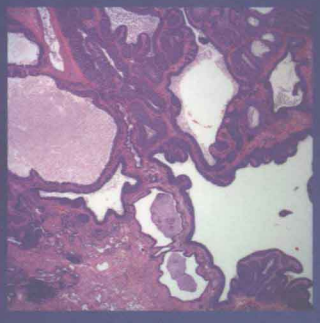
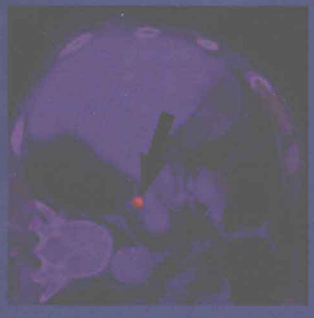
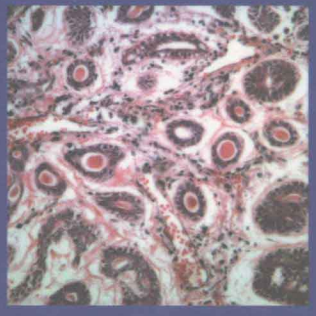
MORAN AND SUSTER

Tumors and Tumor-Like Conditions of the Lung and Pleura







SAUNDERS
ELSEVIER

Tumors and Tumor-like Conditions of the Lung and Pleura

CESAR A. MORAN, MD

Professor and Deputy Chair
Director of Thoracic Pathology
Department of Pathology
The University of Texas
M. D. Anderson Cancer Center
Houston, Texas

SAUL SUSTER, MD

Professor and Chairman
Department of Pathology
Medical College of Wisconsin
Milwaukee, Wisconsin

SAUNDERS
ELSEVIER

SAUNDERS
ELSEVIER

1600 John F. Kennedy Blvd.
Ste 1800
Philadelphia, PA 19103-2899

TUMORS AND TUMOR-LIKE CONDITIONS OF THE LUNG AND PLEURA

ISBN: 978-1-4160-3624-1

Notices

Knowledge and best practice in this field are constantly changing. As new research and experience broaden our understanding, changes in research methods, professional practices, or medical treatment may become necessary.

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds, or experiments described herein. In using such information or methods they should be mindful of their own safety and the safety of others, including parties for whom they have a professional responsibility.

With respect to any drug or pharmaceutical products identified, readers are advised to check the most current information provided (i) on procedures featured or (ii) by the manufacturer of each product to be administered, to verify the recommended dose or formula, the method and duration of administration, and contraindications. It is the responsibility of practitioners, relying on their own experience and knowledge of their patients, to make diagnoses, to determine dosages and the best treatment for each individual patient, and to take all appropriate safety precautions.

To the fullest extent of the law, neither the Publisher nor the authors or editors, assume any liability for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

Library of Congress Cataloging-in-Publication Data
Moran, Cesar.
Tumors and tumor-like conditions of the lung and pleura / Cesar A. Moran, Saul Suster.—1st ed.
p. ; cm.
Includes bibliographical references.
ISBN 978-1-4160-3624-1
1. Lungs—Tumors. 2. Lungs—Pleura. I. Suster, Saul. II. Title.
[DNLM: 1. Lung Neoplasms—diagnosis. 2. Diagnostic Imaging—methods. 3. Pleural Neoplasms—diagnosis. WF 658 M829t 2010]
RC280.L8M625 2010
616.99'424—dc22

2010001329

Publishing Director: Bill Schmitt
Developmental Editor: Katie DeFrancesco
Project Manager: David Saltzberg
Design Direction: Lou Forgione

Printed in the United States

Last digit is the print number: 9 8 7 6 5 4 3 2 1

Tumors and Tumor-like Conditions of the Lung and Pleura

To our families
Susan, Jenny, Elisa Jean, Dana, Kate, and David
for their continuous support

CONTRIBUTORS

EDITH M. MAROM, MD
Professor of Diagnostic Radiology
Department of Diagnostic Imaging
The University of Texas
M. D. Anderson Cancer Center
Houston, Texas
Chapter 1: Imaging Tumors of the Lung and Pleura

DAVID J. STEWART, MD
Professor and Deputy Chair
Department of Thoracic and Head and Neck Oncology
The University of Texas
M. D. Anderson Cancer Center
Houston, Texas
Chapter 14: Clinical Management of Lung Cancer

GARRETT L. WALSH, MD
Professor of Surgery
Department of Thoracic Surgery
The University of Texas
M. D. Anderson Cancer Center
Houston, Texas
Chapter 2: Staging of Thoracic Malignancies: A Surgeon's Perspective

PREFACE

This textbook gives surgical pathologists a practical approach to the diagnosis of the different tumors and tumor-like conditions that may affect the lung and pleura. The book has been arranged and subdivided based on the different families of tumors that may seed those structures. When important, historical background is provided so that the surgical pathologist becomes more familiar with the different terminologies used over the years. Current concepts and definitions are also presented so that their importance and the difficulties they may pose to the surgical pathologist are apparent. The text focuses on the morphologic approach to the different tumoral conditions and the use of ancillary methods to corroborate the morphologic diagnosis. When appropriate, important advanced studies, such as molecular pathology information, are also provided.

Additionally, the text provides important radiologic, surgical, and oncologic information that must be considered when dealing with the different conditions presented. In presenting these components, which are essential to understanding the pathology of the lung and pleura, we are indebted to Edith Marom, MD, for her contribution on diagnostic imaging; Garrett L. Walsh, MD, for his contribution on surgical staging, and to David J. Stewart, MD, for his contribution on the clinical management of lung cancer. They provide important information that is of great benefit to all involved in the diagnosis and treatment of patients with lung and/or pleural lesions.

This textbook will be useful not only to surgical pathologists but also to oncologists, surgeons, and radiologists who want to get better acquainted with the diverse histologies that may be present in the lung and pleura. Additionally, we hope this text enhances communication among all the different specialties involved in the treatment of patients with tumors of the lung and pleura.

Cesar A. Moran, MD
Saul Suster, MD

CONTENTS

1

Imaging Tumors of the Lung and Pleura

Edith M. Marom

In the past few decades, the use of computers has revolutionized imaging, with the introduction of technologies such as computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography, positron emission tomography (PET), and, more recently, PET-CT, which integrates anatomic (morphologic) and physiologic aspects of imaging. With the ever-greater subspecialization of the different areas of practice within medical oncology—surgical oncology, radiation oncology, and diagnostic radiology—and the expanding use of picture archiving systems, radiologist and clinician may encounter each other only rarely, if at all. Optimal patient outcomes, however, require careful planning of imaging for diagnosis, staging, and follow-up, best achieved through direct communication between the clinician and the radiologist. This chapter presents a general overview of lung and pleural tumor imaging, with an emphasis on the strengths and weaknesses of specific techniques in evaluating different tumor types, to help in selection of the ideal imaging modality for each patient.

PRIMARY MALIGNANT LUNG TUMORS

Screening

Despite new diagnostic techniques, the overall 5-year survival rate for patients with lung cancer, the leading cause of cancer death, remains approximately 15%, and most patients still present with advanced disease.[1] This high death rate is presumed to reflect a combination of difficulty in detecting early-stage disease and lack of significant curative treatment. Abrogating cigarette smoking would be highly effective in reducing the prevalence of lung cancer but would not abolish it altogether, because effecting lifestyle change in an entire population is very difficult; moreover, previous smokers would still be at risk for lung cancer. Detection of the disease at the stage at which cure or control is possible is the theoretical rationale for screening for lung cancer.

Because tumors of the lungs are encased by the rib cage, early diagnosis by physical examination is not possible. Chest radiographs are ideal for demonstrating pulmonary abnormalities that differ significantly from the surrounding structures in density. The lungs contain air, the density of which differs significantly from the soft tissue density of tumor. Early screening studies for lung cancer, therefore, used chest radiography, which fulfills the criteria for a suitable screening test by being simple to perform, inexpensive, painless, and relatively safe, with relatively limited radiation exposure.[2] Nonrandomized, uncontrolled screening studies in the 1950s[3–6] gave way to nonrandomized, controlled trials,[7,8] which showed that persons in the screened group were more likely to have lung cancer detected in the early stages, were more likely to have resectable disease, and enjoyed better survival rates. No clear reduction in lung cancer–associated mortality, however, was documented.

Although survival (number of persons alive after diagnosis of the disease relative to the total number of persons diagnosed with the disease) is commonly reported in screening trials, this statistic can be misleading because it is subject to lead time, study duration, and overdiagnosis biases. An impact on mortality rather than survival is therefore sought,

to validate potential screening methods.[9] Accordingly, in the 1970s, four major randomized, controlled trials looked at approximately 37,000 male smokers[10–13] and found that chest radiograph screening yielded no change in mortality. In the screened cohort, patients demonstrated higher 5-year survival rates but no reduction in the number of advanced cancers (i.e., no stage shift). A follow-up study more than 20 years after the Mayo Lung Project confirmed no significant difference in lung cancer mortality.[14] Because of its failure to reduce lung cancer mortality, chest radiograph screening for lung cancer was not recommended.

In the late 1990s, the issue of screening began to reemerge because of the ongoing debate about the validity of the findings on chest radiograph studies and in light of revolutionary developments in CT that enabled detection of pulmonary nodules smaller than 1 cm, in one breathhold, with a reduced radiation dose to the patient—low-dose CT (LDCT). The studies of lung cancer screening with CT conducted so far have been single-arm studies without a comparative group, or 1-year feasibility randomized, controlled trials.[15] These studies showed that chest CT scans have greater sensitivity than chest radiographs for the detection of pulmonary nodules (Fig. 1-1). Noncalcified nodules could be detected in as many as two thirds of the persons screened, all of whom underwent follow-up or workup to exclude malignancy, but 99% of these nodules were benign.[16] Nodules that remained suspect for lung cancer after workup or follow-up required resection. Nevertheless, more than one third of the nodules resected were associated with benign conditions.[16,17]

Despite the published 10-year survival rate of 88% for patients with stage I disease,[18] and the increased likelihood that cancers detected by LDCT would be operable, LDCT yielded no decreases in the number of advanced lung cancers detected or in the number of deaths from lung cancers compared with predictive historical models of an unscreened population.[19]

More recently, the National Lung Screening Trial (NLST) was launched to directly assess whether screening with LDCT is effective for early detection of lung cancer. NLST compared the effectiveness of two screening tests, LDCT and chest radiograph, on net lung cancer–specific mortality in persons who were at high risk for the development of the disease. Between September 2002 and April 2004, the trial accrued 34,614 participants, who underwent annual imaging. The trial involves follow-up questionnaires administered over 6 to 8 years and thus is still monitoring these patients; prevalence data have not yet been published. In the meantime, patients are encouraged to wait for the results of the NLST, or to be screened as part of a randomized, controlled trial, because it has not been shown that screening with LDCT is effective in reducing mortality.

Early Detection: Solitary Pulmonary Nodule

A solitary pulmonary nodule (SPN), defined as a nodule less than 3 cm in greatest dimension surrounded by lung (see Fig. 1-1), is a common incidental radiologic finding. Its incidence has increased with the growing use of chest CT over the past few decades and in screening studies in asymptomatic populations. Because of concern about lung cancer, further evaluation of such nodules often is suggested. The goal of imaging is to differentiate between nodules that are benign and those that are malignant, so that patients who require surgery are correctly identified; the mean postoperative mortality rate after lung cancer resection in the United States is 5%.[20]

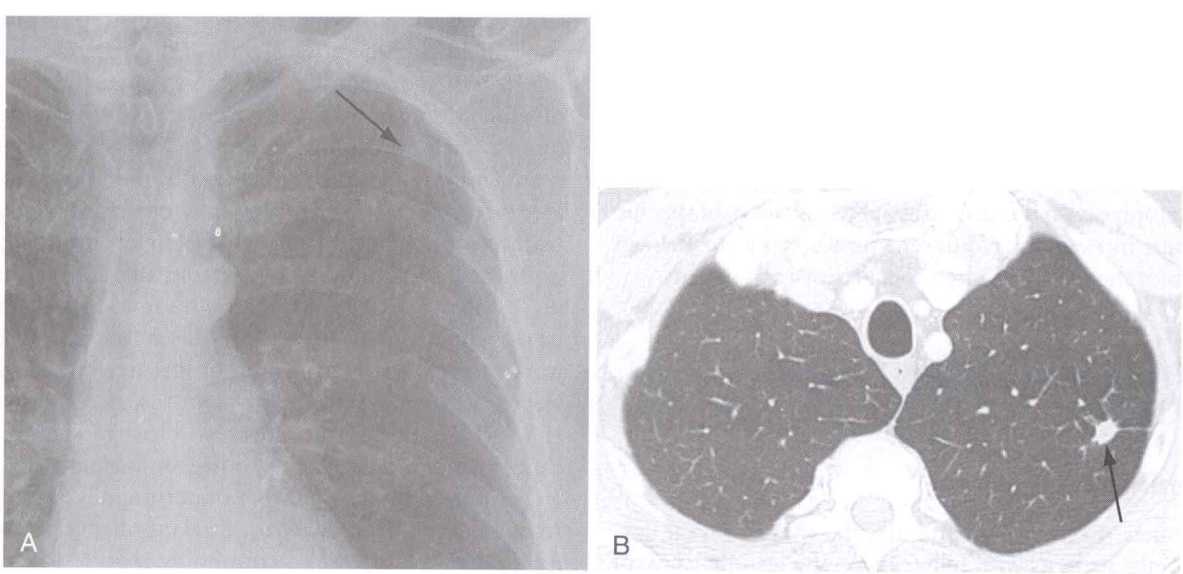


Figure 1-1 **A**, Incidental nodule in a 67-year-old man was discovered on a routine chest radiograph. The small nodule is barely visualized because it is superimposed on ribs *(arrow)*. **B**, Contrast-enhanced chest CT scan shows a spiculated 1.3-cm nodule *(arrow)*. Transthoracic needle biopsy revealed respiratory epithelial cells and histiocytes in a background of extensive necrosis but no malignancy. The nodule nearly completely disappeared without therapy over a period of 3 years, confirming the benign diagnosis.

Chest Radiography

Evaluation of the SPN entails several steps. When a nodule is large enough to be seen on a chest radiograph, this study will be the first step in the investigation. Chest radiography is inexpensive, delivers very little radiation to the patient, and provides an image that often can be compared easily with preexisting radiographs. The initial determination is whether the nodule is indeed within the lung, because mimics of pulmonary nodules are numerous, such as rib fracture, bone island, skin lesion, or overlapping normal structures (see Fig. 1-1). Review of old films or old CT scans is the most cost-efficient way to assess an SPN. If no old images are available, shallow oblique images, fluoroscopy, or chest CT scan can be used.

Once the nodule has been confirmed to be within the lung, it should be assessed for features suggesting benign origin. The ability of chest radiography to discern between malignant and benign pulmonary nodules remains limited, however. Numerous studies in the 1940s and 1950s attempted to address this issue as the use of chest radiography increased exponentially. Before the advent of CT, positive preoperative diagnosis of asymptomatic SPN was rare; early exploratory thoracotomy was strongly urged for patients with these nodules.[21,22] Although larger nodules are more likely to be malignant, no size criterion allows exclusion of malignancy.[23] Two methods of distinguishing benign from malignant nodules were developed, both of which are in use today: documentation of stability of the nodule over a period of 2 years and identification of benign-appearing calcifications. Both methods are problematic: Stability was not found by robust and scientifically valid evidence to be a reliable criterion; the original data from the 1950s suggested a positive predictive value of 65% for benignity.[24] Identifying calcifications on radiographs as benign was shown by a later study to be a subjective judgment.[25]

Computed Tomography

In the absence of a chest radiograph from at least 2 years previously to provide a baseline for judging SPN stability, patients are referred for chest CT scan. CT is superior to chest radiography in establishing the margins and, more important, the internal characteristics of the pulmonary nodule. Spiculated margins are highly suggestive of, although not pathognomonic for, a malignant nodule (Fig. 1-2). This feature can reflect the presence of fibrosis in surrounding lung parenchyma, direct infiltration of the cancer into adjacent lung parenchyma, or localized lymphangitic spread.[26,27] In a study looking at 634 nodules, 50 of 53 (94%) that exhibited diffuse spiculation and 134 of 165 (81%) that showed focal spiculation were primary lung carcinomas.[28] On the other hand, 8 of the 66 (12%) smoothly marginated, nonlobulated nodules were primary lung cancer, 6 (1%) represented a solitary metastasis, and 52 (87%) were benign. Lobulation (Fig. 1-3) implies uneven growth, which often is associated with malignancy,[23] but it is not useful in distinguishing benign from malignant nodules. Of 350 smoothly marginated lobulated nodules, 91 (26%) were primary lung cancer, 57 (16%) were metastatic disease, and 202 (58%) were benign.[28]

With its ability to evaluate the internal characteristics of the SPN, CT revolutionized investigation of these findings. With its improved contrast resolution, elimination

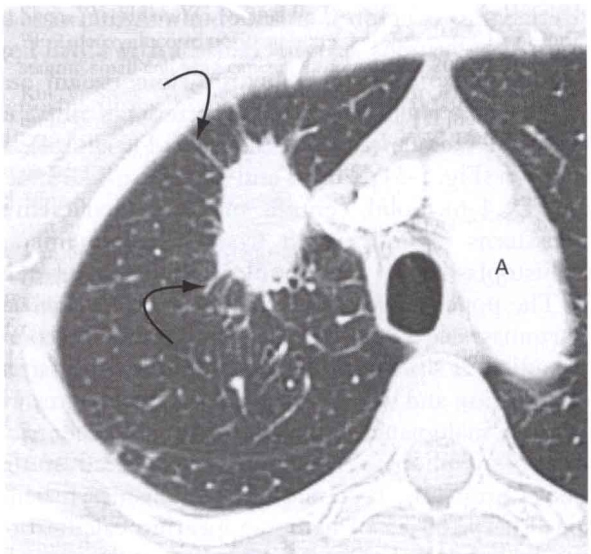


Figure 1-2 Adenocarcinoma with spiculations in a 61-year-old woman. Contrast-enhanced chest CT scan at the level of the transverse aorta (A) demonstrates a 2.8-cm nodule with spiculations *(arrows)*.

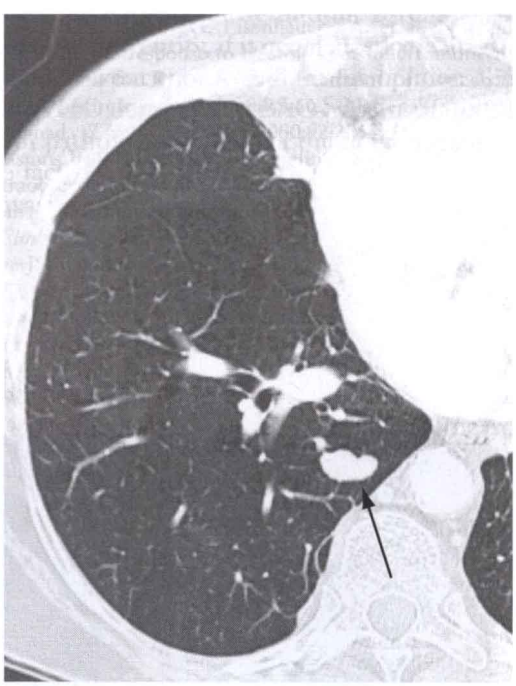


Figure 1-3 Adenocarcinoma with lobulation in a 79-year-old woman. Contrast-enhanced chest CT scan shows a lobulated 1.9 × 1-cm nodule *(arrow)*.

of overlapping structures, and slicing into thin sections, obvious calcifications can be visualized readily. For a nodule to be considered benign, obvious calcifications must be of the benign type. Characteristics of benign calcification include central, diffuse solid (Fig. 1-4), and lamination (Fig. 1-5) patterns and a popcorn-like appearance (Fig. 1-6). Solid, central, and laminated calcification patterns typically result from a remote infection with histoplasmosis or tuberculosis (see Figs. 1-4 and 1-5). The popcorn-like calcification pattern is seen with hamartomas (see Fig. 1-6). For a nodule to be considered benign, it should display one of these four patterns of calcification and should exhibit no other features worrisome for malignancy. If calcifications are eccentric or if a nodule is bilobate, irregular, or spiculated or abuts a central bronchus, it should not be considered benign despite the presence of benign-appearing calcifications, because essentially benign calcifications can be engulfed by malignancy.[28] In addition, because pulmonary metastatic disease from osteosarcoma or chondrosarcoma can manifest as benign-appearing calcified nodules, the calcification pattern cannot be used to differentiate benign from malignant nodules in patients with a history of one of these cancers. In such patients, benignity is established by long-term nodule stability. Another type of calcification, the sandlike, amorphous form, is seen in 6% of lung cancers imaged by CT.[29] Such calcifications can be seen

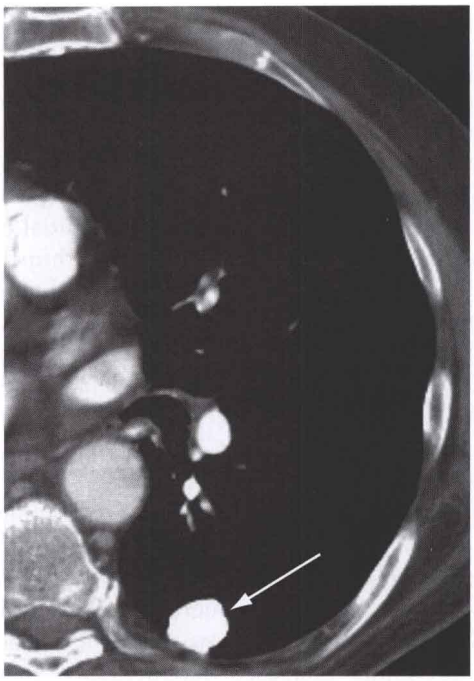


Figure 1-4 The patient was a 73-year-old man who had undergone right lower lobectomy for squamous cell lung cancer 2 years previously. Contrast-enhanced chest CT scan shows a benign, heavily and diffusely calcified nodule in the left lower lobe *(arrow)*. Note that calcification is denser than contrast in the vessels. The nodule proved to be stable on future imaging.

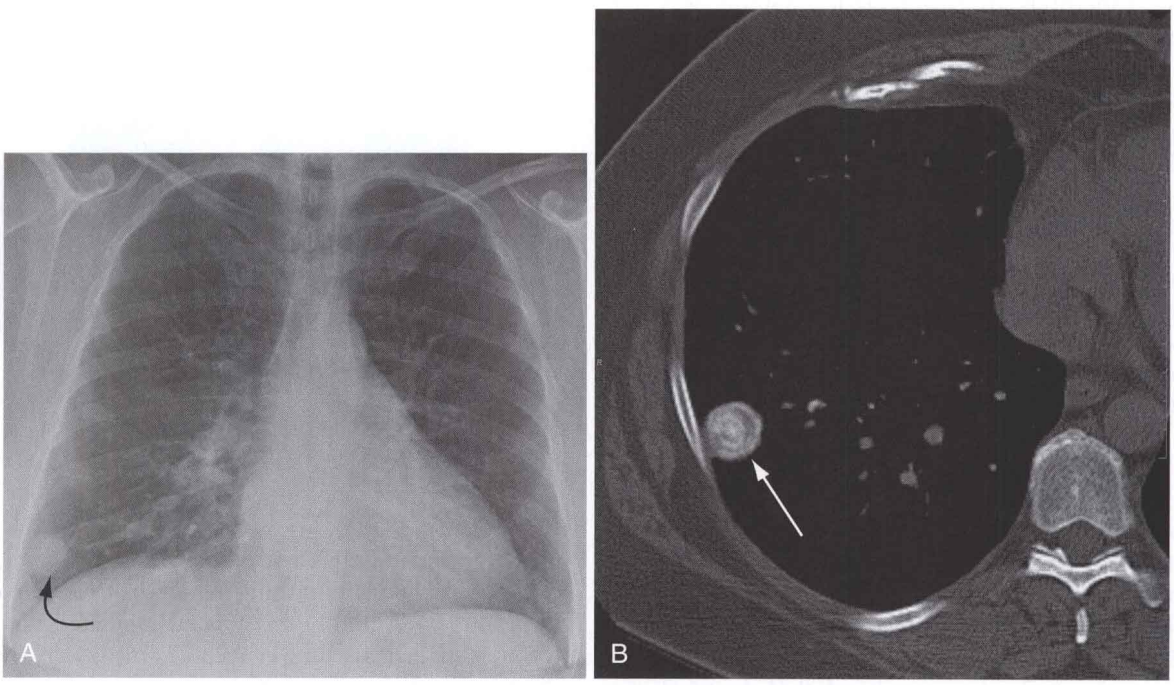


Figure 1-5 **A**, Incidental nodule *(arrow)* was discovered on a routine chest radiograph in a 47-year-old woman. **B**, Non–contrast-enhanced chest CT scan demonstrates laminated calcifications typical for previous infection with histoplasmosis *(arrow)*. The nodule remained stable at 5-year follow-up evaluation by chest CT *(not shown)*.

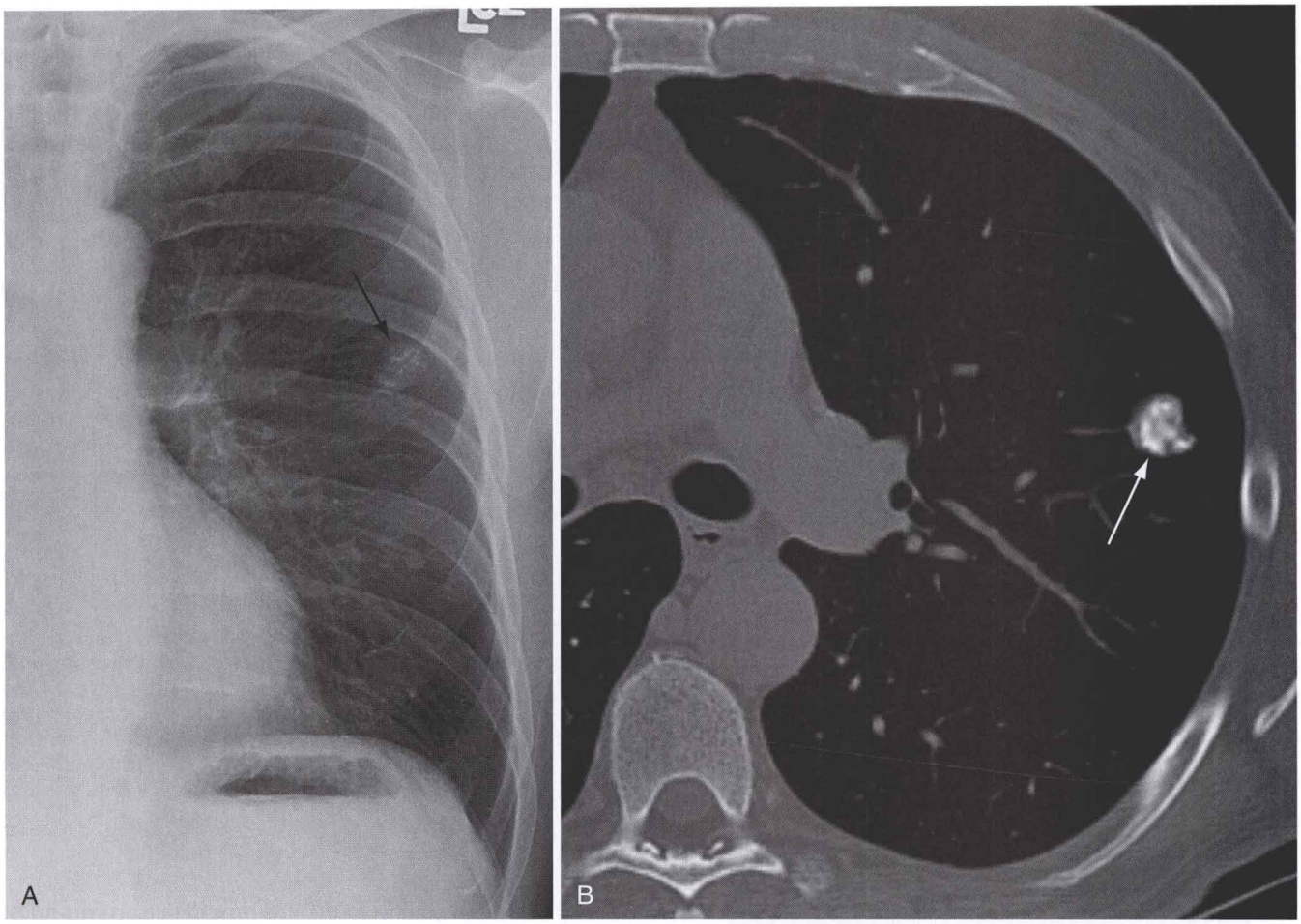


Figure 1-6 Treated non–small cell lung cancer of the right lung in a 59-year-old man. Left upper lobe nodule shows popcorn-like calcifications *(arrow)* on the chest radiograph (**A**) and non–contrast-enhanced chest CT scan (**B**), consistent with a pulmonary hamartoma. This nodule remained stable at 7-year follow-up evaluation by chest CT *(not shown)*.

in both benign and malignant disease and thus are not be useful in diagnosis (Fig. 1-7).

Although most nodules detected by CT are not obviously calcified, CT scans can objectively measure density with Hounsfield units (HU). In some previous attempts to identify subtle calcifications, not obvious to the human eye, measurements of density in HU were used to establish a threshold above which nodules were to be considered calcified and therefore benign.[30,31] These attempts were based on historical studies showing that malignancies with calcifications had been identified on radiographs in less than 1% of patients.[32–34] The assumption was that increased CT sensitivity would lead to identification of more benign nodules, with no false negatives, thereby reducing the number of futile thoracotomies. Subsequently, however, more than 10% of nodules evaluated as having a density higher than the established threshold of 185 HU (above which nodules should have been benign) were found to be malignant. This threshold was abandoned because it did not reliably distinguish between benign and malignant nodules.[31]

Fat is readily recognized on CT scans. A well-demarcated nodule containing fat and having a density between −40 and −120 HU is considered benign, usually a hamartoma (Fig. 1-8). A nodule consisting of fat alone or in combination with calcifications is seen in 60% of hamartomas on thin-section (using 2-mm slices) CT scans.[35] Such a nodule, even if slow-growing (with a doubling time longer than 2 years), is considered to represent a hamartoma. Popcorn-type calcification is a typical finding in hamartoma, although other benign-type calcifications can be seen as well. A third of hamartomas do not contain calcifications or fat on CT scan and remain indeterminate nodules.

The presence of an air bronchogram within a pulmonary nodule is rare (6%) in benign nodules, but this pattern is readily identified by CT scan (Fig. 1-9). Such an appearance is almost always associated with lung cancer of all cell types but is seen most commonly in adenocarcinoma (with or without bronchioloalveolar features).[36] CT scan also can differentiate among solid nodules, those with a ground-glass appearance (in which the lung vessels can

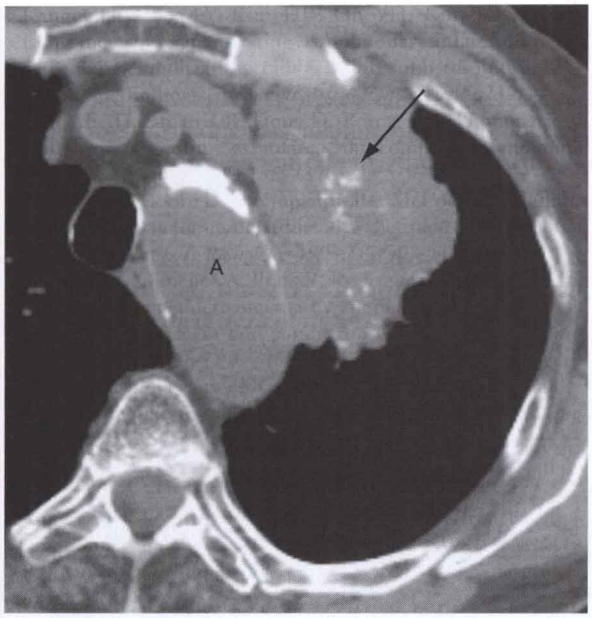


Figure 1-7 Adenocarcinoma of the left upper lobe in a 71-year-old woman. Non–contrast-enhanced chest CT scan at the level of the transverse aorta (A) shows a lobulated mass with amorphous calcifications within it *(arrow)*.

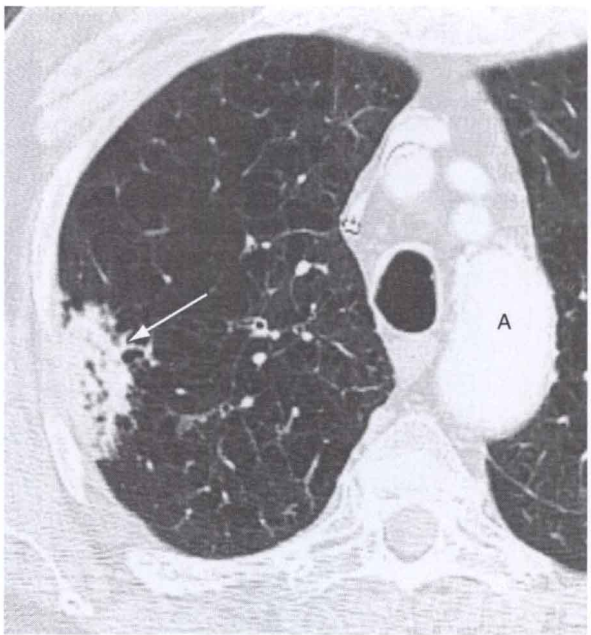


Figure 1-9 The patient was an 82-year-old man who underwent follow-up CT because of a prior history of gastrointestinal stromal tumor. Contrast-enhanced chest CT at the level of the transverse aorta (A) shows a new right upper lobe consolidated mass *(arrow)*. Tubular black structures within the mass represent the air bronchogram. Examination of a biopsy specimen *(not shown)* proved this to represent an adenocarcinoma of lung origin.

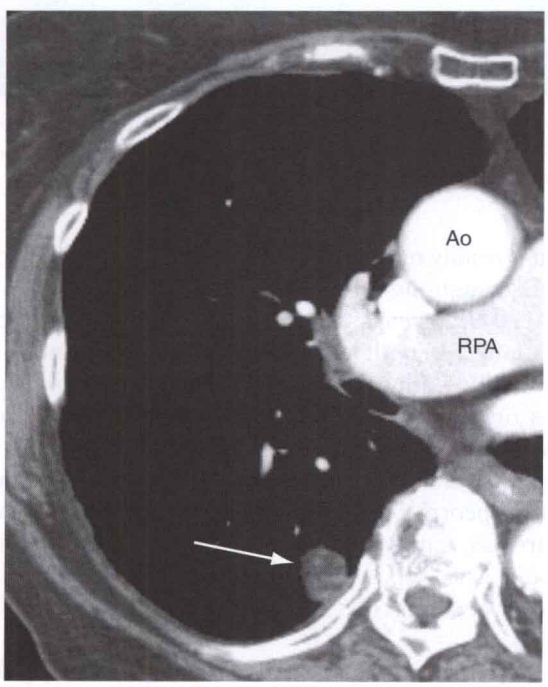


Figure 1-8 The patient was an 80-year-old woman in whom imaging was performed as follow-up for treated esophageal cancer. Contrast-enhanced chest CT scan shows a 2-cm nodule in the right lower lobe *(arrow)*. The nodule is of mixed attenuation and contains fat that is similar in CT appearance to the subcutaneous fat, with attenuation of −80 HU, consistent with a hamartoma. The nodule showed no significant growth at 4-year follow-up evaluation by chest CT *(not shown)*. Ao, aorta; RPA, right pulmonary artery.

be seen through the nodule), and mixed-pattern nodules, which combine a solid portion and ground-glass portion (Fig. 1-10). The malignancy rate is highest for mixed-pattern nodules (63%) and is higher for ground-glass nodules (18%) than for solid nodules (7%).[37]

Despite the superior sensitivity of CT over radiography for detection of benign nodules by identifying fat and calcium, a majority of nodules investigated by the initial CT scan remain indeterminate. The vessels supplying tumors differ both quantitatively and qualitatively from those supplying benign growths and tend to be more "leaky." This inherent difference in blood supply between malignant and benign nodules can be shown by changes in HU values in the pulmonary nodule after intravenous contrast injection. This method, in which the indeterminate nodule is imaged at intervals before and after intravenous contrast administration, was perfected by Swensen and associates.[38,39] Absence of significant lung nodule enhancement (density of 15 HU or less) on CT is suggestive of benignity. Although the method has only 77% accuracy and 58% specificity, it does identify 98% of malignant nodules and therefore is useful in guiding follow-up or intervention.

The CT features described here will identify those patients who have nodules with benign features that do not require follow-up (benign calcifications or fat), those who would benefit from an immediate biopsy, and those who

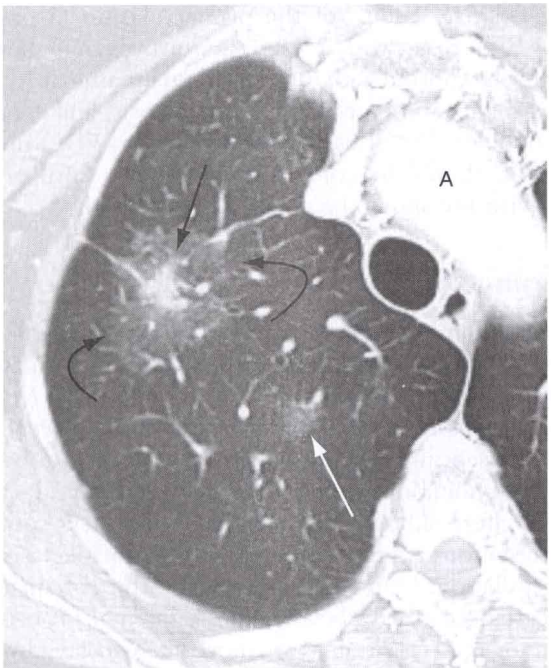


Figure 1-10 Multifocal bronchioloalveolar cell carcinoma in a 68-year-old woman. Contrast-enhanced chest CT scan at the level of the transverse aorta (A) shows one focus of her cancer to be a nodule with a ground-glass appearance *(white arrow)* and another focus as a mass of mixed attenuation: ground-glass opacity *(curved arrows)* with a solid center *(black straight arrow)*.

would benefit from CT monitoring of the nodule to assess its growth. The determination takes into account not only patient risk factors such as age and smoking exposure but also the CT features statistically recognized to be strongly associated with malignancy (e.g., large size, spiculation, mixed solid and ground-glass appearance). Of note, however, stability over a 2-year period is not an invariably valid criterion for benignity. In general, this criterion applies to nodules that are solid and larger than 1 cm.

Reliable detection of growth in nodules smaller than 1 cm can be difficult. For a nodule to double its volume, its diameter must increase by approximately 25%. It is difficult, even with CT, to visually detect the doubling of a 4-mm nodule, which is a change in diameter from 4 mm to 5 mm. Thus, small lung tumors can double in volume yet appear stable. Even computerized volume measurements, rather than diameter measurements, are not invariably accurate with such small nodules, which can appear to change size with differences in inspiratory effort and slice selection.[40] Nodules with a ground-glass appearance or with a mixed solid and ground-glass pattern are detected by CT scan, not by chest radiograph, and a stability criterion for benignity, such as the 2-year stability rule used with nodules detected by chest radiograph, has not been established for such nodules on CT. In fact, such nodules, which often are detected incidentally or by screening chest CT studies, can have very long doubling times. In a screening study in Japan,[41] the mean doubling time for ground-glass-pattern malignant nodules was 813 ± 375 days, for mixed ground-glass and solid tumors 457 ± 260 days, and for solid tumors 149 ± 125 days. In fact, 20% of the nodules in this study had doubling times exceeding 2 years, and these tended to be of the ground-glass type or mixed type. Thus, when a nodule smaller than 1 cm is monitored by CT to establish its benign nature, the follow-up period should be longer than 2 years.

Magnetic Resonance Imaging

The *contrast* resolution of MRI is superior to that of CT. This feature is exploited once cancer is diagnosed, because MRI is superior for evaluation of soft tissue involvement by cancer, such as in determining chest wall or nerve involvement. However, MRI does not serve effectively in early identification of lung cancer. Identifying pulmonary nodules smaller than 1 cm is hampered by the inferior *spatial* resolution of MRI, which is particularly poor in the lungs, as a consequence of characteristics both of the lungs themselves, such as low proton density and numerous air-tissue interfaces, and of the examination, such as motion artifacts from respiratory and cardiac motion. Dynamic contrast-enhanced MRI has been shown in small studies to have sensitivity rates for differentiation of malignant from benign SPNs that were comparable with those obtained with dynamic contrast-enhanced CT, but the nodules investigated usually were larger than the incidental nodules discovered by CT.[42–44]

Positron Emission Tomography

PET imaging with ^{18}F-fluorodeoxyglucose (FDG) has emerged as an additional tool for evaluation of the SPN. FDG-PET is a physiologic imaging modality, with poor spatial resolution in comparison with morphologic imaging modalities such as chest CT or radiograph. This technique assesses use of glucose by different body structures based on the preferential uptake of ^{18}F-FDG by metabolically active tissue. Because many cancers, including non–small cell lung cancer (NSCLC), have a higher metabolic rate than that of surrounding normal tissue, they accumulate ^{18}F-FDG more intensely and therefore appear "hot" on PET images. For nodules that are indeterminate on CT investigation, PET scan can help identify patients who may benefit from immediate biopsy. Initial studies showed that FDG-PET was effective in the differentiation of benign from malignant pulmonary lesions, and several early reports suggested that PET examinations reduce the number of patients with indeterminate nodules who undergo unnecessary thoracotomy, with overall sensitivity, specificity, and accuracy estimated to be 96%, 88%, and 94%, respectively.[45–51] PET is neither uniformly specific nor sensitive, however, particularly if the abnormality is small. Nodules smaller than 1 cm are not measured accurately and sometimes fall below the resolution of the PET scan.[52,53]

Although the combination of PET with a CT scan, or *integrated PET-CT*, has been shown to provide significantly greater specificity than that for either study alone,[54] the quantification of FDG uptake with use of CT for attenuation correction can introduce an artifact related to different breathing states in the CT and PET scans. FDG uptake in nodules, particularly those in the lower lungs, which suffer greater motion from the breathing cycle, will then erroneously appear to be lower than is actually the case.[55]

Cell type also influences FDG uptake. Indolent cancers, such as carcinoid tumors, well-differentiated adenocarcinomas, or bronchioloalveolar cell carcinoma (BAC), demonstrate less FDG activity than that seen in other NSCLCs and in some cases show no increased FDG activity.[48,53,56–60] The typical features of some of these cancers, such as proximity to a bronchus as is common with carcinoid tumors or the consolidative or ground-glass nodule in some BACs, are taken into account in interpreting the results of the PET-CT scan. The negative PET result thus serves as a tool, not a definite marker of benignity. If biopsy is deferred, the SPN with the negative PET result is monitored with serial chest CT scans for growth of the lesion. The data gathered thus far indicate that PET-negative nodules are indolent cancers; accordingly, this approach should not adversely affect patient outcome.[53]

The positive predictive value of PET in most patients is high (90% if the patient is older than 60 years).[61,62] False-positive studies of the primary lesion (a positive FDG-PET result with a lesion that proves to be benign) have been reported with infectious and inflammatory processes such as tuberculosis, histoplasmosis, and rheumatoid nodules.[50,61–66] Lesions with increased FDG uptake, however, should be considered malignant until proven otherwise and should be managed accordingly.

Imaging of Lung Cancer Subtypes

Imaging cannot replace histologic sampling of lung masses, but certain subtypes of lung cancer can manifest with typical imaging features.

Squamous cell carcinoma typically originates centrally, so the presenting manifestation frequently is postobstructive pneumonia or atelectasis, which is readily identified on the chest radiograph[34,67,68] (Fig. 1-11). Less common manifestations are mucoid impaction, bronchiectasis, and hyperinflation.[34,68,69] Approximately one third of squamous cell carcinomas arise beyond the segmental bronchi.[34,68] Squamous cell carcinomas are more likely to cavitate than the other histologic subtypes of lung cancer.[68] Cavitation occurs in 10% to 30% of these cancers and is more common in large peripheral masses and poorly differentiated tumors.[68] Because most squamous cell carcinomas grow slowly and become symptomatic because of their central location, extrathoracic metastases are encountered less commonly in imaging at presentation.[68]

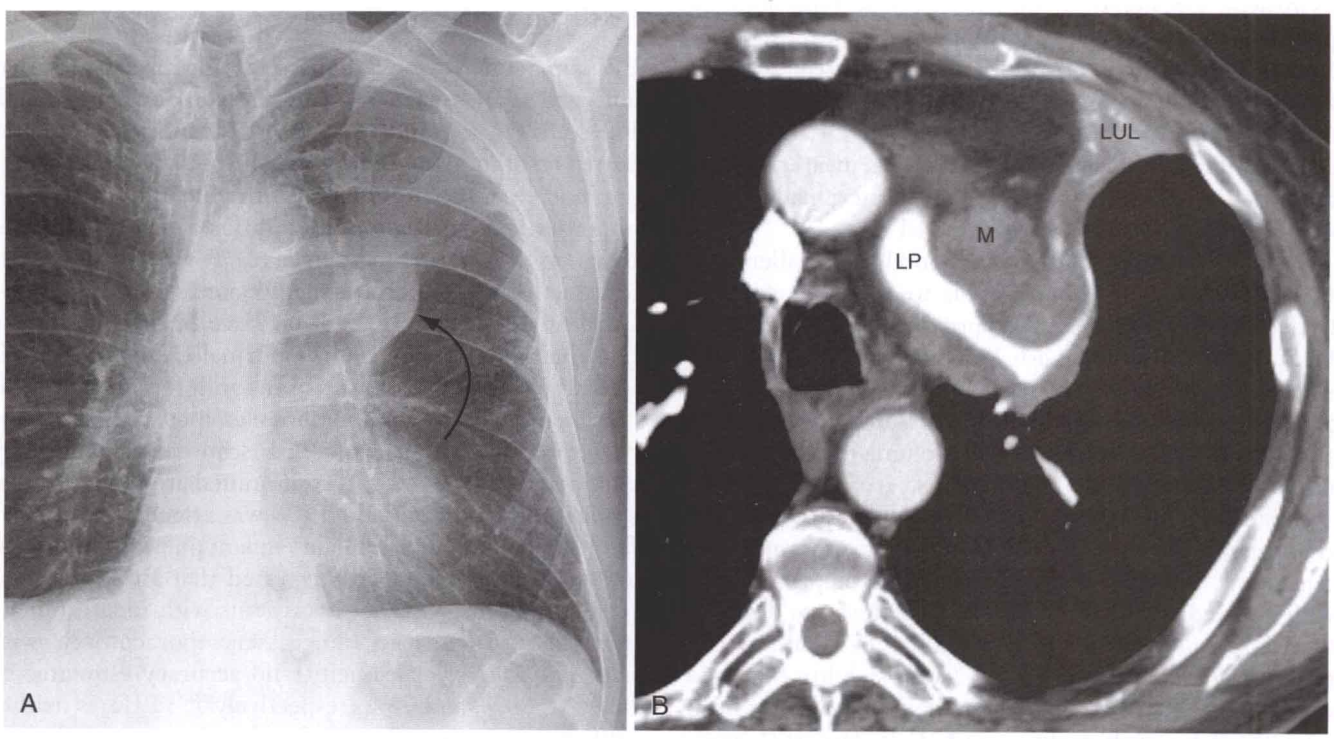


Figure 1-11 Newly diagnosed poorly differentiated squamous cell lung cancer in a 71-year-old man. **A**, Chest radiograph at presentation shows a central left hilar mass *(arrow)*. The hazy opacity above the arrow represents the collapsed left upper lobe. **B**, Contrast-enhanced chest CT scan at the level of the left pulmonary artery (LP) shows the central mass (M) encasing and narrowing the left pulmonary artery, causing left upper lobe (LUL) collapse.

Adenocarcinomas typically manifest as peripheral SPNs (see Fig. 1-9). Historically, nodules have been described as typically having soft tissue attenuation and an irregular or spiculated margin.[34,68] With the expanding use of CT and screening studies, however, an increasing number of adenocarcinomas manifest as nodules with a ground-glass appearance on CT or with mixed ground-glass and solid components (see Fig. 1-10). A correlation has been found between these CT appearances and the classification proposed by Noguchi and coworkers, whereby small (2 cm or less in greatest dimension) peripheral adenocarcinomas are classified into six types based on tumor growth patterns: type A, localized BAC; type B, localized BAC with foci of structural collapse of alveoli; type C, localized BAC with active fibroblastic proliferation; type D, poorly differentiated adenocarcinoma; type E, tubular adenocarcinoma; and type F, papillary adenocarcinoma with a compressive growth pattern.[70–72] Ground-glass attenuation of nodular opacities has been reported to be more frequent in types A to C than in types D to F, whereas soft tissue attenuation is more frequent in types B to F.[70] The soft tissue attenuation component tends to be absent or less than a third of the opacity with type A and greater in extent (more than two thirds) in types D to F. Mixed nodules, with both ground-glass and solid components, have a higher likelihood of being invasive and of higher stage than nodules with a pure ground-glass appearance.[73,74]

Although BAC is known to manifest with the unusual appearance of consolidation, this presentation is seen in only 30% of the cases; the rest of these tumors manifest as SPNs (43%) or multiple nodules (30%).[75] The SPNs are usually peripherally located and can remain stable in size for many years, with doubling times greater than 2 years. They can be of the ground-glass type or mixed type,[70,76] with cystic changes or cavitation occurring rarely, in up to 7%.[77,78] When a nodule exhibits multiple small, focal low-attenuation regions (pseudocavitation) or air bronchograms, the diagnosis of BAC should be suspected.[27,75,78,79] On PET-CT scans, BAC can show low FDG activity, lower than expected for malignancy.[57,80,81]

Large cell carcinoma usually manifests as a peripheral, poorly marginated large mass (larger than 7 cm in greatest dimension).[34,67,68,82–84] Although growth typically is rapid, cavitation is uncommon.

The most common presentation of carcinoid tumors is that of a central endobronchial mass, with or without atelectasis or consolidation, or, less commonly, a well-demarcated pulmonary nodule.[85,86] The tumors usually are less than 3 cm in diameter (Fig. 1-12), although occasionally they may be as large as 10 cm.[85,87–89] Calcification is seen in 25% of carcinoids by CT.[86] Carcinoids can show low FDG uptake on PET-CT studies, lower than expected for malignancies.[53,56,90]

The primary tumor of small cell lung cancer (SCLC) typically is small, in a central location, and associated with marked hilar and mediastinal adenopathy, frequently with engulfment of the primary lesion until it is no longer identifiable[34,67,83,91] (Fig. 1-13). With the increased use of CT and screening CT scans, the number of SCLCs encountered as early, small peripheral SPNs without intrathoracic adenopathy has increased. In the literature, detection of such early disease was reported in only 5% of the cases.[91,92]

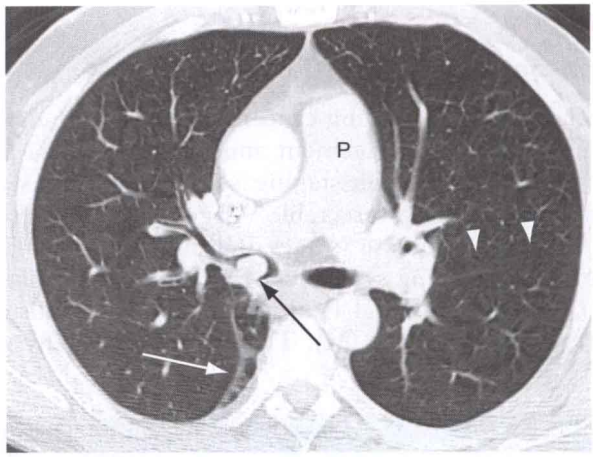


Figure 1-12 The patient was a 47-year-old man who presented with a new cough. Contrast-enhanced chest CT scan shows a nodule *(black arrow)* within the bronchus intermedius, causing some atelectasis of the right lower lobe, as depicted by the displacement of the right major fissure *(white arrow)*. Compare the normal position of the left major fissure *(white arrowheads)*. Nodule was removed endobronchially and proved to represent carcinoid. P, main pulmonary artery.

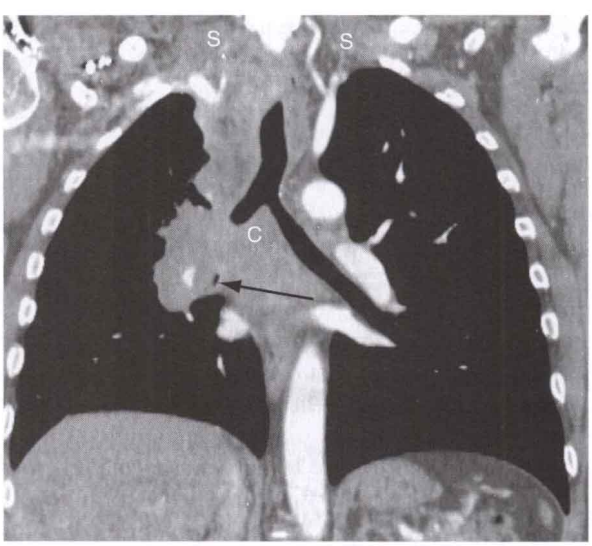


Figure 1-13 Newly diagnosed small cell lung cancer in a 52-year-old man. Coronal contrast-enhanced chest CT scan shows conglomerate lymphadenopathy involving the right hilum, subcarinal region (C), and bilateral paratracheal regions extending to involve the bilateral supraclavicular regions (S). This process obliterates the right main bronchus and significantly narrows the right lower lobe bronchus *(arrow)*. Note that the primary cancer cannot be differentiated from the extensive lymphadenopathy.