Lung Cancers Associated With Cystic Airspaces: Natural History, Pathologic Correlation, and Mutational Analysis

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Purpose: The aim of the study was to investigate the natural history of non–small cell lung cancers (NSCLCs) associated with cystic airspaces, including histopathology and molecular analysis.

Materials and Methods: A total of 34,801 computed tomographic (CT) scans of 2954 patients diagnosed with NSCLC between 2010 and 2015 were evaluated for association with a cystic airspace. Characteristics on serial CT, 18F-fludeoxyglucose positron emission tomography, and pathologic analysis were recorded.

Results: Cystic airspaces were associated with 1% of NSCLC cases (12 men and 18 women; median age, 66 y [range, 44 to 87 y]). Of the total number of patients, 97% had a smoking history. Twenty-four adenocarcinomas, 4 squamous cell carcinomas, and 2 poorly differentiated carcinomas were distributed throughout all lobes and were predominantly peripheral. Some cystic airspaces appeared in previously normal lungs, whereas others were preceded by subcentimeter nodules. Twenty of 30 cases demonstrated increased soft tissue due to wall thickening, increased loculations, enlargement and/or increased attenuation of a mural nodule, or replacement by a mass. 18F-fludeoxyglucose uptake was present if solid components measured >8 mm. Twenty of 30 patients demonstrated >1 cystic lesion or ground-glass nodule, lymphadenopathy, or evidence of prior lung resection. Pathologic analysis revealed that cystic airspaces correspond to a check-valve mechanism, adenocarcinoma superimposed on emphysema, cystification, and adenocarcinoma parasitizing a preexisting bulla. Fourteen of 26 tumors and 64% of adenocarcinomas tested positive for an alteration of *KRAS* with or without other alterations.

Conclusions: Cystic airspaces preceded by nodules can evolve into NSCLCs. Wall thickening and/or mural nodularity may develop. Location in the periphery of the upper lobes, emphysema, additional cystic lesions or ground-glass nodules, lymphadenopathy, and prior lung cancer should further increase suspicion. Cystic airspaces on CT can be due to a check-valve mechanism obstructing the small airways, lepidic growth of adenocarcinoma in an area of emphysema, cystification of tumor due to degeneration, or adenocarcinoma growing along the wall of a preexisting bulla. *KRAS* mutations are the predominant genetic alterations.

Key Words: lung cancer, computed tomography, positron emission tomography, molecular analysis, lung cancer screening

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The United States Preventive Services Task Force has endorsed lung cancer screening using low-dose computed tomography (CT).[1] Lung cancer–screening services are currently covered for eligible beneficiaries by the Centers for Medicare and Medicaid Services and private insurance companies.[2,3]

Lung cancers associated with cystic airspaces have been observed in 3.7% of cases in the International Early Lung and Cardiac Action Program (I-ELCAP) study and have also been reported in a European lung cancer–screening cohort.[4,5] A cystic airspace is a circumscribed parenchymal air-containing lesion with a well-defined wall at the interface with a normal lung. Even though this is a rare manifestation of lung cancer, radiologists involved in lung cancer screening are likely to encounter these lesions given that millions of Americans qualify for lung cancer screening.[6] Although it is the purpose of screening to identify cancers early, little is known about the early indicators that a cystic airspace is a part of lung cancer and not a benign pulmonary cyst that can occur in 8% of patients over 40 years old.[7] Neither the current version of the Lung Imaging Reporting and Data System (Lung-RADS), a structured reporting and management system for lung cancer–screening CT examinations, nor Fleischner Society guidelines provide specific guidance for cystic lesions.[8–10]

A recent analysis of missed carcinomas visible on lung cancer–screening CT examinations performed during the Dutch-Belgian lung cancer–screening group showed that 23% (5/22) of missed cancers were "bulla with wall thickening or a mural nodule," which qualify as lung cancers associated with cystic airspaces.[11] This suggests that timely detection and treatment of these lesions requires a better understanding of the early manifestation of lung cancers associated with cystic airspaces.

The purpose of this study is to investigate the natural history of non–small cell lung cancers (NSCLCs) associated with cystic airspaces, including histopathology and molecular analysis.

MATERIALS AND METHODS

Patient Population

With approval from the Institutional Review Board, 2954 consecutive patients newly diagnosed with NSCLC at a tertiary care hospital between January 2010 and 2015 were retrospectively identified in an institutional database.

Medical Record Review

Patient demographics, smoking history, clinicopathologic tumor stage at diagnosis, and history of prior or subsequent lung cancers were extracted from the medical records. Clinical notes, operative reports, and pathology reports were reviewed. Survival was censored 2 years after diagnosis.

CT and 18F-Fludeoxyglucose Positron Emission Tomography (FDG-PET)

All CT examinations that showed a part of the lung before the date of histopathologic diagnosis of lung cancer were identified in the picture archiving and communication system (PACS). This included CT examinations of the neck, chest, abdomen, and thoracic spine, as well as CT images obtained in conjunction with FDG-PET. Images were acquired between 2000 and 2015 on CT scanners from three manufacturers (General Electric, Siemens, Philips), both with and without intravenous contrast. The slice thickness for each study was between 1.25 and 5 mm, and thinner sections predominated in the recent years of data collection.

Patients were excluded if not >1 CT examination showed the location of the lung cancer, or if the date between the first and the last CT examination before histopathologic diagnosis (observation period) was <6 months.

Evaluation of Imaging Studies

A total of 34,801 CT examinations obtained before lung cancer diagnosis in 2954 patients were evaluated on a PACS workstation (Agfa HealthCare, Greenville, SC) for the presence of a cystic airspace at the site of the subsequently diagnosed lung cancer with a fixed lung window setting (width, 2000; level, -500). Cystic airspace was defined as a circumscribed parenchymal air-containing lesion with a well-defined wall at the interface with a normal lung.

First, a fellowship-trained thoracic radiologist (F.J.F., 7 y of experience; reader 2) and a medical student (J.K.B.) reviewed the CT images. Reader 1 was intimately familiar with the published literature on cystic lung cancers and had been trained to identify cyst-associated lung cancers using PACS on a series of 15 cases collected at our institution. The task of reader 1 was to screen the database with maximum sensitivity and to flag all lung cancers that demonstrate air within or next to the tumor at some point leading up to the histologic diagnosis. If available, coronal and sagittal reformats were reviewed in addition to axial images. Flagged cases were forwarded for review by reader 2 who assessed whether cystic airspaces were present and if any of the following exclusion criteria applied: (a) airspace in the center of a previously solid lesion suggesting cavitation; and (b) airspace cannot be differentiated from the surrounding emphysema, bronchiectasis, or cystic interstitial lung disease. Reader 2 also randomly selected 3% of cases not forwarded by reader 1 to check whether reader 1 had missed any cases of cyst-associated lung cancers.

Second, CT examinations identified by reader 2 as showing a cystic airspace associated with the lung cancer were analyzed by 2 senior thoracic radiologists (S.R.D. and J.O.S., 12 and 30 y of experience, respectively) blinded to all data except for date of lung cancer diagnosis and lung cancer location. Readings were performed independently, and if there were differences they were resolved through consensus.

The presence of pulmonary emphysema was visually assessed and scored as either present or absent. Emphysema was defined as abnormal enlargement of airspaces distal to the terminal bronchioles without a discernable wall.

The following parameters were recorded for each cancer at each time point: (1) lobe of the lung; (2) location (peripheral if the lesion was observed within the outer third of the lobe; otherwise, it was considered central); (3) lesion type (nodule, cystic airspace, both); (4) maximum axial diameter (cystic airspaces were measured from inner wall to inner wall); (5) maximum wall thickness and consistency (solid, nonsolid, or part solid); (6) extent of wall thickening in degrees (0 degree representing no thickening and 360 degrees representing circumferential wall thickening); and (7) size and consistency (solid, nonsolid, or part solid) of the dominant mural nodule, if present. Measurements were made with an electronic caliper-type measurement tool.

The first CT showing a cystic airspace associated with a cancer was referred to as first observation. The presence of additional cystic lesions, ground-glass nodules, lymphadenopathy, and evidence of prior lung resection was assessed on the last chest CT examination obtained before histopathologic diagnosis. If an FDG-PET examination had been obtained within a month before histopatholgic diagnosis, the FDG uptake associated with the lesion was scored as absent (isointense to lung), moderate (isointense to adjacent mediastinal blood pool), or marked (hyperintense to adjacent mediastinal blood pool) based on qualitative visual analysis.

Tumor Morphology

Lung cancers were classified by morphology on each CT obtained during the observation period using a modified classification system based on work by Mascalchi et al.[5] The modified classification scheme consisted of a number, optional uppercase letters, and a lowercase letter (Fig. 1). The number 0 indicates a thin-walled cystic airspace (maximum wall thickness of 1 mm). Number 1 denotes a cystic airspace with an endophytic nodule. Number 2 denotes a cystic airspace with an exophytic nodule. Number 3 refers to a thick-walled cystic airspace (wall thickness >1 mm). The optional uppercase letters indicate the consistency of a nodule, mural nodule, or wall thickening: "S" stands for solid, "NS" for nonsolid (also known as ground glass), and "PS" for part solid (part solid, part ground glass). The lowercase letter indicates whether the cystic airspace is unilocular (u) or multilocular (m).

Pathologic Analysis

A subspecialized pulmonary pathologist (M.K., 15 y of experience) and a pathology resident (W.R.J., 1 y of experience) reviewed available histopathologic slides to identify the etiology of the cystic airspace. A fellowship-trained thoracic radiologist (F.J.F.) displayed representative CT images of the lesion obtained just before histopathologic diagnosis to help identify the most relevant pathologic sections. Tissue diagnosis was compared with the pathology report issued as part of routine clinical care.

A subset of the cohort underwent molecular testing with SNaPshot[12] and/or fluorescence in situ hybridization assays for *ALK*, *ROS1*, and *RET* fusions and/or amplifications of *EGFR*, *MET*, *FGFR1*, and *PDGFRA*. Depending on what was standard of care at our institution at the time of diagnosis, SNaPshot Version 1, 2, 3, or 4 was used.

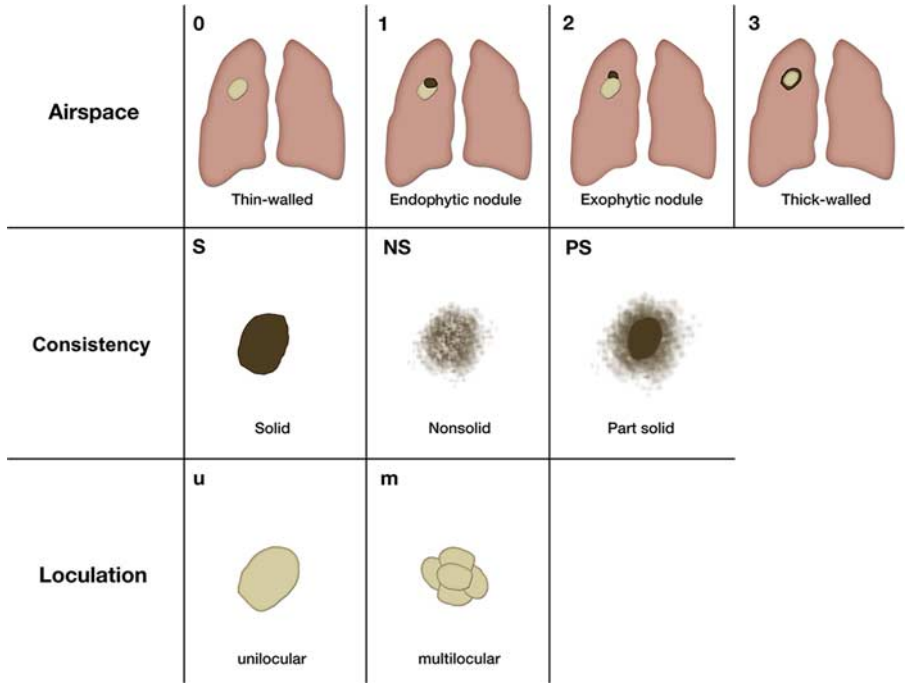

FIGURE 1. Classification scheme of lung cancers associated with cystic airspaces. full color online

The results of the mutational analysis were retrieved from the pathology database.

Statistical Analysis

Data were collected and analyzed in Excel (Microsoft, Redmond, WA). Descriptive data were presented as means with range, medians with 25th and 75th interquartile range (IQR), or as percentages for categorical variables. Sex, age at diagnosis, smoking history, and pack-years of patients with cyst-associated lung cancers were compared with those of patients who did not have a cyst-associated lung cancer. Comparisons were made using the Fisher exact test with a 2-tailed *P*-value. Statistical significance was set at $P \leq 0.05$. Doubling time was calculated for maximum cyst diameter, wall thickness, and mural nodules according to Schwartz.[13]

RESULTS

Cystic airspaces were identified in or adjacent to primary lung cancers in 30 of 2954 patients (1%) at some point leading to histologic diagnosis. A total of 2924 patients were excluded, including 325 patients with an observation period of < 6 months or lack of serial CT examinations. No patients were excluded because of cystic interstitial lung disease or bronchiectasis.

The observation period for each included cancer was on average 4.4 years (range, 0.5 to 12.3 y). A total of 176 CT examinations were performed during the observation period with a median of 5 time points per patient (IQR, 3 to 7). The median time between CT scans was 5.8 months (IQR, 2.8 to 10.4 mo). The median time between the first observation of a cystic airspace and lung cancer diagnosis was 25.5 months (IQR, 10.8 to 45.3 mo).

Characteristics of the Study Population

The group of patients with cyst-associated NSCLC consisted of 12 men (40%) and 18 women (60%), with a mean age of 66.2 years (range, 44 to 87 y) at the time of diagnosis (Table 1). Eleven patients were current smokers, and 18 patients were former smokers. One patient was a never smoker. The mean number of pack-years among smokers was 45 (range, 15 to 110). At the time of histopathologic diagnosis, 18 cases were stage I (60%), 5 cases were stage II (17%), 2 cases were stage IIIA (6%), and 5 cases were stage IV (17%). Fourteen patients (47%) had prior or subsequent lung cancers (Table 1).

The group of patients whose lung cancer was not associated with a cystic airspace comprised 1301 men (45.5%) and 1623 women (55.5%), with a mean age of 65.3 years (range, 14 to 96 y) at the time of diagnosis. A total of 631 patients were current smokers and 1714 patients were former smokers; 579 patients never smoked. The mean number of pack-years among smokers was 46 (range, 15 to 110).

There were significantly fewer never smokers among patients with cyst-associated NSCLC compared with patients whose lung cancer was not associated with a cystic airspace ($P = 0.0194$). No other statistically significant difference was identified between the 2 groups with regard to sex, age at diagnosis, smoking history, and pack-years.

Two years after diagnosis, 12 of 29 patients (41%) were found to have died, and 1 patient was lost to follow-up.

Serial CT Findings

Pulmonary emphysema was present in all patients with a smoking history. Tumors were uniformly distributed throughout the lung, with 6 in the right upper lobe (20%), 3 in the right middle lobe (10%), 8 in the right lower lobe (27%), 7 in the left upper lobe (23%), and 6 in the left lower lobe (20%). Lesions were predominantly peripheral (80%) rather than central (20%).

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TABLE 1. Characteristics of Patients With Cyst-associated NSCLC

Patient	Sex	Age (y)	Pack-Years	Clinicopathologic Stage at Diagnosis	Prior or Subsequent Lung Cancer
1	F	67	40	I	Yes
2	M	84	60	I	Yes
3	M	76	110	II	Yes
4	F	80	63	I	No
5	F	59	49	IV	Yes
6	F	73	60	I	Yes
7	F	69	20	I	No
8	M	84	70	II	Yes
9	F	61	45	II	No
10	F	52	30	I	Yes
11	F	63	25	I	Yes
12	M	87	0	IV	No
13	M	77	40	I	No
14	F	73	25	I	No
15	F	59	20	I	Yes
16	F	64	60	I	No
17	F	65	40	IV	No
18	F	48	68	I	Yes
19	M	66	40	I	Yes
20	M	61	47	I	Yes
21	M	60	54	II	Yes
22	F	77	50	I	Yes
23	M	76	60	IV	No
24	M	58	30	I	No
25	F	55	20	I	No
26	F	69	50	IV	No
27	F	49	60	IIIA	No
28	M	55	40	I	No
29	M	44	15	IIIA	No
30	F	74	20	II	No

F indicates female; M, male.

CT was available before the appearance of a cystic airspace in the location of the lung cancer in 12 cases. A nodule was observed to precede the cystic airspace in 50% (6/12) of cases. These nodules were solid in 2 cases, measuring 4 and 7 mm, and ground glass in 3 cases, measuring 6, 6, and 10 mm. One nodule was part solid and measured 5 mm. When preceded by a nodule, the cystic airspace appeared after a median of 16.1 months (IQR, 9.4 to 18.6 mo), either in the location of the nodule or abutting the nodule. Normal lung without focal lesion was demonstrated in the location where the cystic airspace subsequently appeared in 50% (6/12) of cases (Table 2).

At first observation, 24 cystic airspaces were unilocular and 6 were multilocular. During the observation period 6 cystic airspaces changed from unilocular to multilocular. One lesion (patient 6) changed from unilocular to multilocular and back to unilocular. All lesions that started out as multilocular stayed multilocular.

At first observation, the median diameter of the cystic airspaces was 11 mm (IQR, 5 to 15 mm). The median diameter at the end of the observation period was 14 mm (IQR, 10 to 21 mm). Cyst diameter increased in 16 cases with a doubling time of 454 days (IQR, 160 to 844 d). Cyst diameter decreased in 7 cases because of increased wall thickness and remained constant in 7 cases. The cystic airspace of 1 patient (patient 7) disappeared intermittently (Table 2).

At first observation, the median wall thickness of cystic airspaces was 2 mm (IQR, 1 to 4 mm). Wall thickness remained unchanged during the observation period in 9 cases and increased in 21 cases with a median doubling time of 188 days (IQR, 134 to 477 d) to a median 5 mm (IQR, 3 to 6 mm) at the end of the observation period. In 7 of these cases the cancer was located in an exophytic or endophytic mural nodule. No decrease in wall thickness was observed. If present, wall thickening involved a median of 180 degrees (IQR, 0 to 360 degrees) at first observation and 360 degrees (IQR, 270 to 360 degrees) at the end of the observation period.

A mural nodule was present at first observation in 19 of 30 cystic airspaces. Nodules were solid in 12 cases, part solid in 6 cases, and nonsolid in 1 case. The median maximal diameter was 6 mm (IQR, 4 to 12 mm). A mural nodule was absent in 11 cystic airspaces at first observation: 5 lesions were thin walled and unilocular, and 2 lesions were thin walled and multilocular. Two lesions were thick walled and unilocular, and 2 lesions were thick walled and multilocular. Mural nodules developed in 6 of the thin-walled lesions and in 2 of the thick-walled lesions after a median period of 25 months (IQR, 11 to 92 mo). At the end of the observation period, there was a mural nodule in 18 of 30 cases (16 solid, 1 part solid, and 1 nonsolid). The median maximum diameter of the mural nodule at the end of the observation period was 11 mm (IQR, 8 to 16 mm) with a median doubling time of 250 days (IQR, 130 to 388 d). In 7 cases the diameter of the mural nodule remained unchanged throughout the observation period. Nine lesions had developed a thick wall at the end of the observation period,

TABLE 2. Evolution of Tumor Morphology on Serial CT Examinations During the Observation Period

	Time Point													
Patient	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
1	0u	0u	0u	0u	0u	0u	3NSu	3PSu	3PSu					
2	S	1Su	1Su	1Su										
3	NS	NS	1Su	3Su										
4	Normal	1Sm	1Sm											
5	Normal	0u	3PSm											
6	Normal	1Su	1Su	1Sm	1Sm	1Sm	1Sm	1Sm	2Su	2Su	2Su	2Su	2Su	2Su
7	3Su	PS	3NSu	3NSu	3NSu	3NSu								
8	1PSu	1PSu	1Su											
9	Normal	0m	1Sm	1Sm	1Sm									
10	1Su	1Su	1Su	1Su	1Su	1Sm								
11	PS	PS	3PSu	3PSm	3PSm									
12	1PSu	1PSu	1Su	S										
13	NS	NS	NS	1NSu	1NSm	1NSm								
14	Normal	0u	0u	0u	0u	0u	1Su	1Su	3Su					
15	NS	1Su	1Su	1Sm	1Sm	1Sm	1Sm	1Sm	1Sm	1Sm	1Sm	1Sm	1Sm	1Sm
16	S	1Su	1Su											
17	3PSm	3PSm	1Sm											
18	1PSu	1PSu	1Su	1Sm	1Sm	1Sm								
19	Normal	1Su	1Su	1Sm	1Sm	1Sm								
20	2Su	2Su	2Su	2Su										
21	2Su	S												
22	0m	0m	0m	0m	0m	0m	0m	0m	0m	3Sm	3Sm	3Sm	3Sm	1Sm
23	0u	1PSu	1PSu	2Su	2Su	2Su	2Su							
24	3NSu	0u	1NSu	1NSu	1NSu	1NSu	1PSu	1PSu	1PSu					
25	3NSm	3NSm												
26	1Su	1Su	1Su	1Su										
27	0u	0u	0u	2NSu	2Su	2Su	2Su							
28	1PSu	1Su	3Su											
29	1PSu	1Su	1Su	1Su	S									
30	1PSm	1PSm	1PSm	1Sm	3Sm									

Lesions are classified using the classification scheme detailed in Figure 1.

and the cystic airspace was replaced by a solid mass in 3 patients. Overall, the soft tissue component of 67% of cases (20/30) increased during the observation period, either due to development of wall thickening, increased attenuation of a mural nodule, increased number of loculations, or replacement of the airspace by a solid mass.

The last chest CT obtained before histopathologic diagnosis demonstrated at least one of the following in addition to the index lesion in 20 patients (67%): a cystic airspace in addition to the index lesion was present in 7 patients (23%), 4 of which were subsequently diagnosed as metachronous primary lung cancers (follow-up, 1 to 4 y); persistent multifocal ground-glass opacities were present in 6 patients (20%); hilar and/or mediastinal lymphadenopathy was present in 5 patients (17%); and evidence of prior lung resection was present in 6 patients (20%) and was related to lung cancer treatment.

FDG-PET Findings

FDG-PET examinations were available for 21 (70%) patients. FDG uptake was associated with a mural nodule in 16 lesions: moderate in 4 cases and marked in 12 cases. There was FDG uptake associated with the wall of 13 lesions: moderate in 2 and marked in 11. In 3 cases only the nodule demonstrated FDG uptake, whereas the wall of the cystic airspace did not. The solid component of mural nodules not associated with FDG uptake measured < 8 mm. Wall thickening of cystic airspaces without a dominant mural nodule (patients 5, 28, and 30) demonstrated FDG uptake when the solid component measured > 8 mm.

Histopathology

Histopathologic diagnosis for routine care was established with wedge resection specimens (n = 10), lobectomy specimens (n = 14), transthoracic needle biopsy (n = 4), and mediastinoscopy (n = 2) (Table 3). There were 24 cases of adenocarcinoma (80%), 4 cases of squamous cell carcinoma (13%), and 2 cases of poorly differentiated carcinoma (7%). Slides from 27 (70%) cases underwent joint review. Whereas slides of 6 cases (4 transthoracic needle biopsies and 2 mediastinoscopies) did not demonstrate the cystic component, it was identified on sections of 12 lobectomy specimens and 9 wedge resection specimens of 18 lung adenocarcinomas and 3 lung squamous cell carcinomas. The slides of 1 wedge resection and 2 lobectomy specimens prepared for adenocarcinoma could not be located.

The initial tissue diagnosis was confirmed in all reviewed cases, and necrosis was found to be absent in all cases. Four patterns were identified in the location of the cystic airspace seen on CT: a check-valve mechanism involving the small airways leading to outflow obstruction was suspected in 38% (8/21) of cases and was associated with the presence of scar tissue (Fig. 2). Lepidic growth of adenocarcinoma superimposed on destroyed alveolar walls due to emphysema was observed in 29% (6/21) of cases (Fig. 3). Cystification of tumor was observed in 19% (4/21) of cases: in 3 squamous cell cancers and in 1 adenocarcinoma (Fig. 4). The lesions measured between 1.2 and 4.1 cm in diameter at the time of diagnosis, and one of them (patient 16) presented as a 4 mm solid nodule before the appearance of a cystic airspace. Cytomorphologic features observed in lesions demonstrating cystification suggested degeneration of a solid tumor due to vascular insufficiency but no necrosis was identified. Growth of adenocarcinoma along the wall of a preexisting bulla was identified in 14% (3/21) of cases (Fig. 5).

TABLE 3. Specimen Type and Histologic Analysis

Patient	Specimen Type	Histology	Key Histologic Feature
1	Wedge resection	ADC	Bulla
2	Wedge resection	ADC	Emphysema
3	Lobectomy	ADC	Emphysema
4	Lobectomy	ADC	Check-valve
5	Wedge resection	ADC	Emphysema
6	Wedge resection	SqCC	Cystification of tumor
7	Lobectomy	ADC	Emphysema
8	Lobectomy	ADC	NA
9	Lobectomy	ADC	Check-valve
10	Wedge resection	ADC	Check-valve
11	Wedge resection	ADC	Check-valve
12	PTNB	Poorly differentiated	NA
13	Lobectomy	ADC	Emphysema
14	Lobectomy	ADC	Check-valve
15	Wedge resection	ADC	Check-valve
16	Lobectomy	SqCC	Cystification of tumor
17	PTNB	ADC	NA
18	Wedge resection	ADC	NA
19	Lobectomy	SqCC	Check-valve
20	Wedge resection	ADC	Bulla
21	Lobectomy	ADC	NA
22	Lobectomy	ADC	Bulla
23	PTNB	Poorly differentiated	NA
24	Wedge resection	ADC	Check-valve
25	Lobectomy	ADC	Emphysema
26	PTNB	ADC	NA
27	Mediastinoscopy	ADC	NA
28	Lobectomy	SqCC	Cystification of tumor
29	Mediastinoscopy	ADC	NA
30	Lobectomy	ADC	Cystification of tumor

ADC indicates lung adenocarcinoma; NA, pathology slides not available for review or cystic airspace not sampled; PTNB, percutaneous needle biopsy; SqCC, lung squamous cell carcinoma.

Mutational Analysis

Mutational analysis was available for 26 (87%) cases (Table 4). As expected in patients with significant smoking history, 54% (14/26) of all tumors and 64% of 22 adenocarcinomas tested positive for an alteration of *Kirsten rat sarcoma viral oncogene homolog* (*KRAS*) with or without other alterations. Among tumors with a *KRAS* mutation, G12C was the most common subtype (7/14). Of 4 squamous cell carcinoma cases, 1 harbored mutation of *discoidin domain receptor tyrosine kinase 2* (*DDR2*), *phosphoinositide-3-kinase, catalytic, α polypeptide* (*PIK3CA*), and *TP53*, whereas *fibroblast growth factor receptor 1* (*FGFR1*) and *epidermal growth factor* (*EGFR*) amplification were present in 1 each. No alterations in the examined genes were identified in a poorly differentiated tumor from a never smoker as well as in 7 adenocarcinomas.

DISCUSSION

This study shows that NSCLCs associated with cystic airspaces are statistically more likely to occur in smokers and are associated with emphysema. Tumors can occur in any lobe, more likely peripheral than central. The cystic

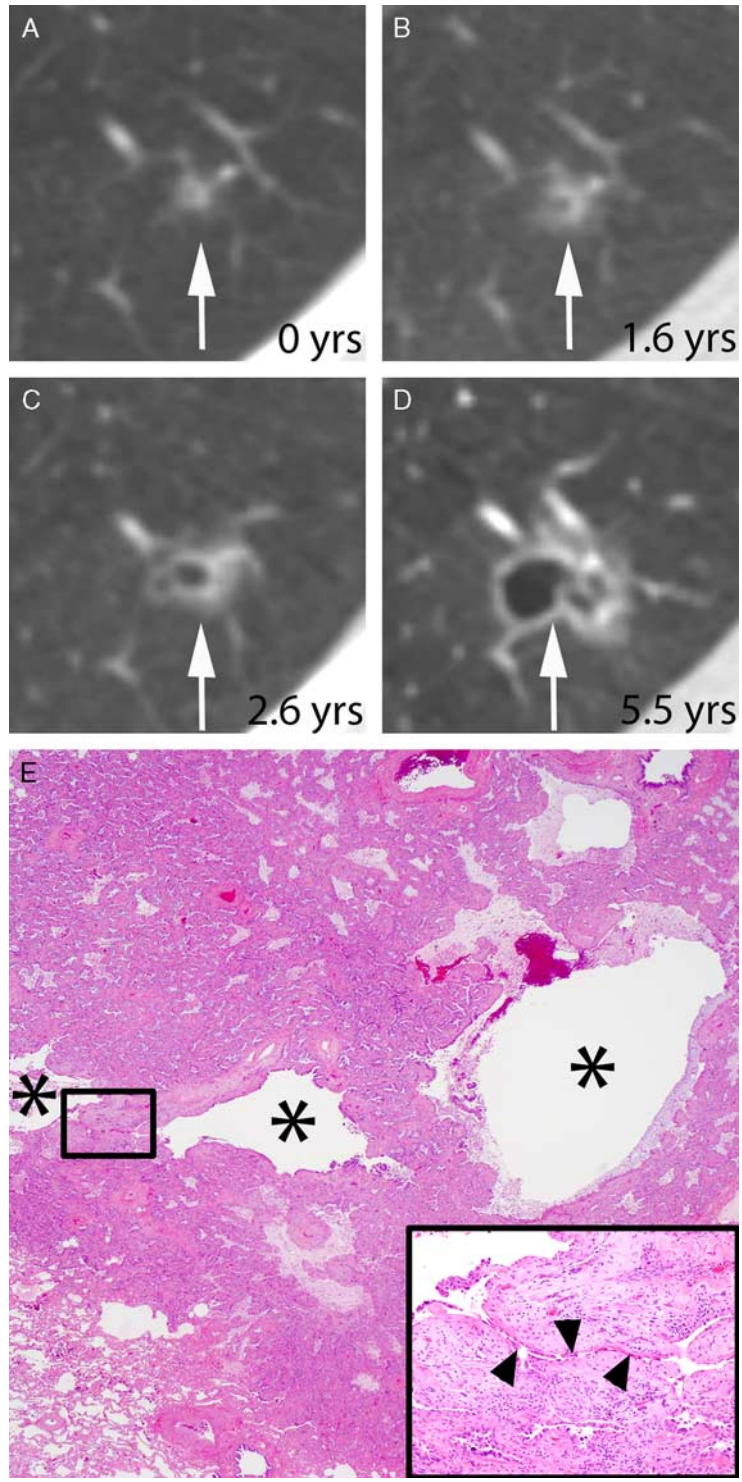

FIGURE 2. A, Composite of serial CT images of a 63-year-old female patient with a 25 pack-year smoking history (patient 11) demonstrating evolution of a part solid 5 mm left lower lobe nodule (A, arrow) into a 17 mm multilocular cystic airspace with a thick wall demonstrating both solid and ground-glass components (D, arrow) corresponding to an adenocarcinoma over 5.5 years. The second (B) and third (C) time points were obtained 1.6 and 2.6 years after baseline (A). E, Histologic image (hematoxylin and eosin stain, $\times 2$) of patient 11 demonstrates adenocarcinoma containing cystic airspaces (asterisks) separated by areas of scar narrowing small airways, thereby creating a check-valve mechanism. The inset shows a magnified view of the airflow passage (arrowheads) narrowed by scar tissue. full color online

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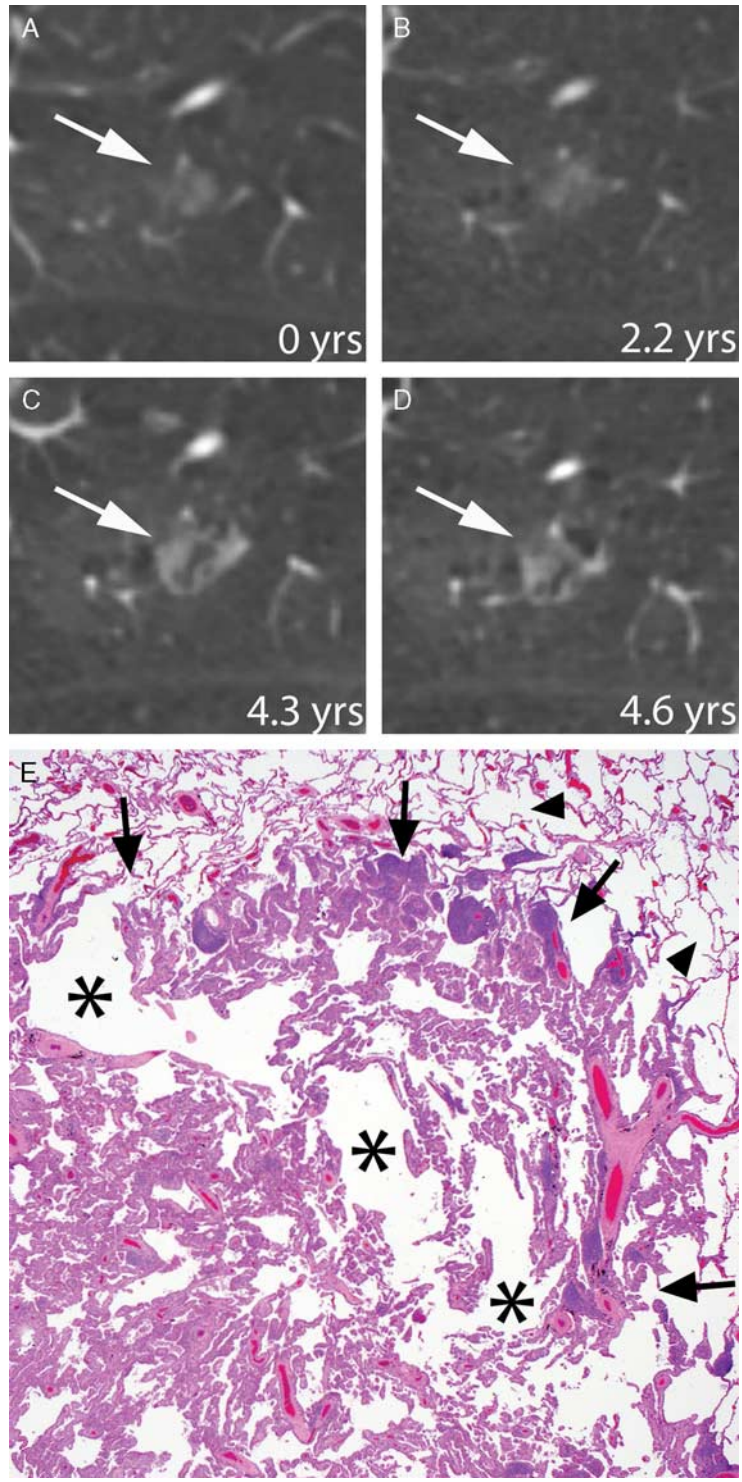

FIGURE 3. Composite of serial CT images of a 77-year-old male patient with a 40 pack-year smoking history (patient 13) demonstrating evolution of a nonsolid (ground glass) 8 mm left upper lobe nodule (A, arrow) into an 18 mm multilocular cystic airspace with an endophytic nonsolid (ground glass) nodule (D, arrow) corresponding to an adenocarcinoma over 4.6 years. The second (B) and third (C) time points were obtained 2.2 and 4.3 years after baseline (A). E, Histologic image (hematoxylin and eosin stain, ×2) of patient 13 demonstrates lepidic growth adenocarcinoma (arrows) superimposed on emphysema resulting in multilocular cystic airspaces (asterisks) surrounded by tumor. Destroyed alveolar walls without tumor are best appreciated in the top right corner (arrowheads). full color online

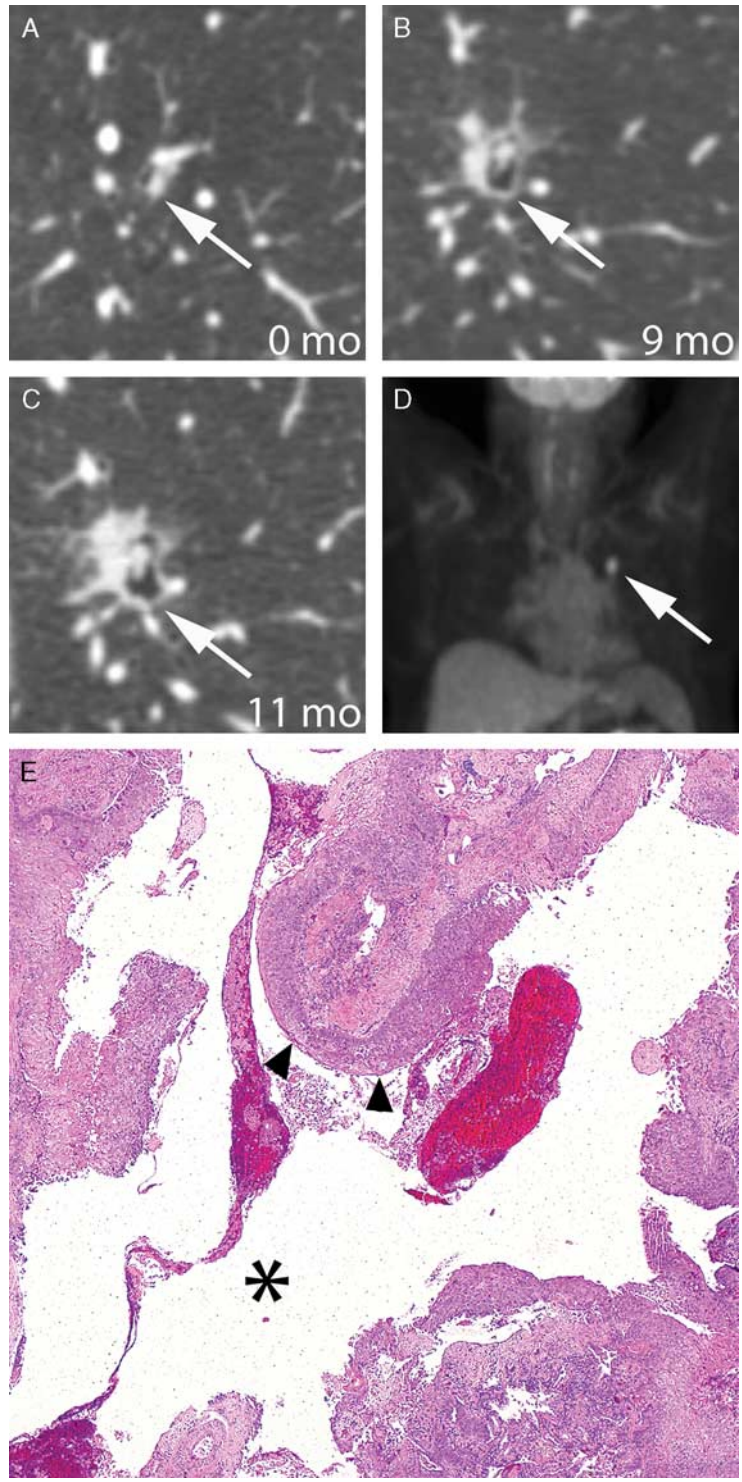

FIGURE 4. Composite of serial CT images (A–C) and an FDG-PET image (D) of a 64-year-old female patient with a 60 pack-year smoking history (patient 16) demonstrating evolution of a 6 mm left upper lobe solid nodule (A, arrow) adjacent to a bronchus into a 19 mm unilocular cystic airspace with an endophytic solid nodule (C, arrow) corresponding to a squamous cell carcinoma over 11 months. The second (B) time point was obtained 9 months after baseline (A). There is marked FDG uptake associated with this lesion (D, arrow). E, Histologic image (hematoxylin and eosin stain, ×2) of patient 16 demonstrates a cystic airspace (asterisk) and a residual thick fibrovascular core lined by a thick layer of squamous cell carcinoma (arrowheads). No necrosis was identified. full color online

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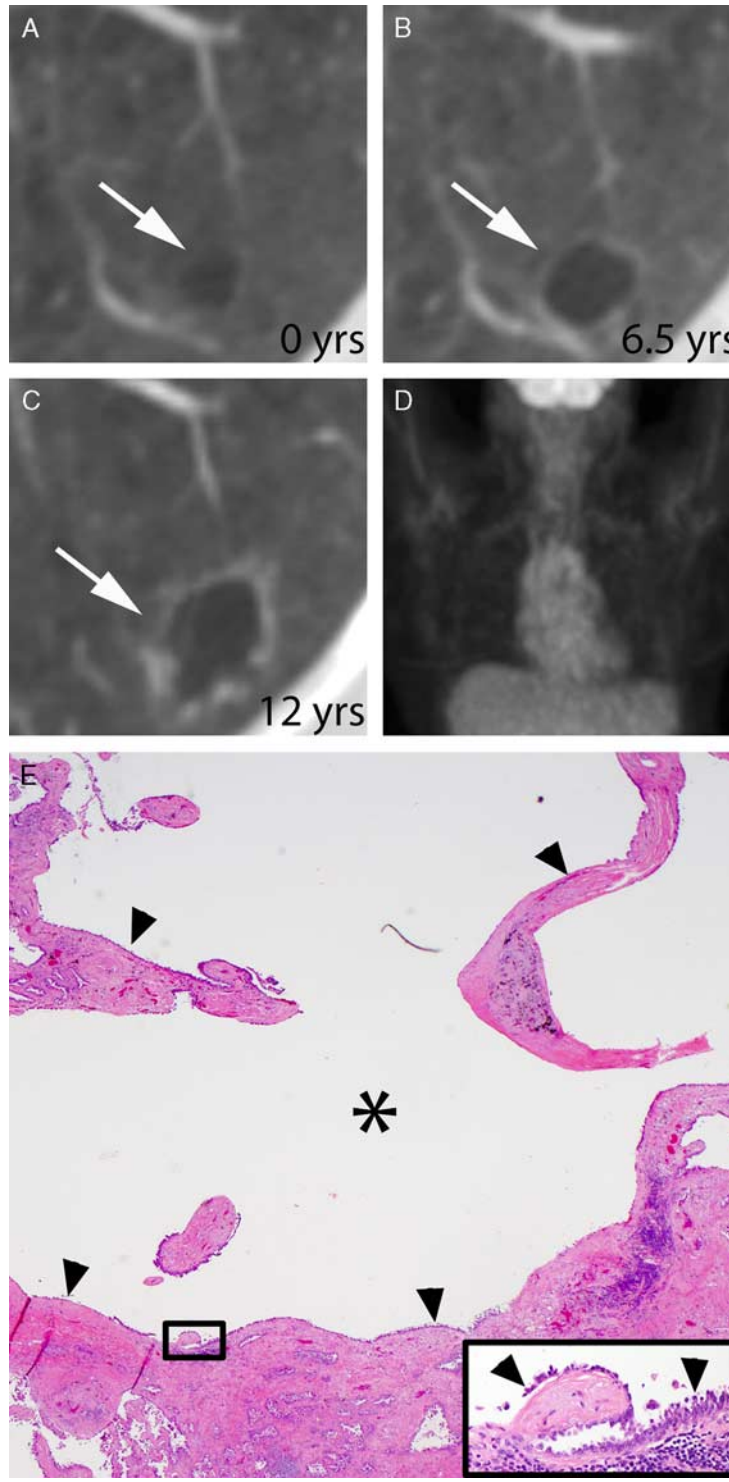

FIGURE 5. Composite of serial CT images (A–C) and an FDG-PET image (D) of a 67-year-old female patient with a 40 pack-year smoking history (patient 1) demonstrating evolution of a 7 mm left lower lobe thin-walled unilocular cystic airspace (A, arrow) into a 24 mm unilocular cystic airspace with a thick wall demonstrating both solid and ground-glass components (C, arrow) corresponding to an adenocarcinoma over 12 years. The second (B) time point was obtained 6.5 years after baseline (A). No FDG uptake is associated with this lesion (D). E, Histologic image (hematoxylin and eosin stain, ×4) of patient 1 demonstrates a part of a preexisting bulla (asterisk indicates lumen) with lepidic growth of adenocarcinoma lining the wall (arrowheads). The inset shows a magnified view of lepidic adenocarcinoma spreading along the bulla wall (arrowheads). full color online

TABLE 4. Mutational Analysis

	Mutations							
Patient	***KRAS***	***PIK3CA***	***TP53***	***EGFR***	***FGFR1***	***MAP2K1 (MEK1)***	***CDKN2A***	***DDR2***
1	G12C	N	N	N	N	N	N	N
2	G12V	N	N	N	—	N	—	—
3	G12C	H1047L	N	N	—	N	—	—
4	N	N	N	N	N	N	N	N
5	G12D	N	N	N	—	—	—	—
6	N	N	N	Amp	—	N	—	—
7	N	N	N	N	—	—	—	—
8	G12A	N	N	N	N	N	—	—
9	N	N	R175H	N	—	K57N	—	—
10	—	—	—	—	—	—	—	—
11	G12V	N	N	N	N	N	N	N
12	N	N	N	N	—	N	—	—
13	N	N	N	N	N	N	N	N
14	G12C	N	N	N	N	N	N	N
15	N	N	N	N	—	N	—	—
16	N	N	N	N	Amp	N	—	—
17	G12C	N	R248L	N	—	N	—	—
18	G12C	E542K	N	N	—	—	—	—
19	—	—	—	—	—	—	—	—
20	G12C	N	N	N	—	N	—	—
21	G12A	N	N	N	—	N	—	—
22	N	N	N	N	—	N	—	—
23	—	—	—	—	—	—	—	—
24	N	N	N	N	—	—	—	—
25	—	—	—	—	—	—	—	—
26	G12V	N	N	N	—	N	—	—
27	N	N	N	N	—	N	—	—
28	N	Q542K	V157F	N	N	N	N	S732R
29	G12D	P104L	L194R	N	N	N	R58*	N
30	G12C	N	N	N	N	N	N	N

Amp indicates amplification; CDKN2A, cycline dependent kinase inhibitor; DDR2, discoidin domain receptor tyrosine kinase 2; EGFR, epidermal growth factor; FGFR1, fibroblast growth factor receptor 1; KRAS, Kirsten rat sarcoma viral oncogene homolog; MAP2K1, mitogen-activated protein kinase kinase 1; MEK1, mitogen-activated protein kinase kinase 1; N, tested, but not present; PIK3CA, phosphoinositide-3-kinase, catalytic, α polypeptide; TP53, tumor protein p53.

airspace can be preceded by a small nodule. The number of loculations may increase over time, wall thickening may develop or become more extensive, and one or more mural nodules may appear, enlarge, and/or increase in attenuation. Additional cystic lesions or ground-glass nodules, lymphadenopathy, or evidence of prior lung resection for lung cancer is present in 67% of patients. FDG-PET is helpful for characterization if the solid component of the lesion measures 8 mm or more.

This observational study focuses on the temporal evolution of lung cancers associated with cystic airspaces. It has been well documented that a cystic airspace that develops wall thickening and/or mural nodularity is suspicious for lung cancer.[4] However, it has not yet been determined what precedes the cystic airspaces.

This study showed that some cystic airspaces appear in a previously normal lung. This implies that, although a new thin-walled cyst may represent a benign postinfectious or posttraumatic pneumatocele, the appearance of a new cyst merits attention on subsequent examinations to assess for development of wall thickening and/or nodularity.

Other cystic airspaces were preceded by a subcentimeter nodule. To our knowledge, the information that a small nodule can precede a cystic airspace associated with a lung cancer has not previously been reported. This finding might be helpful to determine whether a new cyst identified on CT is a benign pulmonary cyst or a lesion suspicious for lung cancer. Araki et al[7] demonstrated that benign pulmonary cysts appear in 8% of patients older than 40 years of age. Benign pulmonary cysts are most likely solitary, in the peripheral area of the lower lobes, and mostly remain unchanged or slightly increase in size over time. Although benign pulmonary cysts can occur in smokers, there is no association with emphysema.[7] In contrast, lung cancers associated with cystic lesions occur throughout the lung, more likely peripheral than central, and present as multiple cystic lesions 23% of the time and were more frequently observed in smokers in this study.

Prior studies of lung cancers associated with cystic airspaces have described a linear process during which a cystic airspace first develops wall thickening, which then transforms into a mural nodule, or the cystic airspace is replaced by a solid mass.[4,5] The report of Farooqi and colleagues is based on serial CT findings in 13 patients. Serial CT findings in 30 patients presented in this study confirm that development of wall thickening and/or mural nodules, and replacement of the cystic airspace by soft tissue, indicates that a cystic airspace is part of a lung cancer. This holds true for preexisting benign bullae that are parasitized by cancer and for new cystic airspaces that are preceded by a nodule. Farooqi et al[4] observed that

cystic airspaces developed wall thickening and/or a mural nodule after a median of 35 months, similar to the median of 25 months to the emergence of a mural nodule documented in this study. Median doubling times were 250 days for mural nodules and 188 days for wall thickening. However, this study documents that the emergence of a mural nodule is independent of the presence or increase of wall thickening. Indeed, in 7 of 9 cases with stable wall thickness the cancer was located in an exophytic or endophytic mural nodule. Consistency of mural nodules and of the wall itself can evolve to become more solid over time as is expected in malignancy.[14]

The incidence of lung cancers associated with cystic airspaces has been reported as 0.5% in a surgical series and as 3.7% in a lung cancer–screening cohort.[4,15] The high incidence of cyst-associated lung cancers in screening cohorts could be due to the association with smoking, as screening programs focus on patients with a significant smoking history. The patients included in this study represent ~1% of all newly diagnosed NSCLCs at a tertiary referral center within a 5-year period. As 325 cases were excluded because of an observation period of <6 months or for lack of serial CT examinations, the true incidence is likely slightly higher than >1%.

Mascalchi et al[5] reported FDG uptake in cystic airspaces associated with lung cancers to be variable and sometimes absent. In this study, focal FDG uptake was observed if the solid component of a lesion measured at least 8 mm, in keeping with the current understanding that only lung cancers with solid components larger than 8 mm are expected to demonstrate focal FDG uptake.[16] Importantly, however, negative PET-CT does not preclude malignancy, and cystic airspaces with increasing soft tissue on CT should be considered highly suspicious for lung cancer.[4]

Histopathology revealed adenocarcinoma to predominate among lung cancers associated with cystic airspaces, similar to prior studies.[4,5,15] Histopathologic analysis demonstrated for the first time that a cystic airspace on CT is a shared endpoint for several processes, most commonly for a check-valve mechanism obstructing the small airways, followed by lepidic growth of adenocarcinoma in an area of emphysema, cystification of tumor due to degeneration, and adenocarcinoma growing along the wall of a preexisting bulla. That obstruction of small airways by lung cancer can result in cystic airspaces has previously been postulated but not shown,[17] while growth of tumor along the wall of a preexisting bulla has already been demonstrated.[4] Interestingly, the morphologic features observed in cases of tumor cystification more or less resembled those of pancreatic pseudopapillary neoplasms.[18] Similar to the pancreatic neoplasm the cystic changes could be due to a solid lesion undergoing degeneration except for areas adjacent to large blood vessels. The cystic space appears once the degenerative content is absorbed. Neither cystification of tumor nor lepidic growth of adenocarcinoma in an area of emphysema has previously been described as explanations for a cystic airspace on CT.

Mutational analysis revealed *KRAS* mutations as the predominant alterations. Although *KRAS* mutations are known to occur in approximately 25% of all lung cancers in the western population, this study documents an overrepresentation with over 50% of the patients harboring these mutations.[19] Relative overrepresentation for adenocarcinoma is expected in heavy smokers.[20] This finding is important as *KRAS* mutations have been associated with decreased overall survival.[21] Interestingly, Guo et al[15] encountered 3 instances of *EGFR* but no *KRAS* mutations in their analysis of 8 lung cancers associated with cystic airspaces. The difference in the prevalent mutations reported by Guo and colleagues and this study is likely due to the difference in ethnicities, as *EGFR* mutations are the most frequent driver alterations in the Asian population.[22]

Study limitations include the retrospective design and that imaging studies were obtained at variable intervals. However, the rarity of the entity under investigation makes a prospective design impractical. This largest study of lung cancers associated with cystic airspaces compiles longitudinal observations with an average of 6 time points (range, 2 to 14) per patient obtained during an average observation period of 4.4 years (range, 0.5 to 12.3 y).

In summary, longitudinal observations of treatment-naive NSCLCs associated with cystic airspaces suggest that cystic airspaces preceded by nodules can evolve into lung cancer. Wall thickening and/or mural nodularity may develop. Location in the periphery of the upper lobes, emphysema, additional cystic lesions or ground-glass nodules, lymphadenopathy, and prior lung cancer should raise suspicion. FDG-PET is useful for workup of lesions with a solid component bigger than 8 mm. Cystic airspaces on CT can be due to a check-valve mechanism obstructing the small airways, lepidic growth of adenocarcinoma in an area of emphysema, cystification of tumor due to degeneration, or adenocarcinoma growing along the wall of a preexisting bulla. *KRAS* mutations are the predominant genetic alterations.

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