tumor cell surface in antigen presentation and immune recognition. This is regarded as the first evidence of somatic cancer genome alterations evading the immune system by changing their surface antigens. Potential therapeutic targets were identified in most tumors, offering new therapeutic avenues of investigation for targeted therapy in lung cancer.

CLINICAL PRESENTATION

Initial symptoms of lung cancer are usually nonspecific—cough, dyspnea, sputum production, chest pain, and weight loss—and are often attributed to bronchitis or pneumonia. The cancer has often invaded adjacent structures or metastasized when first recognized, causing symptoms that reflect the site of involvement, such as hemoptysis, pleuritic chest pain, and pleura or chest wall invasion; hoarseness (left recurrent laryngeal nerve); pleural effusion related to direct tumor involvement of the pleura or obstruction of lymph flow from the mediastinal nodes (E-Fig. 56-8); dysphagia (esophageal involvement); *malignant pericardial effusion,* which can progress to *cardiac tamponade*; *spinal cord compression;* and brain metastasis. A malignant pleural effusion precludes resection. Superior vena cava obstruction may result in the *superior vena cava syndrome,* with edema of the face and upper extremities due to impaired venous return.

The Physical examination can be normal but may reveal changes in the lungs that reflect the effect of the tumor, such as crackles (e.g., postobstructive pneumonia [E-Fig. 56-9]); inspiratory wheezes, suggestive of airway obstruction; dullness to percussion at the lung bases from underlying pleural effusion; and lymph node enlargement in the supraclavicular (E-Fig. 56-10) or cervical and axillary (distant) areas. The most common sites of metastases are the lymph nodes, liver (E-Fig. 56-11), brain, adrenal glands, kidneys, and lungs.

Lung cancers that occur in the apex of the chest and invade apical chest wall structures are known as *superior sulcus* or *Pancoast tumors* (E-Fig. 56-12). The classic description involves a syndrome of pain radiating down the arm due to tumor erosion into the brachial plexus. Tumor erosion into the cervical sympathetic chain causes *Horner syndrome,* with ptosis, miosis, and anhydrosis over the face and forehead.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Diagnostic and Staging Work-Up

When possible lung cancer is identified, either incidentally or because of symptoms, a tissue diagnosis is essential unless the patient is not eligible for treatment because of comorbidity. After assessment for metastases, the site of biopsy should be chosen to determine the greatest extent of spread or highest stage of the tumor, if this is feasible. If the apparent tumor is confined to the chest, bronchoscopy is appropriate for central masses, and a transthoracic needle aspiration would be suitable for peripheral lesions. Pleural effusion should be sampled to assess for malignant cells, which would indicate metastatic-stage disease (M1a).

Solitary Pulmonary Nodule

A *solitary pulmonary nodule* (SPN) is a single, rounded lesion in the lung that is 3 cm in diameter or smaller. Although these lesions are commonly lung cancers in certain patient populations, the differential diagnosis of SPN includes many other malignant and benign etiologies. In addition to primary lung cancer (adenocarcinoma; see E-Fig. 56-5), other possible causes include bronchial carcinoid tumors and metastases from extrapulmonary malignancies (e.g., malignant melanoma, sarcoma, colon, kidney, breast, and testicle). Benign etiologies include benign tumors of the lung (hamartomas) (E-Fig. 56-13), infectious granulomas (from fungal diseases including histoplasmosis and coccidioidomycosis as well as mycobacterial disease), lung abscess, vascular abnormalities (arteriovenous malformation), rounded atelectasis, and pseudotumor (pleural fluid trapped within a fissure).

Accurate and early determination is essential and can potentially lead to cure in the case of a malignant tumor. In a benign nodule, it may preclude surgery with its associated risks and complications. Diagnostic evaluation should consider the patient's age, gender, smoking history, family history of lung and other types of cancer, and other relevant risk factors.

Radiographic features of an SPN can be helpful diagnostically. **L**arger lesions are more likely to be malignant. Lesions 4 to 7 mm in diameter in patients without a history of cancer have a 0.9% chance of being malignant; this probability rises to 18% for lesions 8 mm to 2 cm in diameter, and 50% for those larger than 2 cm. **B**enign tumors tend to have smooth and discrete borders, whereas irregular and spiculated borders are more likely in malignant SPNs. **A** benign tumor tends to have a diffuse, central, laminated (onion-skin), or popcorn calcification pattern. Conversely, lesions with peripheral or eccentric (asymmetrical) calcifications are more likely to be malignant. It is important to assess the rate of occurrence of an SPN and its stability by comparing imaging studies with previous scans whenever available. An SPN that has not changed in size for more than 2 years is unlikely to be malignant.

Once a diagnosis of lung cancer is established, staging is necessary for prognostication and treatment. Staging in NSCLC determines whether surgical resection for cure or chemotherapy or radiation therapy is indicated. The tumor-node-metastasis (TNM) system is used (Table 56-3). For staging of SCLC, the Veterans Administration Lung Study Group designations of limited-stage (confined to one hemithorax) and extensive-stage (beyond one hemithorax) are used. Combined chemoradiation therapy with curative intent is considered for the former, but palliative chemotherapy is the treatment of choice for the latter.

Chest computed tomography (CT), including images of the abdomen, is useful to delineate the location and size of the primary tumor and to examine for mediastinal lymph nodes, pleural disease, and adrenal or liver metastases. However, CT has limited ability to distinguish benign from malignant lymphadenopathy in the mediastinum. Positron emission tomography (PET) using 18-fluorodeoxyglucose (FDG) is more sensitive and more specific than CT in the detection of mediastinal lymph node metastases and may also detect unexpected metastases elsewhere. In principle, any suspected mediastinal or extrathoracic metastases identified by imaging alone should be confirmed with tissue sampling before the patient is excluded from being considered an operative candidate. Techniques for invasive staging of the mediastinal lymph nodes include bronchoscopic transbronchial needle aspiration and mediastinoscopy. Mediastinoscopy can also assess mediastinal spread of disease in patients