Doubling Times and CT Screen–Detected Lung Cancers in the Pittsburgh Lung Screening Study

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Rationale: As computed tomography (CT) screening for lung cancer becomes more widespread, volumetric analyses, including doubling times, of CT-screen detected lung nodules and lung cancers may provide useful information in the follow-up and management of CT-detected lung nodules and cancers.

Objectives: To analyze doubling times in CT screen detected lung cancers and compare prevalent and nonprevalent cancers and different cell types on non-small cell lung cancer.

Methods: We performed volumetric and doubling time analysis on 63 non-small cell lung cancers detected as part of the Pittsburgh Lung Screening Study using a commercially available VITREA 2 workstation and VITREA VITAL nodule segmentation software.

Measurements and Main Results: Doubling times (DT) were divided into three groups: rapid (DT < 183 d), typical (DT 183–365 d), and slow (DT > 365 d). Adenocarcinoma/bronchioloalveolar carcinoma comprised 86.7% of the slow DT group compared with 20% of the rapid DT group. Conversely, squamous cell cancer comprised 60% of the rapid DT group compared with 3.3% of the slow DT group. Twenty-eight of 42 (67%) prevalent and 2 of 21 (10%) nonprevalent cancers were in the slow DT group ($P < 0.0001$; Fisher's exact test). Twenty-four of 32 (75%) prevalent and 1 of 11 (9%) nonprevalent adenocarcinomas were in the slow DT group ($P < 0.0002$; Fisher's exact test).

Conclusions: Volumetric analysis of CT-detected lung cancers is particularly useful in AC/BAC. Prevalent cancers have a significantly slower DT than nonprevalent cancers and a higher percentage of adenocarcinoma/bronchioloalveolar carcinoma. These results should affect the management of indeterminate lung nodules detected on screening CT scans.

Keywords: lung cancer; doubling times; lung cancer screening

Computed tomography (CT) screening for lung cancer has been under study for over a decade. With the publication of results from the National Lung Screening Trial (NLST) (1), CT screening for lung cancer may become widespread. We have accumulated over 150 lung cancers as part of the Pittsburgh Lung Screening Study (PLuSS), which started enrolling subjects in 2002 (2). Although there have been several studies of volumetric evaluation of lung nodule doubling times (DTs) for differentiating benign versus malignant pulmonary nodules (3–5), there is less information about DTs in screening-detected lung cancers. We present software volumetric evaluation of DTs in 63 non-small cell lung

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

There is limited information on doubling times and volumetric computed tomography (CT) analysis in CT screening-detected lung cancers.

What This Study Adds to the Field

This study presents information on doubling times and volumetric CT analysis of CT screening-detected non-small cell lung cancer from the Pittsburgh Lung Screening Study and on the management of indeterminate lung nodules detected on screening CT scans.

cancers (NSCLCs) from PLuSS and compare the doubling times in prevalent and nonprevalent cancers.

METHODS

PLuSS involved 3,642 subjects and was approved by the Institutional Review Board of the University of Pittsburgh. Written informed consent was obtained from all participants, and the study was compliant with the Health Insurance Portability and Accountability Act. At the time of this study, 148 lung cancers had been diagnosed; 63 were suitable for volumetric nodule analysis.

CT Imaging and Nodule Classification Protocol

CT scans evaluated for volumetric analysis included lung cancer screening studies and clinical studies prescribed for the management of CT-detected abnormalities or intervening symptoms. The lung cancer screening protocol used a single breath-hold, helical, low-dose technique (40–80 mA; 140 kVp) to obtain axial images reconstructed with a high-spatial-frequency lung algorithm at contiguous 2.5-mm intervals. Using standard doses, clinical studies typically reconstructed images at 2.5- to 5.0-mm intervals. Volume analysis was performed by a radiology resident (A.R.), a pulmonologist (D.O.W.), and a thoracic radiologist (C.F.). Lung lesions were automatically segmented on a Vitrea 2 workstation (Vitrea Vital Images, Minnetonka, MN) using software supplied with the workstation. The nodule segmentation algorithm is an intensity/density based algorithm that uses tissue density (Hounsfield unit values) to separate nodules from background tissues. To get accurate segmentation of nodules, the algorithm also uses constrained morphological operations to separate nodules from attached vessels and airways. After automatic segmentation, lesion margins were manually corrected, whenever necessary, to include all grossly visible tumor and to exclude adjacent structures such as vessels, chest wall, mediastinum, hilar structures, and atelectasis. Such manual corrections were necessary in approximately 20% of cases. In these cases, the margins were determined based on mild attenuation differences between tumor and air space disease and by excluding linear elements that appeared to represent air space disease. If a distinct nodule could not be manually and reproducibly outlined, the case was excluded. Direct, computer-generated volumes were then automatically displayed.

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Two investigators (A.R. and D.O.W.) independently used Vitrea Vital software to complete 126 nodule volume measurements (63 subjects with a tumor nodule measured independently on two CTs separated in time). If a volume measurement differed by more than 5% ($n = 15$), a third investigator (C.F.) independently measured nodule volumes on both CTs. Data analyses used the geometric mean of the volume measurements for the two investigators in closest agreement.

Cancers visible, possibly in retrospect, as a nodule on an initial or baseline screening CT were considered prevalent. Nonprevalent cancers were not visible on the initial screening CT but were newly visible on a follow-up CT performed for any reason.

Data Analysis

Tumor doubling time estimates used tumor volumes (V_o and V_i) on the first and last available and evaluable pretherapeutic CT, the time interval T_i (in days) between the two exams, and the following formula:

$$\frac{\ln 2 \cdot T_i}{\ln V_i - \ln V_o}$$

Determinations of the statistical significance of DT differences used standard two-sided, nonparametric rank sum tests (SAS version 9.2) for two-group (Wilcoxon test), nonordered multiple-group (Kruskal-Wallis test), and ordered multiple-group (Jonckheere-Terpstra test) comparisons.

RESULTS

Of the initial 148 lung cancers detected in PLuSS, 63 NSCLCs are included in this analysis (Figure 1). Analyses excluded 85 cases for the following reasons: small cell histology ($n = 20$), absence

Figure 1. Workflow of included and excluded lung cancers. CT = computed tomography; NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer.

TABLE 1. COMPARISON OF EVALUABLE SUBJECTS AND EXCLUDED SUBJECTS

Attribute	Evaluable ($n = 63$)		Excluded ($n = 65$)		P Value (χ^2)
	n	%	n	%	
Sex					0.22
Men	32	50.8	40	61.5	
Women	31	49.2	25	38.5	
Age at diagnosis, yr			(1)		0.46
51–59	12	19.0	18	28.1	
60–69	27	42.9	26	40.6	
70–82	24	38.1	20	31.3	
Race					0.54
White	59	93.7	59	90.8	
Nonwhite	4	6.3	6	9.2	
Smoking status					0.65
Current	44	69.8	43	66.2	
Former	19	30.2	22	33.8	
Pack-years					0.16
<50	27	42.9	20	30.8	
≥50	36	57.1	45	69.2	
Lung function (GOLD)					0.42
Normal	13	20.6	14	21.5	
Restriction	5	7.9	10	15.4	
GOLD I	11	17.5	11	16.9	
GOLD II	26	41.3	18	27.7	
GOLD III–IV	8	12.7	12	18.5	
Emphysema score					0.41
None	21	33.3	14	21.5	
Trace	14	22.2	16	24.6	
Mild	18	28.6	19	29.2	
Moderate-severe	10	15.9	16	24.6	
Histology					<0.0001
Adenocarcinoma/BAC	46	73.0	22	33.8	
Squamous cell	8	12.7	23	35.4	
Other/unknown	9	14.3	20	30.8	
Stage			3		0.01
I–II	45	71.4	30	48.4	
III–IV	18	28.6	32	51.6	
Dead					0.02
No	44	69.8	32	49.2	
Yes	19	30.2	33	50.8	

Definition of abbreviations: BAC = bronchioloalveolar carcinoma; GOLD = global initiative for obstructive lung disease.

of two CT scans more than 90 days apart ($n = 41$), cancer detected after screening completed ($n = 15$) with diagnostic CT scans not available for volumetric analysis, and inability to segment the cancer ($n = 9$). We excluded 15 cases because cancer was detected after screening was completed and diagnostic CT scans were not available for volumetric analysis. We corrected the manuscript accordingly. With respect to the 15 cases in question, eight did not have any nodules detected on any screening CT, five had only tiny (< 0.5 cm) nodules detected on screening CT, and two had indeterminate nodules (the largest was 1.0 cm) detected on screening CT. In the latter two cases, lung cancers were diagnosed at outside institutions 3 and 5 years after the last CT screening. There were three bronchioloalveolar carcinoma (BAC)/ground glass cancers in the combined adenocarcinoma (AC)/BAC group, all of which were amenable to the volumetric nodule analysis. All three cases required hand segmentation and were in the group that all three investigators measured to achieve consistent results. There was no BAC in the excluded group. Only 63 of 128 (49%) NSCLCs were amenable to the volumetric/DT analysis.

Table 1 compares the 63 evaluable and 65 excluded subjects with NSCLC. The excluded group had fewer adenocarcinomas, a higher proportion of locally advanced stage III and IV cancers (52 vs. 29%), and more deaths.

TABLE 2. ATTRIBUTES (PERCENT DISTRIBUTION) OF SUBJECTS GROUPED ACCORDING TO CANCER RATE OF GROWTH, AS REPRESENTED BY THE NODULE DOUBLING TIME

Attribute	Doubling Time			P Values	
	<183 d (n = 10)	183–365 d (n = 23)	>365 d (n = 30)	KW	JT
Sex				0.17	
Men	70.0	52.2	43.3		
Women	30.0	47.8	56.7		
Age at diagnosis, yr				0.52	0.33
51–59	20.0	8.7	26.7		
60–69	40.0	47.8	40.0		
70–82	40.0	43.5	33.3		
Smoking, PLuSS entry				0.93	
Current	90.0	56.5	73.3		
Former	10.0	43.5	26.7		
Pack-years, PLuSS entry				0.50	
<40	50.0	30.4	50.0		
≥40	50.0	69.6	50.0		
GOLD, PLuSS entry				0.15	0.15
Normal	10.0	8.7	33.3		
Restriction	10.0	4.3	10.0		
GOLD I	20.0	21.7	13.3		
GOLD II	60.0	47.8	30.0		
GOLD III–IV	0.0	17.4	13.3		
Emphysema, PLuSS T0				0.94	0.90
None	50.0	26.1	33.3		
Trace–mild	40.0	52.2	53.3		
Moderate–severe	10.0	21.7	13.3		
Histology				0.0009	
AC/BAC	20.0	78.3	86.7		
Squamous cell	60.0	4.3	3.3		
Other	20.0	17.4	10.0		
Stage				0.57	
I–II	60.0	73.9	73.3		
III–IV	40.0	26.1	26.7		
Dead				0.65	
No	70.0	65.2	73.3		
Yes	30.0	34.8	26.7		
Manner of detection				<0.0001	
Nonprevalent	70.0	52.2	6.7		
Prevalent	30.0	47.8	93.3		

Definition of abbreviations: AC = adenocarcinoma; BAC = bronchioloalveolar carcinoma; GOLD = global initiative for obstructive lung disease; JT = Jonckheere-Terpstra test; KW = Kruskal-Wallis test; PLuSS = Pittsburgh Lung Screening Study.

Table 2 summarizes the attributes of the 63 included subjects grouped according to cancer rate of growth, as represented by the nodule DT, rapid growth (DT < 183 d), typical growth (DT 183–365 d), and slow growth (DT > 365 d). There were 10 (15.8%) cancers in the rapid DT group, 23 (36.5%) in the typical DT group, and 30 (47.6%) in the slow DT group. These groups differed according to histology and manner of detection (i.e., primary tumor seen vs. not seen on the prevalent screening CT). AC/BAC cell carcinoma comprised 86.7% of the slow DT group compared with 20% of the rapid DT group. Conversely, squamous cell cancer comprised 60% of the rapid DT group compared with 3.3% of the slow DT group. Of the 42 prevalent cancers, 28 (67%) were in the slow DT group, and only 3 (7%) were in the rapid DT group. Of the 21 nonprevalent cancers, 2 (10%) were in the slow DT group, and 7 (33%) were in the rapid DT group. Expressing results in terms of DT, 7 of 10 (70%) rapid DT tumors were nonprevalent cancer, and 28 of 30 (93.3%) slow DT tumors were prevalent cancer ($P < 0.0001$: Fisher's exact test) (Table 2). Twenty-four of 32 (75%) prevalent and 1 of 11 (9%) nonprevalent adenocarcinomas were in the slow DT group ($P < 0.0002$; Fisher's exact test).

Table 3 shows median DT by manner of detection (prevalent vs. nonprevalent) and histology (AC/BAC vs. squamous cell). Prevalent cancers had a median DT of 514 versus 237 days for nonprevalent cancers ($P < 0.0001$). AC/BACs had a median DT of 387 versus 160 days for squamous cell cancers ($P = 0.0031$).

Twenty-five percent of AC/BACs had a DT > 711 days, with a maximum of 1,435 days.

DISCUSSION

We report on 63 subjects with NSCLC and lung tumors that were amenable to segmentation by the VITAL/VITREA 2 algorithm. These cancers represent 42% of the lung cancers detected to date as part of the ongoing PLuSS (Figure 1). The 63 subjects with NSCLC included in the analysis and the 65 subjects with NSCLC excluded from analysis were similar with respect to sex, age, race, smoking history, lung function (GOLD), and a CT measure of emphysema (Table 2). The group excluded from analysis contained more non-AC/BAC, more NSCLC diagnosed at advanced stage (III/IV), and more subjects dying before the end of follow-up. By requiring two CT scans separated by more than 90 days, the DT calculation effectively excluded lung cancer presenting as a large primary tumor, as a central airway abnormality, or as a tumor with lymph node enlargement at screening. This situation, accounting for 29 of 65 excluded cases, appropriately demanded more immediate biopsy intervention and explained the histology, stage, and outcome differences observed between cases excluded and included for DT analysis.

Two factors—histology and manner of detection—differed by DT. AC/BAC histology and prevalent detection characterized

TABLE 3. MEASURES OF THE DISTRIBUTION OF DOUBLING TIME BY MANNER OF DETECTION AND HISTOLOGY

	n	Doubling Time (days)				P Value (Wilcoxon)
		Median	25th Percentile	75th Percentile	Maximum	
All	63	357	236	630	4263	
Manner of detection						<0.0001
Nonprevalent	21	237	141	292	449	
Prevalent	42	514	301	775	4,263	
Histology						0.0031*
AC/BAC	46	387	277	711	1,435	
Squamous cell	8	160	91	238	449	
Other	9	263	202	624	4,263	
Manner of detection and histology						
Nonprevalent						0.44*
AC/BAC	12	260	193	297	382	
Squamous cell	5	99	84	306	449	
Other	4	192	115	250	263	
Prevalent						0.01*
AC/BAC	34	529	316	775	1,435	
Squamous cell	3	160	159	170	170	
Other	5	624	364	1,271	4,263	

Definition of abbreviations: AC = adenocarcinoma; BAC = bronchioloalveolar carcinoma.

*Comparing AC/BAC vs. squamous cell.

cases with slow DT (Table 2). Equivalently, AC/BAC histology and prevalent cases had longer DT (Table 3).

Other studies have looked at DTs in lung cancer (6–10). Several studies have compared DT in squamous cell carcinoma (SCC) and AC, showing significantly shorter DT in SCC than in AC (6–8). Hasegawa and associates reported on DT in early-stage SCC versus AC in a CT screening–detected population from Japan (6). They reported mean DTs for 8 SCC versus 49 AC of 97 versus 533 days. There is one study that showed no significant difference among histologic types of lung cancer and DT; this study included 21 of 149 subjects (14%) that did not grow between the two CT scans (10). Our study is the first to compare prevalent and nonprevalent NSCLC. In light of the recently announced results from the NLST, it is likely that screening CT scans in high-risk individuals will become much more mainstream. If this occurs, many more lung nodules will be found that will require follow-up. The risks of finding indeterminate pulmonary nodules in high-risk individuals include morbidity from overly aggressive diagnostic procedures and radiation exposure from follow-up imaging (2). Tools that allow enhanced prediction of individual lung cancer risk will be critical to the management of CT-detected lung nodules. We and others have published clinical predictive formulas for individual lung cancer risk (11–13). The use of DT data for indeterminate peripheral lung nodules could potentially aid in the risk stratification and follow-up management.

A study by van Klaveren and colleagues has advocated using DT to predict benign versus malignant lung nodules detected on CT screening (14). Focusing on nodules 50 to 500 mm³, these authors report that a DT > 400 days on a follow-up CT scan at 3 months had a point estimate negative predictive value of 99.7%. These data are relevant to indeterminate small pulmonary nodules in a CT screening population. Our data focus on screening-detected lung cancers and show a wide range of DTs (72–4,263 d). Our results are similar to Hasegawa (6) with respect to slower DT for AC. We also found slower DT in prevalent cancers, the majority of which (34/42 [81%]) were ACs (Table 3). The slower DT in prevalent lung cancers is not unexpected. Compared with cancer detected shortly after an initially normal screening, the pool of cases found at an initial screening typically includes a higher proportion of slower-growing prevalent tumors

existing in the population for longer and indefinite periods of time. One could argue that the more rapid DT in nonprevalent cancers should be a factor that informs the management of newly detected lung nodules on follow-up CT scans done serially in high-risk patients. It is known that new nodules not previously seen on prior CT scans are more likely to be cancer than indeterminate nodules of unknown duration. Thus, the management of these nodules should be more expectant with shorter-interval follow-up and a lower threshold to biopsy. With respect to using DT data for peripheral indeterminate lung nodules of unknown duration, our data suggest that following nodules detected on prevalence CT scans for 2 years may be inadequate (15). Table 3 shows that 25% of ACs had a DT > 711 days, suggesting that there is a wide range of growth rates for this type of lung cancer. One can hypothesize that in slow-growing prevalent nodules suggestive of adenocarcinoma there is the potential for overdiagnosis and therefore a more conservative diagnostic management approach might be considered in selected patients.

There are reports that CT slice thickness and type of software package can affect the accuracy of volumetric measurements, especially for small (< 10 mm) nodules (16). To minimize this effect, it has been suggested to use the same section thickness and overlap and the same segmentation software for all studies, a protocol we adhered to. In our experience, the VITREA/VITAL nodule segmentation software appears to be robust to slice thickness and other image acquisition parameters. Nodule characteristics (e.g., central location or proximity to vessels or airways), not technical parameters (e.g., slice thickness), explained our inability to segment the nine nodules excluded from volumetric analysis.

We have presented DT data on lung cancer appearing in PLuSS, a study using CT to detect early lung cancer. Using currently available technology, only 63 of 148 (43%) of all lung cancer and 63 of 128 (49%) of NSCLCs were amenable to DT analysis. AC/BAC comprised 46 of 63 (73%) of cancer amenable to DT analysis but 26 of 30 (87%) with slow DT. Squamous cell cancers comprised 8 of 63 (13%) of cancers amenable to DT analysis but 6 of 10 (60%) with rapid DT. Prevalent cancers had significantly slower DT than nonprevalent cancers. These results are most applicable to peripheral indeterminate nodules that are suitable for follow-up with serial CT scan, in contrast to more suspicious nodules that are more appropriate for

immediate biopsy. As the field of quantitative CT analysis evolves with improved software and computerized segmentation algorithms incorporating freehand sketching of nodules into automated segmentation, volumetric nodule analysis will be easier and more reproducible. We believe the results presented in this manuscript represent a tip-of-the-iceberg phenomenon with respect to quantitative CT analysis of lung nodules, with future studies incorporating new radiology informatics and imaging biomarkers. If the promise of the NLST is to be fulfilled, the many indeterminant lung nodules detected by CT screening will call for a more standardized approach to their clinical management. These results should affect the management of peripheral indeterminant lung nodules detected on screening CT scans.

Author disclosures are available with the text of this article at www.atsjournals.org.

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