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Volume doubling time of lung cancers detected in a chest radiograph mass screening program: Comparison with CT screening

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Abstract. The aim of this study was to evaluate the volume doubling time (VDT) of lung cancer detected in our annual chest radiograph screening program and to compare it with those previously reported for computed tomography (CT) screening. In total, 209 patients who had a measurable tumor shadow and a history of participating in our chest radiograph mass screening program between 2006 and 2009 were included in this study. Indirect roentgenograms for patients with lung cancer were converted into digital images, and the section showing the tumor was enlarged on the monitor to a size of 0.01 mm. The mean VDT for all the patients was 158 days. Only 3.8% of the patients had a VDT of more than 400 days. In 140 patients with adenocarcinoma, the mean VDT was 177 days, and 5.0% of these patients had a VDT of more than 400 days. In the 44 patients with squamous cell carcinoma, the mean VDT was 133 days, and only 2.3% of these patients had a VDT of more than 400 days. These results were different from those previously reported for CT screening. In several reports on CT screening, more than 20% of the lung cancers had VDTs of more than 400 days. Since it is common knowledge that there are 'indolent' lung cancers with a VDT of more than 400 days, screening by annual chest radiography with rare overdiagnosis may need to be reconsidered.

Introduction

Accurate diagnosis of nodule changes is required for the survival of lung cancer patients. Therefore, application of diagnostic tools that are able to distinguish benign from malignant nodules is crucial in deciding whether a nodule should be examined using an invasive procedure. The volume doubling time (VDT) of a nodule, defined as the number of days in which the nodule doubles in volume, is a key parameter in lung cancer screening (1). Since 2000, a number of reports of VDT detected on chest computed tomography (CT) screening have been published (2-7). However, a comparison of VDT detected on chest radiograph screening with that detected on CT screening has yet to be performed. Yankelevitz *et al* defined lung cancers with a VDT of more than 400 days as being prone to overdiagnosis (8), a definition that has come to be generally accepted by other researchers. According to this definition, fewer than 10% of lung cancers detected by chest radiograph mass screening programs would be considered to be overdiagnosed (8). By contrast, this rate was higher than 20% in a chest CT screening program (2-5).

The purpose of this study was to report the VDTs of lung cancer detected in our annual chest radiograph screening program and to compare them with previously reported VDTs for lung cancer detected on CT screening (2-7).

Patients and methods

Patient characteristics. The local government of the Ibaraki Prefecture (in eastern Japan) and the Ibaraki Health Service Association have formulated and managed an annual lung cancer screening program for over 40 years. We conducted this study using the data collected from the 703,047 individuals who participated in this program, between April 2006 and March 2009. All of the participants underwent an annual chest radiograph examination by 100x100 mm miniature postero-anterior photofluorography. Each chest radiograph was examined by two chest physicians or thoracic surgeons separately. If an abnormal shadow was detected, an additional chest physician or thoracic surgeon evaluated the radiograph again.

During the study period, 343 patients were pathologically diagnosed as having lung cancer. Among them, 209 patients who had a measurable tumor shadow and a history of undergoing a radiograph examination under this program were

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included in the study. We excluded the remaining 134 patients: 80 patients with an immeasurable tumor due to atelectasis or pleural fluid and 54 patients who did not undergo radiographic screening under this program.

Methods. The above-mentioned 100x100 mm radiographs from patients with lung cancer were converted into digital images. The section of the image showing the tumor part was enlarged on the monitor to a size of 0.01 mm. The VDT was calculated using the Schwartz formula (9). The size of the tumor on the radiograph and the size of the tumor as measured by a pathologist following excision were strongly correlated in the 147 patients who underwent resection of a pathologically sized tumor (correlation coefficient, 0.85; P<0.0001).

This study was approved by the ethics committee of the Ibaraki Health Service Association.

Statistical significance between the two groups was determined using the Mann-Whitney U test and Chi-square test. P<0.05 was considered statistically significant.

Results

Patient characteristics. In total, 209 patients, 135 males (64.6%) and 74 females (35.4%), 94.5 (45.2%) of whom were ≥70 years of age, were included in this study (Table I). One hundred forty patients (67.0%) had adenocarcinoma, 44 (21.1%) had squamous cell carcinoma, 14 (6.7%) had large cell carcinoma, 5 (2.4%) had small cell carcinoma and 6 (2.8%) had other variants. One hundred fifty-one patients (72.2%) were surgically treated, 44 (21.1%) underwent chemotherapy and/or radiotherapy, and 14 (6.7%) underwent supportive care.

VDT of lung cancer by chest radiograph and CT screening. Of the total 209 lung cancer patients, the mean VDT was 158 days (median, 106 days; range, 32-1493 days). Only 8 patients (3.8%) had a VDT of more than 400 days. The mean VDT in the 135 male patients was 134 days and the mean for the 74 female patients was 202 days, with a statistically significant difference between them (P=0.005). These data were compared with previously reported VDTs of lung cancer detected on chest radiograph screening and CT scan screening (Table II). The VDT of lung cancer detected on chest radiograph screening was apparently shorter than that detected on CT screening.

VDT in adenoma and squamous cell carcinoma. VDTs were reported for the 140 patients with adenocarcinoma and for the 44 patients with squamous cell carcinoma (Table III). The mean VDT in the patients with adenocarcinoma was 177 days (median, 134 days; range, 46-1493 days). Seven of those patients (5.0%) had a VDT of more than 400 days. The mean VDT in the patients with squamous cell carcinoma was 133 days (median, 99 days; range, 40-712 days). Only one of those patients (2.3%) had a VDT of more than 400 days. The mean VDTs in the patients with small cell carcinoma and large cell carcinoma were 82 days (median, 67 days; range, 50-228 days) and 134 days (median, 89 days; range, 32-361 days), respectively. None of the patients with these cell types had a VDT of more than 400 days.

Our data were compared with previously reported VDTs of patients with adenocarcinoma or squamous cell carcinoma detected on chest radiograph and CT screening (Table III). For adenocarcinoma, but not for squamous cell carcinoma, the VDT detected on chest radiograph screening was apparently shorter than that detected on CT screening.

Table I. Characteristics of 209 patients with lung cancer.

Characteristic	No. of patients
Age (years)	Median, 73; range, 47-89
Gender	
Male	135 (64.6%)
Female	74 (35.4%)
Histology	
Adenocarcinoma	140 (67.0%)
Squamous cell carcinoma	44 (21.1%)
Large cell carcinoma	14 (6.7%)
Small cell carcinoma	5 (2.4%)
Adenosquamous cell carcinoma	2 (0.5%)
Pleomorphic carcinoma	1 (0.5%)
Unclassified carcinoma	3 (0.5%)
Treatment	
Surgery	151 (72.2%)
Chemotherapy and/or RT	44 (21.1%)
Supportive care	14 (6.7%)

RT, radiotherapy.

Discussion

VDT is defined as the number of days in which a nodule doubles its volume (9). VDT helps to differentiate between benign and malignant pulmonary nodules (1) and is a key parameter in lung cancer screening. Shorter VDT may reflect greater histological tumor aggressiveness, suggesting that lung cancers with a short VDT are associated with a poor prognosis (10). Traditionally, the absence of lesion growth over a 2-year period was regarded as a benign status. Nodules that remain stable over a period of at least 2 years have a low probability of malignancy (12,13), although 2-year stability does not guarantee a 'benign' nodule because some malignant nodules have a long VDT. Lillington (11) noted that the VDTs of most benign pulmonary nodules were more than 450 days, whereas those of malignant lesions were usually less than 400 days. Spratt *et al* reported that a tumor with a VDT slower than 500 days was usually benign (1). Low VDT indicates rapid growth, and a VDT of less than 400 days has recently been suggested as the best cut-off value to distinguish between 'indolent' and malignant lesions (14,15). Opinions have also been expressed that lung cancers with a VDT of 400 days or more are overdiagnosed cases (3,16).

As for mass screening for lung cancer, chest radiography and sputum cytology were performed until the 1990s (10,17,18). Thereafter, a number of studies involved chest CT screening, which is more sensitive for nodule detection (2-7). VDT detected on CT screening is different from that

Table II. Volume doubling time of lung cancer detected by chest radiograph and CT scan.

Modality	No. of tumors	Mean VDT (days)	Ratio of VDT >400days	Authors, year	Refs.
Radiograph	64	101	Not shown	Fujimura *et al*, 1979	17
Radiograph	174	164	Not shown	Usuda *et al*, 1994	10
Radiograph	44	101 (median)	2.0% (MLP)	Yankelevitz *et al*, 2003	16
Radiograph	43	144 (median)	7.0% (MSK)	Yankelevitz *et al*, 2003	16
CT scan	61	452	44.1% (>450)	Hasegawa *et al*, 2000	2
CT scan	48	518	27.1%	Lindell *et al*, 2007	3
CT scan	46	Not shown	23.9%	Honda *et al*, 2009	4
CT scan	38	497	23.7%	Sone *et al*, 2010	5
CT scan	46	976	Not shown	Oda *et al*, 2011	6
Radiograph	209	158	3.8%	Kanashiki *et al*, 2012	-

VDT, volume doubling time; MLP, the Mayo Lung Project; MSK, memorial Sloan-Kettering Cancer Center.

Table III. Volume doubling time of adenocarcinoma and squamous cell carcinoma detected by chest radiograph and CT scan.

		Volume doubling time			
Modality	No. of tumors	Mean	Median	Authors, year	Refs.
Adenocarcinoma					
Radiograph	31	116	Not shown	Fujimura *et al*, 1979	17
Radiograph	60	161	Not shown	Geddes[a], 1979	21
Radiograph	86	223	Not shown	Usuda *et al*, 1994	10
CT scan	49	533	Not shown	Hasegawa *et al*, 2000	2
CT scan	22	746	343	Lindell *et al*, 2007	3
CT scan	35	976	258	Honda *et al*, 2009	4
CT scan	19	466	Not shown	Sone *et al*, 2010	5
CT scan	12	202	Not shown	Oda *et al*, 2011	6
CT scan	53	292	227	Dhopeshwarkar *et al*, 2011	7
Radiograph	140	177	134	Kanashiki *et al*, 2012	-
Squamous cell carcinoma					
Radiograph	22	94	Not shown	Fujimura *et al*, 1979	17
Radiograph	111	88	Not shown	Geddes[a], 1979	21
Radiograph	67	105	Not shown	Usuda *et al*, 1994	10
CT scan	8	129	Not shown	Hasegawa *et al*, 2000	2
CT scan	8	103	88	Lindell *et al*, 2007	3
CT scan	11	126	131	Honda *et al*, 2009	4
Radiograph	44	133	99	Kanashiki *et al*, 2012	-

[a]Review.

reported in studies on chest radiograph screening (Table II). This difference may be due to the screening methods and high proportion of 'indolent' types of lung cancer. Small nodules with VDTs longer than 400 days were found on chest CT screening that were not detectable by radiography (2,3,14-16, 19,20). In previous reports based on mass screening by chest radiography, the VDT was apparently longer in adenocarcinoma than in squamous cell carcinoma (10,16,17). In chest radiograph screening, the mean VDT was approximately 110-220 days for adenocarcinoma and 90-130 days for squamous cell carcinoma (Table III) (10,16,17,21,22). In the present era of chest CT screening, this difference has become more evident. The reported VDT of adenocarcinoma is extremely long at 400-800 days on average (2-4), whereas the VDT of squamous cell carcinoma remains unchanged (2-4,10,17,21,22). This difference in VDTs indicates the detection of 'indolent'

adenocarcinoma but of unchanged VDT in squamous cell carcinoma even on the CT scan (2-4,10,17,21,22). Furthermore, bronchioloalveolar cell carcinoma, which has an extremely long VDT, has been detected only on chest CT scan screening (5-7).

It has been estimated that up to 25% of screening-detected lung cancers may not become lethal even if left untreated (3). This so-called overdiagnosis bias results not only from the biological properties of an 'indolent' cancer itself, but also from the two competing diagnostic morbidities that may or may not overdiagnose even an 'indolent' cancer. In studies based on chest radiograph mass screening, less than 10% of the patients had a VDT of more than 400 days (16). In the current study, only 3.8% of the 209 patients had a VDT of more than 400 days. By contrast, this rate was 27-57% in reports based on chest CT mass screening (2,3). These results suggest that the significance of chest radiograph mass screening should be re-evaluated given the current data regarding the existence of 'indolent' types of lung cancer.

The results of this study suggest several important points. Firstly, in overall lung cancer, VDT detected on CT screening was longer than that detected on chest radiograph screening. Secondly, this difference was apparent for adenocarcinoma, but not for squamous cell carcinoma, of the lung. Thirdly, a large percentage of lung cancers with more than 400 days of VDT were included in the CT scan screening. By contrast, less than 10% of cancers with more than 400 days of VDT were included in the chest radiography screening.

Despite the novel findings of the current study, there are several limitations. The key limitations are its retrospective nature and the lack of a control group allowing a comparison with non-screening-detected lung cancers. Furthermore, a technical limitation of our study was the bidimensional measurements used to assess growth rates, which are operator-dependent when the nodules are non-solid or poorly defined. In addition, our study did not evaluate the impact on mortality, which remains the key unresolved issue in the context of lung cancer screening. We also did not compare the cost-performance and economic efficacy of mass screening by chest radiography with those by chest CT scan screening.

Since 2000, several reports describing higher diagnostic efficiency in chest CT screening have been published (2-7), but a comparison of VDT detected on chest CT screening with VDT detected on chest radiograph screening has not been reported. In the present study, we compared VDTs of lung cancer in our patients with those of previous reports. Since it is common knowledge that there are 'indolent' lung cancers with more than 400 days of VDT, screening by annual chest radiography with its rare overdiagnosis may need to be reconsidered.

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References

1. Spratt JS and Spratt JA: The prognostic value of measuring the gross linear radial growth of pulmonary metastases and primary pulmonary cancers. J Thorac Cardiovasc Surg 71: 274-278, 1976.
2. Hasegawa M, Sone S, Takashima S, *et al*: Growth rate of small lung cancers detected on mass CT screening. Br J Radiol 73: 1252-1259, 2000.
3. Lindell RM, Hartman TE, Swensen SJ, *et al*: Five-year lung cancer screening experience: CT appearance, growth rate, location, and histologic features of 61 lung cancers. Radiology 242: 555-562, 2007.
4. Honda O, Johkoh T, Sekiguchi J, *et al*: Doubling time of lung cancer determined using three-dimensional volumetric software: comparison of squamous cell carcinoma and adenocarcinoma. Lung Cancer 66: 211-217, 2009.
5. Sone S, Matsumoto T, Honda T, *et al*: HRCT futures of small peripheral lung carcinomas detected in a low-dose CT screening program. Acad Radiol 17: 75-83, 2010.
6. Oda S, Awai K, Murao K, *et al*: Volume-doubling time of pulmonary nodules with ground glass opacity at multidetector CT: assessment with computer-aided three-dimensional volumetry. Acad Radiol 18: 63-69, 2011.
7. Dhopeshwarkar MR, Roberts HC, Paul NS, Dong Z, Tsao M and Menezes RJ: Screen-detected lung cancer: a retrospective analysis of CT appearance. Acad Radiol 18: 1270-1276, 2011.
8. Yankelevitz DF and Henschke CI: Does 2-year stability imply that pulmonary nodules are benign? AJR 168: 325-328, 1997.
9. Schwartz M: A biomathematical approach to clinical tumor growth. Cancer 14: 1272-1294, 1961.
10. Usuda K, Saito Y, Sagawa M, *et al*: Tumor doubling time prognostic assessment of patients with primary lung cancer. Cancer 74: 2239-2244, 1994.
11. Lillington GA: Management of solitary pulmonary nodules. Dis Mon 37: 271-318, 1991.
12. Viggiano RW, Swensen SJ and Rosenow EC III: Evaluation and management of solitary and multiple pulmonary nodules. Clin Chest Med 13: 83-95, 1992.
13. Cummings SR, Lillington GA and Richard RJ: Estimating the probability of malignancy in solitary pulmonary nodules. A Bayesian approach. Am Rev Respir Dis 134: 449-452, 1986.
14. Xu DM, Gietema H, de Koning HJ, *et al*: Nodule management protocol of the NELSON randomized lung cancer screening trial. Lung Cancer 54: 177-184, 2006.
15. Xu DM, van der Zaag-Loonen HJ, Oudkerk M, *et al*: Smooth or attached solid indeterminate nodules detected at baseline CT screening in the NELSON study: cancer risk during 1 year of follow-up. Radiology 250: 264-272, 2009.
16. Yankelevitz DF, Kostis WJ, Henschke CI, *et al*: Overdiagnosis in chest radiographic screening for lung carcinoma: frequency. Cancer 97: 1271-1275, 2003.
17. Fujimura S, Suda S, Yamauchi A, *et al*: Tumor doubling time and PPD skin test reactivity in resectable lung cancer. J Jpn Lung Cancer Soc 19: 135-142, 1979.
18. Satoh H, Ishikawa H, Yamashita YT, *et al*: Outcome of patients with lung cancer detected by mass screening versus presentation with symptoms. Anticancer Res 17: 2293-2296, 1997.
19. Hayabuchi N, Russell WJ and Murakami J: Slow-growing lung cancer in a fixed population sample: radiologic assessments. Cancer 52: 1098-1104, 1983.
20. Awai K, Fujikawa K, Nakamura S, *et al*: Serial changes in CT findings of small peripheral pulmonary adenocarcinomas followed up for more than one year. Jpn J Lung Cancer 38: 19-28, 1998.
21. Geddes DM: The natural history of lung cancer: a review based on rates of tumour growth. Br J Dis Chest 73: l-17, 1979.
22. Filderman AE, Shaw C and Matthay RA: Lung cancer: Part I. Etiology, pathology, natural history, manifestations, and diagnostic techniques. Invest Radiol 21: 230-239, 1986.