

Radiological and pathological analysis of LDCT screen detected and surgically resected sub-centimetre lung nodules in 44 asymptomatic patients



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ABSTRACT

Purpose: Once lung cancer is detected due to clinical symptoms or by being visible on chest X-ray, it is usually high stage and non-operable. In order to improve mortality rates in lung cancer, low-dose CT (LDCT) screening of “high risk” individuals is gaining popularity. However, the rate of malignancy in LDCT detected sub-centimetre lung nodules is not clear. We aimed to analyze surgically resected specimens in this patient group to explore cost effectiveness and recommendations for clinical management of these nodules.

Material & methods: Our hospital pathology database was searched for sub-centimeter lung nodules detected by LDCT screening which were resected. The patient demographics were collected and the radiologic and pathologic characteristics of those nodules were analyzed.

Results: From the records, 44 patients with 46 resected subcentimetre nodules were identified. Patients were selected for surgery based on an irregular shape, growth in size during follow up, family history of lung cancer or personal history of cancer of other sites, previous lung disease, smoking and personal anxiety. Of the 44 patients, 33 were women and the ages ranged from 43 to 76 years (56.75 ± 8.44). All nodules were equal to, or less than 10 mm with a mean diameter of 7.81 ± 1.80 mm (SD). Out of 46 nodules, the pathological diagnoses were: invasive adenocarcinoma (ACa) in 4 (8.7%); adenocarcinoma in situ (AIS) or atypical adenomatous hyperplasia (AAH) in 29 (63%); benign fibrosis/fibrotic scar with inflammation or calcification in 12 (26.1%); an intrapulmonary benign lymph node in 1 (2.2%). Of the ACa, AIS and AAH groups (a total of 31 patients), 77% were women (24 vs. 7). The cancer or pre-cancer nodules (ACa, AIS and AAH) tended to be larger than benign fibrotic scars ($P = 0.039$). Amongst all characteristics, significant statistical differences were found when the following radiological features were considered: reconstructed nodule shape ($P = 0.011$), margin ($P = 0.003$) and ground glass pattern ($P = 0.000$). The patient's age, the axial morphology of the lesion, relationship to major vessels or visceral pleura and location within the lung parenchyma were not predictive of the pathologic diagnosis. Only one of the 31 patients with a cancer or pre-cancer nodule was a smoker.

Conclusion: ACa, AIS and AAH nodules detected on LDCT included more women (77%) than men in our cohort. Smoking as inclusive criteria for LDCT screening of lung cancer needs to be further evaluated in the Chinese population. The reconstructed nodule shape, density and margin may help radiologists to identify small cancer and pre-cancer nodules from benign conditions.

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Globally, lung cancer has the highest mortality rate [1]. By the time lung cancer is clinically symptomatic or can be detected by chest X-ray, it is already at a high stage and is not curable [2,3]. In China, due to the concern of the relationship between air pollution and lung cancer and in the hope to catch the disease at an early stage, LDCT screening of “high risk” individuals is gaining in popularity [4]. However, the pathologic characteristics and particularly,

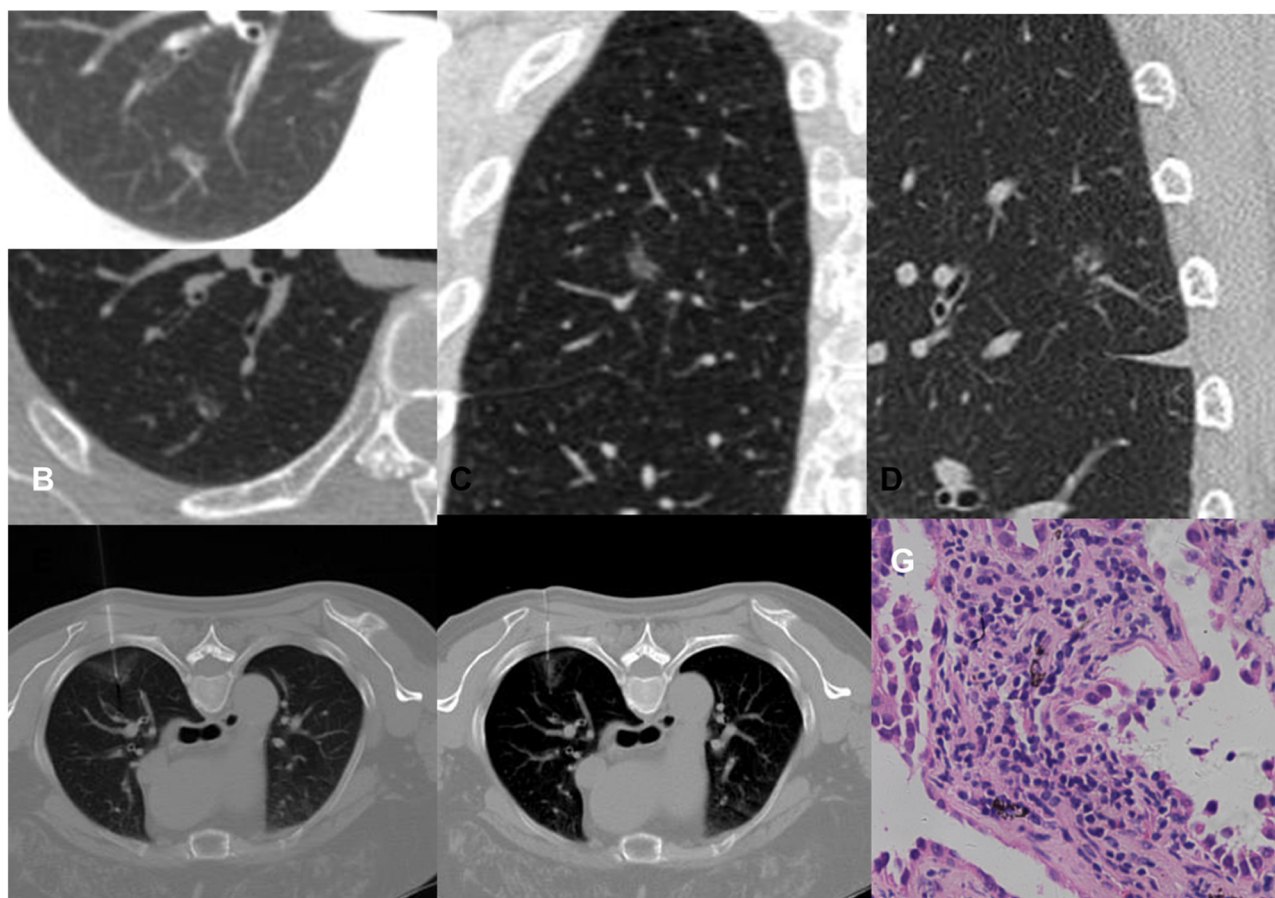


Fig. 1. 63 year old female. A. Right lower lobe opacity; B. Reconstructed image of 0.67 mm section thickness using high-frequency algorithms and displayed at standard window setting showing solid opacity. C, D: Reconstructed crown and sagittal images showing irregular border and micro vasculature passing through. E & F: CT-guided hookwire localization before VATS. G: Histology HE $\times 400$ showing AAH.

the rate of malignancy in CT detected sub-centimeter lung nodules is not clear [5–7]. Analysis of surgically resected specimens in this patient group may provide insights into the demographic characteristics of these sub-centimeter nodules, the cost effectiveness of such screening and, importantly, recommendations on the subsequent clinical management.

1. Material & methods

From July 2013 to March 2015, 44 asymptomatic patients with 46 sub-centimeter lung nodules (two patients each had 2 nodules) that were detected by LDCT screening and subsequently underwent CT-guided hook-needle localization and video-assisted thoracoscopic surgery (VATS) were retrospectively selected from the pathology database of Northern Campus of Shanghai No. 9 People's Hospital. The patient's demographics and the radiologic and pathologic characteristics of these nodules were collected from the records and included gender, age, nodule location, size, shape, density, relation to major vessels, relation to visceral pleura, history of smoking and the major reasons for surgery. CT scanning Brilliance-64, MX-8000 IDT CT scanner (Philips Medical Systems, Cleveland, OH) was acquired at the end of inspiration and performed from the thoracic inlet to the upper portion of the kidneys. The scanning parameters were as follows: 120 kVp, 40–60 mAs, and a pitch of 0.875. Thin-section CT images were reconstructed into 0.675 mm section thicknesses using high-frequency algorithms and displayed at standard window setting (width, 1600 HU;

level, –400 HU). In some cases, follow-up CT scans were performed at 3-, 6- and 12- months. All CT images were anonymized and reviewed by two radiologists. The image analyses were based on the 2013 recommendations by the Fleischner Society [7,8]. The following thin-section reconstruction CT measurements were recorded: lesion size, distance to pleura, pulmonary location, shape on transverse and reconstruction imaging (round or oval, polygonal, irregular), margin (smooth, lobulated, spiculated), border (well-defined, ill-defined), density (solid opacity, mixed ground-glass, pure ground-glass), relation to vascular structure (pass through, convergence, unrelated). Lesion size was measured based on the average of long and short axial dimensions. The distance to pleura was defined between the center of the lesion and visceral pleural. Patients all underwent CT-guided hook-needle localization of the suspected nodules (PAJUNK, Mammography, Germany, 275S090120S 20G $\times 120$ mm) before VATS. At the time of wedge resection, frozen sections performed for initial diagnosis. All specimens were then submitted for permanent section with formalin fixation and paraffin embedding for final diagnosis. All diagnoses were confirmed by 2 pathologists (Figs 1–4).

Statistical analysis was performed using SPSS version 19.0. The independent sample *t* test was used for continuous variables, such as age, lesion size and distance to pleura. The chi-square test was used for categorical data to compare CT image findings. A value of $P < 0.05$ was considered statistically significant. Due to the subjectivity of the differential diagnostic criteria, nodules previously diagnosed as AAH and AIS were combined into one group for sta-

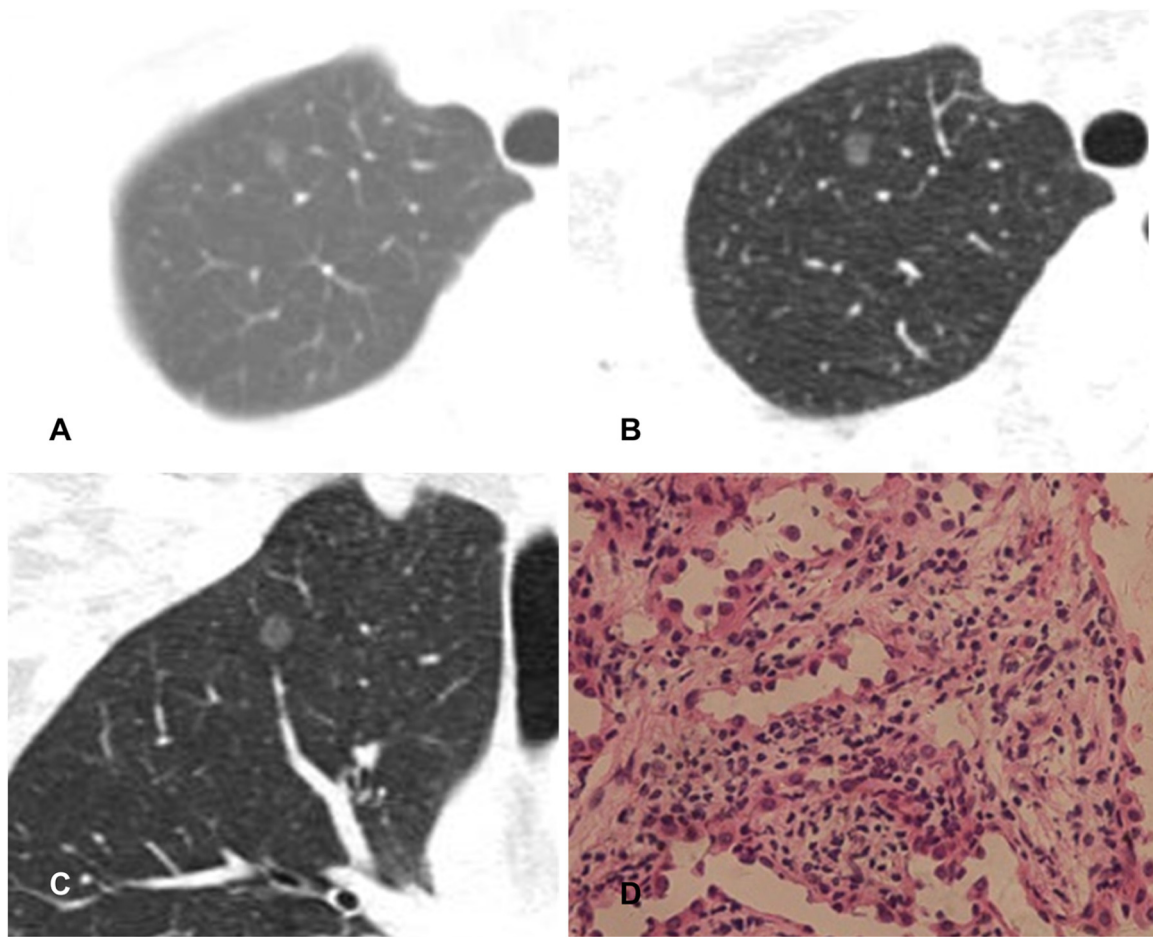


Fig. 2. 46 year old female. A. Right lower lobe opacity; B, C. Reconstructed image of 0.67 mm section thickness using high-frequency algorithms and displayed at standard window setting showing solid opacity. D. Post CT-guided hookwire localization VATS histology diagnosis is AIS (HE $\times$ 400).

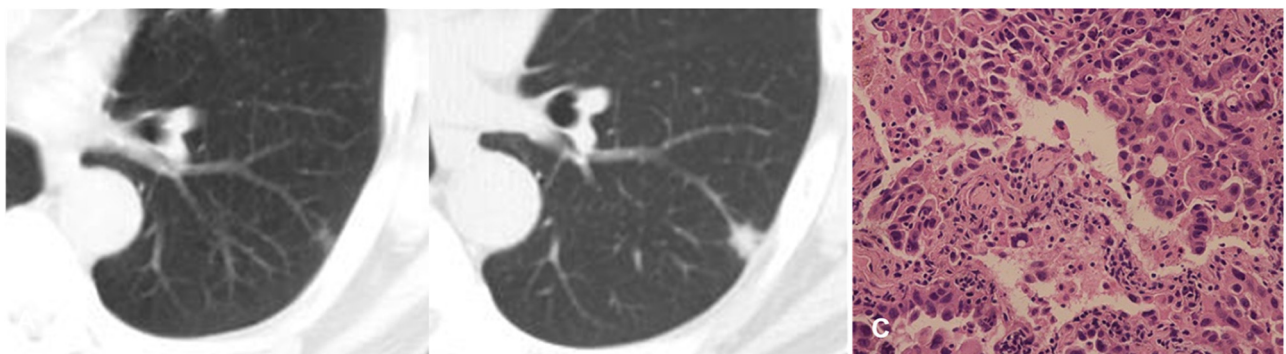


Fig. 3. 63 year old man. CT screen show left lower lobe lung irregular opacity. B. one year later, follow up CT show the lesion is increasing in size and density. The lesion also has speculated shape, ill-defined boarder and uneven density. C. wedge resection and subsequent lobectomy show well differentiated invasive adenocarcinoma (H&E $\times$ 400).

tistical analysis. There were 29 nodules in this group with, only two <5 mm; based on current WHO criteria, the majority of these nodules are qualify for the diagnosis of AIS.

2. Results

As shown in Tables 1 and 2, Patients were selected for surgery due to the following reasons: growth in size during the 3–12 month follow up periods (5 cases); family history of lung cancer (2 cases); personal history of cancers of other sites (11 cases); previ-

ous chronic lung disease, including chronic bronchitis and COPD (8 cases); smoking (1 case) and for many cases, personal anxiety about the CT detected lung nodules played a significant role (19 cases). All resected nodules were also classified by radiologists to be suspicious based on their experience. Of the 44 patients, 33 were women and 11 were men, age range 43–76 years (56.75 ± 8.44 SD). Of the 46 nodules (two patients had 2 nodules), pathological diagnoses were: invasive adenocarcinoma (ACa) in 4 (8.7%); adenocarcinoma in situ (AIS) and atypical adenomatous hyperplasia (AAH) in 29 (63%); benign fibrosis/fibrotic scar with inflammation or calcifica-

Table 1
Case summary.

Final pathology diagnosis			Gender	Age	Location	Reason of Operation	Size (mm)	Distance to pleura	Transverse Shape	Reconstructed Shape	Margin	Border	Density	Vascularity
AAH & AIS	1	f	48	Right Upper	Anxiety	9.90	18.00	Round/oval	Round/oval	Lobular	Well-defined	Pure GGOs	Unrelated	
	2	f	46	Right Lower	Anxiety	3.50	5.30	Round/oval	Polygonal	Lobular	Well-defined	Part-solid GGO	Pass through	
	3	f	52	Right Upper	Enlarged	10.00	7.30	Round/oval	Irregular	Lobular	Ill-defined	Part-solid GGO	Convergence	
	4	f	68	Left Upper	Thyroid CA	9.20	10.60	Irregular	Polygonal	Speculated	Well-defined	Part-solid GGO	Convergence	
	5	m	51	Right Upper	Hx of Lung disease	10.00	20.90	Round/oval	Round/oval	Lobular	Well-defined	Pure GGOs	Pass through	
	6	f	49	Left Lower	Thyroid CA	7.60	6.30	Round/oval	Round/oval	Lobular	Well-defined	Pure GGOs	Unrelated	
	7	f	55	Right Upper	Anxiety	7.30	11.40	Round/oval	Round/oval	Lobular	Well-defined	Pure GGOs	Pass through	
	8	f	53	Right Lower	Smoking	9.00	5.50	Round/oval	Round/oval	Lobular	Well-defined	Part-solid GGO	Pass through	
	9	f	53	Left Lower	Anxiety	6.30	5.90	Polygonal	Polygonal	Lobular	Well-defined	Part-solid GGO	Pass through	
	10	f	70	Left Upper	Breast CA	8.60	12.30	Polygonal	Polygonal	Lobular	Well-defined	Pure GGOs	Convergence	
	11	m	68	Right Upper	Anxiety	8.90	6.40	Round/oval	Round/oval	Lobular	Well-defined	Pure GGOs	Pass through	
	12	.	.	Right Upper		5.00	23.90	Round/oval	Round/oval	Lobular	Well-defined	Pure GGOs	Unrelated	
	13	f	54	Right Upper	Family Hx lung CA	8.30	26.50	Round/oval	Round/oval	Lobular	Well-defined	Pure GGOs	Pass through	
	14	m	51	Left Upper	Family Hx lung CA	9.90	12.30	Round/oval	Round/oval	Lobular	Well-defined	Pure GGOs	Convergence	
	15	f	48	Right Upper	Anxiety	7.70	17.20	Round/oval	Round/oval	Lobular	Well-defined	Pure GGOs	Convergence	
	16	f	52	Right Upper	Anxiety	8.80	4.20	Round/oval	Round/oval	Lobular	Well-defined	Pure GGOs	Convergence	
	17	f	49	Left Upper	Anxiety	7.00	19.50	Polygonal	Polygonal	Lobular	Well-defined	Pure GGOs	Unrelated	
	18	f	67	Left Lower	Hx of Lung disease	7.00	5.80	Irregular	Irregular	Lobular	Well-defined	Pure GGOs	Pass through	
	19	f	75	Left Lower	Hx of Lung disease	9.20	4.40	Round/oval	Round/oval	Lobular	Well-defined	Pure GGOs	Convergence	
	20	f	52	Right Lower	Hx lung CA	9.40	41.80	Round/oval	Round/oval	Lobular	Well-defined	Pure GGOs	Unrelated	
	21	m	64	Left Upper	Enlarged	10.00	28.90	Polygonal	Polygonal	Lobular	Well-defined	Part-solid GGO	Convergence	
	22	f	51	Left Upper	Anxiety	4.80	15.90	Round/oval	Round/oval	Lobular	Well-defined	Pure GGOs	Unrelated	
	23	.	.	Left Upper		7.20	29.00	Round/oval	Round/oval	Lobular	Well-defined	Pure GGOs	Unrelated	
	24	f	55	Right Lower	Anxiety	5.10	7.20	Polygonal	Polygonal	Lobular	Well-defined	Pure GGOs	Unrelated	
	25	f	63	Right Middle	Hx of Lung disease	5.40	9.70	Round/oval	Round/oval	Lobular	Well-defined	Solid opacity	Unrelated	
	26	f	54	Left Lower	Anxiety	8.20	13.60	Polygonal	Polygonal	Lobular	Well-defined	Pure GGOs	Pass through	
	27	f	49	Left Lower	Anxiety	9.30	14.00	Polygonal	Irregular	Lobular	Well-defined	Pure GGOs	Convergence	
	28	m	50	Right Lower	Anxiety	7.70	16.50	Round/oval	Round/oval	Lobular	Well-defined	Part-solid GGO	Convergence	
	29	f	62	Right Lower	Anxiety	8.50	23.00	Irregular	Irregular	Lobular	Well-defined	Part-solid GGO	Convergence	
Total (N)	N	27	27	29	27	29	29	29	29	29	29	29	29	29
Fib & ch inf	1	f	53	Right Lower	Hx of Lung disease	7.60	19.30	Polygonal	Irregular	Lobular	Well-defined	Part-solid GGO	Convergence	
	2	f	47	Right Lower	Hx of Ovarian CA	4.90	6.90	Polygonal	Polygonal	Spiculated	Well-defined	Part-solid GGO	Convergence	
	3	f	51	Right Lower	Hx of Lung disease	8.50	8.80	Irregular	Irregular	Lobular	Well-defined	Solid opacity	Unrelated	
	4	m	56	Left Lower	Hx of Lung disease	8.50	14.20	Polygonal	Irregular	Spiculated	Well-defined	Solid opacity	Convergence	
	5	f	54	Left Lower	Hx of Breast CA	8.30	9.20	Polygonal	Irregular	Lobular	Well-defined	Solid opacity	Pass through	
	6	f	48	Left Lower	Hx of Breast CA	5.50	3.50	Polygonal	Polygonal	Lobular	Well-defined	Part-solid GGO	Convergence	
	7	f	71	Right Upper	Hx lung CA	8.60	5.60	Irregular	Irregular	Lobular	Ill-defined	Pure GGOs	Convergence	
	8	m	76	Left Lower	Hx of Lung disease	6.80	9.90	Round/oval	Round/oval	Lobular	Well-defined	Part-solid GGO	Pass through	
	9	m	65	Left Upper	Anxiety	4.70	9.80	Round/oval	Irregular	Lobular	Well-defined	Solid opacity	Unrelated	
	10	f	43	Right Middle	Hx of Breast CA	9.90	6.20	Irregular	Irregular	Spiculated	Ill-defined	Part-solid GGO	Convergence	
	11	f	67	Right Upper	Enlarged	8.50	11.30	Round/oval	Round/oval	Lobular	Well-defined	Solid opacity	Convergence	
	Total (N)	11	11	11	11	11	11	11	11	11	11	11	11	11
ACa	1	f	56	Right Upper	Anxiety	9.60	8.10	Irregular	Irregular	Lobular	Well-defined	Part-solid GGO	Pass through	
	2	m	58	Right Middle	Enlarged	10.00	14.10	Polygonal	Polygonal	Spiculated	Well-defined	Part-solid GGO	Pass through	
	3	f	53	Left Upper	Anxiety	8.70	24.30	Round/oval	Round/oval	Lobular	Well-defined	Pure GGOs	Pass through	
	4	m	63	Left Lower	Enlarged	10.00	3.00	Polygonal	Polygonal	Spiculated	Well-defined	Part-solid GGO	Convergence	
	Total (N)	N	4	4	4	4	4	4	4	4	4	4	4	
Benign LN	1	f	58	Right Lower	Anxiety	5.60	7.30	Round/oval	Round/oval	Lobular	Well-defined	Solid opacity	Unrelated	
	Total (N)	N	1	1	1	1	1	1	1	1	1	1	1	
Cal.	1	m	69	Right Upper	Anxiety	5.10	7.00	Polygonal	Irregular	Lobular	Well-defined	Part-solid GGO	Unrelated	
Total	Total (N)	N	1	1	1	1	1	1	1	1	1	1	1	
Total	N	44	44	46	46	46	46	46	46	46	46	46	46	46

Abbreviations: CA: carcinoma. ACa: invasive adenocarcinoma. AIS: adenocarcinoma in situ. AAH: atypical adenomatous hyperplasia. LN: lymph node. Cal: calcification. Abs: abscess. Fib & Ch Inf.: fibrosis & chronic inflammation. Hx of: history of.

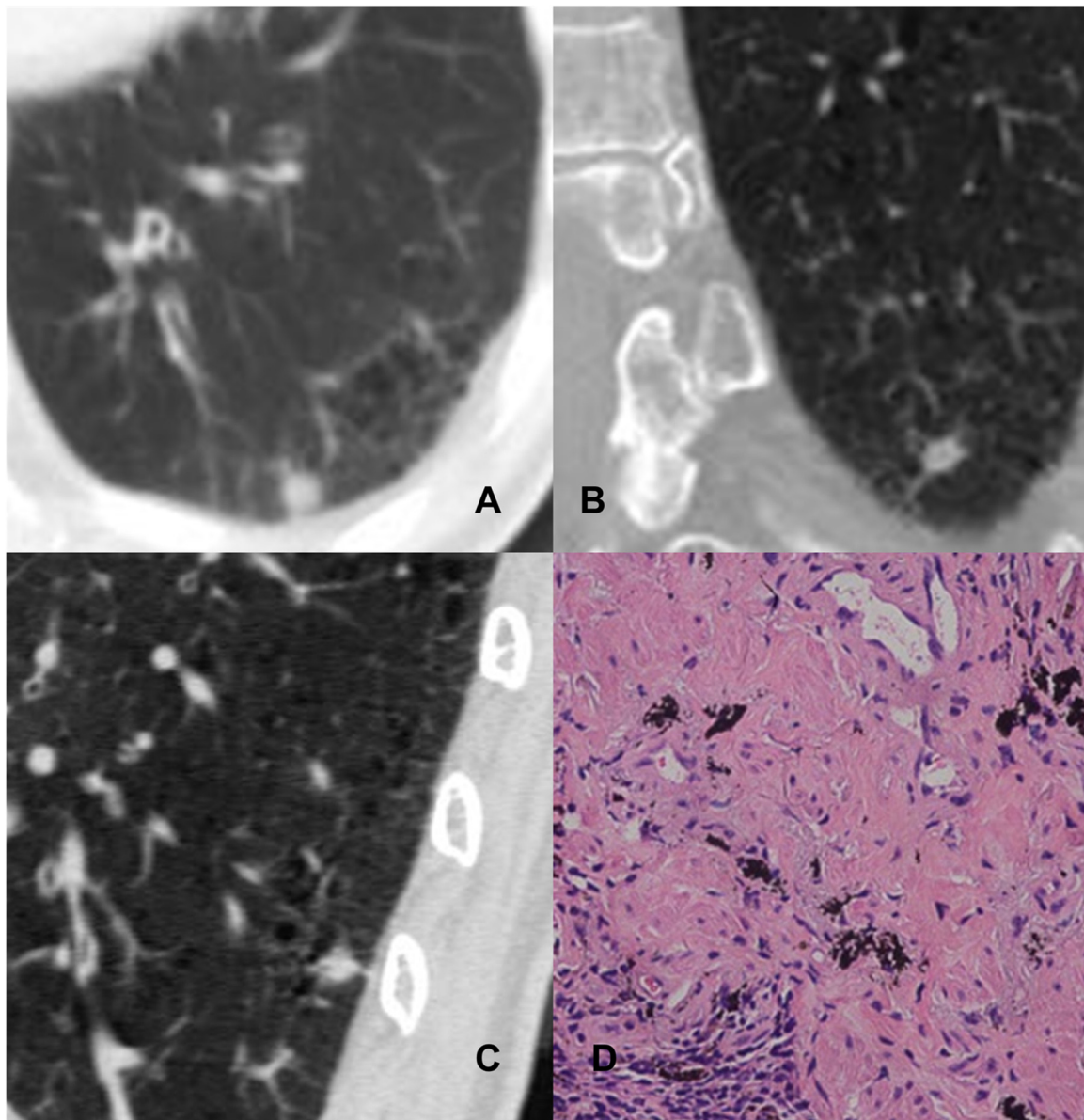


Fig. 4. 75 year old man with history of COPD. A. Screening CT show left lower lobe dense opacity. B & C. Reconstructed crown and sagittal images show irregular speculated lesion shape but defined borders with surrounding lung parenchyma. D. CT-guided hookwire VATS wedge resection show fibrous scar (H&E $\times 400$).

tion in 12 (26.1%); intrapulmonary benign lymph node in 1 (2.2%). Of the ACa, AIS and AAH groups (a total of 31 patients), 77% were women (24 vs. 7). Interestingly, only one out of 31 patients in this group was a smoker.

Amongst all characteristics, significant statistical differences were found between the ACa/AIS/AAH nodule group and benign nodule group when the following radiological features were considered: reconstructed nodule shape ($P=0.011$), margin ($P=0.003$) and ground glass opacity density ($P=0.000$). The patient's age, the axial morphology of the lesion, relationship to major vessels or visceral pleura and location of the nodule within the lung parenchyma were not predictive of the pathologic diagnosis. Only one of the 31 patients with a cancer or pre-cancer nodules was a smoker. All 46 nodules were equal or less than 10 mm, mean $\pm$ SD is 7.81 ± 1.81 mm. Respectively, mean size was, adenocarcinoma, 9.57 mm, AIS, 8.16 mm and AAH, 4.15 mm, although there was no statistical difference in size among all groups, cancer and pre-cancer nodules put together as one group tended to be larger than

benign fibrotic scars ($P=0.039$). The average distance between the nodules to the pleura was 9.18 mm, and there was no statistical difference in the distance to the pleura.

3. Discussion

This is a retrospective study based on a single hospital pathology practice. We focused on surgically resected lung nodules that were detected by LDCT screening of asymptomatic individuals. Although the study is limited by the relatively small sample size and single centre practice, there were some interesting findings. First, among the 31 patients with cancer and pre-cancer conditions (i.e. AAH, AIS and ACa), 24 were female (77%) and 7 were men. This is in contrast to the prevailing paradigm that lung cancer is a male predominant disease [1]. It is possible that the pre-cancerous/pre-invasive (AAH and AIS) nodules grow very slowly and are therefore more likely to be included in this group of sub-centimeter incidental nodules. It is also possible that female patients were more likely

Table 2

Comparison of LDCT image characteristics between cancer/pre-cancer lesions (ACa, AIS, AAH) and Other benign lesions (Fib., LN, Cal).

	Others (13)	ACa/AIS/AAH (33)	P value
Shape Transverse			
Irregular	3 23.1%	4 12.1%	0.181
Polygonal	6 46.2%	9 27.3%	
Round/oval	4 30.8%	20 60.6%	
Shape Reconstructed			
Irregular	28 61.5%	5 15.2%	0.011
Polygonal	2 23.1%	10 30.3%	
Round/oval	3 23.1%	18 54.5%	
Margin			
Smooth	7 53.8%	5 15.2%	0.003
Lobular	3 23.1%	25 75.8%	
Speculated	3 23.1%	3 9.1%	
Border			
Ill-defined	2 15.4%	1 3.0%	0.188
Well-defined	11 84.6%	32 97.0%	
Density			
Part-solid GGO	6 46.2%	11 33.3%	0.000
Solid opacity	6 46.2%	1 3.0%	
Pure GGOs	1 7.7%	21 63.6%	
Surrounding vascular			
Pass through	2 15.4%	12 36.4%	0.385
Convergence	7 53.8%	12 36.4%	
Unrelated	4 30.8%	9 27.3%	
Location			
Left lower	4 30.8%	7 21.2%	0.640
Left upper	1 7.7%	8 24.2%	
Right middle	1 7.7%	2 6.1%	
Right lower	4 30.8%	6 18.2%	
Right upper	3 23.1%	10 30.3%	

to request removal of their incidental lung nodules due to anxiety. Genetic differences from the western population, on which much of the present studies are based, may explain our findings [9]. It is known that EGFR mutations in lung cancer are more common in women, in patients who have never smoked tobacco and in East Asians [10], and there is some evidence that EGFR mutations are over-represented in more low-grade lung cancers [11]. However, we do not have this data for our group. Another interesting finding was that of the 31 patients with cancer and pre-cancer nodules, only one (a woman), was a smoker. The inclusion criteria “at least a 30 pack-year smoking history who smoke or quit smoking <15 years ago” is used in most LDCT screening programs [12–14], which are based on data generated from North America or European population. Therefore our findings raise an important question – will screening programs based on these inclusion criteria

exclude a significant proportion of the population that may benefit from screening, at least in the Chinese population. Most published studies indicate that the malignancy ratio in LDCT detected lung nodules is very small with a false positive rate of approximately 96% [12–16], but these papers are based on Western populations and we do not know how applicable this is in our population. Currently, there are no recommendations or guidelines for LDCT lung cancer screening in China. Due to the concerns that air pollution is a risk factor for lung cancer, many companies include LDCT screening as part of an employee's annual physical exam, as is the case for the patients in our study. The patients were selected for surgery based on a combination of the experience of the radiologists and surgeons experiences and the individual patient's anxiety level. It is clear that more studies investigating different screening inclusion criteria and standardized “lung nodule management algorithms” are necessary to determine the optimal practice in the Chinese population. The newly published NELSON data concluded that measurement of nodule volume may provide better prediction on the risk of incidental lung nodules [17]. Our study also showed that reconstructed nodule shape, lobulated margin and ground glass density on 0.67 mm section thickness scans using high-frequency algorithms displayed at standard window setting may help to identify high risk nodules.

4. Conclusion

In conclusion, although this was a relatively small study from a single center, our findings suggest that the current published inclusion criteria for LDCT screening for lung cancer in China might exclude a significant number of patients who are at risk. Further studies are required in this area.

Conflict of interest

Authors declare no conflict of Interest.

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