Lung Cancers Associated with Cystic Airspaces: Underrecognized Features of Early Disease[1]

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Abbreviation: FDG = fluorine 18 fluorodeoxyglucose

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See discussion on this article by Yankelevitz (pp 717-718).

SA-CME LEARNING OBJECTIVES

After completing this journal-based SA-CME activity, participants will be able to:

- Recognize nodules arising adjacent to cystic spaces in the lung that can reflect early lung carcinomas and thus prompt early detection and treatment of malignancy.
- Discuss the current understanding of the pathogenesis of lung cancers associated with cystic airspaces.
- Identify nonmalignant processes that can mimic pericystic lung cancers and key factors that increase suspicion for malignancy.

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Early lung cancers associated with cystic airspaces are increasingly being recognized as a cause of delayed diagnoses—owing to data gathered from screening trials and encounters in routine clinical practice as more patients undergo serial imaging. Several morphologic subtypes of cancers associated with cystic airspaces exist and can exhibit variable patterns of progression as the solid elements of the tumor grow. Current understanding of the pathogenesis of these malignancies is limited, and the numbers of cases reported in the literature are small. However, several tumor cell types are represented in these lesions, with adenocarcinoma predominating. The features of cystic airspaces differ among cases and include emphysematous bullae, congenital or fibrotic cysts, subpleural blebs, bronchiectatic airways, and distended distal airspaces. Once identified, these cystic lesions pose management challenges to radiologists in terms of distinguishing them from benign mimics of cancer that are commonly seen in patients who also are at increased risk of lung cancer. Rendering a definitive tissue-based diagnosis can be difficult when the lesions are small, and affected patients tend to be in groups that are at higher risk of requiring biopsy or resection. In addition, the decision to monitor these cases can add to patient anxiety and cause the additional burden of strained departmental resources. The authors have drawn from their experience, emerging evidence from international lung cancer screening trials, and large databases of lung cancer cases from other groups to analyze the prevalence and evolution of lung cancers associated with cystic airspaces and provide guidance for managing these lesions. Although there are insufficient data to support specific management guidelines similar to those for managing small solid and ground-glass lung nodules, these data and guidelines should be the direction for ongoing research on early detection of lung cancer.

Introduction

The evolution of lung cancer screening programs is evidence of the clinical benefits of early detection and treatment of lung carcinoma (1,2). This article highlights the underrecognized appearances of early carcinoma occurring in association with small cystic airspaces in the lung parenchyma. These abnormalities are often initially misinterpreted as inflammatory changes or infection. This group of lesions is increasingly being identified as a cause of missed or delayed diagnoses of cancer. With large patient cohorts participating in lung cancer screening programs or undergoing serial cross-sectional imaging to monitor other conditions, the prevalence and natural history of lung cancers arising in association with cystic airspaces are becoming more apparent and providing new insights into the pathogenesis of early lung cancer.

TEACHING POINTS

- Progressive wall thickening or the emergence of a nodule in a cystic airspace in the lung of a patient at high risk for cancer should be regarded as a suspicious lesion that warrants further surveillance or investigation to rule out early lung cancer.
- In practice, a change in the morphologic features of a cyst or pericystic nodule should raise suspicion for cancer.
- The patient's clinical background is important when determining the appropriate follow-up or investigation of pericystic lesions. The combination of signs and symptoms of acute infection, rapid onset of radiologic abnormalities (assuming the availability of previous imaging data), and multifocal lesions points to a benign cause of these lesions.
- Cyst wall thickening and/or nodularity at the interface between normal and fibrotic lung parenchyma should raise suspicion for malignancy.
- The uptake of fluorine 18 fluorodeoxyglucose (FDG) in a small pericystic lesion can be difficult to measure, and a negative PET result does not reliably exclude malignancy.

The nomenclature for these lesions is not well established owing to limited understanding of them, with different groups referring to these neoplasms as "cancers arising from lung cysts" or "cancers associated with cystic airspaces" (3–5). The description "cancers associated with cystic airspaces" is admittedly cumbersome; however, it reflects the terminology used in the studies referenced in this article. In addition, we believe that it best encompasses the variety of causes and morphologic appearances represented, which at present can be reliably differentiated by pathologists only. It is important to emphasize that these lesions are not cavitary; rather, they are nodules or eccentric thickening associated with the wall of the cystic airspace. The term *cystic airspace* is itself broad and serves as an umbrella term encompassing congenital cysts, emphysematous bullae, fibrotic cysts, bronchiectatic airways, subpleural blebs, and cystic dilatation of distal airways arising de novo from small cancers owing to obstruction—a condition that is increasingly becoming apparent. This is not an exhaustive list. For brevity and clarity, we hereafter use the term *cyst* to refer to all of the histologic types of cystic airspaces described.

Lung cancers associated with cystic airspaces have been identified as a cohort of malignancies that are at risk for delayed diagnosis. These lesions pose a diagnostic challenge, as their small size often makes them difficult to assess with biopsy, and their position adjacent to cystic areas increases the risk of procedural complications such as pneumothorax. It is important to recognize that not all lesions associated with cystic airspaces are malignant. In fact, many other conditions in the lung can mimic them, complicating the diagnosis. Many of these mimicking entities are more frequently seen with underlying conditions that also predispose individuals to lung cancer, such as emphysema and interstitial fibrosis (6).

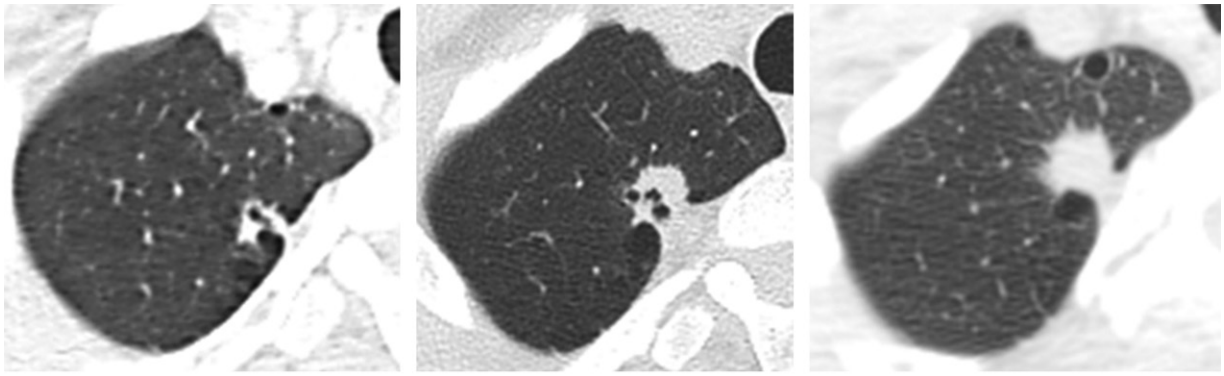
In this article, we review the appearances, evolution, incidence, and histopathologic features of lung cancers arising next to cystic airspaces—according to our experiences and data in large published studies. In addition, we provide a synopsis of the current understanding of the potential pathogenesis of these lesions and a framework for analyzing them, and propose guidance for identifying lesions that warrant further monitoring and/or investigation. Radiologists must be mindful that many cystic airspace–related abnormalities can be benign, and indiscriminate surveillance has the potential to increase the imaging burden on radiology departments and the radiation burden on patient populations.

Missed and Delayed Diagnoses

In the International Early Lung Cancer Action Plan, a total of 706 lung cancers (from a screening population of 48 037 individuals) (7) were identified at baseline examination and annual screening. From these cancers, Farooqi et al (3) identified 26 (3.7%) lesions that were abutting lung cysts. The cyst sizes at baseline ranged from 4 mm to 58 mm. In all 26 cases, a cystic component was present at baseline, and it most often had a thin-walled appearance. A nodular component was present in half of the cases. Development of a solid lung cancer was consistently characterized by progressive wall thickening followed by the eventual emergence of a nodule in or abutting the cyst wall. When a nodular component was present at baseline, there was a greater degree of wall thickening, which was postulated to reflect aggressive lesions that progress quickly to cyst infilling, with resultant solid lesion formation.

The variability in the nature of the cystic airspaces was highlighted by histologic data. Information regarding the nature of the cyst was available for 15 of the 26 cases: Seven cysts were bullae, five were bronchiectatic airways, and three were pleural blebs. Therefore, progressive wall thickening or the emergence of a nodule in a cystic airspace in the lung of a patient at high risk for cancer should be regarded as a suspicious lesion that warrants further surveillance or investigation to rule out early lung cancer.

In the NELSON (Nederlands-Leuvens Longkanker Screenings Onderzoek [Dutch-Belgian Lung Cancer Screening Trial]) lung cancer screening trial, cancers associated with cystic lesions were again identified as a cause of missed cancers (8,9). In that study, 7155 patients underwent lung cancer screening, and 248 cancers were detected. Sixty-one of these malignancies were first diagnosed as



a. b. c.

Figure 1. Pericystic lesion similar to that in a case of delayed diagnosis in the NELSON lung cancer screening trial. There is also apical paraseptal emphysema. **(a)** Initially obtained axial computed tomographic (CT) scan shows thickening around the periphery of an apical bulla, which was misinterpreted as inflammation. **(b)** Axial CT scan obtained 11 months later shows that the bulla had progressed to an eccentric nodule. **(c)** Axial CT scan obtained 16 months after the baseline examination shows continued growth of the bulla. At biopsy, the lesion was proven to represent a primary lung adenocarcinoma.

interval or postscreening carcinomas. This means that they were not first detected at baseline imaging or screening rounds. Rather, they were detected between planned screening examinations or later, after completion of the screening protocol. In a retrospective analysis of these cases, 22 of the 61 cancers were identified as a radiologic abnormality that either was not detected or was misinterpreted at prior screening or baseline examination. Five of these cancers were characterized as focal wall thickening in a bulla. Three lesions had uniform wall thickening, and two had focal nodular thickening. Another case was due to a peribullous nodule that was attributed to apical scarring. A similar example from our experience is shown in Figure 1.

In their department of thoracic surgery, Guo et al (10) identified 15 cases of "lung cancer presenting as cysts" from 3268 surgical resection cases during a period of 5.5 years. Thus, 0.46% of operable lung cancers manifested as cysts. This group distinguished a cyst from a cavity on the basis of a wall thickness of less than 4 mm. They also resected 306 benign cysts during the same period, suggesting a rate of malignancy in pulmonary cystic lesions of 4.7% (15 cancers in 321 cysts). These data provide limited insight into the prevalence of cancers associated with cystic airspaces, which had not been available in other studies.

Classification of Cancers

Having determined that small cancers associated specifically with bullous lung disease are a cause of missed or delayed diagnoses, Maki et al (11) devised a morphology-based classification system in 2006. Based on this system and their own additional findings, Mascalchi et al (4) modified the Maki et al classification to develop a new system for categorizing all lung cancers associated with cystic airspaces in general rather than those associated with bullous disease exclusively (Fig 2). They retrospectively identified 24 lung cancer diagnoses at their institution during a 5-year period. In these 24 cases, a purely cystic airspace preceded the formation of a lung cancer. In the resulting classification system, four morphologic types of pericystic cancers are described: Type I is that of a nodule abutting the external aspect of a lung cyst. Type II is that of a nodule arising from the cyst wall and projecting into the cystic space. Type III is that of cyst wall thickening. Type IV, an addition to the classification system devised by Maki et al (11), is that of a multicystic lesion that contains areas of soft-tissue attenuation. Among the 24 cases included in the study, there was a broad distribution in terms of the number of each morphologic type represented at initial detection, with, respectively, five, four, eight, and seven type I, type II, type III, and type IV cancers seen (4).

In a more recent retrospective study, Fintelmann et al (5) identified and assessed 30 lung cancers from a total of 2954 primary lung cancers diagnosed at their institution. In these 30 cases, cysts were in or adjacent to the cancers at some point leading up to the histologic diagnosis. In 20% of the cases, the cystic airspace was multilocular when it was first identified. Twenty-five percent of the remaining cystic airspaces that were unilocular at first visualization evolved to have a multilocular appearance over the course of observations. None of the initially multilocular lesions evolved to have a unilocular morphology.

It may be difficult to distinguish a type III lesion from a cavity, especially if the wall thickening becomes circumferential. Type III lesions are distinguishable from cavities in that they progress from a preexisting thin-walled cystic airspace, in contrast to cavities, which form from a solid

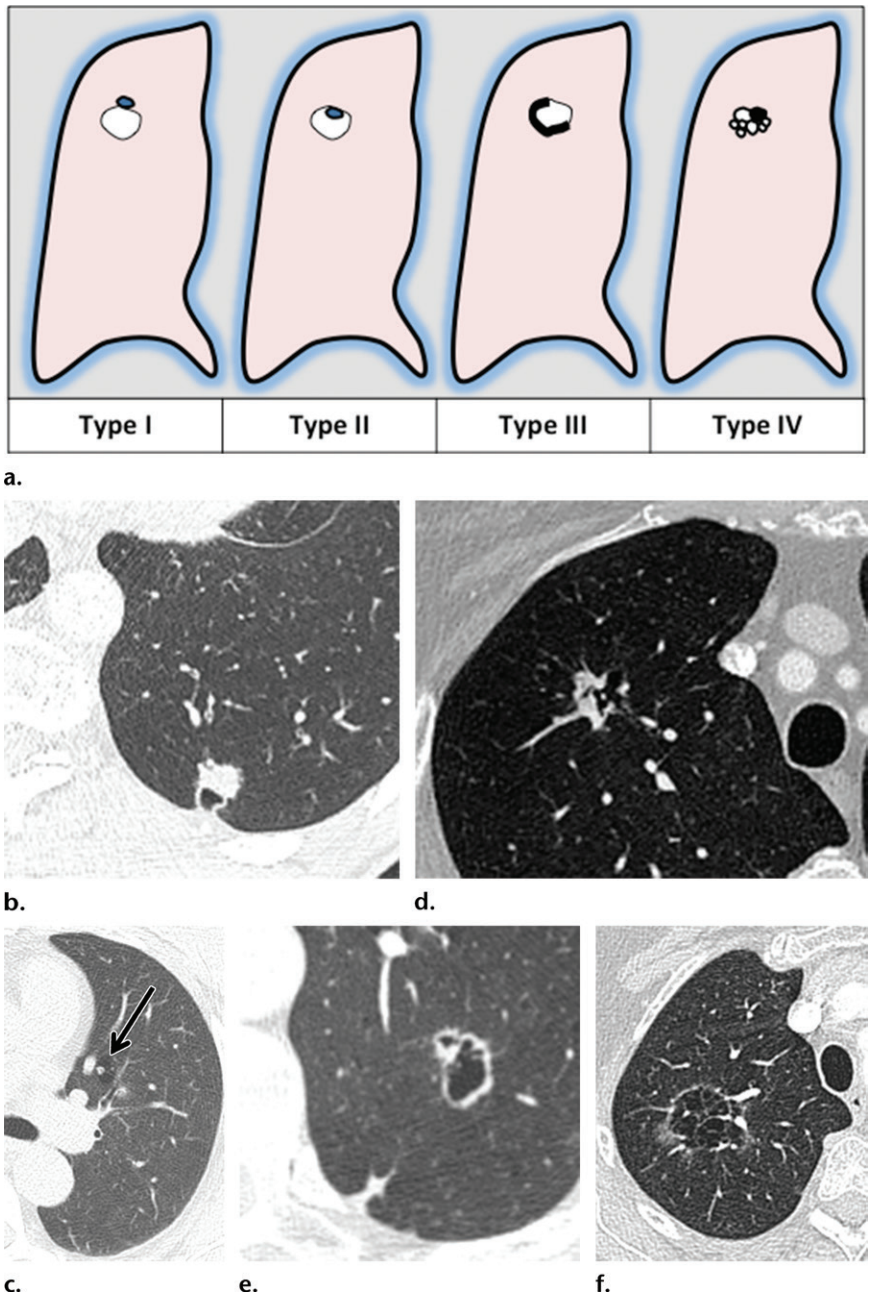


Figure 2. **(a)** Drawing illustrates the system for classifying cancers associated with cystic airspaces according to the method of Mascalchi et al (4), which is based on a previous classification developed by Maki et al (11). Type I represents a nodule outside the cystic airspace and abutting the wall. Type II is that of a nodule projecting into the cystic airspace from the wall. Type III is that of cyst wall thickening, which may not necessarily be circumferential, without an area of focal nodularity. Type IV is a multicystic lesion with focal soft-tissue elements; this is an addition to the existing classification system. **(b–f)** Axial CT scans show the four cystic airspace–related cancer types: type I **(b)**, type II (arrow) **(c)**, type III **(d, e)**, and type IV **(f)**. (Adapted, with permission, from reference 4.)

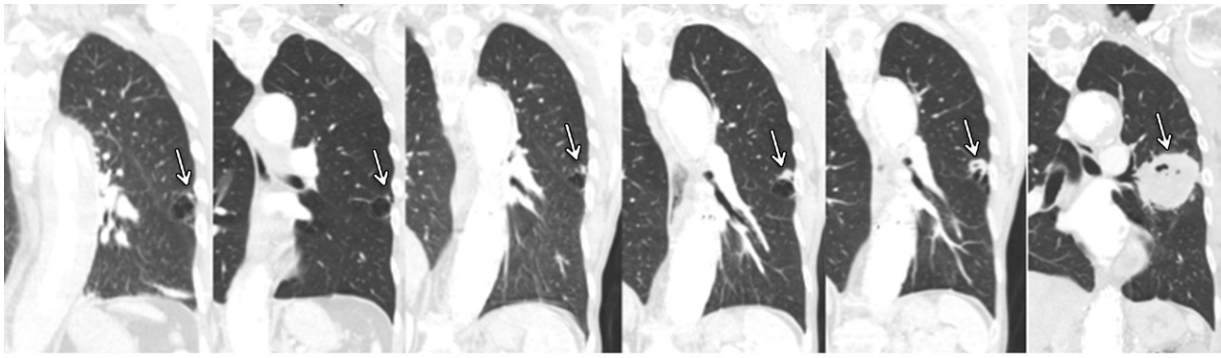
lesion or parenchymal airspace abnormality. Owing to this distinction, thick-walled abnormalities were excluded from the Mascalchi et al study and classification (4) if prior imaging data were not available to show a definitive progression from a thin-walled abnormality rather than a solid lesion or airspace abnormality.

Because none of these proposed classification systems provides prognostic information, their value is not yet proven. However, in our experience, these classifications can be useful for stratifying the risk of a pericystic abnormality representing malignancy. Type I and type IV cystic airspace–related cancers are more likely to be miscategorized as benign lesions, whereas types II and III have a broader range of differential diagnoses, including infection and inflammation. Type III lesions may be difficult to distinguish from cavities without prior imaging data.

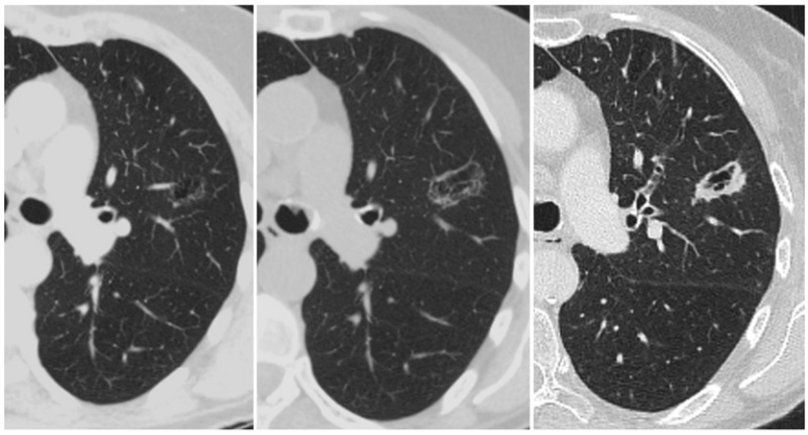
CT Morphology and Evolution

The data acquired at serial CT of cystic airspace–related malignancies offer insight regarding the growth patterns of these early lesions. After establishing a classification system, Mascalchi et al (4) proceeded to identify patterns of disease progression among the lesions. There is often a transition between types as cystic airspace–related lesions progress. For example, a nodule may emerge from uniform cyst wall thickening, or wall thickening may occur in a previously more focal type I or type II lesion.

Figure 3. Patterns of progression of proven cancers that began as nodules associated with cystic airspaces. **(a)** Coronal multiplanar CT reconstructions obtained during a period of 5.5 years show the progression of a type I nodule (arrows) that was misinterpreted during follow-up of aortic disease. The baseline scan (far left) and repeat scans obtained at 2 months (second from left), 15 months (third from left), 33 months (fourth from left), 45 months (fifth from left), and 69 months (far right) are shown. The lesion was initially misinterpreted as an inflammatory abnormality, and the patient was subsequently lost to follow-up. At 45 months, the lesion had transitioned from a type I to type III cancer; nearly complete filling of the cystic component with cancer growth followed. **(b)** Axial CT scans obtained at baseline (left), 30 months (middle), and 36 months (right) in a different patient show a multicystic type IV lesion that gradually developed circumferential wall thickening (type III), with concurrent enlargement of the cystic space and progressive infilling (right).



a.



b.

Solid nodules increase in size, usually with a resultant decrease in the size of the cystic airspace. Six of the 24 cancers in the Mascalchi et al study (4) showed progressive cyst enlargement alongside the solid elements.

In the Fintelmann et al study (5), six of the 30 evaluated cancers were first identified as noncystic lesions, and seven were first identified as purely thin-walled cysts. The remaining lesions were first visualized as thick-walled cysts (n = 4) or nodules inside or adjacent to a thin-walled cyst (n = 13). During the observation period for all lesions in this retrospective study, there was a progressive increase in the solid component in 20 (67%) of the 30 evaluated cases due to wall thickening, increasing attenuation of mural nodules, an increased number of loculations, or a solid mass replacing the airspace.

In our experience, although cystic airspace–related lesions undergo morphologic changes and progression, they can be missed or misinterpreted and often are not detected for prolonged periods (Fig 3). In practice, a change in the morphologic features of a cyst or pericystic nodule should raise suspicion for cancer.

Pathogenesis

Lung cancer associated with cystic airspaces has been reported since the 1940s (11). At that time, the preponderance of this disease was related to congenital lung abnormalities such as congenital pulmonary airway malformations. More recently, a definite risk of mucinous adenocarcinomas arising in congenital cystic malformations has been shown—even in young patients (12,13). Lantuejoul et al (13) established that proliferations of mucinous cells in type I congenital pulmonary airway malformations have the same profile as mutations of mucinous adenocarcinoma of the lung. Lung cancers arising from bullous emphysematous disease also are the subject of a number of anecdotal case reports, as well as a study whose results indicated "poorer cell differentiation and

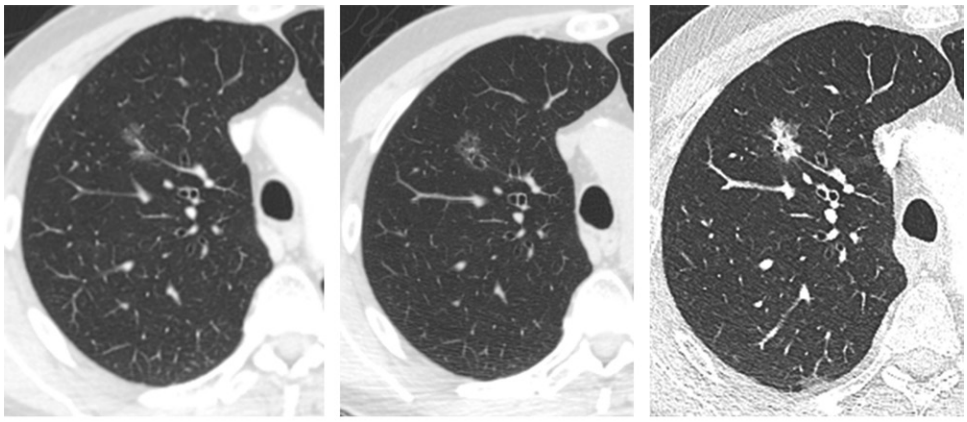


Figure 4. Pathogenesis of adenocarcinoma. Axial CT scans show a ground-glass lesion that was initially suspicious for adenocarcinoma in situ **(a)** and then became multicystic **(b)** before it evolved into a solid lesion **(c)**. An adenocarcinoma was resected.

accelerated proliferative activity" in lung cancer arising from emphysematous bullae (14–16).

Findings in the majority of cases in our experience and in the recent radiologic literature emphasize that these often missed nodules arise from acquired cystic airspaces such as emphysematous bullae rather than from congenital cystic airspaces. However, it is possible that some of the pathogenetic elements of acquired airspaces are translatable from the congenital cases. In some cases from screening trials with histologically confirmed noncongenital cystic airspaces, cysts had been present for at least 6 years before the emergence of wall thickening or a solid nodule. This progression parallels the process described in the congenital cyst cases. However, in most of these screening cases, as compared with the cases of congenital cysts, *nonmucinous* pericystic adenocarcinomas developed (3).

None of the 15 histologically confirmed cysts in the Farooqi et al study (3) were congenital or part of a diffuse cystic lung disease such as Langerhans cell histiocytosis or Birt-Hogg-Dubé syndrome. Rather, these lesions represented emphysematous bullae, dilated airways, and pleural blebs. Histologic cyst analysis was not performed in the Mascalchi et al study (4); however, the cystic airspace pattern preceding the formation of lung cancer was consistent in the 24 cases in that study.

Histologic cyst data on 21 of 30 cases were available in the Fintelmann et al (5) study. Eight (38%) of these 21 cases involved a "check-valve" mechanism of small airway dilatation with scar tissue; six (29%) cases, lepidic growth of adenocarcinoma on emphysematous destruction lesions; four (19%) cases, cystification of tumor; and three (14%) cases, growth of adenocarcinoma along a preexisting bulla wall (5).

In many cases, lung cancers associated with cystic airspaces appear to arise from preexisting cysts. However, there is alternative evidence that some visible cysts are induced by early nonvisible microscopic tumor cell growth, the macroscopic soft-tissue component of which later becomes visible. Our group has rarely seen the second evolution pattern. More commonly, cystic components increase in size or number after a tumor manifests and then persist or become enveloped by the growing lesion. The putative mechanism of pathogenesis of such tumors is that whereby microscopic cancer formation leads to a check-valve effect in the peripheral airways, causing formation of a lung cyst (3) (Fig 4). This theory is supported by cysts that increased in size as the solid components grew in a quarter of the patients in the Mascalchi et al (4) and Farooqi et al (3) studies and in more than half the patients in the Fintelmann et al study (5).

Under surveillance, the natural evolution of many of these untreated lesions—whereby they ultimately become solid tumors, with no evidence of the prior cystic components—may indicate that the number of lung cancers that begin as pericystic lesions is underestimated (Fig 5).

Cystic and pericystic lung cancers are predominantly of the non–small cell adenocarcinoma type. This is especially true of multicystic (type IV) lesions, which are recognized manifestations of lepidic-predominant adenocarcinomas, minimally invasive adenocarcinomas, and adenocarcinoma in situ lesions (17). However, a small number of other cell types—mainly squamous cell but also carcinoid—have been seen consistently in relatively recent case series (3–5,10) (Table). It is notable that nodule progression patterns do not appear to vary with histologic types, although the total number of cases remains limited. In the setting of fibrotic interstitial lung disease, Oh et al (18) identified a predisposition of lung cancers to arise at the junction between fibrotic cysts and normal lung tissue, and amid the fibrotic cysts in patients with idiopathic interstitial pneumonia. It has been suggested that fibrosis predisposes individuals to malignancy owing to atypical or dysplastic epithelial changes.

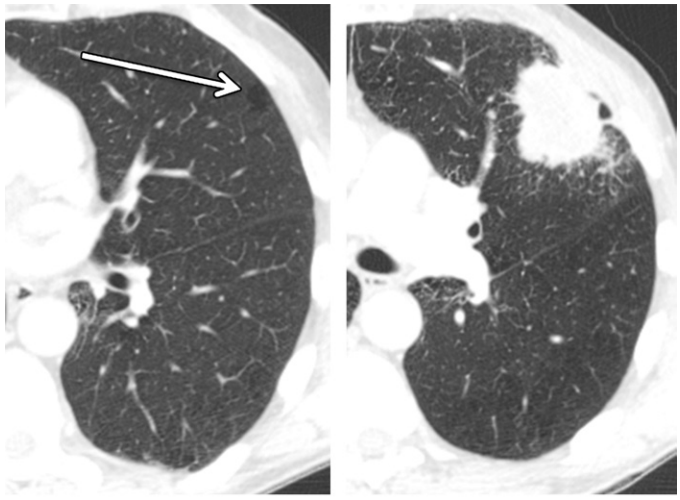


Figure 5. Lung adenocarcinoma that began as a pericystic lesion. Axial CT scans obtained 6 years apart show a solid primary lung adenocarcinoma **(b)** that arose in a region of preexisting cystic airspaces (arrow in **a**).

Cell Types in Pericystic Cancers Reported in Four Studies

Study	No. of Patients	Adenocarcinoma*	Squamous Cell Carcinoma*	Other Cancer*
Fintelmann et al (5)	30	24 (80)	4 (13)	2 (7)
Farooqi et al (3)	26	23 (88)	1 (4)	2 (8)
Mascalchi et al (4)	24	17 (71)	7 (29)	0
Guo et al (10)	15	10 (67)	2 (13)	3 (20)

Note.—Adenocarcinoma is the predominant cell type in pericystic cancers. However, these cancers may also be of the squamous cell type or other cell types such as atypical carcinoid and poorly differentiated carcinoma.
*Data are numbers of patients with the given malignancy. Numbers in parentheses are percentages of patients.

In the setting of lung cancers arising from preexisting parenchymal abnormalities, the concept of scar carcinomas merits attention. Scar carcinomas are a somewhat controversial topic that has become less frequently discussed in the past few decades. The historic theory that adenocarcinomas are predisposed to arise from scarring in the lungs was attributed to local inflammation associated with the scarring and healing processes. However, this concept has been challenged owing to evidence that neoplasms themselves induce localized collagen deposition. Hence, the cause-and-effect relationship between scarring and cancer induction remains unclear (19).

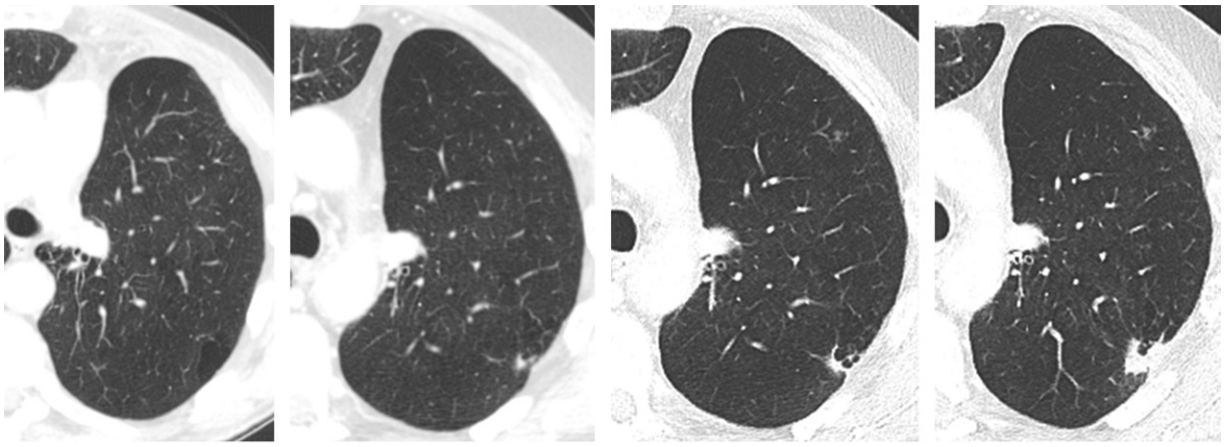
The phenomenon of multifocal or synchronous lepidic-predominant adenocarcinoma, minimally invasive adenocarcinoma, or adenocarcinoma in situ is well recognized and poses a management challenge for surgeons who may be required to consider multiple-site lobar or sublobar resection of lung tissue. In our experience, lesions associated with cystic airspaces, which most frequently represent adenocarcinoma, can often also be synchronous or metachronous lesions that are presumed to be second primary cancers rather than metastases (Fig 6).

Mimics of Cystic Airspace–related Cancer

One of the greatest challenges for radiologists is the fact that patients with bullous lung disease or other causes of cystic airspaces are often at increased risk of both infection and cancer, and, thus, their underlying lung condition can result in atypical appearances of both of these entities at cross-sectional imaging. Acute infection or inflammation can cause bulla wall thickening and irregular cysts or cavities, and fungal infections can cause nodular wall thickening or large abutting masses in the form of mycetomas (Fig 7).

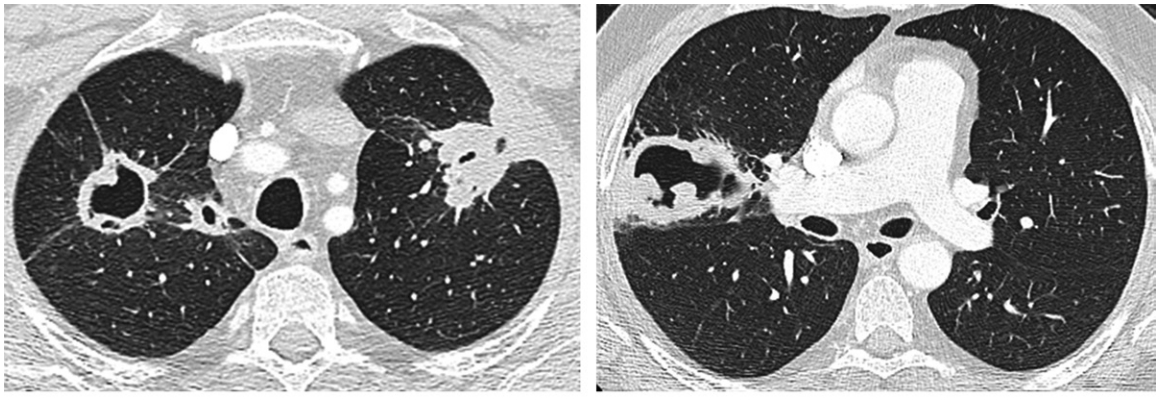
A number of clinical and radiologic findings can help stratify risk. Patients with signs and symptoms of acute infection in conjunction with radiologic features of airway or parenchymal inflammation and multifocal pericystic lesions may be considered to have lower cancer risk. When previously obtained images are available, the rapid progression of findings can also indicate an infective or inflammatory cause of the lesions (Figs 8, 9).

In smokers, cystic airspaces in the form of paraseptal emphysema are concentrated in the lung apices, where apical scarring and extra-



a. b. c. d.

Figure 6. Metachronous cancers in a patient undergoing surveillance after left upper lobectomy for the large primary lung adenocarcinoma seen in Figure 5. **(a)** Axial CT scan obtained before the lobectomy shows a left lower lobe cystic airspace. **(b–d)** Axial follow-up CT scans obtained 7 years after the lobectomy show eccentric cyst wall thickening **(b)**, which rapidly progressed to a solid lesion during the 8th year **(c, d)** and was proven to represent a second primary lung adenocarcinoma. Hyperinflation of the left lower lobe after the lobectomy also is apparent.



a. b.

Figure 7. Thickened cystic airspace walls with nodules in a patient with *Aspergillus* infection. Axial CT scans obtained at different anatomic levels show multiple lesions and preexisting cavities from granulomatosis with polyangiitis. Diagnostic examination results were positive for *Aspergillus* infection. The cyst sizes are large compared with the average sizes of cysts reported in the Mascalchi et al (4) and Farooqi et al (3) studies: 17 mm and 10 mm, respectively.

pleural fat proliferation can simulate apparent pericystic thickening. Careful inspection with both lung and soft-tissue window settings can reveal fat attenuation in the extrapleural space as the cause of apparent bulla wall thickening in lung windows (Fig 10).

The lung is a common site for metastases from other primary cancers. These metastases can occur adjacent to preexisting cysts and may closely reflect the patterns of progression of primary pericystic lung cancers, as described earlier. Compared with primary cancers, metastases tend to be associated with faster growth rates, and the presence of a separate known primary cancer or other metastases alters the differential diagnosis (Fig 11). Furthermore, treatment of metastatic disease with chemotherapeutic or antiangiogenic agents can cause cavitation, which also can lead to the appearance of thick-walled cysts. Knowledge of the patient's clinical history, combined with the likelihood of multiple lesions that typically would be expected to demonstrate a synchronous treatment response, is key to delineating lesions caused by chemotherapeutic or antiangiogenic treatment of metastases (Fig 12).

Rarer causes of pericystic nodules include amyloidosis, especially when it is associated with lymphoid interstitial pneumonitis; vasculitides such as granulomatous polyangiitis (formerly Wegener granulomatosis); and less common infections such as those caused by *Nocardia* species.

The patient's clinical background is important when determining the appropriate follow-up or investigation of pericystic lesions. The combination of signs and symptoms of acute infection, rapid onset of radiologic abnormalities (assuming

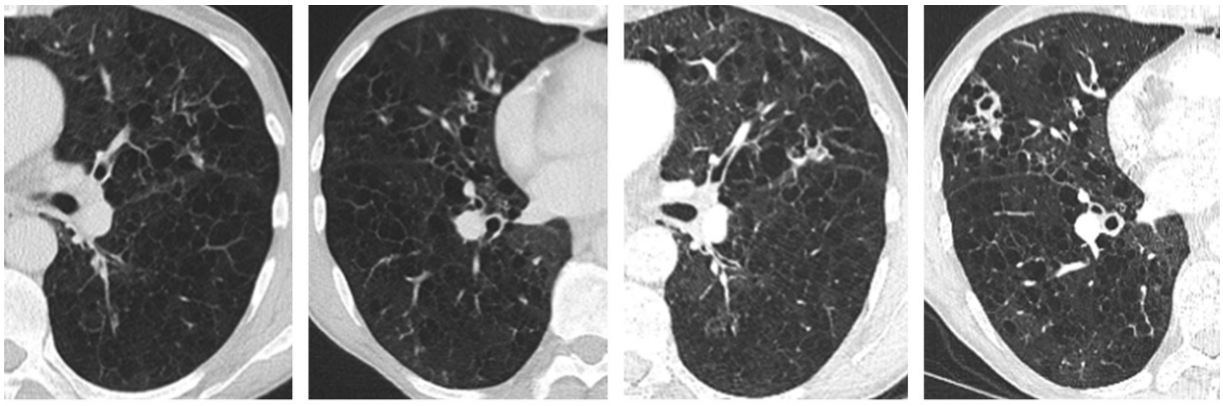


Figure 8. Cystic airspaces related to infection. **(a, b)** Axial baseline left-lung **(a)** and right-lung **(b)** CT scans show widespread emphysema. **(c, d)** Axial left-lung **(c)** and right-lung **(d)** CT scans obtained 3 months later show multifocal thickened cyst walls accompanied by increased bronchial wall thickening. These findings coincided with clinical signs of infection-related exacerbated chronic obstructive pulmonary disease.

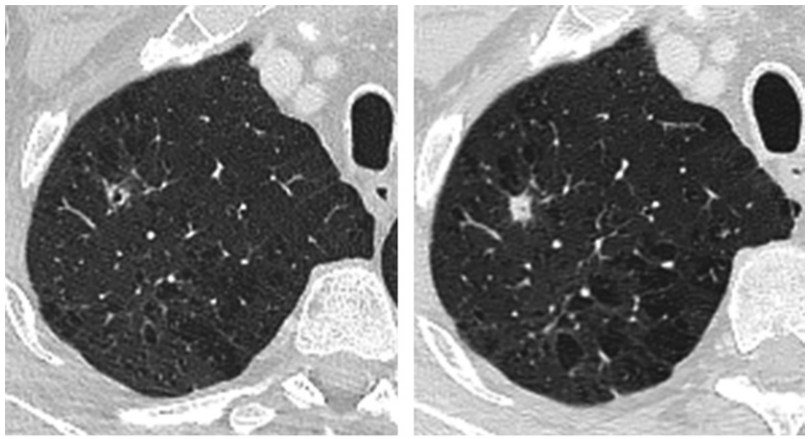


Figure 9. Cystic airspace–associated lesions caused by inflammation. **(a)** Axial follow-up CT scan shows wall thickening in an apical emphysematous bulla. **(b)** Axial CT scan obtained 3 months later shows almost complete infilling of the cystic airspace. Biopsy revealed nonnecrotizing granulomatous inflammation.

the availability of previous imaging data), and multifocal lesions points to a benign cause of these lesions.

Diffuse Lung Disease

Patients with diffuse lung disease, such as emphysema and fibrotic interstitial lung disease, are at increased risk of developing lung cancer, regardless of how frequently they smoke (20,21). The cause of the increased risk remains somewhat unclear, but the chronic inflammatory processes in the lung are likely to be a factor.

Interpreting pericystic changes in patients who have diffuse disease—namely emphysema or fibrosis—as opposed to an isolated pericystic lesion in otherwise normal lung parenchyma is particularly challenging. The often complex appearances of the lung parenchyma on CT images, as well as the predisposition for concurrent acute infection or inflammatory conditions, indicate that cysts with apparent wall thickening and/or nodularity are not an uncommon finding. Solid dense foci adjacent to cysts in fibrotic interstitial lung disease may also be due to focal areas of fibrosis.

Patients with diffuse lung disease are frequently encountered in lung cancer screening populations, or they may undergo serial examinations for surveillance of the lung disease or identified focal abnormalities. Mascalchi et al (4) found that 17 of 24 patients with lung cancer also had emphysema, and two of these 17 patients had combined pulmonary fibrosis and emphysema. Farooqi et al (3) found that 11 of 26 patients with pericystic lung cancer also had emphysema.

Evaluating lung nodules or cancers in diffuse fibrosis of the lung parenchyma is especially complicated. Oh et al (18) identified 63 patients with early-stage T1 cancers in a background of interstitial lung fibrosis. They found a predilection for the lower lobe, and the cancers were closely related to diffuse interstitial fibrosis: More than 50% of the tumors occurred at the interface between fibrotic cysts and unaffected lung tissue. Thirty-one percent of the cancers were located centrally

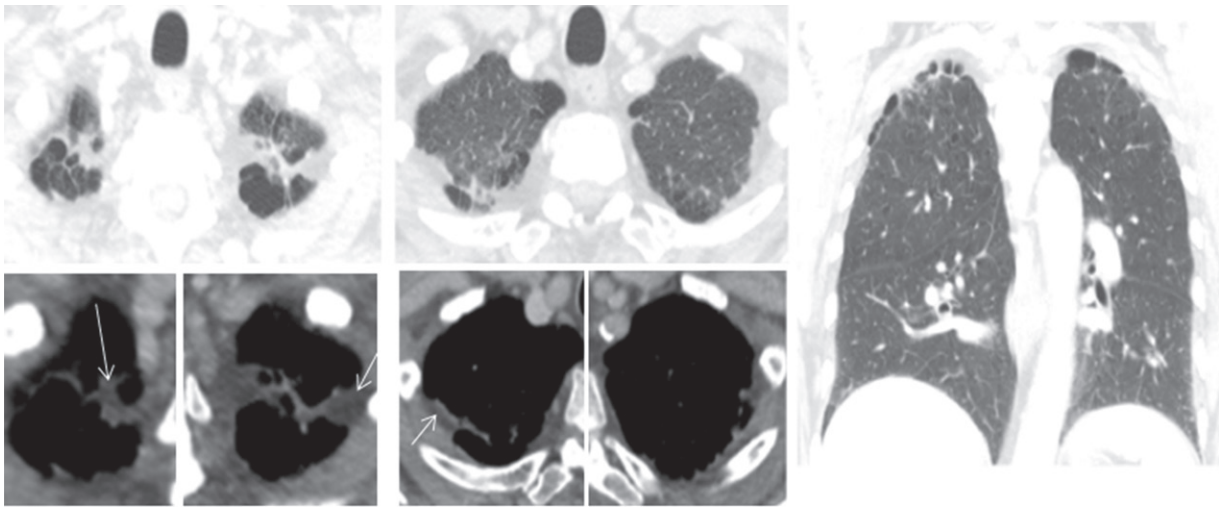
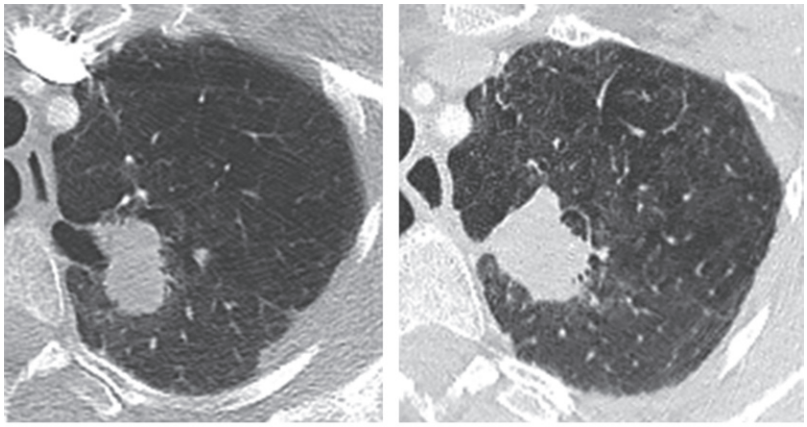


Figure 10. Bullous thickening mimicking pericystic cancer. Axial (top left and top right) and coronal (far right) lung-window CT scans show bilateral apical peribullous thickening, which appears to be related to pericystic cancer. However, the same axial scans obtained with soft-tissue window settings (bottom left and bottom right) show extrapleural fatty proliferation (arrows), as a result of scarring, to be the cause of the bulla wall thickening.



a. **b.**

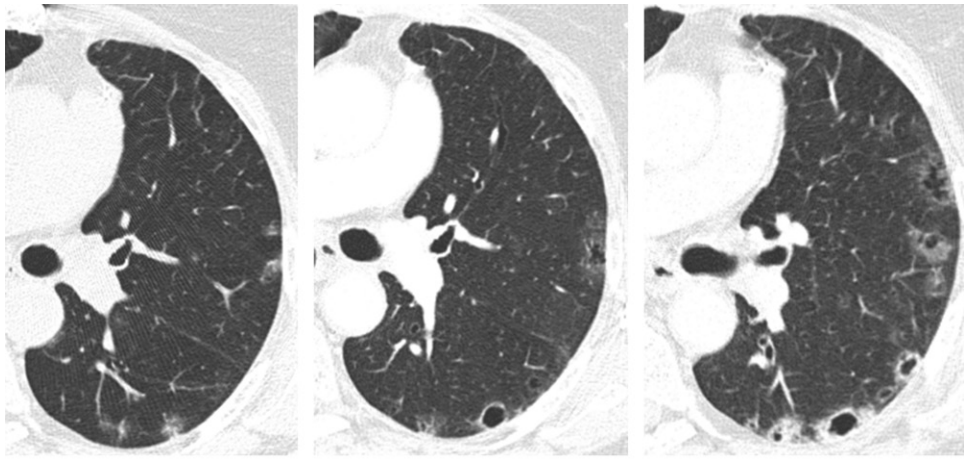
Figure 11. Pericystic lesion in a patient with paraseptal emphysema and a history of previous colorectal carcinoma. **(a)** Axial CT scan shows a large pericystic nodule in the left lung apex. **(b)** Although biopsy revealed metastasis, the axial CT scan obtained at 4 months shows lesion progression, with a pattern of infilling of the cystic airspace similar to that reported with pericystic primary lung cancers.

in the area of fibrosis (18). Therefore, cyst wall thickening and/or nodularity at the interface between normal and fibrotic lung parenchyma should raise suspicion for malignancy (Fig 13). It is possible that many more lung cancers associated with interstitial lung disease arise from cysts than are currently appreciated, as the importance of their position amid fibrotic cystic lungs may be disregarded, compared with the importance of lung cancers arising from a solitary cystic lesion in a patient without diffuse lung disease.

Given the increased risk of lung cancer in patients with pulmonary fibrosis, it could be argued that for surveillance of interstitial disease, it is preferable to perform volumetric CT rather than interspaced noncontiguous thin-section CT—at which emerging nodules might not be visualized. At our institutions, noncontiguous thin-section CT is reserved for monitoring lung disease in young (<40 years) patients, in whom minimizing the radiation dose is an important concern and incidentally discovered malignancies are rare. With use of modern scanners, volumetric CT of the lungs can be a relatively low-dose examination. In addition, owing to the balance of risk (radiation exposure) and benefit (identifying early lung cancers) with volumetric CT, it is preferred for older patients.

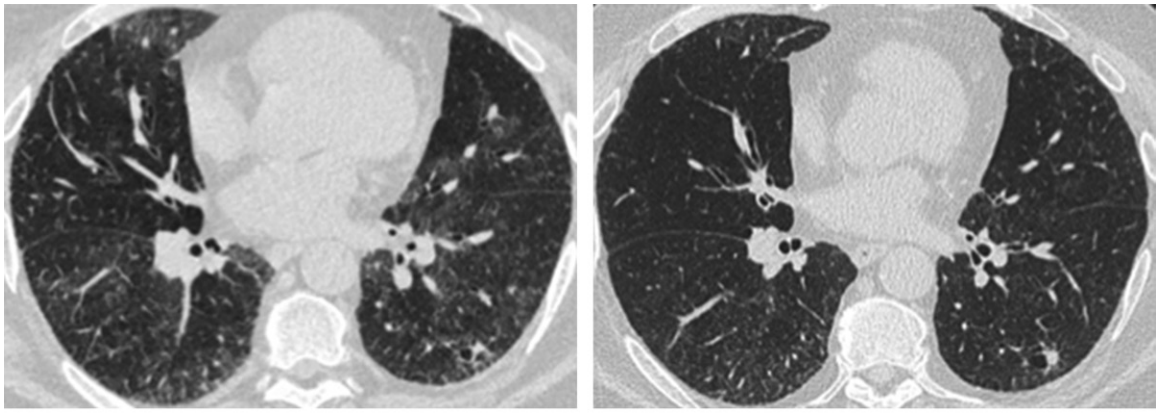
Clinical Implementation and Effect

Many evidence-based guidelines such as the Fleischner Society criteria are intended to rationalize and reduce the frequency of surveillance (22,23). In lung cancer screening trials, standardized lesion classification systems such as the Lung Reporting and Data System (Lung-RADS) (24) are used to determine the appropriate management. At present, it is unclear where lesions associated with cystic airspaces belong in either of these systems. It can be challenging to characterize, accurately and reproducibly measure, and assign size-based criteria to circumferential thickening in particular. For



a. b. c.

Figure 12. Cystic lesions in a patient with metastatic pancreatic adenocarcinoma who was treated with antiangiogenic agents. **(a)** Axial baseline CT scan shows multifocal ground-glass lesions. Combination antiangiogenic therapy with bevacizumab and erlotinib caused cystic liquefactive necrosis. **(b, c)** Axial follow-up CT scans at different anatomic levels obtained at 6 weeks show rapid synchronous progression to cystic lesions.



a. b.

Figure 13. Nodule associated with cystic airspace in a patient with fibrotic interstitial lung disease. **(a)** Axial CT scan shows an enlarging nodule in the left lower lung lobe. **(b)** Axial follow-up CT scan shows the progression of the nodule at 9 months. Note the concurrent enlargement of the cystic airspace. The patient's lung function precluded a definitive diagnosis and local therapy. The nodule was presumed to be cancer and managed with surveillance.

lesions with smooth thin cystic walls, we base our management on the maximal dimension of the solid portion of the disease, without including thin cystic components, because pathologically, the cystic component usually does not represent cancer unless it is thickened. For lesions with thickened cystic walls, the entirety of the cystic and solid components is measured. In the absence of other guidance to date, our follow-up protocols for incidental nodules are based on current Fleischner Society recommendations, and those for screening cases are based on Lung-RADS guidelines.

Determining which CT protocol to use is important, as subtle changes in these small complex lesions may not be well characterized at low-dose follow-up nodule examinations, and often thin-section standard-dose acquisitions may be appropriate. However, this should be decided on a case-by-case basis. In our opinion, full-volume thoracic surveillance of these lesions is prudent. Many of these lesions are seen in patients who have had lung cancer previously, and they are often associated with other similar lesions. Fintelmann et al (5) found that seven of 30 patients had another cystic lesion elsewhere in the lungs, and four of these seven cysts were later proven to represent synchronous lung cancer. An additional six patients had persistent multifocal ground-glass opacities (5).

In many screening studies, the findings in cohorts of patients with missed cancers associated with cystic airspaces are highlighted. However, there is a lack of data regarding the percentages of these lesions that are ultimately diagnosed as malignant, and this paucity should prompt pro-

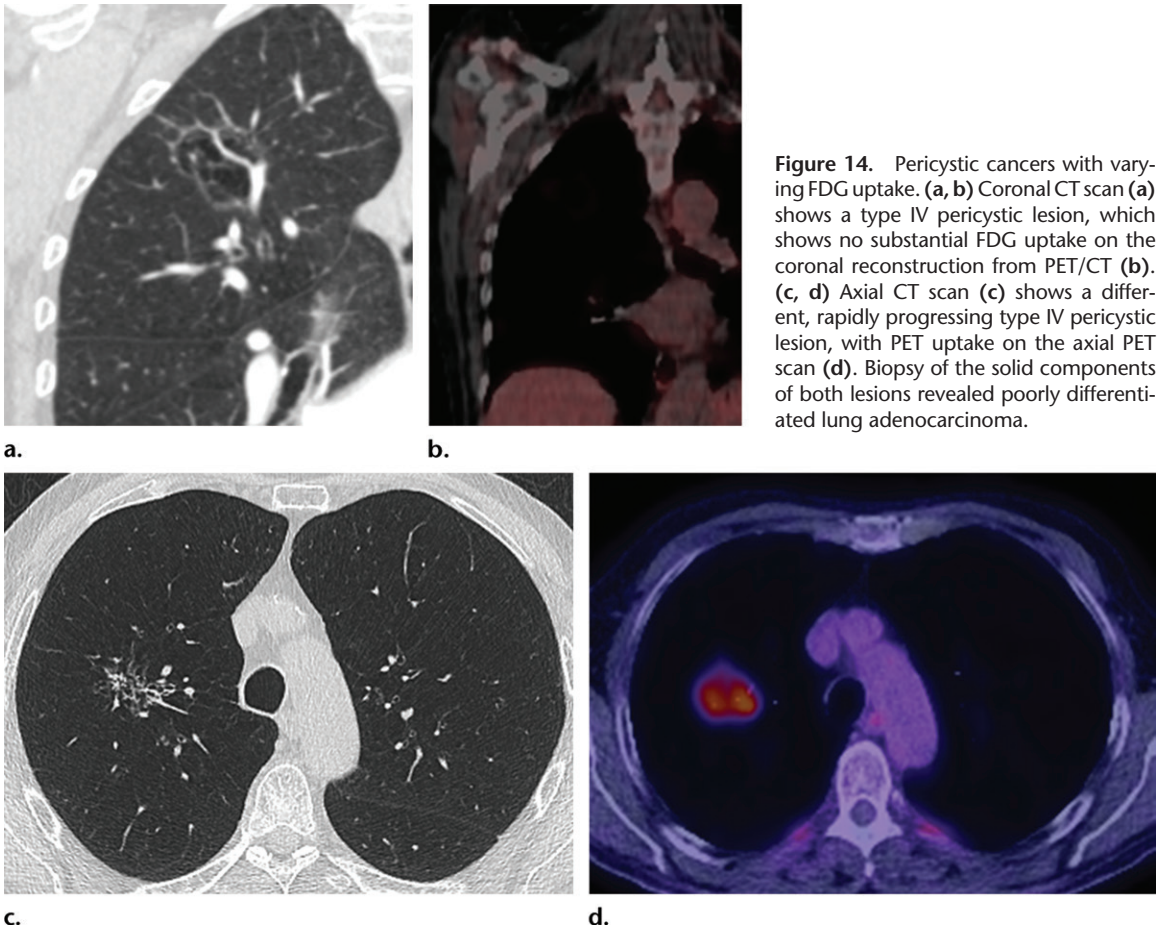


Figure 14. Pericystic cancers with varying FDG uptake. **(a, b)** Coronal CT scan **(a)** shows a type IV pericystic lesion, which shows no substantial FDG uptake on the coronal reconstruction from PET/CT **(b)**. **(c, d)** Axial CT scan **(c)** shows a different, rapidly progressing type IV pericystic lesion, with PET uptake on the axial PET scan **(d)**. Biopsy of the solid components of both lesions revealed poorly differentiated lung adenocarcinoma.

spective research trials. Guo et al (10) provided minimal insight, with 4.7% of resected cystic lesions reflecting cancer in their study. However, this percentage cannot be extrapolated to lesions identified at imaging. In addition, these data are limited to patients who were physiologically capable of undergoing surgical resection and reflect an unusually large rate of benign cyst resections. The authors justified these resections because they led to reduced risks of complications such as infection, hemorrhage, and rupture into the pleural space (10).

Until there are more data on this subject, it will be reasonable to have a low threshold for surveillance when small areas of pericystic thickening or nodularity are encountered. However, indiscriminate follow-up of any lesion has consequences such as strained health care resources and increased patient anxiety and radiation dose.

Positron emission tomography (PET) combined with CT (PET/CT) has an important role in the investigation and staging of lung cancers. However, using PET/CT to characterize metabolic activity in small or subsolid lesions, including those associated with cystic airspaces, has a number of drawbacks. Lesions smaller than 1 cm are often too small to address, and cystic airspace—multicystic type IV in particular—may reduce the overall density of metabolically active cells. The majority of cancers associated with cystic airspaces are of the adenocarcinoma type. The spectrum of subsolid adenocarcinomas, including lepidic-predominant adenocarcinoma, minimally invasive adenocarcinoma, and adenocarcinoma in situ, is the least reliably assessed with PET owing to the low rate of metabolic activity in these often slow-growing tumors or the low density of tumor cells (25,26).

Other issues that are universal to all lung cancers include misregistration artifact due to the tumor's position in relation to moving structures such as the heart and diaphragm. This may be more challenging in patients with diffuse lung disease. The uptake of fluorine 18 fluorodeoxyglucose (FDG) in a small pericystic lesion can be difficult to measure, and a negative PET result does not reliably exclude malignancy. PET uptake was mild or absent in seven of the 24 cases of pericystic lung cancer in the Mascalchi et al study (4), and all seven of these cancers were histologically proven adenocarcinomas. In the cases in which FDG PET/CT data were available in the Fintelmann et al study (5), lesions were found to be FDG avid when the solid components were larger than 8 mm (Fig 14).

Despite the fact that lung cancers associated with cystic airspaces are at risk for delayed diagnosis, there is no evidence that outcomes are worse in this subgroup of lung cancers. Results of an earlier study of lung cancers arising in bullous emphysema (16) indicated that despite the apparently more aggressive pathologic features of these malignancies, the overall prognosis was not substantially different from that of patients who had lung cancer not associated with bullae. However, additional outcome data from screening studies and prospective evaluations are required to validate this clinical impression.

In our experience, cystic airspaces with wall thickening and/or associated nodules of any attenuation warrant surveillance and investigation. For findings potentially related to infection, follow-up imaging is usually sufficient. For more suspicious or persistent lesions, a negative FDG PET result is not necessarily reassuring unless there is a sizeable (>10 mm) solid component. For many of these lesions, percutaneous needle biopsy of the solid or subsolid elements ultimately will be required, provided that these components are large enough and accessible. The imaging and interventional management of lesions that persist, grow, or demonstrate morphologic change should be considered at a multidisciplinary level, with the clinical context and patient's preferences incorporated.

Conclusion

The prevalence of lung cancers arising in association with cystic airspaces is still unknown, and the risk of cysts developing into lung cancer is unquantified. However, owing to the growing numbers of patients undergoing lung cancer screening or serial CT for surveillance of other conditions, these cancers are an increasingly recognized phenomenon. Furthermore, they have been identified as a cause of missed or delayed cancer diagnoses in screening trials and radiologists' daily practice.

Lung cancers associated with cystic airspaces are still poorly understood; this fact is emphasized by the varying nomenclature used to describe these lesions. Classification systems can aid in decision making, but they do not provide prognostic information because the numbers of cases evaluated are too small.

The emerging cohort of study data and evolving pathogenetic theories should prompt the radiologic community to conduct prospective evaluations of these lesions to determine the absolute risk and establish standardized management. Future formal management guidelines should be based on the review of large datasets from either screened patients, which can be retrospectively evaluated, or prospective studies.

***Disclosures of Conflicts of Interest.*—I.V.** *Activities related to the present article:* disclosed no relevant relationships. *Activities not related to the present article:* research software support from Siemens Medical Systems and GE Healthcare. *Other activities:* disclosed no relevant relationships.

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Invited Commentary: Early Lung Cancer and Cystic Airspaces

From:
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In this issue of *RadioGraphics*, Sheard et al (1) provide an overview of lung cancers associated with cystic airspaces, emphasizing the need to recognize findings associated with early disease. In reading their review, what becomes striking is the extent to which our overall knowledge base for studying this topic is limited. This lack of information persists despite the fact that lung cancer is the leading cause of cancer-related death and CT screening for lung cancer is focused on early detection in high-risk individuals—many of whom have emphysema. Also, findings such as increased cyst wall thickening and nodularity have long been known to be associated with lung cancer.

With all of these factors, it seems that there would be a wealth of information regarding cystic airspace–related cancers. However, this review is primarily focused on results reported in four articles (2–5), with 30 or fewer examples from each of them. This lack of data is no fault of the authors. Rather, it demonstrates that little information on these lesions has been compiled, and the authors clearly recognize the need for additional data to be accrued in a systematic fashion.

Sheard et al (1) carefully describe the results reported in the four articles (2–5), pointing out that there are different manifestations of cancers associated with cysts. These manifestations include nodularity inside or outside of the cyst wall and thickening of the wall—usually in an irregular fashion. They also point out that these cysts may be unilocular or multilocular. They note that the causes of cystic airspaces are quite heterogeneous and include various types of congenital cysts, bullae, blebs, and postinflammatory lesions. These authors also include as cysts lesions associated with bronchiectasis and distended distal airspaces.

The walls of each of these cysts differ in histologic composition, and as would be expected, the cancers associated with them also are somewhat heterogeneous. In essence, this group is describing a wide range of illnesses whose commonality is that they involve an air-filled space that is visible on CT scans. This heterogeneity limits the ability to identify an underlying factor that might be the cause of the cancer in these cases, although chronic inflammation is considered to be a likely cause of many of them. The authors point out that even the overall prevalence of cancers associated with cystic airspaces is unknown, let alone the prevalences of cancers associated with different cyst types.

Although the causes of cystic airspaces are dissimilar and even the types of cancers that occur with them are not uniform, from the perspective of the radiologist, the need to appreciate the morphologic changes associated with developing cancer should be recognized. These morphologic changes are often nonspecific, but they mimic those that occur with cancer in general. Thus, the development of nodules in the wall of a cyst that is persistent and growing, and a change in the thickness of the cyst wall, especially if the wall thickening is irregular, are findings that should raise suspicion for cancer.

Sheard et al (1) describe the limitations of PET/CT in the context of cystic airspace–related cancer, as the nodules are often small and below