Indolent, Potentially Inconsequential Lung Cancers in the Pittsburgh Lung Screening Study

Prashanth M. Thalanayar¹, Nejat Altintas², Joel L. Weissfeld³, Carl R. Fuhrman⁴, and David O. Wilson⁵

¹Department of Medicine, University of Pittsburgh Medical Center, McKeesport, Pennsylvania; ²Department of Pulmonary, Sleep and Critical Care Medicine, Namik Kemak University, Tekirdag/Turkey; and ³Department of Epidemiology, ⁴Department of Radiology, and ⁵Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania

Abstract

Rationale: The finding of indolent, potentially inconsequential cancers (overdiagnosis) is inherent to cancer screening in general, and there is a growing body of literature about this concept in lung cancer screening.

Objectives: We report on indolent, potentially inconsequential lung cancers in the Pittsburgh Lung Screening Study (PLuSS) population screened for lung cancer with annual low-dose computed tomography.

Methods: We identified 93 subjects with screen-detected prevalence cancers in PLuSS. We defined indolent, potentially inconsequential cancers as stage I prevalence lung cancer cases that had volumetric doubling time >400 days (when available) and maximal standardized uptake value max on positron emission tomography (PET) scan ≤ 1 (when available).

Measurements and Main Results: Approximately 18.5% (n = 17) of all 93 screen-detected prevalence lung cancers in PLuSS were

indolent, potentially inconsequential cancers. All such cancers except for one were adenocarcinomas by histology. Median tumor size of such cancers at the time of final diagnosis was 10 mm (range, 7–22 mm). Median doubling time was significantly longer in this group when compared with the rest of the prevalence stage I cancers (752 vs. 284.5 d).

Conclusions: Although the precise definitions may vary, the existence of indolent, potentially inconsequential cancers in low-dose computed tomography lung cancer screening is real. Clinicians involved in managing patients with low-dose computed tomography–detected slow-growing nodules, especially with a standardized uptake value ≤ 1 on PET scan, should consider the possibility of indolent, potentially inconsequential cancer in the longitudinal management of these nodules.

Keywords: lung cancer screening; low-dose computed tomography; PLuSS

(Received in original form December 15, 2014; accepted in final form May 16, 2015)

Supported by the University of Pittsburgh Lung Cancer SPORE: NCI P50-CA90440, 1P50 HL084948, University of Pittsburgh Cancer Institute, and University of Pittsburgh Medical Center.

Author Contributions: Conception and design: P.M.T., J.L.W., C.R.F., and D.O.W. Analysis and interpretation: P.M.T., N.A., C.R.F., J.L.W., and D.O.W. Drafting manuscript and intellectual content: P.M.T., N.A., J.L.W., and D.O.W.

Correspondence and requests for reprints should be addressed to David O. Wilson, M.D., UPMC Shadyside Cancer Pavilion, 5150 Centre Ave, Suite 4C, Pittsburgh, PA 15232. E-mail: wilsondo@upmc.edu

Ann Am Thorac Soc Vol 12, No 8, pp 1193–1196, Aug 2015

Copyright © 2015 by the American Thoracic Society

Originally Published in Press as DOI: 10.1513/AnnalsATS.201412-577OC on June 24, 2015

Internet address: www.atsjournals.org

The National Lung Screening Trial (NLST) showed a 20% relative mortality benefit from low-dose computerized tomography (LDCT) screening for lung cancer, compared with chest X-ray. Part of the downside of LDCT screening for lung cancer is the complications related to the evaluation of positive screens, especially in

individuals who do not have lung cancer. Significant psychosocial stress, capital and time expenditure, and radiation exposure are part of the lung nodule work-up (1).

Indolent or potentially inconsequential malignancy is inherent to cancer screening and can be defined as a cancer that would not become symptomatic in a patient's

lifetime and would not contribute to death. Indolent, potentially inconsequential lung cancer is a relatively new concept, owing to two factors. First, lung cancer has a high case fatality rate such that the idea of clinically inconsequential lung cancers never had much traction in the clinic. Second, lung cancer screening was

nonexistent until the recent advent of LDCT as a research tool in the early 2000s, so these tumors were rarely identified

In the past decade, there have been several studies that have looked at overdiagnosis in lung cancer screening in chest X-ray (2) and LDCT screening (3–6) using variable methodologies and definitions. The range of estimated indolent lung cancers is 2 to 25% (2, 4). Most recently, a modeling study from the United States Preventive Services Task Forces (USPSTF) estimated a 10 to 12% overdiagnosis in screen-detected lung cancer (6). We report on indolent potentially inconsequential cancers in the Pittsburgh Lung Screening Study (PLuSS), the largest single institution LDCT lung cancer screening cohort in the United States (7).

Methods

Patient Selection and Diagnostic Criteria

PLuSS involved 3,642 subjects enrolled from 2002 to 2005 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. The protocols and details of enrollment of PLuSS have been previously published (7).

Our retrospective study includes all 93 cases of prevalence lung cancer detected in PLuSS. A prevalence cancer is defined as a cancer present, even on retrospect, on the first screening LDCT. Data pertaining to the health status and cause of death were collected from medical records and/or death certificates. The follow-up data of these patients in this study span until June 2013. The details of the mode of diagnosis and treatment of the 93 cases of cancer are beyond the scope of this article.

The investigators reviewed the nodule database and CT images up to the point of biopsy or initiation of treatment and documented nodule size and characterized nodules as nonsolid or solid. Computed tomography (CT) scans evaluated for volumetric analysis included lung cancer screening studies and clinical studies prescribed in the management of CT-detected abnormalities or intervening symptoms. The lung cancer screening

protocol, volume analysis methodology, and volumetric doubling time calculation are described in our previous publication (8). For the purposes of this study, we defined slow growth as volumetric doubling time >400 days and rapid growth as volumetric doubling time ≤400 days.

We defined an indolent cancer as including all of the following criteria: clinical stage I nodule on prevalence LDCT scan with a volumetric doubling time >400 days and maximal standardized uptake value (SUVmax) ≤1 on positron emission tomography (PET) scan (when available).

PET and PET/CT scans were ordered during the course of clinical evaluation of lung nodules. The PET protocol and methodology for SUVmax calculation have been previously described (9). PET scan radiology reports (when available) and images were reviewed to note the presence of increased 18-FDG uptake quantified by maximum standardized uptake value (SUV). In addition, nodule size was accounted for in all cases of negative PET scan findings (or SUV ≤1).

Statistical Methods

Data on sex, age at diagnosis, smoking status with number of pack-years, solidity and size of nodule, histological subtype, presence or absence of emphysema, observed FEV₁, volumetric doubling times, and SUVs were analyzed using Fisher's exact test and

nonparametric Wilcoxon models with the help of SAS version 9.3 (SAS Institute, Inc., Cary, NC).

Results

Review of the initial 149 lung cancers detected in PLuSS revealed 93 prevalence lung cancers (Figure 1). Overall, men and women were equally distributed. Out of 45 prevalence stage I cancers, there were 29 solid nodules and 16 nonsolid cancers. There were 17 nodules (18.5% of 93 prevalence cancers) with volumetric doubling time >400 days and SUVmax <1, meeting the criteria for indolent, potentially inconsequential, screen-detected cancers (Figure 1).

In Table 1, the characteristics of the 17 indolent cases (group A) are compared with the rest of the stage I prevalence cancers (group B; n = 28). Over 78% of group B cases (n = 22) were adenocarcinomas. There were more current smokers than former smokers in each group. Likewise, emphysema was equally distributed in both populations. There were no statistically significant differences in age, sex, mean pack-years, FEV₁, nodule size, or length of follow-up. Median doubling time was significantly longer in the indolent group when compared with the rest of the prevalence stage I cancers (752 vs. 284.5 d). Of note, only 20 of 28 cases from group B

Figure 1. Workflow of screen-detected lung cancer using indolence criteria. PLuSS = Pittsburgh Lung Screening Study.

Table 1. Comparison of indolent, potentially inconsequential cancers (group A) and other prevalence stage I cancers (group B)

Variables	Group A (n = 17)	Group B (n = 28)	P Value
Age, yr	64 (50–76)*		0.93 [†]
Smoking, pack-years	48.75 (21.75–101.25)	55.63 (24–126)	0.97 [†]
FEV ₁ , observed, liters	2.035 (0.65–3.79)	2.18 (0.23–5.15)	0.90 [†]
FEV ₁ , % predicted	69.55 (28.5–112.8)	77.2 (11.3–109)	0.56 [†]
Emphysema score	2 (0–3)	1.5 (0–4)	0.81 [†]
Nodule size, mm	10 (5–25)	13.5 (4–40)	0.07 [†]
Volumetric doubling time, d	752 (409–17,906)	284.5 (45–4,277) (n = 19)	0.002 [†]
Length of follow-up, yr	9.79 (3.0–11.33)	9.38 (0.50–12)	0.96 [†]
Men, n (%)	8 (47.06)	14 (50.0)	0.85 [‡]
Adenocarcinoma, n (%)	16 (94.12)	22 (78.57)	0.23 [‡]
Others, n (%)	1 (5.88)	6 (21.43)	
Current smoker, n (%)	10 (58.82)	15 (53.57)	0.77 [‡]
Former smoker, n (%)	7 (41.18)	13 (46.43)	
No emphysema, n (%)	5 (29.41)	9 (32.14)	0.85 [‡]
Yes emphysema, n (%)	12 (70.59)	19 (67.86)	
Nonsolid nodule, n (%)	8 (47.06)	8 (28.57)	0.33 [‡]
Solid nodule, n (%)	9 (52.94)	20 (71.43)	

*Values are means (range) unless otherwise noted.

[†]Nonparametric Wilcoxon test.

[‡]Fisher's exact test.

had data on volumetric doubling time (indicated in Table 1 as n = 20).

Discussion

Indolent, potentially inconsequential lung cancer (overdiagnosis) is a relatively recently characterized concept. In PLuSS, we estimate approximately 18.5% of screen-detected prevalence cancers may be indolent. These findings are consistent with previously published reports on lung cancer indolence (2–5) and the recent USPSTF estimate (6). In 2003, Yankelevitz and colleagues published data from chest X-ray screening from the Mayo Lung project and the Memorial Sloan Kettering Cancer Center trial (2). Using doubling times >400 days on chest X-ray, the estimated rate of indolent cancer was between 2 and 7%. Regarding low-dose CT screening trials, Lindell and colleagues reported a 25% rate of indolent cancers in a single-arm prospective CT screening study using a similar cut-off for doubling times from two-dimensional tumor measurements and the Schwartz equation of exponential growth (3). Veronesi and colleagues reported a rate of 25% among incident cancers from the Italian COSMOS cohort study using doubling times from volumetric analysis (4). It should be pointed out that Veronesi and colleagues included cancers present in retrospect as incident cancers

and some prevalence cancers where doubling time could not be calculated in their study. The NLST defined indolent cancers as the number of excess cancers compared with the control group and estimated a rate of 18 to 22.5% (5). A modeling study from the USPSTF estimated a 10 to 12% overdiagnosis in screen-detected lung cancer (6). Each of these studies used different methodologies.

A major strength of our study is that the definition for indolence included both volumetric and PET data. We are the first group to incorporate PET scan findings to define indolence. We used an SUV cut-off of 1 to indicate that any metabolic activity above background physiological activity could be suggestive of a more aggressive tumor. Small nodules (<8–10 mm) are probably below the resolution of PET (9), and two of nine indolent cancers in our series were <10 mm, with SUV ≤1. Another unique feature of our study is the focus on prevalence cancers only. Although this may potentially result in an underestimation of indolence, assuming that some incidence screen-detected lung cancers could be indolent, this approach would result in a more consistent definition of indolence of lung cancer in a screened population.

In contrast to our approach, Veronesi and colleagues focused on incident cancers (although many of the cancers included in our study, defined as prevalence cancers, met their definition of incidence cancer) and

proposed that slow-growing cancers with volumetric doubling time >400 days may represent indolent cancers in COSMOS (25% of incident cancers) (4). In PLuSS, incidence cancers are more aggressive, with a higher percentage of small cell and squamous cell histologies, and only 6.7% of incidence cancers had volumetric doubling time >400 days in our previous study (8). Although there are likely some incident cancers that are indolent, it is a more likely phenomenon in prevalence cancers in a screened population. Our estimate of 18.5% is consistent with the recent estimate from the NLST (18–22.5%) (6).

Tumor growth may not always be linear and could instead be sigmoid shaped or accelerate after a dormant period of no growth (10). Thus, dependence on volumetric doubling time calculated during a limited period of observation of tumor growth to predict long-term indolence may be a study design weakness. The same can be said for using SUV at a single point in time. Thus, prolonged follow-up for such indolent nodules or cancers is essential.

The characterization of small pulmonary nodules remains a challenge for clinicians. The data on indolence suggest that there is a subgroup of lung nodules/cancers detected in the context of LDCT screening usually that are nonsolid; these nodules/cancers may be suitable for follow-up imaging. They would have low metabolic activity on PET (SUV <1) and slow growth (volumetric doubling time >400 d), would likely be adenocarcinoma, and may have different biological behavior than the usual clinical lung cancers. Additional studies to further elucidate the defining characteristics and long-term biological behavior of indolent lung cancer would help address this potential conundrum in lung cancer screening.

In conclusion, indolence in LDCT lung cancer screening may account for 18.5% of all prevalence cancers in PLuSS. Possible indolent cancers include nodules with slow volumetric doubling time and physiologic PET uptake (SUV <1). Educational efforts aimed at increasing awareness of indolence and additional studies to further elucidate the defining characteristics and long-term biological behavior of indolent lung cancer would help limit overtreatment, patient anxiety, and the overall costs of screening. ■

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

References

- 1 Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, Gareen IF, Gatsonis C, Marcus PM, Sicks JD; National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011;365:395–409.
- 2 Yankelevitz DF, Kostis WJ, Henschke CI, Heelan RT, Libby DM, Pasmantier MW, Smith JP. Overdiagnosis in chest radiographic screening for lung carcinoma: frequency. *Cancer* 2003;97:1271–1275.
- 3 Lindell RM, Hartman TE, Swensen SJ, Jett JR, Midthun DE, Tazelaar HD, Mandrekar JN. Five-year lung cancer screening experience: CT appearance, growth rate, location, and histologic features of 61 lung cancers. *Radiology* 2007;242:555–562.
- 4 Veronesi G, Maisonneuve P, Bellomi M, Rampinelli C, Durlì I, Bertolotti R, Spaggiari L. Estimating overdiagnosis in low-dose computed tomography screening for lung cancer: a cohort study. *Ann Intern Med* 2012;157:776–784.
- 5 Patz EF Jr, Pinsky P, Gatsonis C, Sicks JD, Kramer BS, Tammemägi MC, Chiles C, Black WC, Aberle DR; NLST Overdiagnosis Manuscript Writing Team. Overdiagnosis in low-dose computed tomography screening for lung cancer. *JAMA Intern Med* 2014;174:269–274.
- 6 de Koning HJ, Meza R, Plevritis SK, ten Haaf K, Munshi VN, Jeon J, Erdogan SA, Kong CY, Han SS, van Rosmalen J, *et al.* Benefits and harms of computed tomography lung cancer screening strategies: a comparative modeling study for the U.S. Preventive Services Task Force. *Ann Intern Med* 2014;160:311–320.
- 7 Wilson DO, Weissfeld JL, Fuhrman CR, Fisher SN, Balogh P, Landreneau RJ, Luketich JD, Siegfried JM. The Pittsburgh Lung Screening Study (PLuSS): outcomes within 3 years of a first computed tomography scan. *Am J Respir Crit Care Med* 2008;178:956–961.
- 8 Wilson DO, Ryan A, Fuhrman C, Schuchert M, Shapiro S, Siegfried JM, Weissfeld J. Doubling times and CT screen-detected lung cancers in the Pittsburgh Lung Screening Study. *Am J Respir Crit Care Med* 2012;185:85–89.
- 9 Degirmenci B, Wilson D, Laymon CM, Becker C, Mason NS, Bencherif B, Agarwal A, Luketich J, Landreneau R, Avril N. Standardized uptake value-based evaluations of solitary pulmonary nodules using F-18 fluorodeoxyglucose-PET/computed tomography. *Nucl Med Commun* 2008;29:614–622.
- 10 Friberg S, Mattson S. On the growth rates of human malignant tumors: implications for medical decision making. *J Surg Oncol* 1997;65:284–297.