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ONCOLOGY

Inter-observer agreement on the morphology of screening-detected lung cancer: beyond pulmonary nodules and masses

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Abstract

Objectives Pulmonary nodules and masses are the typical presentations of lung cancer. However, a spectrum of focal opacities cannot be defined as either "pulmonary nodule" or "mass," despite representing cancer. We aimed to assess the morphology of screening-detected lung cancers at low-dose computed tomography LDTC and to evaluate inter-observer agreement in their classification.

Methods Four radiologists with different experiences in thoracic imaging retrospectively reviewed 273 screening-detected lung cancers. Readers were asked to assess if morphology at the time of diagnosis was consistent with the Fleischner Society definition of pulmonary "nodule" or "mass." Cancers not consistent were defined as "non-nodular/non-mass" (NN/NM) and sub-classified as follows: associated with cystic airspaces, stripe-like, scar-like, endobronchial, or not otherwise defined (NOD). Inter-observer agreement was evaluated using Cohen's K statistic among pairs of readers and modified Fleiss' kappa statistic for overall agreement.

Results Two hundred forty-one of the 273 (88%) lesions were defined as pulmonary nodule or mass by complete agreement, while 20/273 (7.3%) were defined as NN/NM. Six (2.2%) of 273 were sub-classified as lesions associated with cystic airspace, six (2.2%) as scar-like, five (1.8%) as endobronchial, and one (0.7%) as NOD by complete agreement. The concordance in defining morphology was excellent (261/273; 96%, 95%CI 92–98%; *k* 0.85, 95%CI 0.75–0.92) and also in the sub-classification (18/20; 90%, 95%CI 68–99%, *k* 0.93, 95%CI 0.86–1.00). There was incomplete agreement regarding lesion morphology in 4.4% (12/273) of cases.

Conclusions A non-negligible percentage of screening-detected lung cancers has a NN/NM appearance at LDCT. The concordance in defining lesion morphology was excellent. The awareness of various presentations can avoid missed or delayed diagnosis.

Key Points

- *A non-negligible percentage of screening-detected lung cancers have neither nodular nor mass appearance at low-dose CT.*
- *The awareness of various LDCT presentations of lung cancer can avoid missed or delayed diagnosis.*
- *Optimal protocol management in CT screening should take into consideration lung nodules as well as various other focal abnormalities.*

Keywords Lung cancer · Mass screening · Solitary pulmonary nodule · Observer variation

Cristiano Rampinelli and Marta Minotti have given an equal contribution in the ideation, data management, and realization of this study.

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Abbreviations

CT	Computed tomography
LDCT	Low-dose computed tomography
NLST	National Lung Cancer Screening Trial
NN/NM	Non-nodular/non-mass
NOD	Not otherwise defined

Introduction

The National Lung Cancer Screening Trial (NLST) has demonstrated that low-dose computed tomography (LDCT) reduces lung cancer mortality by 20% in high-risk subjects compared with chest X-ray screening [1].

As non-calcified pulmonary nodules are the typical presentation of early-stage lung cancer, worldwide computed tomography (CT) screening protocols and study designs are based on the detection and management of pulmonary nodules. According to the definition of the Fleischner Society, the pulmonary nodule appears as "a rounded or irregular opacity, well or poorly defined, measuring up to 3 cm in diameter" [2].

Screening-detected lung cancers can appear also as a mass, typically when advanced-stage, which is defined by the Fleischner Society as "any pulmonary, pleural, or mediastinal lesion seen as an opacity greater than 3 cm in diameter."

However, there is a wide spectrum of focal opacities seen on LDCT that can be defined neither as pulmonary nodule nor as mass, but actually represent manifestation of primary lung cancer and have been reported in the literature among the causes of missed diagnosis of lung cancer in patients undergoing CT screening [3–5]. In particular, in a recent retrospective evaluation of interval and post-screen carcinomas from the Dutch-Belgium lung cancer trial, the authors found that detection error can occur for endobronchial cancers and interpretation error for bulla with wall thickening [6].

Previous studies aimed to retrospectively review the appearance of CT screening-detected lung cancers [7–9], but few have focused their attention on the different morphology of these lesions [4, 6].

Early identification of any focal lesion, even if not manifesting as a pulmonary nodule or mass, is crucial because cancer is typically curable when it is in early stage [10].

Therefore, the aim of this study was to assess the morphology of screening-detected lung cancers at LDCT, with particular regard to lesion with neither nodular nor mass appearance, and to evaluate the inter-observer agreement in the classification of these lesions.

Materials and methods

Study population

The clinical dataset for the present study was obtained from a single-center screening program, carried out in our Institute from 2004 to 2015 (COSMOS screening trial). Each subject enrolled in the trial provided written consent. The design, enrolment procedure, and management protocol of suspicious lesions of the trial were reported previously [11–13].

Briefly, 5203 asymptomatic volunteers ($\geq$ 50 years old, with a smoking history of at least 20 pack-years, current or former smokers within 10 years of quitting, having no history of previous malignancies) were enrolled to perform annual LDCT for 10 consecutive years. During the screening period, 280 lung cancers were diagnosed.

CT images were obtained on two 64-detector row spiral scanners (Discovery CT750 HD and Optima CT660, GE Healthcare) with the following technical parameters: tube voltage 100 kVp, tube current 30 mA, pitch 1.75, rotation time 0.5 s, slice thickness 2.5 mm, reconstruction interval 1.25 mm, kernel standard.

Study design

In this study, we evaluated only LDCT scans from the COSMOS trial. Therefore, out of the 280 lung cancers detected in the COSMOS cohort during the study period, seven cases were excluded because the diagnosis was made using a standard dose CT not performed in our institute.

Eventually, 273 primary lung cancers, all proved by histology, in 255 patients were considered. Patient and tumor characteristics are summarized in Table 1.

Four radiologists with different experiences in thoracic imaging (reader A, 3 years of experience; reader B, 10 years; reader C, 20 years; reader D, 30 years) retrospectively reviewed, independently, the LDCT scan performed prior to histological diagnosis for each of the 273 lung cancers. The readers were aware of the specific lesion location; in particular, they knew the pulmonary lobe and CT slice number. To define the morphology of screening-detected lung cancers, each reader was asked to assess if the lesion at the time of diagnosis was a pulmonary "nodule" or a "mass," according to the Fleischner Society definitions. Lesions categorized as neither nodule nor mass were defined as "non-nodular/non-mass" (NN/NM) and sub-classified as follows: associated with cystic airspaces, stripe-like, scar-like, endobronchial, and not otherwise defined (NOD).

The subtype "associated with cystic airspaces" (Fig. 1) was applied to lesions that abutted or were in the wall of cystic airspaces (dilated airways, emphysematous bullae, blebs), irrespective of the presence of emphysema elsewhere [14].

Table 1 Characteristics of screening-detected lung cancers

Characteristic	*N* (%)			
	Pulmonary nodule or mass,* *N* = 241	NN/NM lesions,* *N* = 20	Discordant lesions,§ *N* = 12	All, *N* = 273
Age (mean ± SD)	63.3 ± 6.3	64.2 ± 6.1	63.2 ± 4.3	63.3 ± 6.2
Sex				
Male	168 (70%)	14 (70%)	10 (83%)	192 (70%)
Female	73 (30%)	6 (30%)	2 (17%)	81 (30%)
Incidental tumor				
No	156 (65%)	18 (90%)	9 (75%)	183 (67%)
Yes	34 (14%)	1 (5%)	0 (0%)	35 (13%)
Present at first CT	51 (21%)	1 (5%)	3 (25%)	55 (20%)
Site				
Upper left	62 (26%)	5 (25%)	6 (50%)	73 (27%)
Upper right	81 (34%)	10 (50%)	4 (33%)	95 (35%)
Lower left	34 (14%)	1 (5%)	1 (8%)	36 (13%)
Lower right	44 (18%)	3 (15%)	1 (8%)	48 (18%)
Medium	17 (7%)	1 (5%)	–	18 (7%)
Ilo	3 (1%)	–	–	3 (1%)
Histology				
ADK	182 (76%)	14 (70%)	11 (92%)	207 (76%)
SCC	31 (13%)	3 (15%)	–	34 (12%)
SCLC	14 (6%)	1 (5%)	–	15 (5%)
Others	14 (6%)	2 (10%)	1 (8%)	17 (7%)
T				
T1	164 (72%)	10 (56%)	10 (91%)	184 (72%)
T2	44 (19%)	6 (33%)	1 (9%)	51 (20%)
T3	9 (4%)	–	–	9 (4%)
T4	10 (4%)	2 (11%)	–	12 (5%)
Missing	14	2	1	17
Tumor stage				
I	161 (71%)	14 (78%)	9 (82%)	184 (72%)
II	25 (11%)	1 (6%)	1 (9%)	27 (11%)
III	31 (14%)	3 (17%)	1 (9%)	35 (14%)
IV	10 (4%)	–	–	10 (4%)
Missing	14	2	1	17

SD, standard deviation

*Defined by complete agreement among the four radiologists

§ Disagreement in defining "pulmonary nodule" or "mass" versus "NN/NM" lesions

Focal lesions with a linear appearance, where one diameter in any plane clearly predominates over the other, were defined "stripe-like" lesions (Fig. 2).

Irregular lesions with spiculated margins, evaluated in any plane, with or without retraction of the adjacent parenchyma, were defined as "scar-like" (Fig. 3). Radiologists were asked to refer to a focal lesion as scar-like if they would report it as a scar in clinical routine (i.e., apical scar).

Lesions growing into the lumen of a central or peripheral airway were named "endobronchial" (Fig. 4).

Lesions that did not meet any of the above features were classified as "NOD." In this subtype, we included, for example, cancers presenting as consolidation (Fig. 5) [2]. The anatomical site (lobe) and histological type were assessed for each lung cancer.

TNM stage was assessed for 256/273 patients.

Finally, we also reviewed the previous annual LDCT scans of all lung cancers detected after the baseline (218/273), in order to assess whether the lesion was already visible 1 year before the diagnosis. When the lesion was not present the year before, we defined it as "incidental."

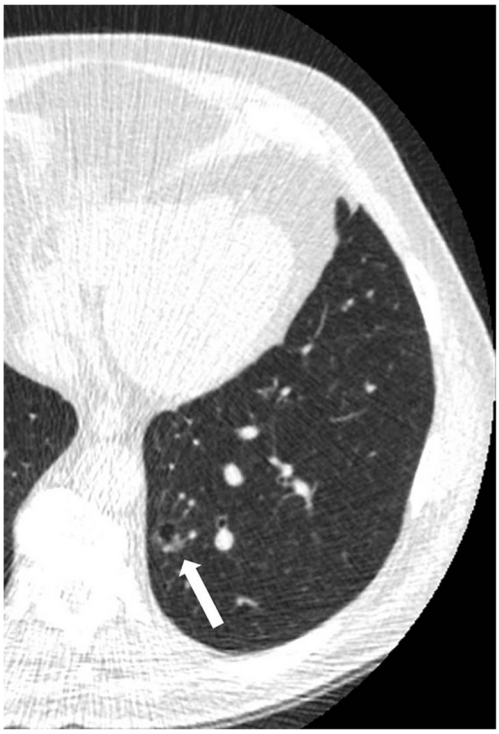

Fig. 1 Lung adenocarcinoma in a 54-year-old woman. Axial LDCT shows an irregular thickening of the wall of a bulla (arrow) in the left-lower lobe. This lesion was defined as NN/NM (associated with cystic airspaces) by all the readers

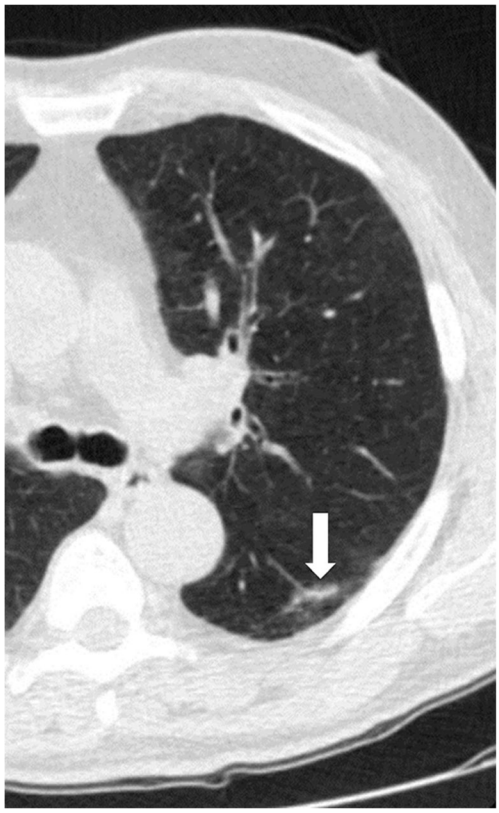

Fig. 2 Lung adenocarcinoma in a 69-year-old man. Axial LDCT shows a focal abnormality with a linear appearance in the left-lower lobe. This lesion was defined as NN/NM by all the readers; in particular, it was classified as stripe-like by one reader and as NOD by the other three readers

Statistical analysis

Tumor characteristics were reported as frequencies and percentages. Inter-observer agreement in the definition of morphology was evaluated using Cohen's K statistic, with 95% confidence interval (CI), among pairs of readers, and the modified Fleiss' kappa statistic for overall agreement among the four different readers. Fleiss' kappa 95%CIs were calculated with 1000 bootstrap replications [15]. Conventionally, a value of kappa lower than 0.2 is considered poor agreement, between 0.21 and 0.40 fair, between 0.41 and 0.60 moderate, between 0.61 and 0.8 substantial, and greater than 0.8 perfect [16].

Statistical analysis was performed using SAS (SAS Institute Inc.), version 9.4 and STATA (STATA Corp.) version 13.1.

Results

Of the 273 lung cancers evaluated, 241 (88%) lesions were defined as pulmonary nodule or mass by complete agreement among the readers.

Between 8 and 10% of lung cancers were defined as NN/NM lesions depending on the radiologist (Table 2; reader A, 28/273 (10%); reader B, 22/273 (8%); reader C, 26/273 (9.5%): reader D, 27/273 (9.8%)) while 7.3% (20/273) were defined as NN/NM lesions by complete agreement among all four radiologists.

There was an incomplete agreement between the radiologists regarding lesions morphology in just 4.4% (12/273) of cases (Table 3).

Frequency and sub-classification of NN/NM lesions according to each radiologist are reported in Table 2.

The concordance between the four readers in defining lung cancer morphology was excellent, as shown in Table 4 (overall percent of concordance, 261/273; 96%, 95%CI 92–98%; *k* 0.85, 95%CI 0.75–0.92). The greatest concordance was obtained between the two most experienced radiologists (reader C and reader D; overall percent of concordance, 270/273; 99%, 95%CI 97–100%; *k* 0.94, 95%CI 0.87–1.00). The concordance was also excellent in the sub-classification of NN/NM lesion subtypes, as shown in Table 5 (overall percent of concordance, 18/20, 90%, 95%CI 68–99%, *k* 0.93, 95%CI 0.86–1.00).

Among the 20 lung cancers defined as NN/NM lesions by complete agreement among the four radiologists (Table 2), six were classified as lesions associated with cystic airspaces (2.2%, 6/273), six as scar-like (2.2%, 6/273), five as

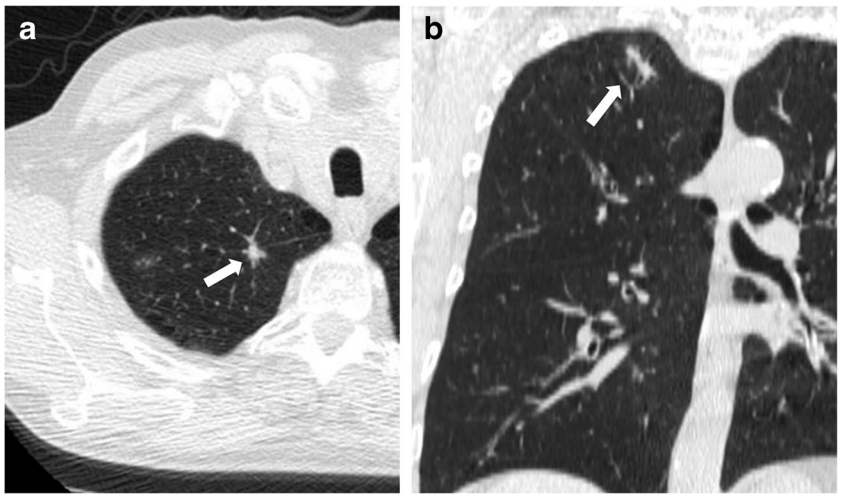

Fig. 3 Adenocarcinoma presenting as a scar-like lesion in a 74-year-old man. LDCT shows a lesion in the right-upper lobe with spiculated margins in both axial (**a**) and coronal reconstruction (**b**). This lesion was defined as NN/NM (scar-like) by all the readers

endobronchial (1.8%, 5/273), and one as NOD (0.4%, 1/273). The radiologists were discordant about the sub-classification of two NN/NM lesions: the first was classified as stripe-like by one reader and as NOD by the other three readers (Fig. 2); the second was classified as NOD by three readers and as scar-like by others (Fig. 6). There was a better agreement in defining lung cancer morphology for lesions with higher T stages (Table 1).

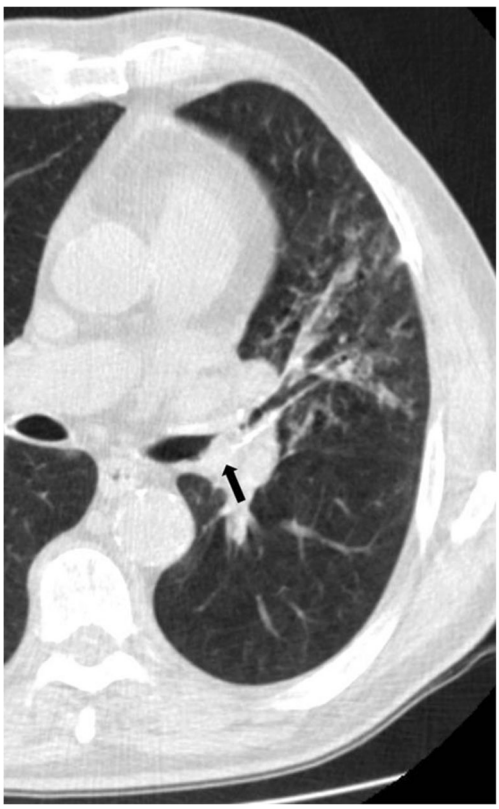

Fig. 4 Endobronchial squamous cell carcinoma in a 72-year-old man. Axial LDCT shows a solid tissue (arrow) in the left-upper bronchus with significant airway reduction. This lesion was defined as NN/NM (endobronchial) by all the readers

Eighteen out of the 20 lung cancers defined as NN/NM lesions by complete agreement among the four radiologists were already visible in the previous annual low-dose CT scan (Table 1); four were endobronchial, six were lesions associated with cystic airspaces, six were scar-like, and two were discordant lesions (one lesion was classified as stripe-like by three readers and as NOD by one reader; one was classified as NOD by three readers and as scar-like by one reader).

Adenocarcinoma was the predominant histological subtype among the NN/NM lesions (14/20; 70%) and 75% (15/20) of

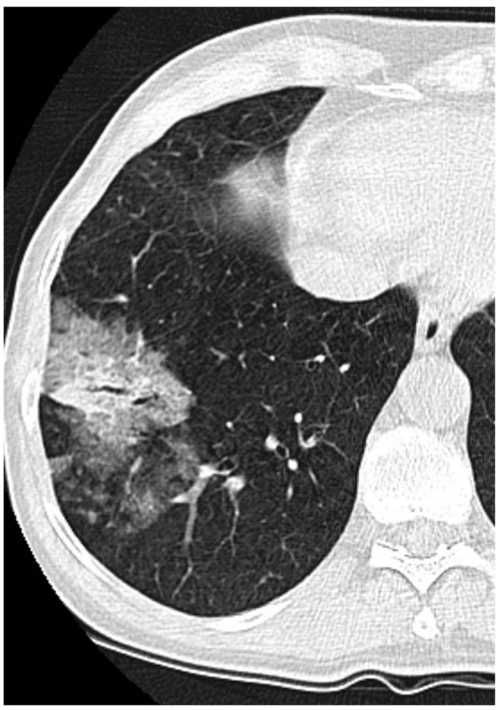

Fig. 5 Lung adenocarcinoma in a 55-year-old woman. Axial LDCT shows a parenchymal consolidation in the right-lower lobe with irregular shape and peripheral ground-glass opacities. This lesion was defined as NN/NM (NOD) by all the readers

Table 2 Frequency of NN/NM lesions among 273 screening-detected lung cancers according to each radiologist and overall

Reader	Lesion type	*N*° NN/NM lesions (%)
A	All	28 (10%)
	Associated with cystic airspaces	7 (2.6%)
	Stripe-like	3 (1.1%)
	Scar-like	11 (4%)
	Endobronchial	5 (1.8%)
	NOD	2 (0.7%)
B	All	22 (8%)
	Associated with cystic airspaces	7 (2.6%)
	Stripe-like	1 (0.4%)
	Scar-like	7 (2.6%)
	Endobronchial	5 (1.8%)
	NOD	2 (0.7%)
C	All	26 (9.5%)
	Associated with cystic airspaces	6 (2.2%)
	Stripe-like	1 (0.1%)
	Scar-like	9 (2.9%)
	Endobronchial	5 (1.8%)
	NOD	5 (1.8%)
D	All	27 (9.8%)
	Associated with cystic airspaces	6 (2.2%)
	Stripe-like	4 (1.5%)
	Scar-like	9 (2.9%)
	Endobronchial	5 (1.8%)
	NOD	3 (1.1%)
All NN/NM*	All	20 (7%)
	Associated with cystic airspaces	6 (2.2%)
	Stripe-like	–
	Scar-like	6 (2.2%)
	Endobronchial	5 (1.8%)
	NOD	1 (0.4%)
	Discordant^	2 (0.7%)

NOD, not otherwise defined

*Defined by complete agreement among the four radiologists

^ One lesion was classified as "stripe-like" by one reader and as "NOD" by three readers; one lesion was classified as "NOD" by three readers and as "scar-like" by one reader

these lesions were in stages I and II at the time of diagnosis (Table 1).

Discussion

Non-calcified pulmonary nodules and parenchymal masses are the typical presentations of lung cancer.

In particular, pulmonary nodule is the finding all radiologists look for to diagnose early-stage lung cancer in healthy subjects enrolled in CT screening programs. It is currently defined by the Fleischner Society as "a rounded or irregular opacity, well or poorly defined, measuring up to 3 cm in diameter" [2]. To embrace a broader spectrum of abnormalities, the actual definition is more comprehensive than the previous published in 1996, in which a lung nodule was defined as "a round opacity, at least moderately well marginated and no greater than 3 cm in maximum diameter."

Unfortunately, there is still a level of uncertainty in the interpretation of some focal opacities, which implies that not all radiologists might agree in defining them as a nodule or a mass (Figs. 2 and 6). In fact, as previously argued, "all nodules are focal abnormalities, but not all focal abnormalities are nodules" [3].

This problem may be amplified in lung cancer screening, where the detected lesions are generally smaller than in clinical routine, and where low-dose images are noisier than the standard dose ones [5, 17].

In the present study, four radiologists with different experiences in thoracic imaging identified a rather high percentage (8–10%) of screening-detected lung cancers as presenting with neither nodular nor mass appearance.

This finding is noteworthy since all lung cancer screening guidelines and management protocols are based on the concept of pulmonary nodules [18–23], while the detection of non-nodular abnormalities is not taken into consideration and could result in missed or delayed diagnosis [6, 24, 25].

Xu et al showed, in fact, that some cancers among the International ELCAP series were misclassified as benign findings, due to radiologists' lack of experience in detecting cancer with neither nodular nor mass presentation [7]. A methodical assessment of any focal pulmonary opacity, through a careful comparison with the prior scan and/or a follow-up LDCT, is therefore recommended to assess any change that could suggest early signs of lung cancer.

On retrospective review of the previous annual LDCT scans for the 20 NN/NM lesions, we found that in 18 cases (18/20, 90%), a focal abnormality was already present 1 year before. Four of these 18 persistent opacities were overlooked endobronchial cancers; in the other 14 cases, the lesions were interpreted as benign dystrophic alterations due to their neither nodular nor mass morphology and the radiological diagnosis of malignancy was based on the lesion's changes and growth at the subsequent screening round.

However, 80% of the 20 NN/NM lesions were T1 or T2 at the time of diagnosis (75% were stage I or II), suggesting that even if not recognized as suspicious at prior CT scan, these abnormalities might have an indolent growth. Therefore, it could be argued that in the setting of lung cancer screening in healthy subjects, where false-positives remain the most important limitation, overlooking NN/NM lesions with indolent growth may not be actually a damage for patients if this results in fewer lesions misinterpreted as cancers. Further studies are

Table 3 Morphology of discordant lesions among 273 screening-detected lung cancers

All discordant lesions*	12 (4.4%)	Defined as nodular by radiologists (*N* lesions)
Associated with cystic airspaces	1 (8.3%)	C and D (1)
Stripe-like	2 (16.7%)	B and C (1); B (1)
Scar-like	6 (50.0%)	A and B (1); B, C and D (3); B (1); C (1)
Endobronchial	0 (0%)	–
NOD	2 (16.7%)	A, B and D (1); A and B (1)
Discordant^	1 (8.3%)	A and B (1)

NOD, not otherwise defined

*Disagreement in defining "pulmonary nodule" or "mass" versus "NN/NM" lesions, defined as nodular by at least one radiologist

^ One lesion was classified as "stripe-like" by one reader and as "NOD" by one reader

therefore required to better understand the characteristics and behaviors of unusual presentations of lung cancer. Moreover, several questions about the optimal management protocols of such unusual lesions remain unanswered and should be addressed through future research [26].

As well, for most lesions defined as pulmonary nodule or mass, a focal abnormality was already visible 1 year before the diagnosis in 156/241 cases (65%). The difference between the percentages of non-incidental tumor in nodule/mass versus NN/NM lesions does not reach statistical significance (*p* value 0.07).

We observed that lesions associated with cystic airspaces and scar-like lesions were slightly predominant compared with endobronchial lesions, while the radiologists were not concordant in the definition of stripe-like lesions. Lung cancer associated with cystic airspaces is an uncommon but known presentation of lung cancer [4, 14, 27]. The International ELCAP study reported that 3.6% of lung cancers detected were associated with cystic airspaces (compared with the 2.2% of our series) [14], while in the NELSON study, 22% (5/22) of missed carcinomas originally presented as bulla wall thickening on CT [6].

Delayed diagnosis is also common in endobronchial lesions, in particular for unenhanced low-dose CT images, because radiologists can overlook them [28]. The NELSON screening study reported that 5/22 missed lung cancers were attributable to overlooked endobronchial lesions [6]. Therefore, any opacity within the lumen of an airway, bronchial wall thickening, or stenosis should be carefully evaluated in subjects at high risk for lung cancer.

Beyond lesions associated with cystic airspaces and endobronchial lesions, other non-nodular appearances of lung cancer have been reported previously in the context of CT screening, confirming that early-stage lung cancer has a wide spectrum of presentations. In particular, in the ITALUNG study, among 20 incident lung cancers detected at annual screening rounds, seven had a non-nodular complex or a stripe-like shape [4]; the authors concluded that all persistent focal pulmonary abnormalities should be carefully monitored in subsequent LDCT for possible growth or increase in density suggestive of cancer [4].

In our study, there was disagreement in defining the morphology of 12/273 lesions (4.4%). These lesions were classified as "pulmonary nodule" or "mass" by some radiologists

Table 4 Concordance and kappa of agreement for definition of morphology of cancers

Readers comparison	Percent of concordance (95%CI)	Kappa of agreement* (95%CI)
A-B	267/273 (98%; 95–99%)	0.87 (0.76–0.97)
A-C	263/273 (96%; 93–98%)	0.79 (0.67–0.92)
A-D	266/273 (97%; 95–99%)	0.86 (0.76–0.96)
B-C	265/273 (97%; 94–99%)	0.82 (0.69–0.94)
B-D	266/273 (97%; 95–99%)	0.84 (0.73–0.96)
C-D	270/273 (99%; 97–100%)	0.94 (0.87–1.00)
All	261/273 (96%; 92–98%)	0.85 (0.75–0.92)

CI, confidence intervals

*Fleiss kappa for more than two raters with bootstrap confidence intervals ($N = 1000$)

Table 5 Concordance and kappa of agreement for diagnosis of NN/NM lesions according to lesion type

Readers comparison	Percent of concordance (95%CI)	Kappa of agreement* (95%CI)
A-B	22/22 (100%; 85–100%)	1.00 (1.00–1.00)
A-C	20/22 (91%; 71–99%)	0.88 (0.72–1.00)
A-D	24/24 (100%; 86–100%)	1.00 (1.00–1.00)
B-C	18/20 (90%; 68–99%)	0.86 (0.69–1.00)
B-D	21/21 (100%; 84–100%)	1.00 (1.00–1.00)
C-D	22/25 (88%; 69–97%)	0.84 (0.68–1.00)
All	18/20 (90%; 68–99%)	0.93 (0.86–1.00)

CI, confidence intervals

*Fleiss kappa for more than two raters with bootstrap confidence intervals ($N = 1000$)

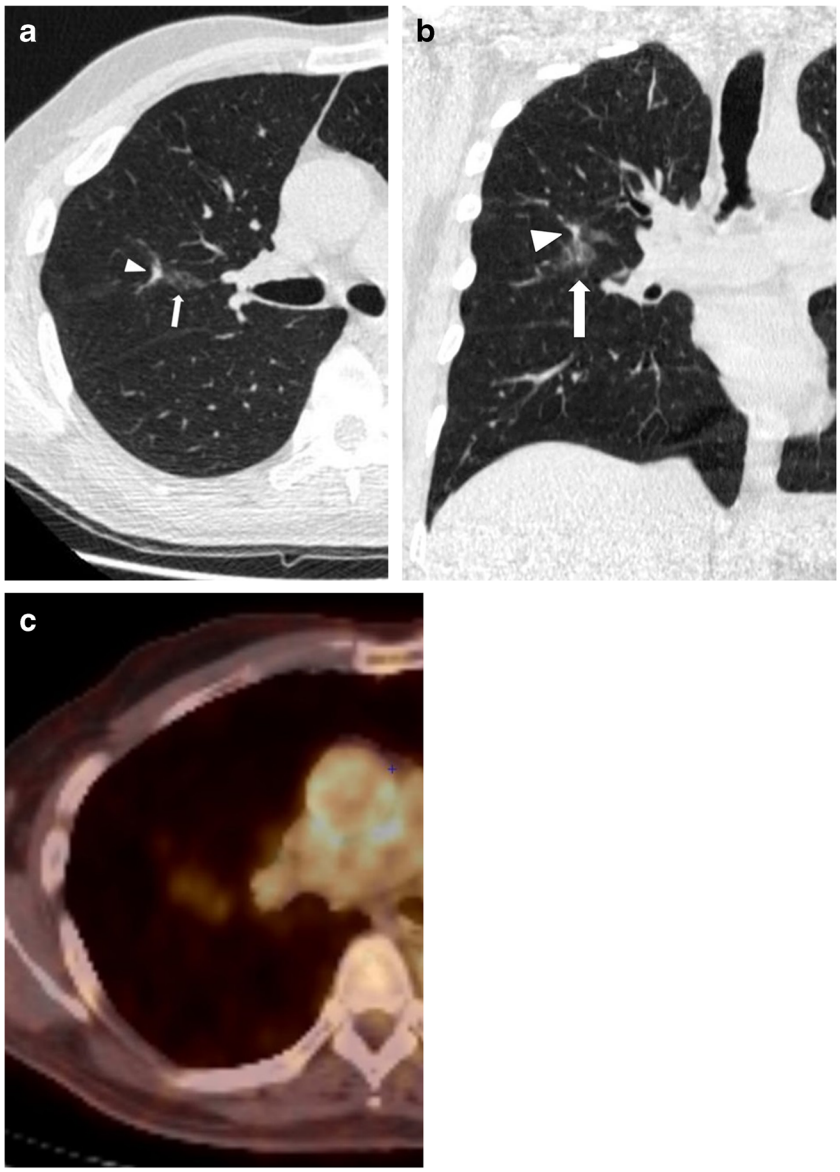

Fig. 6 Lung adenocarcinoma in a 60-year-old man. Axial (**a**) and coronal (**b**) LDCT scans show a NN/NM lesion in the right-upper lobe characterized by a complex morphology and shape, with both a solid (arrowhead) and ground-glass (arrow) component. **c** PET/CT scan shows fluorodeoxyglucose uptake of the whole lesion. This lesion was classified as scar-like by one reader and as NOD by the other three readers

and as NN/NM by others. Out of these 12 discordant lesions, scar-like subtype was predominant, highlighting the difficulty in discerning these lesions from spiculated nodules.

This study has several limitations. Firstly, only histologically proven malignant cases were considered; thus, we are not aware of the frequency of NN/NM presentations among screening-detected benign lesions and therefore we do not know the positive and negative predictive value of such morphologies. Moreover, we evaluated the concordance of the four radiologists with different levels of experience in thoracic imaging, but all were from a single institution and were not blinded to the aim of the study. Therefore, this might have partially overestimated the results.

Additionally, the definitions of stripe-like and scar-like subtypes are descriptive and depend on reader's interpretation, leading to the variability of the results; part of further investigation of NN/NM lesions should involve careful definition of the various types in order to minimize the risk of misclassification between observers. Finally, radiologists did not report the size of NN/NM lesions; thus, we do not know the inter-observer variability in the measurement of these lesions and how this could influence the management of such findings.

In conclusion, a non-negligible percentage (8–10%) of screening-detected lung cancers are lesion with neither nodular nor mass appearance at low-dose CT, with a predominance of lesions associated with cystic airspaces and scar-like lesions. Therefore, in CT screening, any focal abnormality should be carefully evaluated to detect potential radiological signs of early-stage lung cancer. The awareness of various CT appearance of lung cancer can avoid missed or delayed diagnosis, while further studies are required to define their optimal management protocol.

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Compliance with ethical standards

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Statistics and biometry Two of the authors, Dr. Bagnardi Vincenzo and Dr. Raimondi Sara, provided statistical advice for this manuscript.

Informed consent Written informed consent was obtained from all patients in the original COSMOS screening trial.

Ethical approval Institutional Review Board approval was obtained for the original COSMOS screening trial.

Methodology
- Retrospective
- Observational
- Performed at one institution

References

1. National Lung Screening Trial Research Team, Aberle DR, Adams AM, Berg CD et al (2011) Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 365:395–409
2. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Muller NL, Remy L (2008) Fleischner Society: glossary of terms for thoracic imaging. Radiology 246:697–722
3. Armato SG III et al (2004) Lung image database consortium: developing a resource for the medical imaging research community. Radiology 232(3):739–748
4. Mascalchi M, Picozzi G, Falchini M et al (2014) Initial LDCT appearance of incident lung cancers in the ITALUNG trial. Eur J Radiol 83:2080–2086
5. Rampinelli C, Calloni SF, Minotti M, Bellomi M (2016) Spectrum of early lung cancer presentation in low-dose screening CT: a pictorial review. Insights Imaging 7(3):449–459
6. Scholten ET, Horeweg N, de Koning HJ, Vliegenthart R, Oudkerk M, Mali WPTM et al (2015) Computed tomographic characteristics of interval and post screen carcinomas in lung cancer screening. Eur Radiol 25:81–88
7. Xu DM, Yip R, Smith JP, Yankelevitz DF, Henschke CI for the I-ELCAP Investigators (2014) Retrospective review of lung cancers diagnosed in annual rounds of CT screening. AJR Am J Roentgenol 203:965–972
8. Lindell RM, Hartman TE, Swensen SJ, Jett JR, Midthun DE, Tazelaar HD et al (2007) Five-year lung cancer screening experience: CT appearance, growth rate, location, and histologic features of 61 lung cancers. Radiology 242:555–562
9. Horeweg N, van Rosmalen J, Heuvelmans MA et al (2014) Lung cancer probability in patients with CT-detected pulmonary nodules: a prespecified analysis of data from the NELSON trial of low-dose CT screening. Lancet Oncol 15:1332–1341
10. International Early Lung Cancer Action Program Investigators (2006) Survival of patients with stage I lung cancer detected on CT screening. N Engl J Med 355:1763–1771
11. Veronesi G, Travaini LL, Maisonneuve P et al (2015) Positron emission tomography in the diagnostic work-up of screening-detected lung nodules. Eur Respir J 45(2):501–510
12. Veronesi G, Maisonneuve P, Spaggiari L et al (2014) Diagnostic performance of low-dose computed tomography screening for lung cancer over five years. J Thorac Oncol 9(7):935–939
13. Veronesi G, Bellomi M, Scanagatta P et al (2008) Difficulties encountered managing nodules detected during a computed tomography lung cancer screening program. J Thorac Cardiovasc Surg 136(3):611–617
14. Farooqi Ali O, Matt C, Lijuan Z, Beasley MB, Austin JH, Miller A et al (2012) Lung cancer associated with cystic airspaces. AJR Am J Roentgenol 199:781–786
15. Reichenheim ME (2004) Confidence intervals for the kappa statistic. Stata J 4:421–428
16. Kundel HL, Polansky M (2003) Measurement of observer agreement. Radiology 228:303–308
17. Rampinelli C, Origgi D, Bellomi M (2013) Low-dose CT: technique, reading methods and image interpretation. Cancer Imaging 12:548–556
18. International Early Lung Cancer Action Program Investigators Group. I - ELCAP Protocol. Available from: http://www.ielcap.org/sites/default/files/I-ELCAP-protocol.pdf. Published July 1, 2016. Accessed Dec 2018
19. Lung-RADS Assessment Categories, Version 1.0. American College of Radiology. Lung CT Screening Reporting and Data System (Lung-RADS™). Available from: http://www.acr.org/Quality-Safety/Resources/LungRADS. Published April 28, 2014. Accessed Dec 2018
20. Wood DE Lung cancer screening, Version 3.2018 - Clinical practice guidelines in oncology. J Natl Compr Canc Netw 16(4):412–441
21. Baldwin DR et al (2015) The British Thoracic Society guidelines on the investigation and management of pulmonary nodules. Thorax 70:794–798
22. Kauczor HU et al (2015) ESR/ERS white paper on lung cancer screening. Eur Respir J 46:28–39
23. Oudkerk M et al (2017) European position statement on lung cancer screening. Lancet Oncol 18(12):e754–e766
24. Wahidi MM, Govert JA, Goudar RK, Gould MK, McCrory DC (2007) Evidence for the treatment of patients with pulmonary nodules: when is it lung cancer? ACCP evidence-based clinical practice guidelines (2nd Edition). Chest 32:94S–107S
25. Li F, Sone S, Abe H et al (2004) Malignant versus benign nodules at CT screening for lung cancer: comparison of thin-section CT findings. Radiology 233:793–798
26. Devaraj A (2015) Missed cancers in lung cancer screening – more than meets the eye. Eur Radiol 25:89–91
27. Mascalchi M, Attinà D, Bertelli E et al (2015) Lung cancer associated with cystic airspaces. J Comput Assist Tomogr 39(1):102–108
28. Han NJ, Song KS, Lee KH et al (2002) Superficial endobronchial lung cancer: radiologic-pathologic correlation. Korean J Radiol 3(4):229–234