Five-year Lung Cancer Screening Experience:

CT Appearance, Growth Rate, Location, and Histologic Features of 61 Lung Cancers[1]

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Purpose: To retrospectively evaluate the computed tomography (CT)-determined size, morphology, location, morphologic change, and growth rate of incidence and prevalence lung cancers detected in high-risk individuals who underwent annual chest CT screening for 5 years and to evaluate the histologic features and stages of these cancers.

Materials and Methods: The study was institutional review board approved and HIPAA compliant. Informed consent was waived. CT scans of 61 cancers (24 in men, 37 in women; age range, 53–79 years; mean, 65 years) were retrospectively reviewed for cancer size, morphology, and location. Forty-eight cancers were assessed for morphologic change and volume doubling time (VDT), which was calculated by using a modified Schwartz equation. Histologic sections were retrospectively reviewed.

Results: Mean tumor size was 16.4 mm (range, 5.5–52.5 mm). Most common CT morphologic features were as follows: for bronchioloalveolar carcinoma (BAC) (n = 9), ground-glass attenuation (n = 6, 67%) and smooth (n = 3, 33%), irregular (n = 3, 33%), or spiculated (n = 3, 33%) margin; for non-BAC adenocarcinomas (n = 25), semisolid (n = 11, 44%) or solid (n = 12, 48%) attenuation and irregular margin (n = 14, 56%); for squamous cell carcinoma (n = 14), solid attenuation (n = 12, 86%) and irregular margin (n = 10, 71%); for small cell or mixed small and large cell neuroendocrine carcinoma (n = 7), solid attenuation (n = 6, 86%) and irregular margin (n = 5, 71%); for non–small cell carcinoma not otherwise specified (n = 5), solid attenuation (n = 4, 80%) and irregular margin (n = 3, 60%); and for large cell carcinoma (n = 1), solid attenuation and spiculated shape (n = 1, 100%). Attenuation most often (in 12 of 21 cases) increased. Margins most often (in 16 of 20 cases) became more irregular or spiculated. Mean VDT was 518 days. Thirteen of 48 cancers had a VDT longer than 400 days; 11 of these 13 cancers were in women.

Conclusion: Overdiagnosis, especially in women, may be a substantial concern in lung cancer screening.

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Early detection of lung cancer may improve patient mortality. Computed tomography (CT) as a screening tool has been evaluated in several large screening trials for early lung cancer detection (1–6). Our institution was involved in a National Cancer Institute–sponsored lung cancer screening trial in which individuals underwent annual screening chest CT for 5 years. The final results of this screening trial have been reported (6). The purpose of our current study was to retrospectively evaluate the CT-determined size, morphology, location, morphologic change, and growth rate of incidence and prevalence lung cancers detected in high-risk individuals who underwent annual screening chest CT for 5 years and to evaluate the histologic features and stages of these cancers.

Materials and Methods

Study Participants

The original prospective screening trial and this retrospective study were approved by our institutional review board and compliant with the Health Insurance Portability and Accountability Act. Written informed consent was obtained from all participants in the prospective trial, and informed patient consent was waived for this retrospective review.

In the original prospective screening trial, annual screening chest CT and sputum cytology were performed in 1520 high-risk participants for 5 years. High-risk participant was defined as a man or woman aged 50 years or older with a smoking history of at least 20 pack-years. Participants had to have no prior history of cancer, no need for supplemental oxygen, and a life expectancy of at least 5 years. If a participant had stopped smoking, he or she had to have quit less than 10 years prior to the study onset. Enrollment took place from January 20, 1999, to December 15, 1999. Final CT scanning was completed in December 2003, with the results of follow-up reported through May 26, 2004.

In the 1520 participants enrolled in the study, 68 lung cancers were diagnosed in 66 patients. For our current study, 61 of these cancers (24 in men, 37 in women; age range, 53–79 years; mean, 65 years) in 59 patients had a primary tumor that could be identified at CT. For four of the seven excluded cancers, the primary tumor could not be identified: Two were extensive multifocal or metastatic tumors, one was extensive right hilar and mediastinal lymphadenopathy with a postobstructive nodular infiltrate, and one was identified at sputum analysis only and was not visible at CT. Three of the excluded cancers were seen only on unavailable outside CT scans. Forty-eight lung cancers were depicted at more than one CT examination before treatment and therefore could be evaluated for growth rate and morphologic change.

CT Imaging

Screening chest CT examinations were performed with a four-section multidetector helical CT scanner (LightSpeed QX/i; GE Medical Systems, Milwaukee, Wis) by using a 5-mm section width, 3.75-mm reconstruction interval, high-speed mode, pitch of 1.5, exposure of 0.8 second per rotation, table feed of 30 mm per rotation, 120 kVp, and 40 mA. All screening CT scans were obtained without contrast material. Screening CT scans were obtained initially and every 12 months thereafter for 5 years. Standard chest CT examinations were ordered at the discretion of a board-certified pulmonologist (including J.R.J. and D.E.M.) and were performed without contrast material by using an eight-section multidetector helical CT scanner (LightSpeed Ultra-8; GE Medical Systems) and a 5-mm section width, 5-mm reconstruction interval, pitch of 1.35, exposure of 0.5 second per rotation, table feed of 13.5 mm per rotation, 120 kVp, and 430 mA. CT scans had been prospectively read in cine mode by one of four thoracic radiologists at a computer workstation. The experience after board certification of these radiologists (including T.E.H. and S.J.S.) ranged from 7 to 26 years (mean, 15.5 years).

Image Review

For our current study, lung cancers were retrospectively reviewed on all preoperative CT scans, including the screening and standard images. After the original reports were reviewed, tumor size, morphology, and location were assessed by one chest radiologist (R.M.L.) at a computer workstation.

Advances in Knowledge

- Thirteen of 48 CT screening–detected lung cancers had a volume doubling time longer than 400 days and therefore may have been overdiagnosed.
- The majority of the possibly overdiagnosed cancers occurred in women.
- The most common CT appearance of CT screening–detected lung cancers was an irregular semisolid or solid nodule with a mean size of 16.4 mm.
- If the CT morphology of a lung cancer changed over time, it most commonly increased in attenuation and/or became more irregular or spiculated.
- A minority of lung cancers became smaller, decreased in attenuation, or became more smoothly marginated at CT.

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Abbreviations:
BAC = bronchioloalveolar carcinoma
GG = ground glass
MLP = Mayo Lung Project
NSCLC-NOS = non–small cell lung cancer not otherwise specified
SCLC-NEC = mixed small cell and large cell neuroendocrine carcinoma
VDT = volume doubling time

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Measurements were made to the nearest millimeter by using computer electronic calipers on transverse scans in lung windows. Tumor size was determined by calculating the average of two diameters. Diameters were measured according to the longest horizontal axis and the maximum diameter perpendicular to this axis. If thin-section CT analysis was performed, measurements were taken from the thin-section scans. A nodule was defined as a focal round or oval opacity that measured less than 30 mm in diameter. If the measured tumor was equal to or greater than 30 mm in greatest diameter, it was defined as a mass. If a tumor had multiple linear opacities projecting from it, it was defined as spiculated. Spiculations were not included in the tumor diameter measurements. If two nodules or masses within one lobe were histologically positive for cancer with no evidence of metastases (ie, stage T4), the measurements of the tumor that was identifiable on the most CT scans or was oldest were taken. If the tumors appeared simultaneously on the scan, only the larger nodule or mass was measured.

When the tumor size measured at more than one CT examination was available, the volume doubling time (VDT) was calculated by using a modified Schwartz equation of exponential growth (7–9) (Appendix, Fig A1). If data from more than two CT examinations were available, the measurements from the first and last examinations were used to calculate the VDT. The VDT was compared with the patient's sex and the histologic type, transaxial location, attenuation, and stage of the tumor.

Tumor morphology (ie, attenuation and margins) was assessed on each CT scan. Tumor cavitation or the presence of air bronchograms also was noted. If a tumor was a faint hazy opacity, its attenuation was described as ground glass (GG). If a tumor had both hazy attenuation and solid elements, its attenuation was described as semisolid. Otherwise, a tumor's attenuation was categorized as solid. Tumor margins were characterized as smooth, irregular, or spiculated. Tumor attenuation was compared with the patient's sex and the stage and VDT of the tumor.

If a tumor was imaged at more than one CT examination, the change in its morphology was assessed. Change in tumor attenuation was described as an increase (ie, GG to semisolid or solid, semisolid to solid, or attenuation increase without change in category) or decrease (ie, solid to semisolid or GG, semisolid to GG, or attenuation decrease without change in category). Tumor margin changes were noted as smoother (ie, spiculated to irregular or smooth, irregular to smooth) or more irregular or spiculated (ie, smooth to irregular or spiculated, irregular to spiculated). If a tumor's attenuation or margins changed in more than one way over subsequent CT examinations (ie, increased attenuation on one scan then decreased attenuation on another), the change was described as variable. If there was no change in tumor attenuation or margins, this was noted also.

Tumor location also was assessed on each CT scan. The tumor's transaxial location was described as peripheral if the center of the nodule or mass was within 2 cm of the interface of the lung and chest wall; otherwise the location was described as central. The lobar location within the lung also was noted.

A nodule or mass was defined as an incidence cancer if the tumor was not reported at the participant's first screening CT examination and as a prevalence cancer if it was reported at the first screening CT examination. Note was made of incidence cancers that were present at first screening CT but not reported at the first reading (ie, noted only in retrospect).

Other Data

Patient age was documented as the age on the date of tumor resection or, if resection was not performed, the age on the date that tissue was obtained at biopsy. All histologic sections of the tumors were retrospectively reviewed by two pathologists (including H.D.T., with 20 years experience in chest abnormalities) in consensus and classified according to the 2004 World Health Organization schema (10). In two cases (both non–small cell lung cancers not otherwise specified ([NSCLC-NOS]), histologic data were unavailable for retrospective review and therefore were retrieved from the clinical notes. All bronchioloalveolar carcinomas (BACs) were diagnosed according to findings in resected specimens. For the purposes of this study, the term *non-BAC adenocarcinoma* refers to nonpure BAC adenocarcinomas. The stages of the non–small cell carcinomas were retrieved from the clinical notes and compared with the CT-determined tumor size, VDT, and attenuation.

Results

Histologic Analysis

The 61 tumors were classified histologically as follows: nine (15%) BACs in one man and eight women, 25 (41%) non-BAC adenocarcinomas in 14 women (with 16 tumors) and nine men, 14 (23%) squamous cell carcinomas in eight men and six women, five (8%) small cell carcinomas in one man and four women, two (3%) mixed small cell and large cell neuroendocrine carcinomas (SCLC-NECs) in two men, five (8%) NSCLC-NOS tumors in two men and three women, and one (2%) large cell carcinoma in a man. Two of the nine BACs were mucinous. One of the two patients who had two lung cancers had two metachronous grade 3 non-BAC adenocarcinomas that were resected within 2½ years of each other. The other patient had two grade 3 non-BAC adenocarcinomas that were resected within a year of each other, although both were present at first screening CT. The largest and most suspicious lesion was resected first.

Incidence and Prevalence

There were 31 incidence and 30 prevalence cancers. Incidence cancers included six BACs, seven non-BAC adenocarcinomas, nine squamous cell carcinomas, three small cell carcinomas, one SCLC-NEC, four NSCLC-NOS tumors, and one large cell carcinoma. Prevalence cancers included three BACs, 18 non-BAC adenocarcinomas, five squamous cell carcinomas, two small cell carcinomas, one

SCLC-NEC, and one NSCLC-NOS. Of the 31 incidence cancers, nine were present in retrospect at first screening CT: three BACs, five non-BAC adenocarcinomas, and one NSCLC-NOS.

Tumor Size

Mean tumor size was 16.4 mm ± 12.1 (standard deviation) (median, 12 mm; range, 5.5–52.5 mm). Mean cancer sizes by histologic type were as follows: BACs, 11.1 mm; non-BAC adenocarcinomas, 13.8 mm; squamous cell carcinomas, 15.6 mm; small cell carcinomas, 29.4 mm; SCLC-NECs, 52.0 mm; NSCLC-NOS tumors, 23.5 mm; and large cell carcinomas, 11.5 mm. There were 54 non–small cell carcinomas, and all of them had been staged. Table 1 summarizes the stages of these lung cancers according to size range: less than 10 mm, 10–20 mm, 21–30 mm, and greater than 30 mm. Of the 50 non–small cell carcinomas that were 30 mm or smaller, six (12%) were stage III, and there were no stage IV cancers.

Cancer Growth Rate

The 48 cancers in which VDT could be calculated (ie, that were imaged at more than one CT examination) included all nine (100%) BACs, 22 (88%) of 25 non-BAC adenocarcinomas, eight (57%) of 14 squamous cell carcinomas, three (43%) of seven small cell or SCLC-NECs, all five (100%) NSCLC-NOS tumors, and the one (100%) large cell carcinoma. Mean VDT was 518 days ± 1094 (median, 166 days; range, 10–5810 days). Although all VDTs were positive, four tumors became smaller at some point during the study according to both visual and computer caliper assessment. These were two BACs (one from 5 × 5 mm to 4 × 4 mm, one from 9 × 11 mm to 9 × 9 mm) and two non-BAC adenocarcinomas (one from 9 × 12 mm to 8 × 11 mm, one from 7 × 11 mm to 3 × 4 mm) (Fig 1). Mean VDTs are cited according to patient sex and tumor histologic type, transaxial location, attenuation, and stage in Table 2. Thirteen (27%) of the 48 tumors (three BACs, 10 non-BAC adenocarcinomas) had a VDT longer than 400 days; 11 (85%) of these 13 tumors were in women, and two (15%) were in men. The tumors with a VDT longer

Table 1

Sizes and Stages of 54 CT Screening–detected Lung Cancers

Cancer Size (mm)	Tumor Stage						
	IA	IB	IIA	IIB	IIIA	IIIB	IV
<10	15	0	1	0	2	2	0
10–20	18	2	3	0	2	0	0
21–30	4	1	0	0	0	0	0
>30	0	0	0	1	2	1	0

Note.—Data are numbers of cancers. Of the total 61 lung cancers, seven were small cell carcinomas and therefore were staged as limited or extensive.

Figure 1

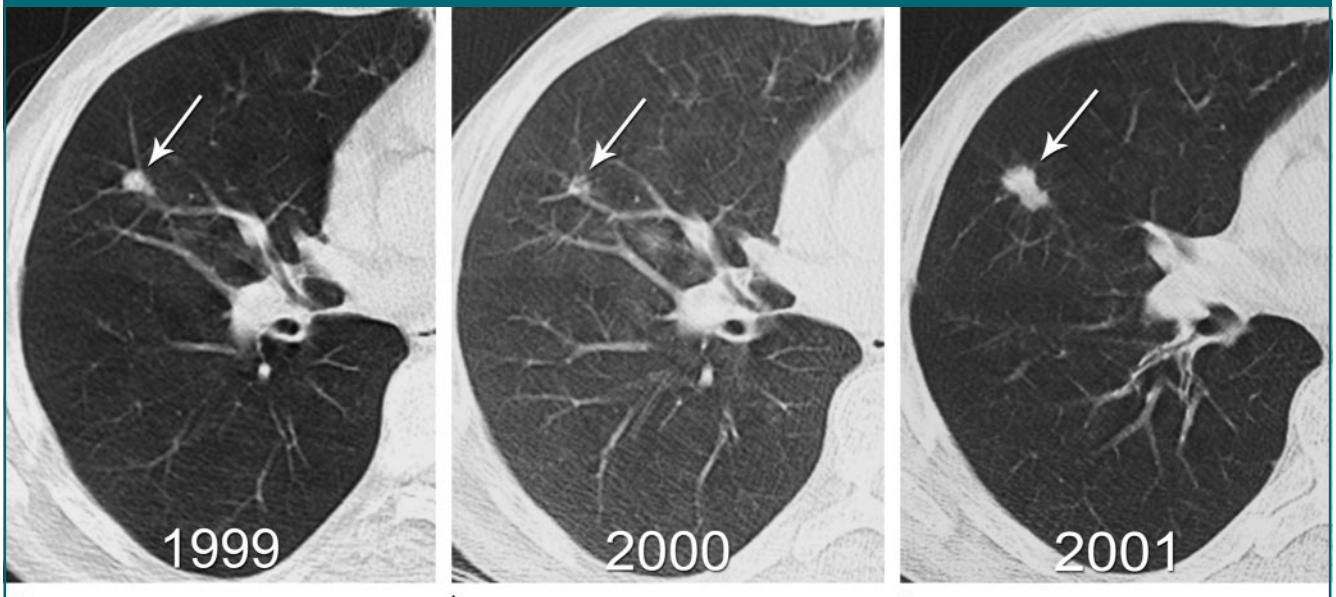


Figure 1: **(a–c)** Three sequential transverse CT scans (5-mm section width) obtained 1 year apart show a grade 3 non-BAC adenocarcinoma (arrow) in the right middle lobe that became smaller after initial screening CT but enlarged on the subsequent scan.

than 400 days were stages IA (n = 10), IB (n = 1), and IIA (n = 2).

CT Morphology and Morphologic Changes

CT attenuation categorized according to histologic type (Appendix, Table A1) was as follows: GG (Fig 2a) in six (67%) and semisolid in three (33%) BACs; GG in two (8%), semisolid in 11 (44%) (Fig 2b), and solid in 12 (48%) non-BAC adenocarcinomas (Fig 2c); semisolid in two (14%) and solid in 12 (86%) squamous cell carcinomas; semisolid in one (14%) and solid in six (86%) small cell carcinomas or SCLC-NECs; semisolid in one (20%) and solid in four (80%) NSCLC-NOS tumors; and solid in the one (100%) large cell carcinoma. BACs were equally distributed among those with smooth (n = 3, 33%), irregular (n = 3, 33%), or spiculated (n = 3, 33%) margins. Non-BAC adenocarcinoma margins were more commonly irregular (n = 14, 56%) or spiculated (n = 8, 32%). The one large cell carcinoma had a spiculated margin. The margins of the remaining tumors were most commonly irregular (10 [71%] squamous cell carcinomas, five [71%] small cell carcinomas or SCLC-NECs, three [60%] NSCLC-NOS tumors).

Sixteen (26%) of the 61 tumors had air bronchograms. The majority of these tumors were BACs (three [33%] of nine) and non-BAC adenocarcinomas (10 [40%] of 25). The other three tumors with air bronchograms were one small cell carcinoma (the only peripheral small cell carcinoma), one NSCLC-NOS tumor, and the one large cell carcinoma. Only one tumor, a squamous cell carcinoma, demonstrated cavitation. Tumor attenuation is categorized according to patient sex and tumor stage and VDT in Table 3.

Of 48 tumors that were imaged at more than one CT examination, 21 (44%) had attenuation changes and 20 (42%) had margin changes. Attenuation changes in 21 tumors were as follows: Twelve (57%) tumors had increases (from semisolid to solid in six, from GG to solid in one, from GG to semisolid in one, no category change in two with GG and in two with semisolid attenuation); five (24%), decreases (from solid to semisolid in four, no category change in one with semisolid attenuation); and four (19%), variable attenuation changes. In the 20 tumors with margin changes, the margins became more irregular or spiculated in 16 (80%) tumors, became smoother in three (15%), and were variable in one (5%).

Table 2

VDTs Categorized according to Patient Sex and Histologic Type, Transaxial Location, Attenuation, and Stage of Tumor

Characteristic	No. of Cancers (n = 48)*	Mean VDT (d)†	Median VDT (d)
Patient sex			
Male	18	234 ± 447	92
Female	30	688 ± 1321	217
Tumor histologic type			
BAC	9	780 ± 1545	210
In male patients	1	210	210
In female patients	8	851 ± 236	236
Adenocarcinoma (non-BAC)	22	746 ± 1238	343
In male patients	8	427 ± 635	204
In female patients	14	928 ± 1470	403
Squamous cell	8	103 ± 58	88
In male patients	4	77 ± 25	72
In female patients	4	128 ± 74	102
Small cell or SCLC-NEC‡	3	49 ± 36	58
In male patients	2	34 ± 34	34
In female patients	1	81	81
NSCLC-NOS	5	81 ± 31	77
In male patients	2	75 ± 36	75
In female patients	3	85 ± 35	77
Large cell§	1	49	49
Tumor transaxial location			
Central	23	423 ± 1026	94
Peripheral	25	605 ± 1168	237
Tumor attenuation			
GG	8	469 ± 452	236
Semisolid	15	568 ± 1222	210
Solid	25	503 ± 1188	110
Tumor stage			
IA	31	652 ± 1303	197
IB	3	292 ± 104	275
IIA	5	632 ± 827	101
IIB	1	55	55
IIIA	4	116 ± 88	74
IIIB	1	83	83
Limited‖	3	50 ± 36	58

* Same as numbers of patients.

† With the exception of data for the one BAC in a male patient, the one small cell or SCLC-NEC in a female patient, the one large cell carcinoma, the one stage IIB tumor, and the one stage IIIB tumor, data are mean VDTs ± standard deviations.

‡ For the categorization in this table, the SCLC-NEC tumors were combined with the small cell lung cancers.

§ One male patient had large cell lung cancer.

‖ Small cell or SCLC-NEC.

Tumor Location

Tumors (n = 61) occurred more often in the right (n = 36, 59%) than in the left (n = 25, 41%) lung. The majority of tumors were in the upper lobes (n = 34, 56%), and tumors were more often located in the right upper lobe (n = 19, 31%) than in the left upper lobe (n = 15, 25%). There was no substantial lo-

bar predominance based on tumor histologic type. Tumor transaxial location was almost equally divided between the central (n = 32, 52%) and peripheral (n = 29, 48%) regions. Non-BAC adenocarcinomas (n = 25) were most commonly peripheral (n = 16, 64%), while squamous cell and small cell carcinomas were most commonly central (10 [71%] of 14 and seven [88%] of eight tumors, respectively). BACs (n = 9) were nearly equally central (n = 4, 44%) and peripheral (n = 5, 56%), as were NSCLC-NOS tumors (n = 5: three [60%] central, two [40%] peripheral). Both SCLC-NECs were central. The large cell carcinoma was peripheral.

Table 3

Tumor Attenuation Categorized according to Patient Sex and Tumor Stage and VDT

Characteristic	GG	Semisolid	Solid
Patient sex			
Male	0	8	16
Female	8	10	19
Tumor stage			
IA	7	15	15
IB	1	0	2
IIA	0	1	4
IIB	0	0	1
IIIA	0	1	5
IIIB	0	1	3
IV	0	0	0
Limited*	0	1	4
Tumor VDT (d)			
<100	0	4	12
100–400	5	7	7
>400	3	4	6

Note.—Data are numbers of cancers. All 61 cancers (in 61 patients) were analyzed according to patient sex and tumor stage. However, VDT was analyzed in 48 cancers (in 48 patients).

* Small cell lung cancer.

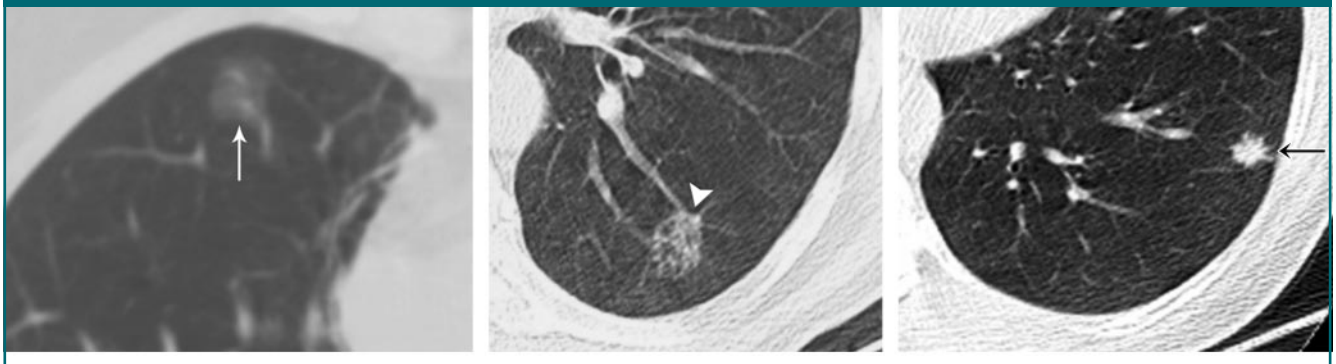
Discussion

Investigators in the Mayo Lung Project (MLP) (11) examined 9211 male smokers older than 12 years to see if performing screening chest radiography and sputum cytology would reduce lung cancer mortality. Of the 9211 participants, 4618 underwent chest radiography and sputum cytology every 4 months for the first 6 years (intervention arm), while the others were advised to undergo the same examinations annually (usual-care arm). No significant reduction in lung cancer mortality was observed in the intervention arm. Marcus et al (12) extended the follow-up in the MLP by retrospectively examining the data of the participants for the 13 years after the MLP had ended. Again, no significant reduction in lung cancer mortality was observed, but the intervention arm participants had better survival than did the usual-care arm participants (16 vs 5 years). One important issue raised in that study was that overdiagnosis may account for the improved survival rates without improved mortality. Specifically, a number of indolent cancers that would never have been detected in the absence of screening may have been detected in the intervention arm. This possibility of overdiagnosis was viewed as a very important limitation of using chest radiography for screening.

Yankelevitz et al (13) examined the issue of overdiagnosis in the MLP and in another similar screening trial, the Memorial Sloan-Kettering Cancer Center Project, (14), by examining the VDT of the stage I lung cancers detected in these studies. Overdiagnosed cancers were defined as those having a VDT longer than 400 days. They found that among the stage I cancers, 2% of the MLP cancers and 7% of the Memorial Sloan-Kettering cancers could be considered overdiagnosed. They concluded, contrary to prior observations in these studies, that screening chest radiography did not lead to a high proportion of overdiagnosed stage I lung cancers.

In our study, 33% of 48 tumors had a VDT shorter than 100 days; 40%, a VDT of 100–400 days; and 27%, a VDT longer than 400 days. If we used the definition of overdiagnosis proposed by

Figure 2



a. b. c.

Figure 2: Tumor attenuation on transverse CT scans (5-mm section width). **(a)** Scan obtained through the right middle lobe shows a grade 2 BAC (arrow) with hazy increased attenuation, through which underlying lung architecture can be seen, consistent with a GG attenuation nodule. **(b)** Scan shows a grade 2 non-BAC adenocarcinoma (arrowhead) in left lower lobe with both GG and solid elements, consistent with a semisolid nodule. **(c)** Scan obtained through left lower lobe shows grade 3 non-BAC adenocarcinoma (arrow) with solid attenuation and spiculated margins.

Yankelevitz et al, 27% (n = 13) of the lung cancers in which VDT was calculable would be considered overdiagnosed. All of these were operable tumors: 10 were stage IA, one was stage IB, and two were stage IIA. If we recalculated these findings for stage I tumors only, 25% (10 of 40) of our stage I tumors would be considered overdiagnosed. This rate is much higher than the rate of 2%–7% reported by Yankelevitz et al (13).

This discrepancy in the percentage of possibly overdiagnosed cancers may be due to a number of factors. First, it may be partially explained by the differences inherent of the modalities used in the two studies: The MLP and Memorial Sloan-Kettering studies involved screening chest radiography while ours involved screening chest CT. CT is more sensitive for nodule detection, so there may have been small nodules with VDTs longer than 400 days that were not detectable at radiography in the other study. A second important possibility is that because cancer overdiagnosis occurs primarily in women, the MLP and Memorial Sloan-Kettering study overdiagnosis rates were lower because they involved men only. In our study, 11 (85%) of 13 tumors with a VDT longer than 400 days were in women versus two (15%) that were in men. If we considered only the men in our study, then the cancers in two (11%) of the 18 men in whom VDTs were calculable—8% (two of 24) of all the men in our study—would be considered overdiagnosed. These percentages are more similar to those reported by Yankelevitz et al (13).

In contrast, Hasegawa et al (9) examined 61 lung cancers detected at annual screening chest CT in 38 men and 23 women and calculated VDTs by using the modified Schwartz equation. The total percentage of tumors with VDTs longer than 400 days was not stated in that study, but it was stated that 27 adenocarcinomas had a VDT longer than 450 days, so the overdiagnosis rate was possibly at least 44% (27 of 61 tumors). This is higher than the overdiagnosis rate in both our study and the Yankelevitz et al investigation. It is unclear if these cancers were primarily in men or women, but a longer mean tumor VDT in women than in men was reported. Last, variation in VDT calculations among the studies also may contribute to the discrepant overdiagnosis rates.

Comparison of sex-based differences in VDT between our study and the Hasegawa et al study revealed that in both studies, the mean tumor VDT was longer in women, although the difference between the sexes was greater in our study. We calculated mean tumor VDTs of 688 days for women and 234 days for men (a 454-day difference), and Hasegawa et al calculated mean tumor VDTs of 559 days for women and 387 days for men (a 172-day difference). In our study, the longer mean VDT for women seemed to reflect the higher incidence of less aggressive tumor histologic types in women: 24 (65%) of the 37 cancers in women versus 10 (42%) of the 24 cancers in men were BACs or non-BAC adenocarcinomas. Interestingly, nearly every tumor histologic subtype in the women had a longer mean VDT than did the subtypes in the men. The exception was large cell carcinoma, which occurred in only one patient, so a comparison was not possible.

Hasegawa et al (9) reported that almost all tumors with long VDTs (>342 days) had GG or semisolid attenuation. This was not the case in our study, as GG and semisolid tumors together comprised only a slight majority of the tumors with VDTs longer than 400 days. Six (46%) of the 13 tumors with VDTs longer than 400 days had solid attenuation; four (31%), semisolid attenuation; and three (23%), GG attenuation. Furthermore, the mean VDT for each tumor attenuation category was similar: 469 days with GG attenuation, 568 days with semisolid attenuation, and 503 days with solid attenuation, in contrast to 813, 457, and 149 days, respectively, in the Hasegawa et al study. These findings reflect the fact that we observed a higher percentage of solid tumors and a lower percentage of tumors with GG attenuation in the less aggressive histologic categories BAC and non-BAC adenocarcinoma. In the Hasegawa et al study, 19 (42%) of the 45 adenocarcinomas (including BACs) had GG attenuation; 19 (42%), semisolid attenuation; and seven (16%), solid attenuation. In our study, eight (24%) of the non-BAC adenocarcinomas and BACs combined (n = 34) were GG; 14 (41%), semisolid; and 12 (35%), solid.

The mean VDT of 518 days in our study was similar to the mean VDT of 452 days reported by Hasegawa et al. In contrast, the standard deviation in our study, 1094 days, was longer than that in the Hasegawa et al study, 381 days. Our shortest and longest VDTs were more extreme—10 and 5810 days, respectively—than those calculated by Hasegawa et al—52 and 1733 days, respectively. In our study, non-BAC adenocarcinomas had a longer mean VDT (746 days) than did squamous cell (103 days) and small cell (49 days) carcinomas, as in the Hasegawa et al study (533, 129, and 97 days, respectively). These findings are consistent with the known higher tumor aggressiveness of squamous cell and small cell carcinomas.

The right lung and upper lobe predominance of cancer in our study is consistent with the lung cancer predominance reported in previous studies (15–17). The central predominance of squamous cell and small cell carcinomas versus the peripheral predominance of non-BAC adenocarcinomas also is in agreement with previously published study results (18–20).

Although our study represents, to our knowledge, one of the largest series of CT screening–detected lung cancers, it was limited by the relatively small numbers of lung cancers. Another limitation was the accuracy of the two-dimensional measurements used to calculate tumor volumes. Although volumetric analysis might have been more accurate, it was not available for our study.

In summary, the screening CT–detected lung cancers in high-risk individuals were most commonly non-BAC adenocarcinomas. CT most commonly depicted a semisolid or solid nodule with irregular margins and a mean size of 16.4 mm. A small number of tumors became smaller, decreased in attenua-

tion, or became more smoothly marginated. Therefore, such changes should not negate follow-up of an indeterminate tumor. Tumor VDTs were, on average, longer than 1 year, and the range of growth rates was wide. Of 48 tumors with calculable VDTs, 13 had a VDT longer than 400 days (observed most commonly in women) and could be considered overdiagnosed; this is a confounding factor in lung cancer screening.

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Appendix

Figure A1

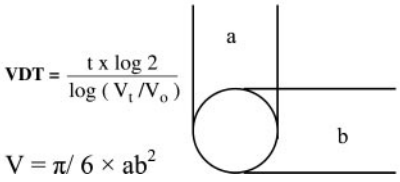

Figure A1: Modified Schwartz equation. a = largest diameter of the tumor, b = largest diameter perpendicular to a, t = interval between the two CT scannings, V = tumor volume, V_o = tumor volume at initial CT scanning, V_t = tumor volume at last CT scanning.

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Table A1

Attenuation, Attenuation Change, Margin, and Margin Change Categorized according to Tumor Histologic Type

Tumor Histologic Type	Attenuation			Attenuation Change			Margin			Margin Change		
	GG	Semisolid	Solid	Increased	Decreased	Variable	Smooth	Irregular	Spiculated	Smoother	More Irregular or Spiculated	Variable
BAC (n = 9)	6	3	0	1	0	2	3	3	3	2	0	1
Adenocarcinoma, non-BAC (n = 25)	2	11	12	8	3	0	3	14	8	1	8	0
Squamous cell (n = 14)	0	2	12	1	1	1	3	10	1	0	4	0
Small cell or SCLC-NEC (n = 7)	0	1	6	1	0	0	2	5	0	0	0	0
NSCLC-NOS (n = 5)	NA	1	4	1	1	0	1	3	1	0	3	0
Large cell (n = 1)	NA	NA	1	NA	NA	1	NA	NA	1	NA	1	NA
Total	8	18	35	12	5	4	12	35	14	3	16	1

Note.—Data are numbers of cancers. Attenuation and margin characteristics were analyzed in 61 cancers, and attenuation change and margin change were analyzed in 48 cancers. NA = not applicable.