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Impact of lung-RADS classification system on the accurate diagnosis of pulmonary nodular lesions in oncology patients

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Abstract

Background: Lung assessment is highly recommended in the management of oncology patients as it is the commonest affected site in metastatic dissemination. The low-dose CT with nodule reporting system based on Lung Reporting and Data System (lung-RADS) is a promising non-invasive tool for the characterization of incidentally detected pulmonary nodules. The authors aimed to assess the accuracy of the "lung-RADS" classification system as a non-invasive tool for the characterization of any newly developed pulmonary nodules among oncology patients. Ethics committee approval and informed written consent were obtained from the studied patients. A non-contrast LDCT study was performed on all patients with a nodule reporting system based on the lung-RADS classification system applied for evaluation of each detected pulmonary nodule. Diagnoses were established using the help of either histopathology or follow-up clinical results as a gold standard.

Results: In this prospective study, we enrolled 187 known malignancy patients with 200 suspicious newly developed pulmonary nodules. Their mean patient age was 48.4 ± 9.7 years. The studied 200 pulmonary nodular lesions were categorized using a nodule reporting system based on the lung-RADS into 6 sub-groups with 122 lesions found to be malignant and 78 lesions were of benign etiology, which showed a high sensitivity of 92.08%, specificity of 78.79%, and accuracy of 85.50% with 81.58% positive predictive value and 90.70% negative predictive value in the diagnosis of pulmonary nodules in cancer patients.

Conclusion: Low-density CT with a nodule reporting system based on the lung-RADS classification system was found to be an accurate non-invasive tool to characterize and to risk stratify pulmonary nodules in oncology patients.

Keywords: Lung-RADS, Pulmonary nodules, Oncology

Background

In daily clinical practice, radiologists and pulmonologists are faced with incidental findings of pulmonary nodules that require an optimal decision in management and, meanwhile, to avoid morbidity and increased costs which are caused by invasive and unwarranted procedures for benign disease [1]. The differential diagnosis for pulmonary nodules is extremely broad, including both benign and malignant causes [2]. There is no consensus or guidelines regarding the investigation of pulmonary nodules in patients with extra-pulmonary malignancies. Retrospective data in populations of patients with cancer shows a high frequency of benign lesions (up to 58%) and primary lung cancers (up to 50%) found after biopsies or surgery [3]. Computed tomography (CT) is the most widely used modality for detecting lung metastases [4]. While the interpretation of CT scans for lung screening in pulmonary nodules remains challenging, various protocols and scoring systems have been developed [5]. The Reporting and Data System

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Table 1 Summary of Lung-RADS category [9]

Category descriptor	Category malignancy	Probability management	Recommendation
Negative	1	< 1%	Continue annual screening with LDCT in 12 months
Benign appearance or behavior	2	< 1%	Continue annual screening with LDCT in 12 months
Probably benign	3	1–2%	6-month LDCT
Suspicious	4A	5–15%	3-month LDCT; PET/CT may be used when there is a ≥ 8 mm solid component
	4B 4X	> 15%	Chest CT with/without contrast, PET/CT, and/or tissue sample that depends on the probability of malignancy and comorbidities. PET-CT may be used when there is a ≥ 8-mm solid component

(lung-RADS) was introduced to standardize the reporting and management of patients undergoing screening to facilitate data collection and monitoring of patient outcomes [6]. In this system, a specific lung-RADS category is assigned to each low-dose computed tomography (LDCT) examination. Each category measures the likelihood of malignancy for the dominant finding and offers specific recommendations regarding management [7]. The primary goal of lung-RADS is to minimize variation in the management of detected lung nodules that can be implemented effectively in radiology practices outside the purview of a clinical trial [8].

The purpose of the work was to assess the accuracy of the "lung-RADS" classification system as a non-invasive tool for characterization of any newly developed pulmonary nodules among oncology patients using the help of either histopathology or follow-up clinical results as a gold standard.

Methods

Patients' demographic data

This prospective cross-sectional analytic study included 187 patients (109 females and 78 males) with a known history of malignancy who are under management and followed up with 200 newly developed pulmonary nodules that are suspicious of a metastatic etiology. The

patient's age ranged from 21 to 78 years old with the mean age 48.4± 9.7 years.

Ethics committee approvals in addition to informed written consent were obtained from all patients.

Inclusion criteria

Patients with a known history of treated malignancy (either surgical, radio, or chemo-therapy) with newly developed pulmonary nodule/s on a follow-up CT chest study were included in the study.

Patients who had general contraindications for CT examination or respiratory distress that made them unable to tolerate breath-hold were excluded.

CT protocol and technique

The non-contrast LDCT study was performed using a 16–Multislice CT scanner (GE) Aquilion machine. All patients were trained to achieve a full end-inspiratory breath-hold before the start of the LDCT exam. They were scanned at the end of the full inspiration CT protocol: 120–140 kVp, 40–100 mA, and reconstructed section width 1.0 to 3.2 mm, with reconstruction scan intervals of 1–2.5 mm and a pitch of 1–2.

Post-processing

All CT images were magnified and reviewed by two radiologists who had prior experience with chest imaging and were informed of the patient's history, using GE PACS in axial images and reconstructed with soft tissue and lung windows. Axial maximum-intensity projections (16–2.5 mm). Coronal and sagittal multiplanar reformatted images were reconstructed and used for interpretation. The window setting for lung parenchyma used was between – 560 and – 1135 HU by the visual method to detect any pulmonary nodular lesions as well as the associated parenchymal abnormalities. According to the lung-RADS classification system (Table 1), nodules can be categorized into 1–4A, B, and X subgroups [9]. CT image interpretation was performed by two radiologists in consensus with adequate experience in CT lung screening using lung-RADS guidelines and nodule

Table 2 Demographics

Variable	Overall	Percent (%)
Number	187 pts with 200 nodules	100%
Age	21–78 (± 48.4) years	-
Sex	109 females	58.28%
	78 males	41.71%
Known primary neoplasm		
-Breast Ca	83	41.5%
-Lung Ca	68	34%
-Prostate Ca	19	9.5%
-GIT Ca	12	6%
-Thyroid Ca	5	2.5%

Table 3 Final clinico-pathological diagnosis results of the all studied nodular lesions (no. = 200)

Final lesion clinical/pathology diagnosis		No.	Percent %
Group I: Benign lesions		**78**	39%
a) Ground glass nodules	**26/0**	26	13%
b) Pre-fissural nodules	**17/0**	17	8.5%
c) Inflammatory nodules	**13/0**	13	6.5%
d) Follow-up static small nodules	**10/0**	10	5%
e) Fat/calcifications containing nodules	**12/0**	12	6%
Group II; Malignant lesions		**122**	61%
a) Metastatic nodules	**19/78**	87	43.5%
b) Sequamus cell carcinoma	**0/19**	19	9.5%
c) Adeno-carcinoma	**0/7**	7	3.5%
d) Alveolar lung cancer	**0/6**	6	3%
e) Small cell carcinoma	**0/3**	3	1.5%
Total		200	100%

follow-up algorithms. Nodules are considered positive for malignancy and are categorized as 4A, 4B, and 4X.

Assessment of nodule size and density
On CT images, each pulmonary nodule was studied for:

The lesion size is given in millimeters

Leurion texture, which is expressed as soft tissue attenuation "solid," sub-solid, which could be divided into either pure ground-glass attenuation with pulmonary vessels and bronchi that may be seen within, or a semi-solid/part-solid that contains both ground glass and soft-tissue attenuation components. The categorization of a pulmonary nodule is important in that it predicts the likelihood of malignancy.
Histo-pathological and final clinical diagnosis as a gold standard
CT findings with the lung-RADS classification system were correlated by either histopathological results for very suspicious large malignant lesions or follow-up of final clinical diagnosis for benign featuring small nodular lesions in all patients. The nodules were classified as benign or malignant based on the final diagnosis.

Statistical analysis
The statistical calculations were done using the Statistical Package for Social Science, version 19, in which data is described in terms of range, mean, standard deviation, frequencies & percentages. Sensitivity, specificity, accuracy, positive predictive value, and negative predictive value for CT results with a lung-RADS classification system for pulmonary nodules were calculated.

Results
This prospective study included 187 patients who had a positive history of treated cancer (83 breast cancer, 68 lung cancer, 19 prostate cancer, 12 GIT cancer, and 5 thyroid cancer) and were under management and follow-up with 200 newly developed pulmonary nodules that were suspicious of metastatic etiology. The patients' ages ranged from 21 to 78 years (M = 43.4 ± 9.7 years) (Table 2).

Gold standard
The histopathological results for the biopsed103 nodules were as follows: 72 metastatic nodules, 9 Seq. cell Ca, 7 adeno-Ca, 6 alveller Ca, 3 small cell Ca, and 6 inflammatory lesions, while the final clinical diagnoses based on the clinical and follow-up (for 18–24 months) results of the remaining 97 inaccessible small/benign featuring lesions were as follows: 25 metastatic lesions that showed either increase in size or number in follow-up CT images. However, 72 lesions were categorized as benign nodules which were stationary on CT follow-up studies up to 2 years duration. Table 3 shows the classification of all pulmonary nodular lesions studied (no = 200) into two groups: group I: benign nodular lesions (78 lesions; 39%) and group II: malignant nodular lesions (122 lesions; 61%).

The diagnosis of lung RADS necessitates the examination of 200 nodules
Eighty-six lesions were diagnosed as benign (score 1–3), although 8 of them were found to be malignant

Table 4 Categorization of benign lung nodules (lung-RRADS score 1–3): "group I" (no. = 86 nodules)

RADS score	Size	Lesion density	Lesion no.	% for all lesions	Radio-diagnosis
1	**Any**	Fully-pop corn calcification	**13**	**6.5%**	**Benign**
	Any	Fatty containing	**5**	**2.5%**	
2	6–< 30 mm	Solid pre-fissural/+ground glass appearance	**29**	**14.5%**	**Benign**
	< 6 mm	Sub-solid/semi-solid	**13**	**6.5%**	
3	≥ 6 to < 8 mm	Solid	**17**	**8.5%**	**Benign**
	≥ 6 mm with solid component < 6 mm,	Part solid	**6**	**3%**	
	≥ 30 mm	Non-solid	**3**	**1.5%**	
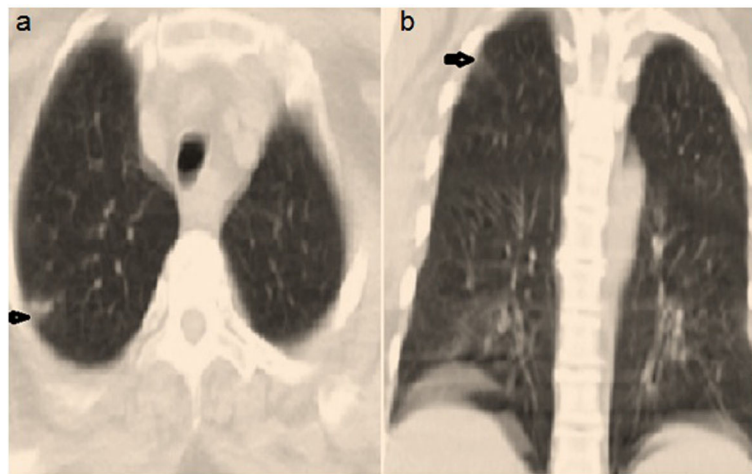
Fig. 1 "A 47-year-old male patient with a history of rectum cancer." MCCT exam revealed a small well-defined solid nodule about 6 x3mm at the posterior aspect of the Rt. Upper lung lobe (**a**) axial (**b**) coronal image that is categorized as lung-RADS score III "benign solid nodular lesion" that is proved on follow-up for 24 months to be static small begin nodule

metastatic lesions (false negative). Five of these lesions showed significant growth in the follow-up study and 3 were accompanied by the appearance of other newly developed nodules that were not included in this study (Table 4; Figs. 1 and 2). On the other hand, 114 nodules were diagnosed as malignant lesions (score 4A, 4B, and 4 X), with 21 of them proving to be of benign etiology (false positive; 12 inflammatory granulomas according to histopathology and 9 lesions were static in follow-up CT images up to 18 months), (Table 5, Figs. 3, 4 and 5).

Sensitivity, specificity, and accuracy of lung-RADS for final diagnosis of all studied 200 nodular lesions

Lung-RADS was found to show a high sensitivity of 92.08%, specificity of 78.79%, and accuracy of 85.50% with 81.58% positive predictive value and 90.70%

negative predictive value in the diagnosis of pulmonary nodules in cancer patients (Table 6).

Discussion

Pulmonary metastasis is seen in 20–54% of extra-thoracic malignancies [9]. Lung-RADS reporting is standardized per CT lung screening, which accounts for pulmonary nodules and other findings concerning carcinoma, as well as any significant incidental findings [10, 11].

The present study included 200 newly developed pulmonary nodules in 187 known cured cancer patients that were categorized by the lung-RADS calcification system into 6 sub-groups, 1-4A, 4B, and 4X, and we considered scores of 4A, 4B, and 4X as malignant. We found 86 lesions to be benign that were categorized as
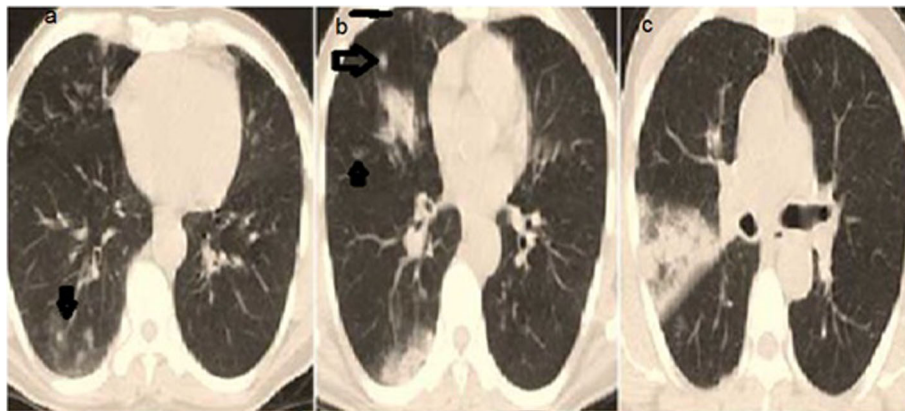
Fig. 2 "A 44-year-old female patient with a history of breast cancer."| MCCT exam axial views revealed multiple well-defined small solid nodules scattered at the periphery of the Rt. upper and lower lung lobes (**a**, **b**) that categorized as lung-RADS score 4X, "malignant metastatic solid nodular lesions" that is on follow-up after 1 month (**c**) proved to be benign inflammatory granuloma according to final clinical diagnosis
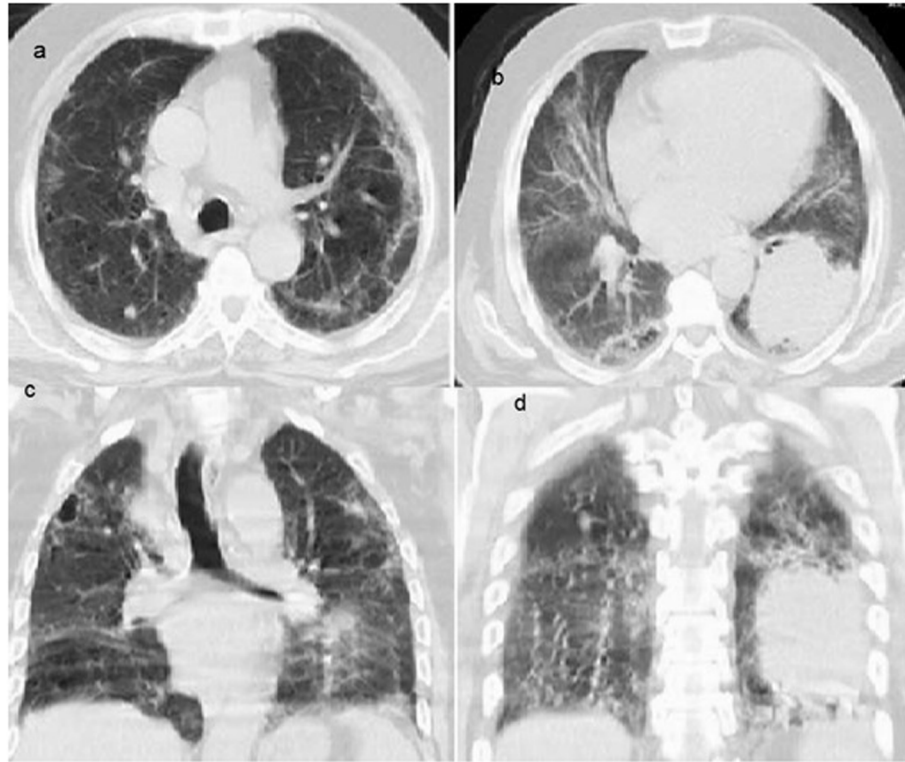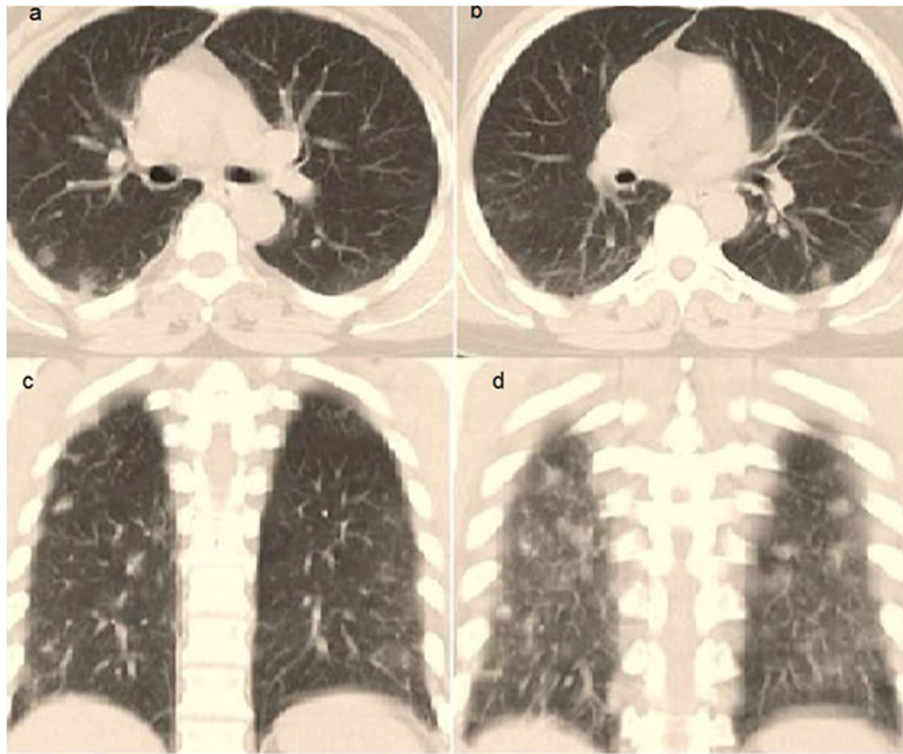
Fig. 3 "A 63-year-old male patient with a history of prostate cancer." MCCT exam revealed a well-defined small solid nodule at the Rt. lower lung lobe and a sizable soft tissue mass lesion at the Lt. lower lung lobe (**a**, **b**) axial and (**c**, **d**) coronal images that categorized as the lung-RADS score 4X, "malignant solid nodular lesions." The Lt. side lesion was pathology proved as newly developed adenocarcinoma and Rt. side considered as a metastatic lesion

lung-RADS 1–3 scores. However, 8 of them were found to be malignant metastatic lesions (false negative) in line with histopathology and follow-up results. While we diagnosed 114 nodules as malignant lesions with lung-RADS 4A, 4B, and 4X scores, 21/114 proved to be of benign etiology (false positive): 6 inflammatory granulomas per histopathology results and 15 showed static appearance on LDCT chest follow-up after 18–24 months. Our findings were consistent with those of Caparica et al. [3], who conducted a similar study) on 228 patients and

metastatic disease was found in 146 patients (64%). On biopsy, 60 patients (26.3%) were found to have a second primary lung tumor, while 22 patients (9.6%) were found to be cancer-free. Other series have also found different rates of malignant nodules on histologic analysis. In a large study with 1104 patients undergoing PNs resection, Mery et al. [12] observed a 63% malignancy rate in 337 patients with a previous cancer history. A lower rate by Khokhar et al. [13] discovered malignant pulmonary nodules in oncologic patients; 28% of small pulmonary

Table 5 Categorization of malignant lung nodules (lung-RADS score: 4A, B, and X). "Group II" (no. = 114 nodules)

RADS score	Size	Lesion density	Lesion no.	% for all lesions	Radio-diagnosis
4A	≥ 8 to < 15 mm	Solid	9	4.5%	**Malignant**
	≥ 6 mm + solid comp. measuring ≥ 6–< 8 mm	Part solid	7	3.5%	
	Measuring 9.3 mm	Endo-bronchial	1	0.5%	
4B	≥ 15 mm	Solid	32	16%	**Malignant**
	With a solid component measuring > 8 mm.	Part solid	14	7%	
4X 4A/4Bwith	With	Other solid lesions	29	14.5%	**Malignant**
		Speculation	11	5.5%	
		Lymphadenopathy	4	2%	
		Growth on follow-up	7	3.5%	

Fig. 4 "A 56-year-old female patient with a history of thyroid cancer." MCCT exam revealed multiple well-defined solid nodules scattered throughout both lung parenchyma (**a**, **b**) axial and (**c**, **d**) coronal images that are categorized as lung-RADS score 4X, "malignant metastatic solid nodular lesions" that showed an increase in size and number in follow-up examinations which proved to be metastatic malignant nodules

nodules detected on the initial CT will increase in size, suggesting metastasis. However, Reginald et al. [14] concluded that in the majority of clinical settings, an interval increase in the size of a single pulmonary nodule is considered evidence of metastasis, this size increase tends to occur early, and follow-up CT in 3 and 6 months would be appropriate for further evaluation. On the opposite hand, Meng et al. [15] divided ground-glass nodules into three groups: benign disease (inflammations), pre-invasive group, and invasive group
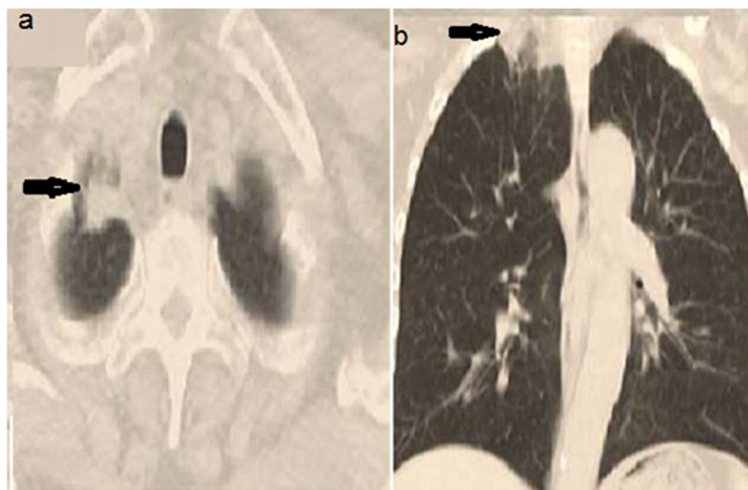
Fig. 5 "A 52-year-old female patient with a history of treated breast cancer since 1.5 years." Follow-up MCCT exam revealed an irregular well-defined semi-solid nodule at the anterior segment of the Rt. upper lung lobe (**a**) axial (**b**) coronal image that is categorized as lung-RADS score 4A "malignant nodular lesion." Pathology results newly developed small cell carcinoma

Table 6 Sensitivity, specificity, and accuracy of lung-RADS for all studied lesions

Modality	Sensitivity	Specificity	Accuracy	PPV	NPP
Lung-RAD**S**	92.08%	78.79%	85.5%	81.58%	90.70%

(adenocarcinoma) in line with the pathologic findings of type IV, strongly suggesting a high likelihood of malignancy, while Kim et al. [16] stated that pulmonary subsolid nodules (SSNs) are frequently encountered within the screening CT with their main concern being lung adenocarcinoma and its precursors. Results from the National Lung Screening Trial showed that carcinoma screened by CT significantly reduced carcinoma mortality, and benign nodules were primarily confirmed by stability or shrinkage on repeat CT scans over a 2-year follow-up period [17]. Chung et al. [18] found that the typical false-positive rate was 7% for category 3 nodules, 7% for category 4A nodules, and 19% for category 4B nodules.

Lung-RADS may be a tool that facilitates standardized reporting and management of abnormal findings at LCS CT [8].

Our findings revealed that the lung-RADS arrangement had a high sensitivity of 92.08%, specificity of 78.79%, and accuracy of 85.50% in the diagnosis of pulmonary nodules in oncology patients, with 81.58% positive predictive value and 90.70% negative predictive value. These results were in agreement with McKee et al. [19], who said that ACR lung-RADS reduced the general positive rate from 27.6 to 10.6%. No false negatives were present within the 152 patients with > 12-month follow-up reclassified as benign. Applying ACR lung-RADS increased the positive predictive value for diagnosed malignancy in 1603 patients with follow-up from 6.9 to 17.3% and by Kessle et al. [20], who concluded that lung-RADS produced 9 false-positives and 16 false-negative findings, whereas VRC with a 5% threshold resulted in 29 false-positives and 10 false-negative findings. Overall sensitivity and specificity for lung-RADS was 58.0% and 98.0%, and for VRC with a 5% threshold was 73.7% and 93.5%, respectively ($P = .313$, $P = .001$, respectively).

Limitations
Due to the relatively low number of lesions and the small size of most nodules, which made biopsy and histopathology difficult, we relied on a follow-up clinical diagnosis of up to 24 months, which is acceptable in oncology patients.

Conclusion
Low-density CT with a nodule reporting system based on the lung-RADS classification system was found to be an accurate non-invasive tool to characterize and to risk stratify pulmonary nodules in oncology patients.

Abbreviations
CT: Computed tomography; Lung-RADS: Lung Reporting and Data System; LDCT: Low-dose computed tomography

Authors' contributions
The author(s) read and approved the final manuscript.

Declarations

Ethics approval and consent to participate
This study was done after approval from the AL-Azhar University Hospital, Faculty of Medicine Assuit, and the after patient agrees verbal consent (as the patients were not exposed to any type of surgical or intervention maneuver). This study was done from January 2019 to October 2020. The number of meeting code is 3 and the number of paper code is 7.

Consent for publication
All patients included in this research gave written informed consent to publish the data contained within this study. If the patient was less than 16 years old, deceased, or unconscious when consent for publication was requested, written informed consent for the publication of this data was given by their parent or legal guardian.

Competing interests
The authors declare that they have no competing interests.

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