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Lung Cancer

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Lung cancer is the most frequently occurring cancer in the world, and in the United States it is the second most common cancer diagnosed. Accurate staging by imaging can have a significant impact on appropriate treatment and surgical options. Familiarity with the different histologic subtypes of lung cancer and the typical and atypical appearances of lung cancer is vital. Radiologists serve a critical role in the diagnosis, staging, and follow-up of patients with lung cancer.

Incidence

Lung cancer is the most frequently occurring cancer in the world; 1.2 million new cases or 12.3% of the world's total cancer incidence were diagnosed in the year 2000. In the United States, lung cancer is the second most common cancer diagnosed in men and women. An estimated 174,470 new cases of lung cancer will be diagnosed in 2006, accounting for 13% of cancer diagnoses of which 92,700 cases will be in men and 81,770 cases among women [1]. The incidence is declining significantly in men, from a high of 102.1 per 100,000 in 1984 to 79.8 in 2000. In the 1990s, the increasing trend previously noted among women leveled off with an incidence at 52.8 per 100,000. The long-term trends in the age-adjusted incidence among men and women are consistent with the historic pattern of tobacco use, which reflects a 30-year lag time between increasing prevalence of smoking in women and development of lung cancer as compared with men. The lifetime probability of developing lung cancer in men in the United States is 1 in 13; for women the probability is 1 in 17. This is based on data from 1998 to 2000 [2].

Incidence rates of lung cancer also differ by ethnicity. African Americans and Native Hawaiians

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are at a significantly greater risk of lung cancer than whites, Japanese Americans, and Latinos among those who smoked no more than 20 cigarettes per day. At levels exceeding 30 cigarettes per day, however, these differences were not significant [3]. African Americans have the highest rate of smoking (29%) but smoke the fewest number of cigarettes per day and have higher nicotine levels after same number of cigarettes smoked. This may represent variation in metabolism of nicotine and differences in smoking behavior (ie, depth and frequency of inhalation) that may underlie exposure to carcinogens.

Mortality

Lung cancer is the leading cause of death in smokers and the leading cause of cancer mortality in men and women in the United States. There will be an estimated 160,460 deaths from lung cancer in the United States in 2006. An estimated 90,330 deaths among men and 72,130 deaths among women will account for about 29.8% of all cancer deaths in the United States [1]. In 2006, the American Cancer Society described a historic drop in cancer death from lung cancer by 369 total cancer deaths. Death rates have continued to decrease significantly in men since 1991 by 1.8% per year. The rate of increase in women, which had continued to increase, has slowed since the early 1990s. Mortality rates remain closely related to smoking patterns and lung cancer incidence rates. The decrease in smoking rates observed have reflected the decline in smoking observed over the past 30 years, although smoking patterns among women lag behind those of men. Overall, lung cancer mortality rates and trends are similar to those observed for incidence, because survival for lung cancer is poor.

Histologic types

Non–small cell lung cancer

Adenocarcinoma is the most common cell type representing 50% of all cases and is the most common cell type in nonsmokers. CT usually demonstrates a solitary peripheral pulmonary nodule or mass, which can be spiculated or lobulated. It is often subpleural and asymptomatic because of its peripheral location (Fig. 1). It may be associated with concomitant lung disease, such as focal and diffuse fibrosis. It is a slower-growing tumor; however, it can metastasize early. Subclassification is very difficult, with mixed subtype as the most common subtype. This is a glandular epithelial tumor with acinar, papillary, or solid growth patterns. In the 1981 World Health Organization classification, four subtypes of lung

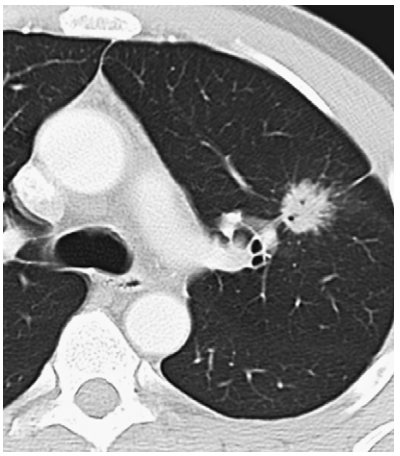

Fig. 1. A 41-year-old male smoker presenting with spiculated left upper lobe nodule with linear extension to the pleura. Histologically proved to be poorly differentiated adenocarcinoma.

adenocarcinoma were recognized including acinar, papillary, bronchioloalveolar (BAC), and solid carcinoma with mucus production.

BAC subtype of adenocarcinoma represents 3% of lung cancers. According to the 2004 World Health Organization classification the strict definition of BAC is that of a noninvasive tumor with no stromal, vascular, or pleural invasion and mantling of pre-existing airspaces "lepidic growth" along alveolar walls [4]. There are three radiologic patterns. A solitary nodule is the most common appearance, similar to adenocarcinoma. It represents 60% to 90% of presentations of this histologic subtype. Ground glass density can be seen especially peripherally within the lesion, representing the classic lepidic growth (along the alveolar walls) that is associated with this tumor. The second most common appearance is the pneumonic process, which is dense consolidation that can have air bronchograms similar to pneumonia. This presentation is seen in up to 20% of cases. Nodules can also be seen in association with this appearance, which can be bilateral because it is spread by the tracheobronchial tree and can disseminate throughout both lungs. A large dominant mass with satellite nodules within the same lobe or multiple nodules in more than one lobe can also be seen. The least common appearance is multiple small subcentimeter irregularly marginated nodules.

There are three histologic subtypes that have important clinical associations. The nonmucinous subtype is associated with a solitary nodule and a better clinical outcome. The mucinous subtype presents as a pseudopneumonic or multifocal-multinodular appearance and has a worse clinical outcome. Histologically, this type shows mucin

production with mucin pooling in alveolar spaces. The third subtype is a mixed mucinous and nonmucinous type. These different appearances have different clinical implications. Diffuse or multicentric growth patterns can be seen with both nonmucinous and mucinous BAC, but this is more characteristic of mucinous tumors.

Most lung adenocarcinomas with a BAC pattern are not pure BAC, however, but rather adenocarcinomas, mixed subtype with invasive patterns. This applies to tumors presenting with a diffuse-multinodular and solitary nodule pattern. The percent of BAC versus invasive components in lung adenocarcinoma seems to be prognostically important [4].

Atypical adenomatous alveolar hyperplasia is a premalignant lesion thought to be a precursor to BAC and found in lung adjacent to areas of invasive adenocarcinoma. Small BAC can be indistinguishable, however, from atypical adenomatous alveolar hyperplasia both histologically and radiologically.

Squamous cell carcinoma represents approximately 30% of all lung cancers. It is associated with the best prognosis. Although it generally grows locally rapidly, distant metastases occur at a later phase. There is a strong association with smoking.

Most tumors are between 3 and 5 cm when detected and centrally located, resulting in postobstructive atelectasis or pneumonia (Fig. 2). Patients may also present with signs and symptoms related to invasion of adjacent central structures, such as involvement of the recurrent laryngeal nerve. Hemoptysis, which is associated with central tumors, can also be a presenting symptom with squamous cell carcinoma. When these lesions occur peripherally they may be large before presentation and can lead to chest wall invasion and Pancoast's syndrome. Pancoast's syndrome refers to involvement of the brachial plexus and cervical sympathetic nerves associated with severe pain in the shoulder region radiating toward the axilla and scapula; atrophy of hand and arm muscles; Horner syndrome (constellation of signs produced because of interruption of the sympathetic innervation); and compression of blood vessels with edema. Pancoast's tumors can occur with any histology but are more common with both squamous cell and adenocarcinoma. The term "superior sulcus" tumor refers to its location in the superior pulmonary sulcus at the lung apex, from which it can invade locally the chest wall and brachial plexus.

Undifferentiated large cell carcinoma represents up to 5% of lung cancers. It generally presents as a large peripheral mass (>70% tumors are >4 cm on presentation) with rapid growth and early metastases, especially to mediastinum and brain. This histology generally has a poor prognosis and has a strong association with smoking (Fig. 3). There are several histologic subtypes of this tumor. Giant cell has a more aggressive behavior. Large cell neuroendocrine carcinoma also is more aggressive and can have a similar prognosis to small cell carcinoma. It differs histologically from small cell neuroendocrine tumors in appearance and response to chemotherapy, which is generally poorer. For the poorly-differentiated high-grade tumors, electron microscopy or immunohistochemistry may be needed to confirm endocrine features and diagnose this subtype.

The histologic distinction between these categories may not always be clear and different portions of a tumor may have different histologies. Poorly differentiated squamous cell carcinoma can be difficult to distinguish from a high-grade adenocarcinoma or undifferentiated large cell carcinoma.

Small cell lung cancer

Small cell lung cancer (SCLC), previously called "oat cell carcinoma" for the small, round cell shape of the cancer cells, is an aggressive tumor often presenting with generalized symptoms and distant metastases. Although these tumors respond initially to chemotherapy, most patients develop drug resistance. SCLC represents approximately 20% all lung

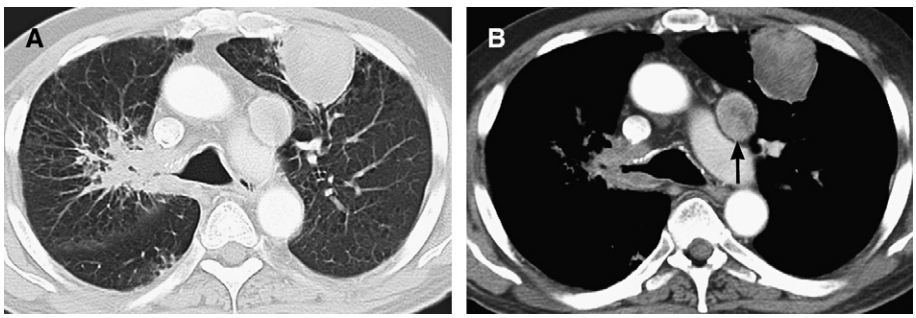

Fig. 2. A 75-year-old smoker with metastatic squamous cell carcinoma. (*A*) Note spiculated right central mass with encasement of the right main stem bronchus. A contralateral metastasis is seen in the left upper lobe. (*B*) Mediastinal lymphadenopathy (*arrow*).

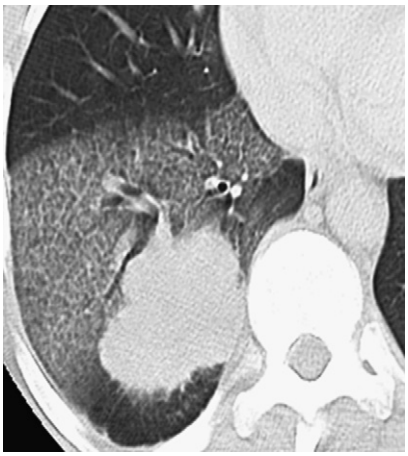

Fig. 3. Large right lower lobe mass with adjacent ground glass density consistent with hemorrhage. Patient presented with hemoptysis.

cancer cases. It has the greatest association with tobacco use, with almost 98% of patients with SCLC having a history of smoking [5]. The proportion of patients with SCLC has decreased over the last decade. SCLC is of a high-grade morphology and pathologic diagnosis is usually made on light microscopic findings, although electron microscopy or immunohistochemistry can be helpful.

Multiple primary carcinomas

Synchronous lesions are defined as the presence of two tumors at the same time or closely following initial diagnosis. The incidence of synchronous multiple primary tumors is less than 3.5% of all lung cancers [6]. This number may even be higher depending on the cell type and how carefully further primary tumors are sought and the rigidity of the criteria used to define the tumors as primary lesions. Difference in cell type is an accepted criterion; however, tumors of the same histologic type must be physically quite separate and separated by noncancerous lung tissue (Fig. 4) [7]. Metachronous lesions are defined as the second cancers appearing after a time interval, usually 12 months or more. The peak incidence is between the third and eighth postoperative years. These lesions comprise at least two thirds of multiple pulmonary neoplasms. Ten percent to 32% of patients surviving resection for lung cancer may develop a second primary tumor. The reported incidence has increased presumably because second primary lung cancer can be distinguished from recurrence and satellite disease. These lesions are regarded as multiple primary lesions only if they show unique histologic features. Adenocarcinoma has replaced squamous cell cancer as the most common histologic type of multiple carcinoma [8,9].

Screening

Surveillance and early detection

Lung cancer has a poor prognosis because it is typically diagnosed at an advanced stage as a result of a patient's symptoms, by which time it is incurable. The possibility of detection of early stage lung cancer, and which if treated aggressively by surgery could result in a high cure rate, has long been of interest.

Efforts using induced bronchial sputum cytology to detect early lung cancer did not prove successful [10–12]. The use of chest radiograph to detect early lung cancer had decidedly mixed results, with some centers detecting stage I lung cancer in

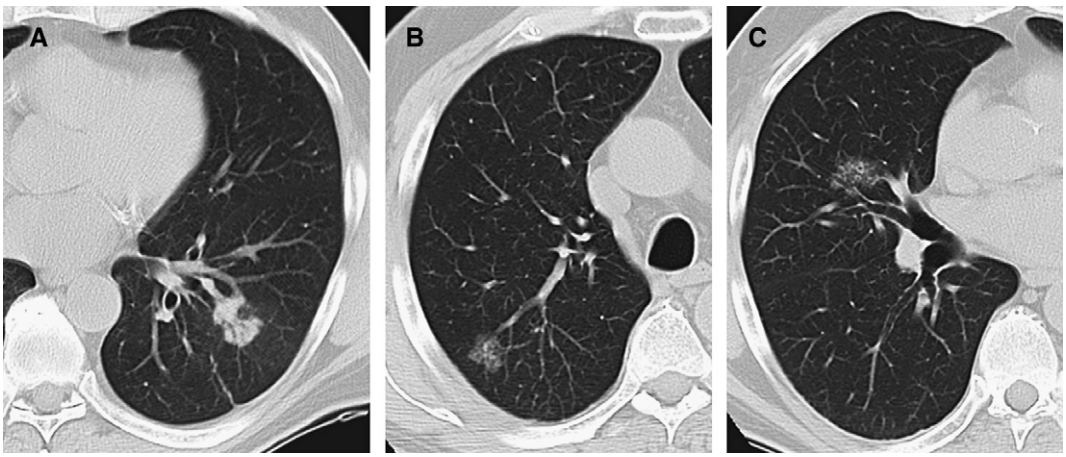

Fig. 4. A 68-year-old smoker with synchronous adenocarcinoma of the lung. (*A*) Left lower lobe nodule with air bronchograms. (*B*) Right upper lobe ground glass nodule. (*C*) Right middle lobe ground glass nodule. All were of slightly different histologies.

approximately 40% of patients. This was accompanied by the failure of these efforts to impact on mortality from lung cancer [13], resulting in a long pause in attempts at screening high-risk asymptomatic patients, lasting through the 1980s and most of the 1990s.

Those supporting imaging screening claimed that the study group and observation groups, particularly in the Mayo Clinic study, which compared a randomized study group receiving quarterly chest radiographs with an observation group for which only periodic clinical follow-up was recommended, were contaminated by noncompliance in the study group, and by the tendency of the observation patients to get tested [13,14]. The numbers of patients entered was claimed to be insufficient to answer the screening efficacy mortality question (ie, the study was "underpowered") [13]. Those opposing imaging screening claimed that there were various kinds of statistical bias introduced which caused a spurious increase in the diagnosis of small or early stage lung cancers accompanied by no decrease in late stage diagnosed lung cancers with any decrease in lung cancer mortality in the study group. These most notably included lead time bias [15] (screening diagnosis does not lead to a real increase in life span); length bias [15] (screening misses tumors that progress rapidly); and overdiagnosis bias [16] (diagnosis of pseudodisease [ie, nodules or "tumors" that would not have resulted in the patient's death because of an extremely slow rate of growth]).

The issue of lung cancer screening resurfaced in the early 1990s with the development of more advanced CT technology allowing faster breathhold scanning of the chest. During the 1990s Japanese investigators established the feasibility of CT screening to detect early lung cancer, and noting an increase in the number of early stage cancers diagnosed [17,18]. In 1999, Henschke and coworkers [19] published a prevalence study of CT scanning of 1000 high-risk patients. Twenty seven lung cancers were diagnosed and treated, of which 23 were stage I (85%). This paper was controversial because it proposed universal screening. A methodologic dispute followed as to whether follow-up studies of screening CT should be single arm or a randomized controlled trial (ie, whether all patients should receive the low-dose CT screening alone or whether they should be randomly assigned either to receive the test or not receive the test, or to receive another screening test, such as chest radiograph, with the results being compared between the two groups). This latter method was considered to be definitive for eliminating the possibility of significant bias and for detecting real differences in mortality from lung cancer between the two groups.

Henschke and coworkers [20] embarked on an international single-armed study that enrolled more than 25,000 participants: lung cancer continued to be detected on initial screening and on follow-up at stage I in 80% of patients. Moreover, this group claimed to have devised an imaging method for accurately differentiating benign noncalcified nodules from small lung cancers, involving careful follow-up and evaluation of size, both on measurement and by three-dimensional volumetric study, and use of sophisticated percutaneous biopsy procedures [21].

Swensen and coworkers [22], in a single-armed study of 1500 patients, demonstrated an apparent increase in diagnosis of small, early stage tumors. In comparing mortality from the CT study with their prior chest radiograph study from the 1980s, however, no difference in mortality between these two groups could be confirmed. In addition, the Mayo Clinic study found a significant incidence of work-up (including invasive procedures) of noncancerous masses to eliminate false-positive diagnoses.

It is thought that a large randomized trial of low-dose CT versus chest radiograph will be able to answer the issues raised by the overdiagnosis claim [23] and to this end a large randomized study sponsored by the National Cancer Institute and the American College of Radiology Imaging Network [24] has enrolled, with initial examination, 53,000 individuals into a randomized study involving comparison of CT and chest radiograph screening. Initial accrual has been completed and results, including early mortality results, should be available in the next several years.

Asymptomatic patients

With the increasing awareness of the relationship between smoking and lung cancer, individuals at risk are requesting low-dose CT screening outside of a clinical research study. Low-dose CT scans (40 mA, compared with conventional 200–300 mA CT dose) have the advantage of offering a diagnostic procedure at a radiologic dose that is comparable with plain posteroanterior and lateral chest radiographs. The potential reward is the diagnosis of lung cancer in a high-risk patient when it is both smaller and at an earlier stage. The downside of screening is the diagnosis of false-positives, with consequent morbidity and potential mortality associated with invasive diagnostic procedures [22]. At this time, screening has not shown a decrease in lung cancer mortality. Experience with diagnosing early lung cancer in a screening setting in asymptomatic patients has resulted in some guidelines in the evaluation of small pulmonary nodules [20–25].

- **Nodules <5 mm are seldom caused by lung cancer.**
- **Growth of nodules is ominous and should be aggressively evaluated, including by percutaneous biopsy. Growth is the screening gold standard for lung cancer diagnosis. There are, however, instances of growth of benign nodules.**
- **Lack of growth over time of 5- to 10-mm nodules should be confirmed over a 2-year time period.**
- **Small foci of clustered nodules are usually inflammatory or postinflammatory in origin.**
- **Randomly distributed nodules are nonspecific. They have a large differential diagnosis including inflammatory, inhalational, and neoplastic processes, both metastatic and primary in the lung.**

Symptomatic patients

Symptomatic patients with lung cancer frequently present on chest radiograph or CT with pleural effusions, mediastinal lymphadenopathy, or distant metastasis, all hallmarks of advanced disease. Patients with advanced lung cancer may present with fever and cough, blood-tinged sputum, brain or bone symptoms, weakness, weight loss, or other clinical indications of advanced disease. Whether the patient is symptomatic or asymptomatic, histologic confirmation is crucial, usually obtained either by percutaneous lung biopsy; bronchoscopy with biopsy (or alveolar lavage); or surgical exploration by open thoracotomy or video-assisted thoracoscopic surgery procedures.

Diagnosis

Imaging diagnosis of lung cancer frequently occurs in the context of screening or detection of nodules on a routine CT scan or chest radiograph in asymptomatic patients. These tumors tend to be smaller at diagnosis and not to have spread beyond their local confines. Diagnosis of lung cancer in patients whose work-up is precipitated by the development of symptoms, however, usually results in diagnosis of later-stage lung cancer, which is generally larger in size and may have spread regionally or distantly.

The location of these lesions can be described as central or peripheral. The shape of the borders of these lesions can be suggestive, but is not diagnostic of malignancy. In particular the presence of spiculation (Fig. 5) is thought to indicate a higher likelihood of malignancy [26]. Clearly defined edges [27] may indicate an inflammatory process. Cavitation, frequently an indication of long-standing or advanced lung cancer, is most commonly seen with squamous cell lung cancer (Fig. 6) [28].

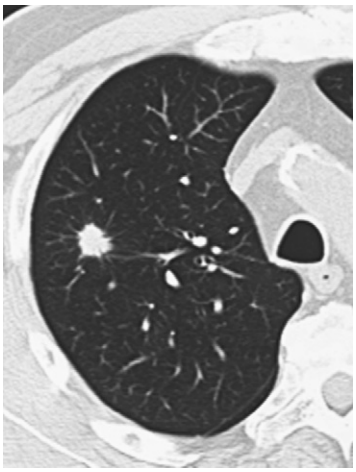

Fig. 5. A 68-year-old man with squamous cell carcinoma, moderately differentiated, of right upper lobe. Peripheral spiculated nodule with corona radiata. The spiculation suggests a malignant lesion with aggressive behavior.

In recent years, particularly with the development of surveillance programs, which tend to detect tumors at a smaller size, debate continues to occur as to whether detection and treatment of these small tumors, which seem to be earlier-stage lung cancers, translates into improved mortality. Yabuuchi and coworkers [29] correlated CT characteristics of small peripheral lung tumors with well-differentiated and poorly differentiated adenocarcinoma. Smoothness of tumor margin and a solid tumor appearance without air-bronchograms were more commonly found in poorly differentiated adenocarcinoma (all patients in this study had

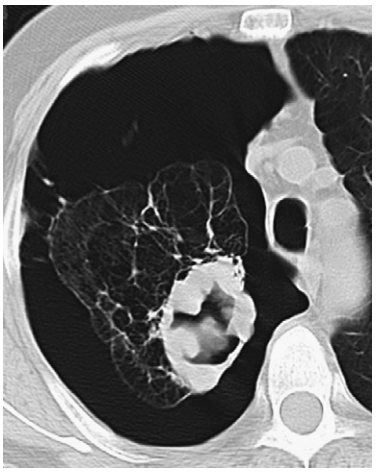

Fig. 6. A 60-year-old man with a cavitated mass that represents squamous cell cancer. Note the large pneumothorax.

lung cancer). The presence of air-bronchograms was associated with well-differentiated adenocarcinoma. Henschke and coworkers [30] in analyzing their data from the Early Lung Cancer Action Project divided their group of 233 noncalcified nodules into three groups: (1) solid (Fig. 7), (2) part solid (Fig. 8), and (3) nonsolid–ground glass opacity (Fig. 9). Nodules detected at screening that were part solid (ie, containing a solid and ground glass [nonsolid] component) had the greatest chance of being malignant (63%). Nonsolid nodules, composed of ground glass material, had an 18% chance of being malignant, whereas purely solid nodules had only a 7% chance of being malignant.

Lee and coworkers [31] in evaluating T1 stage non–SCLC (NSCLC), including imaging and histopathologic findings, found that T1 lung cancers with a large ground glass attenuation component (50% or more of tumor volume) had a better prognosis and less likelihood of mediastinal nodal or extrathoracic metastasis. Solid T1 lesions with a spiculated margin or with bronchovascular bundle thickening in the surrounding lung more frequently demonstrated local vessel invasion, regional lymph node metastasis, and distant metastatic disease. They suggest that patients with these morphologic features should have a work-up for extrathoracic metastases, including positron emission tomography scan, brain MR imaging, or mediastinoscopy. Li and coworkers [32] described three morphologic characteristics of screening detected or small peripheral lung nodules: nodules with pure ground glass opacity and that had a round shape were found more often to be malignant. These pure ground glass opacity lesions, especially when small, may represent premalignant atypical adenomatous hyperplasia. Mixed ground glass opacities (ie, with ground glass opacity at the periphery and a high attenuation zone at the center) were more often seen in malignant lesions than in benign, which agreed with Henschke's observation. Among solid nodules a polygonal shape or a smooth or somewhat smooth margin was present less frequently in malignant than in benign lesions. They concluded that certain morphologic characteristics at thin-section CT can be helpful in differentiating small malignant nodules from benign ones. These characteristics of screening-detected small nodules may reflect radiographic characteristics of the very early development of lung cancers rather than the well-described appearance of more advanced lung cancers.

Up to one half of patients with central tumors exhibit signs of locally advanced tumor with peripheral lung collapse or obstructing pneumonia [33]. The central location of these tumors results in early involvement of adjacent structures (vessels, lymph nodes, and bronchi) resulting, in the latter instance, in peripheral lung collapse or obstructive pneumonia (Fig. 10). In some instances, the peripheral consolidation or collapse of the lung may be distinguished from central tumor on contrast-enhanced CT scans, allowing visualization of the normal enhanced peripheral anatomy distinct from the central inhomogeneously enhanced or necrotic tumor (Fig. 11) [34]. The role of MR imaging in this area is questionable [35]. The presence of a persistent segmental or lobar pneumonia or an incompletely healed infiltrate, despite appropriate antibiotic therapy, should precipitate a careful search for a central obstructing pulmonary neoplasm. Rate of growth is measured by volume-doubling times and is not, in general, reliable for distinguishing tumor from a benign process. Recent CT volumetric analysis indicates a wide range of doubling times with more than 20% exhibiting markedly slow growth (doubling time greater that 465 days) [36].

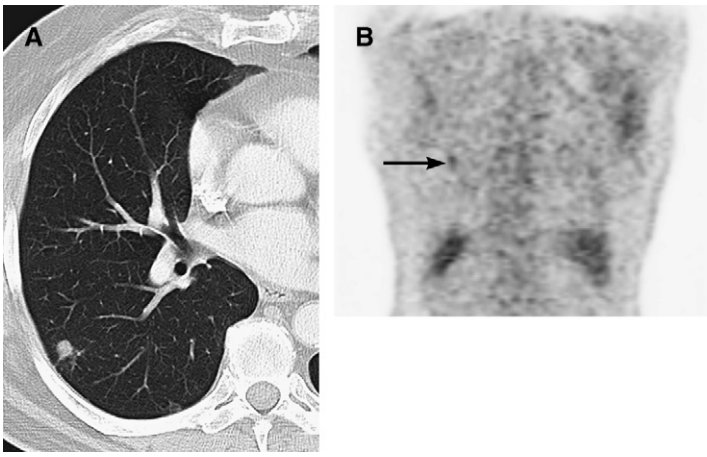

Fig. 7. (*A*) Small solid nodule detected in an asymptomatic 69-year-old man. In Henschke's data, this has a 7% chance of being malignant. (*B*) The positron emission tomography scan was weakly positive (*arrow*). This increases the likelihood of malignancy, but remains a nonspecific finding. Following resection, pathology revealed histoplasma granuloma.

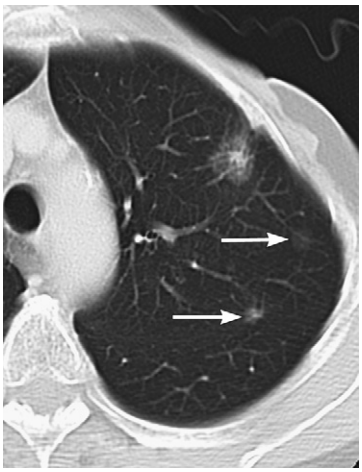

Fig. 8. A 65-year-old woman with a left upper lobe nodule with a solid core and large nonsolid periphery. At histology this was adenocarcinoma with bronchioalveolar features. Note two smaller lesions adjacent (*arrows*).

Common cell types of lung cancer as described previously have certain typical radiographic appearances; however, recognizing unusual presentations and suggesting the correct diagnosis is also of primary importance. Adenocarcinoma when located peripherally may directly invade the pleura and grow circumferentially around the lung and mimic diffuse malignant mesothelioma [37], pleural metastases, or metastatic involvement of the pleura by thymoma. Centrally located tumors may directly invade mediastinal structures or extend by the pulmonary veins into the left atrium. BAC most commonly presents as a solitary nodule with surrounding ground glass opacity. Although less common, consolidation and multiple small pulmonary nodules are other forms of presentations (Fig. 12). Unusual radiographic appearances include lobar atelectasis, expansile consolidation without air bronchograms, or elongated lobulated opacity resembling mucoid impaction [38,39].

Squamous cell carcinoma less commonly may present as a solitary peripheral nodule with or without cavitation. When the tumor cavitates, the inner wall is typically thick and irregular, and if secondarily infected may develop an air-fluid level. The unusual appearance of undifferentiated large cell carcinoma is a centrally located mass.

Fluorodeoxyglucose positron emission tomography scanning

Malignant tumors have a higher rate of metabolism because of the higher glucose use. Glucose and fluorodeoxyglucose (FDG) uptake by malignant cells is higher compared with surrounding tissues. After intravenous administration FDG is taken up by cells in a similar fashion to unlabeled D-glucose, which is then converted to FDG-6-phosphatase after being phosphorylated by hexokinase. FDG-6-phosphatase cannot then be further dephosphorylated or degraded by the glycolytic pathway [40]. FDG is ultimately filtered by kidneys and resorbed by glucose transporters.

The standardized uptake value (SUV) or standardized uptake ratio is used to provide an objective measurement of positron activity in the region of interest. SUV is calculated as maximum activity concentration detected in the lesion divided by injected activity and corrected for body weight.

It has been shown that FDG uptake in untreated primary NSCLC is related to the expression of glucose transporter-1 expression [41]. There is correlation between the degree of differentiation of lung adenocarcinoma and both Glut-1 expression and

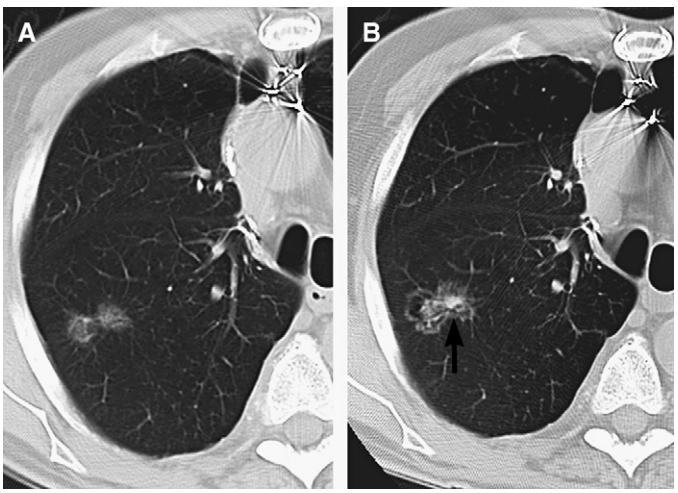

Fig. 9. An 81-year-old man with non–small cell lung cancer. (*A*) CT scans with two separate foci of ground glass density (nonsolid) in the right lung. This nonsolid appearance is frequently seen in bronchioloalveolar carcinoma. (*B*) Same levels in the right lung 1 year later. The tumor densities have increased in size and have developed small central solid cores (*arrow*), suggesting evolution to more aggressive adenocarcinoma in the central region.

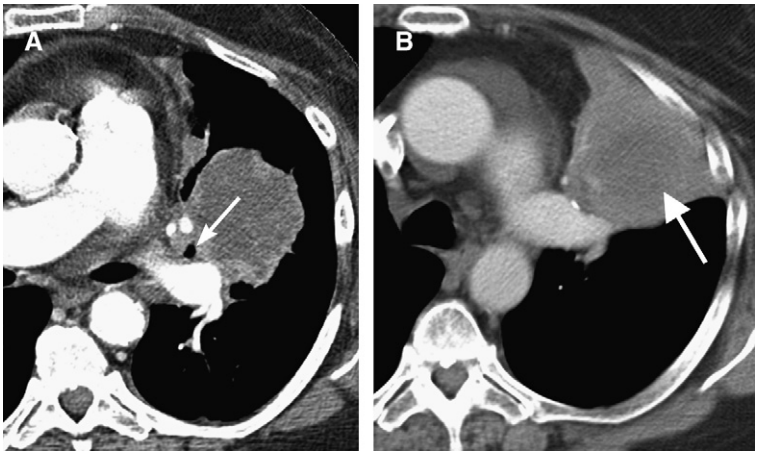

Fig. 10. (*A*) Largely central necrotic mass encasing the left upper lobe bronchus (*arrow*) and left hilar vessels. (*B*) More superiorly the mass extends into the left upper lobe, again demonstrating central necrosis (*arrow*) with some associated peripheral collapse.

FDG uptake. That is likely why FDG uptake has been shown to be significantly lower in BACs [42].

FDG-PET has a sensitivity ranging from 90% to 100% and specificity ranging from 69% to 95% [43–45] in detecting malignancy in a solitary nodule (Fig. 13). Small nodules (<7 mm) may not be detected by FDG-PET imaging because the amount of FDG uptake in these lesions cannot be reliably resolved [44] and may be below the threshold of resolution of current PET-CT scanners. An FDG-PET scan is indicated when the appearance of a nodule on CT is discordant with the pretest probability of cancer [46]. An SUV value >2.5 in a pulmonary lesion is highly suggestive of a malignant process [47] or active infection or inflammation. It has been observed that an SUV <2.5 has a 100% specificity for benign lesions >1.2 cm [48]. Similar findings have been reported, however, in the evaluation of lung lesions as small as 7 mm [44].

False-positive results on a PET scan can be caused by metabolically active infectious or inflammatory lesions. Granulomatous diseases like sarcoidosis, tuberculosis, or fungal infections can commonly produce significant FDG accumulation [49]. In geographic locations where prevalence of pulmonary fungal infections is high, there is low specificity and negative predictive value of FDG-PET in the evaluation of pulmonary lesions [50].Occasionally, adenocarcinoma <1 cm can have relatively less FDG accumulation and can result in a high false-negative rate of cancer detection [51,52]. A recent retrospective study evaluating the role of FDG-PET in indeterminate lesions <1 cm reported a sensitivity of 93%, specificity of 77%, positive predictive value of 72%, and negative predictive value of 94%. In this series, the prevalence of malignancy was found to be 39% [43].

Note that focal or pure BAC can result in a false-negative FDG-PET scan [53,54]. Similarly, in carcinoid tumors, an FDG-PET scan can yield false-negative results [55]. In about 5% of T1 indolent cancers, such as a focal nodular pure BAC or a carcinoid tumor, there is no significant FDG uptake [31].

Staging of non–small cell lung cancer

The process of staging, although separate from diagnosis, usually takes place in tandem with diagnostic procedures. The International System for Staging Lung Cancer, which follows the standard TNM

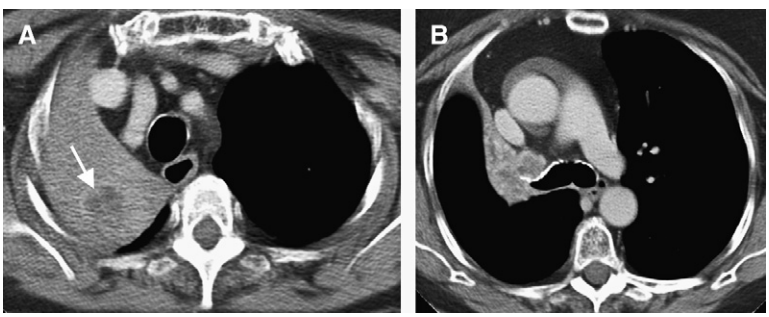

Fig. 11. A 79-year-old woman with non–small cell carcinoma. Patient with advanced, symptomatic lung cancer. (*A*) CT scan demonstrates a 3-cm right lung tumor within right upper lobe collapse (*arrow*). (*B*) Central hilar adenopathy (N2) with occlusion of the right upper lobe bronchus. MR image of brain (not shown) also detected a metastasis (M1 disease).

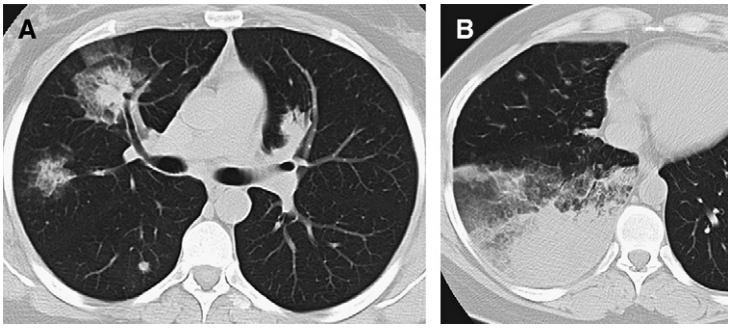

Fig. 12. A 35-year-old nonsmoking woman with multifocal bronchioalveolar carcinoma. (*A*) CT image demonstrates bilateral masses with ground glass and solid components. (*B*) Dense consolidation in the right lower lobe and smaller nodules in the right middle lobe.

format (Fig. 14) [56], is universally accepted and provides a useful framework for NSCLC staging. Small cell cancer is staged and treated differently (see later).

In the past there have been two competing systems for mapping mediastinal lymph nodes, but in 1996 the two systems were unified and adapted by the American Joint Committee on Cancer (Fig. 15) [57,58]. The new unified system provided for a numbered and a descriptive classification for lymph node staging, resulting in a standardized and easily understood system of reproducible lymph node mapping. The staging for NSCLC is not perfect, however, reflecting some intrinsic problems with the system and the complex anatomy in the thorax and the consequent variety of possibilities of regional and distant spread of disease. It is frequently difficult or impossible to determine the extent of tumor because of the presence of other abnormalities (eg, the true size of a tumor mass may be obscured by surrounding lung infiltrate or consolidation or a large pleural effusion). There are several descriptive ambiguities associated with this staging system, of which three examples are given below:

- **N2 tumor, which invades mediastinal structures (Fig. 16). Is this considered a meaningful N2 or is it more advanced disease?**
- **Recurrence of tumor following surgery: in lung, brain, bone, and so forth. There is no staging for this situation. It is designated recurrent disease.**
- **Two synchronous lung cancers are staged separately and independently. Prognosis is determined by the most advanced-stage tumor (Fig. 17).**

Pathologic staging more accurately reflects the patient's true extent of disease than clinical staging, because of the fact that it is performed during the actual surgical removal of tumor and

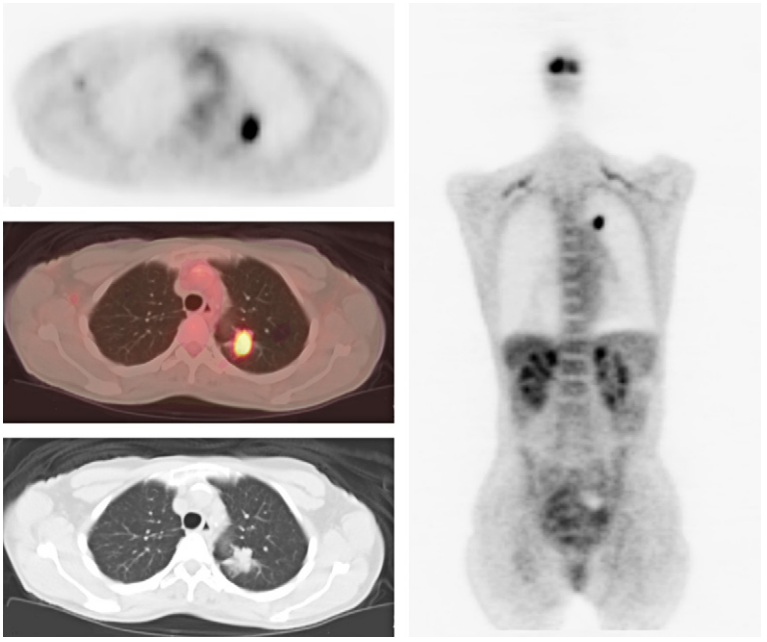

Fig. 13. A 65-year-old woman with lung nodule for evaluation. FDG-PET scan showed increased uptake in a nodule in the left upper lobe consistent with malignancy. Biopsy demonstrated poorly differentiated adenocarcinoma.

TNM	Stage	Percent surviving 5 years after treatment	
		Clinical stage (% with 95% CI)	Pathological stage (% with 95% CI)
CIS	0		
T1N0M0	IA	**61**	**67**
T2N0M0	IB	**38**	**57**
T1N1M0	IIA	**34**	**55**
T2N1M0	IIB	**24**	**39**
T3N0M0	IIB	**22**	**38**
T3N1M0	IIIA	**9**	**25**
T1-3N2MO	IIIA	**13**	**23**
T4N0-2M0	IIIB	**7**	–
Tany N3M0	IIIB	**3**	–
Tany Nany M1	IV	**1**	–

Primary tumor (T)

TX Malignant cells in Sputum or bronchial washings but primary not visualized.
T0 No Primary tumor
Tis Carcinoma in *situ*
T1 Tumor ≤ 3 cm in greatest dimension, surrounded by lung ir visceral pleura.
T2 Tumor with any of the following features of size or extent: > 3 cm in greatest dimension. Involves main bronchus ≥ 2 cm distal to the carina. Invades the visceral pleura. Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung.
T3 Tumor of ant size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium; or tumor in the main bronchus < 2 cm distal to the carina, but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung.
T4 Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; or tumor with malignant pleural or pericardial effusion, [a](see below) or with satellite tumor nodule(s) within the ipsilateral primary-tumor lobe of the lung.

Regional lymph nodes (N)

NX Regional lymph nodes cannot be assessed.
N0 No regional lymph node metastasis.
N1 Ipsilateral peribronchial and/or hilar lymph nodes, and intra pulmonary nodes involved by direct extension.
N2 Metastasis to ipsilateral mediastinal and/or subcranial lymph node(s).
N3 Metastasis to contralateral mediastinal or hilar lymph node(s), any scalene or supraclavicular lymph node(s).

Distant metastasis (M)

MX Presence of metastasis cannot be assessed.
M0 No distant metastasis.
M1 Distant metastasis; separate metastatic tumor nodule(s) in the ipsilateral non primary-tumor lobe(s) of the lung.

[a]Most pleural effusions are due to tumor. However, there are a few patients in whom multiple cytopathologic examinations of pleural fluid show no tumor. In these cases, the fluid is non bloody and is not an exudate. When these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and disease should be staged T1, T2, or T3. Pericardial effusion is classified according to the same rules.

Fig. 14. International system for Staging Lung Cancer and Lung Cancer Survival by Stage. (*Data from* Mountain CF. Revisions in the International System for Staging Lung Cancer. Chest 1997;111:1710–7.)

the anatomic relationship of the tumor to surrounding structures may be ascertained (eg, adjacent to or invading a particular structure). Also, other foci of tumor may be found that were not seen on presurgical procedures (satellite nodules or regional lymph nodes containing tumor). Once diagnosis is achieved, detailed clinical staging must be performed, which is defined as staging procedures that occur before the definitive therapeutic intervention. Surgical staging comprises all staging information from the therapeutic surgical procedure, including findings at surgery and confirmatory pathologic findings, representing a further refinement of clinical staging. In patients who undergo operation, the clinical preoperative staging is subject to verification by the surgical and pathologic findings, which not infrequently uncover more advanced disease than the clinical staging. Surgical staging frequently results in an upgrade of the clinical stage. This may be fairly simple in cases of early or small lung cancer. A CT scan alone in the presence of a small nodule <7 mm demonstrating growth over time, if negative for regional abnormality, may suffice as the sole preoperative diagnostic procedure, although some clinicians advocate extensive preoperative work-up for all patients diagnosed with cancer, including small T1 lesions. If, however, there are equivocal or abnormal findings (eg, borderline-size nodes or an adrenal

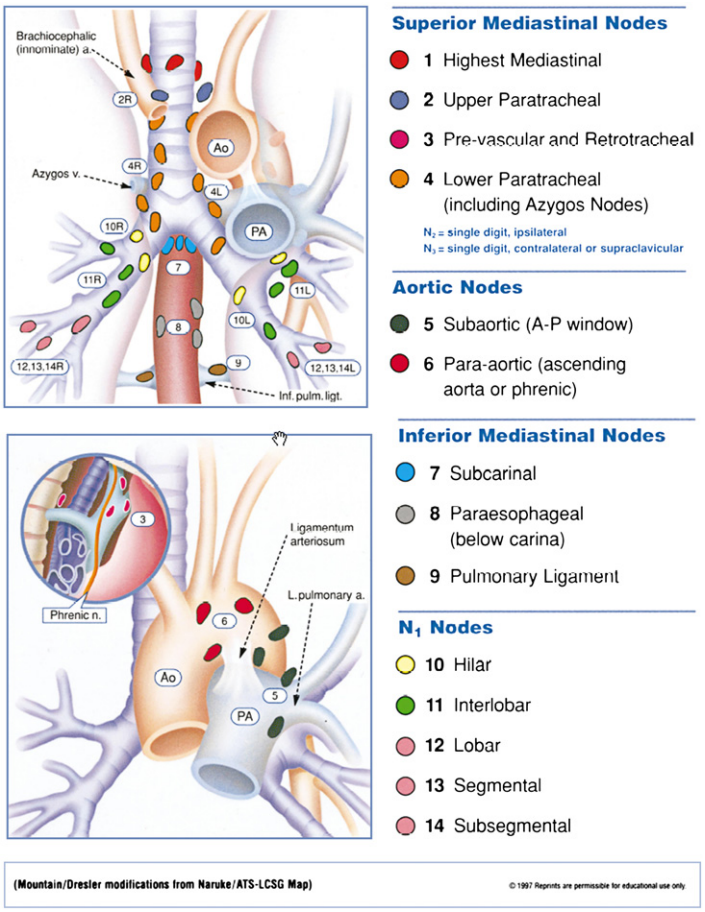

Fig. 15. Mediastinal lymph node mapping figure. (*From* Mountain CF, Dresler CM. Regional lymph node classification for lung cancer staging. Chest 1997;111:1718–23; with permission.)

mass), further work-up may be indicated. FDG-PET scan (discussed later) may be considered in these situations. In cases of advanced lung cancer at presentation (eg, regional lymph nodes, pleural effusion), when the efficacy of surgery may be questioned, a complete staging work-up should be performed. This should include CT of the chest, FDG-PET scan, brain MR imaging, and other procedures as may be clinically warranted, including MR imaging of other organs, as indicated by the patient's symptoms, to determine if the patient is truly a candidate for useful surgical intervention.

In advanced lung cancer (stage III B/IV) surgery is contraindicated because it represents incurable disease. There is no surgical-pathologic staging because surgery is not performed. Surgery is contraindicated in these patients with advanced tumor, including those patients with T4 tumor (ie, with invasion of central mediastinal structures [including spine] or malignant pleural effusion or satellite tumor nodules within the primary-tumor lobe of lung). Some surgeons resect satellite tumor nodules if they are in the same lobe as the primary tumor, reasoning that they are part of the local-regional process and are potentially completely resectable. Patients with stage III B by virtue of positive contralateral mediastinal or hilar nodes, or either contralateral or ipsilateral scalene or supraclavicular nodes, are not considered resectable. Any M1 (distant metastasis) is unresectable.

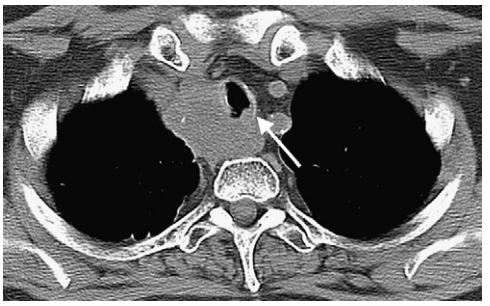

Fig. 16. Extensive mediastinal adenopathy invading the trachea (arrow). This N2 disease is more extensive (involving or invading mediastinal structures in a manner described for T4 primary lung masses) than standard enlarged mediastinal metastatic disease contained within a lymph node capsule.

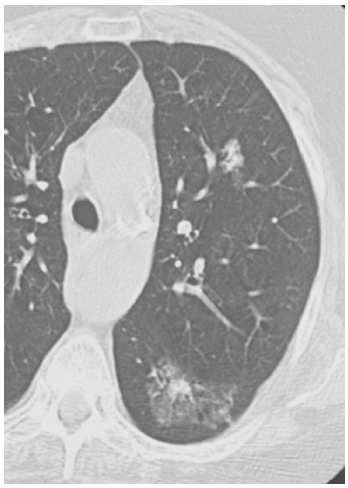

Fig. 17. Left upper lobe solid nodule with an irregular shape. A mass in the superior segment of the left lower lobe is of ground glass opacity with a central core. Although both were adenocarcinomas, they differed significantly in their morphology and immunohistologic staining properties, causing the pathologist to designate them as two separate primary lung cancers.

By its nature, pathologic staging uncovers equal or more advanced neoplasm than clinical staging and is more accurate. It seldom results in downstaging of a neoplasm; occasionally, it may diagnose benign disease in a lesion previously thought malignant. This delineation of more advanced tumor by surgical intervention explains the improved 5-year survival seen in Fig. 8 in patients who are staged pathologically for each stage: clinical staging discovers less advanced disease; pathologic staging uncovers tumor involvement not seen on clinical staging. This more accurate pathologic appraisal results in a greater percentage of patients in each staging group actually belonging to that group, and not having more advanced disease, as in the clinical staging group, accounting for the apparent superior 5-year survivals with pathologic staging.

CT and positron emission tomography in staging of mediastinal lymphadenopathy

In the era before CT, plain chest radiography was the most commonly used noninvasive method for preoperative evaluation of lung cancer. Earlier reports of CT scanning in patients with lung cancer aroused great optimism in the radiologic community concerning the ability of this modality accurately to stage lung cancer. Indeed, early reports, which were poorly controlled and not correlated with surgical-pathologic findings, indicated high accuracy for CT in detecting regional, mediastinal, and distant metastases. A standard morphologic criterion for abnormality of lymph nodes was a short axis measurement of 10 mm or more. It seems clear now that this somewhat simplistic approach to lung cancer staging was flawed. Eventually, larger series of patients undergoing pretreatment CT were analyzed with more rigorous criteria for truth testing, including thoracotomy, mediastinoscopy, and other invasive procedures designed accurately to determine the ability of CT to evaluate mediastinal and hilar lymph nodes, raising serious doubts concerning exaggerated claims for CT's accuracy in this regard [59,60]. The cooperative Radiology Diagnostic Oncology Group, in comparing the accuracy of CT and MR imaging in staging lung cancer in the mediastinum, found that the two procedures were equally inaccurate, with sensitivity for CT and MR imaging at 52% and 48%, respectively, and specificity for CT and MR imaging at 69% and 64%, respectively [36]. McLoud and coworkers [60] in a study of CT accuracy in diagnosing mediastinal involvement with excellent surgical-pathologic correlation reported a sensitivity and specificity of CT on a per patient basis of 64% and 62%. The sensitivity for CT in individual nodal stations involved with tumor was 44%. A significant number of false-positives (benign enlarged lymph nodes) and false-negatives (normal-sized lymph nodes containing tumor) were encountered. Other carefully performed studies placed the overall percent accuracy of CT in detecting mediastinal lymph node metastasis in the upper 60s to low 70s.

Initially, MR imaging with its ability to scan in any plane was proposed as a replacement for CT in staging lung cancer, justified by its claimed intrinsic diagnostic superiority related to its ability to scan in all planes. The Radiology Diagnostic Oncology Group study, however, demonstrated no advantage for MR imaging over CT in staging lung cancer. In addition, MR imaging was considerably more xpensive and time consuming to perform. There does seem to be some advantage for MR imaging in evaluating extent of invasion of superior sulcus tumors through the lung apex into the lower neck [61].

CT, although clearly useful in describing the properties of the primary tumor (T stage) and in detecting distant metastatic disease (frequently in patients who are symptomatic), was demonstrated to be a flawed modality in the evaluation of mediastinal lymphadenopathy. Some observers in the surgical community suggested a return to more invasive staging procedures as a routine, such as cervical mediastinoscopy [62].

Dales and coworkers [63] reviewed all available studies of CT in the detection of mediastinal metastasis between January 1980 and 1988. A total of 42 studies were pooled and a meta-analysis was

performed, indicating a sensitivity, specificity, and accuracy of 79%. This was considered unreliable as a truth test because of the unacceptable number of false-positive and false-negative examinations, potentially resulting in unnecessary surgery in patients with advanced disease or depriving patients of potentially curative surgery in the mistaken belief that they had advanced disease. At the end of the article the author stated "we believe that no clinically important advances (in detection of mediastinal lymph node tumor involvement) will be made until lymph node size is replaced by a fundamentally different indicator of lymph node pathology."

FDG-PET is useful in the evaluation and staging of lung cancer and assessment of prognosis and treatment response [64]. It has been shown that FDG-PET can be more accurate than CT for staging of NSCLC. In patients with potentially resectable disease it can help in reducing the rate of unnecessary surgical procedures [65,66] because an FDG-PET scan can identify involved lymph nodes, although they may be normal sized. M and N staging is better assessed with FDG-PET than with CT imaging. Additionally, FDG-PET scanning can be more accurate than CT scanning or endoscopic ultrasound for the detection of mediastinal metastases [67]. FDG-PET can be particularly helpful and more accurate than CT for the detection of N1 and N2-N3 disease (Fig. 18).

In patients with suspected or proved NSCLC considered resectable by standard staging procedures, FDG-PET can prevent unnecessary thoracotomy in one out of five patients [68]. In a multicenter randomized trial involving 188 patients with NSCLC, conventional staging work-up as compared with conventional work-up plus FDG-PET was evaluated and it was concluded that unnecessary surgery in one of five patients was prevented by the addition of FDG-PET to the conventional work-up. Additionally, 27% of patients were upstaged based on the FDG-PET findings [69].

In a prospective study of 102 patients with NSCLC, the sensitivity and specificity of FDG-PET in detecting mediastinal lymph node metastasis were 91% and 86%, respectively, and the investigators concluded that invasive procedures, such as mediastinoscopy, are probably not necessary in patients with negative mediastinal findings on FDG-PET scan. Detection of local and distant metastases in patients with NSCLC can improve with a FDG-PET scan (Fig. 19) [70].

The prognostic value of FDG-PET has been investigated by several groups. In a study of a group of 155 patients with NSCLC median survival was compared with the SUV of the primary tumor. As the mean SUV increased, the median survival decreased [71]. A retrospective study of 100 patients demonstrated that in a group with an SUV >9, the 2-year survival rate was 68%, whereas with those in the group with an SUV <9, the survival rate increased to 96% [72]. Another study that included 162 patients with stage I to IIIB NSCLC of which 93 patients were treated with surgery and 69 patients were treated with radiotherapy concluded that the SUV for the primary tumor was the most significant prognostic factor among that group of patients. Patients with a low SUV ≤ 5 showed significantly better disease-free survival than those with a high SUV >5 [73].

In patients with stage I NSCLC, the FDG-PET uptake had a significant independent postoperative prognostic value for recurrence. The incidence of metastases was high if the SUV was high [74]. The SUV values, however, had a wide range from 5 to 20 [75].

A recent multicenter trial evaluating 465 patients with NSCLC noted that obtaining an FDG-PET study initially after first presentation does not decrease the overall number of diagnostic tests, although invasive procedures, such as mediastinoscopies, were performed significantly less often if a PET-CT scan was obtained. There were limitations with this study, however, such as different levels of clinical experience with FDG-PET interpretation, which varied among institutions, and also the fact that the PET scans were not read in conjunction with the CT scan [76].

For small, peripherally located T1 or T2 tumors, however, FDG-PET has no demonstrable benefit in the diagnosis, staging, or determination of prognosis of these patients. Only 55% of these tumors were FDG-PET avid after the exclusion of BAC [77]. Another study involving patients with stage I-II NSCLC found that PET provides potential for more appropriate stage-specific treatment but may not lead to a significant decrease in the actual number of thoracotomies avoided [78]. In locally advanced NSCL patients, FDG-PET was found to have additional value over CT in monitoring response to induction chemotherapy. It may be feasible to predict response and patient outcome even after one course of induction chemotherapy [79]. It has been shown that in patients with known or suspected lung cancer evaluated with FDG-PET, the results had major impact on staging and management of their lung cancer [80]. PET-CT is also more accurate than PET and CT alone for staging NSCLC [81].

Staging of small cell lung cancer

SCLC is not staged according to the TNM system. It is described as either limited-stage disease or extensive-stage disease. Standard staging procedures for SCLC include CT scans of the chest and abdomen, bone scan, and CT scan or MR

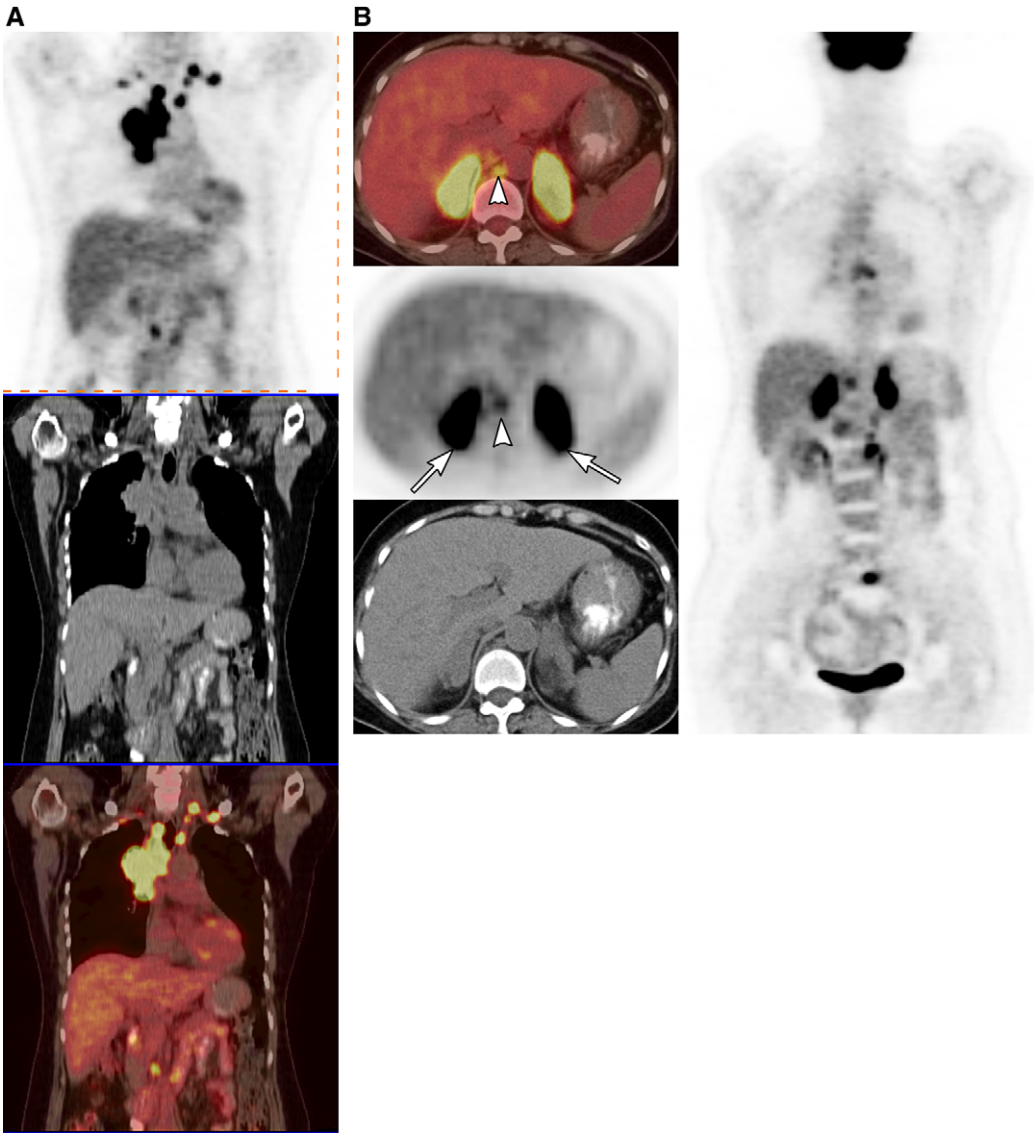

Fig. 18. A 56-year-old woman with non–small cell lung carcinoma. (*A*) FDG-PET scan demonstrates increased uptake in the right upper lung in a paramediastinal mass with lymph node metastases bilaterally in the lower neck, paratracheal region, and the para-aortic region in the upper abdomen. (*B*) There is also increased activity in the adrenal glands (*arrows*) and in a retrocrural lymph node (*arrowhead*) consistent with metastases.

imaging of the brain. Patients with limited-stage disease have involvement restricted to the ipsilateral hemithorax within a single radiation port (Fig. 20). Extensive-stage disease is defined as the presence of metastatic disease. Limited-stage disease is treated with curative intent with chemotherapy and radiation therapy. The median survival time for patients with limited-stage disease is approximately 18 months. A small subset of these patients present with a single solitary nodule that can be resected. These cases are considered very early stage limited disease and have a better prognosis. Extensive-stage disease is treated primarily with chemotherapy, with a median survival time of approximately 9 months [82]. These tumors are usually centrally located and present as a hilar or perihilar mass associated with extensive bilateral mediastinal lymphadenopathy [83]. The primary tumor may be obscured by adenopathy and which may lead to associated lobar collapse. It is the most common cause of superior vena cava syndrome. Less commonly seen are peripheral lesions with associated hilar adenopathy.

There are limited data regarding the role of FDG-PET in the work-up of patients with SCLC [84]. Some preliminary data with a small number of

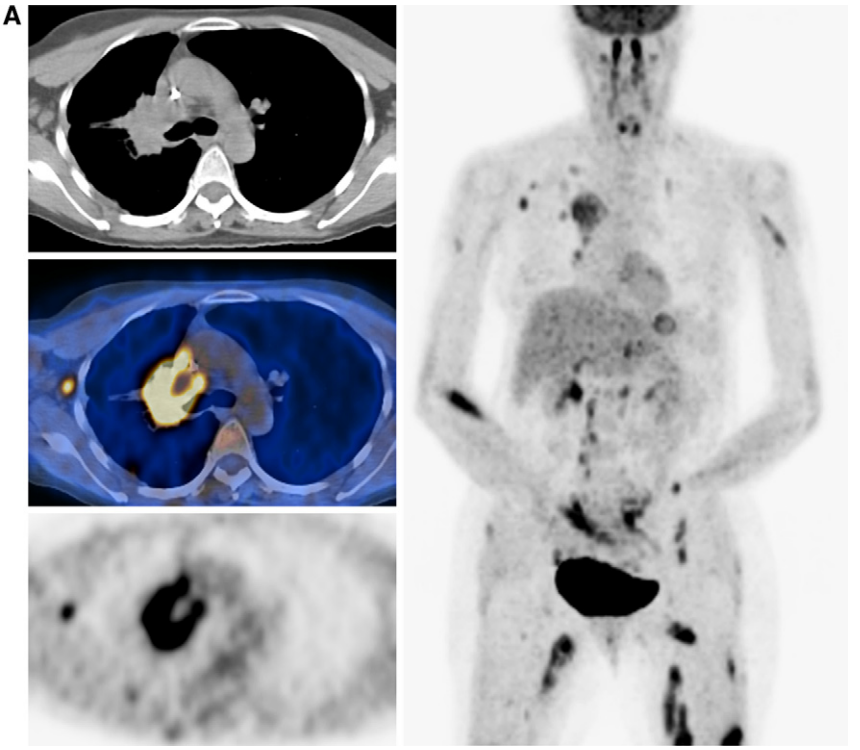

Fig. 19. A 54-year-old woman with adenocarcinoma of the right lung. (*A*) FDG-PET showed increased uptake in the right hilar mass. Whole body maximum intensity projection image demonstrates extensive nodal metastases in the chest and abdomen. (*B*) Note musculoskeletal metastases in the legs.

patients provided a potential use of FDG-PET for the staging of patients with SCLC (Fig. 21) [85]. FDG-PET influences staging and can help in improving management of patients with SCLC. A study by Brink and coworkers [86] evaluated the clinical impact of FDG-PET on primary staging of patients with newly detected SCLC. In this study, FDG-PET showed 100% sensitivity in the detection of the primary tumor. The sensitivity of FDG-PET was significantly better than that of CT in the detection of extrathoracic lymph node involvement and distant metastases, with exception of brain where a brain MR image or CT is more sensitive than an FDG-PET scan.

Follow-up imaging

Immediate postoperative period

In the immediate postoperative period, chest radiography is performed to assess for lobar collapse, tension pneumothorax, pulmonary edema, or other acute processes. In the weeks and months after surgery, postoperative pneumothorax decrease in size and are replaced by fluid or compensatory expansion of the remaining lung. Patients with pneumonectomy usually have complete opacification of the hemithorax with shift of the mediastinum into the surgical side. Occasionally, air fluid levels may persist; however, if it is stable or the patient is asymptomatic, it is not clinically significant. An increase in the air component of the postoperative hydropneumothorax should raise concern, however, for a bronchopleural fistula.

The radiologic follow-up of patients after the immediate postoperative period varies according to the referring surgeon. Follow-up examinations generally include chest radiography and chest CT. Extrathoracic imaging is not usually ordered unless there are clinical symptoms that are suggestive of potential metastatic disease. Assessing for recurrent disease and for metastatic disease is vital for the radiologist interpreting the CT scan or radiograph.

Long-term follow-up

The standard treatment of choice for localized stage I through IIIA remains surgical resection with and without chemoradiation therapy. Unfortunately, the 5-year survival for all stages of lung cancer remains at 15% [1]. Careful follow-up may lead to earlier detection of recurrences or earlier detection of a second primary bronchogenic carcinoma. The risk of developing a second lung cancer in patients

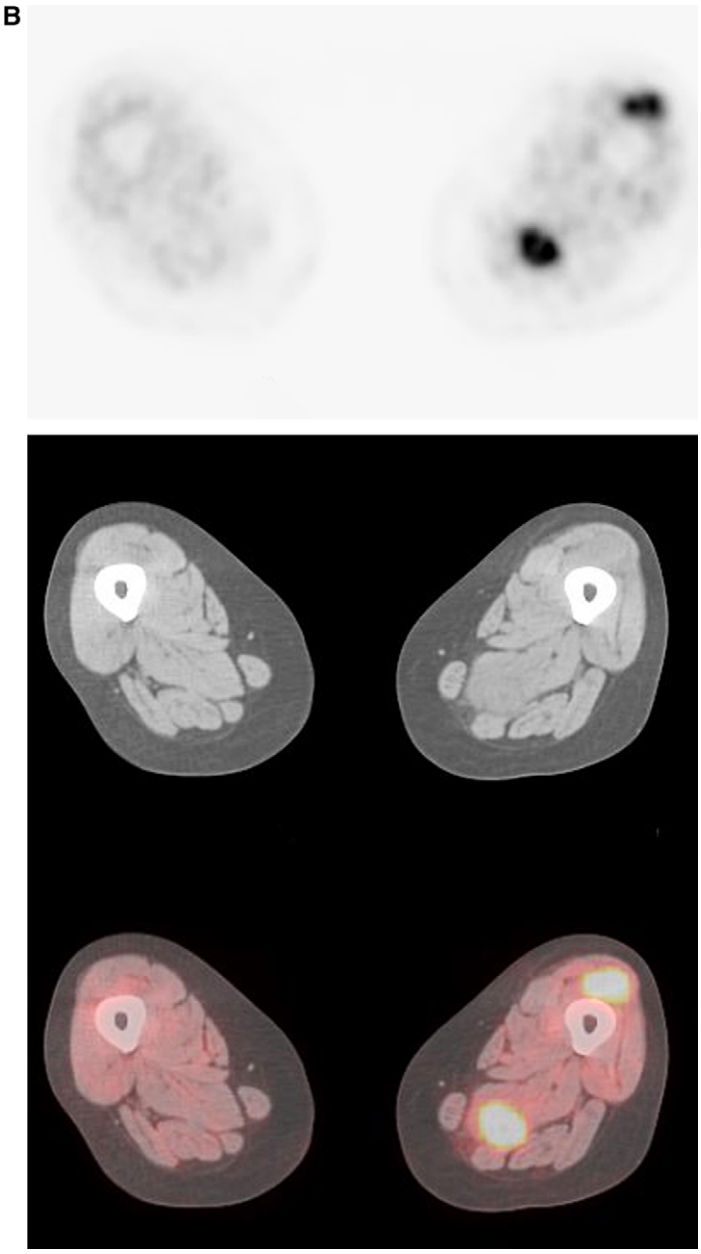

Fig. 19 (*continued*)

who survived resection of a NSCLC is approximately 1% to 2% per patient per year and for SCLC survivors it is approximately 6%. Ten years after the initial treatment in those who survived SCLC, the risk increases to greater than 10% per patient per year. This risk of developing a second primary lung cancer can translate into an important cumulative risk [87]. This cumulative risk can make death from a second lung cancer a common cause of death in lung cancer survivors.

The current recommendations for routine follow-up after complete resection of NSCLC at the authors' institution are as follows: for 2 years following surgery a contrast-enhanced chest CT scan every 6 months and then yearly noncontrast chest CT scans. Recurrence on CT is the primary goal in the initial years and a contrast-enhanced scan should be obtained optimally to evaluate the mediastinum. Because identifying an early second primary lung cancer becomes of more clinical

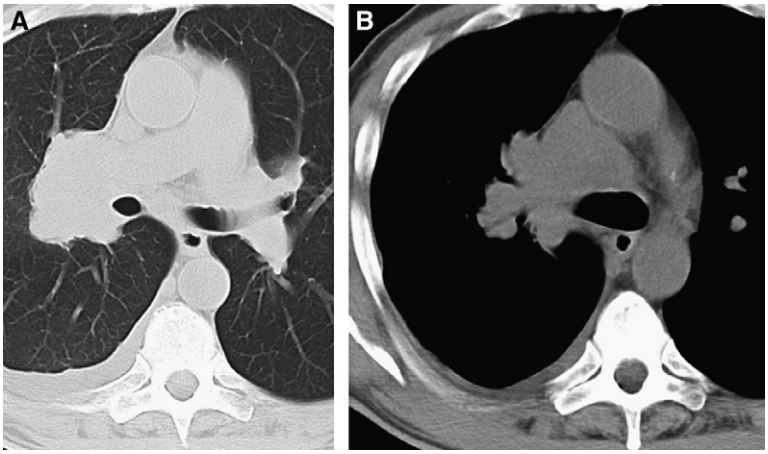

Fig. 20. A 56-year-old man presenting with limited stage small cell lung cancer. Note larger right hilar mass (*A*) and mediastinal lymphadenopathy (*B*) that can be contained in a single radiation port.

importance in the subsequent years a noncontrast scan suffices to evaluate the lung parenchyma.

Posttreatment imaging

Radiation therapy changes

All references should be related to the end of the radiation therapy treatment period. Imaging performed within 3 months of the conclusion of therapy may show ground glass opacities, which may indicate radiation pneumonitis. This may occasionally appear nodular but is within the lung that was treated with radiation. At follow-up imaging, the nodules are seen to coalesce into areas of consolidation and eventually become a component of the radiation fibrosis. Radiation fibrosis consists of a well-defined area of consolidation associated with volume loss and bronchiectasis. Fibrosis can progress slowly over 3 to 12 months after radiation therapy ends but stabilize within 2 years (Fig. 22). Most fibrosis occurs within the first 12 months

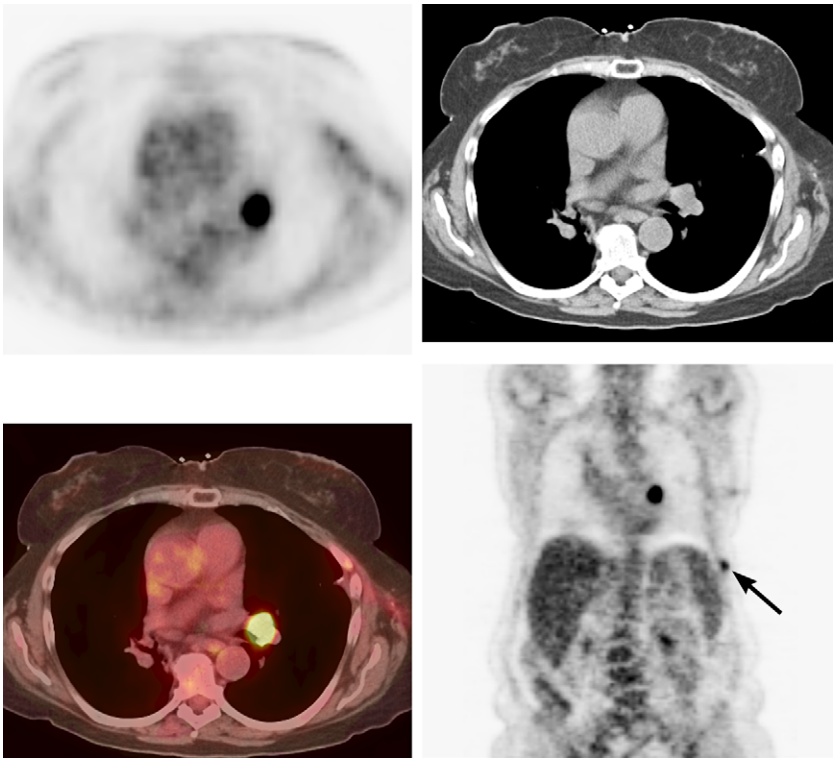

Fig. 21. A 64-year-old woman following chemotherapy and radiation treatment for small cell carcinoma of the right lung developed a left hilar mass, which had increased uptake on an FDG-PET scan consistent with tumor recurrence. Focus of uptake in a left lower rib (*arrow*) is consistent with a new rib metastasis.

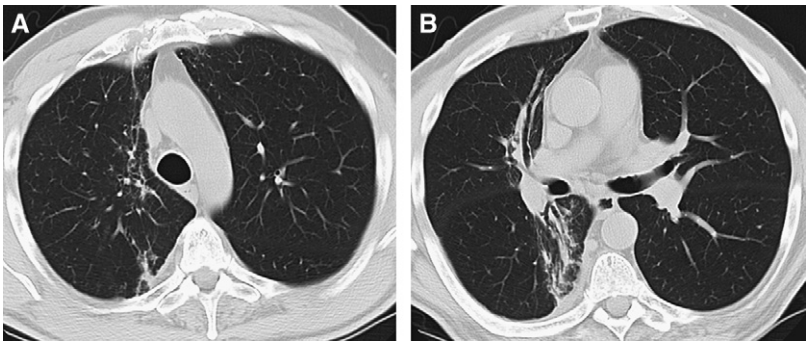

Fig. 22. (*A*) Right paramediastinal fibrotic changes within the radiation port. (*B*) Three years later after treatment with radiation and chemotherapy demonstrates typical postradiation changes of right paramediastinal consolidation and traction bronchiectasis.

and has a well-defined border [88]. Changes occurring within radiation fibrosis that had previously been confirmed to have stabilized could represent recurrent tumor or infection. Recurrent tumor may manifest as a convex bulge in the border of the radiation fibrosis or as a tumor extending into adjacent structures, such as the mediastinum or chest wall. Filling in of the bronchiectasis within the fibrosis is also an indication of recurrent tumor and may occur without any other evidence of recurrence [89]. Infection within the radiation fibrosis can have a similar manifestation, however, with opacities filling the bronchiectasis.

Thermal ablation

The use of imaging-guided thermal ablation, which includes radiofrequency, microwave and cryoablation, is a relatively new application in the treatment of lung neoplasms. It may be used in those patients who may not be surgical candidates or in those patients who are not candidates for conventional radiation (external beam or brachytherapy) and chemotherapy because of coexisting morbidities or of the higher stage of their inoperable tumor that may respond poorly to conventional treatment. On the immediate post–radiofrequency ablation CT, the most common imaging finding is ground glass opacity adjacent to the treated tumor. Between 1 and 3 months after radiofrequency ablation most patients have resolution of this ground-glass opacity and can develop cavitation within the treated tumor (Fig. 23). This is more common if a lesion is located in the inner two thirds of the lung or in close proximity to a segmental bronchus. Pleural thickening and scar formation in the region of pleura traversed by the radiofrequency electrode is often seen. Tumor size can be variable in the first 6 months after radiofrequency ablation. If there is growth of the lesion beyond 6 months it is usually consistent with residual or recurrent disease [90].

Future directions

Despite "better treatment for lung cancer," survival remains poor. Treatment up until recently was focused on surgery, radiation therapy, and chemotherapy. New molecular and genetic understanding of tumor biology has led to research involving targeted therapies. There may be genes that may make certain individuals susceptible to lung cancer. More recently, research has been centered on identifying patients who respond and may have mutated forms of an epidermal growth factor receptor on their tumors and may respond to a drug that targets epidermal growth factor receptors. Drugs that take advantage of those molecular differences and thereby block the activity of molecules necessary for cancer cells to survive are being developed. Such dugs as gefitinib and erlotinib have led to unexpected insight that mutations are found in a substantial number of NSCLCs, particularly in never-smokers with adenocarcinoma. These discoveries promise to alter the approach toward lung cancer [91,92]. Molecular imaging of lung cancer may in the future aid in earlier diagnosis of lung cancer.

Computer-aided diagnosis

The goal of lung cancer screening with CT is to detect small cancers. Computer-aided diagnosis has been reported to be effective in facilitating detection of small pulmonary nodules at CT. Most computer-aided diagnosis schemes that are used to facilitate detection of focal lung lesions are designed and optimized for solid nodules. It has been postulated that a program can be developed by combining the texture and pixel attenuation features of localized ground glass opacity with an artificial neural network classification to facilitate detection of localized ground glass opacity in the lung at CT [93]. Lung cancers missed at low-dose CT screening have been studied with the use of computer-aided diagnosis. Li and coworkers

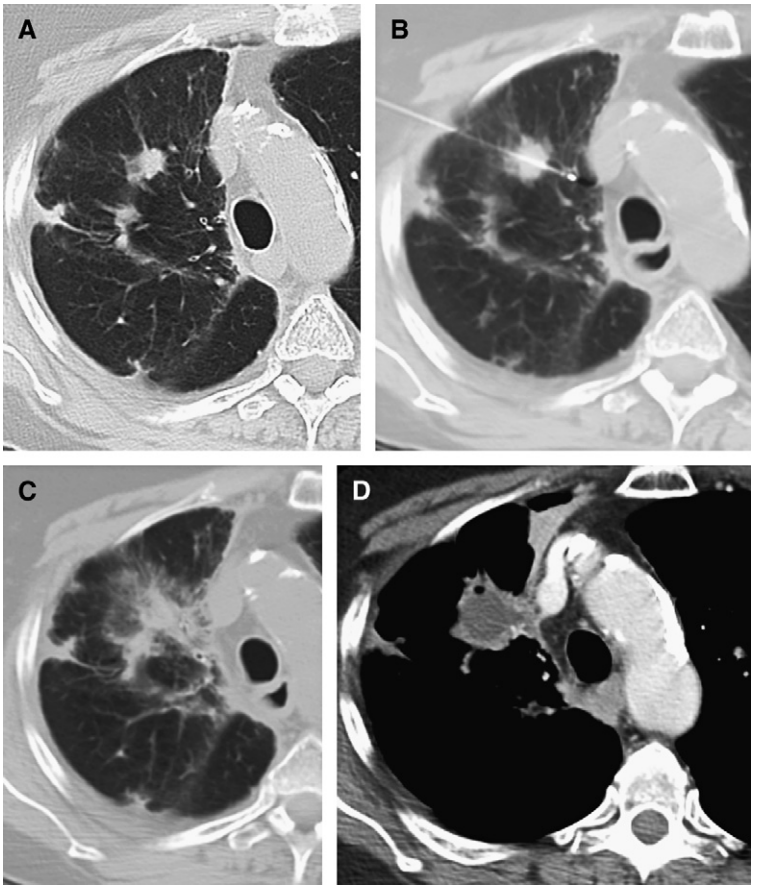

Fig. 23. A 72-year-old man with small cell lung cancer. (*A*) Nodule seen in the right upper lobe. (*B*) Radiofrequency probe within the nodule. (*C*) Nodule immediately postradiofrequency treatment demonstrates peripheral ground glass density representing adequate treatment. (*D*) Three months after treatment lesion is low in density consistent with necrotic tumor.

[94] evaluated whether a computer-aided diagnosis scheme can help radiologists detect missed lesions at least 6 mm. They included lesions with pure ground glass opacity, mixed ground glass opacity, and solid opacity. Lung cancers missed at low-dose CT were very difficult to detect, even in an observer study. The use of computer-aided diagnosis, however, did improve radiologists' performance in the detection of these subtle cancers. Future development may improve the radiologists' performance in the detection of these subtle cancers. Growth of lung nodules in the future will likely be assessed by automated three-dimensional volumetric measurements. This may lead to the more accurate measurement of growth of a nodule and also possibly may help discriminate malignant versus benign disease based on growth patterns and rates.

Summary

Lung cancer prevention by smoking cessation is an important aspect in discussions on lung cancer. Survival for lung cancer is clearly better for earlier-stage tumors, and whereas it sounds reasonable that early detection in an asymptomatic population is beneficial, there are no definitive data that screening for lung cancer leads to a decrease in mortality.

Accurate staging by imaging can have a significant impact on appropriate treatment and surgical options. Staging of newly diagnosed NSCLC is performed according to the International System for Staging Lung Cancer using the TNM system. Because the extent of the disease determines whether the patient is treated by means of surgical resection, radiation therapy, chemotherapy, or a combination of these modalities, radiologic imaging plays an important role in the staging evaluation [90]. SCLC is not staged according to the TNM system but rather as limited-stage disease or extensive-stage disease. Accurate staging by imaging of SCLC is also extremely important. Staging by combined modalities, such as CT and FDG-PET, has been shown to be more accurate than CT or PET alone.

Radiologists need to be aware of entire spectrum of manifestations of lung cancer. Familiarity with the different histologic subtypes of lung cancer and the typical and atypical appearances of lung cancer is vital. Radiologists serve a critical role in the diagnosis, staging, and follow-up of patients with NSCLC. This includes suggesting the

possibility of synchronous and metachronous lung cancers because it has serious implications in the staging and prognosis of these patients.

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