Clinical Radiology 79 (2024) 842–850

Contents lists available at ScienceDirect

Clinical Radiology

journal homepage: www.clinicalradiologyonline.net

The impact of cystic lesions on the postoperative prognosis of non-small cell lung cancer: a comparative study

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ARTICLE INFORMATION

Article history:
Received 15 June 2024
Received in revised form
7 August 2024
Accepted 8 August 2024

AIM: Due to the rarity of lung cancer with cystic imaging manifestations, we explore the clinical features and survival prognosis of such tumors.

MATERIALS AND METHODS: Imaging characteristics were used to categorize 3,556 patients who underwent surgery for isolated primary lung cancer into one of three groups: those with cystic lung cancer (149), solid lung cancer (1,399), and ground-glass lung cancer (1,160). Propensity score matching by sex and age was performed to analyze the differences in clinical characteristics of lung cancer among the three groups and the correlation between clinical characteristics of cystic lesions and progression-free survival (PFS).

RESULTS: The three groups of patients differed in various aspects, including pathological type, smoking history, tumor stage, type of surgery, histological grading, and PFS ($P < 0.05$). The results of the multifactorial analysis indicated that lung cancer type, pathological type, lymph node metastasis, tumor stage, and histologic grading were independent prognostic factors for lung cancer ($P < 0.05$). After comparison, there was a difference in prognosis between cystic lung cancer and ground-glass lung cancer ($P < 0.05$).

CONCLUSION: The clinical features of cystic lung cancer are significantly different from those of ground-glass lung cancer and solid lung cancer. Cystic lesions are independent influencing factors affecting lung cancer, and the prognosis of cystic lung cancer is worse than that of ground-glass lung cancer.

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https://doi.org/10.1016/j.crad.2024.08.012

Introduction

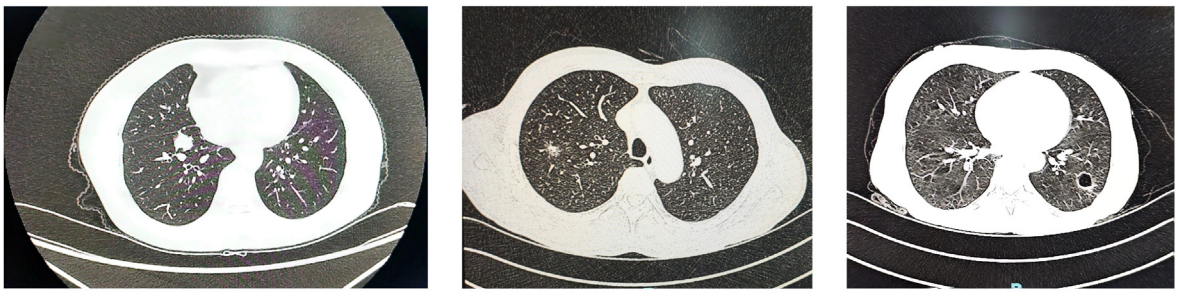
Lung cancer is currently the second most common cancer and the leading cause of cancer deaths. In males, lung cancer ranks first in incidence and mortality, while In females, it comes in second in terms of mortality, following breast cancer, and third in terms of incidence, behind colorectal cancer and breast cancer.[1] Computed tomography (CT) is currently the most common and important follow-up method. It is a major challenge for clinicians to determine the benign or malignant nature of a lung nodule or mass and diagnose lung cancer based on the imaging morphology.[2] In the clinic, based on imaging features, lung cancer can be categorized into solid lung cancer and non-solid lung cancer, in which non-solid lung cancer is mainly manifested as ground glass.[3] On chest radiographs, solid opacity refers to an exudate or other product of disease that replaces alveolar air, rendering the lung solid, and ground-glass opacity appears as an area of hazy increased lung opacity, usually extensive, within which margins of pulmonary vessels may be indistinct[3] (Fig 1). In recent years, lung cancer associated with cystic airspaces (LCCAs), a type of non-solid lung cancer, has attracted more attention from clinicians. In 1941, Womack and Graham[4] first reported lung cystic disease associated with lung cancer, after which this cystic lung cancer appeared in case reports with various forms of names.[5–10] Sheard *et al.* summarized the data from previous studies and suggested that cystic lesions may be a specific form of early lung cancer.[11] As a specific form of non-solid lesion, cystic lesions are as complex as ground-glass lesions and can be the manifestation of lung inflammation, lung infection, pulmonary fibrosis, etc., as well as malignant tumors or pre-cancerous lesions.[12] In this paper, LCCAs are defined as lung cancer diagnosed pathologically with cystic lesions on imaging, with or without solid or ground-glass lesions[11] (Fig 1). There are no definitive studies that have reported that the clinical feature of the particular morphology is different from solid and ground-glass lung cancer, and cystic lesions imply a poor prognosis.

In this study, 149 cases of cystic, solid, and ground-glass lung cancer were followed up and investigated, including 447 patients, respectively. The objective was to explore the differences between patients with cystic lung cancer and patients with solid and ground-glass lung cancer in terms of clinical characteristics. Additionally, the study revealed the postoperative prognosis of lung cancer and the relevant factors affecting the postoperative prognosis of lung cancer.

Methods

Research objectives

A total of 3,556 patients who underwent lung surgery for isolated primary lung malignancy in the Department of Thoracic Surgery and Department of Cardiothoracic Surgery between January 2019 and September 2023 were retrospectively collected. A total of 149 patients with LCCAs were included as the cystic group based on the imaging manifestations of chest CT, and the other 1,160 patients with imaging manifestations of ground-glass lesions were included as the ground-glass group (M group), and 1,399 patients with solid lesions on imaging were included in the solid group (S group). The inclusion criteria were as follows: ① malignant nodules confirmed after surgery; ② non-small cell lung cancer suggested by postoperative pathology; ③ patients' age was greater than or equal to 18 years old; ④ those who did not use chemotherapy, immunotherapy, targeted drug adjuvant therapy before surgery; ⑤ those who did not have chest CT images from our hospital before surgery; ⑥ those with poor control of their respiratory function were unable to produce images of good quality. ⑦ patients with multiple lung lesions; ⑧ no combination of other malignant cancers such as breast, kidney, liver, prostate, and so on. ⑨no previous history of lung surgery. A total of 447 patients with 149 cases each of cystic, solid, and



(a) (b) (c)

Figure 1 (a–c) are three types of lung cancer. (a) There is a homogeneous hyperdense nodular shadow in the right lower lung. (b) There is a mixed ground-glass nodule in the right upper lung. (c) There is a thin-walled cystic cavity lesion in the left lower lung.

Table 1
Age and gender characteristics of the three groups before and after PSM.

	Before PSM				After PSM			
	Group N	Group S	Group M	P	Group N	Group S	Group M	P
Age	59 (53 , 67)	64 (56 , 68)	55 (46.25 , 63)	< 0.001	59 (53 , 67)	59 (53 , 67)	59 (53 , 67)	0.999
Sex				< 0.001				0.973
Male	85	901	402		85	83	84	
Female	64	498	758		64	66	65	

Group N represents the LCCAs group, Group S represents the solid lung cancer group, and Group M represents the ground-glass lung cancer group.

ground-glass lung cancer were screened by propensity score matching (PSM). Clinical data, demographic characteristics (age, gender, smoking history, and family history of malignancy), laboratory tests, imaging tests, pathological examinations, and surgical data were recorded for the 447 matched patients. The maximum diameter was used for the tumor size, and tumor staging was based on the 2015 International Association for the Study of Lung Cancer (IASLC) 8th edition of the lung cancer TNM (tumor node metastasis) staging system, and pathological staging was based on the 2021 WHO (World Health Organization) lung tumor classification criteria.

Imaging

The instrumentation was a Siemens spiral CT machine. Scanning order: from lung apex to lung base; scanning range: neck to upper abdomen. Observations: Under the same criteria, both mediastinal window and lung window images were independently read by two thoracic surgeons with senior titles under double-blind conditions, and the diagnostic conclusions of the two were deliberated if they were controversial.

The classification criteria of three types of lung cancer: On chest radiographs, solid lung cancer presents as hyperdense lesions; ground-glass lung cancer presents as an area of hazy increased lung opacity; LCCAs present as cystic lesions with or without solid or ground-glass lesions.

Evaluation of clinical outcomes

Patients were followed for prognosis by accessing the electronic medical record system or by telephone. The last follow-up date was February 1, 2024. Progression-free survival (PFS) is defined as the time from diagnosis to first recurrence (local or distant metastasis) or death from any cause, whichever outcome was first observed, with recurrence assessed by clinical follow-up, imaging, and histological manifestations.

Statistical methods

PSM was implemented using R4.2.2 language to balance the baseline data of the three groups of cystic, solid, and ground-glass nodules. The solid and ground-glass groups were used as the control group, and the data of the three groups were matched 1:1:1, with gender and age as covariates using the nearest match method, and the caliper value was set at 0.5. Statistical analysis of the data was performed using SPSS 25.0, with non-normally distributed variables expressed as medians and categorical variables expressed as percentages. The chi-square test was used to compare the differences between the cystic and ground-glass groups, as well as the cystic and solid groups. Survival rates were estimated by using the Kaplan-Meier method, and comparisons of survival rates among the three groups were performed using the log-rank test. Patient survival curves were plotted by using GraphPad Prism 9.5.1. Lung cancer prognosis-related factors were analyzed by using Cox univariate regression, and statistically significant indicators were included in the multivariate Cox regression model. All tests were two-sided, and $P < 0.05$ was considered statistically different.

Results

Demographic characteristics

Age and sex

The differences in the distribution of the three groups of patients in terms of gender and age before matching were statistically significant ($P < 0.001$). A total of 149 pairs of patients were successfully matched, and after matching, there was no difference in the distribution of the three groups of patients in terms of age and age status ($P > 0.05$), and the distribution of the groups reached equilibrium (Table 1).

Symptom

Of the 447 patients in this study, 105 patients in group N had asymptomatic physical examination findings, and 44 had symptoms; 80 patients in group S had asymptomatic physical examination findings, 69 had symptoms, and 110 patients in group M had asymptomatic physical examination findings, and 39 had symptoms (Table 2).

Table 2
Initial symptoms in the three groups after PSM.

Symptomatic	Group N	Group S	Group M
Physical examination (asymptomatic)	105 (70.5)	80 (53.7)	110 (73.8)
fever	0 (0)	2 (1.3)	3 (2.0)
hemoptysis	4 (2.7)	9 (6.0)	1 (0.7)
cough	16 (10.7)	37 (24.8)	24 (16.1)
dyspnea	1 (0.7)	3 (2.0)	0 (0)
chest distress	14 (9.4)	8 (5.4)	6 (4.0)
chest pain	9 (6.0)	10 (6.7)	5 (3.4)

Differences in clinical characteristics between the three groups

The clinical characteristics of the three groups of lung cancer patients were compared, and the differences between the three groups were statistically different ($P < 0.05$) in terms of pathological type, smoking history, tumor stage, type of surgery, histological grading, presence or absence of invasion of the pleura of the visceral layer, presence or absence of spread through air spaces, presence or absence of nerve invasion, presence or absence of invasion of the peripheral tissues, size of the CT imaging, the time between detection of the nodule and the diagnosis of the tumor, and the PFS(Table 3).

There was a statistical difference between the cystic lung cancer group and the solid lung cancer group in terms of smoking history, tumor stage, tumor size, histological grading, presence or absence of invasion of the pleura of the visceral layer, presence or absence of spread through air spaces, presence or absence of nerve invasion, presence or absence of invasion of peripheral tissues, and time to PFS ($P < 0.05$). The tumors in the cystic lung cancer group were smaller 1.8 (1.3, 2.6) vs. 2.2 (1.5, 3.3) and statistically different from the solid lung cancer group ($P < 0.001$). In terms of pathological type, most of the cystic lung cancer group were adenocarcinomas, whereas 20.1% of the patients with squamous carcinoma were in the solid lung cancer group. The proportion of squamous cell carcinoma was much higher in the solid lung cancer group than in the cystic lung cancer group (20.1% vs 6.0%). Notably, the time from nodule detection to tumor diagnosis was greater in the cystic group than in the solid group and was statistically significant ($P < 0.001$). As can be concluded from the survival curves of the two groups (Fig 2), there was no statistically significant difference in PFS between groups N and S ($P > 0.05$, HR = 1.321 95%CI 0.6520 − 2.677).

The differences between the cystic lung cancer group and the ground-glass lung cancer group were statistically different in terms of smoking history, tumor stage, type of surgery, histological grading, presence of spread through air spaces, tumor size, time from nodule discovery to tumor diagnosis, and PFS ($P < 0.05$). As can be concluded from the survival curves (Fig 2), there was a statistical difference in PFS between groups N and M ($P < 0.05$, HR = 0.0186 95%CI 0.06729 − 0.5186).

Prognostic factors associated with lung cancer

COX univariate regression analysis was performed on the prognosis of 447 lung cancer patients (Table 4), in which the type of lung cancer, smoking history, tumor stage, histological grading, CT imaging size, pathological type, peripheral tissue invasion, and lymph node metastasis were statistically significant. The above indicators were included in the COX multivariate regression equation, and it was found that lung cancer type, pathological type, lymph node metastasis, tumor stage, and histological grading were independent prognostic factors for lung cancer ($P < 0.05$). Lung cancer patients with the pathological type of squamous carcinoma, lymph node metastasis, tumor stage 3, and histological grading of moderately differentiated had a poorer prognosis. After excluding the effects of pathological type, tumor stage, histological grading, and presence of lymph node metastasis, the association between the imaging manifestations of cystic and the prognosis of lung cancer was statistically significant ($P < 0.05$). Compared with cystic lung cancer, the prognosis of ground-glass lung cancer was better ($P = 0.010$, HR = 0.131, 95%CI 0.028–0.613) (Table 5).

Discussion

In recent years, cystic lung cancer has received widespread attention and has been reported and described by an increasing number of scholars. These types of lung cancers have the same features as CT, namely isolated thin-walled air-containing cavities. Due to the rarity of LCCAs, only a few small cohort studies or case reports have discussed the pathological and imaging features of this particular imaging lung cancer. In addition, due to the different definitions of cystic lung cancer in various studies, there are no clear conclusions about the clinical features and prognosis of LCCAs, which also indicates that people lack knowledge about this type of lung cancer. In 2008, the Fleischner Society summarized the terminology of lung imaging and used terms such as airspace, blisters, bubbles, cavity, and cavern to describe the gas-filled space in the lungs on CT imaging.[13] Gas-filled spaces have distinct borders with the lung parenchyma and wall structures. For non-solid nodules, the Fleischner Society believes that an annual review can be done to assess the progression and that a 12-month interval is still safe. However, no definitive recommendation is given for such nodules or masses with cystic lesions.[3] In this study, we explored the time from detection to diagnosis of tumors in three groups of lung cancers. We found that cystic lung cancers took longer (Table 3) and were statistically different from solid and ground-glass lung cancers ($P < 0.001$), which are neglected in clinical practice. In conjunction with the prognostic comparisons between the latter two groups, cystic lesions are an independent risk factor for lung cancer. It is essential to develop follow-up guidelines for cystic lung cancer.

Similar to the results of previous studies, the median age of patients with cystic lung cancer in this study was 59, and the gender distribution of patients with cystic lung cancer varied from study to study. Shen,[14] Guo,[15] and Mascalchi *et al.*[16] found that the incidence of cystic lung cancer was greater in men than in women, while Fintelmann *et al.*[17] found a greater incidence of cystic lung cancer in women than in men. Farooqi[18] and Fintelmann *et al.* suggested that cystic lung cancer is associated with emphysema, which reflects the association of cystic lung cancer with smoking status. However, in our study, we found that the smoking history of cystic lung cancer patients was not statistically different from that of solid and ground-glass lung cancers. The reason for this inconsistency in the results may be due to the fact that most of the cases in the previous studies had

Table 3
Comparison of clinical and pathological features of different types of lung cancer.

		Group N	Group S	Group M	χ^2/H	P
Pathological type	Adenocarcinoma	139 (93.3)	113 (75.9)	146 (98.0)		
(n , %)	squamous carcinoma	9 (6.0)	30 (20.1)	2 (1.3)		
	Other types	1 (0.7)	6 (4.0)	1 (0.7)	40.154[a]	< 0.001
	χ^2		17.699[a]	4.798[a]		
	P		< 0.001	0.056		
smoking history	No	90 (60.4)	92 (61.7)	112 (75.2)		
(n, %)	Yes	59 (39.6)	57 (38.3)	37 (24.8)	8.824	0.012
	χ^2		0.056	7.438		
	P		0.812	0.006		
family history	No	134 (89.9)	140 (94.0)	139 (93.3)		
(n, %)	Yes	15 (10.1)	9 (6.0)	10 (6.7)	1.974	0.393
	χ^2		1.631	1.092		
	P		0.202	0.296		
Tumor location	Upper lobe of the right lung	44 (29.5)	39 (26.2)	56 (37.6)		
(n, %)	Upper and middle lobe of the right lung	0 (0)	2 (1.3)	0 (0)		
	Lower lobe of the right lung	31 (20.8)	37 (24.8)	29 (19.5)		
	Middle and lower lobe of the right lung	1 (0.7)	1 (0.7)	0 (0)		
	middle lobe of right lung	13 (8.7)	11 (7.4)	10 (6.7)		
	upper lobe of the left lung	35 (23.5)	32 (21.5)	41 (27.5)		
	lower lobe of the left lung	25 (16.8)	27 (18.1)	13 (8.7)	17.626[a]	0.128
	χ^2		3.982[a]	7.618[a]		
	P		0.679	0.209		
Tumor Stage	1	70 (47.0)	67 (45.0)	103 (69.1)		
(n, %)	2	45 (30.2)	21 (14.1)	21 (14.1)		
	3	34 (22.8)	61 (40.9)	25 (16.8)	40.766	< 0.001
	χ^2		16.467	16.395		
	P		< 0.001	< 0.001		
Type of surgery (n, %)	lobectomia pulmonalis	106 (71.1)	134	72 (48.3)		
	segmentectomy	31 (20.8)	13	50 (33.6)		
	wedge-shape excision of lung	12 (8.1)	2	27 (18.1)	63.560	< 0.001
	χ^2		17.773	16.720		
	P		< 0.001	< 0.001		
Histological grade (n, %)	adenocarcinoma in situ /minimally invasive adenocarcinoma	34 (22.8)	84 (56.4)	12 (8.1)	145.282	< 0.001
	Poorly differentiated	15 (10.1)	4 (2.7)	50 (33.6)		
	Moderately differentiated	75 (50.3)	33 (22.1)	79 (53.0)		
	Well differentiated	25 (16.8)	28 (18.8)	8 (5.4)		
	χ^2		44.058	38.229		
	P		< 0.001	< 0.001		
Invasion of the pleura of the	No	139 (93.3)	123 (82.6)	141 (94.6)		
visceral layer (n, %)	Yes	10 (6.7)	26 (17.4)	8 (5.4)	15.703	< 0.001
	χ^2		9.231	0.070		
	P		0.002	0.792		
spread through air spaces	No	107 (71.8)	89 (59.7)	144 (96.6)		
(n , %)	Yes	42 (28.2)	60 (40.3)	5 (3.4)	57.920	< 0.001
	χ^2		5.224	33.625		
	P		0.022	< 0.001		
nerve invasion (n, %)	No	148 (99.3)	133 (89.3)	148 (99.3)		
	Yes	1 (0.7)	16 (10.7)	1 (0.7)	25.952	< 0.001
	χ^2		13.932	-		
	P		< 0.001	1		
invasion of peripheral tissues	No	144 (96.6)	118 (79.2)	146 (98.0)		
(n, %)	Yes	5 (3.4)	31 (20.8)	3 (2.0)	43.372	< 0.001
	χ^2		23.406	0.153[a]		
	P		< 0.001	0.723		
Peripheral tissue lesions (n,	No	143 (96.0)	145 (97.3)	149 (100.0)		
%)	Yes	6 (4.0)	4 (2.7)	0 (0)	4.671[a]	0.124
	χ^2		-	4.138[a]		
	P		0.977	0.059		
lymphatic metastasis	No	141 (94.6)	114 (76.5)	148 (99.3)	48.754	< 0.001
	Yes	8 (5.4)	35 (23.5)	1 (0.7)		
	χ^2		19.812	6.367		
	P		< 0.001	0.012		
CT imaging size (cm)		1.8 (1.3–2.6)	2.2 (1.5–3.3)	1.3 (1.0–1.9)	52.932	< 0.001
(M,P_{25}–P_{75})	U		12847.5	7230.0		
	P		0.019	< 0.001		

Table 3 (*continued*)

		Group N	Group S	Group M	χ^2/H	P
PFS		32 (1.5–57)	33 (0.5–60)	42 (8–60)	67.980	< 0.001
Month (M,P_{25}–P_{75})	U		9349.5	5409.5		
	P		0.018	< 0.001		
Time from nodule detection		25 (13–180)	16 (10–27)	18 (11–76)	20.959	< 0.001
to tumor diagnosis (day)	U		7650.0	9591.0		
(M,P_{25}–P_{75})	P		< 0.001	0.042		

[a] Statistical method is Fisher probabilities. H is the Kruskal-Wallis test.U is the Mann-Whitney U test.

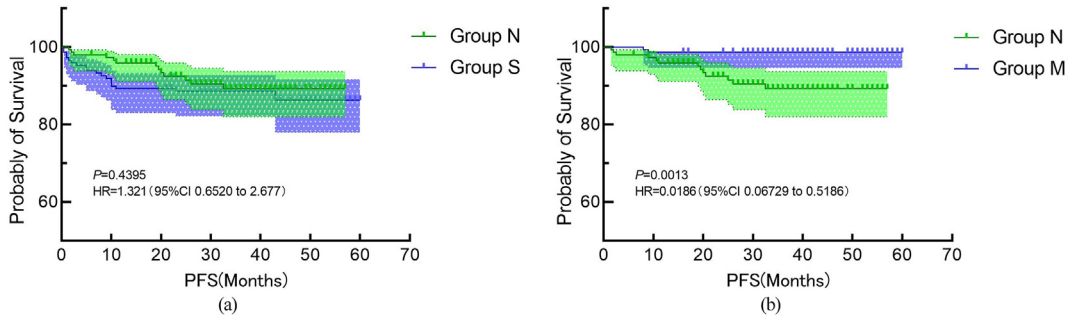


Figure 2 (a) and (b) clear the survival curves for three types of lung cancer. (a) Survival curves of groups N (Group N represents the LCCAs group) and S (Group S represents the solid lung cancer group) Survival curves were not statistically different between the two groups of lung cancer patients (P > 0.05). (b) Survival curves of groups N (Group N represents the LCCAs group) and M (Group M represents the ground-glass lung cancer group), the two group survival curves were statistically different (P < 0.05).

Table 4
COX univariate analysis of the factors associated with the prognosis of lung cancer.

		β	waldχ^2	P	HR (95%CI)
Types of Lung Cancer	N	–	9.635	0.008	–
	S	0.307	0.709	0.400	1.359 (0.665–2.777)
	M	−2.002	6.932	0.008	0.135 (0.030–0.600)
Pathological type	Adenocarcinoma	–	19.412	< 0.001	–
	squamous carcinoma	1.339	10.509	0.001	3.814 (1.698–8.570)
	Other types	2.166	12.363	< 0.001	8.727 (2.609–29.198)
smoking history	No	–	–	–	–
	Yes	1.030	8.541	0.003	2.801 (1.404–5.589)
Family history of tumors	No	–	–	–	–
	Yes	0.260	0.184	0.668	1.297 (0.396–4.252)
Tumor location	Upper lobe of the right lung		8.433	0.208	–
	Upper and middle lobe of the right lung	−9.236	0.000	0.982	0 (0∼0)
	Lower lobe of the right lung	0.903	3.606	0.058	2.469 (0.971–6.269)
	Middle and lower lobe of the right lung	2.349	4.819	0.028	10.480 (1.286–85.373)
	middle lobe of right lung	0.175	0.048	0.827	1.191 (0.247–5.735)
	upper lobe of the left lung	0.397	0.588	0.443	1.487 (0.539–4.102)
	lower lobe of the left lung	-0.083	0.015	0.904	0.920 (0.238–3.561)
Tumor Stage	1		21.093	< 0.001	–
	2	0.743	1.608	0.205	2.102 (0.667–6.629)
	3	1.907	19.087	< 0.001	6.735 (2.862–15.848)
Histological grade	adenocarcinoma in situ /minimally invasive adenocarcinoma		19.703	< 0.001	
	Poorly differentiated	1.651	11.444	0.001	5.215 (2.003–13.576)
	Moderately differentiated	-0.032	0.003	0.953	6.969 (0.336–2.793)
	Well differentiated	0.591	0.951	0.329	1.805 (0.551–5.915)
Invasion of the pleura of the visceral layer	No	–	–	–	–
	Yes	0.800	3.139	0.076	2,226 (0.918–5.393)
spread through air spaces	No	–	–	–	–
	Yes	0.449	1.393	0.238	1.567 (0.743–3.305)
invasion of peripheral tissues	No	–	–	–	–
	Yes	1.304	10.302	0.001	3.685 (1.662–8.171)
lymphatic metastasis	No	–	–	–	–
	Yes	1.739	23.023	< 0.001	5.691 (2.797–11.579)
CT imaging size (cm)		0.363	17.443	< 0.001	1.437 (1.212–1.704)

Table 5
COX multivariate analysis of the factors associated with the prognosis of lung cancer.

		β	waldχ^2	P	HR (95%CI)
Types of Lung Cancer	N	–	6.809	0.033	–
	S	0.342	0.625	0.429	0.710 (0.304–1.658)
	M	2.034	6.657	0.010	0.131 (0.028–0.613)
Pathological type	Adenocarcinoma	–	6.571	0.037	-
	squamous carcinoma	1.069	0.475	0.025	2.911 (1.147–7.390)
	Other types	1.067	0.658	0.105	2.906 (0.801–10.549)
lymphatic metastasis	No	–	–	–	–
	Yes	0.959	4.656	0.031	2.608 (1.092–6.231)
Tumor Stage	1		8.407	0.015	–
	2	0.477	0.628	0.428	1.612 (0.495–5.246)
	3	1.352	7.683	0.006	3.864 (1.486–10.051)
Histological grade	adenocarcinoma in situ /minimally invasive adenocarcinoma	–	10.474	0.015	–
	Poorly differentiated	−0.200	0.110	0.741	0.818 (0.250–2.680)
	Moderately differentiate	−1.609	5.955	0.015	0.200 (0.055–0.729)
	–	–	0.027	0.870	0.902 (0.262–3.110)

a history of smoking (past or present), whereas in the present study, there was a not inconsiderable percentage of female cystic patients (64 cases), and most of the female patients had no history of smoking.

In response to the imaging features of cystic lung cancer, Yang *et al.*[19] systematically elaborated their imaging features and proposed that isolated cystic lung cancer has malignant features of uneven walls, separations, wall nodules, and irregular margins, which helps clinicians to differentiate between benign and malignant features. Zhu *et al.*[20] also demonstrated that polycystic structures, irregular cystic spaces, and the size and attenuation of the tumor diameter are predictive of pathological aggressiveness in cystic lung adenocarcinomas. In our study, there were 116 (77.2%) cases of invasive lung cancer among cystic lung cancer and 90 (60.4%) cases of moderately differentiated and poorly differentiated. It suggests that cystic lesions may be a manifestation of tumor progression to the invasive stage or to a more poorly differentiated stage, which coincides with the conclusion of the study reported by Wang *et al.*,[21] who concluded that cystic airspace is an independent predictor of invasiveness. For the imaging morphology of cystic lung cancer, this study did not explore it in detail. Previous studies reported proposed various morphological classifications, most of which were formulated on the basis of the thickness of the wall, the number of nodules in the wall, and the number of cystic cavities. Mascalchi first proposed a four-classification system, which was later refined by Fintelmann. In 2019, Shen *et al.*[22] proposed a new classification system by grouping exophytic and endophytic wall nodules together and concluded that cystic lung cancer with mural nodules had the worst prognosis by analyzing cystic lung cancer of different morphological subtypes. Jung *et al.*[23] reviewed 98 follow-up images of 27 patients and developed a preliminary progression model for cystic lung cancer, revealing its natural clinical course: in the first stage, the cancer cells appear in the middle of a non-solid nodule; in the second stage, the cancer cells proliferate, and the thickness of the ground-glass wall surrounding the cancer cells remains unchanged (or decreases); in the third stage, the solid component appears at the border of the tumor; and in the fourth stage, the solid wall progressively encases the tumor and its thickness gradually increases while the tumor gradually becomes smaller. However, this study is only a conception based on the fact that the pathological type of the tumor is adenocarcinoma, ranging from non-solid to solid to completely solid. Pathologically, it satisfies the histological progression sequence from atypical hyperplasia to minimally invasive adenocarcinoma to invasive adenocarcinoma. However, the point that cannot be ignored is that the model refers to cystic lesions being formed after tumorigenesis. In clinical practice, cystic lesions are already present at the time of discovery of the lesion, and the pre-disease state cannot be traced, so it is not possible to determine whether a pre-existing cystic lesion in the lung caused the tumorigenesis.

The correlation of prognostic factors in cystic lung cancer, there is no clear conclusion, and previous studies were based on different morphologies to discuss the prognosis of cystic lung cancer. Kaneda *et al.*[24] concluded that lung cancers adjacent to large alveolus showed a poorer prognosis and that patients with emphysema had a higher risk of developing lung cancer. However, this study found that smoking status did not affect the prognosis of cystic lung cancer, which may be caused by the variability of small sample studies and the lack of control for confounding factors such as gender in the study population. Shinohara *et al.*[25] by comparing the postoperative RFS and overall survival (OS) of lung cancer with and without adjacent alveolus, they found that proximity to alveolus may be an independent good factor. However, adjacent alveolar pathology has higher malignant potential, which may be related to the tumor having better differentiation. Shen *et al.*[14] concluded that cystic lung cancer with wall nodules has the worst survival outcome, and they suggested that this imaging presentation is related to the aggressiveness of the pathology, so this lesion should be operated on immediately when detected during follow-up. In this study, we did not investigate the morphological typing and prognosis of cystic lung cancer; we only compared the prognostic

differences from the imaging manifestations divided into cystic, solid, and ground-glass groups. We concluded that in terms of pathological type, the cystic group and the ground-glass group were similar, both of which were predominantly adenocarcinomas, but cystic lung cancer had its own unique manifestations in terms of tumor stage, histological grading, surgical approach, tumor size, and spread through air spaces. Although there was no statistical difference between the cystic and solid groups in terms of prognosis, solid lung cancer had a higher malignant potential in terms of invasion of the pleura of the visceral layer, airway dissemination, nerve invasion, peripheral tissue invasion, and lymph node metastasis. The prognosis of cystic lung cancer was worse than that of ground-glass lung cancer, which may be related to the fact that cystic lung cancer is more aggressive (most ground-glass lung cancers are adenocarcinomas in situ or minimally invasive adenocarcinomas) and that cystic lung cancers are more prone to lymph node metastasis and airway dissemination.

The current guidelines have clear guidance on the follow-up and management of solid and non-solid nodules but are inconclusive about this particular form of lesion. Moreover, the diagnosis of cystic lung cancer is more difficult. Cystic lung cancer is mostly peripheral lung cancer, which is difficult to diagnose by bronchoscope, while percutaneous lung aspiration biopsy may be good for lung cancer with nodules on the wall or wall thickening type, but increases the risk of pneumothorax for cystic lung cancer with thin wall type. At the same time, cystic lesions are non-evaluable lesions in the current RECIST (The Response Evaluation Criteria in Solid Tumors) criteria, and it is also a major difficulty to assess the efficacy of conservative treatment with medications for advanced inoperable cystic lung cancer.[26]

Conclusion

It is a comparative study that reveals that cystic lung cancer is more different from ground-glass lung cancer and solid lung cancer. Cystic lesions are independent influencing factors of lung cancer, and the prognosis of cystic lung cancer is worse than that of ground-glass lung cancer. However, because of the small sample size included, only a preliminary exploration of the clinical characteristics, pathological types, prognosis, and solid and ground-glass lung cancer of cystic lung cancer patients was conducted, and the lack of a long follow-up period of relevant CT and the control of imaging and pathology did not allow for further study of the mechanism of development of cystic lung cancer and the influence of imaging morphology on prognosis. At the same time, because of the small number of patients who had events, other indicators of possible correlation could not be analyzed.

Ethics

This study was approved by the ethics committee. This study used human material or data with identifiable information. in addition, the research project does not involve personal privacy and commercial interests, and the ethics committee exempted all patients from informed consent.

Funding

This work was supported by the National Natural Science Foundation of China (grant numbers 82360474 and 81960523).

Author contribution

1 guarantor of integrity of the entire study:Longhua Sun.
2 study concepts and design:Longhua Sun, Xin Xu.
3 literature research: Xin Xu, Zhi Dong.
4 clinical studies: Xin Xu, Maoyu Zhang, Qi Song.
5 experimental studies/data analysis: N/A.
6 statistical analysis: Jidong Guo, Tianpan Cai.
7 manuscript preparation: Xin Xu.
8 manuscript editing: Wen Chen.

All authors read and approved the final manuscript.

Conflict of interest

The authors declare no conflict of interest.

Data availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Acknowledgments

We wish to thank the timely help given by Dr. Longhua Sun in study concepts and funding acquisition.

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