Staging of Small-Cell Lung Cancer

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Abstract

Small-cell lung cancer (SCLC) is the most common and most aggressive pulmonary neuroendocrine malignancy. SCLCs account for approximately 13% of all lung cancers and are characterized by rapid growth, early development of metastatic disease, dramatic initial response to chemotherapy and radiation therapy, and frequent association with paraneoplastic syndromes. Computed tomography (CT) and positron-emission tomography (PET)/CT are the imaging modalities routinely used in the evaluation of patients with SCLC. On imaging, SCLC usually manifests as a large centrally located lung mass or as mediastinal or mediastinal and hilar lymphadenopathy. Most patients have metastatic disease at presentation. Historically, the Veterans Administration Lung Study Group (VALG) staging system has been used to stage SCLC. More recently, it has been recommended by the International Association for the Study of Lung Cancer (IASLC) that the tumor, node, metastasis (TNM) staging system replace the VALG staging system. Despite characteristic responsiveness to initial therapy, disease invariably recurs and the overall prognosis remains poor.

Keywords

Small-cell lung cancer (SCLC) · Neuroendocrine malignancy · (TNM) staging system · Computed tomography (CT) · Positron-emission tomography/computed tomography (PET/CT)

9.1 Introduction and Clinical Features

Lung cancer is typically divided into non-small cell lung cancer (NSCLC) and small-cell lung cancer (SCLC). SCLC is an aggressive high-grade malignancy that is characterized by rapid growth, early development of metastatic disease, dramatic initial response to chemotherapy and radiation therapy, and frequent association with paraneoplastic syndromes. Among all histologic types of lung cancer, SCLC and squamous cell carcinoma have the highest correlation with ciga-

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rette smoking; approximately 90–95% of patients with SCLC are either current or past smokers [1]. The risk of developing SCLC increases with both the number of cigarettes smoked each day and the duration of smoking [1].

Analysis of the United States National Cancer Institute's Surveillance, Epidemiologic, and End Results (SEER) database from 1973 to 2002 showed that the percentage of SCLC among all cases of lung cancer in the United States peaked in 1986 at approximately 17% and decreased gradually over the next decade and a half to approximately 13% [2]. The proportion of women with SCLC increased during that same period from 28% in 1973 to 50% in 2002 [2]. The slight decrease in overall incidence of SCLC from 1986 to 2002 may be explained by several factors including (1) the decreased percentage of smokers, particularly among men; (2) the change in cigarette composition (e.g., decreased tar and nicotine); and (3) a change in the pathologic criteria for SCLC whereby some cases previously classified as SCLC are now classified as large-cell neuroendocrine carcinoma [2]. Currently, SCLC accounts for approximately 13% of all lung cancers in the United States [3]. Despite modest but statistically significant improvement in 2- and 5-year survival in the SEER study period from 1973 to 2002, outcomes and prognosis remain poor [2]. Median survival ranges from 10 to 18 months in limited-stage (LS) disease and from 7 to 12 months in extensive-stage (ES) disease [4, 5]. Up to 37% of patients with LS-SCLC survive 2 years and 7–18% survive 5 years [4, 6, 7]. ES-SCLC portends a much worse prognosis with 2- and 5-year survival rates of 4% and 1–2%, respectively [4, 5].

Most patients with SCLC are symptomatic at presentation; the majority demonstrate short symptom duration (usually less than 3 months), an indication of rapid tumor progression [8]. Presenting symptoms of SCLC may be constitutional, pulmonary/thoracic, related to extrathoracic metastatic spread, or due to paraneoplastic syndromes [9]. In one series, fatigue (occurring in 79%) was the most common symptom among SCLC patients; decreased activity, cough, decreased appetite, dyspnea, pain, and weight loss were also common, though each occurred in at least half of the patients [10]. Hemoptysis occurred in 14% [10]. Symptoms referable to regional tumor extension to the mediastinum include hoarseness and dysphagia. Hoarseness is a manifestation of vocal cord paralysis and usually represents recurrent laryngeal nerve involvement by tumor although lesions anywhere along the course of the vagus nerve can produce this symptom [11]. Dysphagia can be due to extrinsic compression of the esophagus by tumor/lymphadenopathy or due to direct invasion of the esophagus [11]. Involvement of the superior vena cava (SVC) can result in SVC obstruction/SVC syndrome; in one review, 9% of SCLC patients had signs or symptoms of SVC obstruction (e.g., collateral venous circulation, upper hemibody edema, increased jugular venous pressure, dyspnea, peripheral cyanosis, and confusion) [12]. Approximately 70–80% of patients have overt metastatic disease at presentation and involvement of liver, adrenal glands, and bone is frequently encountered. Hepatic and adrenal metastases are typically asymptomatic; skeletal metastases may manifest as osteolytic lesions, often without bone pain [9]. Vertebral involvement can lead to acute or subacute neurologic deficits, particularly in cases of spinal cord compression (by tumor or a collapsed vertebra) or when spinal cord vasculature is obstructed [11]. In a review of 432 patients with SCLC by Seute et al. 18% were found to have brain metastases at diagnosis though in approximately one-third of cases, the brain metastases did not cause symptoms [13]. When symptomatic, brain metastases may manifest with seizures, alteration in mental status, or ataxia. The 2-year cumulative risk of brain metastases was 49% for patients with LS-SCLC and 65% for patients with ES-SCLC [13].

Paraneoplastic syndromes are more commonly associated with SCLC than with other histological types of lung cancer [14]. Paraneoplastic syndromes are typically the result of either ectopic production of hormones by cancer cells or immune-mediated tissue destruction caused by neural antigen expression

from cancer cells [15]. The most common paraneoplastic syndrome associated with SCLC is the syndrome of inappropriate antidiuretic hormone (SIADH), also referred to as hyponatremia of malignancy [15]. SIADH, which occurs in 15% of patients with SCLC, results from the ectopic production of arginine vasopressin (AVP, also known as antidiuretic hormone or ADH) from tumor cells [15]. Symptoms associated with SIADH/hyponatremia of malignancy include nausea, vomiting, lethargy, and seizures. Cushing syndrome, related to the production of adrenocorticotropic hormone (ACTH), is the second most common paraneoplastic syndrome associated with SCLC, occurring in 5% of patients [15]. In terms of antibody-mediated (neurologic) paraneoplastic syndromes associated with SCLC, Lambert-Eaton myasthenic syndrome (LEMS) is most common, seen in 1–3% of patients at presentation [15]. Features of LEMS include slowly progressive proximal muscle weakness, characteristically worse in the lower extremities, and fatigue. Clinical symptoms of paraneoplastic syndromes frequently precede the diagnosis of SCLC by months to years [13, 15]. Treatment is aimed at the underlying lung cancer; in cases of clearly identifiable serum antibodies, immunosuppression is an alternate option.

9.2 Histological Features

SCLC is a malignant epithelial tumor composed of small round, oval, or spindle-shaped cells with scant cytoplasm, ill-defined cell borders, fine granular nuclear chromatin that is uniformly distributed (yielding a "salt and pepper" appearance), and absent or inconspicuous nucleoli [16]. Cells have a high nuclear/cytoplasmic ratio and nuclear molding is a prominent feature [16]. Mitotic count is high and necrosis is typically extensive [16].

SCLC is defined by light microscopy and the most important stain is a high-quality hematoxylin and eosin (H&E) stain (Fig. 9.1) [17]. Most cases are diagnosed by H&E alone; in difficult cases, immunohistochemical stains can be used to help differentiate SCLC from other tumors [17]. Immunohistochemical stains used in the diagnosis of SCLC include a pancytokeratin antibody such as AE1/AE3 (which helps demonstrate cell lineage, i.e., the tumor is a carcinoma rather than a lymphoma, melanoma, or sarcoma); neuroendocrine markers such as CD56, chromogranin, and synaptophysin; TTF-1 (thyroid transcription factor-1, which helps determine the primary site of malignancy); and Ki-67 (a marker for cellular proliferation; SCLCs show a high proliferation rate by Ki-67, averaging 80–100%) [17–19].

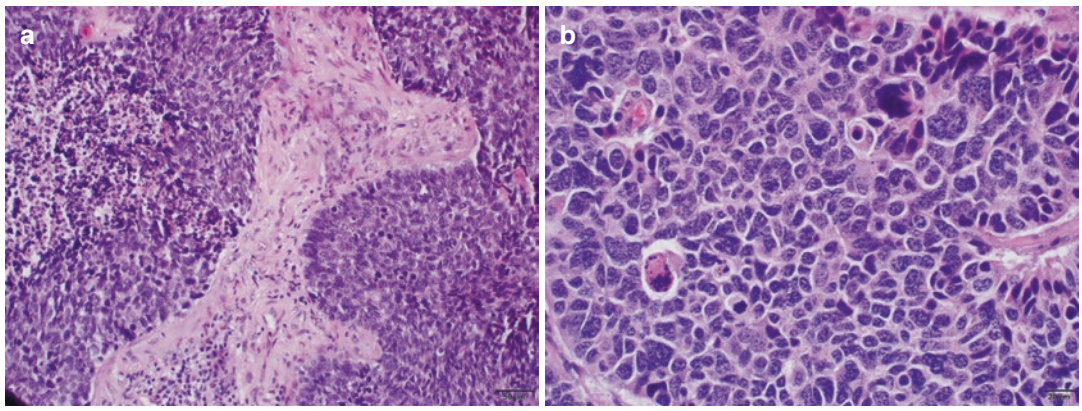

Fig. 9.1 Microscopic features of SCLC. (**a**) High-power photomicrograph (original magnification, ×20; hematoxylin-eosin stain) and (**b**) high-power photomicrograph (original magnification, ×40; hematoxylin-eosin stain) showing tumor composed of predominantly small- to medium-sized malignant cells with high nuclear:cytoplasmic ratio, numerous mitotic figures and apoptotic cells, and abundant necrosis. Nuclear molding, a characteristic but nonspecific feature, can be seen. The chromatin within the nuclei of these neoplastic cells is fine, and prominent nucleoli are not seen

Histologic classification of SCLC has undergone numerous changes over the last half century. SCLC was subdivided by the World Health Organization (WHO) in 1962 into oat cell (roundish to oval cells with sparse cytoplasm and naked nuclei) and polygonal forms [20]. In the first official WHO lung cancer classification (published in 1967), SCLC was subdivided based on morphology into four groups: lymphocyte-like (synonymous with oat cell), polygonal, fusiform, and others [21]. In the 1981 revision, the lymphocyte-like designation was replaced by the term oat cell and the remaining three subtypes were included in an intermediate category. In 1988, a consensus report by the pathology committee of the International Association for the Study of Lung Cancer (IASLC) recommended the following classification: (1) small-cell carcinoma (i.e., all SCLC tumors that have no non-small cell elements; most of the tumors previously categorized as oat cell and intermediate subtypes); (2) mixed small-cell/large-cell carcinoma (i.e., a small-cell carcinoma that contains a subpopulation of cells resembling large-cell lung carcinomas); and (3) combined small-cell carcinomas (i.e., SCLC admixed with areas of differentiated squamous cell or adenocarcinoma). Subsequent revisions to the WHO classification of lung tumors have resulted in further changes—previous classifications and terms such as oat cell carcinoma, intermediate cell type, mixed small-cell/large-cell carcinoma, and others (e.g., small-cell anaplastic carcinoma and undifferentiated small-cell carcinoma) are now considered obsolete and are no longer recognized. The WHO now recognizes two types of SCLC: pure SCLC and combined SCLC [14]. If SCLC has a pure histology, it is classified as SCLC [17]. Combined SCLC is defined as SCLC combined with a non-small cell lung cancer (NSCLC) component such as adenocarcinoma, squamous cell carcinoma, large-cell carcinoma, spindle cell carcinoma, or giant-cell carcinoma [16]. The diagnosis of combined SCLC is accompanied by a description of the NSCLC component or components [18]. To make the diagnosis of combined SCLC/large-cell carcinoma, the tumor should be composed of at least 10% large or giant cells; for other combined SCLCs, there is no percentage requirement for diagnosis [18].

SCLCs, like the other neuroendocrine tumors of the lung, arise from Kulchitsky cells that are normally present in the bronchial mucosa. The neuroendocrine family of lung tumors is comprised of SCLC, large-cell neuroendocrine carcinoma (LCNEC), and typical and atypical carcinoid tumors; these tumors share morphological, ultrastructural, immunohistochemical, and molecular characteristics [14]. Despite being grouped together, there are major differences among the pulmonary neuroendocrine tumors. SCLC and LCNEC are high-grade tumors, atypical carcinoids are intermediate-grade tumors, and typical carcinoids are low-grade tumors. SCLC and LCNEC patients are older, have a worse prognosis, and have a stronger association with smoking than patients with carcinoid tumors [22]. SCLC and LCNEC have higher mitotic rates and more necrosis than carcinoid tumors [22]. SCLC and LCNEC may show combinations with other histologic types of lung cancer. Carcinoid tumors have very few genetic abnormalities compared with the high-grade pulmonary neuroendocrine tumors [22].

Macroscopically, SCLCs are typically tan-white, soft, friable masses with extensive necrosis [16]. Nodal involvement is frequent. In the lung, tumor commonly spreads along bronchi in a submucosal and circumferential manner and frequently involves lymphatics [16].

9.3 Imaging of SCLC

9.3.1 Computed Tomography (CT)

The majority (90–95%) of SCLCs are located centrally and arise from the lobar or main stem bronchi [23]. On CT, SCLCs most commonly manifest either as (1) a large centrally located lung mass or as (2) mediastinal or mediastinal and hilar lymphadenopathy (Fig. 9.2) [24, 25]. A noncontiguous parenchymal lesion (i.e., a parenchymal lesion not contiguous with hilar/mediastinal adenopathy) was seen in 41% of cases in one review [25]. The absence of visualization of a primary lung tumor

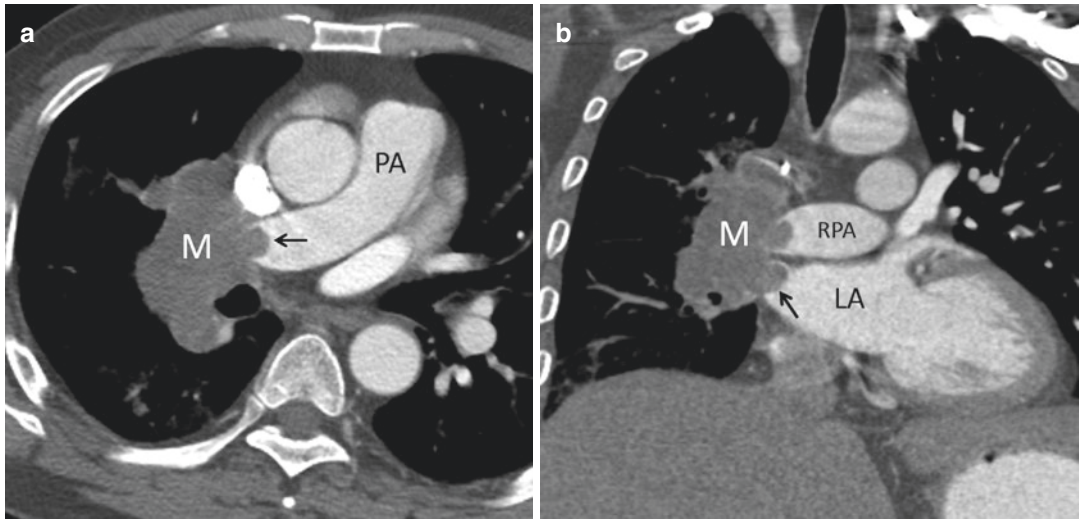

Fig. 9.2 SCLC with invasion of the pulmonary artery and left atrium. (**a**) Contrast-enhanced axial CT shows a right hilar mass (M) invading the right pulmonary artery (arrow). (**b**) Coronal reformation also depicts invasion of the left atrium (arrow). *LA* Left atrium; *PA* Pulmonary artery; *RPA* Right pulmonary artery

even in the presence of bulky lymphadenopathy is not uncommon however. Narrowing of the tracheobronchial tree (either secondary to extrinsic compression or endobronchial growth) and/or displacement of the tracheobronchial tree are frequent findings, occurring in approximately two-thirds of cases [25, 26]. As a result of their central location and propensity to narrow the tracheobronchial tree, SCLCs can result in post-obstructive atelectasis of either a lobe or an entire lung; atelectasis of at least a lobe is found in 30% of cases (Fig. 9.3) [25]. SCLCs may narrow or displace major vessels (present in approximately two-thirds of cases) (Fig. 9.4) [25]. The thin-walled low-pressure venous system is prone to obstruction/invasion by tumor. SVC obstruction, for instance, occurs in up to 9% of cases and manifests with narrowing or obliteration of the SVC by tumor; obstruction of the SVC is accompanied by the development of collateral venous return to the heart from the upper half of the body, most commonly through the azygous venous system (Fig. 9.5). Atypical imaging presentations of SCLC include lymphangitic carcinomatosis (visualized as smooth and/or nodular thickening of bronchovascular bundles and interlobular septa), replacement of an entire lobe by tumor (Fig. 9.6), and consolidation [27]. Metastatic disease to serosal surfaces (i.e., the pleura and pericardium) may manifest as an effusion and/or smooth or nodular thickening (Fig. 9.7). Importantly, the absence of serosal thickening in the presence of an effusion does not exclude metastatic disease. Other common sites of metastatic disease, e.g., lungs, liver,

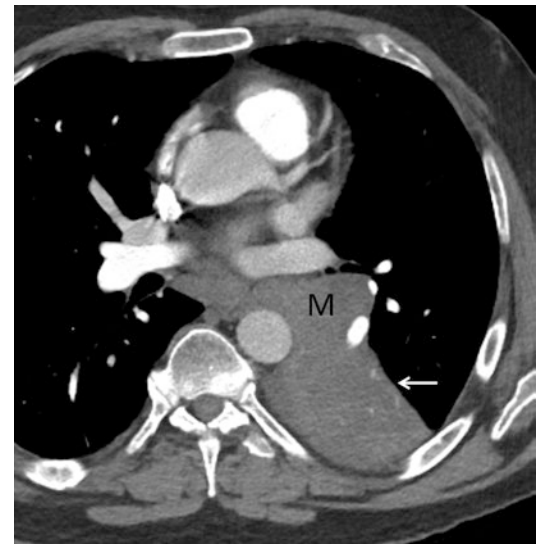

Fig. 9.3 SCLC resulting in lobar atelectasis. Contrast-enhanced axial CT shows a left infrahilar SCLC (M) and associated post-obstructive atelectasis of the left lower lobe (arrow)

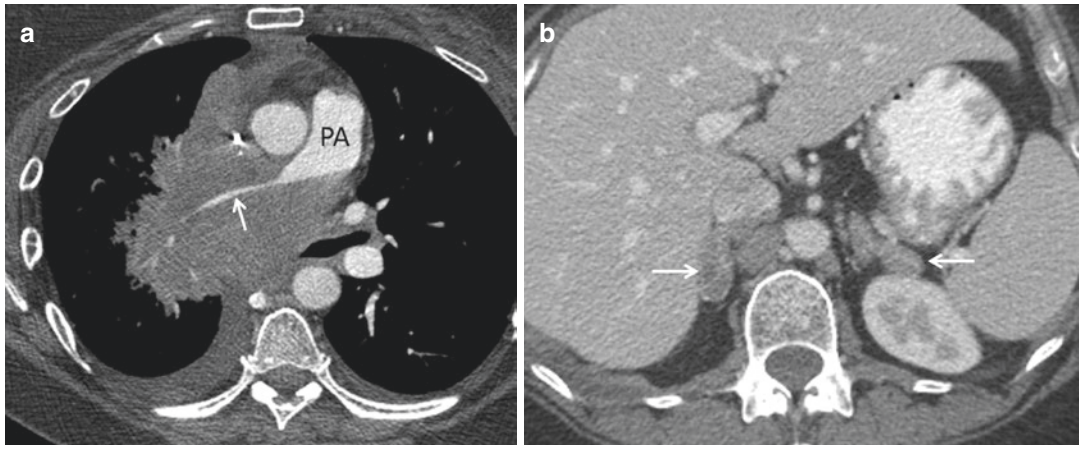

Fig. 9.4 SCLC with mediastinal invasion and adrenal metastases. (**a**) Contrast-enhanced axial CT at the level of the pulmonary artery (PA) shows a large right hilar mass invading the mediastinum and causing slit-like narrowing of the right pulmonary artery (arrow). (**b**) Contrast-enhanced axial CT of the abdomen demonstrates bilateral adrenal metastases (arrows)

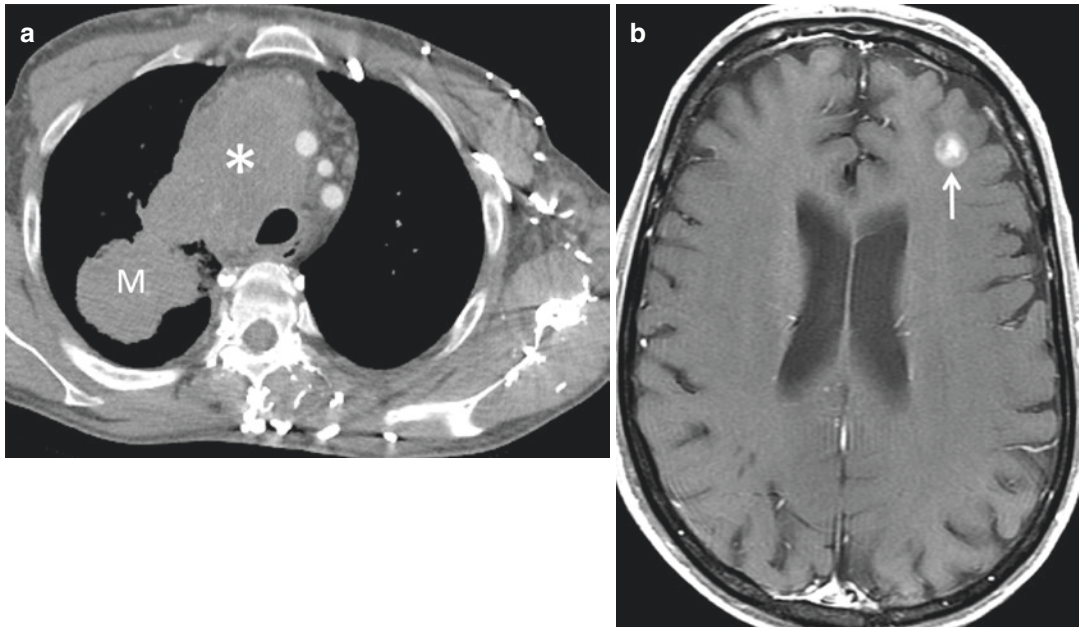

Fig. 9.5 SCLC resulting in superior vena cava syndrome and brain metastasis in a 53-year-old man who presented with facial and neck swelling. (**a**) Contrast-enhanced axial CT shows a right upper lobe mass (M) and bulky mediastinal lymphadenopathy (*) related to SCLC. Lymphadenopathy has obliterated the SVC. Note the extensive collateral venous circulation that has developed in order to return blood to the right heart. (**b**) T1-weighted post-contrast MR imaging of the brain shows a metastasis in the left frontal lobe (arrow) for which the patient was asymptomatic

adrenal glands, and skeleton, are also readily evaluated on CT (Fig. 9.8).

In a minority (5–10%) of cases, SCLC may present as a solitary pulmonary nodule without lymphadenopathy (Fig. 9.9) [18]. SCLCs that present as a solitary pulmonary nodule have a nonspecific appearance. They are usually homogeneous in attenuation, and round or lobulated, and

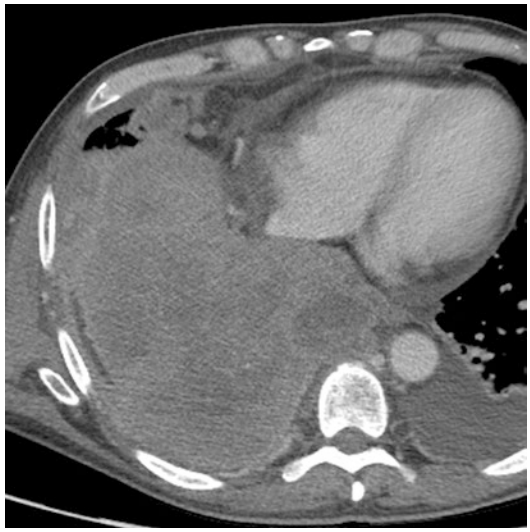

Fig. 9.6 Replacement of a lobe by SCLC. Contrast-enhanced axial CT shows a large tumor replacing the right lower lobe and most of the middle lobe

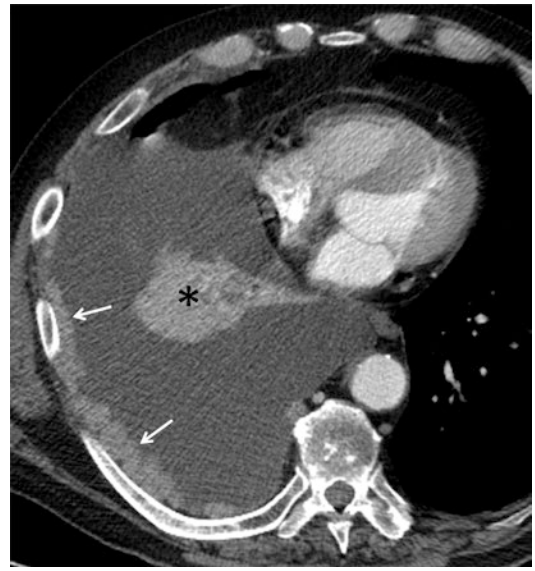

Fig. 9.7 Pleural metastatic disease. Contrast-enhanced axial CT shows a large right pleural effusion and lobular pleural thickening (arrows), consistent with pleural metastatic disease. Note the atelectatic right lower lobe (asterisk)

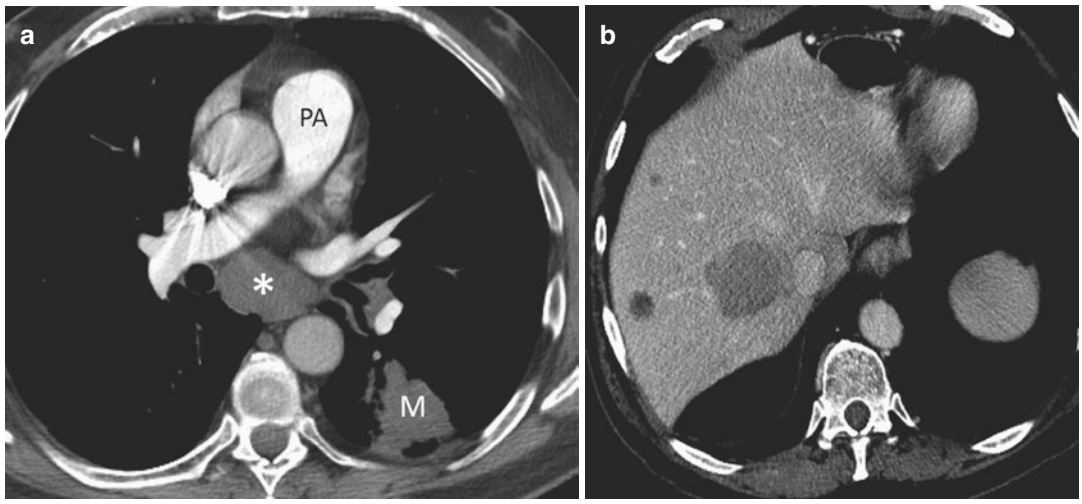

Fig. 9.8 SCLC with lymph node and hepatic metastases. (**a**) Contrast-enhanced axial CT at the level of the pulmonary artery (PA) shows the left lower lobe primary tumor (M) and subcarinal lymph node metastasis (asterisk). (**b**) Contrast-enhanced axial CT of the upper abdomen shows several low-attenuation hepatic lesions, consistent with metastases

have well-defined margins [28]. In some instances, tumor margins may be ill defined with either spiculation (corresponding to vascular, lymphatic, or alveolar invasion) or ground-glass opacity (corresponding to edema, hemorrhage, or intra-alveolar invasion) [28].

9.3.2 Positron-Emission Tomography/Computed Tomography (PET/CT)

^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET/CT combines functional information with anatomic infor-

mation and is an important examination in the evaluation of patients with SCLC [24]. FDG PET/CT plays a role in staging and restaging, guiding of therapy, and suggesting prognosis [24]. Because of the high metabolic activity of SCLC (Fig. 9.10), staging accuracy is better with PET/CT than with conventional imaging [29–31] and PET/CT is superior to PET alone [31]. In their review of 14 studies comparing pretreatment FDG PET to conventional staging procedures in patients with SCLC, Kalemkerian and Gadgeel found that 18% of patients diagnosed with limited disease by conventional imaging were upstaged to extensive disease by FDG PET (Fig. 9.11) [32]. Along similar lines, 11% of patients diagnosed with extensive disease by conventional imaging were downstaged to limited disease based on PET results [32]. PET was more sensitive and specific at most sites of metastatic disease but was inferior to MRI or CT in the detection of brain metastases [32].

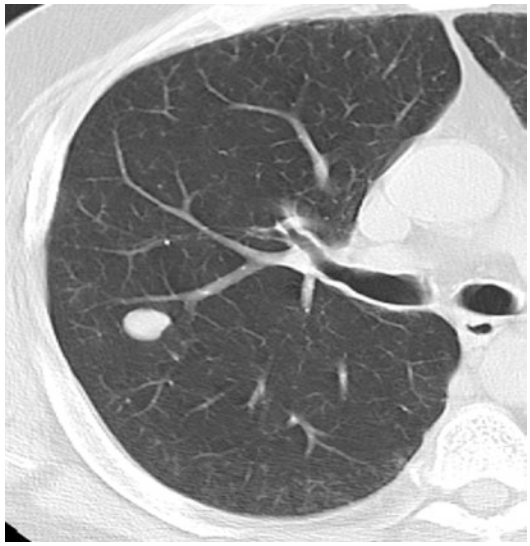

Fig. 9.9 SCLC presenting as a solitary pulmonary nodule. Contrast-enhanced axial CT performed to evaluate a pulmonary nodule detected on chest radiography confirms a solitary nodule in the right upper lobe. There was no lymphadenopathy. The patient underwent right upper lobectomy and was treated with adjuvant chemotherapy and prophylactic cranial irradiation

Several studies have evaluated changes in the initial management of SCLC patients based on PET; in their review of these studies, Kalemkerian and Gadgeel found that PET findings led to a change in initial management in 28% of patients—of patients who had a change in management, 32% had a change in the general treatment plan as a result of change in overall stage and 68% had changes in the extent of the radiation field [32]. In terms of restaging after therapy, studies have shown that 20–57% of patients had more disease while 14–38% had less disease on PET than with CT alone [33–36].

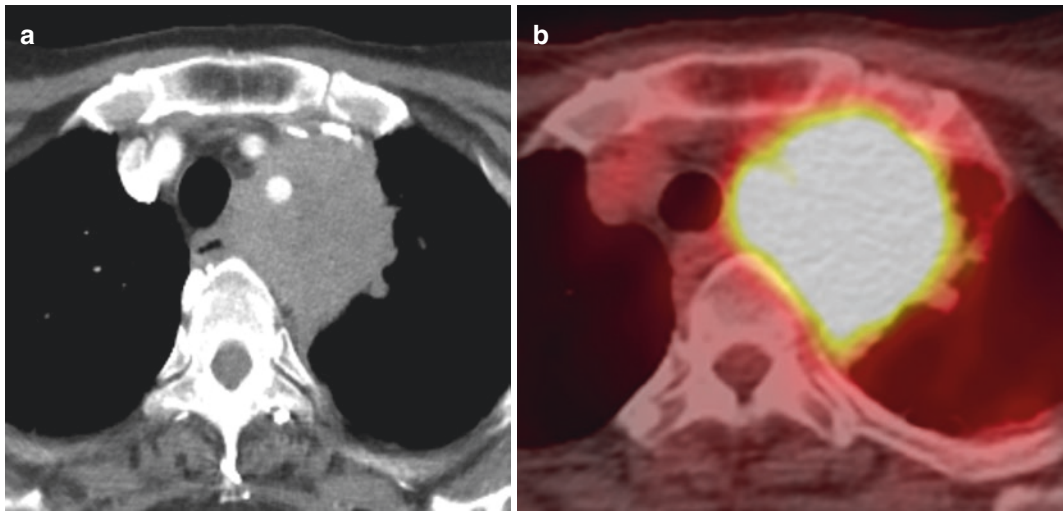

Fig. 9.10 Mediastinal SCLC with characteristic increased FDG uptake. (**a**) Contrast-enhanced axial CT shows a large soft-tissue mass in the left mediastinum. (**b**) Fused axial PET/CT image shows intense FDG uptake with maximum SUV of 14. Because of its high metabolic activity, SCLC typically demonstrates intense FDG uptake on PET/CT

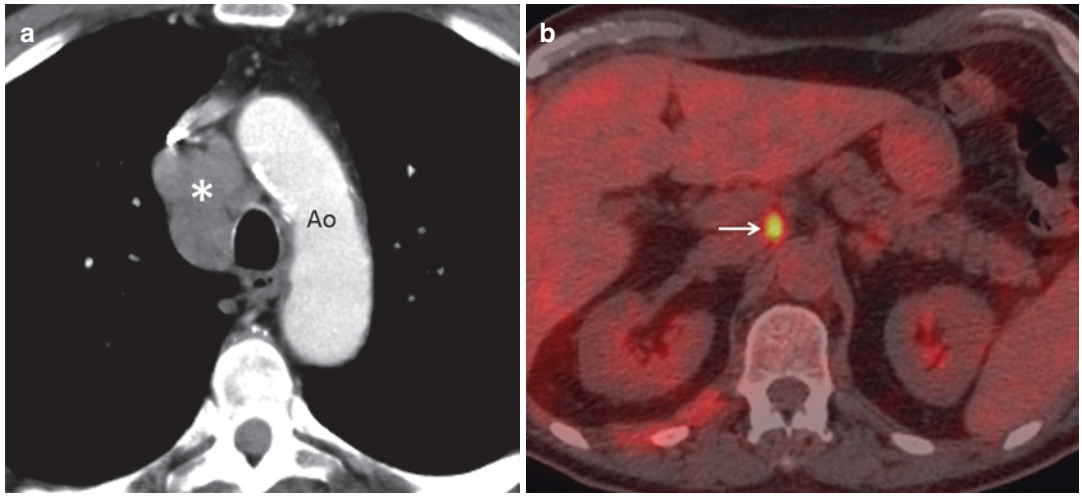

Fig. 9.11 Improved staging accuracy with PET/CT. (**a**) Contrast-enhanced axial CT at the level of the aortic arch (Ao) shows right paratracheal lymphadenopathy (asterisk), proven to represent SCLC. The abdominal CT did not reveal any evidence of metastatic disease. (**b**) Fused PET/CT image reveals an FDG-avid lymph node in the right retroperitoneum (arrow), proven to represent distant metastasis. Staging accuracy is better with PET/CT than with conventional imaging alone

PET imaging provides prognostic information in both staging and restaging of SCLC. In a review by Chong et al., SUV_{max} (maximum standard uptake value) of SCLC before treatment showed a negative correlation with survival time; an SUV_{max} of greater than 13.7 suggested a short survival time [37]. In a review by Pandit et al., patients with a positive FDG PET scan after initial therapy were found to have a significantly worse prognosis than those with a negative study; furthermore, a high SUV_{max} was associated with poor survival [38].

9.4 Magnetic Resonance (MR) Imaging

Thoracic MR imaging is not routinely performed to evaluate patients with SCLC. However, it can be valuable in certain situations, such as the suspected invasion of mediastinal or vascular structures in a patient in whom intravenous contrast is contraindicated (e.g., in cases of renal failure or allergy) [24]. Brain MR imaging is the imaging modality of choice for the evaluation of intracranial metastatic disease; due to the high incidence of brain metastases in SCLC, routine imaging of the brain is warranted in the staging of the tumor [39]. Spinal MR imaging is the modality of choice in the evaluation of suspected cord compression.

9.4.1 Differential Diagnosis

The differential diagnosis of SCLC, especially in cases of ES-SCLC, primarily includes other malignancies such as NSCLC, metastatic disease from another primary malignancy (such as breast cancer, sarcoma, or melanoma), and lymphoma. Other neuroendocrine neoplasms (e.g., of lung or alternate primary site) may also be considered. In the case of a solitary pulmonary nodule, the differential diagnosis is broad and includes other malignancies (primary or metastatic), benign lung tumors, and nonmalignant etiologies such as infection (e.g., bacterial or fungal pneumonia) or inflammation (e.g., nonnecrotizing granulomatous inflammation and granulomatosis with polyangiitis).

9.4.2 Staging

Historically, the TNM staging system was not used in the staging of SCLC since the TNM system relies on surgical confirmation for accuracy

and patients with SCLC rarely present with localized disease amenable to surgical resection [40, 41]. SCLC has instead been traditionally staged using a two-stage system that was introduced by the Veterans Administration Lung Study Group (VALG) in 1957. In the VALG staging system, patients are classified as having either LS-SCLC or ES-SCLC. LS-SCLC was originally defined as tumor involvement limited to one hemithorax that could be treated within a tolerable single radiotherapy port; ipsilateral supraclavicular lymph nodes could be classified as LS-SCLC if they could be included in the radiation port. ES-SCLC was defined as a disease that could not be classified as LS-SCLC and included malignant pleural or pericardial effusions and contralateral hilar and contralateral supraclavicular lymph nodes. Due to a lack of uniformity and controversy in the handling of patients with ipsilateral pleural effusion and of patients with contralateral mediastinal or contralateral supraclavicular lymph node metastases, the IASLC modified the VALG staging system in 1989 [42]. LS-SCLC was redefined as disease restricted to one hemithorax with regional lymph node metastases, including hilar, ipsilateral, and contralateral mediastinal, and ipsilateral and contralateral supraclavicular lymph nodes; an ipsilateral pleural effusion (independent of positive or negative cytology) was also included as LS-SCLC given that no extrathoracic metastases were detected [42]. ES-SCLC was defined as disease at sites beyond the definition of LS-SCLC. In practice, clinicians typically classify contralateral mediastinal and ipsilateral supraclavicular lymph node involvement as LS-SCLC. Controversy still exists with regard to the classification of contralateral supraclavicular or contralateral hilar lymph node involvement; treatment is usually based on the ability to include the area in a tolerable radiotherapy port [32].

In 2007, the IASLC, based on a retrospective analysis of over 8000 patients diagnosed with SCLC between 1990 and 2000, recommended that the (at the time forthcoming) 7th edition of the AJCC/UICC (American Joint Committee on Cancer/Union for International Cancer Control) TNM staging system replace the VALG staging system for SCLC [41]. They found that in patients without hematogenous metastases, both the T and N descriptors were discriminatory for overall survival; clinical stage groupings I–IV were also predictive of overall survival [32, 41]. An updated (8th) edition of the TNM staging system has recently been published based upon an analysis of a new database of patients that were diagnosed with lung cancer (including over 5000 with SCLC) between 1999 and 2010; analysis has again confirmed the prognostic value of TNM staging in patients with SCLC and continued usage of the TNM system in SCLC is recommended [43]. Minor changes to some of the TNM descriptors and TNM stage categories have been introduced in the 8th edition. Using the 8th edition of the TNM system, limited disease corresponds to T(any), N(any), M0 except T3–4 due to multiple lung nodules that do not fit in a tolerable radiation field while extensive disease corresponds to T(any), N(any), M1a/b/c or T3–4 due to multiple lung nodules. The M1b category represents oligometastatic disease in which there is a single metastatic deposit in one distant organ while M1c represents multiple metastases in one or more distant sites.

9.4.3 Treatment Guidelines

Systemic chemotherapy is the mainstay of treatment in all patients with SCLC. Combination therapy with etoposide plus a platinum-based agent (e.g., cisplatin or carboplatin) is the recommended standard chemotherapy regimen [44]. In ES-SCLC, chemotherapy alone is the recommended treatment although radiotherapy may be used for palliation of symptoms (for

example, in cases of SVC syndrome, obstructive atelectasis, painful bone metastases, and spinal cord compression) [44]. In patients with ES-SCLC and brain metastases, chemotherapy is given before or after whole-brain radiotherapy depending on the presence or absence of neurologic symptoms—if asymptomatic, chemotherapy is given first; if symptomatic, whole-brain radiotherapy is administered before chemotherapy unless immediate systemic therapy is required [44]. Patients with LS-SCLC, regardless of the visible extent of tumor, also receive chemotherapy because of the high likelihood of micrometastatic disease and because of the high initial response rate to cytotoxic therapy [32]. The addition of thoracic radiotherapy to chemotherapy in patients with LS-SCLC results in a 25–30% reduction in local failure and a 5–7% improvement in 2-year survival when compared with chemotherapy alone [45, 46]. LS-SCLC is therefore treated with a combination of chemotherapy and early concurrent thoracic radiotherapy, administered with cycle 1 or 2 of chemotherapy. Although SCLC is highly responsive to initial chemotherapy, approximately 80% of patients with LS-SCLC and almost all patients with ES-SCLC develop recurrent or progressive disease (Fig. 9.12) [24]. Second-line therapy may provide palliation and the likelihood of response is dependent on the time from initial therapy to relapse; for instance, if the interval between initial therapy and relapse is less than 3 months, response rates are <10% whereas if the interval is greater than 3 months, response rates are approximately 25% [44, 47].

Due to the high risk of the development of brain metastases, prophylactic cranial irradiation (PCI) is recommended in patients with LS-SCLC and ES-SCLC who have a good response to initial therapy [44]. In patients with LS-SCLC, PCI decreases the incidence of brain metastases and increases overall survival [48, 49]. In terms of patients with ES-SCLC, a study published in 2007 concluded that PCI decreases brain metastases and increases overall survival [50]. A recent Japanese trial, however, showed that PCI did not result in longer overall survival compared with observation in patients with extensive disease [51]. PCI is not administered concurrently with systemic chemotherapy due to the increased risk of neurotoxicity [44].

Surgery may be considered in SCLC patients with clinical stage I (T1–2, N0) disease. Patients with higher T- or N-stage disease do not benefit from surgery [52]. When surgery is being considered, occult lymph node metastasis should be excluded by pathologic mediastinal staging which may include mediastinoscopy, endoscopy (bronchoscopy or esophagoscopy) with ultrasound-guided fine-needle aspiration (FNA) procedures, thoracoscopy, or a combination of these procedures [53]. After confirmation that mediastinal lymph nodes are uninvolved, complete resection (preferably a lobectomy with either mediastinal lymph node dissection or sampling) is performed [44]. Patients without lymph node metastases are treated with postoperative chemotherapy whereas patients with nodal metastases are treated with postoperative concurrent chemotherapy and mediastinal radiotherapy [44].

Conclusions

SCLC is the most aggressive pulmonary neuroendocrine malignancy and is characterized by rapid growth and early development of metastatic disease. On CT, SCLC usually manifests as a large central lung mass or as mediastinal or mediastinal and hilar lymphadenopathy. Although SCLC has traditionally been staged using the modified VALG staging system, utilization of the TNM system is now recommended. Systemic chemotherapy is the mainstay of treatment in all patients with SCLC. Despite characteristic responsiveness to initial therapy, disease invariably recurs and the prognosis remains poor.

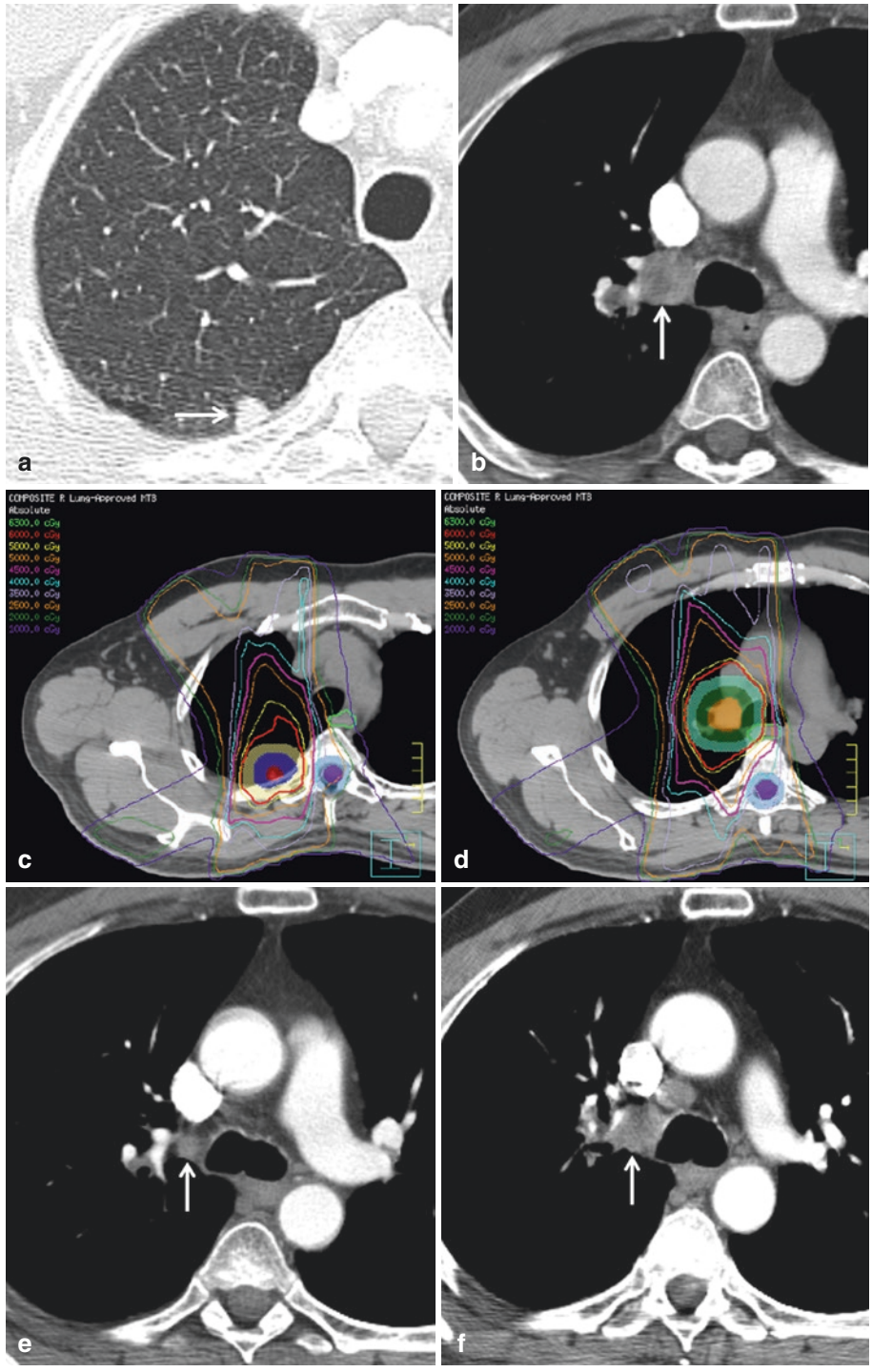

Fig. 9.12 Recurrent SCLC. Axial CTs in lung (**a**) and soft-tissue (**b**) windows show the right upper lobe primary tumor (arrow in **a**) and a right hilar lymph node metastasis (arrow in **b**). Images from the radiation treatment plan (**c**, **d**) show targeting of both lesions for treatment with radiation. (**e**) CT after radiation shows decrease in the treated lymph node metastasis (arrow). The primary tumor (not shown) has also decreased in size. (**f**) CT performed 8 months later shows recurrence of the lymph node metastasis (arrow) and a new right paratracheal lymph node metastasis

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