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Identification of Nonaggressive Pulmonary Nodules Using an Optimized Scoring System

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Purpose: The purpose of this study was to define the optimal scoring method for identifying benign intrapulmonary lymph nodes.

Materials and Methods: Subjects for this study were selected from the COPDGene study, a large multicenter longitudinal observational cohort study. A retrospective case-control analysis was performed using identified nodules on a subset of 377 patients who demonstrated 765 pulmonary nodules on their baseline computed tomography (CT) study. Nodule characteristics of 636 benign nodules (which resolved or showed <20% growth rate at 5 y follow-up) were compared with 51 nodules that occurred in the same lobe as a reported malignancy. Two radiologists scored each pulmonary nodule on the basis of intrapulmonary lymph node characteristics. A simple scoring strategy weighing all characteristics equally was compared with an optimized scoring strategy that weighed characteristics on the basis of their relative importance in identifying benign pulmonary nodules.

Results: A total of 479 of 636 benign pulmonary nodules had the majority of lymph node characteristics, whereas only 1 subpleural nodule with the majority of lymph node characteristics appeared to be malignant. Only 279 of 479 (58%) of benign pulmonary nodules with the majority of lymph node characteristics were intrafissural or subpleural. The optimized scoring strategy showed improved performance compared with the simple scoring strategy with average area under the curve of 0.80 versus 0.55. Optimized cutoff scores showed negative likelihood values for both readers of <0.2. A simulation showed a potential reduction in CT utilization of up to 36% for Fleischner criteria and up to 5% for LUNG-RADS.

Conclusions: Nodules with the majority of lymph node characteristics, regardless of location, are likely benign, and weighing certain lymph node characteristics greater than others can improve overall performance. Given the potential to reduce CT utilization, lymph node characteristics should be considered when recommending appropriate follow-up.

Key Words: pulmonary nodules, intrapulmonary lymph nodes, lung cancer screening

Since the introduction of computed tomography (CT) there has been an effort to classify pulmonary nodules as either benign or malignant.[1–3] Size has proven to be the most reliable metric in determining the probability that a pulmonary nodule may be malignant.[4] Additional characteristics studied have included growth rate, ground-glass attenuation, and irregular and round morphology.[5,6] In conjunction with this initial work came formalized methods for the management of pulmonary nodules: Fleischner Society guidelines for workup of incidental (non–screen-detected) pulmonary nodules[7,8] and LUNG-RADS screening criteria for pulmonary nodules detected for formal lung cancer screening.[9] The Fleischner Criteria Guidelines and LUNG-RADS use size and attenuation as the main characteristics for placing pulmonary nodules into categories that reflect the probability of malignancy. Although the Fleischner Guidelines also mention morphologic features of pulmonary nodules, these are not explicitly formalized in the algorithm summary. Classification algorithms for determining the likelihood that a pulmonary nodule is malignant using quantitative methods have also been proposed and could find their way into refined approaches for pulmonary nodule characterization.[10–14]

One of the concerns with incidentally detected lung nodules and nodules found during lung cancer screening is the inevitability of false positives. This could potentially lead to an increased number of follow-up CT scans, PET/CT scans, or biopsies. A major cause of false-positive nodules are intrapulmonary lymph nodes (IPLNs). Several studies have described the characteristics of IPLNs as generally subpleural or perifissural nodules with angular margins and lower lung predominance.[15–18] When present in a screening population or found incidentally in a patient without known malignancy, they are generally regarded as benign, as shown by a large retrospective study looking at 4026 such nodules.[19] IPLNs may also occur in other locations, and they are characterized by juxtapleural location, sharp margins, angular shape, being adjacent to bronchial bifurcations, and linear densities extending from the nodules representing ectatic lymphatic channels.[20–23] The use of some of these IPLN characteristics has been explored for distinguishing benign from malignant pulmonary nodules in small case studies with limited utility shown for patients with known malignancy.[17,24,25]

In this paper, we propose a lymph node score (LNS) using IPLN imaging characteristics to determine the likelihood that a pulmonary nodule is benign in a nononcologic setting. Subcategorizing these nodules on the basis of an optimal cutoff, we determine how these nodules changed over a 5-year period of time and how such categorization might impact the already defined Fleischner Criteria and LUNG-RADS.

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MATERIALS AND METHODS

Subjects for this study were selected from the COPDGene study, a large multicenter longitudinal observational cohort study. Written informed consent was obtained from each subject, and the study was approved by the institutional review boards of all 21 participating centers. Current and former smokers aged between 45 and 80 years, with ≥ 10 pack-year smoking history, with and without airflow obstruction, were enrolled.[11] Inclusion criteria also included non-Hispanic white or African American race; exclusion criteria included a history of other lung disease except asthma, prior surgical excision involving a lung lobe or greater, active cancer, metal in the chest, and history of chest radiation therapy. The original COPDGene cohort enrolled 10,192 individuals, and for the follow-up phase, subjects were invited to return for repeat CT examination at 5 years. Thin-section thoracic CT scans were acquired at full inspiration (200 mAs) at both visits (Regan et al,[26]). Lung cancer cases were identified through longitudinal telephonic follow-up (LFU) and collection of death certificates. During LFU, if a subject self-reported a new diagnosis of lung cancer, this was verified by review of medical records. In addition, the COPDGene Data Coordinating Center obtained vital statistics data retrieved from the National Death Index by subject Social Security Number. If the death certificate listed lung cancer as a cause of death, the subject was included as a case. Additional lung cancer annotation was performed for those cases in which pertinent medical records were available. Deidentified data were reviewed and verified for accuracy by a medical oncologist. If lung cancer was reported, it was confirmed by histologic records from the site, and the lobe where the cancer was found was recorded.

The current study is summarized in Figure 1 and is comprised of the following: (1) 360 randomly selected subjects who had nodules recorded on the baseline CT for the study, and who subsequently returned for a follow-up CT at 5 years, and who did not have a diagnosis of lung cancer (follow-up nodule group), and (2) 81 subjects who received a diagnosis of lung cancer over the course of the study (lung cancer group). Of those in the follow-up nodule group, 25 were excluded for the following reasons: no qualified nodules were visible on a review of baseline CT (n = 5), CT not available (n = 2), and all nodules were <4 mm in maximum diameter (n = 17). In the lung cancer group, 40 subjects were excluded for the following reasons: no nodules were visible on a review of baseline CT (n = 2), CT not available (n = 2), the lobar location of cancer not known (n = 19), and no visible nodule in the lobe of cancer (n = 17). This yielded a total population of 377 subjects (336 with no documented malignancy, and 41 with documented malignancy).

On review of chest CT scans in these individuals by a radiologist, a total of 765 solid and subsolid nodules were visible on their baseline CT examination. This equates to a little >2 nodules identified per scan. The 765 selected pulmonary nodules were then characterized independently by one cardiothoracic radiology fellow and a radiologist with 12 years of experience, using a standard scoring system, based on common features used to characterize pulmonary nodes including location, margin, shape, linear extension,
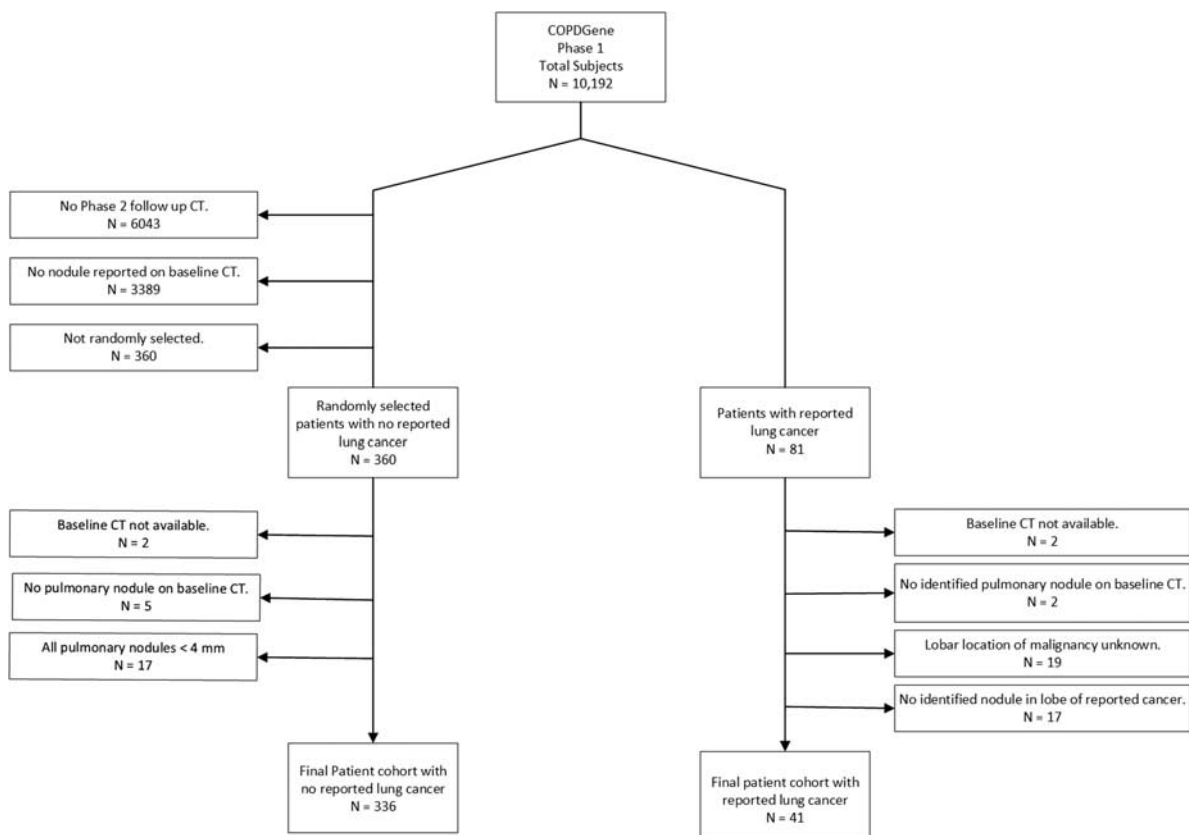

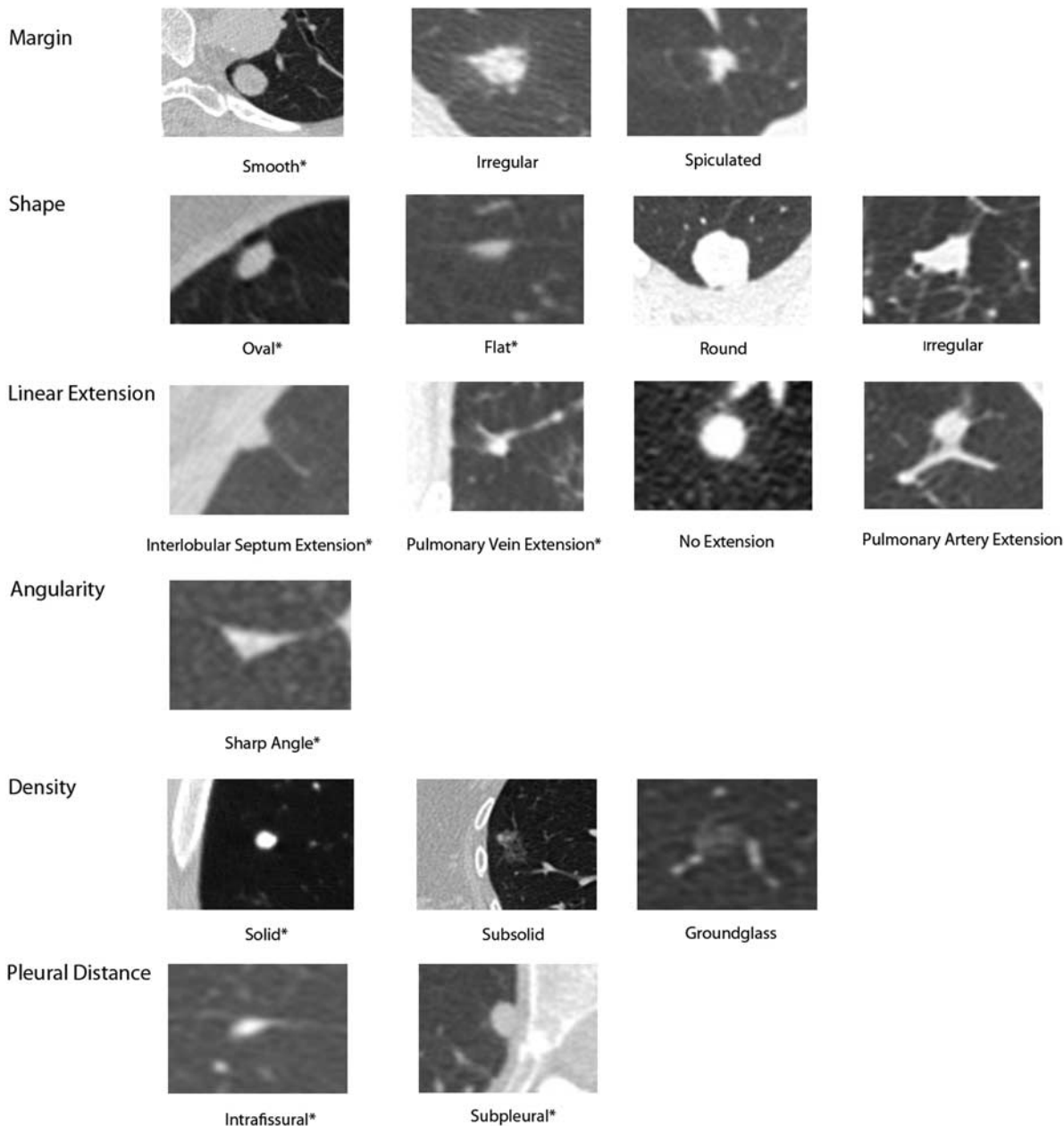**FIGURE 1.** Consort diagram for patient selection.

FIGURE 2. Nodule category types and features. *Features associated with intrapulmonary lymph nodes.

angularity, density, and pleural distance (Fig. 2). Nodules were measured in the anteroposterior, transverse, and craniocaudal planes.

Logistic regression was used to estimate the probability of benign diagnosis using differences in nodule characteristics found between patients without cancer (absence of reported malignancy after 5 y and no significant interval growth in nodules) and those with documented malignancy. The statistical model included a random subject effect (multiple nodules in a subject) and a random radiologist effect (multiple scores for each subject). Two LNS were also created. One LNS weighted all features the same, whereas the other weighted lymph node score (WLNS) was derived on the basis of a category's ability to differentiate presence or absence of

malignancy (Appendix A, Supplemental Digital Content 1, http://links.lww.com/JTI/A126). A weighted κ value was derived to evaluate consistency between readers.

Pulmonary nodules were categorized as true positive (TP), false positive (FP), false negative (FN), or true negative (TN) on the basis of the 2 derived LNS. Pulmonary nodules with LNS below the cutoff in a lobe of known malignancy were categorized as a TP. Pulmonary nodules with a LNS equal to or above the cutoff and either not in a lobe of documented malignancy or unchanged on a 5-year follow-up CT scan were considered TNs. Pulmonary nodules with LNS below the cutoff and not in a lobe of documented malignancy were considered FPs. Pulmonary nodules with LNS at or above the cutoff and located in a lobe of documented

TABLE 1. Demographic Information

	Noncancer	Cancer
N	336	41
Age (y)	61.5 (41-81)	64.2 (48-75)
Sex (n [%])		
Male	173 (51.5)	16 (39)
Female	163 (48.5)	25 (61)
Race (n [%])		
White	244 (72.6)	30 (73.1)
Other	92 (27.4)	11 (26.8)
Average ATS pack years (y)	46 (10-331)	54 (15-118)
Family history of lung cancer (n [%])	55 (16.3)	9 (22)

ATS indicates American Thoracic Society.

TABLE 3. Area Under the Curve for Standard and Weighted Lymph Node Scores at Both the Patient and Nodule Level

	Standard LNS		Weighted LNS	
	Reader 1	Reader 2	Reader 1	Reader 2
AUC (patient)	0.67	0.68	0.81	0.79
AUC (nodule)	0.59	0.49	0.84	0.77

malignancy were considered FNs. Pulmonary nodules located in a lobe of documented malignancy that were accompanied by at least one additional pulmonary nodule that had the opposite categorization on the basis of the cutoff score were excluded. Pulmonary nodules were also excluded if the location of cancer was unknown or not specific enough to categorize a nodule.

On the basis of TP, FP, FN, and TN values derived for various LNS and WLNS cutoff values, negative likelihood ratios (LRn) and receiver operator curve (ROC) curves were used to determine an optimal cutoff value for each score and area under the curve (AUC). Optimal cutoff values and associated LRn were also used to assess the utility of LNS and WLNS at various nodule sizes. We used LRn, as the majority of nodules were benign, inflating the negative predictive value, and we preferred a measurement independent of incidence.

To assess the potential impact on management, the total number of CTs during a 2-year period for the patient population was estimated using the normal Fleischner criteria and LUNG-RADS criteria, and the modified versions using the optimized LNS cutoff, which excluded nodules above the threshold (Appendix B, Supplemental Digital Content 1, http://links.lww.com/JTI/A126). For this analysis, all patients with nodules on baseline CT (430 total) were used irrespective of inclusion criteria. Derived values for both methods were used to determine percent change using both the LNS and WLNS over a 2-year time interval.

RESULTS

Breakdown of the population shows selected patients at high risk for lung cancer. The cancer subjects on average had greater risk factors than the noncancer group, as shown by the higher tobacco exposure in American Thoracic

TABLE 2. Combination of 2 Most Significant Features Extracted From Logistic Regression With Predicted Probability of the Nodule Being Benign

Shape	Border	Pr (Benign)	99% CI	P
Oval, flat	Smooth	0.95	0.93-0.98	0.001
	Lobulated	0.96	0.90-1.00	0.001
	Spiculated	0.82	0.6-1.00	0.01
Round, irregular	Smooth	0.9	0.81-0.98	0.001
	Lobulated	0.9	0.79-1.00	0.001
	Spiculated	0.65	0.35-0.96	0.22

CI indicates confidence interval.

Society pack years and a higher percentage of subjects' family history of lung cancer (Table 1). There was not a significant difference in the 2 groups on the basis of sex, race, or age.

As expected, initial logistic regression analysis showed size to be the dominant feature in determining the potential for a nodule to be benign or malignant. Logistic regression excluding size showed shape and border to be the strongest features for differentiating benign and potentially malignant nodules, with statistically significant *P*-values. Additional features not statistically significant in order of relevance were relationship to pulmonary vasculature, angularity, density, and pleural distance. Table 2 demonstrates the probability of a nodule being benign on the basis of the 2 most significant features. The covariance parameter estimate for the radiologist effect was 0 indicating, on average, the radiologists' scoring of CT characteristics was consistent using this model.

Weighted κ for the LNS and WLNS were 0.66 and 0.49, respectively. ROC analysis of the LNS and WLNS shows that overall AUC improved for both readers using the WLNS (Table 3). Optimal cutoff values for the LNS for the exclusion of benign nodules was 5, as shown by the ROC curve and derived LRn (Figs. 3A, 4A). Optimal cutoff values for the WLNS for the exclusion of benign nodules was 7, as shown by the ROC curve and derived LRn (Figs. 3B, 4B).

The LRn for various sized nodules at the optimal cutoff values is shown in Figure 4. The negative likelihood dramatically decreases for larger nodules (>8 mm) using the WLNS, as shown in Figure 5B, whereas the ratio is not significantly changed for smaller nodules (<8 mm).

There were a total of 479 benign nodules (<20% growth or resolved) on 5-year follow-up, which had at least 4 features of IPLNs. Of these, 279 (58%) were intrafissural or subpleural while 200 (42%) were not intrafissural or subpleural. A total of 379 (79%) were below the level of the carina while 100 (21%) were above the level of the carina. A total of 74 (15%) had a linear extension to the pleura, with only 4 of them showing multiple lines extending to the pleura.

The decreased average growth rate of nodules over 5 years correlated with increasing LNS and WLNS. For example, average growth rates for nodules over 5 years with LNS and WLNS below the optimized cutoff were between 45% and 100% and 36% and 112%, respectively, while average growth rates for nodules over 5 years with LNS and WLNS above the optimized cutoff were between 18% and 20% and 13% and 32%, respectively.

Many nodules showed increased size on 5-year follow-up in patients who did not have reported cancer. In all, there were 91 such patients (131 nodules) who had at least one nodule with >20% increase in maximum diameter after 5 years. Of these, 74 patients (81%) and 100 nodules (76%) had LNS less than optimized cutoff values. All but one nodule were under 1 cm in maximum dimension, with the
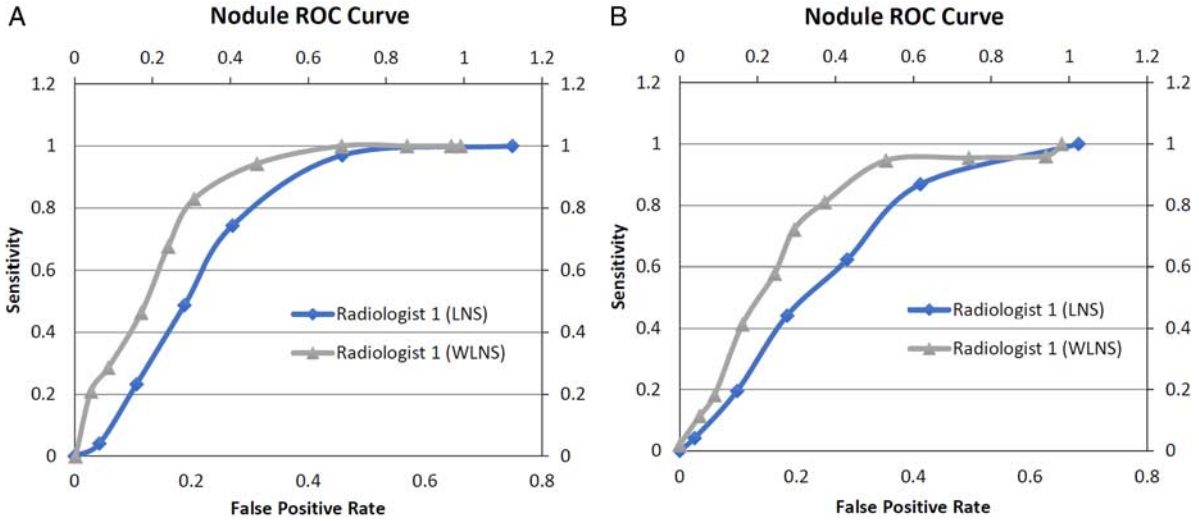
FIGURE 3. A, ROC comparison between the LNS and WLNS for the first radiologist. B, ROC comparison between the LNS and WLNS for the second radiologist. ROC indicates receiver operator curve.

one nodule measuring 1 cm in maximum diameter. There were 19 nodules that had a maximum dimension ≥ 1 cm and showed growth of > 20%. Of these, 18 (95%) had LNS less than the optimized cutoff values.

Using the optimized cutoff scores, the original CT studies were evaluated for change before and following the addition of the optimized LNS cutoff (Table 4). The percent change in management for the LNS showed a potential decrease in utilization of 36% using Fleischner Criteria and 5% using LUNG-RADS. The percent change in management for the WLNS showed a decrease of 22% and 4%, respectively.

DISCUSSION

Excluding size, logistic regression showed that border and shape were the strongest predictive variables for differentiating between benign and malignant nodules with good agreement between the 2 radiologists. This is born out in the improved performance of the WLNS versus the LNS and strongly argues against excluding nodules from

follow-up if they do not have smooth borders and have either a flat or oval shape.

Both LNS and WLNS demonstrate the ability to exclude pulmonary nodules from further follow-up. A high LNS was almost always associated with a benign-appearing nodule. Even in cases wherein the nodule had grown in size on a 5-year follow-up, it often maintained its lymph node characteristics (Figs. 6A, B). Conversely, up to 18 nodules with low LNS and subsequent growth showed changes concerning for malignancy (Figs. 6C, D).

Performance of WLNS is better than the LNS, as shown by the improved AUC for both readers. A specific example of improvement is shown in Figure 7, wherein both readers gave one of the eventual cancers a high LNS but a lower WLNS. While LNS and WLNS need to be relatively high to have confidence that a given nodule is truly a benign IPLN, derived cutoff values still impact management, as shown by the predicted decrease in CT utilization, and should not be ignored. This was in large part due to the high prevalence of such nodules shown on the baseline CTs.
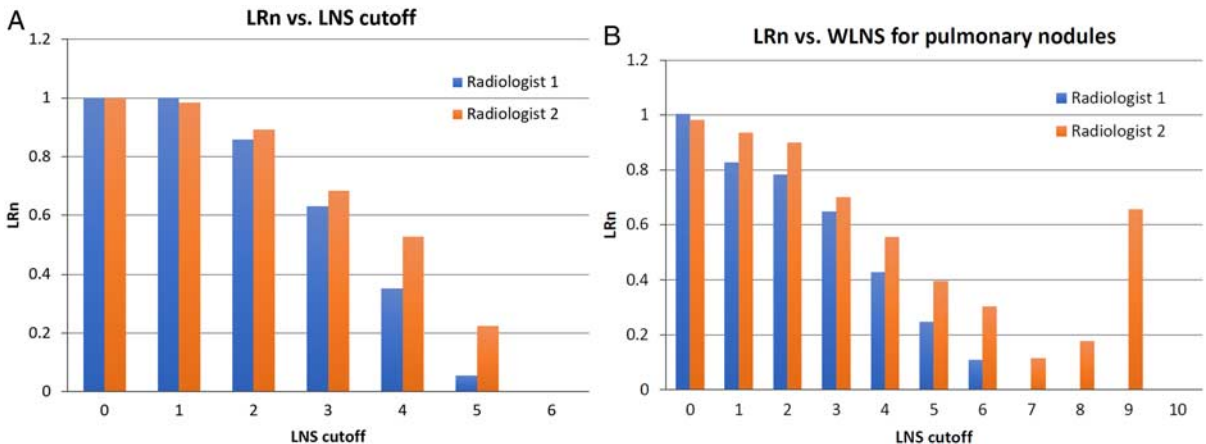

FIGURE 4. A, Comparison of negative log ratio (LRn) for various cutoff values of the LNS for each radiologist. B, Comparison of the negative log ratio (LRn) for various cutoff values of the WLNS for each radiologist.
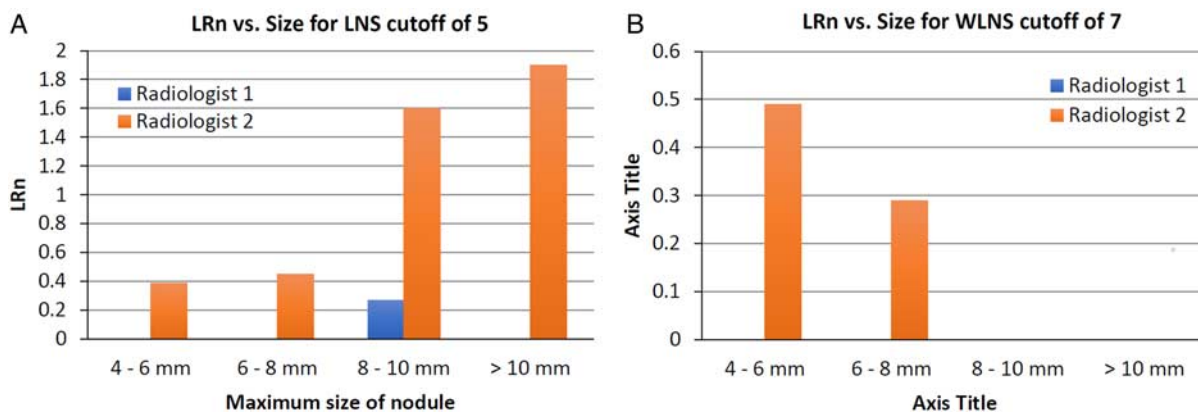
FIGURE 5. A, Comparison of the negative log ratio (LRn) for various sized nodules for each radiologist with a LNS cutoff value of 5. B, Comparison of the negative log ratio (LRn) for various sized nodules for each radiologist with a WLNS cutoff value of 7.

As expected, CT utilization impact was greater for Fleischner criteria compared with LUNG-RADS. This is primarily because LUNG-RADS recommends no specific follow-up for the majority of nodules, which can be followed-up on routine annual screening CT. It is also important to note that the original and updated Fleischner society guidelines recommend excluding IPLNs from consideration but are primarily focused on the perifissural and subpleural nodules. While this knowledge is common among most chest radiologists, some radiologists continue to treat these as pulmonary nodules. Depending on population assumptions and evolution of criteria, the impact of including pulmonary nodules with a high LNS or WLNS will vary.

The relative stability of LRn for the LNS across various lymph node sizes is expected given that it is not affected by prevalence. This is important to note, as the negative predictive value will naturally decrease with increasing size of a nodule, as it is well documented that the prevalence of malignancy will increase with size.[27] Interestingly, there appears to be improved performance of the WLNS for larger-sized nodules. This may be due to the easier characterization of the border and shape for larger nodules.

There is already evidence that suggests subpleural and interfissural nodules with additional lymph node characteristics should be excluded from further consideration as an incidental finding in patients without known malignancy.[19,28] This study reaffirms these findings with 5-year follow-up.

In addition, our study found that pleural distance was a poor indicator for benignity in isolation and that other characteristics were more important. Pulmonary nodules did not require a subpleural or intrafissural location to have high confidence that a nodule was benign—in fact, the distance from the pleura was not a significant discriminator between benign and malignant nodules in this study. The vast majority of the nodules characterized as benign in our study had characteristics of IPLNs, independent of subpleural location.

Our results are comparable to previous work that compared benign and malignant nodules, many of which also found spiculation of nodule border an important imaging feature to increase the probability of a nodule being malignant.[3,28,29] These studies did not take into account lymph node characteristics such as angularity and linear extension as a means to categorize nodules into a benign category and used extensive clinical data to improve the accuracy of their models that may or may not be available to the radiologist. Somewhat surprising is the ability of the WLNS to have relatively good AUC despite not including clinical factors or nodule size. There is potential these models could benefit by giving nodules with lymph node characteristics a much lower probability.

It is important to note that our study did not include nodules <4 mm in greatest dimension. Review of excluded nodules and patients on the basis of these criteria yielded no examples of nodules <5 mm that had the possibility of being a cancer. This was expected given prior results.[3,7,27]

TABLE 4. Results for Number of CT Scans Potentially Used on the basis of Existing Criteria With and Without LNS or WLNS

	No. CT Scans Used		
Category	**Fleischner**	**Fleischner + LNS**	**Fleischner + WLNS**
< 6 mm	114 (228 patients)	66 (132 patients)	83 (166 patients)
6-8 mm	112 (94 patients)	60 (50 patients)	68 (57 patients)
> 8 mm	140 (108 patients)	122 (94 patients)	132 (102 patients)
Total number of CTs	367	248	283
Percent reduction		32%	22%
	LUNG-RADS	**LUNG-RADS+LNS**	**LUNG-RADS+WLNS**
Category 2 (< 6 mm)	228	132	166
Category 3 (6-8 mm)	94	50	57
Category 4A (8-15 mm)	81	67	75
Category 4B (> 15 mm)	27	27	27
Total number of CTs	496	473	477
Percent reduction		5%	4%

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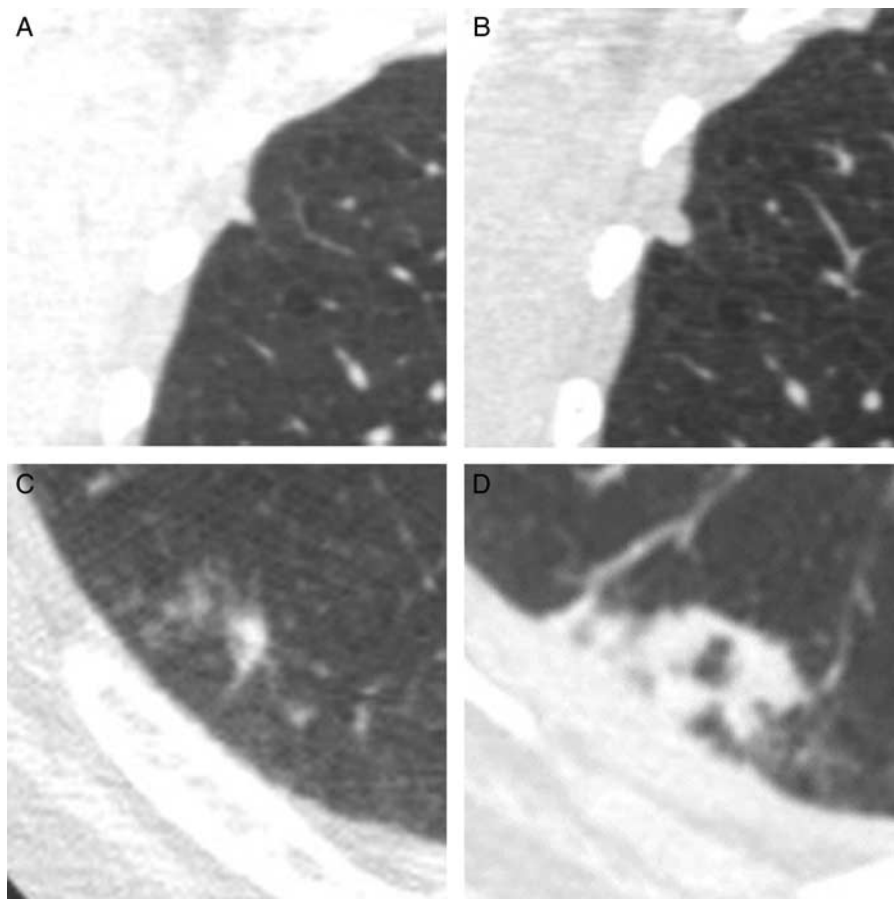
FIGURE 6. A, Initial CT image of pulmonary nodule categorized as a lymph node using both LNS and WLNS using cutoff values of 5 and 7, respectively. B, Same nodule at 5-year follow-up demonstrates an enlarged nodule maintaining lymph node characteristics and score in a patient without malignancy. C, Initial CT image of the nodule with low LNS and WLNS, making this unlikely an intrapulmonary lymph node. D, Same nodule on 5-year follow-up demonstrates increased size in a patient with no documented malignancy.

One of the limitations of this study was its retrospective, case-control design. We believe the size of the cohort, long duration of follow-up, and careful characterization of individuals within the cohort helped mitigate some of the potential biases associated with this type of study.

Another limitation of the study was the lack of specificity as to which nodule was the cancer in a given patient. While many nodules could be elucidated as the cancer from the known lobar location of the cancer, we were often not able to specifically identify which nodule was the cancer, usually because the lobar location of the cancer was not known. We took a more conservative approach to dealing with these nodules by excluding them from the study. We believe our results would have been stronger had we been able to specifically characterize what we believed were cancers on the basis of appearance. It is worth noting that the excluded patients who did not have a documented location of their cancer had at least one nodule with a LNS below the optimized cutoff values. Although we could not confirm it, we believe these nodules were the primary lung cancer.

Despite fair to good interreader agreement between radiologists, as suggested by the κ score and logistic regression model, there were differences in LNS between readers that affected the results. Reader 1 had a more conservative categorization of lymph nodes that resulted in decreased risk of FNs but fewer nodules being excluded and potentially more follow-up CT scans. Reader 2 had a more aggressive categorization, resulting in slightly increased risk of FNs, but a greater number of nodules being excluded. Differences may be partially mitigated by more automated methods for characterization.[11,14] This is particularly true for shape and border, as the WLNS that weighted these more heavily had a lower κ score than the LNS.

It would be ideal to apply our findings to an additional data set to have greater confidence in our findings. However, no comparable independent data set was available to us.

Finally, the impact on implementing LNS will depend on patient population. Some patient populations with a large number of granulomas or other benign nodules may not have the same impact as the studied population. However, the COPDGene study does include several sites with endemic pulmonary granulomatous infection. It will be important in future work to determine whether the time and effort to characterize these nodules are worth the effort if other types of nodules are present.

In conclusion, characterization of lung nodules using lymph node characteristics could help eliminate a substantial number of nodules from follow-up consideration that would potentially result in an overall reduction in CT
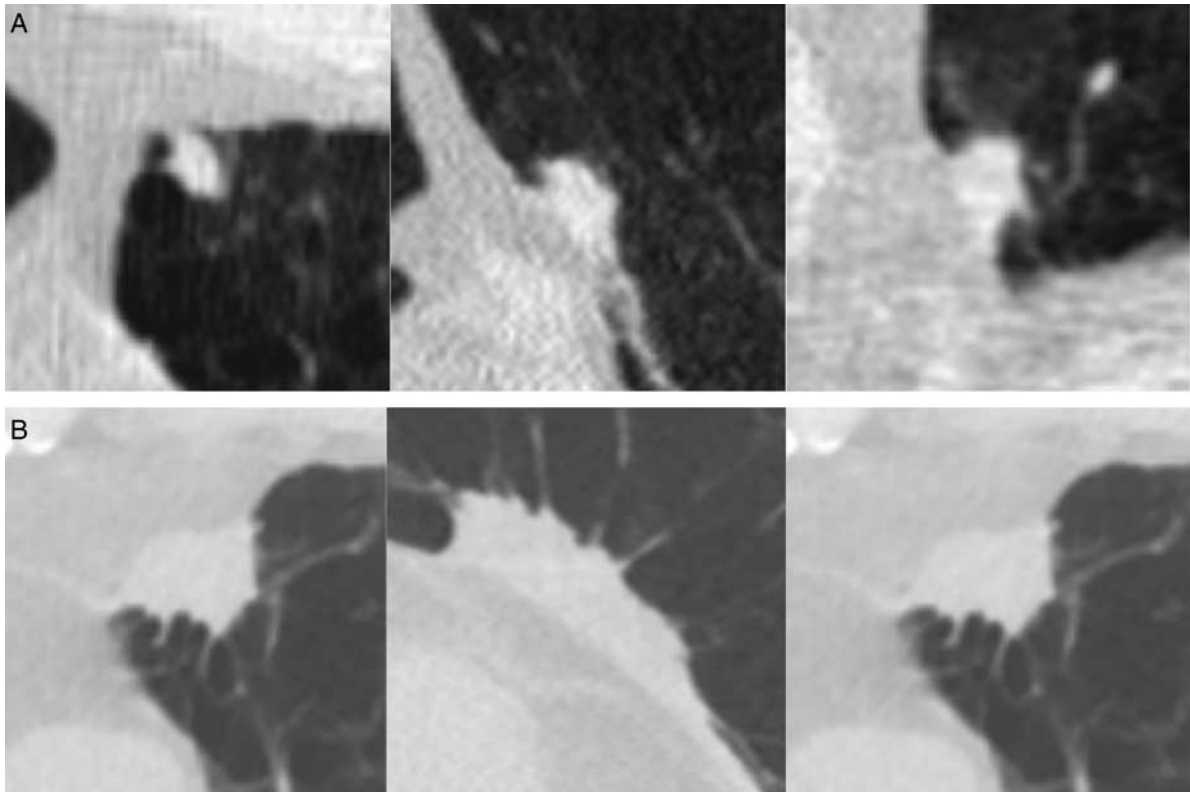
FIGURE 7. A, Initial CT image of a nodule categorized as an intrapulmonary lymph node using the LNS with a cutoff of 5 but excluded using the WLNS cutoff of 7. B, Same nodule at 5-year follow-up demonstrates a malignancy.

utilization. This would have a greater impact on current Fleischner criteria guidelines and a more modest impact on lung cancer screening using LUNG-RADS.

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