for chemotherapy-naive patients with spinal cord compression or symptomatic brain metastasis.

**Follow-Up of Long-Term Survivors**

At present, no standard follow-up protocol exists for patients with cured SCLC or NSCLC. However, at least long-term follow-up should include serial physical examinations once the patient has reached the 5-year mark. There is some controversy about the value of computed tomography (CT) or even chest radiography in the long-term follow-up of these patients. In this vein, retrospective reviews of the literature have revealed that patients with SCLC appear to have the highest rate of second primary tumor development, as high as 30% over the course of their lifetimes, with some studies reporting annual second primary tumor rates of 5% to 10%. Therefore, the concept of chemoprevention appears to have particular merit in these patients.

**Mesothelioma**

Mesotheliomas are uncommon neoplasms derived from the cells lining the pleura and peritoneum. Currently, 2,000 to 3,000 new cases are diagnosed in the United States each year.

**Epidemiology**

**Gender**

Men are affected five times more commonly than women.

**Age**

The median age at diagnosis is 60 years.

**Etiology and Risk Factors**

**Asbestos exposure**

The relationship between asbestos exposure and diffuse pleural mesothelioma was first reported by Wagner (*Br J Ind Med* 1960), who documented 33 pathologically confirmed cases from an asbestos mining region in South Africa. Selikoff et al (*Br J Ind Med* 1988) documented a 300-fold increase in mortality from mesothelioma among asbestos insulation workers in the New York metropolitan region when compared with the general population. The interval between asbestos exposure and tumor formation is commonly 3 to 4 decades. Asbestos fibers are generally divided into two broad groups: serpentine and amphibole. The latter includes crocidolite, the most carcinogenic form of asbestos. The inability of phagocytic cells to digest the fiber appears to initiate a cascade of cellular events that results in free-radical generation and carcinogenesis.

**Diagnosis**

Patients with mesothelioma usually seek medical attention while the disease is limited to a single hemithorax and commonly complain of dyspnea and pain. Dyspnea results from diffuse growth of the tumor on both the parietal and visceral pleurae, which encase the lung in a thick rind. Pain is caused by direct tumor infiltration of intercostal nerves. Chest radiography demonstrates pleural thickening, pleura-based masses, or a pleural effusion. CT of the chest more accurately portrays the extent of disease and frequently reveals chest wall invasion as well as pericardial and diaphragmatic extension.
Potential uses for mesothelioma serum biomarkers

Thoracentesis and pleural biopsy establish the diagnosis in 26% of cases; however, thoracoscopic biopsy yields a diagnosis in 98% of cases and is the gold standard. Light microscopy is often insufficient for differentiating among mesothelioma, metastatic adenocarcinoma, and sarcoma. Immunohistochemistry and electron microscopy are frequently necessary to establish the diagnosis. Small retrospective series have studied three biomarkers: soluble mesothelin-related peptide (SMRP), megakaryocyte potentiation factor, and osteopontin (Table 2). SMRP may predict the development of mesothelioma in asbestos-exposed individuals. Prospective studies are required to validate the utility of these biomarkers for early detection, predicting the extent of disease and determining prognosis.

Pathology

Mesotheliomas may contain both epithelial and sarcomatoid elements and are classified by the relative abundance of each component. Epithelial mesotheliomas are most common (50%), followed by mixed (34%) and sarcomatoid (16%) tumors. Survival of patients with the epithelial type is 22 months, compared with only 6 months for patients with other types.

Staging and Prognosis

The International Mesothelioma Interest Group (IMIG) has developed a staging system based on TNM descriptors. This was adopted by the AJCC (Table 3). Another commonly used staging system for mesothelioma, that of Butchart, is based on inexact descriptions of the extent of local tumor growth or distant metastases (Table 4). Other, more detailed staging systems based on TNM criteria have been proposed. The median survival following diagnosis ranges from 9 to 21 months. Although autopsy series have demonstrated distant metastases in as many as 50% of patients with mesothelioma, death usually results from local tumor growth.

Treatment

Treatment rarely results in a cure.
**Combined-modality treatment options**

Surgical procedures (pleural fluid drainage and talc pleurodesis, or pleurectomy and decortication) to control symptomatic pleural effusions are well accepted. Otherwise, the role of surgery in the potentially curative treatment of mesothelioma remains controversial. In this setting, the goal of surgery is to remove all gross disease; however, microscopic disease is likely to remain. Therefore, surgery is most commonly performed in combination with other treatments (multimodality therapy). The type of operation is also controversial. Pleurectomy and decortication (PD) is designed to remove both the visceral and parietal pleura while preserving underlying lung tissue. Extrapleural pneumonectomy (EPP) removes the pleural envelope and the lung en bloc. The advantages of PD are that the lung is preserved and morbidity and mortality are less; however, adjuvant radiation may be difficult because the lung remains. EPP has a higher mortality rate but adjuvant radiation to the pleural cavity is possible without the risk of radiation pneumonitis because the lung is removed. Recent retrospective studies have reported no difference in overall survival between PD and EPP; however, patients who underwent PD may have had a lower volume of disease at the time of surgery than the patients who underwent EPP. Trimodality therapy (EPP, chemotherapy, and radiation therapy) in some series has resulted in promising results in select patients, particularly those with epithelial histology and negative lymph nodes. Burt et al queried the Society of Thoracic Surgeon General Thoracic Surgery Database and identified 225 patients who underwent either PD or EPP from 2009–2011. Patients undergoing EPP were younger (63.2 ± 7.8 years vs 68.3 ± 9.5 years; \( P < .001 \)) and more likely to have received induction chemotherapy. Multivariate analyses revealed that EPP was an independent predictor of major morbidity or mortality (odds ratio, 6.51; \( P = .001 \)). Lang-Lazdunski and colleagues reported on the use of intraoperative heated povidone-iodine as an adjunct to pleurectomy decortication. This may provide further cytoreduction without the morbidity of intraoperative heated chemotherapy.

Chemotherapy is commonly given either before or after surgical resection. In a further attempt to treat residual microscopic disease, intrapleural therapies, such as heated chemotherapy, or other treatments are being explored. Management of potential toxicities mandates that these treatments be performed at an experienced center.

In the Mesothelioma and Radical Surgery (MARS) trial, after patients received induction platinum-based chemotherapy, they were reassessed and randomized to EPP and postoperative radiation therapy or to no EPP. Of 112 patients registered, only 50 were randomized (because of
disease progression in 33, inoperability in 5, and patient choice in 19 patients). Median survival was 14.4 months (range, 5 months to 19 months) for EPP vs 19.5 months (13 not yet reached) for no EPP (Treasure T et al: *Lancet Oncol* 2011). However, Weder and the members of the International Mesothelioma Interest Group have published their criticisms of this trial.

**Chemotherapy**

The benefit of chemotherapy for patients who have unresectable mesothelioma was clarified in a randomized trial. This study was a single-blind, multicenter, two-arm trial with cisplatin alone in the control arm and cisplatin combined with the multitargeted antifolate pemetrexed in the experimental arm. The study was based on the observation that pemetrexed produced a 16% objective response rate in a previous phase II evaluation. In the randomized trial, patients treated with pemetrexed and cisplatin had an estimated median survival of 12.1 months compared with 9.3 months in those treated with cisplatin alone. On the basis of this improvement in survival, the combination of pemetrexed and cisplatin has received an FDA indication for treatment of unresectable mesothelioma. The same combination is undergoing further evaluation in a neoadjuvant approach to treatment of patients with resectable disease.

**Thymoma**

Thymoma is a rare mediastinal tumor that occurs mainly in the anterosuperior mediastinum. Because thymic malignancies are rare, a multidisciplinary team of clinicians and basic scientists formed the International Thymic Malignancy Interest Group (ITMIG). ITMIG participants can pool their clinical experiences and outcomes in an international database to identify prognostic factors and effective treatments. ITMIG members published consensus papers proposing standardized definitions, terminology, and procedures for staging, imaging, surgery, radiation therapy, chemotherapy, and pathologic evaluations of patients with thymic malignancies.

**Epidemiology**

**Gender**

The tumor affects both sexes equally.

**Age**

Thymoma is most often seen in people in the fourth and fifth decades of life.

**Etiology and Associated Syndromes**

The etiology of thymoma is unknown, and the risk factors have not been identified. Thymoma is a tumor originating within the epithelial cells of the thymus. One-third to half of patients present with an asymptomatic anterior mediastinal mass, one-third of patients present with local symptoms (eg, cough, chest pain, superior vena cava syndrome, and/or dysphagia), and one-third of cases are detected during the evaluation of myasthenia gravis. Distant metastases are distinctly uncommon at initial presentation of this tumor. In addition to myasthenia gravis, which occurs in approximately 30% of patients with thymoma, a host of paraneoplastic syndromes have been seen in association with thymoma. These other syndromes, which occur in fewer than 5% of patients, include pure red cell aplasia, hypogammaglobulinemia, and a variety of other autoimmune disorders.

**Diagnosis**

The most commonly described symptoms are pleuritic chest pain or discomfort, dry cough, and dyspnea. Physical examination may reveal adenopathy, wheezing, fever, superior vena cava syndrome, vocal cord paralysis, and other paraneoplastic syndromes.

**Chest radiography and CT**

A chest radiograph provides an initial basis for diagnosis. The location, size, density, and presence of calcification within the mass can all be determined. Comparison of the film to previously obtained films is usually helpful. Following identification of a mediastinal mass on conventional radiography, contrast-enhanced CT
scanning should be performed. CT scanning can differentiate the cystic form from a solid lesion as well as the presence of fat, calcium, or fluid within the lesion. Magnetic resonance imaging (MRI) is increasingly available for use in the evaluation of mediastinal pathology, but it is less frequently used than CT. MRI is superior to CT scanning in defining the relationship between mediastinal masses and vascular structures and is useful in the assessment of vascular invasion by the tumor.

**Invasive diagnostic tests**

CT-guided percutaneous needle biopsy specimens are obtained using fine-needle aspiration techniques and cytologic evaluation or with larger-core needle biopsy and histologic evaluation. Fine-needle specimens are usually adequate to distinguish carcinomatosis lesions, but core biopsies may be necessary to distinguish most mediastinal neoplasms. Immunohistochemical techniques and electron microscopy have greatly improved the ability to differentiate the cell of origin in mediastinal neoplasms. Most series report diagnostic yields for percutaneous needle biopsy of 70% to 100%.

**Mediastinoscopy**

This is a relatively simple surgical procedure accomplished with the patient under general anesthesia. It is an adequate approach to the superior, middle, and upper posterior mediastinum, and most series report a diagnostic accuracy of 80% to 90%. Anterior mediastinotomy (Chamberlain approach) provides for direct biopsy of tissue and has a diagnostic yield of 95% to 100%. Thoracotomy is occasionally necessary to diagnose mediastinal neoplasms, but its indications have been largely supplanted by video-assisted thoracoscopic techniques, which yield an accuracy of 100%.

The most common tumors in the differential diagnosis of an anterior mediastinal tumor are lymphomas and germ-cell tumors. Immunohistochemical markers are helpful to differentiate thymoma from tumors originating from other cell types.

**Pathology**

Two of the most common classification schemes for thymoma are listed in Table 5. Verley and Hollman propose a classification system based on tumor architecture, cellular differentiation, and predominant cell type. Bernatz et al describe a simpler classification by presenting thymoma based on the percentage of epithelial cells and lymphocytes. In both of these systems, thymoma with a predominance of epithelial cells is associated with a greater incidence of invasion and a subsequently worse prognosis.

**Staging and Prognosis**

The staging system proposed by Masaoka et al has been widely adopted. Stage is an independent predictor of recurrence and long-term survival. The 5-year survival rates are 96% for stage I thymoma, 86% for stage II, 69% for stage III, and 50% for stage IV.

**Treatment**

**Surgical treatment**

All patients whose tumors are potentially resectable should undergo surgery. If the patient has evidence of myasthenia gravis, a preoperative consultation with a clinical neurologist should be considered. The incision of choice is almost always a median sternotomy, which is quick and easy to
make and provides excellent exposure to the anterior mediastinum and neck. Although the surgeon is considered the best judge of a tumor’s invasiveness, it is often difficult to grossly separate tumor invasion from tumor adherence to surrounding tissue. Experience with minimally invasive approaches (such as transcervical thymectomy; video-assisted thoracoscopic surgery, or VATS, thymectomy; and robotic-assisted thymectomy) is growing; however, until longer-term data become available, sternotomy should still be considered the standard surgical approach. Recently, Ismail, Swierzy, and Rückert surveyed the world literature and data obtained from their own extensive experience with robotic thymectomy surgery. They noted that approximately 500 case reports on robotic thymectomy have been published, with low complication rates, short hospital stays, and low rates of early recurrence overall for early-stage thymoma.

Complete resection of thymoma has been found to be the most significant predictor of long-term survival. Several studies have examined the extent of surgical resection on survival and disease-free survival rates. In 241 operative cases, Maggi and colleagues (Ann Thorac Surg 1991) found an 82% overall survival rate in those whose tumors underwent complete resection and a 26% survival rate at 7 years in those who underwent biopsy alone. Other investigators reported similar results in surgical patients. Therefore, regardless of stage, tumor resectability is one of the important predictors of treatment outcome.

**Radiation treatment**

Thymomas are generally radiosensitive tumors, and the use of radiation therapy in their treatment is well established. It has been used to treat all stages of thymoma, either before or after surgical resection. General agreement exists regarding the postoperative treatment of invasive thymoma (stages II and III). The value of adjuvant radiation therapy for invasive thymomas is well documented and should be included in the treatment regimen regardless of the completeness of tumor resection.

**TABLE 6: Common chemotherapy regimens for thymoma**

**Chemotherapy**

Chemotherapy has been used in the treatment of invasive thymomas with increasing frequency during the past decade (Table 6). The most active agents appear to be cisplatin, doxorubicin, ifosfamide, and corticosteroids. Combination chemotherapy has generally shown higher response rates and has been used in both neoadjuvant and adjuvant settings and in the treatment of metastatic or recurrent thymomas. CAP or CAPPr (cyclophosphamide, Adriamycin [doxorubicin], Platinol [cisplatin], and prednisone) regimens have been used in neoadjuvant and/or adjuvant settings. These regimens have also been used for recurrent thymoma.

**Unresectable Thymoma**

Advanced-stage (III/IVA) thymomas usually are difficult to remove completely. Multidisciplinary approaches, including induction chemotherapy followed by surgical resection, postoperative radiation therapy, and consolidation chemotherapy, have been reported. Induction chemotherapy consists of cyclophosphamide (500 mg/m² IV on day 1), doxorubicin (20 mg/m²/d, by continuous infusion, on days 1 to 3), cisplatin (30 mg/m²/d IV on days 1 to 3), and prednisone (100 mg/d PO on days 1 to 5), repeated every 3 to 4 weeks for 3 courses. Twenty-two evaluable patients were consecutively treated from 1990 to 2000 in a prospective phase II study at MD Anderson Cancer Center. After induction chemotherapy, 17 of 22 patients (77%) had major responses, including 3 complete responses. Twenty-one patients underwent surgical resection. All patients received postoperative radiation
therapy and consolidation chemotherapy. With a median follow-up of 50.3 months, overall survival rates at 5 years and 7 years were 95% and 79%, respectively. The rate of disease-progression-free survival was 77% at 5 and 7 years. The multidisciplinary approaches to unresectable thymoma appear to be promising.

Schalke et al performed a single-arm study to evaluate the response of octreotide LAR (long-acting regimen) plus prednisone in patients with inoperable or locally recurrent thymoma. Response was defined as a decrease in tumor volume by more than 20% at 3 months. Seventeen patients with Masaoka stage III thymoma were recruited. The response rate was 88%. Five patients (29%) were found to be operable for radical resection.

Suggested Reading

On Small-Cell Lung Cancer


On Mesothelioma


On Thymoma


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