CT Screening for Lung Cancer: Implication of Lung Biopsy Recommendations

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OBJECTIVE. The purpose of this article is to address the implications of invasive diagnostic procedures recommended by a lung cancer screening protocol. In particular, we assess how many invasive procedures were recommended for benign nodules.

MATERIALS AND METHODS. Between 2003 and 2009, 4782 high-risk current and former smokers were enrolled in a lung cancer screening study. A helical low-dose CT of the chest was performed. Morphologic features targeted were parenchymal nodules. The indication for biopsy was made according to the diagnostic algorithm provided by the International Early Lung Cancer Action Program. We recorded the time points of biopsy recommendation; shape, size, and growth of nodules; types of diagnostic procedures; complication rates; and final pathologic diagnosis.

RESULTS. A total of 128 diagnostic biopsies were recommended for suspicious nodules, and 127 biopsies were performed, including 110 percutaneous CT-guided fine-needle aspiration biopsies (FNABs), nine video-assisted thoracoscopic surgery (VATS) resections, seven bronchoscopies, and one ultrasound-guided biopsy of a lymph node. Of 110 FNABs, 24 had unsatisfactory results, 13 of which were referred for secondary diagnostic VATS resection. The indication for biopsy was made on the basis of shape in 48% of cases (62/128), growth on follow-up in 40% of cases (51/128), and the appearance of new nodules in 12% of cases (15/128). In total, 104 of 124 biopsies (84%) were correctly indicated (true-positive recommendation) for malignancy, 20 were benign (false-positive) (16%), and final results are pending for four cases. The overall false-positive recommendation rate was 0.42% (20/4782); 11.6% of FNABs (16/128) and 3.6% of VATS (5/128) revealed benign nodules, corresponding to an overall false-positive rate of 0.33% for FNAB (16/4782) and 0.10% for VATS (5/4782).

CONCLUSION. The recommended biopsy procedures for screen-detected suspicious pulmonary nodules resulted in a low intervention rate for benign nodules. This rate is minimal when we followed a research protocol that relies on shape and growth.

Keywords: biopsy, false-positive rate, low-dose CT, lung cancer screening

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The advent of low-dose helical CT screening introduced for the early detection of lung cancer in the early 1990s has generated a widespread interest, resulting in the diagnosis of a high number of pulmonary nodules and early-stage peripheral lung cancers [1–6]. In direct comparison with chest radiography, low-dose CT can identify more small pulmonary lesions in the lungs of current and former smokers [1] and more early-stage lung cancers [3]. Recently, a 20% mortality benefit in the CT screening arm (compared with chest radiographs) has been found in the United States [7, 8]; and mortality remains under investigation in European studies as well [9]. Low-dose CT screening has been criticized because of the large number of false-positive results (i.e., lung nodules that after investigations are proven to be benign) [4, 10–12]. These investigations, often invasive, result in related morbidities and mortalities, potentially offsetting the survival benefit from the early lung cancer detection.

The International Early Lung Cancer Action Project (I-ELCAP) developed a straightforward algorithm for assessing indeterminate nodules that would provide the inclusion diagnosis of lung cancer [1]. This study protocol provides a definition for suspicious pulmonary nodules and recommends a diagnostic regimen to be followed once these nodules are described. The protocol provides suggestions only; the exact decision for the follow-up strategies is left to the patient and physician and depends on the expertise of the institution.

The purpose of this article is to assess the impact of biopsy recommendations from a lung cancer screening study that followed the I-ELCAP protocol for conservative and invasive follow-up of lung nodules.

Materials and Methods

Participants and Study Protocol

Between June 2003 and June 2009, the lung cancer screening study at the Princess Margaret Hospital in Toronto enrolled 4782 participants as part of the I-ELCAP. Inclusion criteria were age of at least 50 years, current or former cigarette smoker of at least 10 pack-years, and otherwise self-reported in good health. Exclusion criteria were history of cancer (except nonmelanotic skin cancer). Study participation was voluntary and followed written informed consent; the institutional review board had approved the protocol.

All participants who were enrolled in the study underwent a baseline low-dose CT examination. According to the I-ELCAP diagnostic protocol, the baseline CT scans were negative if there were no nodules at least 5 mm in size. A baseline CT scan was termed positive if at least one indeterminate noncalcified solid or part-solid nodule 5 mm or larger in size or nonsolid nodule 8 mm or larger in size was identified. For annual repeat scans, the result was positive if at least one noncalcified nodule had grown in the interim or was newly seen. Positive low-dose CT scans were followed up depending on the shape and the diameter of the largest nodules. The I-ELCAP protocol recommended biopsy immediately when noncalcified nodules were 15 mm or larger in size, 1 month after receiving antibiotics with no decrease in size of the nodules, and when interval growth was seen.

Imaging Technique

All CT scans were acquired on various MDCT scanners within the Department of Medical Imaging at the University Health Network in Toronto, equipped with different number of channels, ranging from 4- to 64-MDCT scanners, and from various manufacturers (LightSpeed Advantage, GE Healthcare; Aquilion, Toshiba Medical Systems). All scans were performed with a low-dose technique (120 kVp and 40–60 mA) and thin-slice acquisition (1–1.25-mm axial reconstructions).

Image Review and Decision for Biopsy Recommendation

The images were reviewed on a PACS workstation (eFilm, Merge Healthcare). The workstation provided all previous CT studies, if any, for comparison. A standard soft-tissue window (window width, 350 HU; window level, 25 HU) and lung window (window width, 1500 HU; window level, –650 HU) were used. If the nodule's appearance was suggestive of lung cancer, it was discussed between the reviewing radiologist on service (all of whom were chest radiologists with 7–30 years of experience) and the principal investigator (with 10 years of experience), and the decision for follow-up or biopsy recommendation was made by consensus. If patients did not keep their recommended follow-up appointments, their primary care physicians were contacted to ensure that procedures would be performed. The indication for biopsy was made when a solitary nodule measured 15 mm or more, a solid nodule had grown on follow-up scans, or a nonsolid or part-solid nodule persisted in size and did not resolve on 1- or 3-month follow-up scans. The I-ELCAP protocol included PET as an optional noninvasive imaging modality to characterize noncalcified pulmonary nodules larger than 10 mm. PET was not routinely available in our institution, so we relied on nodule size, shape, and growth for making the decision of biopsy recommendation.

Invasive Procedures

We followed the I-ELCAP protocol and predominantly performed transthoracic fine-needle aspiration biopsy (FNAB) as the invasive diagnostic procedure. The FNABs were performed in our institution by the radiologist on service. Between 2003 and 2006, a 4-MDCT scanner (Asterion, Toshiba, Medical Systems) was used for image guidance. Since 2006, a 64-MDCT scanner (Aquilion 64, Toshiba, Medical Systems) has been used. Our protocol included a coaxial technique using a 19-gauge outer coaxial needle (Truguide, C. R. Bard) and a 22-gauge inner disposable biopsy needle (Greene, Cook Medical). The correct needle position was documented on thin-section CT images in all cases. Subsequent aspirates were obtained and immediately reviewed by the collaborating cytopathologist. The number of passes was based on adequacy of the specimen, as assessed by the cytopathologist, and on CT confirmation of the position of the needle tip.

Nodules not accessible for FNAB were referred to thoracic surgery, and video-assisted thoracoscopic surgery (VATS) resections were arranged. In cases of an endobronchial nodule, the thoracic surgeon or pneumologist performed a bronchoscopy.

Assessment of Nodule Characteristics and Other Data

The overall number of suspicious nodules recommended for biopsy was evaluated, as well as the number and results of FNABs and other types of diagnostic procedures. For all surgical resections, the final histopathologic analysis was reviewed to define biopsy recommendations for malignant lesions (true-positive) and benign lesions (false-positive); for cases without histopathologic analysis, the nodule nature was determined by long-term follow-up. We also noted the time point of biopsy recommendation, whether it was the result of a baseline scan, annual repeat, or other. The nodule shape was characterized by size (maximum length in millimeters), attenuation, and rim (solid with smooth, lobulated, or spiculated margins; part-solid; nonsolid; or cavitated). For growth assessment, bidimensional caliper measurements were compared with results from previous scans. To assess the number and types of complications of all nonsurgical and surgical diagnostic procedures

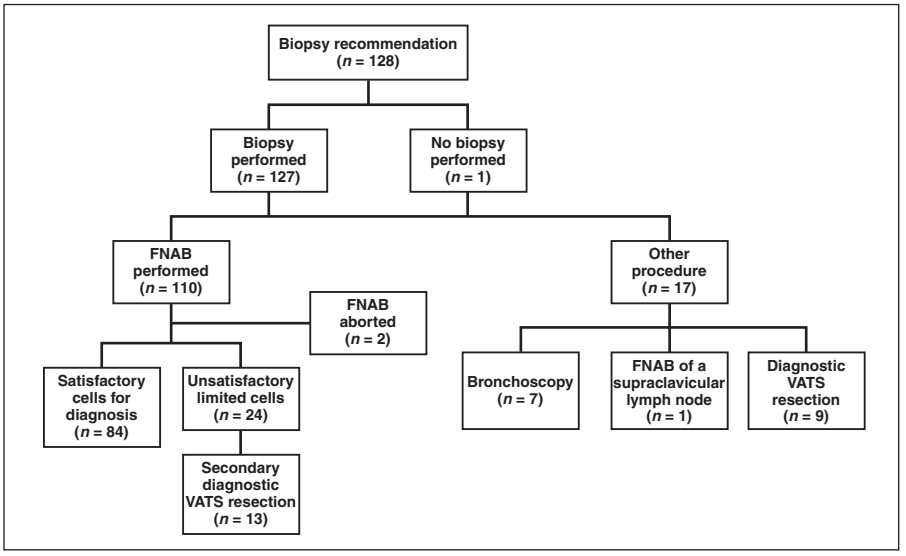

Fig. 1—Flowchart of biopsy recommendation of suspicious pulmonary nodules. FNAB = fine-needle aspiration biopsy, VATS = video-assisted thoracoscopic surgery.

performed, the patients' electronic charts were reviewed. All data were presented as medians including range or percentages.

Results

Subject Demographics

The 4782 study participants included 2127 men (44%) and 2655 women (56%). The median age was 60 years (range, 50–83 years). The self-reported median smoking history was 34 pack-years (range, 10–189 pack-years). There were 1654 current smokers (35%) and 3128 former smokers (65%).

Invasive Procedures

The overview of lung biopsy recommendations and procedures is summarized in Figure 1. Overall, 128 suspicious lesions in 128 participants were recommended for biopsy. For one participant, the supervising surgeon declined any invasive diagnostic procedures because of the subject's advanced age and severe emphysema.

The most common biopsy procedure was a transthoracic CT-guided FNAB (110/128 [86%]). In two participants, an FNAB was recommended because of baseline nodule shape (spiculated, cavitary, or lobulated) and size (12 and 17 mm, respectively), but the procedures were aborted because of interval decreases in size of the targeted nodule, which were documented on the limited planning images obtained immediately before the procedure (Fig. 2). Seventeen participants underwent other invasive diagnostic procedures (13%), including seven bronchoscopies for endobronchial or parahilar lesions, one ultrasound-guided FNAB of an enlarged supraclavicular lymph node, and nine diagnostic VATS resections. These diagnostic VATS resections were performed because three participants were extremely needle phobic. In two other cases, FNAB procedures were abandoned before needle placement because of vasovagal reaction and difficult access of a nodule in an uncooperative individual. In four participants, the pulmonary nodules were positioned in a challenging paraaortic or paracaval location (Fig. 3). In addition, 13 subjects (10%) with inconclusive FNAB results (Fig. 4) underwent subsequent VATS resection as a secondary diagnostic intervention for adequate tissue diagnosis (discussed later in this article).

Shape, Growth, and Size Criteria for Biopsy Recommendation

Shape was the most important criterion that led to biopsy recommendations (62/128 [48%]), especially within the first year (62/79 [78.5%]); 31 of those 79 recommendations (39.2%) were from findings on baseline scans, and 31 others were recommended for biopsy within 1, 3, or 6 months because of lack of regression (Table 1). Most of the nodules within the first year were part-solid (18/62 [29%]) followed by solid (17/62 [27%]), spiculated (13/62 [21%]), nonsolid (9/62 [15%]), and cavitary (5/62 [8%]) nodules. In total, three nodules were recommended for biopsy after a routine annual scan; all of them were growing nodules (two were solid and one was nonsolid).

Growth assessment was the basis for 40% of biopsy recommendations (51/128); 15 of 128 nodules (12%) were new on annual CT scans or later (Fig. 5). The majority of growing nodules were solid (32/51 [63%]), 12 were part-solid (24%), and two had initial nonsolid appearance. Five nodules were nonsolid (Fig. 4), one was spiculated, and one was cavitating. Of all 15 new nodules, 14 were smooth or lobulated solid; one was a cavitating nodule that was detected on a 2-year follow-up scan. In our cohort, 58 of 128 nodules (45%) were recommended for biopsies that were 15 mm or smaller.

Result of Biopsy Recommendation

The results from 108 FNAB procedures showed obvious malignant cells in 79 cases (73%), benign cells in five cases (5%), and inconclusive or unsatisfactory results in 24

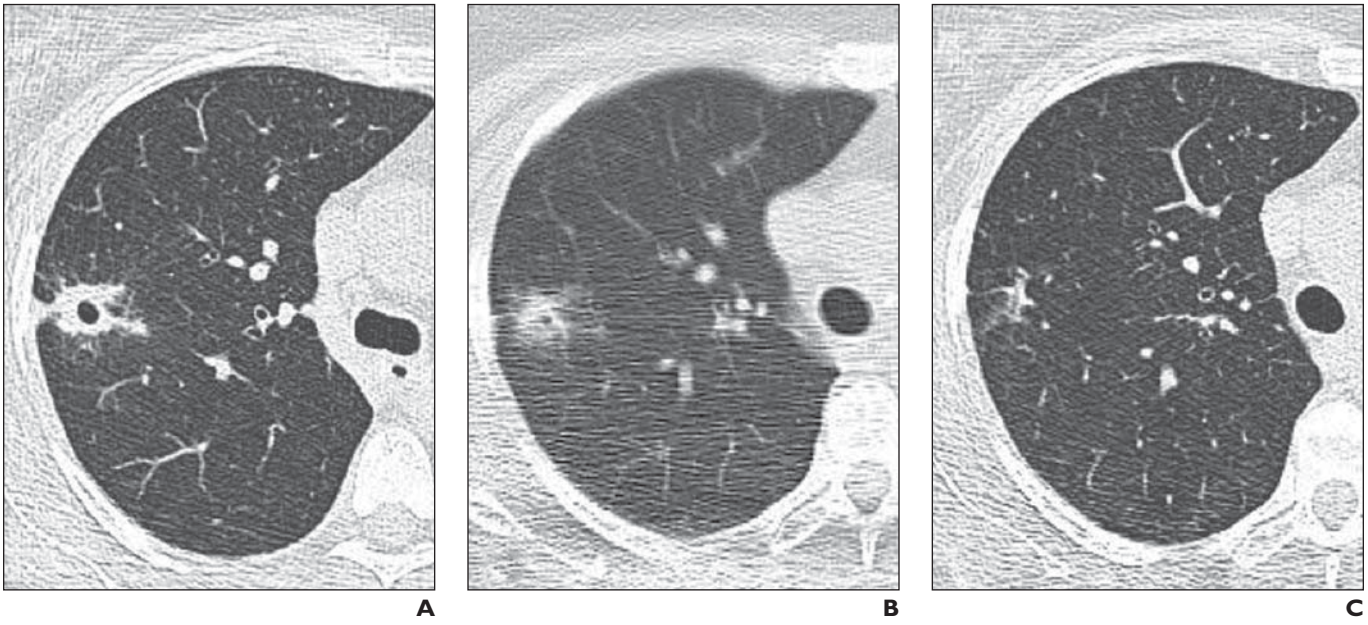

Fig. 2—56-year-old woman with cavitary pulmonary nodule seen on baseline scan.
A, Baseline scan shows evidence of 18 × 18-mm ill-defined nodule in right upper lobe with central cavitation. Immediate biopsy was scheduled.
B, Image shows initial limited scan of pulmonary nodule before biopsy. There was interval decrease in size (13 × 12 mm) and smaller central cavitation. Biopsy was aborted.
C, Twelve-month follow-up low-dose CT of same level shows further markedly decrease in nodule size.

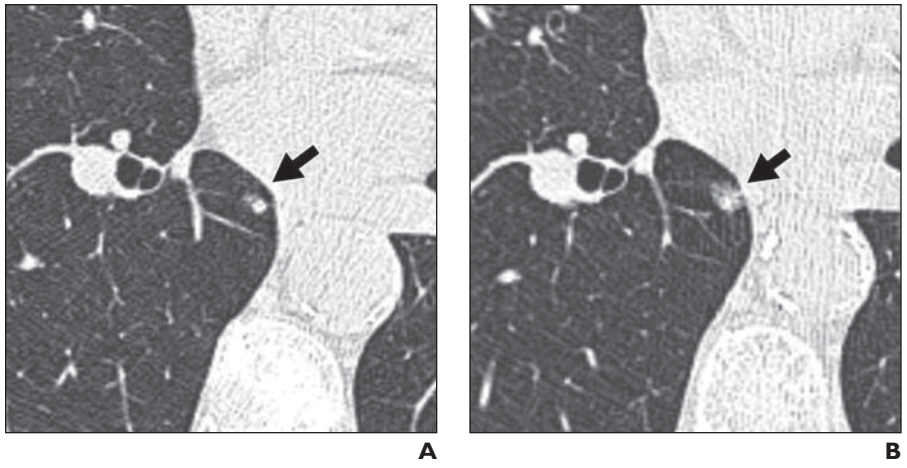

Fig. 3—74-year-old woman with slowly growing part-solid nodule.
A, Baseline scan shows 5-mm part-solid nodule (*arrow*) in mediobasal segment of right lower lobe.
B, Two-year follow-up low-dose CT scan shows interval nodule (*arrow*) growth up to 9 mm. Nodule was recommended for biopsy, but position next to left atrium was contraindicating for fine-needle aspiration biopsy. Participant underwent video-assisted thoracoscopic surgery. Histopathologic analysis revealed atypical adenomatous hyperplasia without malignant cells.

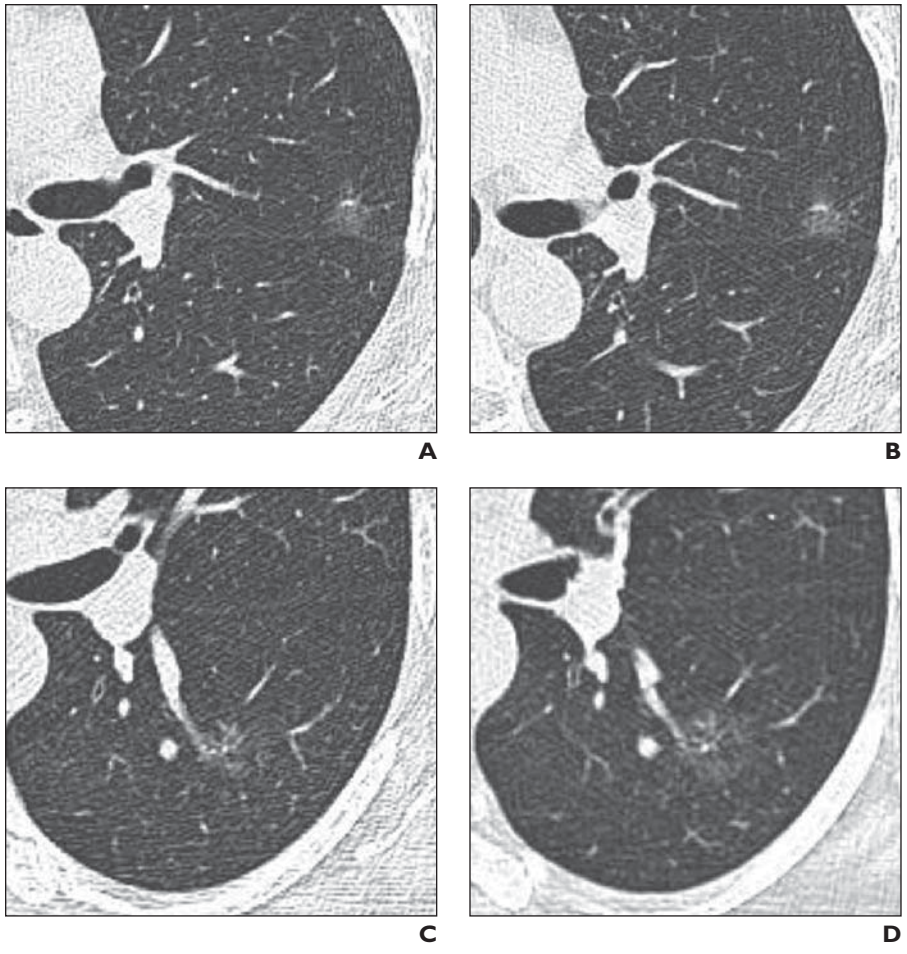

Fig. 4—Two patients with nonsolid nodules with inconclusive results on fine-needle aspiration biopsies (FNABs).
A and **B,** 62-year-old woman. Baseline scan (**A**) shows nonsolid nodule in left upper lobe measuring 10 mm. Follow-up low-dose CT at 2 years and 3 months (**B**) shows minimal growth up to 12 mm. Subsequent FNAB was unsatisfactory. Histopathologic analysis after video-assisted thoracoscopic surgery (VATS) revealed atypical adenomatous hyperplasia.
C and **D,** 57-year-old man. Baseline scan (**C**) shows ground-glass opacity measuring 14 mm. Low-dose follow-up CT scan 1 year and 6 months later (**D**) shows interval increase in size up to 21 mm. Subsequent FNAB was inconclusive. VATS resection revealed malignant cells (bronchoalveolar carcinoma).

cases (22%). This last group included results where the cytopathologist considered that the pulmonary nodule might not have been targeted during the procedure. The two aborted procedures were closely monitored; the nodules were resolving on subsequent low-dose CT scans (Fig. 2). For the 24 cases with unsatisfactory FNAB results, the decisions about further procedures were based on how suspicious the nodules appeared; for 13 participants, a diagnosis was obtained by VATS resection (nine malignant and four benign nodules), and for 11 participants, follow-up low-dose CT scans were performed for at least 2 more years. The latter group showed either resolving or stable nodules in seven cases, which was reassuring for benign nodules. Four nodules remained stable (one solid and three nonsolid); they were considered as either benign (likely atypical adenomatous hyperplasia [AAH]) or possible bronchioalveolar carcinoma, and currently they still remain under active surveillance.

All seven bronchoscopies and one ultrasound-guided lymph nodule biopsy revealed malignant cells. The nine primary diagnostic VATS procedures for parenchymal nodules showed malignancies in eight cases and a benign lesion in one case (Fig. 4). The subject whose FNAB was declined by the supervising surgeon showed no growth of the nodule for 2.5 more years, which was reassuring for a benign nodule.

For four of 128 biopsy recommendations, an FNAB was performed but yielded unsatisfactory results. Three were multifocal bilateral nonsolid nodules with minimal growth on 18- and 24-month follow-up studies, and in one case, there is no growth documented. One participant showed a stable smooth solid nodule on a recent 36-month follow-up study.

TABLE 1: Summary of Evaluated CT Criteria for Pulmonary Nodules Recommended for Biopsy, at Different Time Points After Baseline Scans

Diagnostic Criteria, CT Feature	No. of Subjects (*n* = 128)	First Year[a] (*n* = 79 [61.7%])	Second Year[b] (*n* = 22 [17.2%])	More Than 2 Years[c] (*n* = 27 [21.1%])
Shape				
Solid smooth or lobulated	50/11 (1)	24/6	11/4 (1)	15/1
Solid spiculated	17/0	16/0	1/0	—
Solid cavitary	5/2	4/2	—	1/0
Part-solid	23/4	15/3	2/0	6/1
Nonsolid	9/3 (3)	7/1 (1)	1/0 (2)	1/2
Growth				
Stable	52/9 (1)	24/6 plus baseline 28/3 (1)	—	—
Growth	43/8 (3)	14/3	11/2 (3)	15/3
New	12/3	—	4/2	8/1
Size (mm)				
≤ 10	7/4	0/1	3/2	4/1
11–15	40/6 (1)	28/5	6/0 (1)	6/1
16–20	26/8 (2)	20/5 (1)	1/1 (1)	5/2
21–30	18/2 (1)	8/1	4/1 (1)	6/0
> 30	13/0	10/0	1/0	2/0
Total	104/20 (4)	66/12 (1)	15/4 (3)	23/4

Note—Data are no. of malignant nodules/no. of benign nodules (no. of pending cases). Dash (—) indicates not applicable.
[a]CT performed at baseline and at 3, 6, and 9 months.
[b]CT performed at 12, 15, 18 and 21 months.
[c]CT performed at ≥ 24 months.

The histologic diagnoses of the benign nodules were three AAHs, seven necrotizing granulomata (six mycobacterial and one *Blastomycosis*), one chronic inflammation, one organized phase acute lung injury, and three organized remote pulmonary infarcts. Three nodules are without final pathologic diagnosis but have shown no interval growth for at least 3 years after detection at MDCT, and two cases had resolving nodules. The histologic diagnoses of the confirmed malignancies include 68 adenocarcinomas, nine bronchioalveolar carcinomas, 14 squamous cell carcinomas, seven small cell carcinomas, three large cell carcinomas, and three carcinoids. Of 124 CT-detected nodules that were suggestive of lung cancer, 104 biopsy recommendations (81.3%) were true-positive for malignancy and 20 were false-positive recommendations (15.6%).

Shape of Malignant and Benign Nodules

Nodule characteristics of malignant and benign nodules are summarized in Tables 2 and 3. In both groups, a solid shape was most common. Of note, all spiculated nodules were malignant. The proportions of new nodules were about the same in both groups (11.5% [12/104] of malignant nodules and 15.0% [3/20] of benign nodules). All three new benign nodules were solid and smooth or lobulated in shape, measuring 11–16 mm. The largest proportion of benign nodules were 10–20 mm in size. All masses 30 mm or larger were malignant.

Procedure Complications

Of 108 transthoracic FNABs, 94 participants (87%) were sent home on the same day without serious complications. In 47 cases (44%), a small self-limited pneumothorax occurred. In 14 cases (13%), a postprocedural moderate-to-large pneumothorax occurred, with subsequent tube insertion and overnight hospital stay in 12 cases; two participants (both more than 70 years old) were observed in consensus with thoracic surgery for 24 hours and discharged the next day, but no tubes were inserted. One of 14 participants with chest tube insertion had a biopsy done for a benign nodule. Of the seven bronchoscopies performed, no complications were documented, and participants were sent home the same day. All 22 participants who underwent diagnostic VATS procedures, including four wedge resections in benign cases, were sent home on the third postoperative day without complications noted in the record. There was no obvious difference in hospitalization rates between the patients with benign or malignant results.

Benign Pulmonary Lesions Recommended for Biopsy

Altogether, 20 invasive procedures were recommended for benign lesions; two of them were aborted and, as mentioned previously, one biopsy recommendation was rejected by the supervising surgeon. All characteristics of benign nodules are summarized in Table 3. The majority of benign nodules were smooth or lobulated solid (*n* = 11) (Figs. 5C and 5D), followed by part-solid (*n* = 4) (Fig. 3), and nonsolid (*n* = 3) (Figs. 4A and 4B) shape. Two biopsy recommendations were made for cavitary nodules detected at baseline scan (Fig. 2). Five solid nodules showed interval growth in a time frame of 1–15 months after baseline scan, and one of them showed a rapid increase from 8 to 20 mm within 1 month.

Of all recommended diagnostic interventions, 16 of 128 FNABs (13%) and four subsequent VATS for inconclusive FNAB results, as well as one primary VATS resection for a small but growing part-solid nodule (Fig. 3), were performed for benign nodules (overall rate, 22.7% [5/22]; rate for VATS, 4% [5/128]). The overall false-positive recommendation rates for biopsy were 0.42% for primary and secondary diagnostic biopsies (20/4782) and 0.44% for re-

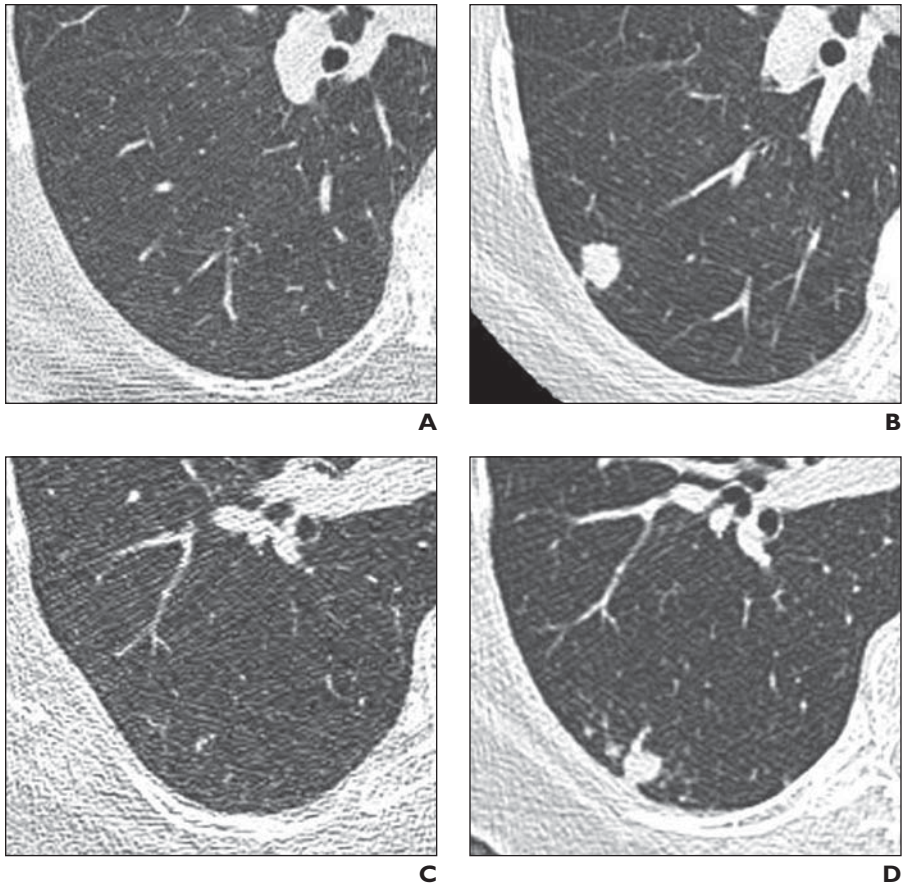

Fig. 5—Two patients with new solid pulmonary nodules with different nature.
A and **B,** 58-year old woman. Baseline scan (**A**) was unremarkable. Annual scan (**B**) shows interval development of 13-mm lobulated solid nodule. Fine-needle-aspiration biopsy (FNAB) was positive for malignancy. Non-small cell lung cancer was confirmed by surgery.
C and **D,** 63-year-old woman. Baseline scan (**C**) was normal. On annual scan (**D**), interval development is seen in 11-mm well-defined solid nodule and adjacent tiny dots. On FNAB, necrotizing granulomatous inflammation was seen.

sections (21/4782). Overall, 0.33% of FNABs (16/4782) and 0.10% of VATS (5/4782) procedures were performed for benign nodules.

Discussion

Our results show that a stringent diagnostic algorithm for follow-up of pulmonary nodules, such as that established by the I-ELCAP, results in a low rate of invasive procedures for benign nodules. Only 20 of 4782 of our participants (0.42%) had invasive procedures performed for benign nodules.

The implication of screen-detected lung nodules, and the "false-positive" diagnoses in particular, represent a heavily discussed issue in the context of the recent lung cancer screening literature. It is well known that low-dose CT screening detects a high rate of lung nodules [1] and also that almost all of the screen-detected nodules are benign [13, 14]. However, all screen-detected lung nodules require follow-up or management, to highlight the few small early-stage lung cancers within the abundant number of benign nodules. Recently, concern has been raised that the often invasive follow-up of the false-positive lung cancer screening studies results in a high number of unnecessary invasive diagnostic procedures and thoracotomies and, as such, causes harm to the mostly healthy individuals participating in lung cancer screening studies [10]. The cumulative probabilities of false-positive results on low-dose CT have been reported to be as high as 21% after baseline screening and as high as 33% after two screenings [12]. The intervention rates for benign nodules have been reported between 20% [15] and 43% [16]. These data are difficult to compare because the definition of a "positive" screening CT scan varies considerably among the different lung cancer screening studies, ranging from nodules of all sizes [1] to the presence of noncalcified nodules larger than 3 mm [17], 4 mm [15], 5 mm [3, 6], or 8 mm [18].

Our data show that a simple but well-defined algorithm to follow up screen-detected nodules results in a very low rate of interventional diagnostic procedures for benign lesions. Adherence to a similarly stringent algorithm has been successfully implemented in other screening studies, such as the NELSON trial, in which the false-positive rate was only 7.9% [19].

The diagnostic algorithm used in this study is based on a combined assessment of nodule

TABLE 2: Summary of Shape and Size of All Histologically Confirmed Malignant Pulmonary Nodules Recommended for Biopsy

Nodule Consistency	No. of Malignant Nodules/Total No. of Nodules Recommended for Biopsy (%)	Nodule Growth Assessment			Nodule Size (mm)				
		Stable[a]	Growth	New	≤ 10	11–15	16–20	21–30	> 30
Solid	50/62 (80.6)	12	27	11	7	18	10	11	4
Spiculated	17/17 (100)	15	2	—	—	7	5	2	3
Cavitary	5/7 (71.4)	3	1	1	—	1	1	1	2
Part-solid	23/27 (85.2)	14	9	—	—	8	8	3	4
Nonsolid	9/15 (60.0)	5	4	—	—	4	4	1	—
Total	104/128 (81.3)	49	43	12	7	38	28	18	13

Note—Except where noted otherwise, data are no. of nodules. Four pending cases are not included. Dash (—) indicates not applicable.
[a]Includes nodules from baseline scans.

TABLE 3: Summary of Shape and Size of All Benign Pulmonary Nodules Recommended for Biopsy

Nodule Consistency	No. of nodules	Nodule Growth Assessment			Nodule Size (mm)				
		Stable[a]	Growth	New	≤ 10	11–15	16–20	21–30	> 30
Solid	11	3	5	3	3	2	5	1	—
Spiculated	—	—	—	—	—	—	—	—	—
Cavitary	2	2	—	—	—	—	1	1	—
Part-solid	4	3	1	—	1	2	1	—	—
Nonsolid	3	1	2	—	—	2	1	—	—
Total	20/128 (15.6%)	9	8	3	4	6	8	2	—

Note—Data are no. of nodules. Dash (—) indicates not applicable.
[a]Includes nodules from baseline scans.

shape, size, and growth. Shape as such is a rather unreliable feature for lung nodule assessment. Only calcifications [20] and perifissural nodules [21] are strongly associated with benign nodules. Other morphologic CT features have been evaluated for nodule characterization with limited success [11, 22–25]. In our cohort, spiculated and lobulated solid nodules were mostly malignant; spiculations were seen only in malignant nodules. We did not find any other morphologic features that would have allowed us to predict the benign nature of the 20 nodules; their attenuation ranged from nonsolid to solid with smooth or lobulated margins. Our numbers are too small for a generalized statement, but we observed the tendency that cavitations were more commonly found in benign nodules. Larger series in the future will have to address whether the presence of cavitations indeed helps characterize a benign nodule.

The importance of follow-up imaging and growth rate computation has been stressed before [26–28] and has been very helpful in most of the screen-detected nodules in our experience as well. Growth rate assessment in the 20 benign nodules, however, showed a wide range, and in most cases was not able to predict their benign nature with the exception of a very slow growing lesion that turned out to be AAH and a fast growing lesion that was an acute inflammatory process.

^{18}F-FDG PET imaging was not routinely available at our institution for further noninvasive characterization of a lung nodule. FDG PET is a recognized tool for noninvasive characterization of indeterminate pulmonary nodules. A recent metaanalysis showed that FDG PET has a high sensitivity (> 95%) and specificity (77.8%) for malignant pulmonary nodules, although few data are currently available for subcentimeter nodules [29]. CT perfusion [30] studies would be additional noninvasive modalities for further characterization of pulmonary nodules, which in the future might be used to reduce the number of false-positive recommendations for invasive procedures in a lung cancer screening environment.

The currently accepted notion is to confirm the malignant nature of a lung nodule with an invasive procedure before planning patient management (i.e., referring the patient to a thoracic surgeon). The exact kind of invasive procedure varies depending on the experience of a particular institution. CT-guided percutaneous FNAB is widely accepted as an accurate and safe procedure for characterizing pulmonary nodules [31]. In our institution, FNAB of pulmonary nodules is common practice and has been valuable in the management of suspicious pulmonary nodules detected at screening [5]; 87% of FNABs were safely performed on an outpatient basis.

The high rate of inconclusive FNAB results in our series is likely explained by the small nodule size: nine of the inconclusively biopsied nodules were 10 mm or smaller in size. The complication rate in our cohort is similar to that in another FNAB series in subcentimeter nodules [32]. The VATS procedure has the advantage of a higher chance of definite diagnosis, both for malignant and benign diseases [33]. Although it has been shown that thoracoscopic surgery has a lower incidence of complication compare with thoracotomy [34], bleeding, prolonged lengths of hospital stay, and chest tube duration are considerable complications compared with FNAB. In our cohort, five VATS wedge resections were performed for benign nodules, corresponding to a rate of 22.7% of all VATS resections. This number is slightly higher compared with reported benign VATS rates in screening trials [35].

As indicated by the current results, in an experienced environment, a stringent algorithm of noninvasive follow-up procedures yields a high positive prediction of a malignant nodule. The rate of intervention for benign nodules was indeed very low and can be further reduced when taking cavitations and very slow or very fast growth rates into consideration. Consequently, it is currently discussed whether a purely diagnostic invasive procedure is required at all. We speculate that with careful assessment of shape and size, in combination with imaging surveillance and growth assessment as well as functional imaging such as PET or perfusion imaging, we would be able to predict the malignant nature sufficiently reliably to refer the individual for surgical treatment without a cytologic diagnosis.

In summary, this retrospective analysis of the biopsy recommendations from our lung cancer screening study confirms that the rate of false-positive recommendations for invasive interventions can be maintained at a very low rate when following a simple yet stringent algorithm. Any algorithm based on nodule shape, size, and growth will help to limit the impact of screen-detected nodules, and it might be further improved with functional imaging.

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