CHEST

Original Research

LUNG CANCER

5-Year Lung Cancer Screening Experience

Growth Curves of 18 Lung Cancers Compared to Histologic Type, CT Attenuation, Stage, Survival, and Size

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Background: **Although no study has prospectively documented the rate at which lung cancers grow, many have assumed exponential growth. The purpose of this study was to document the growth of lung cancers detected in high-risk participants receiving annual screening chest CT scans.**

Methods: **Eighteen lung cancers were evaluated by at least four serial CT scans (4 men, 14 women; age range, 53 to 79 years; mean age, 66 years). CT scans were retrospectively reviewed for appearance, size, and volume (volume [v] = $\pi/6[ab^2]$). Growth curves (x = time [in days]; y = volume [cubic millimeters]) were plotted and subcategorized by histology, CT scan attenuation, stage, survival, and initial size.**

Results: **Inclusion criteria favored smaller, less aggressive cancers. Growth curves varied, even when subcategorized by histology, CT scan attenuation, stage, survival, or initial size. Cancers associated with higher stages, mortality, or recurrence showed fairly steady growth or accelerated growth compared with earlier growth, although these growth patterns also were seen in lesser-stage lung cancers. Most lung cancers enlarged at fairly steady increments, but several demonstrated fairly flat growth curves, and others demonstrated periods of accelerated growth.**

Conclusions: **This study is the first to plot individual lung cancer growth curves. Although parameters favored smaller, less aggressive cancers in women, it showed that lung cancers are not limited to exponential growth. Tumor size at one point or growth between two points did not appear to predict future growth. Studies and equations assuming exponential growth may potentially misrepresent an indeterminate nodule or the aggressiveness of a lung cancer.**

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Abbreviations: BAC = bronchioloalveolar carcinoma; IPF = idiopathic pulmonary fibrosis; NSCLC-NOS = non-small cell lung cancer-not otherwise specified; VDT = volume doubling time

No studies have documented the growth dynamics of screening-detected, untreated, subclinical lung cancers on CT scans. Many prior studies[1–8] evaluating indeterminate nodules or predicting the prognostic outcomes of lung cancers presume exponential growth. Our institution conducted a National Cancer Institute-sponsored lung cancer screening trial that screened high-risk participants with annual

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chest CT scans for 5 years. The final results have been reported.[9,10] Some participants received additional interval scans during the 5 years to evaluate indeterminate nodules in the process of identifying lung cancers. This experience provided the opportunity to review the volume of subclinical lung cancers at multiple points in time, beginning at small sizes. The purpose of this study was to examine lung cancer growth by plotting growth curves (volume, in microliters, as a function of time, in days) to determine whether growth rates were consistent for individual cancers and whether growth curves correlate with histologic type, CT scan attenuation, stage, survival, and initial size.

Materials and Methods

Study Participants

The original prospective screening trial and this study were approved by our Institutional Review Board and were compliant with the Health Insurance Portability and Accountability Act. Written informed consent had been obtained from all participants for the prospective trial, and informed consent was waived for this study.

The original study involved 1,520 participants considered to be at high risk, which was defined as a man or woman $\geq$ 50 years of age with a smoking history of at least 20 pack-years who had undergone annual screening with a chest CT scan and sputum cytology over a 5-year period. No history of cancer, no need for supplemental oxygen, and a life expectancy of at least 5 years were required for participation. If a participant had quit smoking, he or she had to have quit within 10 years of the start of the study. Study enrollment and the initial CT scan took place between January 20, 1999, and December 15, 1999. The final CT scan was completed in December 2003. Cancer growth observation was not planned but, rather, was part of the prospective consequence of the clinical evaluation of nodules detected at CT scan screening.

Recommendations for the workup of indeterminate nodules detected on CT scan screening were as follows. If a nodule was $<$ 4 mm, a low-dose screening CT scan was suggested after 6 months (changed to 12 months toward the end of the study). Nodules 4 to 7 mm in size were followed up with a standard CT scan after 3 months. Nodules 8 to 20 mm in size were worked up with a standard CT scan as soon as possible, and the clinician should have considered performing a solitary nodule enhancement CT scan or PET scan. For nodules of $>$ 20 mm, standard CT scanning was recommended as soon as possible, and PET scanning, biopsy, or resection should have been considered. Nodules were considered to be benign if they were unchanged in size for 2 years or had a benign pattern of calcification. Further management decisions were made by the clinician, surgeon, and patient.

Of the 1,520 participants, 68 lung cancers were diagnosed in 66 patients. There were 48 tumors imaged on more than one CT scan. The identification of lung cancer on at least four CT scans was required to generate a growth curve for the current study. The growth curve was defined as a graph plotting lung cancer volume in cubic millimeters (y-axis) as a function of time in days (x-axis). All prebiopsy and pretherapy CT scans that showed a nodule eventually diagnosed as a lung cancer were included, whether the nodule had been identified at the time of the original reading of the CT scan. There were 18 cancers (4 in men and 14 in women; patient age range, 53 to 79 years; mean age, 66 years; mean age for women, 65 years; mean age for men, 69 years) that met these criteria. Specifically, two cancers were present on 10 CT scans, three were present on 7 CT scans, four were present on 6 CT scans, six were present on 5 CT scans, and three were present on 4 CT scans. Survival includes data up to March 31, 2009. Among the 1,520 participants, 14 benign nodules were resected or biopsied. Four of these nodules were imaged on four or more CT scans and were included in this study for comparison.

CT Scan Imaging

Screening low-dose, non–contrast-enhanced chest CT scans were performed using a four-section, multidetector, helical CT scanner (Light Speed Model QX/I; General Electric Medical Systems, Inc; Milwaukee, WI) using a 5-mm section width, a 3.75-mm reconstruction interval, high-speed mode, a pitch of 1.5, an exposure of 0.8 s per rotation, a table feed of 30 mm per rotation, 120 kVp, and 40 mA. Scans were obtained initially and approximately every 12 months for a total of 5 years. Standard-dose, non–contrast-enhanced chest CT scans were ordered at the discretion of board-certified pulmonologists and were performed using an eight-section multidetector helical CT scanner (Light Speed Model Ultra-8; General Electric Medical Systems, Inc) using a 5-mm section width, a 5-mm reconstruction interval, a pitch of 1.35, an exposure of 0.5 s per rotation, a table feed of 13.5 mm per rotation, 120 kVp, and 300 mA.

Image Review

CT scans were retrospectively reviewed at a computer workstation for lung cancer dimensions and attenuation by one radiologist. Measurements were made to the nearest millimeter using manually placed computer electronic calipers on an axial image using lung windows. If a thin-section analysis had been performed, measurements were taken from the thin-section images. A spiculation, defined as a linear opacity projecting from a lung cancer, was not included in the measurement. Lung cancer volumes were calculated using the equation, volume (v) = $\pi/6(ab^2)$, where a was the longest horizontal axis and b was the maximum perpendicular diameter. If only one dimension decreased by 1 mm on a subsequent CT scan, the decrease was attributed to measurement error rather than to an actual size decrease. If both dimensions showed a decrease of 1 mm, or at least one dimension showed a change of $\geq$ 2 mm, the nodule was evaluated by visual assessment to determine whether the decreased size was valid. Nodule size on the first CT scan was obtained for growth curve comparison and was calculated using the mean of a and b. Volume doubling time (VDT) was calculated using the modified Schwartz equation.[1,2] Attenuation on the last CT scan was obtained for growth curve comparison. Attenuation was described as "ground glass" if it was a faint, hazy opacity; it was described as "semisolid" if both hazy attenuation and solid elements were present; and otherwise it was described as "solid."

Other Data

Resected specimens from 17 of the 18 lung cancers were retrospectively reviewed for consensus by two pathologists (one with 20 years experience and one with 2 years experience in chest pathology) and were classified according to the 2004 World Health Organization schema.[11] The one exception was a review of a transthoracic needle aspiration specimen showing adenocarcinoma in a participant with idiopathic pulmonary fibrosis (IPF), a condition unknown at the time of study enrollment. It was believed that the patient could not tolerate resection due to IPF. Patient age was documented as the age on the date of tumor

resection or, if not resected, on the biopsy date that confirmed lung cancer. In keeping with the World Health Organization classification, the term *bronchioloalveolar carcinoma* (BAC) referred to carcinomas that were purely BAC. The term *non-BAC adenocarcinoma* referred to adenocarcinomas that were not purely BAC, although they may have contained areas of BAC.

To understand the characteristics of this subset of 18 lung cancers and be aware of potential biases, we compared them with the 30 screening-detected lung cancers that were excluded from this study subset because they had been imaged only on two or three CT scans. Notes were made of gender, histologic type, CT scan attenuation, cancer size, VDT, and total elapsed time of tumor observation (time between the first CT scan that showed the tumor and the last CT scan prior to treatment or resection) in both groups.

Results

Growth Curve Patterns

There was a variety of growth curve appearances among the 18 lung cancers (Fig 1). A few growth

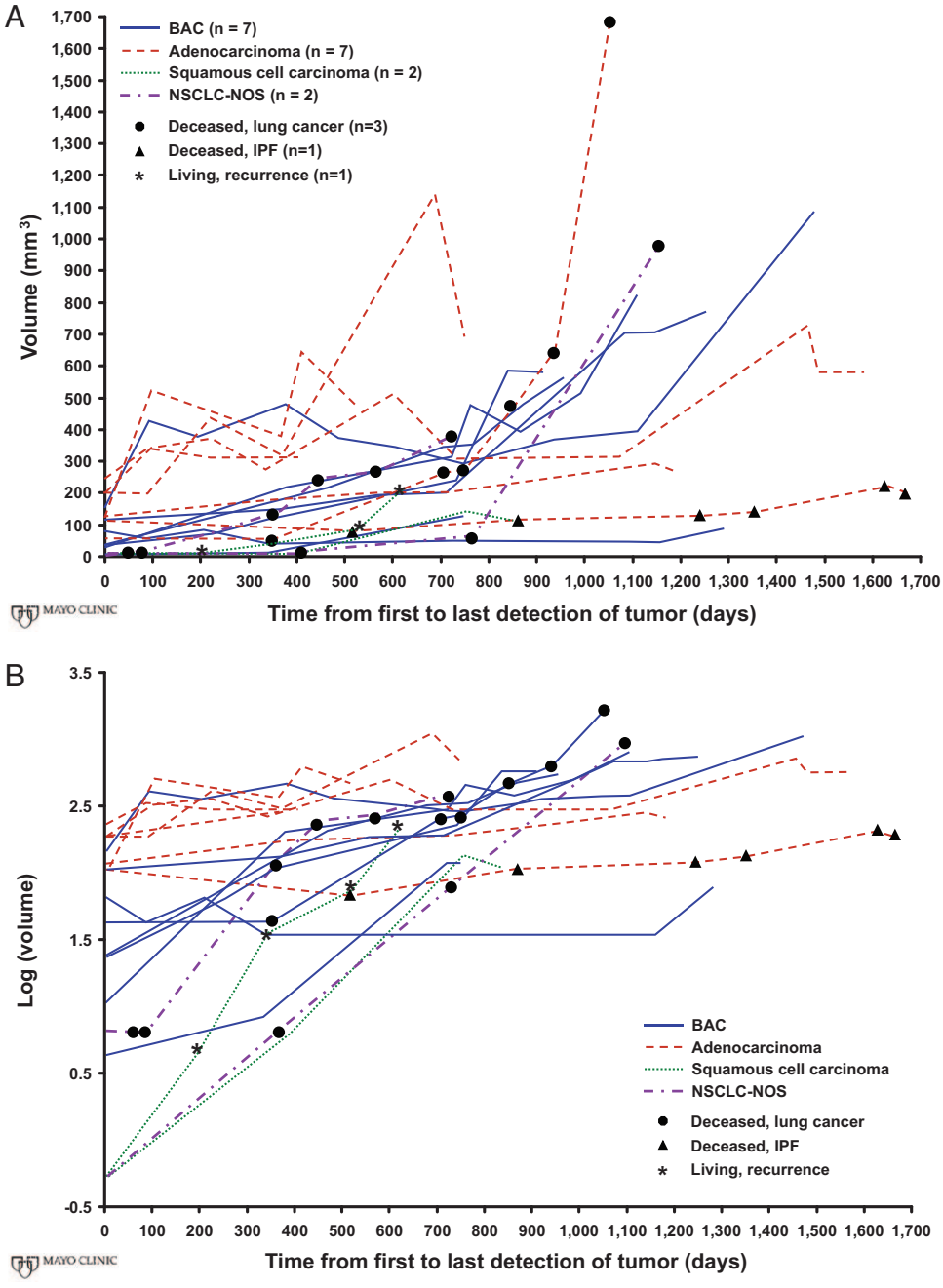

FIGURE 1. Summary of lung cancer growth curves using both linear scales (*A*) and logarithmic scales (*B*). ● = participants who died from metastatic lung cancer; ▲ = one participant who died from IPF; * = a living participant with lung cancer recurrence.

curves were close to horizontal, depicting slow growth. Steeper growth curves appeared to have linear and exponential increments in volume. A few growth curves appeared to have accelerated, steeper-than-exponential growth compared with earlier growth. These curves were analyzed according to histology, CT scan attenuation, stage, survival, and initial size, and are presented in the next section.

Volume Decreases

Of the 18 cancers in this study, 11 growth curves suggested a decrease in volume at some point. Only four of these cancers were considered to have actually decreased in volume according to both visual assessment and diameter measurement criteria. These four cancers included two BACs (one grew from 5 × 5 mm to 4 × 4 mm; one grew from 9 × 11 mm to 9 × 9 mm) and two non-BAC adenocarcinomas (one grew from 9 × 12 mm to 8 × 11 mm; one grew from 7 × 11 mm to 3 × 4 mm).

Growth Curves According to Histology

The 18 lung cancers were histologically classified as follows: seven BACs (39%) in one man and six women; seven non-BAC adenocarcinomas (39%) in one man and six women; two squamous cell carcinomas (11%) in one man and one woman; and 2 non-small cell lung cancer-not otherwise specified (NSCLC-NOS) [11%] in one man and one woman. One BAC was mucinous. The growth curves divided by histology are shown in Figure 2. All subtypes included at least one cancer that had fairly steady linear or exponential increments of growth. BAC and adenocarcinomas also had cancers with close-to-horizontal growth curves. BAC, adenocarcinoma, and NSCLC-NOS each had cancers that underwent accelerated, steeper-than-exponential growth compared with earlier rates.

Growth Curves According to CT Scan Attenuation

The CT scan attenuations of the 18 lung cancers were solid in 7 cancers (39%), semisolid in 6 cancers (33%), and ground glass in 5 cancers (28%) . Growth

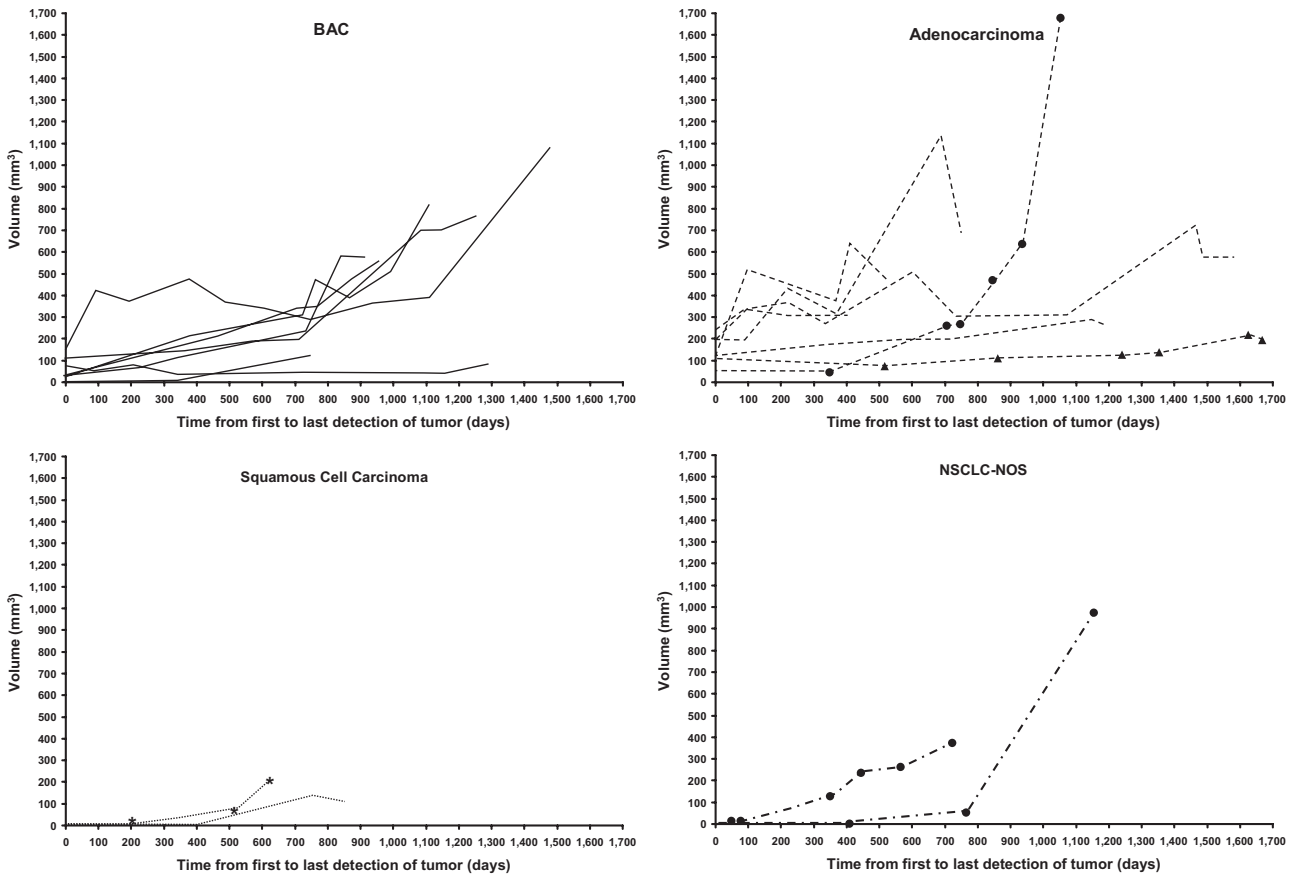

FIGURE 2. Growth curves separated by histology. ● = participants who died from metastatic lung cancer; ▲ = a participant who died from IPF; * = a living participant with lung cancer recurrence.

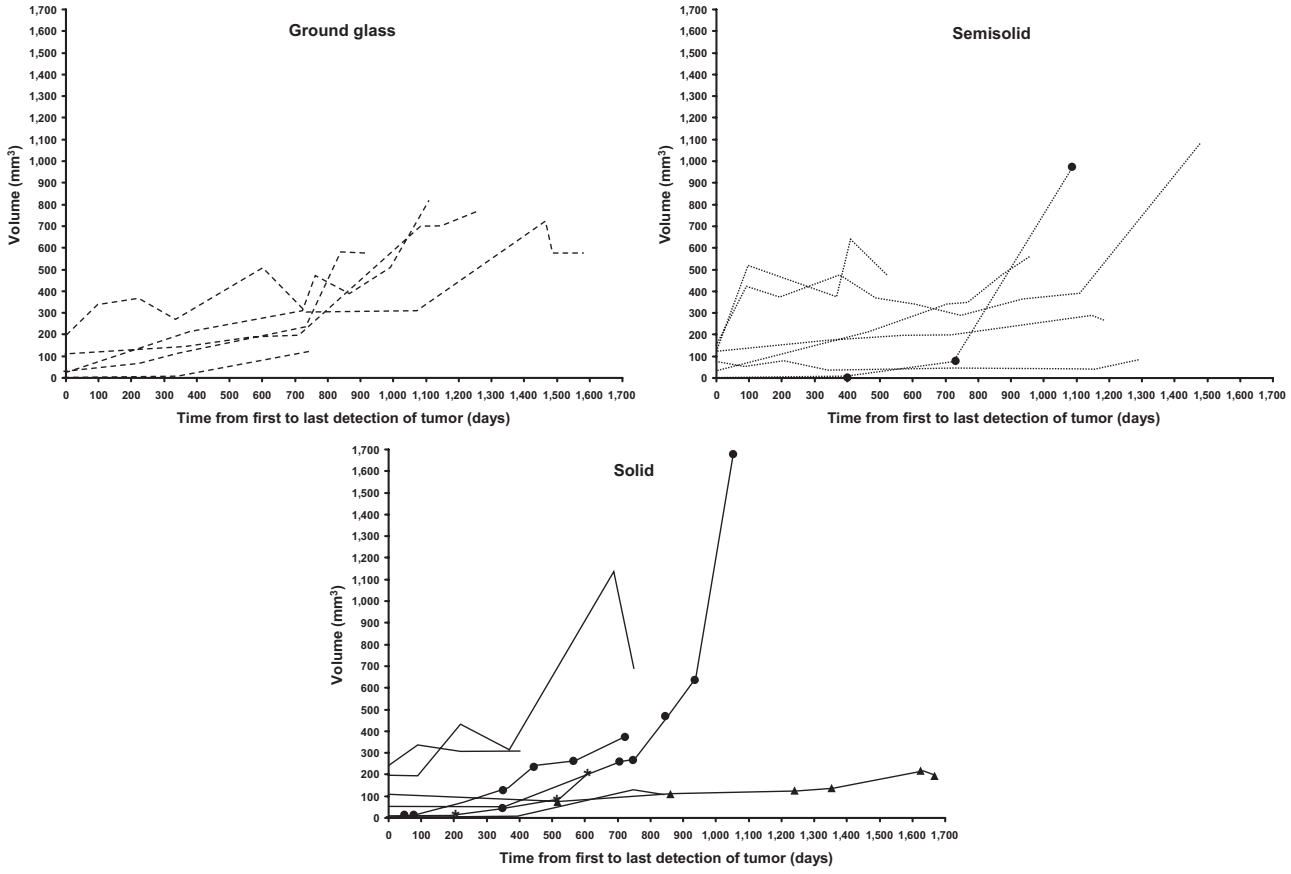

FIGURE 3. Growth curves separated by attenuation on the last CT scan. ● = participants who died from metastatic lung cancer; ▲ = a participant who died from IPF; * = a living participant with lung cancer recurrence.

curves per attenuation are shown in Figure 3 and demonstrate a variety of growth patterns for each attenuation category.

Growth Curves According to Stage

Lung cancer staging at the time of resection of the 18 lung cancers was as follows: stage IA, 13 cancers (72%); stage IB, 2 cancers (11%); stage IIA, 2 cancers (11%); and stage IIIA, 1 cancers (6%). Figure 4 shows growth curves separated by stage.

Growth Curves According to Survival

Fourteen of the 18 participants were living at the time of this study. One of the 14 living participants had lung cancer recurrence; specifically, liver metastases diagnosed 7 years after resection. This was one of the two squamous cell carcinomas, and the growth curve is marked by asterisks on Figures 1 to 5. Of the four deceased participants, three died from recurrent lung cancer after resection (one participant with stage IA NSCLC-NOS, one participant with stage IIA NSCLC-NOS, and one of the two participant with stage IB adenocarcinomas), and one participant died of IPF (stage IIA adenocarcinoma). On Figures 1 to 5, the deceased participants' growth curves are marked with dots (those without IPF) and triangles (the participant with IPF). The stage IA NSCLC-NOS had fairly steady linear-type growth. The stage IB adenocarcinoma and stage IIA NSCLC-NOS showed accelerated, steeper-than-exponential growth compared with earlier fairly steady growth. The stage IIA adenocarcinoma in the participant with IPF had a close-to-horizontal growth curve.

Growth Curve According to Size on First CT Scan

Figure 5 shows growth curves divided by initial lung cancer size using Fleischner criteria categories of ≤ 4 mm (n = 8), > 4 mm and up to 6 mm (n = 2), and > 6 mm and up to 8 mm (n = 8).[12] None of the 18 cancers was > 8 mm on the initial CT scan. There were a variety of growth curves for each size category.

Comparison With Larger Study

In our previous study,[9] there were 48 lung cancers that were imaged on more than one CT scan. The 18

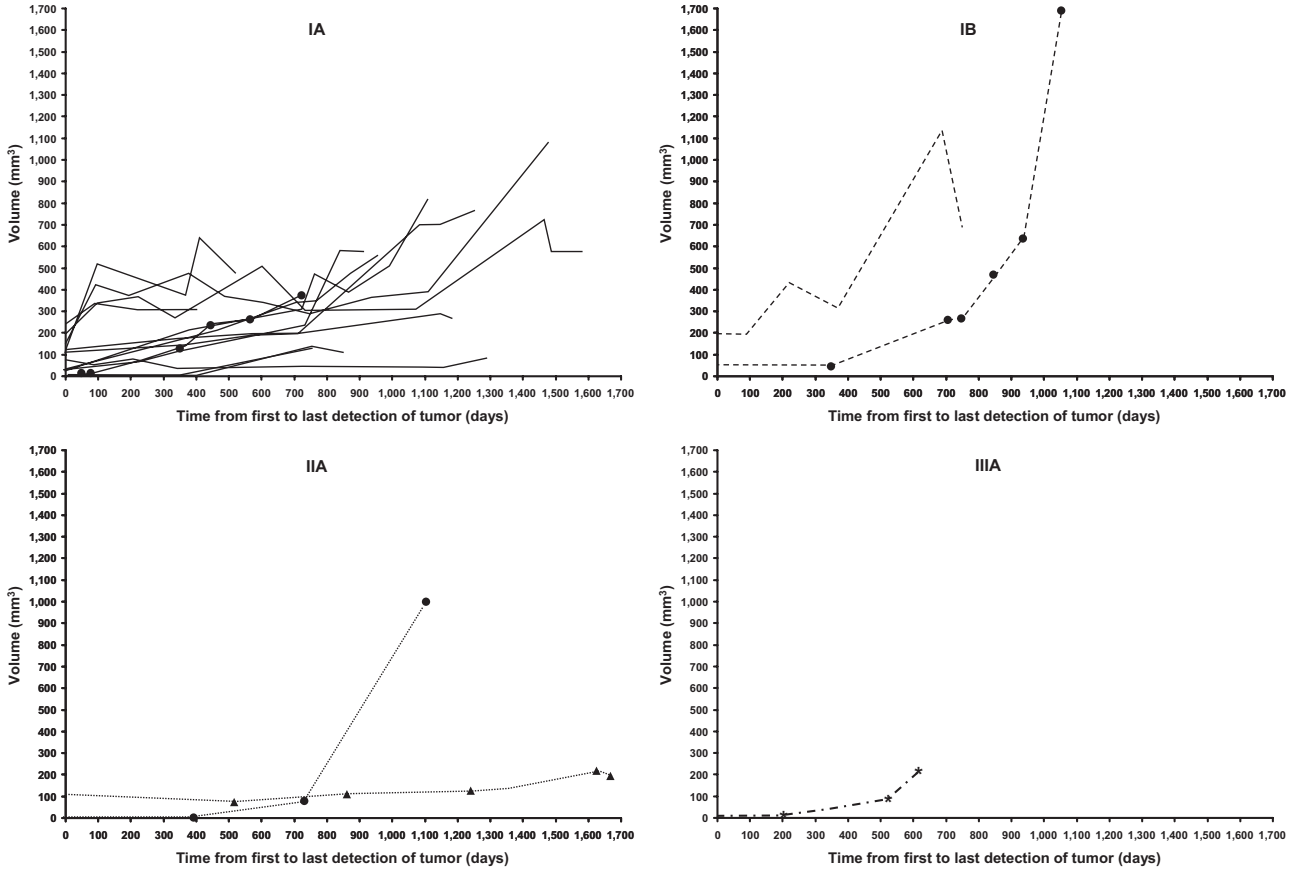

FIGURE 4. Growth curves separated by tumor stage at diagnosis. ● = participants who died from metastatic lung cancer; ▲ = a participant who died from IPF; * = a living participant with lung cancer recurrence.

lung cancers reported for the current study are a subset of the 48 previously reported cancers but were the only cancers that had been imaged on four or more CT scans. Comparison of these 18 cancers with the 30 excluded cancers is outlined in Table 1. The percentage of cancers with a VDT > 400 days was 50% (9 of 18 cancers) in the current study vs 17% (5 of 30 cancers) in the excluded cancers. There was a higher percentage of women (78%; 14 of 18 cancers) in the current study than among the excluded cancers (53%; 16 of 30 cancers). The current study favored the less aggressive subtypes of BAC and adenocarcinoma (78%; 14 of 18 cancers) vs the excluded cancers (57%; 17 of 30 cancers). Finally, there was a lower percentage of solid tumors in the current study (39%; 7 of 18 cancers) vs the excluded cancers (60%; 18 of 30 cancers).

Comparison With Benign Nodules

The four benign nodules included a necrotizing granuloma, benign parenchyma, nonnecrotizing granuloma, and benign fibrotic tissue. Figure 6 demonstrates the growth curves of the benign nodules. There was a variety of growth curves. The necrotizing granuloma and benign fibrotic tissue both showed ground-glass attenuation, and later semisolid attenuation. The benign parenchyma showed ground-glass attenuation with air bronchograms. The nonnecrotizing granuloma showed solid attenuation and was positive on the CT scan solitary nodule enhancement evaluation.

DISCUSSION

The lung cancers in our study had a variety of growth curves and did not uniformly demonstrate linear, exponential, or Gompertzian growth.[3,4] Gompertzian growth is exponential at an early stage and approaches a plateau as the tumor size increases.[4] Most curves showed fairly steady linear or exponential increments of growth, but there also were curves that were close to horizontal and curves that showed accelerated, greater-than-exponential growth compared with earlier rates. It is possible that some cancers were resected prior to reaching the plateau

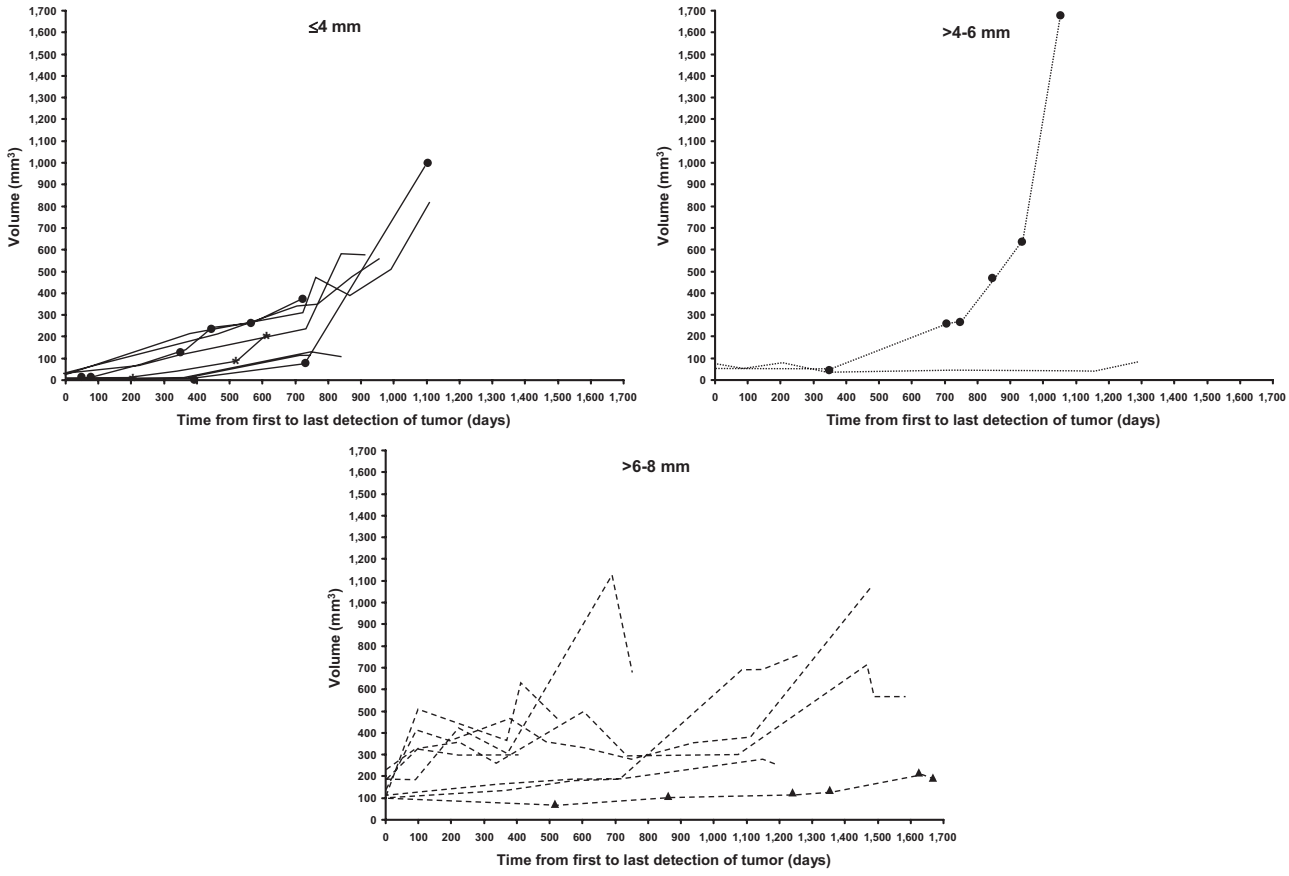

FIGURE 5. Growth curves separated by size when first detectable on CT scan. ● = participants who died from metastatic lung cancer; ▲ = a participant who died from IPF; * = a living participant with lung cancer recurrence.

phase described by Gompertzian growth. Comparison with the benign nodule growth curves showed similar variations in the curves.

The variety of growth curves in our study challenges the use of equations and studies that assume an exponential growth of cancer. For example, the modified Schwartz equation[1,2] that is used to calculate VDT in a cancer is based on exponential growth. The VDT result may be used subsequently to assess the likelihood of an indeterminate nodule being malignant and to assess the aggressiveness of a lung cancer.[5] A lung cancer that does not have the assumed exponential growth may be misinterpreted as benign, or its aggressiveness may be misinterpreted.

Another example of assumed exponential growth is in a study by Gorlova et al[6] that assumed exponential growth in order to estimate the growth rate of lung cancers detected on CT scans based on one or two points in time. Again, our study showed that some lung cancers do not grow exponentially and, furthermore, that the growth of a cancer between two points in time does not predict its future growth.

Our study showed that lung cancers associated with higher stages of disease, mortality, or recurrence had a tendency toward fairly steady linear or exponential growth, or accelerated, greater-than-exponential growth compared with earlier growth, although these types of growth were seen in other lung cancers as well. One exception is the growth curve for the deceased participant with IPF, which was close to horizontal despite being stage IIA. Another exception was the close-to-horizontal growth curve of the patient with stage IIIA squamous cell carcinoma who had liver metastases 7 years after resection. The growth curves of two of the four fatal lung cancers did not appear different than the growth curves of the nonfatal lung cancers. The other two fatal lung cancer growth curves also did not stand out as different from the nonfatal lung cancers until the last scan showed that the nodule growth had rapidly accelerated.

The fact that lung cancers may become smaller prior to treatment has been reported,[7,9] and in our study, four lung cancers became smaller. The fact that cancers have been documented to decreased in size at some point in their development should

Table 1—*Comparison of the 18 Lung Cancers Imaged on Four or More CT Scans to the 30 Excluded Lung Cancers Imaged on Two or Three CT Scans*

Characteristics	Current Study Cancers (n = 18)	Excluded Cancers (n = 30)
Patient sex, No.		
Male	4	14
Female	14	16
Tumor histologic type, No.		
BAC	7	2
Adenocarcinoma	7	15
Squamous cell	2	6
Small cell/mixed small cell	0	3
NSCLC-NOS	2	3
Large cell	0	1
Attenuation on last CT scan, No.		
Ground glass	5	3
Semisolid	6	9
Solid	7	18
Tumor size on the last CT scan, mm		
Mean ± SD	10.3 ± 2.8	16.2 ± 9.9
Median	10.3	13.8
Range	5.5–16	5.5–45
Tumor VDT, d		
Mean ± SD	771 ± 1,150	403 ± 1,058
Median	322	109
Range	71–4,885	10–5,810
Tumor VDT, No.		
< 71 d	0	9
71–400 d	9	16
> 400 d	5	9
Total time from first CT scan to the last CT scan, d		
Mean ± SD	1,025 ± 351	341 ± 255
Median	1,051	342
Range	404–1,666	21–907

have raised questions previously about the utility of equations that assume the exponential growth of lung cancers in order to determine whether a nodule is benign or malignant. Lung cancers that decrease in volume clearly are not exhibiting exponential growth.

Although 4 cancers clearly became smaller during this study, 11 cancers showed decreased volumes by two-dimensional-based volume calculations, demonstrating a limitation of two-dimensional measurements. This apparent discrepancy may be due to the volume equation volume (v) = $\pi/6(ab^2)$, amplifying small differences in diameter measurements. For example, if a nodule does not change size between two examinations, but on one examination it was measured to be 5×5 mm and on the next it was measured to be 4×5 mm, the volume in the first case would be 65.4 mm^3, and in the second case it would be 41.9 mm^3. This would cause a noticeable decline in the growth curve, but the 1-mm difference in diameter could be accounted for by differences in slice technique or the normal variability in human-assisted measuring techniques. Therefore, when nodule volume is based on two-dimensional measurements, it is important to note that some volume decreases may be due to measuring or differences in slice technique rather than to actual size decrease. Visual evaluation of the nodule can help to eliminate some of the measurement variability.

Growth curves varied when plotted according to the histologic types BAC, adenocarcinoma, and NSCLC-NOS. The two squamous cell carcinomas had similar growth curves, but this could be accounted for by their small numbers and their small size at resection. Both squamous cell carcinomas were solid and irregular on CT scan, likely prompting further evaluation based on an aggressive appearance.

Many lung cancers that were first imaged at a size of ≤ 4 mm showed steeper growth curves than cancers that were > 4 mm when first imaged. Furthermore, some of the more aggressive lung cancers were first imaged at ≤ 4 mm in size, including the patient with stage IIIA squamous cell carcinoma, the patient with stage IA squamous cell carcinoma that recurred 7 years later with liver metastases, and the patient with stage IIA NSCLC-NOS, who is now deceased. Our findings support the current Fleischner Society recommendations[12] regarding the need for the follow-up of high-risk patients with nodules ≤ 4 mm in size.

Comparison of this subset of 18 lung cancers with the 30 lung cancers that were excluded for having two or three CT scans showed, not surprisingly, that the current study favored smaller and slower growing tumors. The higher percentage of women in the current study reflects the higher frequency of less aggressive histologic subtypes in women.[2,9] The higher percentage of solid nodules among the excluded cancers (60%; 18 of 30 cancers) vs the included cancers (39%; 7 of 18 cancers) is compatible with the known correlation of less aggressive tumors and ground-glass or semisolid attenuation seen on a CT scan.[2]

To our knowledge, our study is the only one to have evaluated the growth curves of lung cancers using multiple CT scans. Although it was part of one of the largest series of lung cancer CT screening trials, it was limited by the relatively small numbers of lung cancers that were imaged on four or more CT scans. A second limitation was the accuracy of two-dimensional measurements for volume calculation of a tumor, especially in ground-glass and semisolid tumors. Volumetric analysis may have been more accurate but was not available for our study.

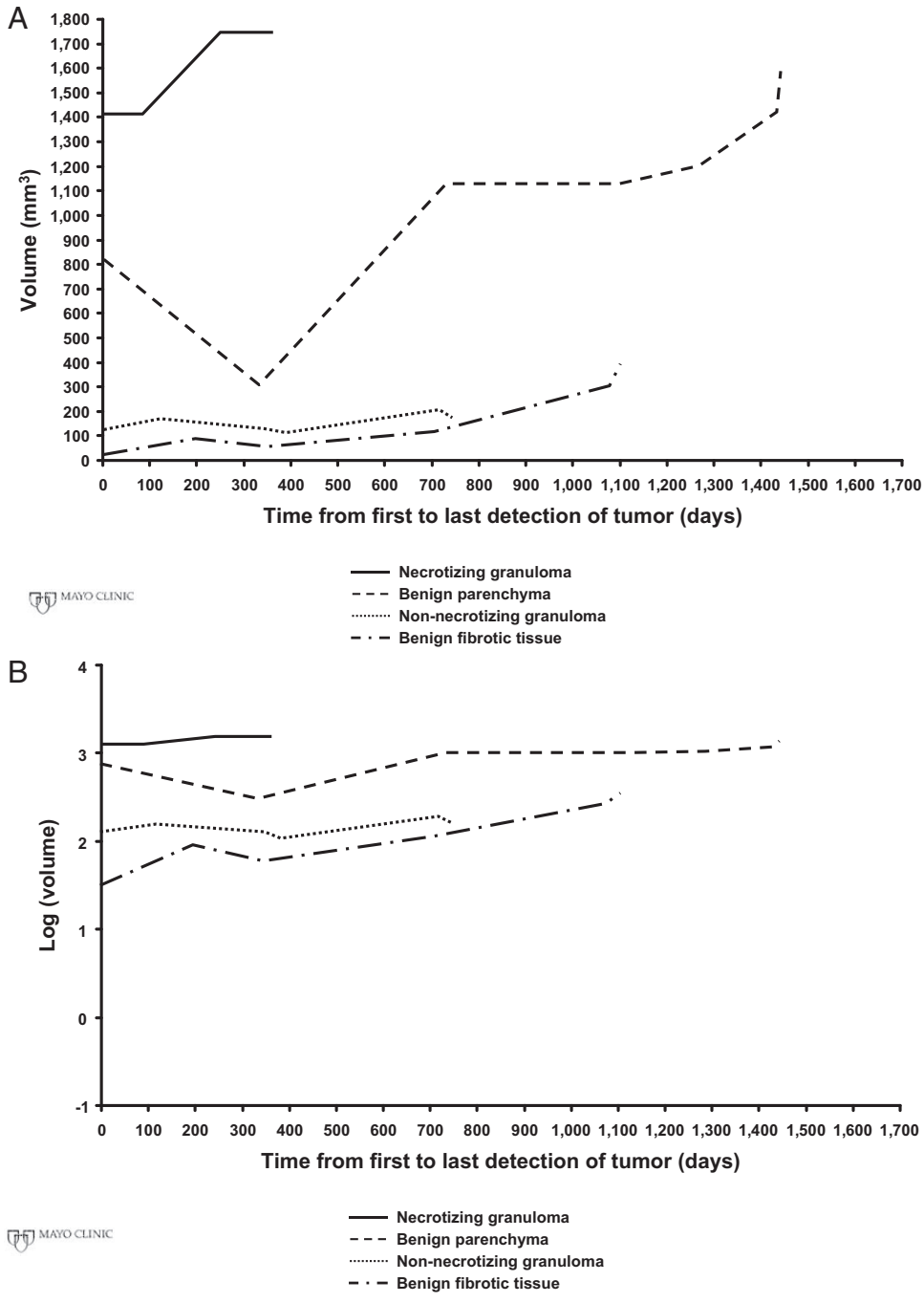

FIGURE 6. Growth curves of benign nodules using both linear scales (*A*) and logarithmic (*B*) scales.

However, two-dimensional measurements may more accurately reflect clinical practice where volumetric measurement may not be available. In addition, the study was not a representation of all lung cancers because it naturally favored smaller and slower growing tumors, as these were more likely to have been imaged on four or more CT scans. Therefore, although the study does not disprove that exponential growth may exist in lung cancers across the spectrum, it does show that there is variation in the growth rate of this subset of cancers over time. It should be noted that this subset included four fatal cancers and one metastatic recurrence.

In conclusion, although the study criteria favored a smaller and less aggressive subset of cancers, it showed that lung cancer growth curves varied and were not limited to exponential growth. Additionally, the size of a lung cancer at one point

in time and the growth rate between two points in time did not predict future growth rates. Hence, studies or equations that assume exponential growth may be misleading in the evaluation of an indeterminate nodule or the aggressiveness of a lung cancer.

Acknowledgments

Author contributions: Dr. Lindell contributed to the data acquisition and analysis. Dr. Mandrekar contributed to the data analysis. All authors contributed to the preparation of the manuscript.

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