Smooth or Attached Solid Indeterminate Nodules Detected at Baseline CT Screening in the NELSON Study: Cancer Risk during 1 Year of Follow-up[1]

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Purpose: To retrospectively determine whether baseline nodule characteristics at 3-month and 1-year volume doubling time (VDT) are predictive for lung cancer in solid indeterminate noncalcified nodules (NCNs) detected at baseline computed tomographic (CT) screening.

Materials and Methods: The study, conducted between April 2004 and May 2006, was institutional review board approved. Patient consent was waived for this retrospective evaluation. NCNs between 5 and 10 mm in diameter ($n = 891$) were evaluated at 3 months and 1 year to assess growth (VDT < 400 days). Baseline assessments were related to growth at 3 months and 1 year by using χ^2 and Mann-Whitney U tests. Baseline assessments and growth were related to the presence of malignancy by using univariate and multivariate logistic regression analyses.

Results: At 3 months and at 1 year, 8% and 1% of NCNs had grown, of which 15% and 50% were malignant, respectively. One-year growth was related to morphology ($P < .01$), margin ($P < .0001$), location ($P < .001$), and size ($P < .01$). All cancers were nonspherical and purely intraparenchymal, without attachment to vessels, the pleura, or fissures. In nonsmooth unattached nodules, a volume of 130 mm^3 or larger was the only predictor for malignancy (odds ratio, 6.3; 95% confidence interval [CI]: 1.7, 23.0). After the addition of information on the 3-month VDT, large volume (odds ratio, 4.9; 95% CI: 1.2, 20.1) and 3-month VDT (odds ratio, 15.6; 95% CI: 4.5, 53.5) helped predict malignancy. At 1 year, only the 1-year growth remained (odds ratio, 213.3; 95% CI: 18.7, 2430.9) as predictor for malignancy.

Conclusion: In smooth or attached solid indeterminate NCNs, no malignancies were found at 1-year follow-up. In nonsmooth purely intraparenchymal NCNs, size is the main baseline predictor for malignancy. When follow-up data are available, growth is a strong predictor for malignancy, especially at 1-year follow-up.

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With the advent of low-dose multidetector computed tomographic (CT) technology and the use of smaller collimations, the detection of small subcentimeter noncalcified nodules (NCNs) of the lung has increased substantially, with prevalence rates between 61% and 92% in different screening programs (1,2). Several investigators (3) have reported that the likelihood of malignancy in NCNs smaller than 5 mm is almost negligible. The category of indeterminate NCNs between 5 and 10 mm is more challenging. They are less amenable than larger nodules for characterization by means of positron emission tomography (PET) or percutaneous biopsy (4), and the accuracy of CT-guided biopsy is substantially lower (5). Therefore, the Fleischner Society (6) recommended two to three follow-up CT scans for incidental nodules between 6 and 8 mm. Only if no growth is observed after 24 months, a nodule can, according to these recommendations, be regarded as benign. Once growth has been observed, the likelihood of malignancy increases, but benign lesions may also grow (5). Intensive observation policies are a financial burden for patients and society, and additional invasive diagnostic procedures, such as CT-guided biopsy, after the assessment of growth may incur patient morbidity. Another limitation of the growth criterion is that two-dimensional measurements are unreliable in the evaluation of small indeterminate nodules and that three-dimensional software is required for reliable estimates (7).

If it were possible to identify NCNs, which are not very likely to be malignant, follow-up CT of these lesions could be avoided, which would reduce radiation exposure, anxiety, and costs. Thus, the purpose of our study was to retrospectively determine whether baseline nodule characteristics at 3-month and 1-year volume doubling time (VDT) are predictive for lung cancer in solid indeterminate NCNs detected at baseline CT screening.

Advances in Knowledge

- In smooth solid indeterminate pulmonary nodules or nodules attached to a fissure, the pleura, or located juxtavascularly (volume between 50 and 500 mm^3), cancer risk is absent at 1 year of follow-up.
- In nonsmooth purely intraparenchymal solid indeterminate pulmonary nodules, volume is the only predictor for malignancy at baseline screening.
- A volume doubling time of less than 400 days at 1-year follow-up has a positive predictive value of 63% for malignancy in solid indeterminate pulmonary nodules.

Materials and Methods

Participants

The Dutch-Belgian randomized lung cancer screening trial (known as the NELSON study) (8) was institutional review board approved. Our study was part of the NELSON study. For our study, participants with one to five solid indeterminate NCNs between 50 and 500 mm^3, corresponding to a diameter of 4.6–9.8 mm at baseline screening, were selected between April 2004 and May 2006 (9). According to the NELSON protocol, all participants with at least one indeterminate NCN were invited to undergo 3-month repeat scanning to determine whether the nodule had grown (9). The NELSON study was approved by the medical ethics committees of all institutions, and all subjects gave their written informed consent. Informed patient consent was waived for this retrospective evaluation.

Data Acquisition

At all four screening sites, 16-section multidetector CT scanners (Mx8000 IDT or Brilliance 16P, Philips Medical Systems, Cleveland, Ohio; Sensation 16, Siemens Medical Solutions, Forchheim, Germany) were used. Scanning of the entire chest was performed in a caudocranial direction. Scanning data were obtained in the spiral mode, with 16 detector rows, 0.75-mm section thickness, and a pitch of 1.5. No contrast material was used. Low-dose settings were applied. Depending on body weight (<50, 50–80, or >80 kg), the peak voltage settings were 80–90, 120, and 140 kVp, respectively, to achieve volume CT dose index values of approximately 0.8, 1.6, and 3.2 mGy, respectively. The tube current–time product settings were adjusted accordingly, depending on the machine used. To minimize breathing artifacts, scans were performed at suspended maximal inspiration after appropriate instruction to the subjects. Data were reconstructed at 1.0-mm section thickness, with a 0.7-mm reconstruction increment.

Image Analysis

All CT images were read at two independent readings. First readings were performed by radiologists with backgrounds varying from 1 to 20 years of experience in reading thoracic CT images. Second readings were performed by two radiologists (D.M.X. and Y.W., both with 6 years of experience). In the case of a discrepancy between the two

Implication for Patient Care

- Smooth or attached (to a fissure, the pleura, or a vessel) solid indeterminate pulmonary nodules require no shorter follow-up than 1 year.

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Abbreviations:
CI = confidence interval
NCN = noncalcified nodule
VDT = volume doubling time

Author contributions:
Guarantors of integrity of entire study, D.M.X., M.O., Y.W., R.V., E.T.S., J.V., M.P., R.J.v.K.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, D.M.X., R.J.v.K.; clinical studies, D.M.X., H.J.v.d.Z.L., M.O., Y.W., R.V., E.T.S., J.V., M.P., R.J.v.K.; statistical analysis, D.M.X., H.J.v.d.Z.L.; and manuscript editing, all authors

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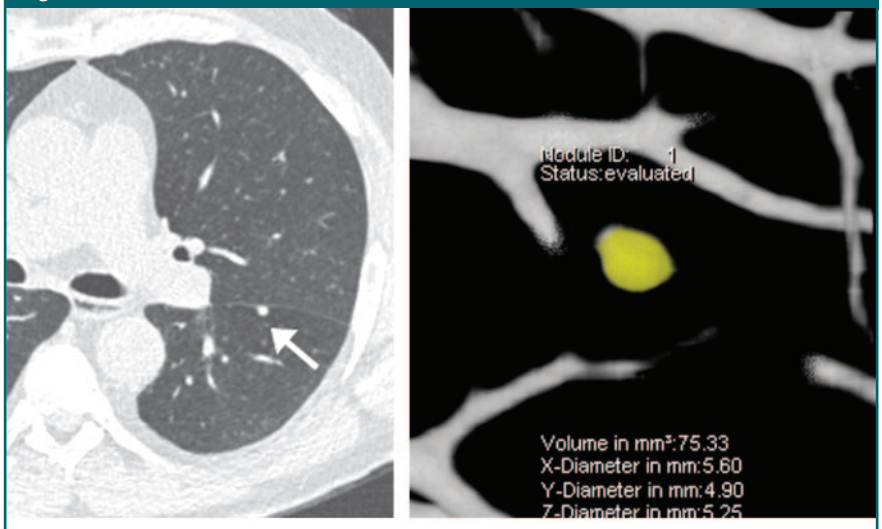
independent readers, a radiologist (M.O., with 15 years of experience in lung CT) made the final decision. A software package (Syngo Lungcare, version Somaris/5 VB 10A; Siemens Medical Solutions, Erlangen, Germany) designed to aid the radiologist in the detection of pulmonary nodules was used with a workstation (Leonardo; Siemens Medical Solutions, Erlangen, Germany), in addition to visual readings. Volumes were calculated by using three-dimensional volumetric computer software (Lungcare). In cases of inappropriate segmentation, the radiologist was able to enter manual measurements as well, which then overruled the automatically generated volume calculations as described earlier (9). Baseline and follow-up images were reviewed and displayed simultaneously on one workstation. All images were interpreted at lung window (window width, 1600 HU; window level, −700 HU) and mediastinal settings (window width, 400 HU; window level, 50 HU).

Nodule Features

An NCN was defined as solid if its lung opacity completely obscured the underlying structures (10). On the basis of morphology, NCNs were classified as either spherical or nonspherical. A nodule was considered spherical if the maximal diameter was less than twice the minimal diameter; otherwise, it was considered nonspherical. The location of the nodule refers to its intrapulmonary position. An NCN was considered attached if the length of the contact surface with other pulmonary structures (fissure, the pleura, or vessel) was more than 50% of the diameter of the nodule at volume-rendered reconstruction or on transverse images; otherwise, it was considered purely intraparenchymal. Subsequently, attached nodules were further classified according to the pulmonary structures to which they were attached: Fissure-attached nodules were attached to a minor or major fissure (Fig 1); pleural-based nodules had pleural contact (Fig 2); and juxtavascular nodules were attached to a vessel, but were not considered juxtavascular if they were attached to the tip of a vessel (Fig 3). Because the 50% contact criterion was difficult to apply to nonspherical nodules due to their irregular shape, these nodules were classified as attached only if the major part of their surface was in contact with these structures; otherwise, they were considered purely intraparenchymal.

NCNs were also classified according to their margin as smooth, lobulated, or

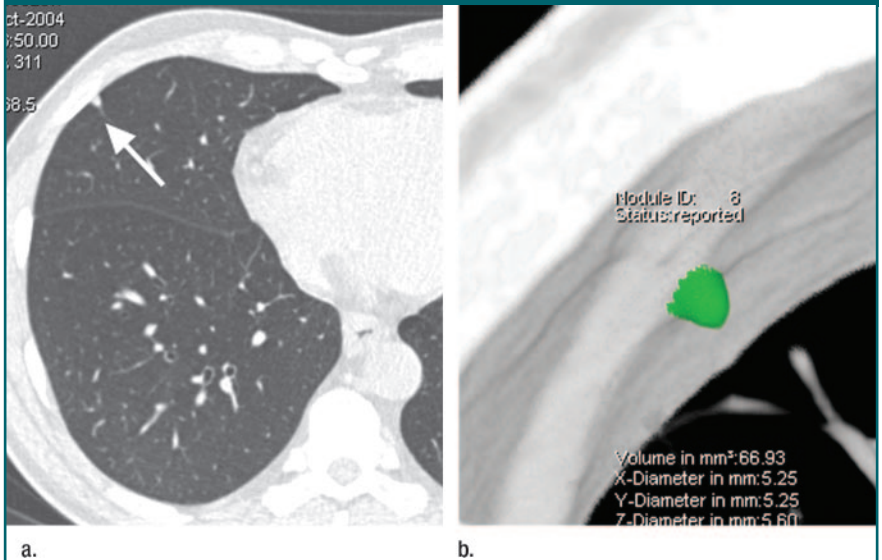
Figure 1



a. b.

Figure 1: **(a)** Transverse thin-section CT and **(b)** volume-rendered reconstruction images show spherical solid fissure-attached pulmonary nodule (arrow in **a** and yellow area in **b**) detected at baseline screening in the NELSON study.

Figure 2

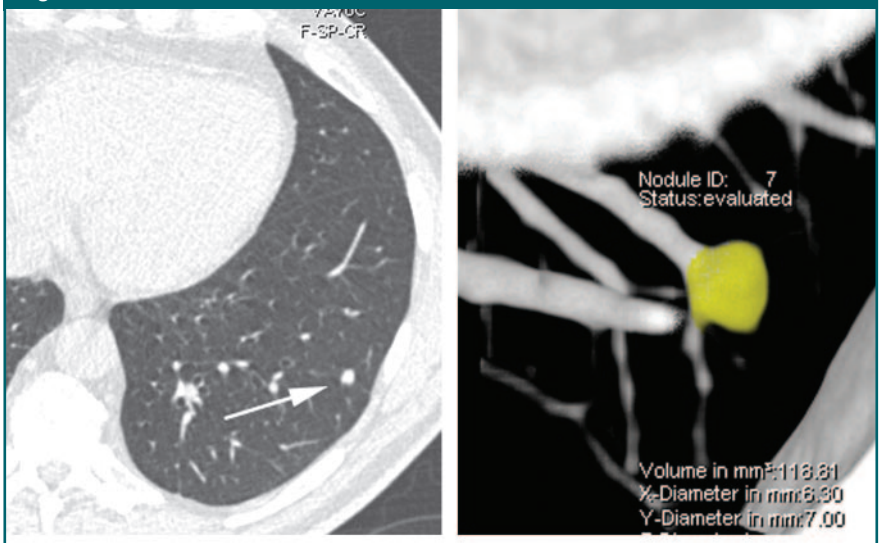


a. b.

Figure 2: **(a)** Transverse thin-section CT and **(b)** volume-rendered reconstruction images show solid pleural-based pulmonary nodule (arrow in **a** and green area in **b**) detected at baseline screening in the NELSON study.

spiculated or irregular (11). Lobulation was defined as an abrupt bulging of the contour of the lesion (12), and spiculation was defined as the presence of thicker strands extending from the nodule margin into the lung parenchyma without reaching the pleural surface (13). According to the NELSON protocol, participants with indeterminate nodules underwent repeat scanning at 3 months to assess growth. Growth was defined as a volume increase of at least 25% after at least a 3-month interval, which corresponded with a VDT of less than 400 days (9). If there was no malignancy detected at 3-month follow-up, a 1-year follow-up CT examination was performed. If the indeterminate nodules were stable at the second-round CT study 1 year later, participants underwent a third-round CT study 2 years later. The total duration of the follow-up period of all participants was 6 years.

Figure 3



a. b.

Figure 3: **(a)** Transverse thin-section CT and **(b)** volume-rendered reconstruction images show solid juxtavascular pulmonary nodule (arrow in **a** and yellow area in **b**) detected at baseline screening in the NELSON study.

Table 1

Distribution of Morphology and Margin in 891 Solid Indeterminate Nodules Detected at Baseline Screening in the NELSON Trial

Variable	Location					Median Baseline Volume (mm³)*
	Total	Intraparenchymal	Juxtavascular	Fissure Attached	Pleural Based	
Morphology						
Spherical	767 (100)	303 (39)	130 (17)	189 (25)	145 (19)	84 (50–492)
Nonspherical	124 (100)	109 (88)	1 (1)	2 (1)	12 (10)†	121 (52–499)‡
Total	891 (100)	412 (46)	131 (15)	191 (21)	157 (18)	86 (50–499)
Margin						
Smooth	654 (100)	264 (40)	102 (16)	149 (23)	139 (21)	81 (50–492)
Lobulated	168 (100)	90 (54)	24 (14)	41 (24)	13 (8)	88 (51–465)
Spiculated	69 (100)	58 (84)	5 (7)	1 (1)	5 (7)§	222 (61–499)‖

Note.—Unless otherwise indicated, data are numbers of nodules, with percentages in parentheses.

* Data in parentheses are ranges.

† χ^2 value of 104.6; degrees of freedom, three; $P < .0001$.

‡ Mann-Whitney *U* test; spherical versus nonspherical; $P < .0001$.

§ χ^2 value of 63.7; degrees of freedom, six; $P < .0001$.

‖ Mann-Whitney *U* test; spiculated versus lobulated or smooth; $P < .0001$.

Study End Points

A participant with one or more indeterminate NCNs with a VDT of less than 400 days at 3 months or 1 year was referred to a pulmonologist for work-up and final pathologic diagnosis (9). An NCN was classified as malignant only on the basis of histologic examination findings of tissue specimens. An NCN was classified as benign when either: *(a)* the nodule was benign at histologic examination; *(b)* extensive work-up by a pulmonologist, including contrast material–enhanced CT, PET, and bronchial washing, had a negative finding; *(c)* the VDT was more than 600 days at 1-year follow-up; or *(d)* the nodule had decreased in volume or completely resolved at 1-year follow-up.

Statistical Analysis

The baseline variables morphology (spherical or nonspherical) and margin (smooth, lobulated, or spiculated) were related to location and size; these relations were tested by using χ^2 and Mann-Whitney *U* tests, respectively. Subsequently, morphology, margin, location, and size were related to the VDT at 3 months. In this analysis, VDT was dichotomized into less than 400 days versus 400 days or longer. A nongrowing tumor had by definition a VDT of 400 days or longer at 3 months. The relations were tested by applying χ^2 and Mann-Whitney *U* tests. Finally, the baseline variables morphology, margin, location, and baseline volume were related to the VDT at 1 year. In this analysis, VDT was categorized into less than 400 days, 400–600 days, or 600 days or longer. A nongrowing tumor at 1 year had by definition a VDT of 600 days or longer. The relations were tested by applying χ^2 and Mann-Whitney *U* tests.

The relations between morphology, margin, location, baseline volume, and VDT at 3 months and 1 year and the presence of malignancy during 1 year of follow-up were studied by using univariate logistic regression analyses, for which malignancy was the dependent variable. Odds ratios and 95% confidence intervals (CIs) were calculated for each independent variable with regard to the presence of malignancy. In this analysis, VDT at 1 year was valued as less than 400 days if the VDT at 3 months or at 1 year of follow-up was less than 400 days. Otherwise, the VDT at 1 year was valued as 400 days or longer. Baseline volume was dichotomized into small (50–130 mm^3) versus large (130–500 mm^3). The cutoff of 130 mm^3 was based on the third quartile (ie, 75% of the nodules were smaller and 25% were larger).

Because smooth or attached nodules were never related to the presence of malignancy, these nodules were excluded from multivariate logistic regression analyses. The first multivariate logistic regression model was based on the variables morphology, margin (lobulated or spiculated), and baseline volume, with malignancy as the dependent variable. In the second model, the VDT at 3 months was added to the significant baseline variables, and in the third model, the VDT at 1 year was added to the significant baseline variables. *P* values less than .05 were considered to indicate statistically significant differences. All analyses were performed with software (SPSS, version 14.01; SPSS, Chicago, Ill).

Results

Participants

Of the 6868 participants who underwent baseline screening between April 2004 and May 2006, 658 participants with a total of 891 solid indeterminate NCNs met the inclusion criteria for this study. The median age of the participants was 62 years (range, 52–78 years). Of them, 631 (95.9%) were men and 27 (4.1%) were women. In 2% (16 of 891) of the indeterminate nodules,

Table 2

Distribution of VDTs at 3-month Follow-up in 875 Solid Indeterminate Nodules according to Variables

Variable	Total VDT	VDT <400 Days	VDT ≥400 Days
Morphology			
Spherical	754	52 (7)	702 (93)
Nonspherical	121	16 (13)	105 (87)*
Margin			
Smooth	643	43 (7)	600 (93)
Lobulated	164	13 (8)	151 (92)
Spiculated	68	12 (18)	56 (82)†
Location			
Intraparenchymal	407	40 (10)	367 (90)
Attached	468	28 (6)	440 (94)‡
Juxtavascular	123	10 (8)	113 (92)
Fissure attached	190	10 (5)	180 (95)
Pleural based	155	8 (5)	147 (95)
Median baseline volume (mm^3)§	875	83 (50–465)	86 (50–499)‖

Note.—Unless otherwise indicated, data are numbers of nodules, with percentages in parentheses. For 16 indeterminate nodules, 3-month repeat scanning was not performed.

* χ^2 value of 5.8; degrees of freedom, one; $P < .05$.

† χ^2 value of 10.3; degrees of freedom, two; $P < .01$.

‡ χ^2 value of 4.5; degrees of freedom, one; $P < .05$.

§ Data in parentheses are ranges.

‖ Mann-Whitney *U* test; difference between VDT groups: $P = .03$.

Table 3

Distribution of VDTs at 1-year Follow-up in 878 Solid Indeterminate Nodules according to Variables

Variable	Total VDT	VDT <400 Days	VDT 400–600 Days	VDT >600 Days
Morphology				
Spherical	759	5 (1)	18 (2)	736 (97)
Nonspherical	119	5 (4)	4 (3)	110 (93)*
Margin				
Smooth	652	2 (0)	14 (2)	636 (98)
Lobulated	162	2 (1)	5 (3)	155 (96)
Spiculated	64	6 (9)	3 (5)	55 (86)†
Location				
Intraparenchymal	400	10 (3)	11 (3)	379 (94)
Attached	478	0	11 (2)	467 (98)‡
Juxtavascular	131	0	3 (2)	128 (98)
Fissure attached	191	0	5 (3)	186 (97)
Pleural based	156	0	3 (2)	153 (98)
Median baseline volume (mm^3)§	878	235 (82–498)	86 (58–470)	85 (50–499)‖

Note.—Unless otherwise indicated, data are numbers of nodules, with percentages in parentheses. For 13 indeterminate nodules, no 1-year CT study was performed.

* χ^2 value of 12.0; degrees of freedom, two; $P < .01$.

† χ^2 value of 44.7; degrees of freedom, four; $P < .0001$.

‡ χ^2 value of 12.3; degrees of freedom, two; $P < .01$.

§ Data in parentheses are ranges.

‖ Mann-Whitney *U* test; difference between VDT of less than 400 days versus 400 days or longer; $P < .01$.

the 3-month repeat study was not performed: One subject (one nodule) was referred to the pulmonologist after baseline screening and underwent second-round screening 1 year later; in eight subjects (eight nodules), the nodules were missed at baseline screening but were retrospectively evaluated at second-round screening; five subjects (seven nodules) did not show up for the 3-month repeat examination. In 2% (13 of 891) of the indeterminate nodules, no 1-year CT scanning was performed: Ten subjects (10 nodules) went to routine clinical care after the detection of lung cancer at 3 months; two subjects (two nodules) went to routine clinical care after surgical resection of a growing nodule at 3 months; one subject (one nodule) did not show up at 1-year follow-up.

Nodule Features at Baseline Screening

Eighty-six percent (767 of 891) of the nodules were spherical, and 14% (124 of 891) were nonspherical; 73% (654 of 891) were smooth, 19% (168 of 891) were lobulated, and 8% (69 of 891) were spiculated or irregular (Table 1). Forty-six percent (412 of 891) were purely intraparenchymal, and 54% (479 of 891) were attached. Smooth or attached indeterminate NCNs comprised 83% (743 of 891) of all indeterminate solid pulmonary nodules detected. Nonspherical nodules were more frequently purely intraparenchymal (with regard to location) than expected, whereas spherical nodules were more often juxtavascular, fissure attached, or pleural based ($P < .0001$). Spiculated or irregular nodules were more frequently intraparenchymal than expected ($P < .0001$) (Table 1).

The median baseline volume of nonspherical nodules was 121 mm^3 (range, 52–499 mm^3; corresponding diameter, 6.1 mm) versus 84 mm^3 (range, 50–492 mm^3; corresponding diameter, 5.4 mm) in spherical nodules ($P < .0001$). The median baseline volume was 222 mm^3 (range, 61–499 mm^3; corresponding diameter, 7.5 mm) in spiculated or irregular nodules versus 81 mm^3 (range, 50–492 mm^3; corresponding diameter, 5.3 mm) in smooth and 88 mm^3 (range, 51–465 mm^3; corresponding diameter, 5.5 mm) in lobulated nodules ($P < .0001$) (Table 1).

Three-month and 1-year Follow-up

VDT at 3 months was assessed in 98% (875 of 891) of the nodules, and 8% (68 of 875) had a VDT of less than 400 days. The VDT at 3-month follow-up was dependent on baseline morphology ($P < .05$), margin ($P < .01$), and location ($P < .05$) but was independent of baseline volume (Table 2). The VDT at 1-year follow-up was assessed in 99% (878 of 891) of the nodules, and 1% (10 of 878) had a VDT of less than 400 days. The VDT at 1-year follow-up was related to baseline morphology ($P < .01$), margin ($P < .0001$), location ($P < .001$), and baseline volume ($P < .01$) (Table 3).

Cancer Cases Detected

Sixteen (1.8%) of the 891 solid indeterminate nodules were malignant, and 875 were benign. After work-up and diagnosis of the 68 growing nodules at 3-month follow-up, 10 (15%) of them were malignant (four squamous cell carcinomas, four adenocarcinomas, one large cell carcinoma, and one neuroendocrine carcinoma). Six of them were spherical, and four were nonspherical; five had a spiculated margin, and five were lobulated. The other 58 nodules with a VDT of less than 400 days were classified as benign after extensive work-up by a pulmonologist, including contrast-enhanced CT, PET, and bronchoscopy with bronchial washing for cytology. All these participants returned into the screening program and underwent second-round CT scanning at 1 year (Table 2).

After work-up and diagnosis of the 10 nodules with a VDT of less than 400 days at 1-year follow-up, five (50%) of 10 were malignant (one squamous cell carcinoma, three adenocarcinomas, and one large cell carcinoma). One of them was spherical, and four were nonspherical; all five malignant nodules had

Table 4

Results of Univariate Logistic Regression Analyses between Variables and Presence of Lung Cancer during 1-year Follow-up in 891 Nodules

Variable	Lung Cancer*	Odds Ratio†
Morphology		
Spherical	0.9 (7/767)	1
Nonspherical	7.3 (9/124)	8.5 (3.1, 23.3)
Margin		
Smooth	0 (0/654)	NA
Lobulated	3.6 (6/168)	1
Spiculated	14.5 (10/69)	4.7 (1.6, 13.5)
Location		
Intraparenchymal	3.9 (16/412)	
Attached	0 (0/503)	NA
Baseline volume (mm^3)		
<130	0.4 (3/668)	1
≥130	5.8 (13/223)	13.7 (3.9, 48.6)
VDT at 3 months (d)‡		
≥400	0.7 (6/807)	1
<400	14.7 (10/68)	23.0 (8.1, 65.5)
VDT at 1 year (d)§		
≥400	0.1 (1/868)	1
<400	50.0 (5/10)	867.0 (85.2, 8822.4)

* Data are percentages, with numbers used to calculate percentages in parentheses.

† Data in parentheses are 95% CIs. NA = not applicable.

‡ For 16 indeterminate nodules, 3-month repeat scanning was not performed.

§ For 13 indeterminate nodules, 1-year CT scanning was not performed.

spiculated margins. The other five nodules with a VDT of less than 400 days were considered benign after extensive work-up by a pulmonologist, including contrast-enhanced CT, PET, and bronchoscopy with bronchial washing for cytology. One cancer had a VDT between 400 and 600 days (adenocarcinoma) (Table 3).

Predictors for Malignancy

According to univariate logistic regression analyses, nonspherical morphology, lobulated or spiculated margins, purely intraparenchymal location, and a larger baseline volume were all significantly related to the presence of lung cancer (Table 4). During follow-up, a VDT of less than 400 days at 1 year was significantly related to the presence of lung cancer (positive predictive value of 63%). None of the smooth nodules were malignant, whereas 14.5% (10 of 69) of the spiculated or irregular nodules and 3.6% (six of 168) of the lobulated nodules were malignant. All cancers were purely intraparenchymal, and no cancer cases originated from attached nodules.

When the group of attached or smooth nodules—in which no cancers originated—was excluded, a large baseline volume (≥130 mm^3) was the only significant baseline predictor for malignancy (odds ratio, 6.3; 95% CI: 1.7, 23.0). The addition of information on the 3-month VDT yielded a second model in which a large baseline volume (≥130 mm^3) was a significant predictor of malignancy (odds ratio, 4.9; 95% CI: 1.2, 20.1), as well as the 3-month VDT (odds ratio, 15.6; 95% CI: 4.5, 53.5). A third model including baseline volume and 1-year VDT showed that a large baseline volume (≥130 mm^3) was no longer a significant predictor of malignancy, but, in contrast, the 1-year VDT (odds ratio, 213.3; 95% CI: 18.7, 2430.9) became a very strong predictor (Table 5). In this series, the baseline probability for having a malignant nodule was 1.8%.

Table 5

Results of Multivariate Logistic Regression Analyses between Variables and Presence of Lung Cancer during 1-year Follow-up in 148 Nodules

Variable	Lung Cancer*	Odds Ratio†		
		Model 1	Model 2	Model 3
Morphology				
Spherical	10.4 (7/67)			
Nonspherical	11.1 (9/81)	NS	NS	NS
Margin				
Lobulated	6.7 (6/90)			
Spiculated	17.2 (10/58)	NS	NS	NS
Baseline volume (mm^3)				
<130	3.7 (3/81)	1	1	1
≥130	19.4 (13/67)	6.3 (1.7, 23.0)	4.9 (1.2, 20.1)	NS
VDT at 3 months (d)‡				
≥400	4.8 (6/125)		1	1
<400	47.6 (10/21)	NI	15.6 (4.5, 53.5)	NI
VDT at 1 year (d)§				
≥400	0.8 (1/131)			1
<400	62.5 (5/8)	NI	NI	213.3 (18.7, 2430.9)

Note.—Smooth or attached nodules were excluded.

* Data are percentages, with numbers used to calculate percentages in parentheses.

† Data in parentheses are 95% CIs. NI = not included in the model, NS = not significant, excluded from the model.

‡ Analysis was based on 146 nodules; two subjects (two nonattached nodules with nonsmooth margins) did not show up at 3-month follow-up.

§ Analysis was based on 139 nodules; 10 subjects went to routine clinical care after the detection of lung cancer at 3 months, and one subject went to routine clinical care after surgical resection of a growing nodule at 3 months.

Discussion

During the past few years, a lot of new information has become available on the value of size, shape, and margin in the discrimination of benign from malignant CT-detected pulmonary nodules (3,5,14–19). Nodules less than 3 mm in diameter have only a 0.2% chance of being malignant; this chance is 0.9% for nodules between 4 and 7 mm, 18% for nodules between 8 and 20 mm, and 50% for those larger than 20 mm (6). In addition to size, the consistency of the nodule (ie, solid, partially solid, nonsolid) and VDT are also predictive for malignancy. Nonsolid nodules (pure ground-glass opacities) tend to grow slowly with VDTs of approximately 800 days and a 34% chance of being malignant. Partially solid nodules have the highest probability of malignancy (40%–50%), with VDTs of around 450 days, while solid nodules (≤10 mm) have VDTs around 150 days and a malignancy rate of 15% (5,20). The group of baseline-detected indeterminate solid pulmonary nodules between 50 and 500 mm^3 in size, with diameters of 5–10 mm, gives rise to diagnostic problems because of their small size. Therefore, the Fleischner Society recommended performing one or more follow-up studies to assess growth (6). Although we confirmed in our study that a VDT of less than 400 days at 1 year is a very strong predictor for malignancy, with a positive predictive value of 63% in indeterminate solid nodules, additional participant (ie, presence of chronic obstructive pulmonary disease) and nodule (ie, location in the upper lobes) features are needed at baseline screening to improve diagnostic accuracy and to avoid repeat CT examinations and the inevitable associated diagnostic interventions. Furthermore, diagnostic accuracy of the growth criterion at 3 months appeared to be relatively low because benign lesions may also grow (5), as was illustrated in our study: Only 15% of the nodules with significant growth at 3 months were malignant.

In our study, we identified, to our knowledge, two new independent negative predictive factors for malignancy in indeterminate solid NCNs detected in a population at high risk for lung cancer

who participated in a multisection CT screening trial for lung cancer. In smooth or attached nodules, no malignancies were found, despite the fact that some of them showed indeterminate or even high growth rates during a 1-year follow-up period. In contrast, all cancers originated from purely intraparenchymal nodules. Smooth or attached indeterminate NCNs comprised 83% of all indeterminate solid pulmonary nodules detected and are as such a common finding. On the basis of these observations, we recommend that, in this type of indeterminate nodule detected at baseline screening, 1-year follow-up CT scanning is sufficient, without additional repeat scanning at 3 or 6 months. The histologic correlates of pleural-based opacities are most often scars, pleural plaques, or small postinfarction fibrotic lesions. The triangular or ovoid nodules adjacent to the fissures may represent intrapulmonary lymph nodes, which may rapidly grow or decrease in size (21,22). The juxtavascular nodules may represent small lymph nodes or small branching vessels, while bronchiolitis or a small bronchiectasis may also appear as a vessel- or fissure-attached nodule.

In nonsmooth purely intraparenchymal NCNs, only baseline volume appeared to be a predictor for malignancy, while morphology and margin were not. When follow-up information on growth was available, a VDT of less than 400 days at 3 months was also a predictor for malignancy. At 1-year follow-up, the only very strong predictor for malignancy was a VDT of less than 400 days. The correlation between baseline nodule volume and cancer risk found in our study is consistent with the results of other studies (3,23,24). When adjusted for baseline size, a spiculated margin appeared no longer predictive at multivariate analysis.

Although our study represents, to our knowledge, one of the largest series of low-dose multisection CT screening–detected indeterminate solid NCNs, it was limited by the relatively small numbers of lung cancer cases detected among them and by the relatively short follow-up period of only 1 year. It might be possible that some of the NCNs detected may be cancer cases after extended follow-up. This might be due to the fact that cancer growth is not always linear and may be sigmoid shaped, with an acceleration phase after a period of apparent absence of growth (25). This was illustrated by the fact that in our study six cancers detected at 1-year follow-up had a VDT of more than 400 days at 3 months. However, Revel et al (26) demonstrated that the negative predictive value for cancer in solid nodules with a VDT of more than 500 days is very high (98%). Therefore, the conclusions of our study could apply for a 1-year follow-up period after baseline screening. Another limitation of our study was the fact that the VDT was a criterion for referral, and the strength of the positive predictive value of this predictor may be caused by partial verification bias. There is, however, no doubt that growth is a strong predictor of malignancy in clinical practice, and the exact quantification of this strength is therefore of little relevance.

In conclusion, no malignancies were found at 1-year follow-up in smooth or attached solid indeterminate NCNs. In nonsmooth purely intraparenchymal NCNs, baseline size was the only predictor for malignancy. When follow-up data were available, growth was a strong predictor for malignancy, especially at 1-year follow-up.

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