The Radiologic Appearance of Lung Cancer

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A solitary pulmonary nodule (SPN) is the most common radiographic presentation of lung cancer. The imaging characteristics of solitary pulmonary nodules are described and illustrated. The appearance and implications of extension of lung cancer to the pleura are explored. Finally, the contribution of various thoracic imaging modalities to the diagnosis and staging of lung cancer are discussed briefly.[ONCOLOGY 11(9):1387-1402]

Introduction

Over 95% of all primary lung tumors are bronchogenic carcinomas. These are subdivided into four main cell types: squamous cell carcinoma, small-cell carcinoma, adenocarcinoma, and large-cell carcinoma. The relative incidence of these four cell types has changed over the last 30 years, with the number of squamous cell tumors decreasing and the number of adenocarcinomas increasing. This reflects a change in the biology of lung cancer.[1]

Although none of the four main cell types is exclusively central or peripheral in location, the majority of small-cell lung cancers and squamous cell carcinomas are centrally located. This is in contrast to most adenocarcinomas and large-cell tumors, which tend to be peripheral. Among the more common central tumors, squamous cell carcinoma is more frequently associated with bronchial obstruction, a hilar mass, and cavitation. Small-cell carcinoma is often characterized by extensive, bulky mediastinal lymphadenopathy. Small-cell carcinoma is less likely than squamous cell carcinoma to produce bronchial obstruction.[2]

The Solitary Pulmonary Nodule

FIGURE 1

A solitary pulmonary nodule (SPN) is a single round or oval opacity in the pulmonary parenchyma measuring < 3 cm in diameter and completely surrounded by pleura (Figure 1). The reported incidence of malignancy in a solitary pulmonary nodule varies from 3% to 6% in mass surveys of the general population to 30% to 60% of resected solitary pulmonary nodules.[3] The radiologic work-up of the solitary pulmonary nodule is pursued to facilitate the resection of potentially curable lung cancers and to minimize the resection of benign nodules. Neoplasm can often be strongly suspected or excluded based on the radiologic characteristics of the solitary pulmonary nodule.

Size/Growth Rate

As a general rule, SPNs > 3 cm in diameter are more likely to be malignant. The growth rate of a solitary pulmonary nodule is quantitated by measuring its doubling time, ie, the time it takes to double in volume.[4] The detection of a solitary pulmonary nodule on chest films depends on its size, density, and edge characteristics.
Nodules must be at least 9 mm in diameter before they can be reliably detected on chest plain films. Work done by Geddes indicates that the natural history of a lung malignancy is to double its volume 40 times before death ensues. On reaching the reliably detectable size of 9 mm, a nodule has already undergone 30 doublings. A single doubling of the volume of an SPN produces a relatively small increase in its transverse diameter. Doubling times of between 7 and 465 days are strongly suggestive of malignancy, whereas doubling times that are either shorter or longer than this suggest a benign etiology.

According to Gurney, a 9-mm SPN with a doubling time of 100 days will measure 1.1 cm at 3 months and 1.4 cm at 6 months. Therefore, should the physician opt for radiographic surveillance following discovery of an SPN, accurate measurement is of the utmost importance. Follow-up radiographs should always be compared to the initial radiograph showing the solitary pulmonary nodule. Discovery of a solitary pulmonary nodule on chest radiographs should prompt every effort to obtain more remote chest films for comparison. A retrospective analysis may yield valuable diagnostic information. The absence of growth over a 2-year period is the most reliable indicator of benignity.

On rare occasions (1 case per 750,000), a bronchogenic malignancy may show spontaneous regression. More frequently, lung cancers may exhibit a temporary reduction in size followed by a resumption of growth. This reduction in size suggests a resolving inflammatory process. It is thought to be due to partial interruption of the tumor's blood supply, resulting in infarction and necrosis of a portion of the mass. The ensuing fibrosis and retraction may result in an overall decrease in the volume of the mass.

Webb notes that, occasionally, as a pulmonary nodule grows, it may become less well defined, and thus, appear smaller on chest films. Cross-sectional CT imaging will provide clarification if the margins of the opacity are unclear on conventional chest films.

Density

Siegelman et al, Proto and Thomas, and Zerhouni et al have extensively investigated nodule densitometry using CT. Compared with conventional chest films, CT is 10 to 20 times more sensitive to differences in density. By using this imaging modality, a number of nodules judged to be noncalcified by conventional radiography can be classified as benign on the basis of their attenuation coefficients.

Huston and Muhm reported that a CT nodule densitometric study (phantom reference) combined with conventional trispiral tomography had a 77% accuracy in the diagnosis of solitary pulmonary nodules. Despite the effectiveness of this technique, almost one-fourth of noncalcified solitary pulmonary nodules remain indeterminate. A number of false-negative densitometry studies have also been reported.

Calcification

Calcification

Calcification Engulfed by a Neoplasm
The distribution of calcification within the SPN is of the utmost diagnostic importance. The presence of a thin layer or layers of calcium in a lamellar pattern is indicative of a granuloma, usually a histoplasmoma (Figure 2). Central calcification may also be seen in granulomas. Caution must be exercised when assessing solitary pulmonary nodules for the presence of central calcification, as, occasionally, a growing lung cancer may engulf a calcified granuloma or a scar carcinoma may arise within a preexisting calcified granuloma (Figure 3).

"Popcorn" calcification is associated with hamartomas. These benign lesions arise from small rests of tissue not normally found in the lung. The presence of cartilaginous elements gives rise to the popcorn calcification.

Calcification may also be seen in both primary and metastatic tumors to the lungs. Specimen radiography performed by O'Keefe et al.[17] demonstrated the presence of calcification in 14% of resected primary lung tumors. Several individual case reports have described malignant pulmonary nodules with high CT numbers and central calcification.[18-20]

**Shape/Margins**

![Figure 4](image)

**Pleural Tag**

![Figure 5](image)

**Lobulation**

Although the interface between the SPN and the normal surrounding lung cannot be used as an absolute indicator of the nature of the lesion, it can provide useful information. A smooth peripheral margin on CT is more frequently associated with benign lesions than with malignant tumors. The converse is also true.

Zwirewich et al.[21] assessed a total of 96 solitary pulmonary nodules (85 malignant, 11 benign) by CT. Spiculation, defined as linear strands extending from the nodule margin into the lung parenchyma but not extending to the pleural margin, was present in approximately 90% of primary carcinomas. It was also seen in 5 of the 11 benign lesions. A pleural tag was defined as a linear area of high attenuation surrounded by aerated lung, originating from the edge of the mass and extending peripherally to contact the pleural surface (Figure 4). Pleural tags were seen in 58% of malignant lesions and 27% of benign lesions. Both spiculation and pleural tags correlated pathologically with a desmoplastic response.

Lobulation (Figure 5) was predominantly associated with malignancy. This finding correlated with nodular excrescences of the tumor at its leading edge.

**Cavitation**

Cavitation is seen in 2% to 16% of lung cancers.[22,23] Usually, the cavity wall is thick (> 5 mm at its thickest portion) and may demonstrate a nodular internal margin due to focal tumor excrescences. Occasionally, a thin-walled cavity may be associated with malignancy.
Cavitary Lesion

Woodring et al[24] evaluated the wall thickness of cavitary SPNs and found that 94% (29/31) of cavities with a wall thickness ≤ 4 mm were benign. The two remaining thin-walled cavities had a maximum wall thickness of 2 mm and were malignancies. In the same series, the authors found that 95% of cavitary solitary pulmonary nodules with a wall thickness > 15 mm were malignant (Figure 6). Lesions with a wall thickness between 5 and 15 mm were almost equally divided between benign and malignant. The authors also noted that a smooth inner wall to the cavity was more commonly observed in lesions of benign etiology. A cavitary solitary pulmonary nodule should always raise the question of malignancy, and, in the absence of a definitive diagnosis, a diagnostic procedure or close radiographic follow-up is required.

Contrast Enhancement

In the 1980s, the radiologic assessment of the solitary pulmonary nodule focused primarily on CT densitometry. In the 1990s, two techniques that focus on vascularity, pathophysiologic features, and pharmacodynamics have been applied to the diagnosis of the solitary pulmonary nodule.

Contrast-Enhanced Thin-Slice CT—The first of these techniques is based on differential nodule enhancement with IV contrast material, as measured with thin-slice CT. It relies on both qualitative and quantitative differences in the blood supply of benign vs malignant lung lesions. Nodule enhancement following the administration of IV contrast material depends on the amount of contrast that enters the extravascular space of the nodule and the vascularity of the nodule.[25,26] Swensen and colleagues[27] found a 20-Hounsfield-unit increase in 24 of 30 solitary pulmonary nodules subsequent to the IV administration of 100 mL of contrast material. Of the 24 nodules showing contrast enhancement, 23 were malignant. This work suggests that assessment of CT enhancement of the solitary pulmonary nodule may be useful in gauging the likelihood of malignancy.

FDG-PET—The second technique currently being evaluated to differentiate between benign and malignant SPNs is PET scanning with 2$^{[F-18]}$-fluoro-2-deoxy-d-glucose (FDG). This technique is based on the increased glucose metabolism characteristic of tumor cells.[28] Nonmalignant entities fail to show glucose hypermetabolism. Gupta et al[29] used FDG-PET imaging to evaluate 30 patients with solitary noncalcified pulmonary nodules. Thirteen biopsy-proven malignant nodules demonstrated increased FDG uptake, whereas seven benign solitary pulmonary nodules showed no increased FDG uptake. These data and work by Patz et al[30] suggest that FDG-PET scanning can accurately distinguish benign from malignant focal lung lesions.

Influence of Cell Type on Radiographic Appearance

A 1978 review of 10,000 cases reported that only 2% of lung tumors had more than one cellular component.[31] Adelstein and colleagues[32] subsequently found that 10% of small-cell lung cancers had non-small-cell components. More recently, in a blinded, randomized study, Roggli and colleagues[33] found that 45 of 100 lung cancers had more than one major histologic cell type present on extensive sampling. In addition to different cellular elements within the same tumor, multiple synchronous lung primaries of the same or different cell types are seen in < 3% of lung cancers.[34] Despite this, certain radiographic appearances are suggestive of specific cell types, as will be detailed in the following sections.

Adenocarcinoma

As mentioned above, the incidence of adenocarcinoma has changed dramatically over the last 30 years. In the 1960s, adenocarcinoma accounted for only 4% to 8% of lung carcinomas.[35,36] More recent work indicates an incidence of up to 30%.[37] The most common radiographic presentation of this tumor is a solitary peripheral/subpleural
pulmonary mass (Figure 1). Almost half of these masses will have hilar or mediastinal involvement at the time of diagnosis.

Adenocarcinoma is also the most common cell type producing the superior sulcus tumor, sometimes referred to as Pancoast tumor (Figure 7). This tumor has a propensity for extension through the visceral and parietal pleural layers into the chest wall. Superior sulcus tumors are often associated with neck or shoulder pain, Horner's syndrome (superior cervical ganglion involvement), wasting of the lumbrical muscles (brachial plexopathy), and bone destruction. Adenocarcinoma may be categorized into four subtypes, depending on the histologic pattern. These include the acinar, papillary, solid, and bronchoalveolar cellular subtypes. The degree of glandular or papillary formation dictates grading of the tumor as well-differentiated, moderately differentiated, or poorly differentiated carcinoma.

Bronchoalveolar Subtype—The bronchoalveolar subtype of adenocarcinoma accounts for up to 6% of primary lung cancers and is increasing in incidence. This subtype demonstrates a broad spectrum of radiographic findings,[38] presenting as a solitary nodule in 43% of cases (Figure 8), multicentric or diffuse disease in 27% (Figure 9), or diffuse consolidation in 30% (Figure 10). The term "bronchoalveolar cell carcinoma" was coined by Liebow[39] in 1960 due to controversy.
over the true cell of origin. The name derives from recognition of two cell types, a columnar type similar to bronchial cells and a cuboidal type reminiscent of type 2 pneumocytes. Bronchoalveolar cell carcinoma is the most histologically distinct type of adenocarcinoma, and its unique radiographic characteristics relate to its growth pattern. It uses the interior alveolar air spaces as a stroma upon which to grow. This results in the radiographic appearance of air space disease (mimicking pneumonia).

Some metastatic lesions, in particular, adenocarcinoma of the pancreas, biliary tree, and colon, may produce a similar appearance when disseminated to the lungs. Like most adenocarcinomas, bronchoalveolar cell carcinoma is found in the lung periphery, and the desmoplastic response it produces will frequently give rise to a spiculated margin and a pleural tag (Figure 9B). Bronchoalveolar cell carcinoma commonly develops in an area of lung fibrosis. The nodular form of the disease tends to be indolent, often without mediastinal involvement at diagnosis. Recurrence following surgical removal is uncommon. In contrast, the diffuse form is characterized by inexorable progression.

Kuhlman et al[40] have reported on the CT findings of bronchoalveolar cell carcinoma; these include a peripheral location, central areas of lucency (pseudocavitation), irregular margins forming a star-like pattern, pleural tags, and heterogeneous attenuation (Figure 9). Although these CT findings are not highly specific, their presence is considered to be sufficiently characteristic to suggest the diagnosis, as they are encountered considerably less frequently in other subtypes of adenocarcinoma and in large-cell carcinoma.FIGURE 11

The propensity of the diffuse infiltrative variety of bronchoalveolar cell carcinoma to grow along the alveolar walls accounts for the "CT angiogram sign" (Figure 11). This sign refers to the identification of normal enhancing pulmonary vasculature within the tumor subsequent to the IV administration of contrast material. The CT angiogram sign was originally thought to be unique to bronchoalveolar cell carcinoma[41] but has subsequently been reported in cases of lymphoma, pneumococcal and tuberculous pneumonias, and other conditions.[42]

Other unusual radiographic manifestations of bronchoalveolar cell carcinoma include expansile pulmonary consolidation without air bronchograms, lobar atelectasis, and single or multiple cavitary lesions. The differential diagnosis for multiple cavitary nodules—the so-called "Cheerios in the chest" (Figure 12)[43,44]—includes metastatic adenocarcinoma, metastatic squamous cell carcinoma, and metastatic sarcoma, as well as several infectious and inflammatory etiologies. Cavitation is unusual in bronchoalveolar cell carcinoma due to the relative lack of necrosis and the tendency for preservation of the normal pulmonary architecture.

Squamous Cell Carcinomas

Approximately two-thirds of squamous cell carcinomas of the lung are located centrally. Since squamous cell lung cancers arise in the cells lining the main stem, or the lobar or segmental bronchi, they are frequently associated with bronchial obstruction.FIGURE 13
Squamous cell tumors may remain within the bronchial lumen or grow into the peribronchial tissues. The intraluminal tumors frequently produce complete lobar atelectasis (Figure 13). In such cases, the resulting volume loss produces striking radiographic features, including ipsilateral mediastinal shift and ipsilateral hemidiaphragmatic elevation.

Alternatively, an obstructive pneumonitis distal to the mass may result in some preservation of volume and a wedge-shaped peripheral opacity, the apex of which converges on the hilum (Figure 14). The presence of a central mass may be evident on the chest radiograph if the mass extends to the peribronchial tissues, producing displacement of the fissure. This reversed "s"-shaped curve seen on the frontal chest film (Figure 14A) in right upper lobe collapse is a well-recognized sign of carcinoma.[45]

Approximately one-third of squamous cell carcinomas are peripheral, arising in smaller bronchi. Occasionally, they may arise in association with a scar (Figure 3). Squamous cell carcinomas can metastasize widely; bone, liver, and the adrenal glands are the most common sites of hematogenous dissemination. Squamous cell tumors also directly invade the mediastinum, compromising the aerodigestive tract and other vital structures (Figure 15).

**Small-Cell Carcinoma**

Small-cell carcinomas are highly malignant, neuroendocrine neoplasms that have usually metastasized at the time of diagnosis. The vast majority (90%) of these tumors are central, and they are frequently associated with bulky mediastinal lymphadenopathy (Figure 16). The remaining 10%
of small-cell carcinomas are peripheral and may present as a solitary pulmonary nodule. This has therapeutic implications: Although surgery is not recommended for most patients with small-cell lung cancer, it is potentially curable in patients who present with a solitary pulmonary nodule.

**Large-Cell Undifferentiated Carcinoma**

Large-cell undifferentiated tumors account for approximately 10% of lung cancers. By definition, they lack the features of glandular, squamous, or small-cell differentiation. Electron microscopic analysis, however, reveals features of adenocarcinoma in 80% of cases and features of other cell types in the remaining 20%.[46] Imaging frequently reveals a large, bulky, peripheral tumor. Necrosis is a common feature.

**Pleural Extension of Bronchogenic Carcinoma**

Invasion of the visceral pleura by a lung cancer indicates a T2 lesion. The cancer becomes a T3 lesion when it involves the parietal or mediastinal pleura. Both T2 and T3 lesions are amenable to surgical resection, assuming favorable nodal (N2 or better) and distant metastatic (M0) status. A malignant pleural effusion indicates a stage T4 lung carcinoma, the presence of which precludes curative surgery. Lung cancer is the most common cause of a malignant pleural effusion. A nonmalignant (benign reactive) pleural effusion has no staging significance. Although there are no specific radiographic findings to distinguish benign from malignant effusions, CT may demonstrate intrapleural masses or pleural nodularity, both of which strongly suggest metastatic disease (Figure 17).

The presence of a pneumothorax may provide useful information for the thoracic surgeon. Complete retraction of the lung from the inner chest wall indicates that local tumor extension is limited by the visceral pleura (Figure 18A). If there is only partial retraction of the lung, and the tumor remains adherent to the inner chest wall, the parietal pleura is involved (Figure 18B). Tumor recurrence following pneumonectomy may be heralded by increasing fluid accumulation in the pneumonectomy space (Figure 19A). Radiographically, this produces inferi or displacement of the ipsilateral hemidiaphragm and movement of the mediastinum back toward the remaining lung (Figure 19B). In these cases, CT may show enlarging pleural masses and/or pleural irregularity (Figure 19C).

**Imaging Modalities in Lung Cancer**

FIGURE 20
Conventional chest radiographs continue to be the initial examination in patients suspected of having lung cancer. Computed tomography is useful in the confirmation and characterization of pulmonary nodules. The transaxial anatomic display allows for the identification of subtle abnormalities not appreciated on chest films. In the presence of a normal chest x-ray, CT remains the study of choice in patients who present with hemoptysis, vocal chord paralysis, or malignant sputum cytology (Figure 20). Fluorodeoxyglucose PET imaging shows promise in differentiating benign from malignant nodules, staging the mediastinum, and detecting recurrent disease following resection.[47] Table 1 lists the features most frequently associated with malignancy. Clinicians evaluating patients with suspected lung cancer need to be vigilant and remember the words of Pasteur, "In the field of observation, chance favors the prepared mind."

**Features Commonly Associated With Solitary Pulmonary Nodules**

Magnetic resonance imaging of the chest has limited application in lung cancer. It remains the best modality for evaluating the brachial plexus. This modality is also useful in the assessment of superior sulcus lung tumors, as it facilitates imaging in the coronal plane, thus permitting better definition of the extent of disease. Magnetic resonance imaging has little application in the pulmonary parenchyma due to respiratory motion artifact (prolonged data acquisition time) and the relative absence of protons in this environment.

**Conclusions**

In the assessment of the solitary pulmonary nodule, the importance of comparing current chest radiographs with previously obtained chest films cannot be overstated. Table 1 lists the features most frequently associated with malignancy. Clinicians evaluating patients with suspected lung cancer need to be vigilant and remember the words of Pasteur, "In the field of observation, chance favors the prepared mind."

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