Radiology

ORIGINAL RESEARCH • THORACIC IMAGING

Radiologic Features of Nodules Attached to the Mediastinal or Diaphragmatic Pleura at Low-Dose CT for Lung Cancer Screening

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This report and the Initiative for Early Lung Cancer Research on Treatment–Mount Sinai Health System database have been funded in part by Simons Foundation International. The screenings in the International Early Lung Cancer Action Program pooled database have been supported in part by the National Institutes of Health (ROl-CA-633931 and ROl-CA-78905); Department of Energy (DE-FG02-96SF21260); City of New York Department of Health and Mental Hygiene; New York State Office of Science, Technology and Academic Research; American Cancer Society; Instituto de Salud Carlos III, Spain (PI 10/01652, PI 07/0792, and RD12/0036/0062); Starr Foundation; New York Community Trust; Rogers Family Fund; Foundation for Lung Cancer: Early Detection, Prevention, and Treatment (primary source from an unrestricted gift in 2000–2003 from the Vector Group, the parent company of Liggett Tobacco); Dorothy R. Cohen Foundation; Jacob and Malka Goldfarb Charitable Foundation; Auen Foundation; H.N. and Frances C. Berger Foundation; Mills-Peninsula Hospital Foundation; Tenet Healthcare Foundation; Ernest E Stempel Foundation; Academic Medicine Development Company (AMDeC); Columbia University Medical Center; Empire Blue Cross Blue Shield; Eastman Kodak; GE HealthCare; Weill Medical College of Cornell University; Cornell University; New York Presbyterian Hospital; Swedish Hospital; ChristianaCare Helen F. Graham Cancer Center; Holy Cross Hospital; Eisenhower Hospital; Jackson Memorial Hospital; and Evanston Northwestern Healthcare.

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Conflicts of interest are listed at the end of this article.

See also the editorial by Goodman and Baruah in this issue.

Radiology 2024; 310(1):e231219 • https://doi.org/10.1148/radiol.231219 • Content codes: CH CT

Background: Pulmonary noncalcified nodules (NCNs) attached to the fissural or costal pleura with smooth margins and triangular or lentiform, oval, or semicircular (LOS) shapes at low-dose CT are recommended for annual follow-up instead of immediate workup.

Purpose: To determine whether management of mediastinal or diaphragmatic pleura–attached NCNs (M/DP-NCNs) with the same features as fissural or costal pleura–attached NCNs at low-dose CT can follow the same recommendations.

Materials and Methods: This retrospective study reviewed chest CT examinations in participants from two databases. Group A included 1451 participants who had lung cancer that was first present as a solid nodule with an average diameter of 3.0–30.0 mm. Group B included 345 consecutive participants from a lung cancer screening program who had at least one solid nodule with a diameter of 3.0–30.0 mm at baseline CT and underwent at least three follow-up CT examinations. Radiologists reviewed CT images to identify solid M/DP-NCNs, defined as nodules 0 mm in distance from the mediastinal or diaphragmatic pleura, and recorded average diameter, margin, and shape. General descriptive statistics were used.

Results: Among the 1451 participants with lung cancer in group A, 163 participants (median age, 68 years [IQR, 61.5–75.0 years]; 92 male participants) had 164 malignant M/DP-NCNs 3.0–30.0 mm in average diameter. None of the 164 malignant M/DP-NCNs had smooth margins and triangular or LOS shapes (upper limit of 95% CI of proportion, 0.02). Among the 345 consecutive screening participants in group B, 146 participants (median age, 65 years [IQR, 59–71 years]; 81 female participants) had 240 M/DP-NCNs with average diameter 3.0–30.0 mm. None of the M/DP-NCNs with smooth margins and triangular or LOS shapes were malignant after a median follow-up of 57.8 months (IQR, 46.3–68.1 months).

Conclusion: For solid M/DP-NCNs with smooth margins and triangular or LOS shapes at low-dose CT, the risk of lung cancer is extremely low, which supports the recommendation of Lung Imaging Reporting and Data System version 2022 for annual follow-up instead of immediate workup.

A major goal of lung cancer screening protocols has been to limit unnecessary workup while not delaying lung cancer diagnoses (1), which means reducing unnecessary workup of benign noncalcified nodules (NCNs) identified at low-dose CT (2).

Lung cancer screening protocols have focused on limiting workup of nodules below a specific size on baseline and annual repeat scans (3,4), and a similar strategy is used on nodules incidentally detected at CT performed for nonscreening indications (5,6). Studies have suggested that nodules attached to or near pleural fissures that have a mean diameter less than 10.0 mm, a smooth margin, and a triangular, lentiform, or oval shape do not require immediate workup and instead can undergo annual follow-up (7–10). Similar recommendations have been made for costal pleura–attached NCNs (11,12).

Abbreviations

I-ELCAP = International Early Lung Cancer Action Program, IELCART-MSHS = Initiative for Early Lung Cancer Research on Treatment–Mount Sinai Health System, LOS = lentiform, oval, or semicircular, Lung-RADS = Lung Imaging Reporting and Data System, M/DP-NCN = mediastinal or diaphragmatic pleura–attached NCN, NCN = noncalcified nodule

Summary

Noncalcified nodules attached to the mediastinal or diaphragmatic pleura with smooth margins and triangular or lentiform, oval, or semicircular shapes at low-dose CT in participants in a lung cancer screening program were not malignant at a median follow-up of 57.8 months.

Key Results

- Of 240 mediastinal or diaphragmatic pleura–attached noncalcified nodules (M/DP-NCNs) identified in 146 lung cancer screening participants, none with smooth margins and triangular or lentiform, oval, or semicircular (LOS) shapes were found to be malignant after a median follow-up of 57.8 months (IQR, 46.3–68.1 months).
- Of 164 malignant M/DP-NCNs identified in 163 participants with lung cancer, none had smooth margins and triangular or LOS shapes (upper limit of 95% CI of proportion, 0.02).

The most recent version of the Lung Imaging Reporting and Data System (Lung-RADS) has extended the recommendations for perifissural nodules to juxtapleural nodules, which include nodules attached to any of the four pleura (fissural, costal, mediastinal, and diaphragmatic); these are now classified as category 2, with a recommendation of 12-month follow-up (4). However, there are no empirical data related to nodules attached to mediastinal or diaphragmatic pleura to support this recommendation.

The purpose of this study was to determine whether NCNs attached to the mediastinal pleura or diaphragmatic pleura with smooth margins and triangular or lentiform, oval, or semicircular (LOS) shapes can safely be surveilled with annual follow-up CT like fissural and costal pleura–attached NCNs.

Materials and Methods

Study Sample

This retrospective study included data from the International Early Lung Cancer Action Program (I-ELCAP) and the Initiative for Early Lung Cancer Research on Treatment–Mount Sinai Health System (IELCART-MSHS). I-ELCAP, a multiinstitutional lung cancer screening cohort study, prospectively enrolled over 80 000 participants between January 1992 and December 2021. All participants in I-ELCAP were 40–90 years of age and had a history of smoking or other high-risk exposure (3). The IELCART-MSHS study included 872 prospectively enrolled participants with lung cancer who were aged 31–90 years, with or without a history of smoking. All participants in IELCART-MSHS were enrolled upon diagnosis of stage I lung cancer and underwent treatment between January 2016 and December 2021 at three hospitals within the Mount Sinai Health System in New York City (13). All participants in I-ELCAP and IELCART-MSHS signed institutional review board–approved, Health Insurance Portability and Accountability Act–compliant consent forms.

A data scientist (R.Y., with more than 15 years of experience) searched the I-ELCAP and IELCART-MSHS databases and identified participants with lung cancer. These participants were included in group A of the current study if the primary lung cancer was diagnosed as a solid NCN that measured 3.0–30.0 mm in average diameter (Fig 1).

The same data scientist (R.Y.) searched the Mount Sinai I-ELCAP lung cancer screening database, containing the data from the Mount Sinai site of I-ELCAP, to identify all participants with solid NCNs, and thereby identify benign nodules. Participants in the database who had at least one solid nodule with a diameter of 3.0–30.0 mm at baseline CT and underwent at least three follow-up CT examinations were included in group B. The reason for excluding participants who had fewer than three follow-up scans in the database was that we used stability over time to document the benign status of the NCNs.

For all data sets, demographic characteristics, smoking history, self-reported comorbidities, and CT findings of nodules, nodule consistency, average nodule diameter, and presence of emphysema (3,14) were documented at the time of enrollment. The average diameter was defined as the average of the maximum longest dimension of the nodule and its width, which was defined as the longest perpendicular to the length.

Imaging Procedures

In I-ELCAP, low-dose screening CT scans before 2000 were obtained at a section thickness of 10.0 mm overlapping at 5.0-mm intervals, and if NCNs were found, another low-dose CT acquisition at a section thickness of 1.25 mm or less was performed (11,15). Since 2000, the screening section thickness has decreased to 1.25 mm or less (16). Low-dose screening CT was performed at 140 kVp or less and at 80 mAs or less using multidetector row CT scanners (HiSpeed Advantage or LightSpeed, GE HealthCare; Somatom Definition Flash, Siemens Healthineers) in a single breath hold without contrast material. CT scans in IELCART-MSHS were obtained using either a standard-dose or low-dose setting on multisection CT scanners with or without contrast material, with a section thickness of 3 mm or less.

Assessment of CT Scans for NCNs Attached to Mediastinal or Diaphragmatic Pleura and Evaluation of Radiologic Features

The CT images in participants with lung cancer in group A were divided between four radiologists (Y.Z., Q.S., P.L., and Q.C., with 10, 14, 15, and 17 years of experience, respectively; Y.Z. interpreted 365 scans, the others 362 each). Each radiologist reviewed the assigned CT scans to identify all solid mediastinal or diaphragmatic pleura–attached NCNs (M/DP-NCNs) (0-mm distance from nodule to the pleura). This initial review yielded 164 M/DP-NCNs that were diagnosed as lung cancers. Scans with initial findings were then reviewed by two senior radiologists (Y.Z. and Q.C.).

For participants in group B, one radiologist (Y.Z.) reviewed all CT scans to identify solid M/DP-NCNs using the same criteria

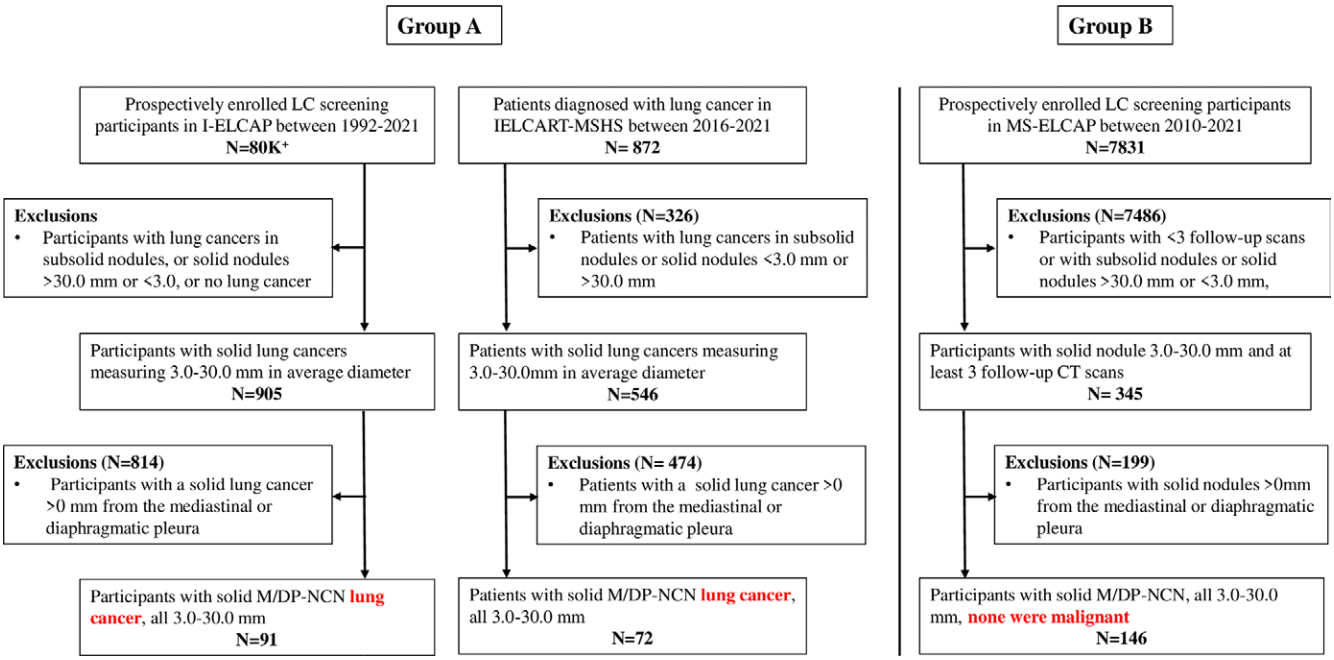

Figure 1: Flowchart of participants. Group A included participants with malignant mediastinal or diaphragmatic pleura–attached noncalcified nodules (M/DP-NCNs) from the Initiative for Early Lung Cancer Research on Treatment–Mount Sinai Health System (IELCART-MSHS) and the International Early Lung Cancer Action Program (I-ELCAP). Group B included participants from a lung cancer (LC) screening program (Mount Sinai I-ELCAP [MS-ELCAP]) with benign M/DP-NCNs screened at three hospitals within the Mount Sinai Health System.

as described for the malignant M/DP-NCNs. We included both baseline and new M/DP-NCNs on annual repeat CT scans.

Two senior radiologists (Y.Z. and Q.C.) independently documented the following characteristics of each M/DP-NCN (13): average diameter (average of maximum length and perpendicular width on a single section), location, margin (smooth or nonsmooth), shape (triangular, LOS, polygonal, round, or irregular), and type of attachment to the mediastinal or diaphragmatic pleura (broad or narrow). The attachment was classified as broad if the length along the pleura divided by the length along the nodule was at least 0.5; otherwise, the attachment was classified as narrow. In addition, emphysema and fibrosis within a 10-mm radius of each nodule were documented as present or not. Upon completion, any disagreement on the characteristics of each nodule was jointly reviewed, and the final classification was made by the consensus of two other senior radiologists (D.F.Y. and C.I.H., both with more than 25 years of experience). For all image reviewing, radiologists were blinded to clinical information and pathology results.

Study of Intra- and Interreader Agreement for Nodule Features

All M/DP-NCNs with average diameter 6.0–9.9 mm were included in the intra- and interreader agreement study. For the evaluation of interreader agreement, three radiologists with different levels of experience (Y.Z., Q.S., and N.P., with 2 years of experience in chest radiology) reviewed the M/DP-NCNs individually to measure nodule features (margin, shape, and pleural attachment), blinded to the clinical information and final pathology results. More than 3 weeks after the initial review, cases were reviewed and nodule features measured again by one radiologist (Y.Z.) to evaluate intrareader agreement.

Statistical Analyses

Continuous variables were summarized as means and SDs for normally distributed data or as medians and IQRs for nonparametric data. Categorical variables were summarized as frequencies and percentages. Differences in distributions of characteristics of benign and malignant M/DP-NCNs were analyzed using the Student *t* test or Mann-Whitney *U* test for continuous variables and the χ^2 or Fisher exact test for categorical variables. $P < .05$ was considered to indicate a statistically significant difference. For inter- and intrareader agreement, κ values were interpreted as follows: 0 or less, no agreement; 0.01–0.20, slight agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, substantial agreement; and 0.81–1.00, almost perfect agreement. All analyses were performed by data scientists (R.Y. and J.Z.) using R software (version 3.6.3; R Foundation for Statistical Computing).

Results

Participant Characteristics

The I-ELCAP database included over 80 000 participants, and the IELCART-MSHS database included 872 participants with lung cancer. Patients were excluded from the current study if they had a lung cancer manifesting as a subsolid nodule or solid nodule with average diameter greater than 30.0 mm or less than 3.0 mm, or no lung cancer. Group A included 905 participants from I-ELCAP and 546 participants from IELCART-MSHS who had a first primary lung cancer manifesting as a solid NCN with average diameter 3.0–30.0 mm. Among these combined 1451 I-ELCAP and IELCART-MSHS participants with lung cancer, 163 (11.2%) had M/DP-NCN lung cancers

Table 1: Demographic Characteristics of Participants with Noncalcified Nodules Attached to the Mediastinal or Diaphragmatic Pleura

Characteristic	Benign (*n* = 146)	Malignant (*n* = 163)	Total (*n* = 309)	*P* Value
Sex				.04
Female	81 (55)	71 (44)	152 (49)	
Male	65 (45)	92 (56)	157 (51)	
Age (y)*	65.0 (59.0–71.0)	68.0 (61.5–75.0)	66.0 (60.0–72.0)	.004
Smoking history				.005
Current	66 (45)	60 (37)	125 (41)	
Former	74 (51)	79 (48)	152 (50)	
Never	6 (4.1)	24 (15)	30 (9.8)	
Pack-years of smoking*†	30.0 (16.9–43.3)	37.5 (10.0–57.5)	33.0 (15.0–51.2)	.5
Follow-up (mo)*	57.8 (46.3–68.1)	47.9 (28.1–123.7)	55.1 (32.9–80.6)	.8

Note.—Except where noted, data are numbers of participants, with percentages in parentheses.
* Data are medians, with IQRs in parentheses.
† For current and former smokers.

Table 2: Characteristics of Noncalcified Nodules Attached to the Mediastinal or Diaphragmatic Pleura When First Identified at Low-Dose CT

Characteristic	Benign (*n* = 240)	Malignant (*n* = 164)	Total (*n* = 404)	*P* Value
Average diameter (mm)				<.001
Median*	4.6 (3.6–6.8)	15.0 (9.8–22.3)	7.0 (4.3–13.3)	
3.0–5.9	166 (69)	8 (4.9)	174 (43)	
6.0–9.9	53 (22)	35 (21)	88 (22)	
10.0–14.9	13 (5.4)	38 (23)	51 (13)	
15.0–30.0	8 (3.3)	83 (51)	91 (23)	
Shape				<.001
Triangular	64 (26.7)	0 (0.0)	64 (15.8)	
LOS	68 (28.3)	2 (1.2)	70 (17.3)	
Polygonal	0 (0.0)	2 (1.2)	2 (0.5)	
Round	34 (14.2)	33 (20.1)	67 (16.6)	
Irregular	74 (30.8)	127 (77.4)	201 (49.8)	
Margin				<.001
Nonsmooth	56 (23.3)	123 (75.0)	179 (44.3)	
Smooth	184 (76.7)	41 (25.0)	225 (55.7)	
Nodule-pleura interface				.7
Broad attachment	165 (68.8)	116 (70.7)	281 (69.6)	
Narrow attachment	75 (31.2)	48 (29.3)	123 (30.4)	
Adjacent parenchyma findings†				
Emphysema	50 (20.8)	50 (30.5)	100 (24.8)	.03
Fibrosis	4 (1.7)	5 (3.0)	9 (2.2)	.5
Nodule location				<.001
Upper or middle lobe	201 (83.8)	93 (56.7)	294 (72.8)	
Lower lobe	39 (16.2)	71 (43.3)	110 (27.2)	
Pleural attachment				<.001
Mediastinal	173 (72.1)	149 (90.9)	322 (79.7)	
Diaphragmatic	67 (27.9)	15 (9.1)	82 (20.3)	

Note.—Except where noted, data are numbers of nodules, with percentages in parentheses. LOS = lentiform, oval, or semicircular.
* Data in parentheses are IQRs.
† Within 10 mm of the nodule.

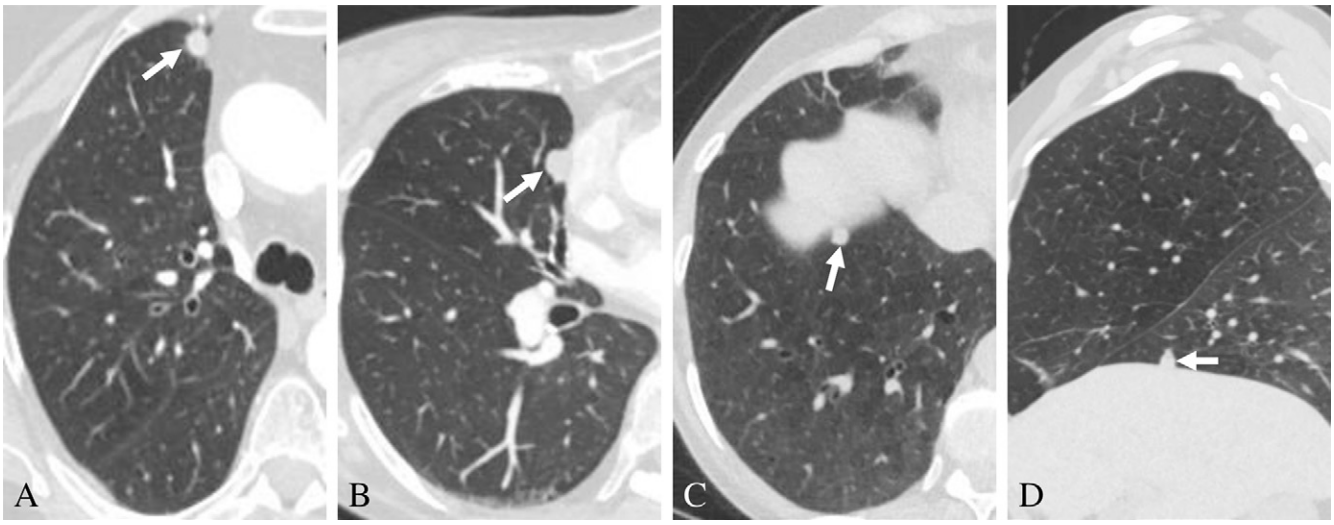

Figure 2: Example low-dose chest CT images of malignant mediastinal or diaphragmatic pleura–attached noncalcified nodules (NCNs) in participants of the Initiative for Early Lung Cancer Research on Treatment–Mount Sinai Health System cohort. **(A)** Axial standard-dose contrast-enhanced CT image in a 77-year-old female participant with adenocarcinoma shows a mediastinal pleura–attached NCN lung cancer (arrow) with a nonsmooth margin and round shape. **(B)** Axial low-dose CT image in a 76-year-old female participant with typical carcinoid shows a mediastinal pleura–attached NCN lung cancer (arrow) with a smooth margin and round shape. **(C)** Axial and **(D)** sagittal low-dose CT images in a 59-year-old female participant with adenocarcinoma show a diaphragmatic pleura–attached NCN lung cancer (arrow) with a smooth margin and round shape.

(91 in I-ELCAP and 72 in IELCART-MSHS). Of these 163 participants with M/DP-NCN lung cancers, 71 (44%) were female and 92 (56%) were male (Table 1). The median age of these participants was 68 years (IQR, 62–75 years), and median pack-years of smoking was 37.5 (IQR, 10.0–57.5 pack-years). One of the 163 participants with lung cancer had two solid M/DP-NCN lung cancers, one in the left lower lobe and the other in the left upper lobe; thus, there were 164 solid M/DP-NCN lung cancers among these 163 participants.

Of the 345 consecutive screening participants in the Mount Sinai I-ELCAP database with a solid NCN with average diameter of 3.0–30.0 mm, 199 were excluded because the solid nodule had a greater than 0-mm distance from the mediastinal or diaphragmatic pleura. Thus, a total of 146 participants with 240 M/DP-NCNs were included in group B. None of the M/DP-NCNs were malignant after a median follow-up of 57.8 months (IQR, 46.3–68.1 months). Of the 146 participants, 81 (55%) were female and 65 (45%) were male (Table 1). The median age of participants was 65 years (IQR, 59–71 years), and median pack-years of smoking was 30.0 (IQR, 16.9–43.3 pack-years).

Radiologic Features of Malignant and Benign M/DP-NCNs

Among the 164 M/DP-NCN lung cancers (group A), 83 (51%) had an average diameter between 15.0 mm and 30.0 mm, 123 (75.0%) had a nonsmooth margin, 127 (77.4%) had an irregular shape, and 116 (70.7%) had a broad pleural attachment (Table 2). Emphysema and fibrosis were seen within 10 mm of 50 (30.5%) and five (3.0%) of the 164 M/DP-NCN lung cancers, respectively. A total of 93 of 164 (56.7%) M/DP-NCN lung cancers were located in the upper or middle lobe. At pathologic examination, 61.6% (101 of 164) were adenocarcinoma, 19.5% (32 of 164) were squamous cell carcinoma, 6.0% (10 of 164) were small cell carcinoma, and 3.0% (five of 164) were large cell carcinoma. Examples of morphologic features of malignant M/DP-NCNs are shown in Figure 2.

Among the 240 benign M/DP-NCNs (group B), 166 (69%) of the nodules had an average diameter of 3.0–5.9 mm, 184 (76.7%) had a smooth margin, 74 (30.8%) had an irregular shape, and 165 (68.8%) had a broad pleural attachment. Emphysema and fibrosis were seen within 10 mm of 50 (20.8%) and four (1.7%) of the 240 M/DP-NCNs, respectively. A total of 201 of 240 (83.8%) M/DP-NCNs were located in the upper or middle lobe (Table 2). Examples of morphologic features of benign M/DP-NCNs are shown in Figure 3.

M/DP-NCN features associated with benignity were size ($P < .001$), shape ($P < .001$), margin ($P < .001$), and lobe location ($P < .001$). Perinodular emphysema was less frequent in benign than in malignant M/DP-NCNs (20.8% [50 of 240] vs 30.5% [50 of 164]; $P = .03$), while type of pleural attachment ($P = .7$) and perinodular fibrosis ($P = .5$) were not significantly associated with benignity or malignancy (Table 2).

Of the M/DP-NCN lung cancers with an average diameter of 3.0–30.0 mm, none had a smooth margin and triangular or LOS shape (upper limit of 95% CI of proportion, 0.02) (Table 3). Among the solid M/DP-NCNs from the Mount Sinai I-ELCAP database with an average diameter of 3.0–30.0 mm, 131 of 240 (54.6%) had a smooth margin and triangular or LOS shape, and none of these were malignant after a median follow-up of 57.8 months (IQR, 46.3–68.1 months). The sensitivity of M/DP-NCNs with smooth margins and triangular or LOS shapes for predicting benignity was 55% (95% CI: 48%, 61%), while specificity was 100% (95% CI: 98%, 100%).

Intra- and Interreader Agreement for Nodule Features

Table 4 summarizes the nodule feature classifications by three radiologists for 88 solid M/DP-NCNs with average diameter of 6.0–9.9 mm. There was perfect intra- and interreader agreement

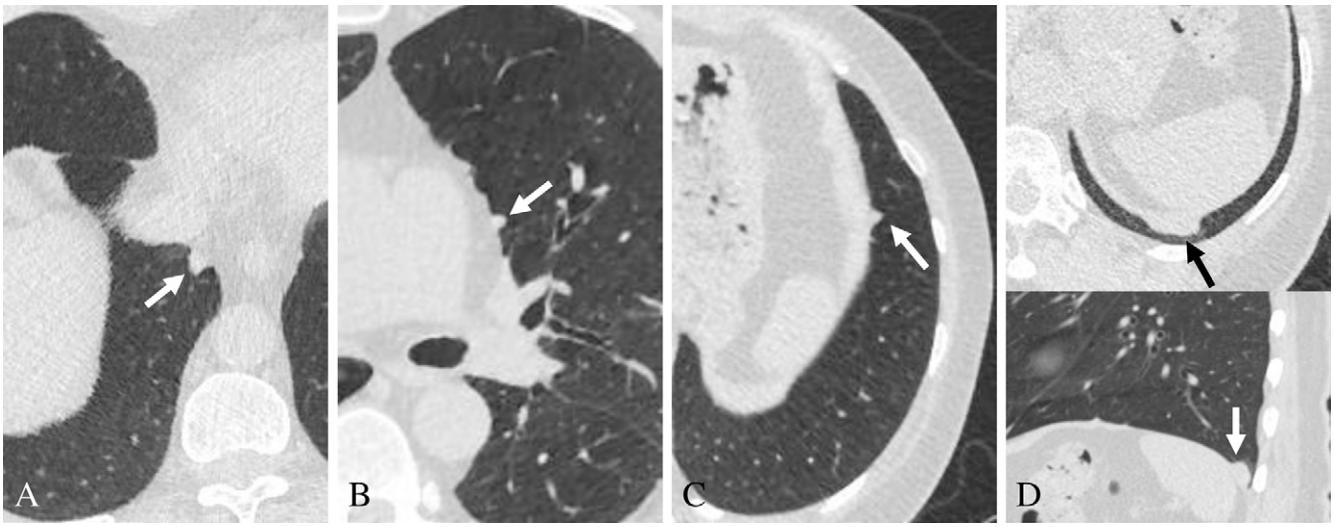

Figure 3: Example low-dose chest CT images of benign mediastinal or diaphragmatic pleura–attached noncalcified nodules (NCNs) in participants of the Initiative for Early Lung Cancer Research on Treatment–Mount Sinai Health System cohort. **(A)** Axial low-dose CT image in a 73-year-old male participant shows a mediastinal pleura–attached NCN (arrow) with a smooth margin and triangular shape. **(B)** Axial low-dose CT image in a 56-year-old female participant shows a mediastinal pleura–attached NCN (arrow) with a smooth margin and oval shape. **(C)** Axial low-dose CT image in a 64-year-old female participant shows a diaphragmatic pleura–attached NCN (arrow) with a smooth margin and triangular shape. **(D)** Axial (top) and sagittal (bottom) low-dose CT images in a 65-year-old female participant show a diaphragmatic pleura–attached NCN (arrow) with a smooth margin and semicircular shape.

Table 3: Combined Characteristics of Noncalcified Nodules Attached to the Mediastinal or Diaphragmatic Pleura

Average Diameter, Margin, and Shape	Benign (*n* = 240)	Malignant (*n* = 164)
3.0–5.9 mm	166/240 (69.2)	8/164 (4.9)
Smooth and triangular or LOS	108/166 (65.1)	0
Nonsmooth and triangular or LOS	1/166 (0.6)	1/8 (12)
Smooth and polygonal	0	1/8 (12)
Smooth and round	25/166 (15.1)	3/8 (38)
Nonsmooth and irregular	19/166 (11.4)	3/8 (38)
Smooth and irregular	13/166 (7.8)	0
6.0–9.9 mm	53/240 (22.1)	35/164 (21.3)
Smooth and triangular or LOS	17/53 (32)	0
Smooth and polygonal	0	1/35 (2.9)
Smooth and round	6/53 (11)	6/35 (17)
Nonsmooth and round	1/53 (2.0)	2/35 (5.7)
Smooth and irregular	6/53 (11)	3/35 (8.5)
Nonsmooth and irregular	23/53 (43)	23/35 (66)
10.0–14.9 mm	13/240 (5.4)	38/164 (23.2)
Smooth and triangular or LOS	5/13 (38)	0
Smooth and round	2/13 (15)	1/38 (2.6)
Nonsmooth and round	0	3/38 (7.9)
Smooth and irregular	0	2/38 (5.3)
Nonsmooth and irregular	6/13 (46)	32/38 (84)
15.0–30.0 mm	8/240 (3.3)	83/164 (50.6)
Smooth and triangular or LOS	1/8 (12)	0
Nonsmooth and oval	0	1/83 (1.2)
Smooth and round	0	11/83 (13)
Nonsmooth and round	0	7/83 (8.4)
Smooth and irregular	1/8 (12)	13/83 (16)
Nonsmooth and irregular	6/8 (75)	51/83 (61)

Note.—Data are numbers of noncalcified nodules, with percentages in parentheses. LOS = lentiform, oval, or semicircular.

for classifying nodules as M/DP-NCNs (κ = 1.0). Interreader agreement for shape was moderate (κ = 0.60 [95% CI: 0.51, 0.69]), with better agreement for triangular or LOS and irregular shapes than for round shape. The interreader agreement for pleural attachment was also moderate (κ = 0.58 [95% CI: 0.46, 0.70]). Of the 88 M/DP-NCNs, 16 (18.2%), 18 (20.5%), and 11 (12.5%) were described as having triangular or LOS shape and a smooth margin by reader 1, 2, and 3, respectively, with substantial interreader agreement (κ = 0.68 [95% CI: 0.56, 0.80]). Intrareader agreement was substantial for shape (κ = 0.71 [95% CI: 0.57, 0.84]), moderate for pleural attachment (κ = 0.59 [95% CI: 0.41, 0.77]), and perfect for classifying M/DP-NCNs as having triangular or LOS shape and a smooth margin (κ = 1.0).

Discussion

Perifissural nodules or costal pleura–attached nodules with smooth margins and triangular or lentiform, oval, or semicircular (LOS) shapes at low-dose CT are recommended for annual follow-up instead of immediate workup. To determine whether this recommendation is appropriate for mediastinal or diaphragmatic pleura–attached noncalcified nodules (M/DP-NCNs) having these same features at low-dose CT, we reviewed all solid M/DP-NCN lung cancers in two large prospective cohort studies. Among 1451 participants with lung cancer, we found 164 solid M/DP-NCN lung cancers with an average diameter between 3.0 mm and 30.0 mm, and none had smooth margins and triangular or LOS shapes. We also reviewed all baseline and new M/DP-NCNs with average diameter of 3.0–30.0 mm in a lung

Table 4: Interreader Agreement for Noncalcified Nodules Attached to the Mediastinal or Diaphragmatic Pleura with Average Diameter of 6.0–9.9 mm

Nodule Feature and Reader	Cohen κ		Fleiss κ
	Reader 2	Reader 3	
Margin*			0.46 (0.34, 0.58)
Reader 1	0.58 (0.40, 0.76)	0.37 (0.18, 0.57)	
Reader 2		0.46 (0.29, 0.63)	
Shape†			0.60 (0.51, 0.69)
Reader 1	0.72 (0.58, 0.87)	0.52 (0.37, 0.68)	
Reader 2		0.57 (0.41, 0.73)	
Triangular or LOS			0.65 (0.53, 0.78)
Round			0.49 (0.36, 0.61)
Polygonal			−0.00 (−0.12, 0.12)
Irregular			0.62 (0.50, 0.74)
Pleural attachment‡			0.58 (0.46, 0.70)
Reader 1	0.62 (0.45, 0.80)	0.49 (0.29, 0.68)	
Reader 2		0.65 (0.46, 0.84)	
Smooth margin and triangular or LOS shape vs other			0.68 (0.56, 0.80)
Reader 1	0.70 (0.49, 0.90)	0.64 (0.43, 0.84)	
Reader 2		0.71 (0.52, 0.91)	

Note.—Cohen κ is given for all pairwise comparisons, and Fleiss κ for comparisons according to nodule features. Values in parentheses are 95% CIs. LOS = lentiform, oval, or semicircular.

* Smooth versus nonsmooth.

† Triangular or LOS, round, polygonal, or irregular.

‡ Broad versus narrow.

cancer screening cohort of individuals without documented malignancy and found that none of the M/DP-NCNs with smooth margins and triangular or LOS shapes were malignant after a median follow-up of 57.8 months.

Previously, we showed that costal pleura–attached NCNs less than 10 mm in average diameter with smooth margins and triangular or LOS shapes could be safely followed up with annual CT rather than having more immediate diagnostic workup (11,12). The results presented in this report suggest that when a solid M/DP-NCN has a smooth margin and triangular or LOS shape, a similar strategy to that for costal pleural and perifissural nodules can be followed (ie, follow-up CT at 1 year rather than immediate diagnostic workup). According to the most recent Lung-RADS classification, such M/DP-NCNs should be classified as Lung-RADS category 2 nodules (4). Our study provides strong empirical data supporting the new recommendations for M/DP-NCNs. For M/DP-NCNs with features other than smooth margins and triangular or LOS shapes, we recommend follow-up according to current guidelines.

M/DP-NCN lung cancers were more frequently located in the upper or middle lobe than the lower lobe (56.7% [93 of 164] vs 43.3% [71 of 164]), similar to costal pleura–attached NCN lung cancers, which also were more frequently located in the upper lung zone than the lower lung zone (baseline NCNs, 56% [five of nine] vs 44% [four of nine]; new NCNs, 62% [13 of 21] vs 38% [eight of 21]) (11,12). These findings are also consistent with those for lung cancers in the Pan-Canadian Early Detection of Lung Cancer Study (66.7% [68 of 102] vs 33.3% [34 of 102]) and a study conducted by the British Columbia Cancer Agency (71.4% [30 of 42] vs 28.6% [12 of 42]) (17).

Emphysema was present within a 10-mm radius of 30.5% (50 of 164) of the M/DP-NCN lung cancers in this study. Perinodular emphysema was less frequent in benign than in malignant M/DP-NCNs (20.8% [50 of 240] vs 30.5% [50 of 164]; P = .027). However, a previous study, which included only 58 cancers and 58 benign nodules, found that perinodular emphysema measurements were not significantly different between malignant and benign nodules (18). Our results are similar to those of a previous large cohort study (615 patients with lung cancer and 64 with benign nodules) (19) that found that a higher regional emphysema score was associated with the presence of a malignant lung nodule (odds ratio, 1.342 [95% CI: 1.112, 1.620]; P = .0022). Over half of the M/DP-NCN lung cancers in our study were adenocarcinoma (61.6%, 101 of 164), followed by squamous cell carcinoma (19.5%, 32 of 164), which is consistent with the frequencies for costal pleura–attached lung cancers (11,12) and fissural pleura–attached lung cancers (9).

Our study had limitations. First, although all diagnosed lung cancers were reviewed for this study, this study does not provide an estimate of the overall prevalence of M/DP-NCNs, including benign ones, in the entire I-ELCAP cohort as only a subset of participants without lung cancer were reviewed, given the large size of the database. Since all screening participants were followed up for lung cancer diagnosis and long-term outcomes, we believe our approach of reviewing all participants diagnosed with lung cancer allowed us to meaningfully estimate how often

lung cancer manifested as a M/DP-NCN with a smooth margin and triangular or LOS shape, while considering the practical constraints of our study. Second, we limited our intra- and interreader agreement studies to M/DP-NCNs with average diameter of 6.0–9.9 mm for both malignant and benign nodules. This size range corresponds to the size range used for recommendations for costal pleural nodules and fissure-based nodules in Lung-RADS, and is of particular importance because of the high frequency of occurrence of nodules of this size. We also recognize the potential difficulties in distinguishing nodule shapes and margins, especially for less-experienced readers; however, the sensitivity of M/DP-NCNs with smooth margins and triangular or LOS shapes as a negative indicator of malignancy is high (82.9%–100%). In our study we reached at least moderate intra- and interreader agreement on nodule characteristics for nodules with average diameter of 6.0–9.9 mm. We would anticipate even higher intra- and interreader agreement for nodules with average diameter of 10.0 mm or greater.

In conclusion, we found that none of the solid mediastinal or diaphragmatic pleura–attached noncalcified nodule (M/DP-NCN) lung cancers in two large prospective cohorts had a smooth margin and triangular or lentiform, oval, or semicircular (LOS) shape. Furthermore, of the solid M/DP-NCNs with smooth margins and triangular or LOS shapes identified in a screening database, none were found to be malignant after a median follow-up of approximately 5 years. The results of our study suggest that the likelihood of diagnosing lung cancer in M/DP-NCNs with these features is very low; therefore, follow-up with annual screening rather than immediate workup may be appropriate, both at baseline and at annual repeat screening scans. Based on these findings, we suggest a similar approach to the management of these M/DP-NCNs as is currently being undertaken with perifissural and pericostal nodules.

Author contributions: Guarantors of integrity of entire study, **P.L., N.T., D.F.Y.**; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agree to ensure any questions related to the work are appropriately resolved, all authors; literature research, **Y.Z., Q.C., N.T., C.I.H., D.F.Y.**; clinical studies, **Y.Z., Q.C., Q.S., P.L., N.P., N.T., C.I.H.**; statistical analysis, **Y.Z., R.Y., J.Z., N.P., N.T., C.I.H.**; and manuscript editing, **Y.Z., R.Y., J.Z., Q.C., N.P., N.T., C.I.H., D.F.Y.**

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Disclosures of conflicts of interest: Y.Z. No relevant relationships. **R.Y.** No relevant relationships. **J.Z.** No relevant relationships. **Q.C.** No relevant relationships. **Q.S.** No relevant relationships. **P.L.** No relevant relationships. **N.P.** No relevant relationships. **N.T.** No relevant relationships. **C.I.H.** Participation on an advisory board without compensation for Lunglife AI; named inventor on a number of patents and patent applications relating to the evaluation of pulmonary nodules on CT scans of the chest that are owned by Cornell Research Foundation (CRF) (since 2009, has not accepted any financial benefit from these patents including royalties and any other proceeds related to the patents or patent applications owned by CRF); and president

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