Review

APPLICATION "LUNG NODULE" SOFTWARE WITH LUNGRADS ON EARLY DETECTION AND FOLLOW UP THE PULMONARY NODULES BY LUNG LOW DOSE CT FINDINGS

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ABSTRACT

Background: *A pulmonary nodule is defined as a rounded or irregular opacity, well or poorly defined, measuring up to 3 cm in diameter. Early detection the malignancy of nodules has a significant role in decreasing the mortality, increasing the survival time and consider as early diagnosis lung cancer*

Content: *The main risk factors are those of current or former smokers, aged 55 to 74 years with a smoking history of at least 1 pack-day.*

Low dose CT*: Screening individuals with high risk of lung cancer by low dose CT scans could reduce lung cancer mortality by 20 percent compared to chest X-ray. Radiation dose has to maximum reduced but respect the rule of ALARA (As Low as Resonably Archivable).*

ACR-LungRADS 2014*: Classification of American College of Radiology, LungRADS, is a newly application but showed many advantages in comparison with others classification such as increasing positive predict value (PPV), no result of false negative and cost effectiveness. "****Lung nodule****" was applied as a smart phone application in order to have a quickly evaluation, especially the malignancy and management face on a pulmonary nodule.*

Keywords: *LungRADS, lung nodule, low dose CT, lung cancer, lung cancer screening*

I. INTRODUCTION

A pulmonary nodule is defined as a rounded or irregular opacity, well or poorly defined, measuring up to 3 cm in diameter. The malignancy rate in solitary lung nodules varies from 5% to 69% according to various disparate scientific researches, which belong to the nodular size and diagnostic modalities. Early detection of malignant solitary lung nodule are considering as lung cancer screening. Actually, most of lung cancer were late diagnosis and the five-year survival rate remain poor, reported at about 13-15%; however, the survival rate would be increasing by up to 70 % - 80 % if the detection and treatment of the lesion applied in the early stage IA [5], [6], [15]. Evaluation solitary pulmonary nodule (SPNs) according to assessment categories of Lung CT Screening Reporting and Data System (Lung-RADS) by American College of Radiology (ACR) that was launch out in 2014, updated new version Lung-RADS 1.1 in 2019 [1]. In the fact that a host of compelling studies shown that Lung-RADS has a bunch of its advantages that boost positive prediction value (PPV) of lung low dose computed tomography (LDCT) in screening lung cancer, and

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no false-negative results have confirmed [7]. In general, the main target of physicians and radiologists are early detection and accuracy diagnostic lung cancers to make correctness clinical decisions and to have reasonable screening campaign low-to-medium cancerous risk of pulmonary solitary nodule, especially in the individuals who have high-risk factors like “heavy smoker”. The combination of “Lung Nodule” and Lung-RADS 1.1 (release 2019) known as “Lung cancer screening kit” updated version 3.0 is an available application could be installed on smartphone iOS, in which just quickly input some basic patient and pulmonary nodule information, the radiologist will receive lung nodule classification in detail as Lung-RADS assessment categories including the malignancy risk proportion and guideline about the clinical decision [1], [7]. The main objective of the present paper is a brief introduction to up-to-date applications in screening and diagnostic solitary pulmonary nodule.

II. SOLITARY PULMONARY NODULE OVERVIEW

2.1. Solitary pulmonary nodule

Widely diverse approaches are to detect lung nodule, commonly accidentally seen on X-rays film, and absolutely on asymptomatic patients. Relying on analyzing CT findings, the solitary nodule could group into a high cancerous risk group, medium cancerous risk group, and low cancerous risk group. Furthermore, it might confirm that completely benign lesion after 24 months follow-up. CT findings of SPNs features on non-contrast enhancement including:

2.1.1. Number and size

The malignant intraparenchymal nodule could be solitary or multifocal. Fleischner 2017 has concluded that the amount of the nodule greater than six classifies as diffuse lesion [8]. When greater than six pulmonary nodules are present on chest CT for an individual patient, the probability of granulomatous lesions or metastases greatly increases.

Generally, small nodules tend to be benign, while larger ones are more likely malignant. The intraparenchymal pulmonary nodule smaller than 8 mm can be benign lesions, in a range of 8 mm to 20 mm can be medium cancerous risk nodule, and from 20 mm to 30 mm is highly cancerous nodules. The nodule located nearby visceral pleura, interlobar fissure, vessels are highly potential benign lesions [2], [6], [15].

Therefore, the SPN diameter can be used as an independent risk factor for differentiating malignant and benign lesions.

2.1.2. Shape and edge characteristics

The edge characteristics provide an important basis for the differentiation between benign and malignant nodules. Malignant SPNs are often associated with irregular contours, spiculated edge and increased lobes. These criteria are evaluated independently among others. High risk of malignancy nodule commonly seen at the lesion larger than 20 mm, multilobulated or spiculated margins with proportion greater than 50%.

The lesion has a round shape, the regular margin is a low risk of malignancy, except multifocal lesion were considers as high risk of metastasis. However, it must be emphasized that a ground glass nodule round in shape suggests malignancy, whereas a polygonal shape with or without concave margins and located next to pleura of a solid as well as a non-solid nodule suggests benignancy

Il-defined, irregular or spiculated margins strongly suggest malignancy. Spiculation was defined as the presence of thicker strands extending from the nodule margin into the lung parenchyma without reaching the pleural surface and has high positive predicting value (PPV) [2] [14], [15].

2.1.3 Density

According to Hounsfield's unit that measured from manual ROI on CT images, pulmonary nodule grouped into three groups as follows: non-solid nodule (pure ground-glass opacity, pure-GGO), solid nodule, and part-solid nodule (mixed-GGO, part-solid GGO). The risk of malignancy in solid nodules is 7% to 11 %, in mixed-GGO nodule is 48% to 63%, and pure-GGO varies in a range of 18% to 59% [9]

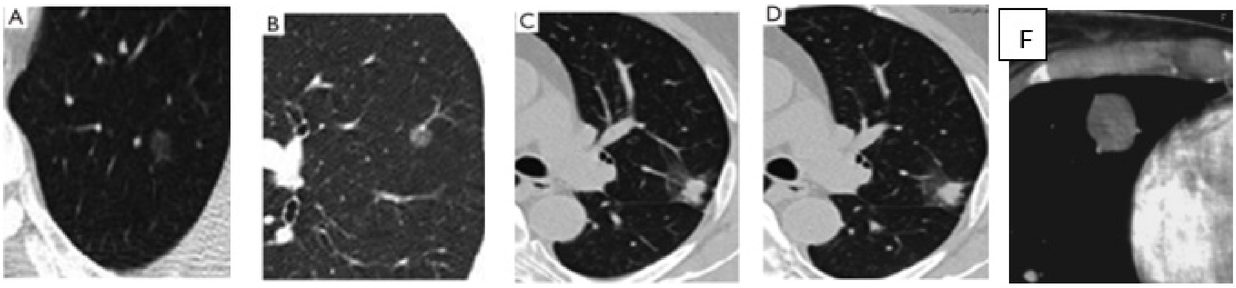

Figure 1: Lung nodules on LDCT [15]
A and B: pure ground glass opacity nodule;
C and D: mixed ground glass opacity nodule; E: solid nodule

2.1.4. Air bronchogram signs

An "air bronchogram and/or pseudocavitation" are more frequently observed in malignant (30%) than benign (5%) lesions. Concerning a malignant nodule, this sign is strongly suggestive of adenocarcinoma, bronchioloalveolar cell carcinoma or lymphoma [2]. Pseudocavities visible within a nodule on CT appear as small round lucencies with well-defined margins, resembling small air bubbles. Air bronchogram and air containing space within a non-solid nodule have also proven to be more frequent in neoplastic than nonneoplastic lesions. The malignancy rate is from 27.5 % to 66.7% depend on distinct researches. Figure 2 shows common types of air bronchogram signs of Tsuboi et al [4], [12]

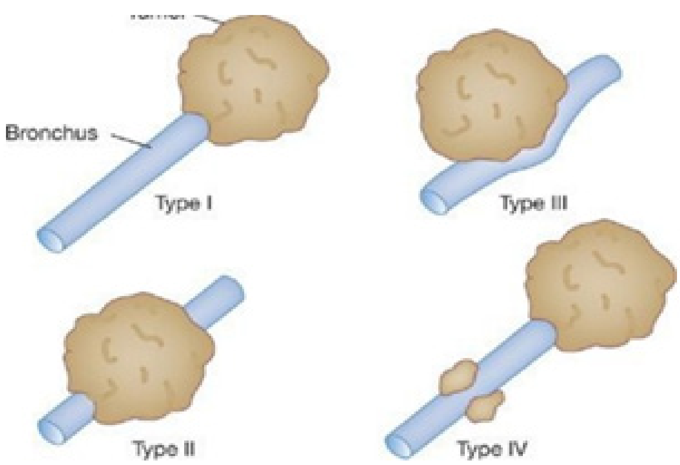

Figure 2: The types of air bronchogram signs following Tsuboi et al [5]
(I) Amputation, (II) Narrowing, (III) Compressing, (IV) Invasive

The cavity-created processes have seen both benign and malignant cases but non specifically. Cavity lung lesion with a thin wall < 4mm and smooth inner margins are more likely non cancerous mass, with a thicker wall > 16 mm and irregular inner margin suggest that highly malignancy.

2.1.5. Types of calcification

High-density components > 200 HU inside the lung nodular are compelling standards to differentiate calcification or non-calcification SPNs. The presence of calcification is always a contributory factor in suggesting malignancy or benignancy. Calcification is more likely benign such as [2], [15]:

- Diffuse calcification: Common reason is calcification from a granulomatous disease so that can confirm as a benign mass. Exceptionally, the patients who have had a history of osteosarcoma, chondrosarcoma, synovial sarcoma, papillary carcinoma, colorectal cancer might have multiple metastasis lesion with calcification.

- Popcorn calcification: normally benign, indicates calcification of cartilaginous origin, and therefore the diagnosis of hamartoma and take place approximately 5% - 50%.

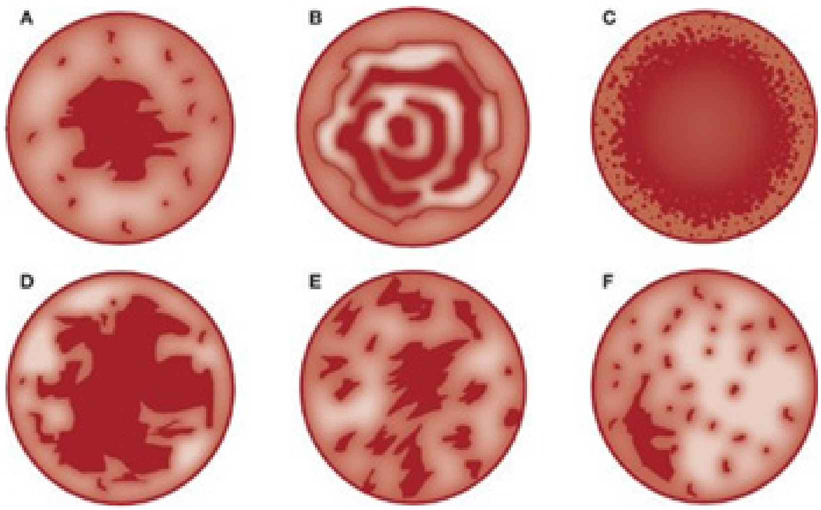

Figure 3: The types of calcification of lung nodule following [5], [13]
A. Central, B. Laminated, C. Diffuse, D. Popcorn, E. Stippled, F.Eccentric

- Central or laminated calcification is usually seen in the patient who have a history of infection. Especially is in tuberculosis or histoplasmoses. This type of calcification occupies > 10 % surface area of the lesion can be considered as benign mass.

- Conversely, eccentric or dispersed calcification is highly suggestive of a malignant lesion and may be seen in 6% of pulmonary cancers. Dispersed punctate calcification can find in bronchial carcinoma and usually grown from a background of calcification lesion of granulomatous before. The difference between granulomatous calcified and this type of malignancy calcification is that calcification usually show at peripheral and just take a small portion entire the tumor [11].

2.1.6. Containing-lipid

The presence of "fat" within a pulmonary nodule is always a formal criterion for benignancy. A density between - 40 and - 120 HU is strongly suggestive of the diagnosis of hamartoma. Detection containing-lipid components in lung node should be performed on thin slices, at the center of the mass to avoid negative influences of partial volume artifact or air-containing patterns in cavity-created lesions with opacity < -200 HU. The presence of fat inside pulmonary nodules confirm benign nodular and is essentially pathognomonic of pulmonary hamartoma or pulmonary chondroma. However, lipid only present in approximately 50% of this pathology. Differentiate diagnostic is necessary with lipoma, lipoid pneumonia, hamartoma, angiomyolipoma, chronic organizing pneumonia and metastasis from liposarcoma [2]for which excision is indicated without delay. However, invasive diagnostic procedures should be avoided in the case of a benign lesion. The objectives of this review article are: [2], [14]

2.1.7. Doubling time

The doubling time of most cancerous lung nodules is approximately 30 to 400 days. If the size of the lung nodule is larger than two times within 30 days, it may be an infection lesion. If the nodule is stable after a 2-year follow-up, the lesion is a benign mass. The doubling time of lung nodules is measured by calculating the volume of the nodule. This measurement has higher accuracy in comparison with the conventional method that measures two dimensions. The lung nodule volume measurement is entire LungCAD software [15]

2.2. Risks to subjects

Risk factors of lung cancer should account as the first line is tabaco. Besides that, exposure to asbestos, radon radiation, passive smoking, or history of extra-pulmonary primary tumors, etc. According to American Lung Association, high-risk factor subjects are 55 - to 74 - year-old men, former or current smokers consume more than 30 pack-year or more than 1 pack per day (heavy smoker) [6. Analyzing contemporary of individual and family history, risk factors, and lung nodule characteristics are useful to determine lung cancer risk on individual patients according to the advice of Fleischner 2017 [10], [14], [15].

III. LUNG LOW DOSE COMPUTED TOMOGRAPHY

3.1. Literature review

The lung is an air-containing organ that potentially significant reduction of radiation dose on CT Scan protocol. CT thorax low dose (Lung low dose CT - LDCT) aims to reduce effective radiation dose for patients, reasonable image quality (poor image quality compared to conventional CT protocol) but the diagnostic value is still acceptable. The reduction is following the ALARA rule (as low as a reasonable archive). Air entire the lung does not absorb much X-ray energy whilst fat in mediastinum still shows as a nature density when using CT low dose protocol.

Corneloup and teammate (2003) performed research with two CT-scan LDCT images (dose reduction 53%) have equal diagnostic valuable compared to the convention CT scan (optimal dose CT protocol) [3]. The state-of-the-art CT machine is integrated with various optimized radiation dose and image quality approaches that can reduce radiation dose more than 50% routinely. The combination brings LDCT protocols becoming a first-line selection for screening lung cancer [3], [9], [11], [15]

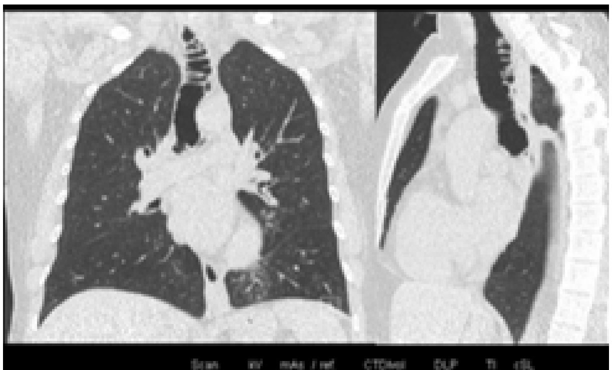

Figure 4: CT low dose, patient 41-year-old, BMI 26.5 kg/m², prolonged cough, present an abnormal at lower left lobe on Xray Chest. CT-DIvol 0.57 mGy and DLP 18 mGy.cm. Effective dose 0.3 mSv equals effective dose of a convention CR Chest AP [15]

However, optimize radiation dose campaign is mainly being an attempt by some institutes or individuals. The meaningful strategy is still not under framework and pressure from national screening.

3.2. Suggested protocol

Application the protocols of National Lung Screening Trial of American (NSLT) or a study of NELSON, or reducing radiation follow body mass index (BMI) depending on authors or medical center. However, effective dose should be reduced as much as possible. The widely using protocol recently shows on the table 1.

Table 1: Suggested CT lung low dose in some institutes.

Parameters	NLST Normal Patients	NLST Overweight patients	NELSON Patients <50kg	NELSON Patients 50-80kg	NELSON Patients > 80kg	BMI ≤30kg/m²	BMI >30-34.9 kg/m²	BMI >35 kg/m²	Hue University Hospital
kVp	120	140	80-90	120	140	110	110	110	80-100
Effective mAs	20-30	20-30	20-30	20-30	20-30	30	30-40	40-50	30
Slice thickness	1,0-3,2	1,0-3,2	1,0	1,0	1,0	1,2	1,2	1,2	1,5
Recontruction	1,0-2,5	1,0-2,5	0,7	0,7	0,7	2,0	2,0	2,0	0,6
Effective dose	1,2	1,4	<1,6	<1,6	<1,6	1,3	1,3-1,6	1,6-2,0	<1,0 (*)

Note (*): Using CARE KV and CARE dose 4D software that available installation in CT machine could be reduced radiation dose up to 50% compared to optimist radiation dose for patient.

3.3. Lung-RADS and classification lung nodule on lung low dose CT

Assessment lung nodule must be using both lung window and mediastinum window with a suitable width, and measure HU. Application LungCARE additionally is to detect pulmonary node, measure volume of lesion while diagnostic, and follow up [1].

April 2014, American College of Radiology has launch Lung Imaging Reporting and Data System (Lung-RADS) 1.0 including Lung-RADS from 0 to 4 aim to assessment and classify lung nodules following malignant characteristics and recommend follow up by CT low dose protocol. Assessment categories of ACR has updated to Lung-RADS 1.1 in 2019.

A comparison of application Lung-RADS to evaluating lung nodule with the classification of National Lung Screening Trial (NLST) published in 2014 by McKee declared that classification base on ACR Lung-RADS increased positive predictive value (PPV) of lung LDCT in screening cancer up to 2.5 times compared to using NLST and no false-negative result have seen. Application ACR Lung-RADS also brings more economic efficiency compared to NLST due to reducing the amount of screening significantly [1], [8]. Lung-RADS 1.1 shows on the Table 2 below.

Table 2: The brief of ACR Lung-RADS 1.1 2019

Groups	Categories	Recommend	Malignancy Risk	% population
LungRADS 0	Incomplete	Necessary compare to previous Xrays examination	**n/a**	1%
LungRADS 1	Negative	LDCT after 12 months	**< 1%**	90%
LungRADS 2	Benign	LDCT after 12 months		
LungRADS 3	Probably Benign	LDCT after 06 months	**1-2%**	5%
LungRADS 4	Suspicious **4A** (*)	LDCT after 03 months, PET/CT maybe used when solid components ≥ 8 mm	**5-15%**	2%
	Very Suspicious **4B, 4X** (*)	Maybe need CTCE Thorax, PET/CT when solid components ≥ 8 mm and or biopsy	**>15%**	2%
Other	**4S**	Depending on clinical to group into LungRADS 0-4	**n/a**	10%

IV. APPLICATION "LUNG CANCER SCREENING KIT" AND LUNG-RADS VERSION 3.0 ON CLINICAL

Lung cancer screening kit is an intelligent application available on smartphones using not only the iOS operating system (iPhone, Ipad) but also on the Android technology platform to help doctors point out quickly advise when face to a solitary pulmonary nodule. Two important information show on screen is the malignancy proportion of nodules and detail guideline for SPNs management [7].

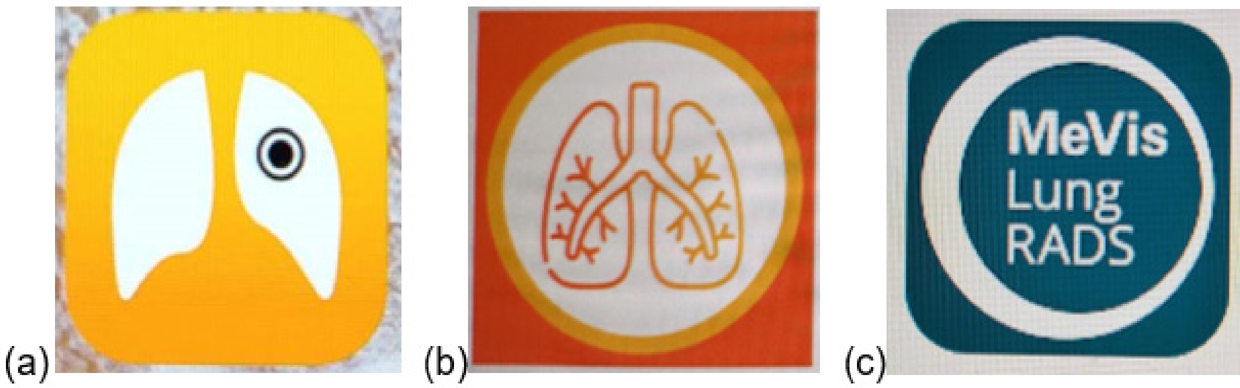

Figure 5: The "software icon" on application about lung nodule flatform

a. *"Lung Nodule": assessment lung nodule according to Lung-RADS and Fleischner 2017, available for IOS (highly recommendation)*

b. *Assessment lung nodule according to Fleischner 2017, available for Android*

c. *Assessment lung nodule according to Lung-RADS, available for Android*

Potential malignancy pulmonary nodule account for nine basic characteristics and some other including patient information, pathology history, CT findings of the node:

- Screening or follow-up CT scan
- Intraparenchymal node or related directly to bronchi lumen.
- Amount and size of the node.
- CT findings to determine benign or malignant mass such as spiculation margin, types of calcification, lipid-containing node, mediastinal lymph nodes.
- Patient and their family member information: age, gender, lung cancer history, and other pulmonary diseases.

Case study (example): Male patient 65-year-old, family history of lung cancer, present a single node intraparenchymal pulmonary on CT scan, the average of the long-and short-axis diameters on plance reveals the greatest dimensions of the nodule is 16.5 mm, located on upper lobe, spiculation margin, non-calcification, non-lipid components entire, no lymph node enlargement, no alveolar dilatation on pulmonary parenchyma surrounding.

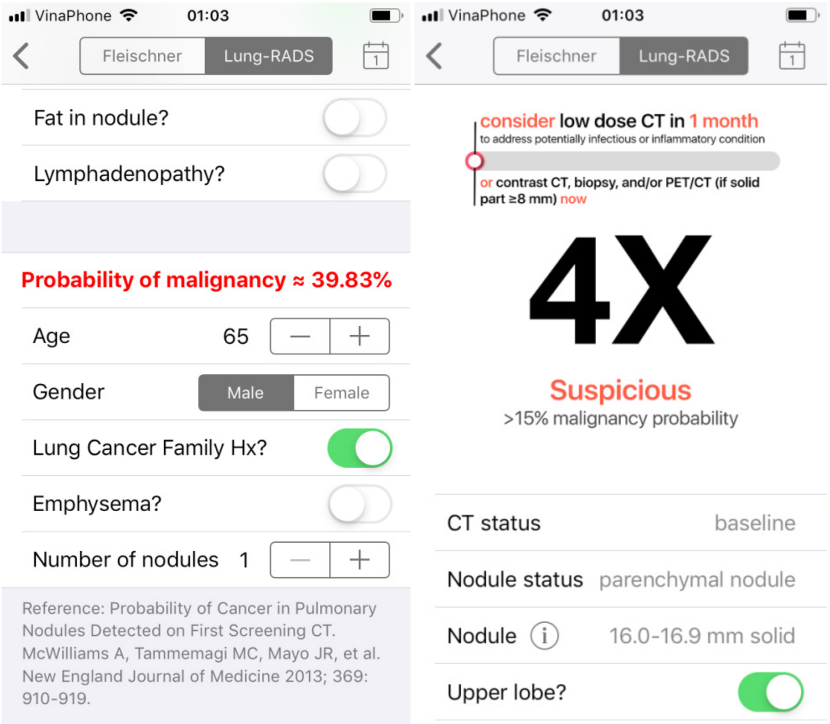

Figure 6: Lung Nodule software shows on Iphone screen that the pulmonary nodule belongs to Lung-RADS 4X, probability of malignancy approximately 39,83%, consider LDCT follow up after 1 month or do an contrast enhancement CT examination, perform biopsy and/or PET-CT if the solid component larger than 8 mm.

V. CONCLUSION

Screening, diagnosing, follow up SPNs on lung LDCT according to assessment categories of Lung-RADS knowns as a new trend and widely applying around the world. All of the high-risk factor individuals suggested should take part in screening by lung LDCT to early detection malignancy intraparenchymal pulmonary lesion. Application of "Lung Nodule" software is available on smartphone helps radiologist, oncologist, pulmonologist to quickly, accurately, and consistently clinical decision making when approaching highly potential malignancy pulmonary lesions.

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