HUE UNIVERSITY
UNIVERSITY OF MEDICINE AND PHARMACY

HOANG THI NGOC HA

VALUE OF CHEST LOW DOSE COMPUTED TOMOGRAPHY IN THE DIAGNOSIS OF PULMONARY NODULES

SUMMARY OF MEDICAL DOCTORAL DISSERTATION

HUE - 2022

This work is completed at
University of Medicine and Pharmacy, Hue University

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MAJOR: RADIOLOGY AND NUCLEAR MEDICINE
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INTRODUCTION

Pulmonary nodules are defined as opacities located in the lung parenchyma, up to 30mm in size, well-defined and without surrounding lung parenchyma pathologies, with a malignant rate ranging from 5 to 69% depending on sample size and research modalities [67], [85], [117], [133], [156]. According to the "Pan-Canadian Early Detection of Lung Cancer Study", the first report about lung cancer screening by computed tomography had a detection rate of malignant nodules of around 3.7-5.5% [92]. Prognosis depended on nodule size when detected and with the 5 year-survival-rate around 15-18% which can be increased to 70-80% when cancer was early detected and operated [63], [71], [145].

According to the results of the American National Lung Screening Trial in the period 2002-2009, the study found that screening individuals with lung low dose computed tomography (LDCT) scanning reduced lung cancer mortality by 20.3% compared to chest X-ray [30], [44], [73]. LDCT also guaranteed imaging quality for diagnosis when reducing the irradiation exposure more than 50% [38], [145]. Therefore, since the early 1990s, most of lung cancer screening studies selected lung LDCT as the screening modality [63], [65], [105], [145], [156]. The biopsy of lung nodules to determine histological nature and confirm the diagnosis of lung cancer is very necessary, but it is an invasive technique and difficult to perform, so computed tomography has been applied widely to classify and screen high risk nodules that need biopsy and at the same time, guide the trans parietal biopsy of these nodules.

The American College of Radiology (ACR) guideline for lung nodule management (Lung-RADS 2019) is effectively applied over the world [35], [37], [35]. 57], [60], [90].

In 2020, Vietnam had the first publication on lung cancer screening by lung LDCT in people over 60 years old with risk factors [3]. However, lung LDCT for screening lung cancer has not been systematically applied, the management of lung nodules has not been unified based on a specific classification guideline; Early lung cancer diagnosis has not been widely applied.

According to the arguments mentioned, we study the subject "**Value of chest low dose computed tomography in the diagnosis of pulmonary nodules**" with two main objectives:

1. Classification of lung nodules according to Lung-RADS 2019 and characterization of chest low dose computed tomography findings of high risk malignant nodules.

2. Investigate the value of chest low dose computed tomography in the diagnosis of high risk nodules.

2. New contributions of the dissertation topic

The thesis has two main contributions: the application of chest Low Dose Computed Tomography (LDCT) and the updated version Lung RADS 2019 from American College of Radiology (ACR) in the diagnosis of pulmonary nodules with high risk of lung cancer.

This study has offered the practical meaning in consider the value of chest LDCT and Lung RADS 2019 in order to encourage the screening of high risk nodules and on the other hand, confirm the scientific meaning of the invidualisation of the guideline.

The research also recommend that it is possible to widely apply the chest LDCT and Lung-RADS 2019 for screening early lung cancer in high risk patients.

3. Structure of the dissertation

This dissertation contains 133 pages, including: Introduction with 2 pages, chapter 1 of Literature Review with 35 pages, chapter 2 of Subjects and Research Methodology with 28 pages, chapter 3 of Research Results with 32 pages, chapter 4 of Discussion with 33 pages, Conclusions with 2 pages, Recommendations with 1 page. The dissertation presents the statistical and visual information with 40 tables, 12 charts, 2 diagrams, and 65 pictures. There are 158 references, including 10 Vietnamese, 05 French and 143 English ones.

Chapter 1
LITERATURE REVIEW

1.1. OVERVIEW OF PULMONARY NODULES

Lung nodule (LN) were defined as nodular lesions localized in the lung parenchyma with a diameter of ≤ 30 mm, including solid, mixed, or ground-glass opacities [15], [67], [70], [73], [80], [97].

1.2. METHODS OF DIAGNOSIS OF LUNG NODULES

The context of detection of nodules is very diverse, of which more than 90% of nodules are detected incidentally [155]. Other detection settings may be nodules on lung radiographs in routine follow-up of cancer patients or in preoperative examinations, screening for metastases from extrapulmonary tumors or in immunocompromised patients. Routine chest X-ray and chest CT are the two main techniques in detecting lung nodules …

Routine chest X-ray

Anterior-posterior (AP) chest radiograph is the most commonly used imaging test. The majority of nodules were detected by radiographs, the rate according to foreign authors was 0.09-0.2% [154].

Normally, LN can be detected on chest X-ray when it is 8-10 mm in size, nodules 5-6 mm in size are more difficult to identify. Chest radiographs provide useful information including size, contour characteristics, calcification status, growth rate of LN and can provide initial assessment of LN [28], [62], [79], [89], [122], [154].

Computed tomography

With outstanding advantages in spatial resolution, structural resolution, CT scan is recently considered the most sensitive technique in detecting lung nodules, included in all recommendations on lung cancer screening applied in the world. In particular, the introduction of multi-slice CT, which can reduce the irradiation dose by more than 50%, has greatly expanded the indications for screening and significantly improved the detection rate of malignant pulmonary nodules [12], [63]], [98], [154].

In addition to using chest LDCT to screen for nodules, classify and diagnose nodules, the monitoring of nodules also plays a huge role in this technique. Follow-up images will be used on the same slice, same plane to compare and contrast to evaluate the progression of nodules [28], [35], [38], [60], [69], [111], [123], [132].

1.3. CLASSIFICATION OF PULMONARY NODULES

The American Radiological Society's 2019 Lung-RADS Classification

In 2011, the National Cancer Institute (NCI) announced the National Lung Cancer Trial (NLST) program to screen cancer with chest LDCT which reduced 20.3% in mortality when compared with chest low-dose CT with radiographic screening [63].

Based on these results, the American Optometric Association (ACR) attempted to standardize and monitor LNs using available imaging data. On April 28, 2014, ACR published the LN evaluation data system on chest LDCT, Lung-RADS version 1.0 [16]

The application of the Lung-RADS classification is widely practiced worldwide, especially in the United States and Asian countries. In 2019, the ACR was updated to the Lung-RADS classification version 1.1 [15], [18].

Prediction of malignancy of nodules

Malignancy risk prediction according to Lung-RADS 2019, developed by author Tammemagi from the Brocks University formula, in addition to predicting malignancy risk in percentage, the calculated results table also displays the content on subgroups of nodules and management strategies of nodules according to Lung-RADS 2019 [95].

1.4. IRRADIATION AND CHEST LOW-DOSE COMPUTED TOMOGRAPHY

Irradiation dose

The irradiation dose for one AP chest X-ray is quite low, about 0.02-0.2mSv (miliSievert) and not more than the natural radiation exposure from radiation of the earth's crust in 3 days. The role of X-ray radiation as a cancer agent in medical irradiation is a complex one. The first reported data source involved survivors of the atomic bomb explosions at Hiroshima and Nagasaki. Mortality from over-irradiation has been reported to be greater than 0.2 Sv (200 mSv) [154].

Application of dose reduction in chest CT

The lung is an anatomical region where a significant reduction in radiation dose on CT can be applied, with the criterion of reduced image quality without loss of diagnostic value. The air in the lungs absorbs very little X-rays, and even mediastinal fat can have a natural

density when used at low doses. According to two main research as NLST and NELSON, the mean of effective dose for chest LDCT in standard patient is 1,2-1,6 mSv [33]. According to NCCN 2018, the effective dose recommended is 1,5 mSv for average body weight, which can be increased to maximum of ≤ 3mSv in patients with BMI ≤ 30kg/m^2 [145].

In radiology as well as in CT, an important difference in dose levels exists, ranging from 1 to 10, from lowest dose to highest dose. With modern CT scanners, a standard chest CT scan, if fully performed, produces about 7mSv radiation dose, whereas a chest LDCT scan only produces about 0.5-1mSv [33]], [145].

Chapter 2
SUBJECTS AND RESEARCH METHODOLOGY

2.1. RESEARCH SUBJECTS

All patients over 18 years old who has clinical visited Hue University of Medicine and Pharmacy Hospital and Da Nang Oncology Hospital between January 2015 and March 2021 for any reason, detected pulmonary nodules size ≤ 30mm on plain chest X-ray and/or conventional abdomen CT, chest LDCT was performed according to a uniform procedure and histopathological examination.

2.1.1. The inclusion criteria

Research sample selection

- Lung nodules in the lung parenchyma ≤ 30mm in patients over 18 years of age, at high risk of malignancy
- Had chest LDCT scan and histopathological results.

Criteria for selecting lung nodules at high risk of malignancy

Nodules indicated for histopathology are pulmonary nodules with high risk of malignancy, including:

- Nodules highly suspected of cancer in the Lung-RADS 4X group: Solid or part solid nodules ≥ 6mm with suspicious imaging features (irregular border or enlarged lymph nodes) [15]
- Nodules with high suspicion of cancer in Lung-RADS 4B group: Solid nodules 15mm or semi-solid nodules with solid parts ≥ 8mm [15]
- Additional group: nodules that do not belong to Lung-RADS 4B, 4X groups but have at least one high risk factor for lung cancer according to David Ost: Nodule size ≥ 23 mm or irregular border

nodules, or other nodules in patients > 60 years old; have a history of cancer; smoking ≥ 1 pack/day; current smoking; have been exposed to pneumoconiosis [104].

2.1.2. The exclusion criteria

- Nodules that have received diagnostic or therapeutic intervention.
- Pneumonia on the same side with nodules interfering image analysis.
- Generalized calcified nodules on AP chest radiograph or CT.
- There are 5 pulmonary nodules on CT or more (considered as the basis for diagnosis of lung metastases or inflammatory lesions) [75].
- The patient did not agree to participate in the study.

2.2. RESEARCH METHODOLOGY

2.2.1. Research methodology: Cross - sectional descriptive study

2.2.2. Steps of research process

Step 1: Select patients 18 years of age or older with detected opacities ≤ 30mm in lung parenchyma on X-ray plan film or other CT, suitable for research subjects.

Step 2: Take chest LDCT and classify nodules according to Lung-RADS 2019.

Step 3: Select high-risk LN that meet the study's inclusion criteria, exclusion criteria, and the study's criteria for high-risk lung cancer opacities to assign diagnostic histopathology tests.

Step 4: Record histopathological results

Step 5: Collect and analyze research data according to a unified questionnaire

2.2.3. Variables

Clinical survey, history and risk factors

Description of the LDCT characteristics of lung nodules

Record images of lung opacities on low-dose computed tomography of the chest to classify nodules according to Lung-RADS 2019: Location, shape, number of nodules, size, density, border and margin, nodule characteristics: fat composition, calcification, cavitation, bronchial tree, pleural retraction, lymph node enlargement...

Classification of nodules

- Classification of lung nodules according to the Lung-RADS 2019 guidelines of the American Society of Radiology to filter out

the group of high-risk lung nodules, which are Lung-RADS 4B, 4X nodules.

- Additional screening for high-risk malignant lung nodules in the remaining group by considering high risk factors for lung cancer according to David Ost, including age, smoking, cancer history, dust exposured lung, size, and contour of the nodule so as not to miss high-risk pulmonary nodules.

Record the last histopathological results of nodules

2.2.4. Study methods

Technical parameters of chest LDCT scan in our study

Chest LDCT scan technique according to a reference study of chest LDCT procedure of the US National Cancer Screening Clinical Trial (NLST) and NELSON study applied on a group of patients's weight in the range of 50-80 kg (BMI < 30 kg/m2) [31], [63], [145]. The specifications are uniformly installed on 16-slice CT scanners at the Department of Radiology within the scope of research sampling as follows:

- Reconstruction mode: 3mm slice thickness, 1.5mm reconstruction slice thickness, 1.2mm reconstruction interval. Images were analyzed on workstation (Syngovia) with a reconstructed slice thickness of 0.6mm. Slices were reconstructed with kernel B41s for mediastinal evaluation, chest wall and kernel B70s for lung parenchymal examination.

- Specifications: 110 kVp voltage, automatic change of bulb current according to CareDose 4D software with principles based on body thickness and X-ray intensity attenuation (reference bulb current, quality ref. mAs 20), bulb rotation speed 0.6 s/rev, collimation opening 16x1.2 mm, pitch 1.5.

Effective dose < 3mSv, reduced patient irradiation dose by more than 50% compared with standard dose, with the dose of a standard chest CT of 7mSv [33]. .

- Application of MPR (MultiPlanar Reformation) thin slice reconstruction and MIP (Maximum Intensity Projection) to analyze image of opacities. Evaluation on both parenchymal and mediastinal windows.

- For patients who have been detected opacities on chest CT of other diseases, low-dose CT chest CT will be performed, focal field of study (FOV) above and below 5cm the opacities to analyze the imaging characteristics of the nodules.

- Injection of contrast agent at a dose of 1ml/kg with a concentration of 300mg Iode/ml, injection rate of 3ml/s. Assess the enhancement of the lesion once during the venous phase of 70-90 seconds [29].

Transthoracic nodule biopsies:

- Indications: Pulmonary nodules with high risk of malignancy.

- Core biopsy of lung opacities under CT guidance for nodules located within the normal lung parenchyma and core biopsy under ultrasound guidance for lesions located close to the chest wall [32]. For each lesion, 3-4 tissue core samples were taken, fixed in a sample bottle containing formalin (formol 10%) and sent to the Department of Pathology for tissue assessment.

- Sampling technique using 16-18G biopsy needle, with satisfactory tissue samples for cutting and processing.

2.2.5. Study of opacities on low-dose computed tomography of the chest

Analytical methods

- Analysis of opacities on chest LDCT images. Identify opacities, solid nodules, semi-solid nodules and measure the exact size of the opacities, averaging the long and short axes in the same plane, reporting with rounding to one decimal place.

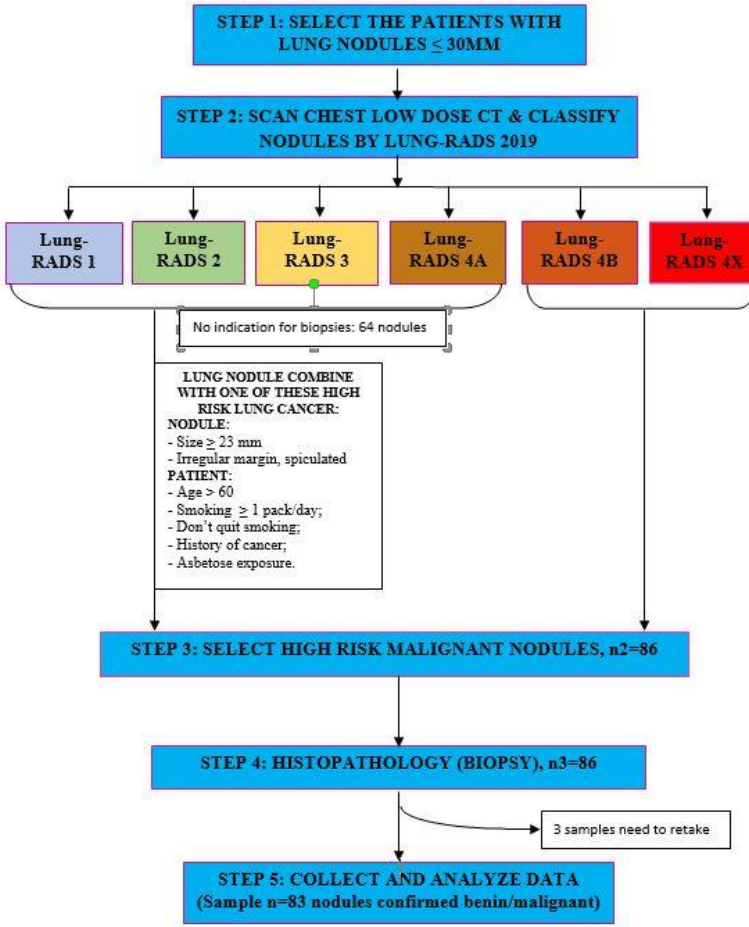
- Analysis of image features:

Classification and treatment of lung nodules

Lung-RADS 2019 nodule classification

- For cases with multiple pulmonary nodules, classify Lung-RADS in patients according to nodules

RESEARCH DIAGRAMS



2.3. DATA ANALYSIS

Statistical analyses were performed using SPSS 18.0

2.4. ETHICS IN RESEARCH

The research was accepted by the ethics committee of University of Medicine and Pharmacy, Hue University.

Chapter 3
RESULTS

This cross-sectional study was conducted between 01.2015 and 03.2021. 83 patients who had pulmonary nodule that fully filled the selection criteria, then received a LDCT scan and had histological are presented below:

3.1. PATIENT CHARACTERISTICS

3.1.1. Demographic characteristics

Table 3.1. Age of patients

Groups of age divided by risk factors	Number of patients (n)	Percentage (%)
< 45	5	6.0
45 - 60	28	33.7
> 60	50	60.2
Total	**83**	**100**
Mean ± Deviation Minimum – Maximum	62.01 ± 12.96 20 – 87	

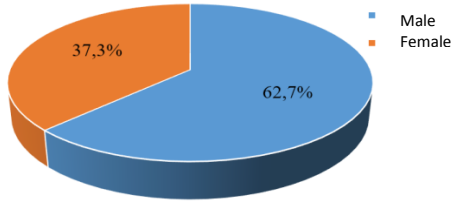


Chart 3.1. Sex distribution of patients (n=83)
(blue: male, orange: female)

Table 3.2. Smoking status of patients

Smoking history		n	%
Smoking	No	55	66.3
	Yes	28	33.7
	Total	83	100
Pack-year	< 30	15	53.6
	≥ 30	13	46.4
	Total	**28**	**100**
	Mean ± Deviation Minimum – Maximum	32.32 ± 23.89 4 – 100	

.3.1.2. Histological results and diagnosis

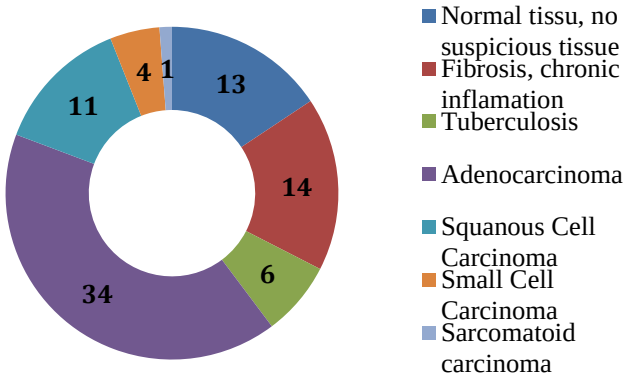


Chart 3.5. Histological evaluation after biopsy or surgery (n=83)
Adenocarcinoma 34/ Infection 14/ Squamous cell carcinoma 11/ TB 6/ Small cell carcinoma 4/ / no malignant cell 13

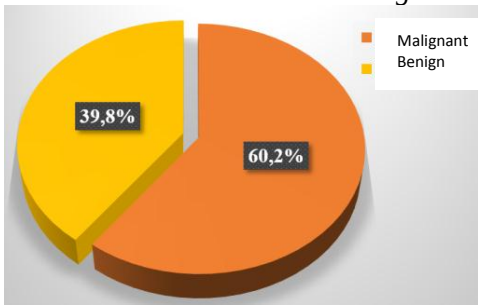


Chart 3.6. Groups of malignancy and benignity divided by histological evaluation (yellow: benign, orange: malignant)
Benign 39,8%/ Malignant 60,2%

Table 3.5. T-staging of early detected lung cancer (n=50)

T-stage	n	%
T1b (UTP >1 and ≤ 2 cm)	9	18
T1c (UTP > 2 cm and ≤ 3 cm)	41	82
Total	50	100

3.1.4. Effective dose

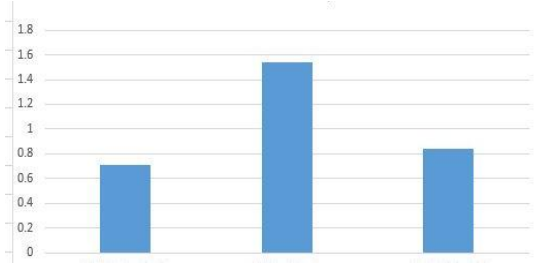


Chart 3.7: CT radiation dose of patients in this study

a. *Chest LDCT non contrast (Ho T S. Effective dose 0,71 mSv)*
b. *Chest LDCT with contrast (Le T T. Effective dose 1,54 mSv)*
c. *Chest LDCT for biopsy – guided (Ho S N. Effective dose 0,84 mSv)*

3.2. CHEST LOW DOSE COMPUTED TOMOGRAPHY FINDINGS AND NODULE CLASSIFICATION BY ACR LUNG-RADS 2019:

3.2.1. Chest LDCT features of lung nodules

Table 3.7. Size, density and lipid-containing component (n=83)

Features		n	%
Size	≥ 15 mm	79	95.2
	< 15 mm	4	4.8
	TB ± ĐLC Smallest – Largest	24.27 ± 4.98 11 – 30	
Density	Part-solid	3	3.6
	Solid	80	96.4
Lipid	No	81	97.6
	Yes	2	2.4

Table 3.8. Types of calcification of lung nodules

Features	Type of calcification	n	%
No calcification	No calcification	67	80.7
Malignant calcification	Dispersed	6	7.2
	Eccentric	7	8.5
Benign calcification	Popcorn	1	1.2
	Laminated	2	2.4
Total	**Total**	**83**	**100**

Table 3.11. Morphologic features of lung nodules (n=83)

Features	Characteristics	n	%
Shape	Triangular	3	3,6
	Round/ Oval	41	49,4
	Polygonal	39	47
Margin	Smooth/Regular	13	15,7
	Irregular/spiculated	57	68,7
	Irregular/Lobulated	13	15,7
Suspicious air bronchogram	Non	44	53
	Compressing or narrowing	6	7,2
	Amputation	26	31,3
	Invasive	7	8,5
Cavity	No	73	88,0
	Yes (cavity with thick wall)	10	12,0
Fissure	Be pulled	67	80,7
	Not be pulled	16	19,3
Necrosis component	No	66	79,5
	Yes	17	20,5

Table 3.13. Associated signs with lung nodules

Associated sign		n	%		n	%
Lymph node(s)	No	27	32.5	No	27	32.5
	Yes	56	67.5	Mediastinal	46	55.5
				Cervical / axillary	10	12.0
	Total	83	100	Total	83	100
Suspicious of metastasis	Suspicious mediastinal/cervical/axillary lymph node(s)				32	38.6
	Hypertrophy of Adrenal gland				4	4.8
	Focal lesion in brain				7	8.4
	Focal lesion in other organs				10	12.0

3.2.2.Nodule classification by ACR Lung-RADS 2019

Table 3.14. ACR Lung-RADS classification of lung nodules (n=83)

Classification	Categories	n	%	Categories	n	%
Lung-RADS 2019 (categories)	Lung-RADS 1.2.3.4A	8	9.6	**1**	5	6.0
				4A	3	3.6
	Lung-RADS 4B. 4X	75	90.4	**4B**	11	13.3
				4X	64	77.1
	Total	**83**	**100**	**Total**	**83**	**100**
Lung-RADS 2019 (malignancy prediction)	High (> 15%)				72	86.7
	Low (≤ 15%)				11	13.3
	Total				**83**	**100**

3.3. LUNG CANCER DIAGNOSTIC VALUE OF LUNG LDCT BY ACR LUNG-RADS 2019

Table 3.17. Value of size in diagnosis of lung nodules (n=83)

Features	Cut-off	Se (%)	Sp (%)	AUC	p	CI 95%
Size (mm)	>22	80.0	45.5	0.637	**0.031**	0.524 - 0.740

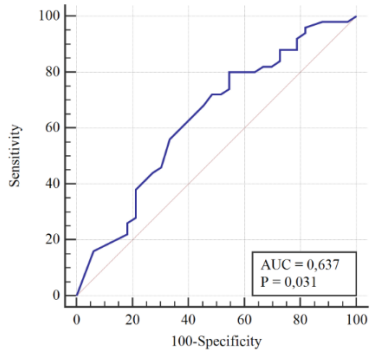


Chart 3.9. ROC curve shows the value of the size threshold in diagnosis of lung nodules (n=83)

Table 3.27. Diagnostic values of significant features (n=83)

Features	Se	Sp	PPV	NPV	Accuracy	p
Size > 22mm	80.0	45.5	69.0	60.0	66.3	0.013
Margin (Spiculated and lobulated)	92.0	27.3	65.7	69.2	66.3	0.018
Calcification	10.0	66.7	31.3	32.8	32.5	0.011
Mediastinal/cervical/axillary lymph node(s)	70.0	60.6	72.9	57.1	66.3	0.006
Suspicious lymph node(s)	50.0	78.8	78.1	51.0	61.4	0.008
Nodule ≥ 15mm and spiculated margin	76.0	45.5	67.9	55.6	63.9	0.041
Nodule ≥ 15mm and mediastinal lymph node(s)	70.0	60.6	72.9	57.1	66.3	0.006
Nodule ≥ 15mm and suspicious lymph node(s)	50.0	78.8	78.1	51.0	61.4	0.008
Nodule ≥ 15mm in upper lobe and had calcification	2.0	84.9	16.7	36.4	34.9	0.034*
Nodule ≥ 15mm in upper lobe and had cavity	0	81.8	0	35.1	0	0.003*
Nodule ≥ 15mm with spiculated margin and enhanced	64.0	66.7	74.4	55.0	65.1	**0.006**

* *Fisher exact test*

Table 3.28. Multivariate logistic regression analysis of LDCT values in diagnosis of lung nodules (n=83)

Values		OR	95% KTC		p
Calcification	Yes	1			
	No	5,79	1,57	21,43	0,008
Nodule size > 22mm	Yes	3,60	1,22	10,60	0,020
	No	1			
Nodule ≥ 15mm with spiculated margin and enhancement	Yes	3,89	1,39	10,85	0,009
	No	1			

Table 3.30. Diagnostic values of significant features in group of Lung-RADS 4B và 4X (n=75)

Image characteristics	Se	Sp	PPV	NPV	Accuracy	p
Nodule size >22mm	81,6	42,3	72,7	55,0	68,0	0,026
Calcification	8,2	73,1	36,4	29,7	30,7	0,041*
Suspicious lymph node	51,0	73,1	78,1	44,2	58,7	0,045
Nodule ≥ 15mm with spiculated margin and enhancement	65,3	65,4	78,1	50,0	65,3	0,011

** Fisher Exact test*

Table 3.31. Diagnostic values of ACR Lung-RADS by categories and predictive malignancy risk (n=83)

Malignancy risk \ Group		Malignant		Benign		Se (%)	Sp (%)	PPV (%)	NPV (%)	Accuracy (%)	p
		n	%	n	%						
Lung-RADS **(malignancy prediction)**	High **> 15%**	48	66.7	24	33.3	96.0	27.3	66.7	81.8	68.7	**0.006***
	Low **≤15%**	2	18.2	9	81.8						
Lung-RADS **(categories)**	High **(4B.X)**	49	65.3	26	34.7	98.0	21.2	65.3	87.5	67.5	**0.006***
	Low **(1→ 4A)**	1	12.5	7	87.5						

** Fisher Exact test*

Table 3.32. Malignancy risk predictive value of ACR Lung-RADS 1.1 in assessing lung nodules (n=83)

Author	Cut-off %	Se (%)	Sp (%)	AUC	p	CI 95%
Lung-RADS	**>29.39**	80.0	54.6	0.652	**0.022**	0.540 - 0.753

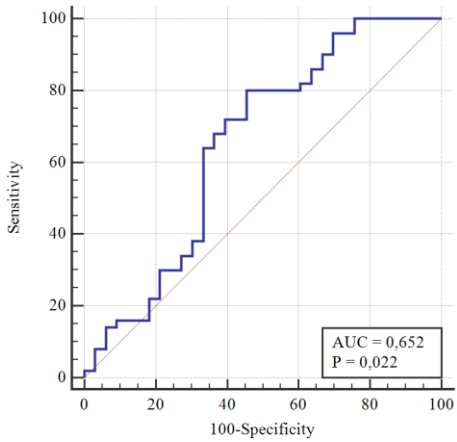


Chart 3.10. ROC curve shows the malignancy risk predictive value of ACR Lung-RADS 1.1 in assessing lung nodules (n=83)

Chapter 4
DISCUSSION

4.1. GENERAL CHARACTERISTICS

In all patients with lung nodule detected at the 2 hospitals, 150 patients had chest LDCT scan that met the criteria for inclusion in the Lung-RADS classification. When combining with high risk factors for lung cancer according to David Ost, 83 patients with 83 high risk nodules identified as benign or malignant nodules were selected for the study sampling.

Age and gender

Average age of 83 patients was 62.01 ± 12.96 years old, the oldest patient was 87 years old, the youngest one was 20 years old. Up to 60.2% of them were in the age group of 60 and above, which is the high-risk group for lung cancer.

Regarding the gender distribution of patients with lung opacities, the percentage of male patients was higher (62.7%) and the male/female ratio was 1.68/1, $p > 0.05$. This result is comparable with most research results in the country and in the world.

The protocol of lung low dose computed tomography applied in the study

The reference protocols were applied in the National Lung Screening Trial (NLST) of National Cancer Institute (USA) and the NELSON study. The latest updated process of NCCN 2018 is quite similar with an allowable effective dose level up to 3mSv for people with BMI ≤30 kg/m2. The above 3 protocols recommend using a multi-detector CT machine with 16 or more slices, taking in 1 breath and without contrast injection [33], [63], [145].

In the study, we used the consistent kVp, mAs, other technical factors and process to obtain an effective dose of < 3mSv for non-contrast-enhancement lung CT examinations; the radiation dose was reduced by ≥ 50% compared to the usual dose, which was based on the Vietnamese body characteristics with an average weight of 50-60kg. We set the protocol to examine the patients. The average effective dose for non-contrast chest CT exam, contrast-enhancement CT (with 2 scan times) and CT-guided biopsy procedure of lung nodule (with at least 3 scan times) were approximately 0.71 mSv, 1.54 mSv and 0.84 mSv, respectively.

We tested the protocol by measuring the signal-to-noise ratio (S/N ratio) and calculating the effective dose when applying it for the model (phantom), voluntary patients and healthy volunteers. The

image quality obtained in 3 circumstances were quite similar while the dose was reduced by >50%, especially when evaluating pulmonary nodules.

4.2. VALUE OF LUNG LOW-DOSE CT IN DIAGNOSIS OF HIGH RISK PULMONARY NODULES

4.2.1. Diagnostic values of main CT findings

Density

Most of the lesions were solid nodules, only 3 cases were mixed nodules while there were no ground glass opacifications. In our study, the density of nodules had sensitivity of 6% and specificity of 100% in diagnosing malignant nodules, p>0.05.

In the ELCAP (Early Lung Cancer Action Project) study (2002), Henschke C.I. et al presented that 81.1% were solid nodules, 12% were GGO and 6.9% were mixed ones, the malignancy proportion of those 3 nodule types were 7%, 28% and 63%, respectively. According to Wahidi (2007), partial solid or mixed nodules had a high malignancy rate of 59-73%, while fully solid ones had a lower malignancy rate of 7-9%.

Size

Our result showed that the threshold of nodule size ≥15mm (according to subgroup 4B of Lung-RADS 2019) to divide nodule into high and low risk groups had Se of 98%, Sp of 9.1% in diagnosis of lung nodules, p>0.05.

According to the ROC curve analysis, the cut-off size that helped diagnose malignant lesions was > 22mm. With that value, Se, Sp, PPV, NPV and accuracy were as follows: 80%, 45.5%, 69%, 60% and 66.3%, respectively, p < 0.05.

This size threshold was close to the value recommended by David Ost (≥ 23mm), which was classified as a high risk factor for lung cancer [104]. This result was consistent with many studies describing relation between risk of malignancy and nodule diameter. For instance, Wang KP showed the malignancy rate of the nodule with the size of 10-20mm was 64-82% and Fleischner presented malignancy rate of 80% in nodules >20-30mm [15], [85], [145].

From result of our study, we recommend taking threshold size of ≥15mm for early lung cancer screening to increase the sensitivity (98%) and taking size of >22mm for diagnosis to improve specificity and accuracy of the technique.

Calcification

As determined by the study result, 31.3% of the calcified nodules were malignant**;** Se and Sp were 10% and 66.7%, respectively, $p < 0.05$. These values were very low, so this characteristic should not be used independently in the diagnosis of lung nodules in clinical practice.

Regarding the calcification in nodules, our result was not similar to those of domestic and international authors. In Vietnam, there are many chronic inflammatory lesions with internal calcifications, such as old pulmonary tuberculosis, lymph nodes of old tuberculosis, chronic pneumonia, granulomas, hamartomas, etc. Therefore, assessment of a benign or malignant calcified lesion was somehow misleading. Moreover, as stated by the literature, there are still malignant nodules with popcorn-like calcifications, so this feature should be analyzed very carefully.

Fat in nodule

In our study sample, there were 2 nodules with fat content inside, accounting for 2.4%, and both were benign, Se and Sp were 100% and 6.1%, respectively, $p>0.05$.

In the Lung-RADS classification, the presence of intranodular adipose tissue is an independent factor and is of absolute value when all other nodular features are reduced to little significance for classifying nodule as Lung-RADS 1. The nodule is considered completely benign and recommended for being re-examined after 12 months [15], [88]

Many other authors also reported that fat tissue in lung nodules is considered a sign of benign nodule with a very high rate [23], [104], [156].

4.2.2. Values of other characteristics

Some other independent imaging features are also significant in diagnosing malignant lung nodules, such as: spiculated and multilobular margin; enlargement of mediastinal, cervical and axillary lymph nodes; suspected metastatic lymph nodes, $p<0.05$.

When analyzing the spiculated margin, Snoecks (2018) suggested that it is necessary to combine with accompanying benign calcifications, morphology of adjacent lung parenchyma and contralateral lung apex lesion, which helps to distinguish real spiculated margin with mimicking images in old TB [120].

The result from analysis of group of criteria including imaging features combined with a nodule Lung-RADS 4B (size $\geq$ 15mm)

showed that the more imaging features combined in the process, the more valuable the chest LDCT technique will be in early diagnosis of lung cancer. Furthermore, this result concretized some imaging features suspicious of malignant nodules in the group of studied patients in Vietnam, which can be considered to rank nodules evaluated as Lung-RADS 3, 4A, 4B to group 4X to avoid missing malignancy.

Besides, a different and discussion-worthy point of our result is that groups of combined features including: nodules ≥ 15mm with malignant bronchogram, even in upper lobes or nodules with spiculated margin in upper lobes or nodules ≥15mm in the upper lobes with spiculated margins did not have diagnostic significance, while many authors in the world have demonstrated independent diagnostic value of these suspicious imaging features [23], [107], [120], [148]. Once again, the study result showed that the history of respiratory diseases in the studied patients greatly affected the diagnosis of lung nodules on chest LDCT images and careful systematic analysis was required to minimize false positive cases.

Linear regression analysis showed that non-calcified nodule group had a 5.79 times higher risk of malignancy than group with calcification (CI 95 %: 1.57-21.43); group of nodules > 22mm had a 3.6 times higher risk of malignancy than nodules ≤ 22mm (CI 95%: 1.22-10.60) and group of Lung-RADS 4B nodules with spiculated margin and enhancement had a 3.89 times higher risk of malignancy than Lung-RADS 4B nodules without these 2 features (CI 95%: 1.39-10.85). This result is quite valuable because we can determine the suitable management strategy when facing a lung nodule, without missing high-risk nodes and unnecessary intervention to low-risk ones.

Author Nguyen Tien Dung (2020) reported that Se, Sp, PPV and NPV of chest LDCT applied in lung cancer screening were: 100%; 81.7%; 9.1% and 100%, respectively [3].

According to Jonas (2021), there have been 24 articles referring to the value of chest LDCT in lung cancer screening. Sensitivity varied from 59 to 100% as stated in 13 studies and > 80 % in 3 studies. Specificity ranged from 26.4% to 99.7% in 13 studies and >75% in 3 studies.

4.2.6. Value of classification and diagnosis of lung nodule according to Lung-RADS 2019

The assessment and classification of lung nodules collected in 2015-2018 period in the study sample has been adjusted when ACR

updated the Lung-RADS 2014 version to Lung-RADS 2019. However, the re-classification did not affect the analysis or management strategy, so the whole sample was uniformly classified into groups using Lung-RADS 2019.

Our study showed that Lung-RADS 2019 classification and Lung-RADS 2019-based malignancy risk prediction software (Lung Nodule) had very high sensitivity (96-98%) and low specificity (21.2-27.3%) in diagnosis of pulmonary nodules, with $p < 0.01$, but the classification had higher sensitivity (Se) and negative predictive value (NPV) than the software. Applying Lung Nodule software included using many related information of patient and his/her nodule, which seemed to towards personalizing recommendations.

Lung-RADS classification recommends that threshold risk of malignancy for Lung-RADS group 4B, 4X is > 15%. In our result Se, Sp of this value were 78.8% and 12.5%, respectively, $p<0.01$. However, the ROC curve analysis (Figure 3.10) showed that the significant threshold in diagnosis of malignant nodules was 29.39% with a clearly improved specificity (Se 80%, Sp 54.6%, AUC 0.652, $p<0.05$). Therefore, it seems that applying a risk prediction threshold of > 29.39% or approximately 30% to classify nodules as high risk ones would reduce intervention in nodules which have a predictive risk of malignancy from 15% to 29.39%. malignancy risk

AUC value of Lung Nodule software in our study was lower than the results stated by Mayo Clinic (AUC 0.895), Brock (AUC 0.902), Veterans Association (AUC 0.735) and Herder PET/CT group (AUC 0.924) [12]. Application of the software to predict the malignancy of lung nodules has become increasingly popular and effective [13], [39], [62], [80], [95], [127], [131], [137]. The results of our study also demonstrated that the prediction of malignancy risk obtained by Lung Nodule software had similar diagnostic values (sensitivity and specificity) to applying the Lung-RADS classification, therefore this software could be widely and conveniently applied.

4.3. LIMITATIONS

- The study did not do the prospective part to follow-up the nodules and assess their progress as Lung-RADS 2019 recommended
- The study objects were only high-risk lung nodules. We did not cover all the nodules in the study, neither did we describe the imaging characteristics of GGO and nodules that did not meet the criteria for biopsy.

- The main facilities of study were two 16-slice CT scan machines and one 128-slice machine at 2 hospitals, thus some modern dose reduction methods such as repeating reconstruction algorithms or AI were not applied.

CONCLUSIONS

In a cross-sectional descriptive study with a sample size of 83 patients with high-risk lung nodules on chest LDCT between January 2015 and March 2021, we have the conclusions as bellow:

1. Classification applied Lung-RADS 2019 and imaging findings of chest LDCT of high risk lung nodules:

- Mean age was 62.01 ± 12.96 (20-87). The age group > 60 accounted for the highest rate with the percentage of 60.2%, the male/female ratio was 1.68/1.

Classifying pulmonary nodules:

- Lung-RADS 2019 classification by categories: 9.6% of nodules belonged to Lung-RADS 1-4A and 90.4% of nodules were Lung-RADS 4B,4X.

- Lung-RADS 2019 based on malignancy risk prediction: 72 patients with high risk of lung cancer (> 15%) accounting for 86.7% and the other 11 patients with a low risk of lung cancer (≤ 15%) accounting for 13.3 %.

Image characteristics of nodules:

- Solitary lung nodules accounted for 67.5%; distributed mainly in the right lung (68.7%) and the upper lobe (57.8%).

- Morphological features referred in the Lung-RADS 2019: 96.4% solid nodules and 3.6% part solid; 95.2% nodules with size ≥ 15mm; 80.7% non calcified and 15.7% with suspected calcification; adipose componants: 2.4%;

- Other chest LDCT findings: 47% of nodules were polygonal, 49.4% were round or oval nodules; spiculated nodules accounted for the highest rate with percentage of 68.7%. Nodules with malignant bronchogram accounted for 47%; 69.9% of nodules had enhancement and 16 nodules (accounting for 19.3%) retracted the interlobar sulcus.

2. Value of low-dose chest computed tomography in the diagnosis of high-risk pulmonary nodules

Diagnostic values of CT imaging features:

- There were 5 significant imaging features dependently suspected high-risk nodules: Size > 22mm (Se 80%, Sp 45.5%); Irregular

margin (spiculated and/or multilobular) (Se 92%, Sp 27.3%); Calcified nodules (Se 10%, Sp 66.7%); enlarged regional lymph node (Se 70%, Sp 60.6%) and suspected lymph nodes (Se 50%, Sp 78.8%), $p<0.05$.

- Non calcified nodules had a 5.79 times higher risk of malignancy than those with calcification (CI 95%: 1.57-21.43); Nodules with size > 22mm had a 3.6 times higher risk of malignancy than those ≤ 22mm (CI 95%: 1.22-10.60); Lung-RADS 4B nodules with spiculated and enhancement had a 3.89 times higher risk than Lung-RADS 4B ones without these two features (CI 95%: 1.39-10.85).

- There were 2 groups of imaging features that were valuable in diagnosing malignancy in Lung-RADS 4B nodules, which meant they would convert a Lung-RADS 4B nodule into 4X. Specifically, when a Lung-RADS 4B nodule was in upper lobe and had calcification (Se 2%, Sp 84.9%) or had spiculated margin and enhancement (Se 64%, Sp 66.7%), it would be classified as Lung-RADS 4X, $p<0.05$.

Value of low-dose chest computed tomography combining with Lung-RADS 2019 in diagnosis of high-risk lung nodules

- When applying Lung-RADS 2019 classification, Se, Sp, PPV, NPV and accuracy were as follows: 98%, 21.2%, 65.3%, 87.5%, and 67.5%, with $p<0.01$.

- When applying Lung-RADS 2019-based malignancy risk prediction software, Se, Sp, PPV, NPV and accuracy were: 96%, 27.3%, 66.7%, 81.8%, and 68.7 %, with $p<0.01$

- The threshold risk for predicting lung cancer risk according to Lung-RADS 2019 was 29.39% (Se 80%, Sp 54.6%, AUC 0.652) with $p<0.05$.

RECOMMENDATIONS

Based on evidence from our result,

1. We recommend using chest LDCT scan for high-risk pulmonary nodules screening and systematically applying Lung-RADS 2019 to stratify as well as predict the malignancy risk of lung nodules, which could greatly contribute to early diagnosis of lung cancer.

2. We suggest that when referring a biopsy for a lung nodule, physicians should take the following circumstances into consideration, besides the group of Lung-RADS 4B, 4X nodules: Patients with at least one high risk factor of lung cancer according to David Ost; nodules with size > 22mm; nodules with predicted malignancy risk ≥ 30%.

PUBLICATIONS OF RESEARCH RESULTS OF THE THESIS

1. Hoang Thi Ngoc Ha, Le Trong Khoan (2015), *Lung-RADS and update of lung nodules screening by low dose computed tomography, Journal of Medicine and Pharmacy*, University of Medicine and Pharmacy, Hue University, 28+29, tr.12–19.

2. Hoang Thi Ngoc Ha, Le Trong Khoan (2017), *The application of acr lungrads and lung low dose computed tomography in diagnosis and follow up lung nodules: early report in 6 case, Journal of Medicine and Pharmacy*, University of Medicine and Pharmacy, Hue University, 5(7), tr.271–280.

3. Hoang Thi Ngoc Ha, Le Trong Khoan (2020), *Application "Lung Nodule" software with Lung-RADS 2019 on early detection and follow up the pulmonary nodules by lung low dose CT findings*, J Clin Med - Hue Cent Hosp, (64), tr.92–100.

4. Hoang Thi Ngoc Ha, Doan Dung Tien, Le Trong Khoan (2020), *Study the value of lung low dose computed tomography in early detection the malignant pulmonary nodule, Journal of Medicine and Pharmacy*, University of Medicine and Pharmacy, Hue University, 4(10), tr. 7–15