Original Article

The influence of different previous cancer histories on the diagnostic efficacy of Lung Imaging Reporting and Data System

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Background: For lung cancer screening in patients with previous malignant tumors, Lung Imaging Reporting and Data System (Lung-RADS) and other lung cancer screening tools are controversial in terms of requirements for the previous cancer history. This study investigated the effect of the length and type of malignancy history on the diagnostic efficacy of Lung Imaging Reporting and Data System (Lung-RADS) 2022 in pulmonary nodules (PNs).

Methods: Chest computed tomography and clinical data of PNs in patients with a history of cancer who underwent surgical resection in The First Affiliated Hospital of Chongqing Medical University from January 1, 2018, to November 30, 2021, were retrospectively collected and evaluated based on Lung-RADS. All PNs were divided into 2 groups: the prior lung cancer (PLC) and the prior extrapulmonary cancer (PEPC) groups. Each group was divided into the ≥5 years and <5 years groups based on the duration of cancer history. The diagnostic agreement of Lung-RADS was evaluated based on the pathological diagnosis of nodules after operation. The diagnostic agreement rate (AR) of Lung-RADS and the composition ratios of different types between different groups were calculated and compared.

Results: A total of 451 patients with 565 PNs were included in this study. These patients were divided into the PLC group (<5 years: 135 cases, 175 PNs; ≥5 years: 9 cases, 12 PNs) and the PEPC group (<5 years: 219 cases, 278 PNs; ≥5 years: 88 cases, 100 PNs). The diagnostic AR of partial solid nodules (93.0%; 95% CI: 88.7–97.2%) and solid nodules (88.1%; 95% CI: 84.1–92.1%) was close (P=0.13), while both were higher than that of the pure ground-glass nodules (24.0%; 95% CI: 17.5–30.4%; all P values <0.001). Within 5 years, the composition ratio of PNs and the diagnostic AR (PLC: 58.9%, 95% CI: 51.5–66.2%; PEPC: 76.6%, 95% CI: 71.6–81.6%) between the PLC and PEPC groups were all different (all P values <0.001), and the others [composition ratio of PNs & the diagnostic AR: PLC (≥5 years) *vs.* PEPC (≥5 years); PLC (<5 years) *vs.* PLC (≥5 years); PEPC (<5 years) *vs.* PEPC (≥5 years)] were similar (all P values >0.05; range: 0.10–0.93).

Conclusions: The length of prior cancer history may affect the diagnostic agreement of Lung-RADS, especially for patients with prior lung cancer within 5 years.

Keywords: Pulmonary nodule; computed tomography; X-ray; previous malignancy; Lung-RADS

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Introduction

Lung cancer is the leading cause of cancer death worldwide, and in 2020, there were 2.21 million new cases and 1.8 million deaths due to lung cancer globally (1). In China, the prevalence of lung cancer is unfortunately very high. In 2022, lung cancer was the leading cause of all new cancers and deaths from cancer in China (2). Therefore, lung cancer screening using low-dose computed tomography (LDCT) in populations at a high risk of developing lung cancer is essential.

In addition to smoking, a history of cancer is a risk factor for developing lung cancer (3). The development of cancer screening technology and the progress of cancer treatment has led to a yearly increase in the number of people with lung cancer and prior malignant tumors (4,5). Previous studies have shown no significant difference in the prognosis and mortality of patients with a history of cancer who develop second primary lung cancer (SPLC) compared with those without prior malignancy (6,7). Hence, screening for lung cancer in patients with a history of cancer should concern clinicians.

The Lung Imaging Reporting and Data System (Lung-RADS), updated in 2022 (8), is a standardized pulmonary nodule follow-up management paradigm for lung cancer LDCT screening reports and plays an important role in the risk assessment and management of pulmonary nodules (PNs) in clinical practice. However, it is unclear whether Lung-RADS is applicable to patients with a history of cancer. Furthermore, the lung cancer screening guidelines of the National Comprehensive Cancer Network (NCCN) clearly exclude people with histories of lung cancer (9). In the classic Mayo prediction model of lung cancer, a history of cancer with 5 years or longer is an independent predictor of malignancy (10). However, the Chinese-based model to predict the malignant risk of PNs focuses only on the presence or absence of a history of malignant tumors without emphasizing the type and length of cancer history (11). Therefore, we conducted a study on the type of previous cancer and the length of cancer history to explore the impact of different cancer histories on the diagnostic efficacy of Lung-RADS. We present the following article in accordance with the STARD reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-22-1039/rc).

Methods

Patients

The chest CT data of patients with prior malignant tumors who underwent surgical resection of PNs in the Department of Cardiothoracic Surgery of The First Affiliated Hospital of Chongqing Medical University (Chongqing, China) from January 1, 2018, to November 30, 2021, were collected. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethical approval was obtained from the Ethics Committee of The First Affiliated Hospital of Chongqing Medical University (No. 2022-K346), and individual consent for this retrospective analysis was waived.

Patients were included if they satisfied the following criteria: they had a definite history of previous cancer, they had a solid nodule (SN) or a partial solid nodule (PSN) ≤30 mm in size [the size of pure ground-glass nodule (pGGN) was not limited], their image information was complete, they had a slice thickness of less than 1.5 mm, their final pathological results were definite, and they had undergone preoperative chest CT scans within 3 months.

Patients were excluded if they fulfilled any of the following criteria: their data was incomplete; the image quality of their data was poor and contained respiratory motion artifacts or metal artifacts; they had nodules that were so close to the hilus of the lung that the size of nodules could not be accurately measured; they had obstructive pneumonia, atelectasis, pneumothorax, or massive pleural effusion; they had a history of 2 or more different types of cancer; their pathological diagnosis was not clearly diagnosed as a benign or malignant disease; and they had a known diagnosis of SPLC.

The enrolled patients were divided into groups. Patients with previous lung or bronchus malignancies were categorized into the prior lung cancer (PLC) group, and patients with previous extrapulmonary malignancies were categorized into the prior extrapulmonary cancer (PEPC) group. Then, these groups were divided into 2 groups (≥5 and <5 years) based on whether the length of previous cancer history was 5 years or more, respectively. The length of a previous cancer history was determined from the date of pathological diagnosis of previous cancer to the date of pathological diagnosis of PNs enrolled in our study.

CT protocol

The noncontrast chest CT scans were performed using SOMATOM Definition Flash (Siemens Healthineers, Erlangen, Germany), SOMATOM Force (Siemens Healthineers), and Discovery CT750 HD (GE Healthcare, Chicago, IL, USA) CT scanners. All patients were asked to place their hands over their heads in a supine position, take a deep breath, and hold their breath. The scan range was from the tip of the lung to the level of the costophrenic angle. The protocol parameters were as follows: tube voltage, 100–120 kV; tube current, 30–50 mA; slice thickness, 5 mm; reconstruction slice thickness, 1 mm; matrix: 512×512; rotation speed, 0.5 or 0.6 s/r; and pitch, 1 or 0.984.

Image analysis

All images were read by 2 radiologists on the picture archiving and communication system in a blind manner. The image window width (WW) and window level (WL) were set as follows: lung window WW =1,500 Hu and WL =–600 Hu; and mediastinal window WW =300 Hu and WL =60 Hu. The manifests and size of nodules were observed and measured on thin images, and the diameters of PNs were measured at the lung window, usually at the transverse slice, unless the longest diameter of the nodule was in the coronal or sagittal position (12). To calculate the nodules' mean diameter, the long and short axes were measured to 1 decimal point, and the mean nodule diameter was measured to 1 decimal point (8).

PNs were classified and evaluated using Lung-RADS 2022 (8) by 2 radiologists (FPS and XLL) in a blind manner. In case of disagreement, the final decision was made via discussion and consensus. When diagnosing benign and malignant PNs, a previous study showed that the optimal diagnostic threshold of Lung-RADS was category 3 (13). Therefore, in this study, a negative screen was defined as categories 1 and 2, and a positive screen was defined as categories 3 and 4. The pathological diagnosis of a benign lesion was defined as negative, and the malignancy was defined as positive. All pathological diagnoses were obtained from the inpatient case system of The First Affiliated Hospital of Chongqing Medical University, and the pathologists were not aware of the relevant details of this study. When the category of Lung-RADS and pathological diagnosis of the same nodule were both positive or negative, this was defined as diagnostic agreement. Therefore, the diagnostic agreement rate (AR) was defined as the number of nodules that met the diagnostic agreement divided by the total number of nodules.

Imaging classification of PNs

A SN was defined as a lesion with a density higher than that of the blood vessels that could be seen in the mediastinal window, while a pGGN was defined as the low density of the nodule that could cover the passing vessels in the lung window. PSN referred to the presence of a solid component in the nodules, with the remaining components being ground-glass density.

Pathological category of PNs

Negative benign lesions included PNs that were pathologically diagnosed as atypical adenomatous hyperplasia (AAH), inflammatory pseudotumor, lung abscess, tuberculosis, and other benign lesions. Pulmonary metastasis (PMT) referred to tumors that had metastasized from the lung or any extrapulmonary organs or tissues and implanted in the lung. SPLC included all other pathologic types of lung malignancies except metastases. Both PMT and SPLC were considered malignant-positive nodules.

Statistical analysis

Quantitative variables are presented as their mean or median. The chi-squared test was used to compare the difference in diagnostic AR and the composition ratio of SN, PSN, and pGGN among the different groups by SPSS 22.0.. Statistical significance was assumed at $P<0.05$. When the sample size was less than 40 or the theoretical frequency was less than 1, the Fisher exact probability method was used.

Results

General data statistics of patients

A total of 451 patients (mean age 58.85 years; range 31–84 years; median age 58 years) comprising 565 PNs were included in this study (*Figure 1*). The patients were divided into the PLC group (144 patients; 187 PNs) and the PEPC group (307 patients; 378 PNs; *Table 1*). In terms of category, 8 nodules were category 1, 213 nodules were category 2, 24 nodules were category 3, 11 nodules were category 4A,

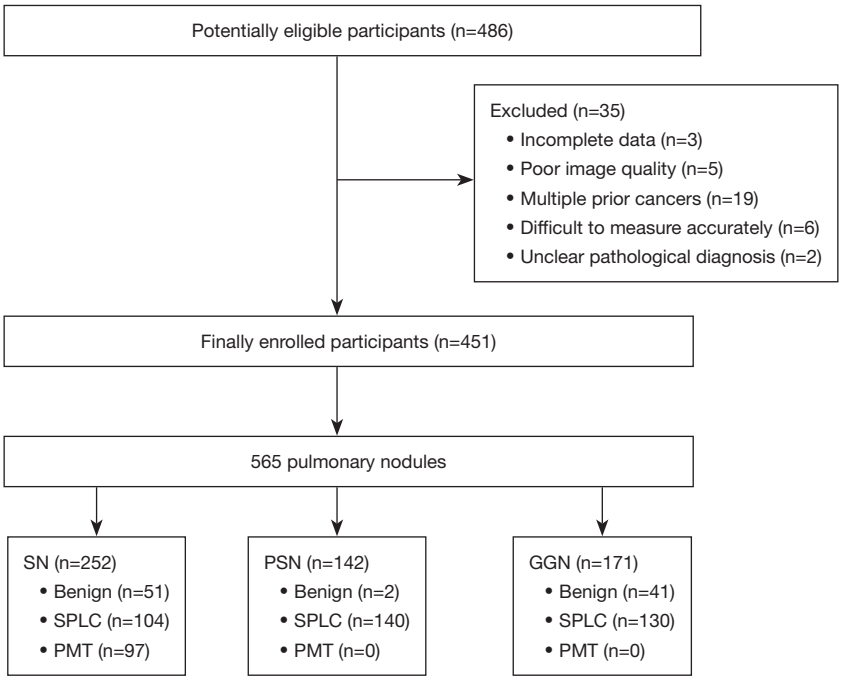

Figure 1 Pulmonary nodules (PNs) recruitment process. SN, solid nodule; PSN, partial solid nodule; GGN, ground-glass nodule; SPLC, second primary lung cancer; PMT, pulmonary metastasis.

Table 1 Baseline demographic and clinical characteristics of participants

Item	PLC		PEPC	
	<5 years	≥5 years	<5 years	≥5 years
Age (years) (mean ± SD)	60.35±9.69	62.89±7.32	56.47±11.22	61.91±9.45
Gender				
Male (n=160)	55	5	71	29
Female (n=291)	80	4	148	59
Smoking history				
Smoker (n=433)	132	9	205	87
Nonsmoker (n=18)	3	0	14	1
Pack years (mean ± SD)	41.73±27.04	40.00±22.30	46.49±29.00	36.88±25.88
Primary cancer				
Head and neck (n=60)	–	–	47	13
Lung (n=144)	135	9	–	–
Breast (n=80)	–	–	50	30
Digestive (n=89)	–	–	69	20
Urogenital (n=67)	–	–	45	22
Bone and joint (n=4)	–	–	3	1
Other (n=7)	–	–	5	2

PLC, prior lung cancer; PEPC, prior extrapulmonary cancer; SD, standard deviation.

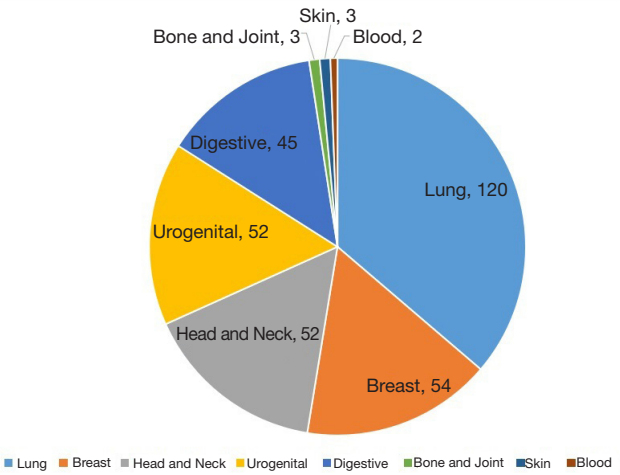

Figure 2 The location of prior cancer in patients with second primary lung cancer.

and 309 nodules were category 4B/X. Moreover, 18 patients (4.0%) had never been smokers, and 433 cases (96.0%) had a smoking history (mean pack years 40.24; range, 0–126). A total of 38 patients had a pack year history of <20 years, and 6 individuals claimed to have quit smoking (cease-smoking time range, 2 months to 30 years). A total of 407 patients (90.4%) underwent 2 or more chest CT examinations with an interval longer than 1 month. The longest follow-up period was 9 years after the discovery of a pulmonary nodule enrolled in the current study.

Table 1 shows the groups and their age and gender compositions, which were as follows: the PLC <5 years group had a mean age of 60.35±9.69 years, with 55 males and 80 females; the PLC ≥5 years group had a mean of 62.89±7.32 years, with 5 males and 4 females; the PEPC <5 years group had a mean age of 56.47±11.22 years, 71 males and 148 females; and the PEPC ≥5 years group had a mean age of 61.91±9.45 years, with 29 males and 59 females.

In the PEPC group, the top 3 types of previous cancers were digestive system (n=89), breast (n=80), and urogenital system cancer (n=67; *Table 1*). In patients who developed SPLC after a previous malignancy, most prior cancers originated in the lung (n=120), the breast (n=54), the head and neck (n=52), and the urogenital system (n=52), as shown in *Figure 2*.

Histology and staging of second primary lung cancer

The most common histological types of SPLC in the present study were invasive adenocarcinoma (165/374, 44.1%), microinvasive adenocarcinoma (101/374, 27.0%), and adenocarcinoma *in situ* (89/374, 23.8%). The most common clinical stage was IA (239/374, 63.9%; *Figure 3*).

Comparison of diagnostic AR of different types PNs using Lung-RADS

The diagnostic ARs for SNs and PSNs were similar (PSN 93.0% *vs.* SN 88.1%; P=0.13). However, the diagnostic ARs were all higher than that of GGNs (24.0%; all P values <0.001; *Table 2*).

Comparison of the composition ratio of PNs of different types between the different groups

The PLC group differed from the PEPC group when the length of malignancy history was less than 5 years (χ^2=29.269; P<0.001). When the time since previous cancer was 5 years or more, there was no difference between the 2 groups (P=0.93). The composition ratio of the same types of previous cancer was similar regardless of the length of cancer history (PLC <5 *vs.* PLC ≥5, P=0.33; PEPC <5 *vs.* PEPC ≥5, P=0.32; *Table 3*).

The difference in the diagnostic AR between the different groups

When the length of malignant tumor history was less than 5 years, there was a statistical difference between the PLC group and the PEPC group (PLC: 58.9%; PEPC: 76.6%; P<0.001). There was no statistically significant difference between the 2 groups (PLC: 50.0%; PEPC: 73.0%; P=0.10) when the length of the malignant tumor history was 5 years or more. As for the PLC group, there was a similar AR between the different timings of cancer history (<5 years: 58.9%; ≥5 years: 50.0%; P=0.55). This trend persisted in the PEPC group (<5 years: 76.6%; ≥5 years: 73.0%; P=0.47; *Table 3*).

Discussion

The chance of developing an SPLC differs depending the type of cancer a patients has previously had (14). In our data, the incidence of SPLC in those with previous lung cancers was the highest, followed by that in those with previous cancer in the breast, head and neck, and urogenital system, which was similar to the findings in the literature

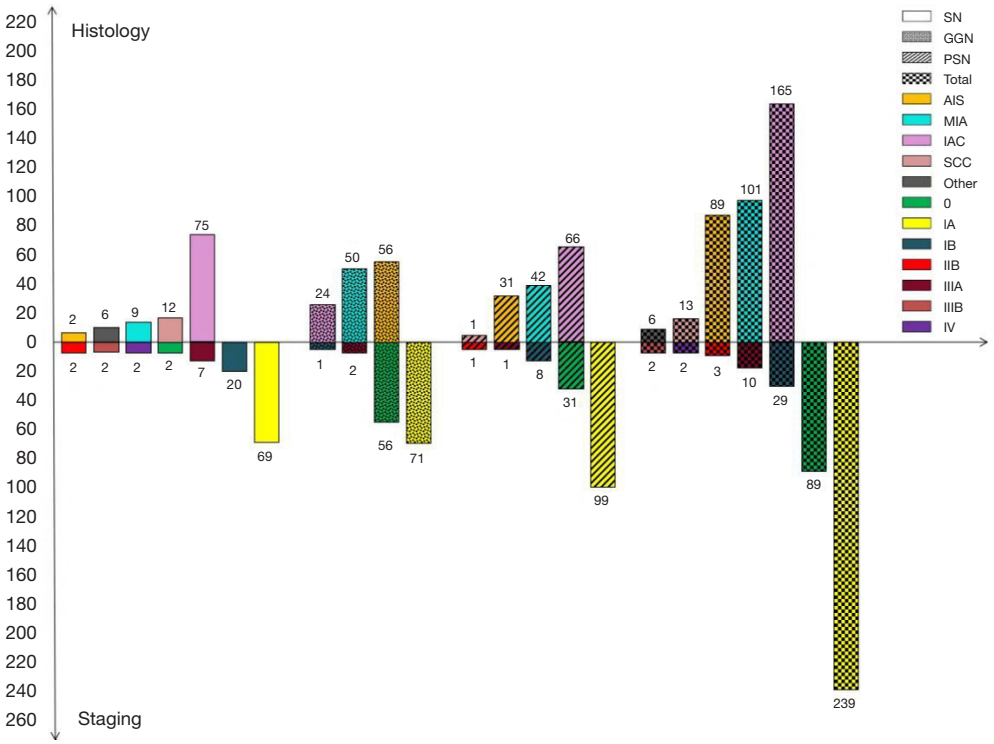

Figure 3 Histology and staging of the second primary lung cancer. SN, solid nodule; GGN, ground-glass nodule; PSN, partial solid nodule; AIS, adenocarcinoma in situ; MIA, microinvasive adenocarcinoma; IAC, invasive adenocarcinoma; SCC, squamous cell carcinoma.

Table 2 Comparison of the diagnostic agreement rate of different PN types

Type	Agreement	Disagreement	Agreement rate (%; 95% CI)	χ^2	P value[#]
GGN	41	130	24.0 (17.5–30.4)	178.086[a]	<0.001
SN	222	30	88.1 (84.1–92.1)	149.319[b]	<0.001
PSN	132	10	93.0 (88.7–97.2)	2.354[c]	0.13
Total	395	170	69.9 (66.1–73.7)	–	–

[a], GGN *vs.* SN; [b], GGN *vs.* PSN; [c], SN *vs.* PSN; [#], P=0.0167; GGN, ground-glass nodule; SN, solid nodule; PSN, partial solid nodule.

(14-16). This finding suggested that it is necessary to screen lung CT for patients with a history of malignant tumors in clinical practice. Although the National Lung Screening Trial (NLST) clearly defines individuals at a high risk of lung cancer that should undergo screening, not all patients underwent screening were at the high risk in clinical practice due to the preference of the individual or clinician. In addition, different countries and regions have different definitions of groups at a high risk of developing lung cancer. For example, in China, groups considered at a high risk of developing lung cancer are defined as those at least 40 years old and with any risk factors for lung cancer (17), such as a history of cancer. Moreover, it was reported that some high-risk patients not meeting the NLST inclusion criteria may benefit from lung cancer screening (18). Halpenny *et al.* (19) conducted lung cancer screening for patients with a previous history of malignancy using Lung-RADS, and the enrolled cases did not fully meet the criteria for high-risk groups of NCCN. Therefore, the age and smoking history of enrolled individuals were not strictly required in the current study. In addition, as a preliminary exploratory study, the indicators compared in this study were objective items, such as nodule diameter and Lung-RADS category, which would not affect the reliability

Table 3 Comparison of the composition ratio and agreement rate of PNs between different groups

Group	Item	PLC	PEPC	χ^2	P value
<5 years	SN	52 (29.7%)	147 (52.9%)	–[a]	0.33*
	PSN	43 (24.6%)	65 (23.4%)	29.269[b]	<0.001
	pGGN	80 (45.7%)	66 (23.7%)		
≥5 years	SN	6 (50.0%)	47 (47.0%)	2.722[c]	0.32
	PSN	3 (25.0%)	31 (31.0%)	–[d]	0.93*
	pGGN	3 (25.0%)	22 (22.0%)		
<5 years	Agreement (AR, 95% CI)	103 (58.9%, 51.5–66.2%)	213 (76.6%, 71.6–81.6%)	0.362[a]	0.55
	Disagreement	72 (41.1%)	65 (23.4%)	16.060[b]	<0.001
≥5 years	Agreement (AR, 95% CI)	6 (50.0%, 16.8–83.2%)	73 (73.0%, 64.1–81.9%)	0.523[c]	0.47
	Disagreement	6 (50.0%)	27 (27.0%)	2.727[d]	0.10

[a], PLC <5 *vs.* PLC ≥5; [b], PLC <5 *vs.* PEPC <5; [c], PEPC <5 *vs.* PEPC ≥5; [d], PLC ≥5 *vs.* PEPC ≥5; *, Fisher exact test; PLC, prior lung cancer; PEPC, prior extrapulmonary cancer; AR, agreement rate.

of the results of this research.

Our study also showed that the diagnostic agreement of Lung-RADS 2022 for PNs was inconsistent between different nodule types. The diagnostic AR of PSNs with Lung-RADS was the highest at 93.0%, meaning that almost all PSNs were malignant. This was consistent with existing literature, which found that early lung adenocarcinoma often presents with PSN (20,21). The diagnostic AR of Lung-RADS for SNs was 88.1%, which was slightly lower than that for PSNs (P=0.13) and slightly higher than the findings in a previous study (22). The possible reason for this finding was related to the different patients selected. The patients in our study were all patients who had undergone surgical resection and had a history of cancer, while the group in the discrepant study was a population of patients who had undergone lung cancer screening. As for pGGNs, the diagnostic AR was the poorest at 24.0%. This finding indicates that more than three-quarters of pGGNs received the wrong diagnoses, which were all false negatives (130/130). This is consistent with the underestimation with Lung-RADS of the malignant risk of subsolid nodules reported in another study (23).

It was noticeable that the proportion of false negatives (146/170, 85.88%) was much higher than that of false positives after a reanalysis of data was conducted. A total of 97.95% (143/146) of false-negative malignant nodules were SPLC. Although adenocarcinoma in situ (AIS) accounted for the largest proportion (64/143, 44.75%), the proportion of microinvasive adenocarcinoma (MIA) and invasive adenocarcinoma (IAC) was more than 50%. Compared to the different types of nodules with diagnoses of false negatives, GGNs accounted for the highest proportion (90.90%, 130/143), and 60.77% (79/130) of them were MIA and IAC. Therefore, it is necessary to complement Lung-RADS for the evaluation of GGNs, which was consistent with the prior study (24). When it came to false positives, we found that all nodules misdiagnosed as malignant lesions were SNs. There are several possible reasons for this finding. First, the nodules in this study to be large in diameter (mean 11.9 mm; maximum 22.8 mm). Second, patients, especially for cancer survivors, were more inclined to choose a nonstandard short-term follow-up or take active surgical treatment because of their fear or anxiety about cancer. In addition, Yu *et al.* (25) found that the probability of absorption and dissipation in chest CT follow-up after anti-inflammatory treatment of SNs was much lower than that of PSNs and pGGNs, at only 22%. Finally, thoracic surgeons may also prefer to perform surgical resection in these patients when there is no obvious absorption in the chest CT follow-up after anti-inflammatory therapy.

In this study, we also found that the length of cancer history could affect the diagnostic agreement of Lung-RADS. The diagnostic AR of Lung-RADS varied according to the type of previous cancer when the length of malignancy history was less than 5 years and disappeared when the time since diagnosis was 5 years or more. This finding was in accordance with the Mayo model of a 5-year history of malignant tumors for malignant risk assessment

of PNs and the NCCN guidelines stated limit of previous lung cancer (9,10). The reason for different diagnostic AR in different type of prior cancer may be related to the different composition ratios of PNs of different types between the PLC group and the PEPC group when the time of malignancy history was less than 5 years. In the PLC <5 years group, the pGGNs accounted for nearly half of the cases, while this proportion was 23.7% in the PEPC <5 years group. However, the composition ratio of PNs of different nodule types between any other 2 groups was close, and the difference was not statistically significant (PLC <5 years *vs.* PLC ≥5 years, P=0.33; PEPC <5 years *vs.* PEPC ≥5 years, P=0.32; PLC ≥5 years *vs.* PEP C ≥5 years, P=0.93, respectively). Correspondingly, the diagnostic AR between the remaining 2 groups was similar, and the difference was not statistically significant (P=0.55, P=0.47, and P=0.10, respectively).

Neither the NCCN guidelines nor the Mayo model is applicable to evaluating PNs in patients with prior lung cancer. The reason for this may be that the PNs in these individuals may be metastatic cancer, thus affecting the accuracy of the assessment. However, regardless of when the previous lung cancer was diagnosed, there was no statistical difference (P=0.55) in the diagnostic AR of Lung-RADS in our study. Moreover, we also noted the relatively small number of patients with previous lung cancer (≥5 years), with only 9 patients with 12 nodules enrolled in the, which may be related to the relatively low 5-year survival rate of lung cancer (26) and the fact that the patients with previous lung cancer included in this cohort all had undergone surgical resection. In contrast, those PNs treated with effective anti-inflammatory therapy or demonstrating long-term stability were not included in this study.

In addition, we sought to determine whether Lung-RADS had a high rate of missed diagnosis for pulmonary metastases. Our results showed that the probability of missed diagnosis was not high. PNs were diagnosed as pulmonary metastases in 73 patients, and 3 cases with 3 PNs were missed. Further analysis found multiple (≥2) pulmonary metastases in 2 patients, and all nodules except those misdiagnosed were correctly identified. Therefore, multiple solid nodules should be considered positive nodules in the future evaluation of PNs in patients with a history of cancer according to Lung-RADS. Of course, since all the nodules included in the present study were surgically resected, it cannot be ruled out that multiple micronodules whose category score may was lower than 2 on Lung-RADS were clinically diagnosed as metastatic tumors without surgical treatment.

This study had several limitations. First, patients with 2 or more types of prior cancer were excluded. Second, there was no comparison with patients who did not have a history of cancer. Third, there was no analysis of the clinical characteristics of patients with SPCL. Finally, this was a single-center study, and the sample size was small. In the future, a prospective, high-quality study with a larger number of cases is needed to verify our results.

Conclusions

In conclusion, when the history of malignant tumor was greater than 5 years, there was no difference in the AR of Lung-RADS for PNs regardless of the previous cancer source. There was also no difference in the coincidence rate of Lung-RADS of PNs for the same type of previous cancer, regardless of the time of previous cancer. The length of the prior cancer history may affect the diagnostic agreement of Lung-RADS, which may be related to the composition ratio of different types of PNs. In particular, it may not be appropriate to assess PNs in those with a history of lung cancer of less than 5 years with Lung-RADS.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-22-1039/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-22-1039/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki

(as revised in 2013). Ethical approval was obtained from the Ethics Committee of The First Affiliated Hospital of Chongqing Medical University (No. 2022-K346), and individual consent for this retrospective analysis was waived.

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