Journal of Cancer Research and Practice 5 (2018) 13–19

Contents lists available at ScienceDirect

Journal of Cancer Research and Practice

journal homepage: http://www.journals.elsevier.com/journal-of-cancer-research-and-practice

Original Article

Evaluating pulmonary nodules to detect lung cancer: Does Fleischner criteria really work?

Muhammad Azharuddin [a, *], Noor Adamo [a], Aamir Malik [b], Douglas S. Livornese [c]

[a] Department of Internal Medicine, Monmouth Medical Center, United States
[b] Department of Internal Medicine, Truman Medical Center Hospital Hill, United States
[c] Department of Pulmonology and Critical Care, Monmouth Medical Center, United States

ARTICLE INFO

Article history:
Received 6 March 2017
Received in revised form
12 May 2017
Accepted 23 May 2017
Available online 29 June 2017

Keywords:
Lung cancer
Low-dose computed tomography scan
Fleischner criteria
Malignancy
Radiology

ABSTRACT

Objective: The Fleischner Society recommends that interval computed tomography (CT) be conducted as a follow-up for managing incidental small pulmonary nodules detected in CT scans. This study evaluated the clinical application of Fleischner criteria using a large cohort of patients at high risk for lung cancer with low-dose CT screening.

Materials and methods: During the years 2012–2016, a retrospective study of 176 patients was reviewed for incidental lung nodules. Patient eligibility included: men and women from 55 to 74 years of age; a 30 pack per year smoking history, and the patient quit smoking in the last 15 years; no cancer history within the last 5 years; and no previous CT chest scan performed. The Fleischner criteria was used to calculate proper patient follow-up and management. Nodules were classified based on several features, including but not limited to size and shape; characteristics of nodules were tabulated and analyzed using the Chi-squared and t-tests.

Results: Out of 176 patients, 117 had nodules with a total of 210 total nodules detected. Table 1 shows the categorization of all nodule features including the Fleischner Criteria. Of the entire cohort, two patients (1.1%) had malignant disease: one was a part-solid nodule of 10.2 mm, and the other was a multiple subsolid ground glass nodule (GGN) of 20.1 mm. Twenty-one patients (17.9%) had undergone unnecessary follow-up CT scans, including those with solitary pure GGNs.

Conclusion: This study emphasizes the need for new Fleischner guidelines to minimize over-diagnosis, unnecessary follow-ups, cost, and dosage of radiation. Such new guidelines will certainly estimate the risk of malignancy with greater accuracy.

1. Introduction

Lung cancer is the most common fatal malignancy for men and women in the United States. Around 175,000 new cases of lung cancer are detected each year, of which 75–80% are non–small cell lung cancer.[1–4] The overall 5-year survival rate in the US is a low 13%, and the 10-year US survival rate is 7%.[5]

1.1. Lung cancer presenting as lung nodules

Ever since the National Cancer Institute showed the positive results of low-dose computed tomography (LDCT) screening to reduce lung cancer mortality by 20%, interest in LDCT has grown more than ever.[2,3] The emergent use of CT has caused a growing number of incidental findings of pulmonary nodules in heavy smokers, increasing detection of lung cancer at an earlier and more curable phase.[3,6]

Noncalcified pulmonary nodules are typically found in screen-detected lung cancers on low-dose CT, including small (<4 mm) pulmonary nodules.[3,4,7–9] Previous CT trials on lung cancer displayed that about 51% of smokers > 50 will have one or more of these nodules, most of which are benign (96.4%).[10] These high-risk populations have a malignancy risk of 0.2% for nodule size <3 mm, 0.9% for nodules 4–7 mm, and 18% for 8–20 mm.[8]Determining the risk of malignancy for these small lesions is critical for prompt diagnosis and treatment.[11]

In 2005, the Fleischner Society published guidelines for the

* Corresponding author. Department of Internal Medicine, Monmouth Medical Center, 300 2nd Ave, Long Branch, NJ 07712, United States.
E-mail address: azhar_uddin203@yahoo.com (M. Azharuddin).
Peer review under responsibility of Taiwan Oncology Society.

http://dx.doi.org/10.1016/j.jcrpr.2017.05.003

incidental detection of small pulmonary nodules during CT scans. Findings were categorized based on the size of the nodule and if the patient was low- or high-risk according to factors such as smoking history and prior malignancy.[7,9,11] Although widely recognized, the 2005 guidelines were not used universally due to inconsistent compliance.[3]

1.2. Updating the definition of pulmonary nodules

Based on the definition of the Fleischner Society, the pulmonary nodule is a rounded or irregular opacity, well or poorly defined, measuring up to 3 cm in diameter.[3,7,11]Most (80%) of nodules <5 mm are benign, commonly representing granulomatous disease. Currently, lung cancer prognosis is poor (16.6% survival at 5 years); however, diagnosis in localized early stage lung cancer can be associated with a 5-year survival of up to 54%.[12]

1.3. Current management guidelines from the Fleischner Society

The original Fleischner guidelines were only based on size and risk, and did not incorporate nodule type.[8] In 2013, the Fleischner Society published recommendations to manage subsolid pulmonary nodules (SSNs), indicating that solid and subsolid (pure ground-glass, pure solid, mixed, semisolid/part-solid ground-glass) nodules react differently, form unique categories of lung nodules, and need different rules that apply for follow-up.[13,14]These new guidelines are helpful in determining the probability of cancer by specifying the classification of nodules based on size, solid portion, and ground-glass opacification, with special protocol for SSNs that persist after initial follow-up CT at three months.[6,14] In addition, an important difference in the new Fleischner recommendations for solid lung nodules is that patients with a smoking history are not always distinguished from ex-smokers, or those who have never smoked.[8]

1.4. The solitary pulmonary nodule

The differential diagnosis for subsolid solitary pulmonary nodules (SPNs) includes infection, inflammation, hemorrhage, and malignancy (commonly lung adenocarcinoma).[15] Assessment of SPNs, both solid and subsolid, is clinically significant as it may be an early sign of lung cancer.[16] According to the American Cancer Society, one in 13 men and one in 16 women will be diagnosed with lung cancer, and about 20–30% of those patients will have an SPN.[16,17]

1.5. CT characteristics

The variables used to assess with CT are nodule size, border characteristics, and density.[3] The size of the pulmonary nodule is a key predictor for malignancy in heavy smokers, as there is a direct relationship between both factors.[18,19] For example, subcentimeter nodules have a relatively low incidence of malignancy.[3] One study of eight CT screening trials showed that malignancy risk was correlated with nodule size, with 0–1% for nodules <5 mm, 6–28% for 5–10 mm, and 64–82% for nodules >20 mm.[3,18,21] The growth of the solid portion of the nodule is more significant in determining its malignancy. Solid nodules usually grow faster than subsolid nodules.[8,20] Border characteristics, including nodules with irregular, lobulated, or speculated borders, are linked with a higher chance of malignancy than smooth border.

Similarly, pure ground-glass or semisolid nodules have a higher probability of malignancy compared to pure solid lesions.[18] One study revealed that the malignancy rate of SSNs (34%) was higher than for solid nodules (7%), and the malignancy rate for part-solid GGNs (63%) was higher than for pure GGNs (18%).[13,14] However, not all SSNs are malignant, as some come from various histologic backgrounds with many benign conditions.[22,23]

Factors that increase risk for developing lung cancer include the following: 1) advanced age; 2) the presence of symptoms; 3) current or past smoking history; 4) history of exposure to asbestos, uranium, or radon; 5) cancer history with resection of small nodules (5 mm or smaller); and 6) history of extrathoracic cancer more than 5 years before nodule detection.[24] During initial clinical manifestation, patients with hemoptysis and an SPN are at increased malignancy risk.[25]

Low-dose CT screening studies have raised issues concerning false-positive findings, cost-effectiveness, over-diagnosis, quality of life, and unnecessary surgical procedure expense, morbidity and mortality, radiation overexposure, and length of follow-up period.[1,26,27] In addition, early detection of lung cancers in the US is less than 15%. Most clinical presentations are during advanced stages of disease, with only 12% of patients presenting at stage I lesions, and 15% at stage II cancers.[28] Thus, effective screening strategies can be beneficial for lung cancer survival and mortality rates.[28] Currently, no organization mandates regular screening for lung cancer, with the general population or with individuals at higher risk due to exposure to tobacco or type of occupation.[29]

This report has evaluated a large cohort of patients at high risk for lung cancer by using screening with low-dose spiral computed tomography (CT) of the chest to determine adherence to the 2005 and 2015 Fleischner Society guidelines. These guidelines are applied in a community hospital setting and the subsequent radiologic findings are assessed. In addition, characteristics of nodules are evaluated to determine risk of malignancy as compared with previous studies.

2. Methods

2.1. Oversight

During January 2012 to December 2016, 176 subjects in Monmouth County, New Jersey underwent LDCT for lung cancer screening at Monmouth Medical Center, Long Branch, New Jersey, USA. Due to institutional policy, ethical approval and informed consent was taken for this retrospective chart review study.

2.2. Study participants

A retrospective cohort study was performed with 176 individuals that were enrolled and underwent baseline (prevalence) CT. We included subjects in the following criteria: (i) men and women, aged 55–75; (ii) former cigarette smokers who smoked at least 30 packs per year, and quit within the last 15 years; (iii) had no history of cancer within the last 5 years; and (iv) had no previous CT chest scan performed. Applicants that were ineligible had a history of any cancer within 5 years other than non-melanomatous skin cancer, cervical cancer in situ, or local prostate cancer. The mean (SD, range) year age for this cohort was 65, of which 95 subjects were male and 81 female (Table 1). Nodules were classified as single or multiple, and by initial size of the largest nodule where multiple.

2.3. Imaging and image review

Patients went through three annual low-dose CT abdomen and chest examinations. Characteristics of pulmonary nodules and additional findings were thereafter tabulated and analyzed. Their follow-up protocol was calculated using the 2005/2013 Fleischner criteria. It was assumed that all nodules were stable in size and that

Table 1
Demographic Features of 176 subjects.

Demographic features	Values
Mean age (yrs)	65
Sex: Male	95
Sex: Female	81
Total follow-up period of CT (number of years)	4
Median follow-up	2.1 (range, 3 months to 4 years)
Mean time lost to follow-up	0.5 and 1.25 years

volume analysis was done. Participants with outstanding lesions (i.e., nodule size >10 mmin diameter) were transferred to a pulmonologist for further evaluation by way of biopsy, PET/CT or short-term follow-up procedures.

In order to use the Fleischner Society guidelines, a proper CT chest must be obtained. First, a thin section (1 mm thickness) of CT was used. Second, the ground-glass component was assessed using the lung window setting, and the solid component was assessed with the mediastinal window setting. Finally, an electronic caliper was used to make bi-dimensional measurements.[14]

The participants' radiology reports were collected and the number of incidental pulmonary nodules with the description was tabulated. All CT images were then reviewed by two radiologists in Monmouth Medical Center to find any true nodules. Patient records, radiology reports, death certificates, and surgical reports were used as sources to study the patients and evaluate their demographics, smoking history, oncology history, and pre-existing pulmonary nodules.[1,4]Next, another thoracic radiologist analyzed the CT images for morphology and size of the subcentimeter nodules.

2.4. Data recording

Findings of the nodules were assessed for nodule size (maximum diameter), nodule growth or stability, nodule location (central and peripheral), nodule position (subpleural, perifissural, parenchymal), nodule attenuation (solid, GGN), nodule shape (round, non-round), nodule margin (smooth, lobulated, spiculated), and additional findings.[1,30]

Nodule diameter was calculated by the average of the length and width of the largest nodule's cross-sectional area. Nodule consistency was considered as solid if the nodule entirely covered the lung parenchyma, partly solid if it partially covered the lung parenchyma, and nonsolid if it did not cover the parenchyma. If the nodules displayed no resolution or growth, biopsy was done, or workup ended.[30] According to our recommendations, CT scans were performed at 3, 6, 18 and 30 months from the index scan.[31]

Abenign nodule was defined as displaying a benign calcification pattern (e.g., fully calcified or popcorn calcification) or having unchanged size of a solid nodule for at least 2 years. Nodules not meeting this protocol were radiologically indeterminate.[1]

2.5. Follow-up and recommendations

CT reports and a physician's letter were sent to the respective participants and their primary physicians. Interval scans for nodule follow-up were obtained, and recommendations were followed first using the 2005 guidelines, including: nodules less than 4 mm required CT in 6 months; nodules 4–8 mm required CT in 3 months; nodules 8–20-mm required CT as soon as possible, with CT nodule enhancement protocol or positron emission tomography; and nodules larger than 20 mm required biopsy.[1]

Follow-up CT examinations also took into account the 2013 Fleischner recommendations, including: 1) solitary, pure GGNs of 5 mm or less did not require follow-up; 2) solitary, pure GGNs larger than 5 mm needed an initial follow-up within three months, with annual surveillance for at least three years for persistence and change; 3) solitary part-solid GGNs with solid component greater than 5 mm were considered malignant unless no growth or change was observed after three months. For part-solid GGNs of 8–10 mm, positron-emission tomography (PET) scan was advised, and biopsy or surgery recommended in some cases. Part-solid GGNs with a solid portion $\leq$5 mm needed yearly surveillance for at least three years. Also, 4) multiple GGNs of 5 mm or less were normally managed with follow-up at two and four years; and 5) multiple pure GGNs larger than 5 mm without a dominant lesion required an initial follow-up at three months, with yearly surveillance for at least three years.[17,32,33] A team of research coordinators contacted all participants at least two times per year, and recorded all data in the database.

3. Theory/calculation

Findings were reported using descriptive summary statistics. Also, the Student's t-test and Chi-square test were used to evaluate the varying parameters and malignancy incidence rates between solid nodules and GGNs. Each scenario used the Fleischner guidelines to ascertain the proper management response. All statistical analyses were done and figures were made using the commercially available software (GraphPad Software; San Diego, CA, USA). Normally distributed data used means and standard deviation, while skewed distribution data used medians with upper and lower quartiles. Proportions were displayed as percentages. A P-value of <0.05 indicated statistical significance, and all P values were two-sided, unless otherwise indicated.

4. Results

4.1. Study participants

A total of 176 persons were enrolled in this study. At the time of the current analysis, the median overall follow-up was 2.1 years (range, 3 months to 4 years).All patients undergoing a thorax CT were between 55 and 75 years of age (median age 65), which was the age criterion for the National Lung Cancer Screening Trial (NLST). During this period, 59 participants (34%) were lost to follow-up. The mean time until loss to follow-up among participants without nodules and those with nodules was 0.5 and 1.25 years, respectively (Table 1).

4.2. CT findings of pulmonary nodules: measurements

During the 4 years of annual screenings, incidental pulmonary nodules were identified in 117 (66.5%) of the 176 patients, with a median age of 62 years (range 55–75). In the 117 patients with nodules, a total of 210 uncalcified pulmonary nodules (including multiple and new nodules) were identified. According to the 2005 Fleischner guidelines, 59.5% (125/210) were $\leq$ 4 mm, 25.7% (54/210) were >4–6 mm, 8.5% (18/210) had nodules >6–8 mm, and 5.7% (12/210) had nodule >8 mm (2005 guidelines). According to the 2013 guidelines, 18 nodules that identified as ground-glass (GGN) and subsolid, and 8/210 (3.8%) were solitary pure GGN $\leq$5 mm, 5/210 (2.4%) were solitary pure GGNs (>5 mm), 2/210 (1.0%) were solitary part-solid nodules, and 3/210 (1.4%) were multiple subsolid nodules (Fig. 1).

The majority of nodules (91.4%, 192/210) were solid in nature. Nonsolid and part-solid nodules accounted for 6.2% and 2.4% of nodules (total 8.6%), respectively (Table 2). The remaining nodules were perifissural, which were not malignant. Fifty-two subjects

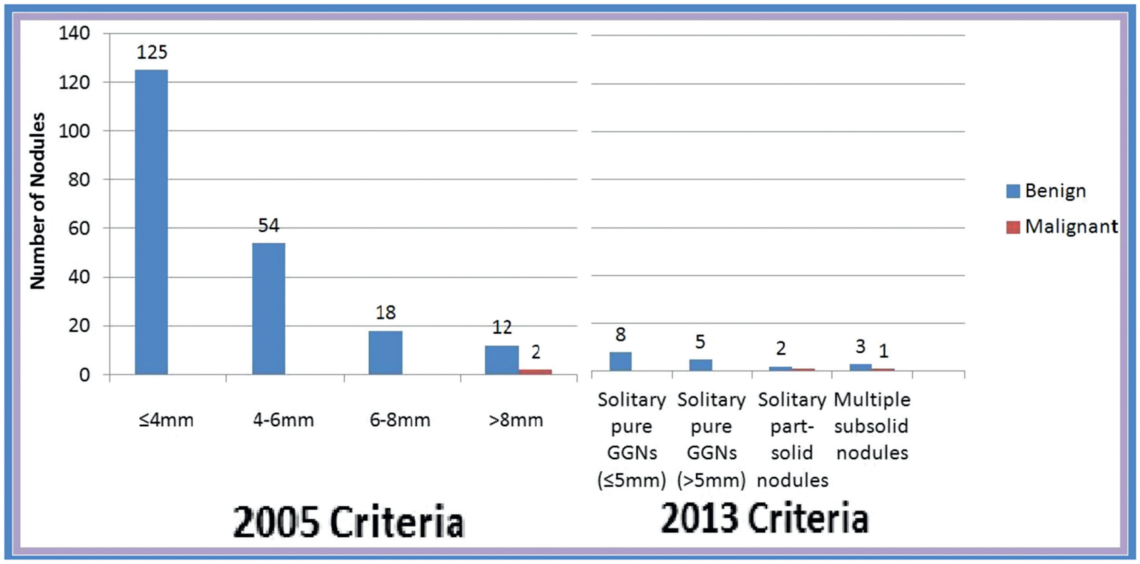

Fig. 1. Characteristics of 210 Detected Nodules using 2005 and 2013 Fleischner Criteria.

Table 2
CT features of 210 nodules detected at baseline screening CT.

Nodule features	Number(n = 210)	P-value
Attenuation of nodule		
Solid	192 (91.4%)	
GGN/SSN	18 (8.6%)	
a) Solitary	a)15 (7.1%)	
b) Multiple	b)3 (1.4%)	
Nodule shape		
Round	164 (78.1%)	
Non-round	46 (21.9%)	
Nodule margin		
Smooth	132 (62.9%)	
Lobulated	71 (33.8%)	P = 0.001[a]
Spiculated	7 (3.3%)	P = 0.001[a]
Location		
Central	36 (17.1%)	
Peripheral	174 (82.9%)	
Position		
Parenchymal	33 (15.7%)	
Subpleural	120 (57.1%)	P < 0.001[a]
Perifissural	57 (27.1%)	P < 0.001[a]
2013 Fleischner criteria:		
Solitary pure GGNs (≤5 mm)	8 (3.8%)	
Solitary pure GGNs (>5 mm)	5 (2.4%)	
Solitary part-solid nodules	2 (1.0%)	
Multiple subsolid nodules	3 (1.4%)	

CT, computed tomography; GGN, ground-glass nodule; SSN, subsolid pulmonary nodule.
[a] Student t-test.

(45.3%) had a single nodule, while 65 subjects (54.7%) had multiple nodules (range 2–5). The median nodule size was 3.6 mm (interquartile range 4 mm).

Characteristics of identified nodules are presented in Table 2. The nodules were round in shape in 78.1% (164/210) and had smooth margins in 62.9% (132/210). In terms of location, most subcentimeter nodules were located in the peripheral (82.9%, 174/210) areas. The mean size of all nodules was 4.5 mm (range, 2–20.1 mm) in diameter and 37.6% (79/210) were 5 mm or larger (2013 guidelines). GGNs were larger than solid nodules in size and volume (P < 0.0001) (Table 3).There was no difference in shape, but the margins were different between the two groups. GGNs tended to have more spiculated or lobulated margins (P = 0.001). In terms of location, solid and GGNs had no statistical differences, but subpleural and perifissural nodules were more common in the solid group (P < 0.001) (Table 2).

4.3. CT follow-up and adherence to Fleischner guidelines

All 176 participants were new patients without prior CT chest exam, with no previous lung nodule found. Ten (8.5%) had one or more new nodules, although none of these new nodules was present in retrospect on the baseline CT scans. Additionally, none of these new nodules was present in retrospect on scans from either the baseline or the first annual CT examinations. The findings were considered clinically important if they required further evaluation (e.g., an adrenal mass) or had substantive clinical implications (e.g., aortic aneurysms).

Most (95%) of the 210 solid nodules which were stable during the initial 2-year follow-up period had no change in size during the remaining 2-year follow-up period. Overall, 104 of the 117 required follow-up according to the Fleischner Society recommendations. Of patients requiring follow-up (n = 104), 48 (41%) of those patients (27% of total cohort) with incidental pulmonary nodules had pending results and require further follow-up. There were no follow-up data for 59, of whom 40 had refused subsequent follow-up, and 19 were discussed at MMC (but no more proposed). In terms of compliance with Fleischner guidelines, 82.05% (96/117) followed the guidelines, whereas 17.9% (21/117) had undergone unnecessary follow-up CT scans, including those with solitary pure GGNs.

4.4. Prevalence of lung cancer and management recommendations

Of the entire cohort, two had malignant disease due to increased size or number, or because the nodule was persistent. One patient had a part-solid nodule of 10.2 mm, and the other had a multiple subsolid GGN of 20.1 mm. Seven patients had nodules larger than 8 mm (2005 criteria), and two of them had malignant disease (2/7, 28.5%). Both were diagnosed with lung cancer, with one status post right upper lobe and left upper lobe lobectomy, and the other one with right lower lobe lobectomy. Of these two cases, one was identified at baseline (prevalence) CT examinations, and the other at subsequent annual (incidence) CT examinations. The prevalence

Table 3
Comparison of features between solid and ground-glass subcentimeter nodules at baseline CT.

	Solid nodules (n = 192)	Ground-glass nodules (n = 18)	P-values
Size (mm)			
Mean ± SD	4.3 ± 2.5	9.2 ± 7.3	<0.0001[a]
Median(min, max)	4 (2, 20.1)	9 (5, 20.1)	
Volume (mm3)			
Mean ± SD	35 ± 65.2	360 ± 93.5	<0.0001[a]
Median(min,max)	73 (10, 1400)	354 (35, 1365)	

SD, standard deviation.
[a] Student t-test.

of lung cancer in the entire group was 1.1% (2/176), and the prevalence of lung cancer in patients with nodules was 1.7% (2/117).

5. Discussion

Previous lung cancer prediction models were hospital-based or clinic-based with a high lung cancer prevalence rate of 23–75%, while this study was community-based with a 1.1% (2/176) malignancy rate in the NLST age group.[34–36] In addition, malignancy rates of solid, semi-solid, and ground-glass nodules was significantly higher than the malignancy rates found in this study (Table 4). It is important to note that the true prevalence may be underestimated, since 48/117 patients required further evaluation and did not have follow-up data accessible to analyze. The amount of subjects lost to follow-up (59/176, 34%) is likely to be significantly higher if smaller nodules were included, emphasizing how important it is to use a systematic approach for follow-up of incidental findings. While screening proved effective in reducing mortality, it was more beneficial for high-risk patients than low-risk patients, as 91% of patients with solid nodules and 59.5% of nodules less than 4 mm were all benign.[37]

Currently, follow-up protocol is based on the size of the largest lesion and changes based on whether the lung nodule is solid, part-solid, or nonsolid. Our study showed that the largest lung nodule was one of the malignant nodules.[8,14,38] Significant predictors for malignancy include older age, current or past smoking history, and extra-thoracic malignancy more than 5 years before detecting nodule.[24] Nodule characteristics linked with higher chance of malignancy are size, spiculation, non-round, central or upper lobe location, and parenchymal position (Table 5).[34] Solid nodules that are stable for more than 2 years or have a benign pattern of calcification require no further work-up. Management is based on nodule size and its risk for malignancy. Patients with no history of cancer and nodules 4 mm or smaller had 0% malignancy, and no further assessment was required (Table 4). For nodules 5–8 mm, serial reassessment is based on nodule size and the clinical risk for malignancy, with more frequent follow-up CT scans for patients with a high risk for malignancy.[39] One study reported that subsolid nodules had a solid component, with more than 50% linked with an increased risk for nodal metastatic disease.[40] For patients with a subsolid lesion, the first 3-month follow-up determines persistence, as infection or inflammation from lesions may resolve in the interval.[8]

Table 5
Characteristics of malignant nodules (n = 2).

Nodule features	Malignant (n = 2)
NODULE ATTENUATION	
Solid	0
GGN/SSN	
Solitary	1
Multiple	1
NODULE SHAPE	
Round	0
Non-round	2
NODULE MARGIN	
Smooth	0
Lobulated	0
Spiculated	2
LOCATION	
Central	2
Peripheral	0
POSITION	
Parenchymal	1
Subpleural	0
Perifissural	1

The strength of the current study is that this is the first investigation of participants with a 30-pack-year history, whereas all other studies focus on participants with 20-pack-year history.[8] However, our findings are perhaps limited since one determines whether the SSN or its solid component is $\leq$ 5 mm or >5 mm. In addition, it is important to classify solid pulmonary nodules into four size categories (<4 mm, 4–6 mm, 6–8 mm and <8 mm), where a similar measurement technique is used.

Our results bring hope that CT screening can be effective in reducing mortality from lung cancer. However, it also raises concern for potential overdiagnosis which could be more harmful, as 21 patients underwent unnecessary CT scans which was no compliant with Fleischner criteria. Symptomatic lung cancer tends to be advanced-stage disease (stage III or stage IV). Overall, low-

Table 4
Comparison of this study's malignancy rate with previous studies (Henschke et al. and Li et al.).

	Solid nodules incidence	Solid nodules malignant	Semi-solid nodules incidence	Semi-solid nodules malignant	Ground glass nodules incidencE	Ground glass nodules malignanT	P-value
Henschke et al.	189/233 (81%)	7%	16/233 (7%)	63%	28/233 (12%)	18%	[a]P < 0.0001
Li et al.	137/222 (62%)	11%	56/222 (25%)	48%	29/222 (13%)	59%	[a]P < 0.0001
Current Study Observations	192/210 (91.4%)	0%	5/210 (2.3%)	20%	13/210 (6.2%)	7.7%	

[a] Chi-Squared test.
SOURCES: [13]: Henschke CI, Yankelevitz DF, Mirtcheva R, McGuinness G, McCauley DI, Miettinen OS. CT screening for lung cancer: frequency and significance of part-solid and nonsolid nodules. AJR 2002; 178:1053–7.[43]: Li F, Sone S, Abe H, Macmahon H, Doi K. Malignant versus benign nodules at CT screening for lung cancer: comparison of thin-section CT findings. Radiology 2004; 233:793–8.

dose CT screening for lung cancer allows for earlier detection and lower mortality.[1]

5.1. Additional findings

All low-dose CT chest scans required further diagnostic testing and/or intervention.[1] Factors that enhance compliance with Fleischner criteria could potentially reduce the number of unnecessary follow-up CT examinations, since previous scientific evidence showed that the follow-up of very small nodules prior to one year is unproductive, even with high-risk smokers.[41] Furthermore, previous CT studies have not provided conclusive evidence that early intervention for detected cancers can lower disease-specific mortality, even in high-risk patients. Thus, follow-up CT scans should not be recommended for every small indeterminate nodule.[42,43]

5.2. Limitations

This study does have certain limitations. First, its limited patient population resulted in poor generalizability of the results and decreases the power of the study. In addition, since this was a retrospective study, not all patients with pulmonary nodules received follow-up due to loss of patient data or patient failure to show up. Instead, only 66% of patients revisited Monmouth Medical Center for 2–4 years. Thus, our data and LDCT follow-up methods defined in this study may not be used to make conclusions about standard guidelines for screen-detected small nodule evaluation.

Data collection required availability and accuracy of radiology reports and medical records. Although all important incidental findings are assumed to be reported, under-reporting of such information could cause greater prevalence of incidental pulmonary nodules. Incomplete medical records make it difficult to determine smoking history.[4] In addition, the most important factor is the danger of overdiagnosis of lung cancer due to unnecessary CT scans. Since subsolid nodules are frequently found in daily clinical practice, a current set of Fleischner recommendations are required. Further refinements and modifications to these recommendations will be coming from information discovered in ongoing research.[14]

6. Conclusion

In conclusion, this study emphasizes the need for new Fleischner guidelines to reduce over-diagnosis, unnecessary follow-ups, cost, and radiation dose. This will more accurately estimate the risk of malignancy. Although most such nodules are benign, lung cancer is an important factor in the differential diagnosis of SPNs. To initiate quick and proper treatment, SPNs should be correctly distinguished based on malignant and benign lesions.[22] Nodules over 8 mm were more likely to be cancerous (28.5% in this study). The results of this study should bring awareness of the Fleischner guidelines to radiologist, and limit the number of unnecessary follow-up CTs and invasive procedures for benign pulmonary nodules. The gap between awareness and implementation of these evidence-based guidelines should be bridged.[9]Data show that we conform to the Fleischner guidelines in 82% of the cases, 27% required further specific investigation, and that 1.1% had malignant disease. Although this is a small number, the practice of follow-up is necessary and stricter adherence to protocol is necessary. Although awareness of the Fleischner recommendations is widespread, both over- and undermanagement are common.

Conflict of interest

The authors have no conflict of interest to declare.

References

1. Swensen SJ, Jett JR, Hartman TE, et al. Lung cancer screening with CT. *Mayo Clin Exp Radiol*. 2003;226:756–761.
2. Shin KE, Lee KS, Yi CA, Chung MJ, Shin M, Choi Y. Subcentimeter lung nodules stable for 2 years at LDCT: Long-term follow-up using volumetry. *Respirol*. 2014;19:921–928.
3. Rampinelli C, Calloni SF, Minotti M, Bellomi M. Spectrum of early lung cancer presentation in low-dose screening CT: a pictorial review. *Insights Imag*. 2016;7:449–459.
4. Hammerschlag G, Cao J, Gumm K, Irving L, Steinfort D. Prevalence of incidental pulmonary nodules on computed tomography of the thorax in trauma patients. *Intern Med J*. 2015;45:630–633.
5. Chirikos TN, Hazelton T, Tockman M, Clark R. Screening for lung cancer with CT; a preliminary cost-effectiveness analysis. *Chest*. 2002;121:1507.
6. Ost DE, Gould MK. Decision making in patients with pulmonary nodules. *Am J RespirCrit Care Med*. 2012;185:363–372.
7. Mets OM, de Jong PA, Chung K, Lammers JJ. Fleischner recommendations for the management of subsolid pulmonary nodules: high awareness but limited conformance – a survey study. *Eur Radiol*. 2016;26:3840–3849.
8. MacMahon H, Austin JHM, Gamsu G, et al. Guidelines for management of small pulmonary nodules detected on ct scans: a statement from the fleischner society. *Radiol*. 2005;237:395–400.
9. Eisenberg RL, Bankier AA, Boiselle PM. Compliance with fleischner society guidelines for management of small lung nodules: a survey of 834 radiologists. *Radiol*. 2010;255:218–224.
10. Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med*. 2011;365:395–409.
11. Esmaili A, Munden RF, Mohammed TH. Small pulmonary nodule management a survey of the members of the society of thoracic radiology with comparison to the fleischner society guidelines. *J Thorac Imaging*. 2011;26:27–31.
12. Choromańska A, Macura KJ. Evaluation of solitary pulmonary nodule detected during computed tomography examination. *Pol J Radiol*. 2012;77:22–34.
13. Henschke CI, Yankelevitz DF, Mirtcheva R, McGuinness G, McCauley DI, Miettinen OS. CT screening for lung cancer: frequency and significance of part-solid and nonsolid nodules. *AJR*. 2002;178:1053–1057.
14. Naidich DP, Bankier AA, Macmahon H, et al. Recommendations for the management of subsolid pulmonary nodules detected at CT: a statement from the Fleischner society. *Radiol*. 2013;266:304–317.
15. Lee HY, Lee KS. Ground-glass opacity nodules: histopathology, imaging evaluation, and clinical implications. *J Thorac Imaging*. 2011;26:106–118.
16. Murrmann GB, van Vollenhoven FHM, Moodley L. Approach to a solid solitary pulmonary nodule in two different settings—"Common is common, rare is rare.". *J Thorac Dis*. 2014;6:237–248.
17. Viggiano RW, Swensen SJ, Rosenow EC. Evaluation and management of solitary and multiple pulmonary nodules. *Clin Chest Med*. 1992;13:83–95.
18. Wahidi MM, Govert JA, Goudar RK, Gould MK, McCrory DC. American College of Chest Physicians. Evidence for the treatment of patients with pulmonary nodules: when is it lung cancer ?: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest*. 2007;132:94S–107S.
19. Bellomi M, Veronesi G, Rampinelli C, Ferretti S, De Fiori E, Maisonneuve P. Evolution of lung nodules 5or ¼5mm detected with low-dose CT in asymptomatic smokers. *Br J Radiol*. 2007;80:708–712.
20. Heuvelmans MA, Oudkerk M, de Bock GH, et al. Optimisation of volume-doubling time cutoff for fast-growing lung nodules in CT lung cancer screening reduces false-positive referrals. *Eur Radiol*. 2013;23:1836–1845.
21. John HM, Austin. The incidental small pulmonary nodule and the fleischner criteria 5 years later have we learned anything more? *J Thorac Imaging*. 2011;26:88–89.
22. Park CM, Goo JM, Lee HJ, Lee CH, Chun EJ, Im JG. Nodular ground-glass opacity at thin-section CT: histologic correlation and evaluation of change at follow-up. *Radiographics*. 2007;27:391–408.
23. Park CM, Goo JM, Lee HJ, Lee CH, Chun EJ, Im JG. Focal interstitial fibrosis manifesting as nodular ground glass opacity: thin-section CT findings. *Eur Radiol*. 2007;17:2325–2331.
24. Herder GJ, van Tinteren H, Golding RP, et al. Clinical prediction model to characterize pulmonary nodules: validation and added value of 18F-fluorodeoxyglucose positron emission tomography. *Chest*. 2005;128:2490–2496.
25. Gurney JW, Lyddon DM, McKay JA. Determining the likelihood of malignancy in solitary pulmonary nodules with bayesian analysis. II. Application. *Radiology*. 1993;186:415–422.
26. van Klaveren RJ. Is CT screening for lung cancer ready for prime time? *J Thorac Imaging*. 2011;26:4–5.
27. Bach PB,Mirkin JN, Oliver TK, et al. Benefits and harms of CT screening for lung cancer: a systematic review. *JAMA*. 2012;307:2418–2429.
28. Wagner H, Ruckdeschel JC. Lung Cancer. In: Reintgen DS, Clark RA, eds. *Cancer Screening*. St. Louis, MO: Mosby; 1996:118–149.
29. Smith RA, Mettlin CJ, Davis KJ, Eyre H. American Cancer Society guidelines for the early detection of cancer. *CA Cancer J Clin*. 2000;50:34–49.
30. Henschke CI, Yankelevitz DF, Libby DM, Pasmantier MW, Smith JP. Survival of patients with stage I lung cancer detected on CT screening. *N Engl J Med*. 2006;355:1763–1771.
31. Reichmann MT, Edwards D, Sivaloganathan A, Drury A, Laws D. P168 outcome of a pragmatic protocol for CT lung nodule surveillance in a UK district general

hospital. *Thorax*. 2012;67:A1–A204.
32. Kim H, Park CM, Koh JM, Lee SM, Goo JM. Pulmonary subsolid nodules: what radiologists need to know about the imaging features and management strategy. *Diagn Interv Radiol*. 2014;20:47–57.
33. McWilliams A, Tammemagi MC, Mayo JR, et al. Probability of cancer in pulmonary nodules detected on first screening CT. *N Engl J Med*. 2013;369: 910–919.
34. Swensen SJ, Silverstein MD, Ilstrup DM, Schleck CD, Edell ES. The probability of malignancy in solitary pulmonary nodules: application to small radiologically indeterminate nodules. *Arch Intern Med*. 1997;157:849–855.
35. Gould MK, Ananth L, Barnett PG. A clinical model to estimate the pretest probability of lung cancer in patients with solitary pulmonary nodules. *Chest*. 2007;131:383–388.
36. Schultz EM, Sanders GD, Trotter PR, et al. Validation of two models to estimate the probability of malignancy in patients with solitary pulmonary nodules. *Thorax*. 2008;63:335–341.
37. Kovalchik SA, Tammemagi M, Berg CD, et al. Targeting of low-dose CT screening according to the risk of lung-cancer death. *N Engl J Med*. 2013;369: 245–254.
38. Wood DE, Eapen GA, Ettinger DS, et al. Lung cancer screening. *J Natl Cancer Compr Netw*. 2012;10:240–265.
39. Patel VK, Naik SK, Naidich DP, et al. A practical algorithmic approach to the diagnosis and management of solitary pulmonary nodules: part 2—pretest probability and algorithm. *Chest*. 2013;143:840–846.
40. Vazquez M, Carter D, Brambilla E, et al. Solitary and multiple resected adenocarcinomas after CT screening for lung cancer: histopathologic features and their prognostic implications. *Lung Cancer*. 2009;64:148–154.
41. Henschke CI, Yankelevitz DF, Naidich DP, et al. CT screening for lung cancer: suspiciousness of nodules according to size on baseline scans. *Radiol*. 2004;231:164–168.
42. Swensen SJ, Jett JR, Hartman T, et al. Screening for lung cancer with CT: mayo Clinic experience. *Radiol*. 2003;226:756–761.
43. Truong MT, Ko JP, Rossi SE, et al. Update in the evaluation of the solitary pulmonary nodule. *RadioGraphics*. 2014;34:1658–1679.