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On the Imaging Modalities for Lung Cancer Screening: Low-Dose CT Scan Could Lead to a Significant Reduction of Mortality Rates of the Patient

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1. Abstract

The NLST- (USA, 2011) [1] and NELSON- (Dutch-Belgian, 2009- 2017) [2,3] randomized control trials on low-dose-CT scans for lung cancer (LDCT) screening have reported a statistically significant reduction of mortality rates of the patient with lung cancers; and the LDCT scan has become an international standard test for screening, being expected to effectively detect curable lung cancers.

Curiously, however, "Japanese lung cancer screening guideline" has long hindered introduction of this screening into a public screening program and the latter is still generally carried out by chest X-ray radiograph (CXR).

Initially, non-comparative observational studies of a fairly large scale had been conducted in Japan and USA to study the performance of LDCT screening in detecting lung cancers at the early curable phase [4-7]. And they reported excellent early detection of lung cancer and high patient survival.

The patient survival rates detected by these are; 5-year survival rates (NAGANO, Japan, 1996-99), 92%, reported in 2007 [5]; and 5-year survival rates (Azumi, Nagano, 2001-2005), 97.1%, reported in 2012 [8]. Further, 10-year survival rates (Nagano, 1996-99), 86%, reported in 2007[5]; and I-ELCAP, USA, 80% among the 484 patients, reported in 2006 [6,7] (Table 1). Of these, Nagano trial (1998) was conducted in a mountainous rural area in Japan (participants of mostly male smokers and female non-smokers) [4], 1998), and (New-York) ELCAP trial, which had been initially named as (NY-) ELCAP (early lung cancer action project 1999) [6], was conducted in a large metropolitan area, New York (with participants limited to smokers); the (NY-) ELCAP was expanded in 1999 to an international research organization, named as International Early Lung Cancer Action Program (I-ELCAP) [7]. Participants in both trials in Nagano and NY had much difference in demographic, geographical and racial features, but showed similarly an excellent detection capability of the lung cancers at the early phase, (Table 2) which led to high survival rates of the patients; a slight difference in survival rates between two trials may be caused by difference on smoking status of the participants in the trials; that is the Nagano trial included female participants of mostly non-smokers [4, 8, 9].

While the survival rates of the patients detected by the traditional chest radiograph (CXR) screening remained poor for a long time, as shown in the Mayo Lung Project [10], caused by a poor performance of this modality in detecting small cancers, at a curable stage [9-12]; a case-control study was further conducted in Miyagi, Okayama, Gunma, Niigata in Japan [12], at nearly the same time as a mobile LDCT trial firstly conducted at Nagano, Japan [4]. Each of these studies by CXR, from 4 prefectures, reported 5-year survival rates ranging 48-61%.

Table 1: Number of participants and stages IA, B or IV cases, survival of patients and over-diagnosis cases

Author, Journal, Year of publication	Number of participants, Stage IA, IB & IV (%)	Survival of patients	over-diagnosis
Sagawa M, et al, Cancer 2001	Case-control study, to evaluate of efficacy of screening between 1990 to 1994, 241 cases, 1557 controls	smoking adjusted odds ratio for those screened within 12 months: 0.54, OR for those screened 12-24 months: 1.24; 5-year survival rate 61%	NA
Sagawa M, et al, Lung Cancer, 2003	Number of cases/controls: Miyagi,328/1886; Gunma, 121/536; Niigata174/801; Okayama 412/3490	Odds ratio who were screened within 12 months/12-24 mos.: Miyagi,0.54/1.24; Gunma,0.68/1.50: Niigata,0.40/1.42; Okayama0.46-0.74/0.79 Survivalrate (LC); 48-61%	NA
Sone S, et al. Lung Cancer, 2007	initial screen, 5483, annual repeat screen,13786, IA 23(initial), 27(1997), 10(1998)	5-year survival rate;92%; 10-year survival, 86%; IA;80.7% IB; 3.5 %, IIB; 1.8%, IIIA; 3.5 %, IV, 0%	13%
Sone S, et al. Eur Radiol, 2012	initial screen, 85 patients with 89 lesions, annual repeat screen,13786, IA 83.	5-year survival rate 97.1%	NA
Henschke CI, et al. N Eng J Med, 2006	baseline screen, 31,567, annual screen, 27,456, clinacal stage I 85%,	10-year survival rate for all participants, 80%	NA

Table 2: TVDT for all 69-cancer cases and for each sub-divided levels (according to smoking status and patient' age and tumor histology) (with Permission by Japanese Journal of Lung Cancer)

	n (%)	Mean	TVDT, number of patients (percentage)						
			VS*	S1*	S2*	S3*	M*	L*	eL*
All cancers	69(100%)	459 days	4(6)	15(22)	5(7)	7(10)	19(28)	14(20)	5(7)
Smoking status									
Smokers	42(100)	364	(10)	(31)	(10)	(7)	(26)	(12)	(5)
Current smokers	28(100)	453	(11)	(32)	(7)	(7)	(18)	(18)	(7)
Ex-smokers	14(100)	187	(7)	(29)	(14)	(7)	(43)	(0)	(0)
Non-smokers	27(100)	606	(0)	(7)	(4)	(15)	(30)	(33)	(11)
Passive-smokers	9(100)	871	(0)	(0)	(0)	(11)	(33)	(33)	(22)
Non-smokers	18(100)	473	(0)	(11)	(6)	(17)	(28)	(33)	(6)
Smoker-group /age									
Smokers-70-	27(100)	245	(11)	(41)	(7)	(11)	(22)	(4)	(4)
Smokers-60-	14(100)	385	(7)	(14)	(14)	(0)	(36)	(21)	(7)
Smokers-50-	1(100)	969	(0)	(0)	(0)	(0)	(0)	(100)	(0)
Non-smoker-70-	15(100)	733	(0)	(0)	(0)	(13)	(33)	(40)	(13)
Non-smokers-60-	9(100)	505	(0)	(22)	(11)	(22)	(0)	(33)	(11)
Non-smokers-50-	3(100)	273	(0)	(0)	(0)	(0)	(100)	(0)	(0)
Histology									
ADC	51(100)	521	(4)	(10)	(8)	(8)	(35)	(25)	(10)
non-ADC	14(100)	173	(7)	(64)	(7)	(7)	(7)	(7)	(0)
LC-NOS	4(100)	119	(25)	(25)	(0)	(50)	(0)	(0)	(0)

To summarize the results of the two types of screening; LDCT screening showed an excellent 5-year survival rate [5] of nearly over 90% as compared with CXR screening, which had a poorer 5-year survival rate of 48-61% [13]. According to the authors of these case control studies, odds ratio (OR) in each program from four prefectures ranged at 0.40-0.68, when they calculated it limited to subjects who died from lung cancer and who had been screened within 12 months before case diagnosis, compared with those not screened; however, as a matter that needs attention, OR was 0.79-1.50 among people screened 12-24 months before the reference date [13]. It seems that the initial small benefits of the screening, shown in the first year of this study, would not last over 12 months; and Japanese case-control studies, using CXR, did not identify odds ratios to indicate the capability in reducing lung cancer mortality in a fairly long term. The CXR screening for lung cancer does not appear to be suitable for local inhabitants, who want their possible lung cancers to be detected at an early stage and to have expectation of a long-term survival.

At present, the guideline for lung cancer screening in Japan recommends the use of chest radiograph (CXR), mainly underpinned by the Sagawa's case-control study [13, 14]. However, comparison of the results shown above between LDCT- and CXR-screening indi-

cates that LDCT is markedly superior to CXR screening [5, 7, 13, 14]; therefore, the basis for recommending the CXR as a screening test for local residents appears weak.

As a diagnostic radiologist, particularly specialized in diagnoses of chest diseases, the author would like to describe next some important findings obtained in our observation study on the LDCT screening (a population-based trial of LDCT screening since 1995, in Nagano, Japan) to help doctors conduct properly the screening. (Table 2) The author strongly hopes that this article (opinion) would be read by the proponents of CXR screening, the doctors, and committees in charge of local CXR screening program and further by the journal reviewers (to put it simply and specific) who are working as the reviewers or members of the editorial board for Japanese Journal of Lung Cancer Society. The author hopes they will be able to understand why CXR screening being not effective in detecting small, early, and curable lung cancers, compared with a LDCT screening, and they will change their management policy, now using CXR in the screening program, to LDCT-screening. This may permit an excellent screening for the local resident in Japan.

To summarize above; the high mortality rate due to lung cancers currently seen in Japan is due to many patients not being diagnosed until they have advanced-stage lung cancers, which may lead to a poor prognosis of the patients. When doctors, in Japan, encounter a situation to explain this fact about lung cancer screening and asked what to do, most of them would say “early detection and treatment is crucial to get a better survival”; however, probably, they do not realize what is the critical tumor size to be pursued in a lung cancer-screening program, and they, together with the clerk in charge of screening examination in the local government, do not really know an appropriate imaging test to depict the curable lung cancers [15, 16].

2. Question 1

2.1. What is the critical tumor size to detect a lung cancer free of nodal involvement and distant metastasis?

Answer 1 [8]

Looking at the scatter diagram, presented by the author for all 89 tumors, including five patients with problematic outcomes (that is, tumor of more advanced p-stage than IA, or with post-surgical recurrence or mortality from lung cancer) (Figure 1), people will understand that the size and CT values of the problematic tumors (which may possibly lead to problematic outcome of the patient, marked by red or orange in the graph) are located at the right upper quadrant of it: having whole tumor size, >18 mm (by 3D-measure), or >14 mm (by 2D-manual measure using a light pen on the monitor), and CT values; > -390 HU (by 3D), or -200HU (by 2Dmanual). The central denser zone (CDZ) diameter; >15mm (by 3D), or >14mm (by 2D manual), and CT values >-70HU (by 3D), or >-40HU (by 2D manual). (*The size of solid tumors is not separately summarized here, because we only occasionally encountered solid nodules; and the author understands the critical size of solid nodule due to small cell lung cancer (SCLC) may probably be less than one centimeter [11,12]).

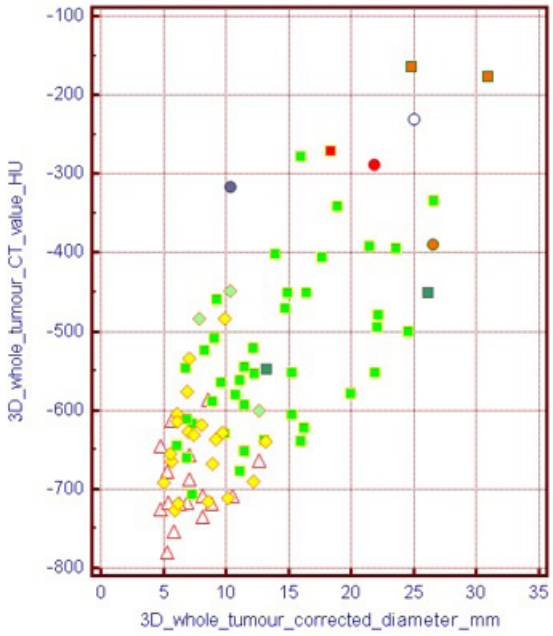

Figure 1: Scatter diagram of the 3D-determined corrected diameter and CT values of the whole tumor for all 89 tumors. Five patients had a problematic outcome (located in the right-upper corner, marked by red or orange on the figure. (under applying for the permission by Eur Radiol)

3. Question 2

3.1. currently most of the guidelines on the LDCT screening recommend for smokers to undergo it. While the Nagano trials have initially conducted the annual LDCT screenings for both smoking- and non-smoking participants. Was it appropriate?

Answer 2

the results of our trials showed that prevalence rates of lung cancer patients for smokers and non-smokers were similarly high, at nearly 500 patients per 100,000 participants. So, the author, personally, considers that it is reasonable for both smokers and non-smokers to undergo prevalence CT screening [15]. And generally speaking, for any non-smoker who is worried about having lung cancer and wants to be tested, the LDCT scan should be done. This helps the doctor consulting with the individuals by preventing detection error of a small curable lesion, which may occur when the individual was tested by other imaging modality (the tumors that should be detected by screening are those small, curable nodules, which could be detected easily on the CT images, but difficult on CXR [11]). CXR is not suitable for this purpose at all; because it has poor detection ability for pure- or part-solid GGO (ground-glass opacity) nodules caused by the adenocarcinoma, which is one of the histologic types of lung cancers detected in the prevalence CT screening.

4. Question 3

4.1. What is the difference of the results by LDCT screening obtained from smokers and non-smokers? [5, 11, 12, 15].

Answer 3 [15]

(Prevalence rate;)among the total of 295 patients, the prevalence rate was similarly high in all smoking categories: that is, 504 patients per 100,000 subjects for entire group: 457 for smoker-, and 542 for non-smokers. (Incidence rate): annual incidence rate (per 100,000 participants) was much lower for all smoking categories. 84 for entire group; 111 for smokers; and 49 for non-smokers (Ratio of prevalence/ incidence); ratio of the prevalence- / annual repeat-cancer was 6.0(504/84) for entire group; with 4.1 for smokers; and 11.0 for non-smokers. (Mean TVDT): 459 days for all 69 lesions; 364 days for smokers; and 606 days for non-smokers.

5. Question 4

5.1. How frequently the repeat LDCT screening should be done?

Answer 4

In considering this, the author expects that repeat scan would be done with an aim to detect most lung cancers at the curable stage, that is before the patient's nodule attains to 14 mm. The author uses assumption in defining an appropriate time of the repeat screening; that any nodule < less than 3 mm may be missed at the previous scanning, and most cancers should be detected at the repeat screening with the tumor size of < 14 mm. In the calculation of the scan interval before the next repeat screening; three parameters should be prepared, those are difference of tumor diameters shown at the initial- and repeat-scans, difference of three-dimensional tumor volume at the initial- and repeat-scans, calculated from tumor diameters or obtained by（semi-）automated volume measurements）and elapsed time between the two scans.

6. Question 5

6.1. How TVDT varies according to the smoking status, age group and gender?

Answer 5

Smokers consisting of 42 patients had mean TVDT of 364 days [15]; it ranged widely from VS (very short, <54 days), 10% of the participants, S1 (quite short, 55-112days), 31%, S2 (moderately short, 113-163 days), 10%, S3 (somewhat short, 164-218 days), 7%, M (moderate, 219-400 days), 26%, L (long, 401-1,499 days), 20% and to eL (extremely long, ≥ 1, 500 days), 5%; while among 27 non-smokers, it ranged from VS (0%), S1 (7%), S2 (4%), S3 (15%), M (30%), L (33) to eL (11%), respectively [12,15]. There were differences in TVDT values between smokers and non-smokers, and the subdivided categories showed a wide distribution pattern of the TVDT values both in the smokers and non-smokers. The TVDT values according to the smoking status/age showed the shortest mean TVDT value in the elderly smokers, whereas a longer mean TVDT value was observed in the elderly non-smokers. These stresses the importance of performing repeat scans at a longer interval for non-smokers.

Annual repeat screening for 60- and 70-year-old smokers may partly fail in detecting lung cancer at the tumor size at < 14 mm, and in some proportion of 60-year-old non-smokers on biennial repeat screening [15].

7. Question 6

7.1. Disadvantage of over-diagnosis has been addressed repeatedly [17]. How often can this occur in LDCT screening program in Nagano, consisting partly of non-smokers?

Answer 6

Over-diagnosis has not been so often observed [5,8,15,16]. Our screening trial in Nagano comprised with the female participants of mostly non-smokers and male participants being mostly smokers. The author estimated the age of the patient at the time that the lesions would have grown to 30 mm, based on the tumor sizes at the initial- and repeat-screening and the calculated TVDTs from these. The author further obtained the expected time of patient's death by adding 2 years to the time when the tumor would have grown to tumor diameter of 30 mm, since it is reported that the patients with lung cancer of 30 mm or larger in size would die of lung cancer in 2 years in average [18]. The expected time of patient's death was compared with people' average life span informed in Japan to define the possible cases of over-diagnosis; the results indicated that our low-dose CT screening in Nagano may be considered to include approximately 13.3% of possible over-diagnosis in total, with 17.9% for male patients and 5.9 % for female patients [15] (The average life span of people in Japan in 2006 was 78.6 years for males and 85.6 years for females, respectively).

Another literature on CXR has discussed on an over-diagnosis and used TVDT of >400 days as a suitable indicator of the over-diagnosis [19] (although the author considers this 400 day may be too short, realistically); when this definition was applied to our trial at Nagano, over-diagnosed cases attained 17% of the smokers and 44% of the non-smokers [15].

8. Question 7

8.1. Quantitative analysis helps doctors in patient's consultation submitting adequate reliable measurements of tumor size, CT value and TVDT [15]. What was an idea in developing the semi-automated quantitative measurements?

Answer 7

When the author conducts work-up examinations on a lung nodule and try to find the presence of any meaningful interval change in nodular size and density, comparing two series of thin section CT images (e.g., initial and follow-up CT images), difficulties may occasionally be encountered, even after a time-consuming close inspection of the many thin-section CT images. To avoid uncer-

tainties in interpreting CT images with the naked-eye observation, the author considered it necessary to develop semi-automatic software to get quantitative information from the CT images. The author wanted to get quantitative measurements on the volume and weight of the whole and each of the sub-divided four different density portions in it [20, 21]. Based on these reliable measurements of the tumor we can avoid over-diagnosis or delay in intervention.

Following this measurement on the lesion seen in the conventional gray-scale image, a color image for the area surrounding the tumor, by four colors, is shown on the monitor (Figure 2) (when the interpreter selects to use the default settings for the CT image display defined by the author, color image will be presented as; pixels in the marked area defined by the interpreter will be colored in red for -750 to -651HU, in yellow for -650 to -351 HU, in green for -350 to -51 HU, in blue for -50 to 50HU; (the current default settings for the CT strata are intended to demonstrate GGO portion in red or yellow, which correspond to alveolar lining tumor growth and cellular portion in green or in blue which represent alveoli-filling tumor growth consisting of moderately dense to highly dense zones of desmoplasia response or solid tumor growth) [20, 21]. (Measurement-results are usually shown at the bottom of the Screen Shot, informing the size and weight for total and each of four strata (Using semi-automated measurement software, the interpreter only needs to manually define the highest and lowest CT images; and when necessary, manual trim off function can be used to exclude pulmonary vessel areas from the nodule).

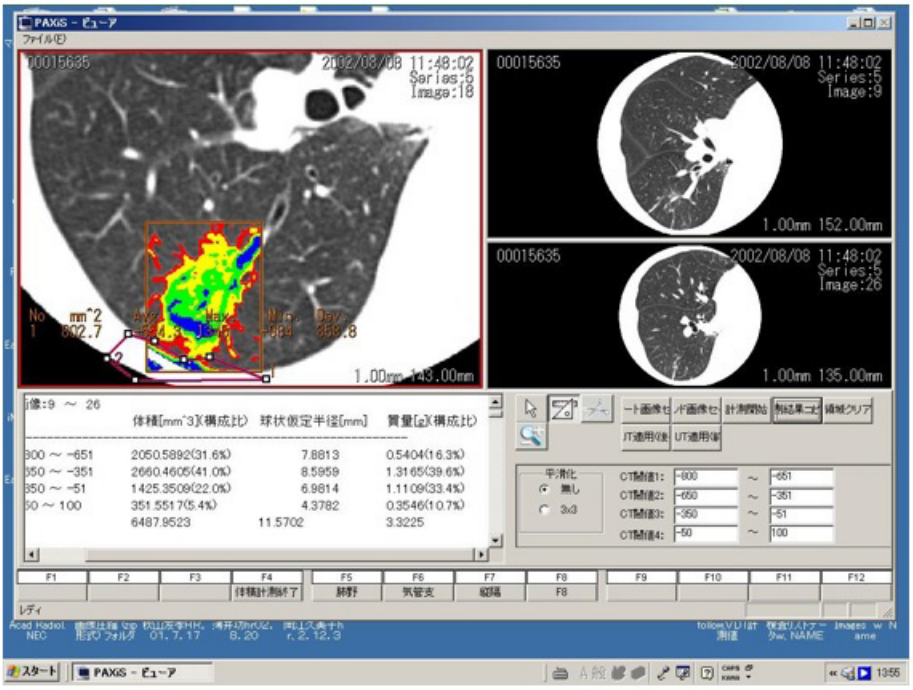

Figure 2: A representative magnified view of the right lower lobe of a 54-year-old non-smoking woman with adenocarcinoma. A partly solid tumor area is colored. Semiautomatic 3-D measured tumor radius, 11.6mm, corrected central denser zone radius occupied 25 % of tumor

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