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Small low-risk pulmonary nodules on chest digital radiography: can we predict whether the nodule is benign?

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AIM: To evaluate digital chest radiography (CR) performance compared to computed tomography (CT) for characterising small low-risk pulmonary nodules detected incidentally in non-oncological patients. A second aim was to assess the prevalence of calcification and possible false-positive findings mimicking nodules.

MATERIALS AND METHODS: Two hundred and seven patients who presented with a pulmonary nodule on CR and underwent CT were included prospectively. Nine radiologists blinded to the CT images reviewed the CRs assessing for the presence of nodules. Afterwards, the same radiologists evaluated the corresponding CT for the presence of nodules, dimensions, and calcification. If the nodule was not present on CT, it was considered a false-positive finding, and possible confounding factors on CR were investigated.

RESULTS: Among all 213 nodules seen on CR, 32.4% were revealed to be false-positive findings on CT, mostly due to images formed by vessels (53.6%), osseous aetiologies (30.4%), and skin lesions (13%). Most nodules <6 mm detected on radiographies had benign calcification on CT (n=90; 67.7%). Comparatively, only 41.2% of nodules ≥6 mm on the CR had benign calcification. Among all nodules <6 mm detected on CR, 95.5% were calcified or not present at CT against 81.2% for those ≥6 mm (p<0.001).

CONCLUSION: The present study demonstrated that 95.5% of pulmonary nodules smaller than 6 mm on CRs are either calcified (benign) or represent a false-positive finding on CT. These results suggest that nodule measures on CR smaller than 6 mm most likely represent a benign finding.

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Introduction

Chest radiography (CR) is one of the most common imaging examinations performed annually worldwide. Pulmonary nodules on CR are very frequent, with an estimated prevalence ranging from 0.09% to 0.2%.[1] The evaluation of a patient with a pulmonary nodule is a common diagnostic dilemma, as some of these nodules may be malignant.[1] Computed tomography (CT) is considered the reference standard to characterise pulmonary nodules, considering characteristics such as size, borders, location, presence of fat, calcifications, and stability over time.[1,2]

Although most nodules are now detected at CT, many are still detected incidentally on CRs that were ordered for some other purpose; however, few studies have examined whether specific CR features were helpful in characterising nodules as malignant or benign, differentiating calcified and non-calcified nodules.[2–10] These features could help in daily practice, mainly in places where accessibility to CT is limited. In addition, those few studies available on literature on this topic have not used digital radiography, the most currently used system for acquisition and processing of CRs, which provides the advantages of better image quality, higher patient throughput, increased dose efficiency, and greater dynamic range of digital detectors with possible reduction of X-ray exposure to the patient.[11]

The purpose of the present study was to determine digital CR performance in the evaluation of small pulmonary nodules incidentally detected in non-oncological patients, comparing to CT images. A second aim was to evaluate the prevalence of calcification and estimate false-positive findings of subtle lung nodules detected at the CR.

Material and methods

Study sample

This prospective study was approved by the Institutional Review Board, and written consent was obtained for all patients. From October 2015 to January 2017, 228 consecutive non-oncological patients who presented a nodular opacity at CR underwent chest CT. Both posteroanterior (PA) and lateral views on CR were included. Patients were excluded if the interval between both studies was >6 months or if there was any suspicion of pregnancy.

Imaging protocols

The digital CR system (Vertix FD, Siemens Medical Solutions; and Pixium 4600, Trixell) consisted of a ceiling-mounted X-ray tube (Opti 150/30/50 HC, Siemens; focal spot size, 0.6 mm), a high-voltage generator, and a motorised receptor wall stand with the flat-panel detector mounted behind a stationary anti-scatter grid. Parameters used were: 10±3 mA and 125 kVp for PA images and 15±5 mA and 125 kVp for lateral images.

CT examinations were performed on a 64-section scanner (LightSpeed VCT; GE Healthcare, Waukesha, WI, USA). Lungs were scanned from the base to the apex in the caudocephalic direction using the following parameters: 120 kVp; 200 mA; and pitch, 1.375. Images were assessed on a PACS (Carestream Health, Rochester, NY, USA), on digital workstations, with dedicated high-resolution monitors. CT was evaluated with pulmonary (WW: 1500 and WL:-800) and soft-tissue (WW:400 and WL:80) windows. Coronal and sagittal reformats were used when necessary. Lung nodules were measured in lung windows, with a high-resolution (bone) filter. A nodule was considered calcified if calcification was visually detected on the CT images on soft-tissue algorithm.

Imaging analysis

Nine dedicated thoracic radiologists who were blinded to the CT findings were asked to review the CR images, assessing for the presence of pulmonary nodules. Additionally, they estimated their degree of confidence on reporting the presence of the nodules (low to high). Findings were analysed according to the Fleischner Society's Glossary of Terms for thoracic imaging.[12] Nodules were also classified according to presence of calcification, ranging from 0 to 3: (0) "definitely not calcified"; (1) "probably not calcified"; (2) "probably calcified"; and (3) "definitely calcified".

After reviewing CRs, the same radiologist would evaluate the corresponding chest CT for presence of nodules, dimensions, and calcification. The calcification pattern was characterised as benign (diffuse solid, central, "popcorn-like", or laminated), or indeterminate (punctate, eccentric). If the nodule was not present on CT, the reader considered the case a false-positive finding and an attempt was made to justify the reason of possible confounding factors on CR (e.g., skin lesion, bone finding, vascular markings, etc.). Additionally, secondary CT findings were analysed, such as moderate–large pleural or pericardial effusions, active infections, and aortic aneurysms.

A second radiologist, blinded to the first reading, who followed the same order of analysis, then reviewed the same case. Data were tabulated on a spreadsheet and reviewed by three dedicated thoracic radiologists. In the case of discrepancies between the initial readers, these other three radiologists would reach a final consensus.

Statistical analysis

All results were analysed using commercial software (SPSS ver. 20, SPSS, Chicago, IL, USA; Excel 2010, Microsoft, Redmond, WA, USA). Continuous variables were reported as means ± standard deviations, and categorical variables were reported as numbers and percentages. Continuous variables were compared using the independent Student's *t*-test for normally distributed variables and the Mann–Whitney U test for non-normally distributed variables. Categorical variables were compared using the

Fisher's exact test. A p-value of <0.05 was considered to indicate statistical significance.

Results

In total, 207 patients matched the inclusion criteria. Most were female (n=104; 50.24%) with a mean age of 50.3±14.6 (range, 12–87) years. The average time between CR and CT was 40 days, with the shortest interval being 0 days (studies performed at the same day) and the longest 176 days.

Table 1
Imaging findings characteristics

Parameter	n (%)
Prevalence on CR (n=213)	
Solitary PN	201 (94.4)
Prevalence on CR and CT (n=144)	
≤5 mm	96 (66.7)
6 mm	21 (14.6)
7–8 mm	17 (11.8)
≥9 mm	10 (6.9)
False positive on CT	69 (32.4)
Due to vessel	37 (53.6)
Due to osseous aetiologies	21 (30.4)
Due to skin or subcutaneous lesions	9 (13)
Calcification on CT	123 (85.4)
<6 mm[a]	90 (93.7)
≥6mm[a]	33 (68.7)
Prevalence on CT according to confidence in reporting on CR	
High confidence	86 (86.7)
Low confidence	29 (28.6)

CR, chest radiography; CT, computed tomography; PN, pulmonary nodule.
[a] Nodule size measured at CR.

Imaging findings characteristics are presented in Table 1. Most patients presented solitary nodules visible on CR (n=201; 91.1%). Only six patients (2.9%) presented two nodules on CR. Among all 213 nodules seen on CR, 65 (32.39%) revealed to be false-positive findings on CT. The most frequent cause of false-positive cases was an image formed by vessels seen on a transverse view (53.6%), followed by osseous aetiologies (enostosis or osteophyte, in 30.4%), and skin or subcutaneous lesions (13%). Most of these false-positive cases were initially detected only in one projection (n=62, 89.9%), either only in PA (n=48, 77.4%) or in lateral (n=14, 22.6%) projections. For those that could be identified on both projections of the CR images (n=7, 10.1%), in only one case the addition of a lateral acquisition would have obviated the necessity of chest CT, as it characterised the nodular lesion identified at PA as corresponding to a nipple shadow. In the remaining cases, a pulmonary nodule could not be discarded at CR, and CT images further revealed to correspond to osseous lesions (n=3), vessels (n=2), or calcified lymph nodes (n=1).

When readers had high confidence to report nodules on the CR, the presence of the lesion was confirmed at CT in 86 (86.7%) cases. Conversely, for low confidence cases, the presence of the nodule was confirmed at CT in 29 (28.6%) cases.

The dimensions of nodules identified at CR and CT did not show differences. Calcification also played some role in nodule detection at CR, as most of the small nodules (<6 mm) detected on radiographies were calcified on CT (n=90; 93.7%; Fig 1). Comparatively, only 68.7% of nodules ≥6 mm on the CR were calcified. When cases were considered

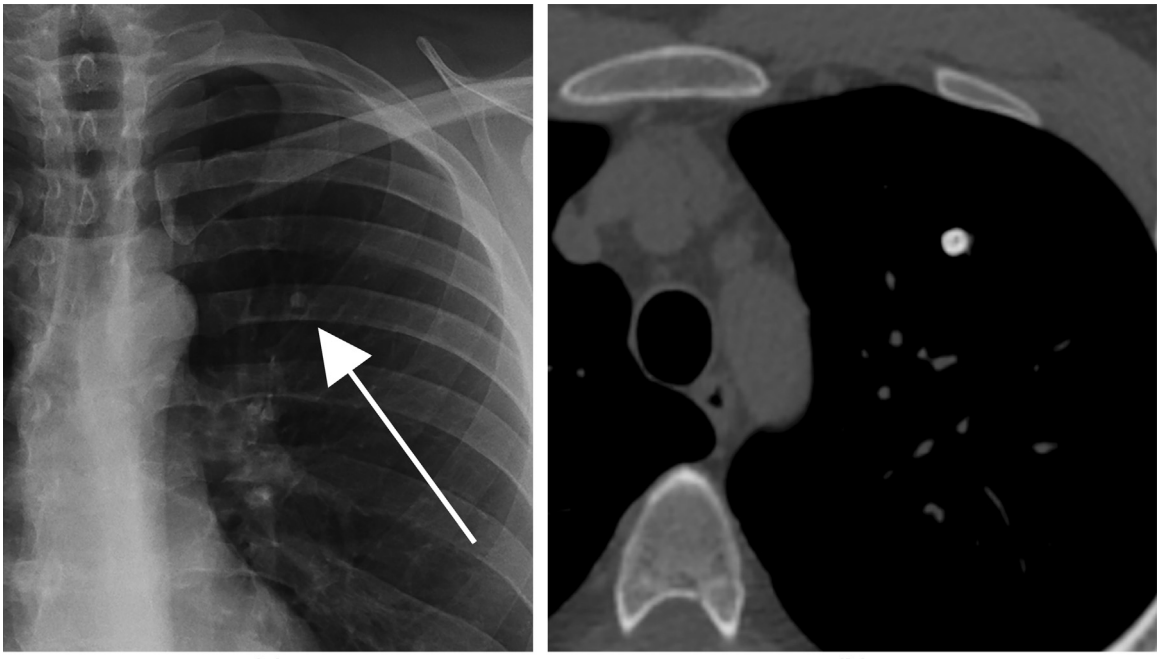

Figure 1 Images from a 46-year-old man with dry cough for 2 months. (a) In the chest radiography, a 5.9-mm nodule is noted in the upper third of the left hemithorax (arrow), categorised as "probably calcified". The CT images (b) demonstrated a diffuse calcified nodule in the left upper lobe.

Table 2
Nodule calcification on CR and CT

		Calcification on CR								Total	
		Definitely not calcified		Probably not calcified		Probably calcified		Definitely calcified			
		n	(%)	*n*	(%)	*N*	(%)	*n*	(%)	*n*	(%)
Calcification on CT	Yes, benign[a]	1	(25)	8	(38.1)	48	(87.3)	63	(98.4)	120	(83.3)
	Yes, indeterminate[b]	0	-	2	(9.5)	1	(1.8)	0	-	3	(2.1)
	No	3	(75)	11	(52.4)	6	(10.9)	1	(1.6)	21	(14.6)
	Total	4	(2.78)	21	(14.58)	55	(38.19)	64	(44.44)	144	

Data are number of cases and percentages are in parenthesis.
CR, chest radiography; CT, computed tomography.
[a] Benign patters: diffuse solid, central, "popcorn-like", or laminated.
[b] Indeterminate patterns: punctate, eccentric.

"definitely calcified" on CR (n=64), CT confirmed calcification in 98.4% (Table 2). On the other hand, readers had an inferior performance for discarding this finding on CR, as calcification was present in 47.6% and 25% of nodules categorised as "probably not calcified" or "definitely not calcified", respectively (Fig 2). Most calcified nodules seen at CT were diffusively calcified. Indeterminate pattern of calcification was observed only in three cases.

Out of the 144 nodules detected on CT, 123 were calcified (85.4%). When analysing this prevalence according to nodule size, 95.5% of nodules <6 mm in CR were calcified (n=90, 67.7%) or not present at CT (n=37, 27.8%). Comparatively, this frequency was 81.2% for those ≥6 mm (calcified, n=33, 41.2%; false-positive, n=32, 40%), and this difference was statistically significant (p<0.001).

Five patients (2.41%) had at least one significant finding on CT not related to the original nodule found on CR: 2 cm thymic nodule, n=1; pneumonia, n=2; moderate pleural effusion related to congestion, n=1; non-specific pulmonary fibrosis, n=1.

Discussion

The results of the present study demonstrated that most nodules <6 mm detected on CR in a non-oncological setting were benign, as 95.5% are either calcified (presumed benign) or false-positive. This finding corroborates the study by Ketai *et al.* (10), which analysed nodules ≤10 mm identified at CT and found that 77% of nodules <7 mm seen on CR were probably calcified. In addition, Ketai *et al.* demonstrated poor CR sensitivity for non-calcified nodules <6 mm (38%), even though reader vigilance for lung nodules was artificially high, with a high false-positive rate (56%; 10).

According to the Fleischner Society 2017 guidelines, for low-risk patients, lung nodules <6 mm would not need any follow-up, and nodules of 6–8 mm should be followed up for 12 months (4). In addition, the American College of Radiology (ACR) published the Lung-RADS, that considered solid non-calcified lung nodules <6 mm as probably benign, with chance of malignancy <1% for nodules <4 mm, and

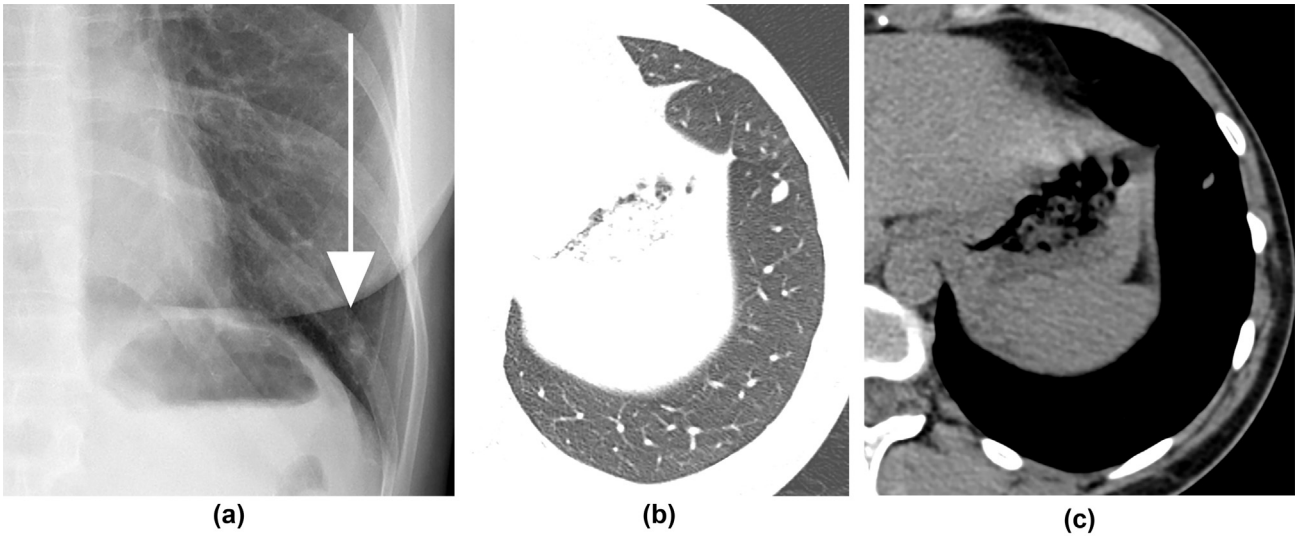

Figure 2 Images from a 36-year-old woman with acute chest pain. (a) In the chest radiography, an 8-mm nodule is noted in the lower third of the left hemithorax (arrow), categorised as "probably calcified". The CT images (b, c) demonstrated a non-calcified nodular opacity in the left lower lobe, more likely to represent a pulmonary lymph node.

1–2% for 4–5 mm.[13] Therefore, in a non-oncological setting, lung nodules <6 mm at CT would be a benign diagnosis, independently of calcification.

In addition, the present data demonstrated that there was better performance for readers predicting nodule calcification rather than excluding this finding. When calcification was probable or definite on CR, CT confirmed this finding in most cases (94.07%). Another study that included 35 nodules varying in size from 6×6 mm to 27×25mm found calcification in 54.3% of lesions, as defined on CT (9).

Direct digital radiography (DR), which also might be further classified as direct and indirect image capture, involves acquiring image data in digital format without laser scanning to extract the latent image. The present study was performed using a DR system, and both similar previous papers did not use digital radiography (9, 10). One focused on small nodules and the other on bigger lesions. Although the present sample consisted mainly of smaller nodules, the present study included all nodule sizes, which is the current practice.

The limitations of the present study include the sample size and the inclusion of a population of an endemic area of granulomatous diseases, what might have influenced the prevalence of nodules and calcifications. Further studies could also assess the cost-effectiveness of the method.

In summary, the present study demonstrated that 95.5% of pulmonary nodules <6 mm on chest radiographies are either calcified (benign) or represent a false-positive finding on CT. These results suggest that nodule measuring <6 mm seen at CR most likely represent a benign finding.

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