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Low-dose computed tomography for lung cancer screening: comparison of performance between annual and biennial screen

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Abstract

Objectives To compare the performance metrics of two different strategies of lung cancer screening by low-dose computed tomography (LDCT), namely, annual (LDCT1) or biennial (LDCT2) screen.

Methods Recall rate, detection rate, interval cancers, sensitivity, specificity, positive and negative predictive values (PPV and NPV, respectively) were compared between LDCT1 and LDCT2 arms of the MILD trial over the first seven (T0-T6; median follow-up 7.3 years) and four rounds (T0-T3; median follow-up 7.3 years), respectively.

Results 1152 LDCT1 and 1151 LDCT2 participants underwent a total of 6893 and 4715 LDCT scans, respectively. The overall recall rate was higher in LDCT2 arm (6.97 %) than in LDCT1 arm (5.81 %) ($p = 0.01$), which was counterbalanced by the overall lower number of LDCT scans. No difference was observed for the overall detection rate (0.56 % in both arms). The two LDCT arms had similar specificity (99.2 % in both arms), sensitivity (73.5 %, in LDCT2 vs. 68.5 % in LDCT1, $p = 0.62$), PPV (42.4 %, in LDCT2, vs. 40.6 %, in LDCT1, $p = 0.83$) and NPV (99.8 %, in LDCT2 vs. 99.7 %, in LDCT1, $p = 0.71$).

Conclusion Biennial screen may save about one third of LDCT scans with similar performance indicators as compared to annual screening.

Key Points

- *Biennial LDCT screening may be as efficient as the annual screening.*
- *Annual and biennial LDCT screening have similar frequency of interval lung cancers.*
- *Biennial screening may save about one third of LDCT scans.*

Keywords Lung cancer screening · Strategy · Biennial screening · Low-dose computed tomography · Interval cancer

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Abbreviations

FN	False negative
FP	False positive
LDCT	Low-dose computed tomography
LDCT1	Annual LDCT screening
LDCT2	Biennial LDCT screening
NCNs	Non-calcified nodules
NPV	Negative predictive value
PPV	Positive predictive value
TP	True positive
TN	True negative

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Introduction

Several differences are evident among the randomised lung cancer screening trials, notably in size thresholds of non-calcified nodules (NCNs) to be deemed a positive finding, as well as in the selection of low-dose computed tomography (LDCT) screening frequency for negative screenees [1–6].

The United States Preventive Services Task Force recommends annual screening with LDCT in selected subjects, according to stratification of risk [7]. The American College of Radiology provided a quality assurance tool to standardize screening LDCT and management, suggesting annual screening for subjects either with no nodules or with nodules with very low likelihood to evolve into clinically active disease [8].

However, there is still substantial uncertainty about the optimization of screening interval for participants with negative screen results. A comparison of annual versus longer screening intervals was retrospectively simulated to identify efficient CT-screening scenarios with optimal balance between prevention of lung cancer deaths and number of CT screens [9]. These findings suggested that biennial screening was less effective in absolute terms, with the advantage to reduce harms (e.g., number of screening examinations per individual, false-positive results, overdiagnosis, and radiation-related deaths from lung cancer) and increase cost effectiveness. However, to date, there is no prospective study testing the performance of longer-than-one-year screening intervals.

The LDCT arm in the MILD trial was peculiarly randomized into two arms with different intervals between LDCT controls, namely annual or biennial screen [2]. Such differentiation was adopted to assess the best screening strategy in terms of health care resources and radiation exposure.

In a prior publication, no difference was found in terms of mortality rate between the two LDCT arms within the first 5 years [2]. In this study, we present detailed findings from the two LDCT arms in order to compare the performance characteristics in terms of recall rate, detection rate, interval cancers, sensitivity, specificity, positive and negative predictive values over the first seven and four rounds, respectively, for LDCT1 and LDCT2 arms.

Materials and methods

Study population

The MILD trial was approved by the Institutional Review Board (IRB) of each collaborating Institution, and written informed consent was obtained from all participants.

Details on the design, eligibility criteria, demographic characteristics of the participants, and lung-cancer-specific mortality rates of the MILD trial are found elsewhere [2, 10]. Consenting participants were randomly assigned into two arms: *1) control arm* undergoing primary prevention program with pulmonary function test and blood sample collection; *2) LDCT arm* undergoing the same primary prevention program and LDCT. The LDCT arm was further randomized into two subgroups: 1) LDCT1 with annual LDCT scan; 2) LDCT2 with biennial LDCT scan. LDCT2 participants with either indeterminate or positive findings underwent diagnostic workup as per protocol, and were then followed with annual LDCT scan.

In the present study, data were collected from the LDCT arms until 31 December 2013, including the first seven screening rounds (T0–T6) for the LDCT1 arm and the first four rounds (T0–T3) for the LDCT2 arm (see also supplemtary material). A total of 2376 eligible subjects were randomized to the LDCT arm. There were 1152 participants who underwent at least one LDCT scan in the LDCT1 arm and 1151 in LDCT2 arm with a rate of adherence to the screening protocol of 96.1 % and 95.1 %, respectively. At recruitment, LDCT1 and LDCT2 subjects were similar for age, gender proportion, and smoking history [2].

Lung nodule management protocol

Imaging method and reading procedure are given in the supplementary material.

Baseline screening

The outcome of screening test was set as negative, indeterminate, or positive based on semiautomated volumetry. A negative result was assigned to subjects without NCN or with NCN < 60 mm^3, nodules with fat or benign pattern of calcification. An indeterminate result was assigned in the case of NCN 60–250 mm^3, which was further investigated by LDCT after 3 months with definite categorization into positive finding if NCN was found, or negative if otherwise. A positive result was assigned in case of NCN > 250 mm^3 at baseline LDCT. Furthermore, LDCT scans were deemed positive, also based on findings such as non-calcified hilar or mediastinal lymphadenomegaly, atelectasis, consolidation and pleural findings. All positive findings were evaluated by PET-CT scanning and/or contrast enhanced CT scan. Participants with lesions showing a positive FDG uptake underwent biopsy and/or lung surgery as jointly established by the senior MILD radiologist (A.M.) and the thoracic surgeon (U.P.) coordinating the MILD trial. Annual LDCT screening interval was therefore administered to subjects with an indeterminate or positive LDCT result that was not classified as tumor by the established workup, despite their LDCT arm of initial randomization (either LDCT1 or LDCT2). The 1-year follow-up by LDCT granted longitudinal volumetry of NCN, notably nodule growth was considered a positive result; otherwise, the test

was considered negative and the participant was scheduled for annual screen (see also supplementary material).

Incidence screenings

In the case of known NCN, the result of the follow-up round was based on volumetric change of NCN (positive result was defined as volume increase > 25 %). When one or more new NCNs appeared on repeat LDCT scan (incidence NCN), a recall LDCT was planned after 3 months for assessment of signs of growth. In the case of NCN, the finding was further characterized by workup as described above for positive baseline screen. Subjects with incidence NCN that did not result in diagnosis of lung cancer were then followed up by yearly LDCT.

Outcomes

Definitions for true-negative (TN), true-positive (TP), false-negative (FN) and false-positive (FP) test results are given in the supplementary material.

For the assessment of the interval lung cancers, two radiologists (M.S., N.S., with 6 and 9 years of experience in lung cancer screening, respectively) retrospectively reviewed screening LDCTs, and reached a consensus on whether or not the lung cancer could retrospectively be identified. Interval lung cancers were classified according to the definitions modified from the study of Horeweg et al. [11]:

- *type 1:* lung cancers diagnosed after a negative screening test, in particular
  - *type 1a:* without sign of disease on previous screening
  - *type 1b:* with retrospectively visible interval cancers
- *type 2:* lung cancers diagnosed after an indeterminate screening test, but without any diagnostic workup being done in the screening program;
- *type 3:* lung cancers diagnosed after a positive screening result if the diagnostic workup initiated for the positive screening result did not yield a diagnosis of lung cancer. Diagnostic workup was defined not to have yielded a diagnosis of lung cancer if it was concluded that the suspicious lesion was not lung cancer and the participant was assigned to annual screening.

All related diagnostic procedures and results were retrieved by certified medical records. Final staging of disease was made according to the histology (pTNM) and the recommendations from the seventh edition of International Association for the Study of Lung Cancer (IASLC) [12]. Lung cancers diagnosed as stage equal to or higher than II were deemed advanced disease.

Data analysis

Recall rate was calculated as the number of participants referred for further investigation after an indeterminate or positive LDCT screen, including repeated LDCT after 3 months and other diagnostic procedures (e.g., standard-dose CT, histological diagnosis and PET) divided by the number of screens. Additionally, we calculated the specific recall rate for interval imaging (including contrast CT scan)—"interval imaging recall rate"—or more invasive diagnostic procedures (e.g., PET examinations, transthoracic needle aspiration, fibrobronchoscopy, or transbronchial needle aspiration), separately. For each LDCT arm, both recall and detection rate were calculated. We defined the detection rates as the number of lung cancers diagnosed after a diagnostic procedure carried out as a result of a positive LDCT screening test, divided by the number of screens.

Definitions of sensitivity, specificity, positive (PPV) and negative (NPV) predictive values are summarized in the supplementary material.

Dichotomous and categorical data were analysed using the contingency table analysis with the Chi-square or Fisher's test, as appropriate. Continuous data were analysed using Wilcoxon's rank-sum test. Confidence intervals were calculated with the use of bootstrapping. Comparisons between proportions were performed using z-test. All tests were two-sided and p values < 0.05 were considered statistically significant. Statistical analyses were performed using STATA statistical software (version 11; StataCorp, College Station, TX, USA).

Results

LDCT1 and LDCT2 participants underwent a total of 6893 and 4715 LDCT scans, respectively (Table 1). A median of 6 ± 1.7 follow-up LDCT1 scans and 3 ± 1.7 follow-up LDCT2 scans over a median follow-up of 7.3 years were obtained. The LDCT arms were similar for age, gender proportion, smoking history and also for nodules number (LDCT1 nodules = 1418 vs. LDCT2 nodules = 1392) [2]. Participants adherence was susbstantially maintained until T6 and T3 rounds for the LDCT1 and LDCT2 participants, respectively (Figs. 1 and 2).

The two LDCT arms screening results are summarized in Figs. 1 and 2. The frequency of positive screens was higher in the LDCT1 arm ($p < 0.0001$), while that of the indeterminate screens was higher in the LDCT 2 arm ($p = 0.0002$). LDCT1 participants underwent PET-CT examinations twice as much as LDCT2 participants. No major surgical resections (i.e., lobectomy or segmentectomy) were performed for benign disease (Table 1).

The overall recall rate in the LDCT2 arm (6.97 %) was higher than that of the LDCT1 arm (5.81 %) ($p = 0.01$), whereas the detection rate was 0.56 % in both LDCT arms (Figs. 1

Table 1 Performance indicators for LDCT1 and LDCT2 arms

	LDCT1	LDCT2	*p* value
Total number of LDCTs/participants (ratio)	6893/1152 (6:1)	4715/1151 (4.1:1)	<0.0001
Indeterminate screens (recall at 3 months)/total number of screens	272/6621 (4.1 %)	252/4461 (5.6 %)	0.0002
PET examinations	79	41	0.0008
Early recall at 1 month following antibiotic therapy	17	16	0.9
Contrast CT examinations	6	3	NA
Invasive diagnostic procedures*			
Benign/Malignant	1/4	3/5	NA
Anatomical resections†			
Benign/Malignant	0/35	0/19	NA
Non anatomical resections§			
Benign/Malignant	0	1/0	NA

* transthoracic needle aspiration, fibrobronchoscopy, or transbronchial needle aspiration

† either lobectomy or segmentectomy

§ wedge resection

and 2). The interval imaging recall rate was higher in the LDCT2 arm (6.1 % in LDCT2 vs. 4.5 % in LDCT1, $p = 0.0002$), whereas the recall rate for invasive procedures was similar (1.1 % in LDCT2 vs. 1.3 % in LDCT1, $p = 0.35$). In the LDCT2 arm, the dection rate was higher among participants who were screened yearly (i.e., due to the presence of indeterminate or positive findings at former screen) than among participants who continued to be screened biennually (1.19 to 2.29 % vs. 0.13 to 0.52 %; Fig. 2).

Incidence, characteristics, and screening detection of lung cancer are stratified for each LDCT arm in Table 2. A total of 42/1152 (3.6 %) and 31/1151 (2.7 %) participants received a diagnosis of lung cancer in LDCT1 and LDCT2 ($p = 0.19$), respectively. No synchronous tumor was detected. The lung cancer incidence rate was 519.1 cases per 100,000 person-years in the LDCT1 arm and 380.8 cases per 100,000 person-years in the LDCT2 arm.

Tumor staging data was available for 41/42 (97.6 %) LDCT1 and 27/31 (87.1 %) LDCT 2 subjects (Table 2). For early stage lung cancer, the overall proportion (22/41, 53.6 % in LDCT1 and 16/27, 59.2 % in LDCT2; $p = 0.65$) and detection rate (16/22, 72.7 % in LDCT1 arm vs. 12/16, 75 % in LDCT2 arm; $p = 0.98$) were similar between the LDCT arms. The incidence of early stage lung cancer was 271.9 cases per 100,000 person-years in the LDCT1 arm , compared to 196.5 cases per 100,000 person-years in the LDCT2 arm.

Histologic data was available for 37/42 tumors (88.1 %) in LDCT1 arm and 26/31 tumors (83.9 %) in LDCT2 arm (Table 2). Adenocarcinoma was the most frequent histological subtype in both LDCT1 (22/37, 59.4 %) and LDCT2 (19/26, 73.1 %). Squamous cell carcinoma was more frequently recorded among tumors detected in the LDCT1 arm (Table 2).

The frequency of participants with interval cancer was similar between LDCT arms (13/1152, 1.1 % in LDCT1 vs. 10/1151, 0.9 % in LDCT2; $p = 0.68$). Frequency, types and characteristics of interval lung cancers are summarized in Table 2. Data on TP and FN screens are summarized in Table 3. Of note, the proportion of interval cancers with no sign of disease on previous screening (*type 1a*) was slightly higher in the LDCT1 ($n = 5$), as compared to LDCT2 ($n = 3$). Reassessment of the LDCTs showed that detection errors (33 % in both arms) and interpretation errors (67 % in both arms) were the causes of the failure to detect type 1b interval cancers. The proportion of interval cancer at advanced stage was similar (6/12, 50 % in LDCT1 vs. 5/9, 55 % in LDCT2, $p = 0.80$) between the LDCT arms.

Specificity (99.2 %, 95 % CI: 99.1–99.4 % in LDCT 2 vs. 99.2 %, 95 % CI: 99.0–99.3 % in LDCT1, $p = 1.0$) and sensitivity (73.5 %, 95 % CI: 55.2–89.9 % in LDCT2 vs. 68.5 %, 95 % CI: 52.8–87.0 % in LDCT1, $p = 0.62$) were similar in the two LDCT arms. The LDCTs arms were similar with respect to both PPV (42.4 %, 95 % CI: 35.9–49.3 % in LDCT2, vs. 40.6 %, 95 % CI: 34.1–46.2 % in LDCT1, $p = 0.83$) and NPV (99.8 %, 95 % CI: 99.5–100 % in LDCT2 vs. 99.7 %, 95 % CI: 99.6–99.9 % in LDCT1, $p = 0.71$) (Table 3).

Discussion

Recall rate and detection rate are high priority targets for optimization of lung cancer screening, along with reduction of screens [13]. This study shows that a biennial screening may be at least as efficient as the annual screening in terms of detection rate, sensitivity, specificity, PPV and NPV. These findings are in keeping with the similar mortality rate previously observed in the two LDCT arms [2]. The slightly higher interval imaging recall rate in the LDCT2 arm was counterbalanced by the lower number of scans; notably, about

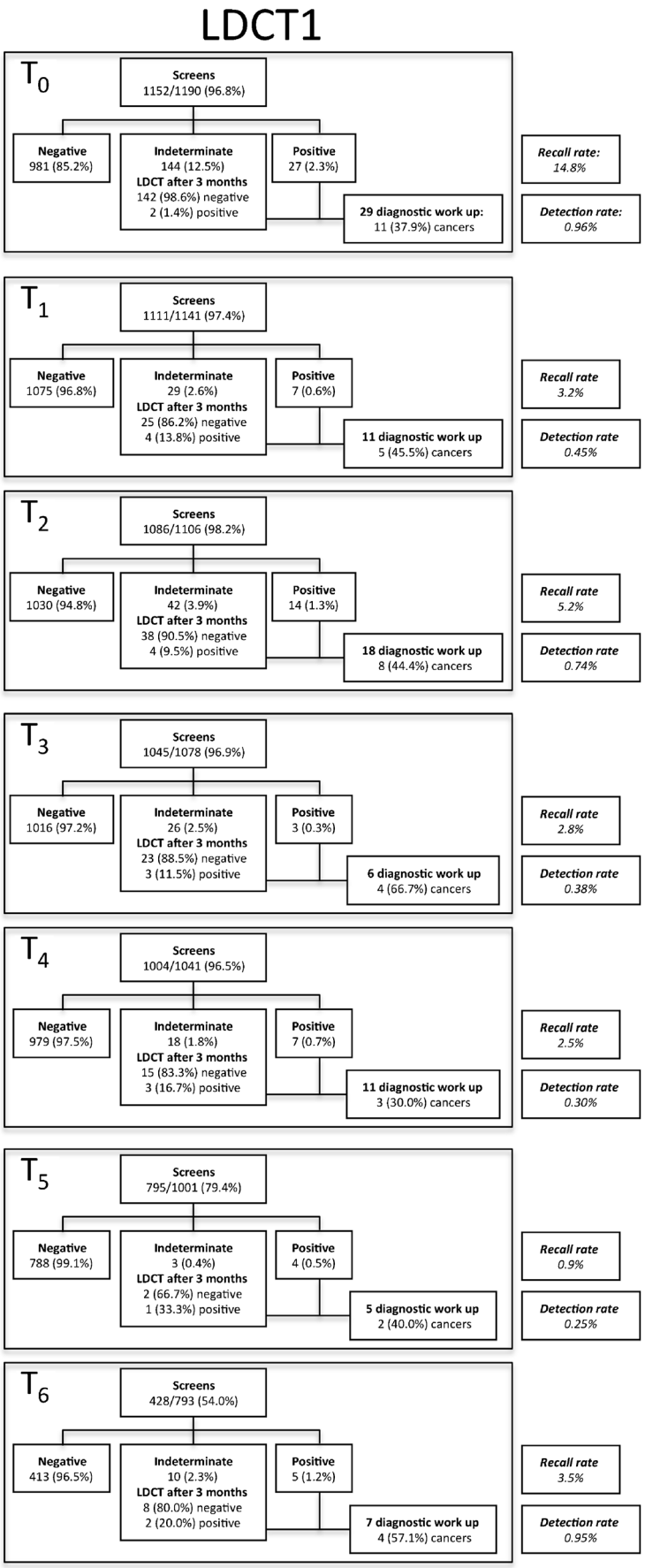

Fig. 1 Results of the first seven rounds of annual low-dose computed tomography screening

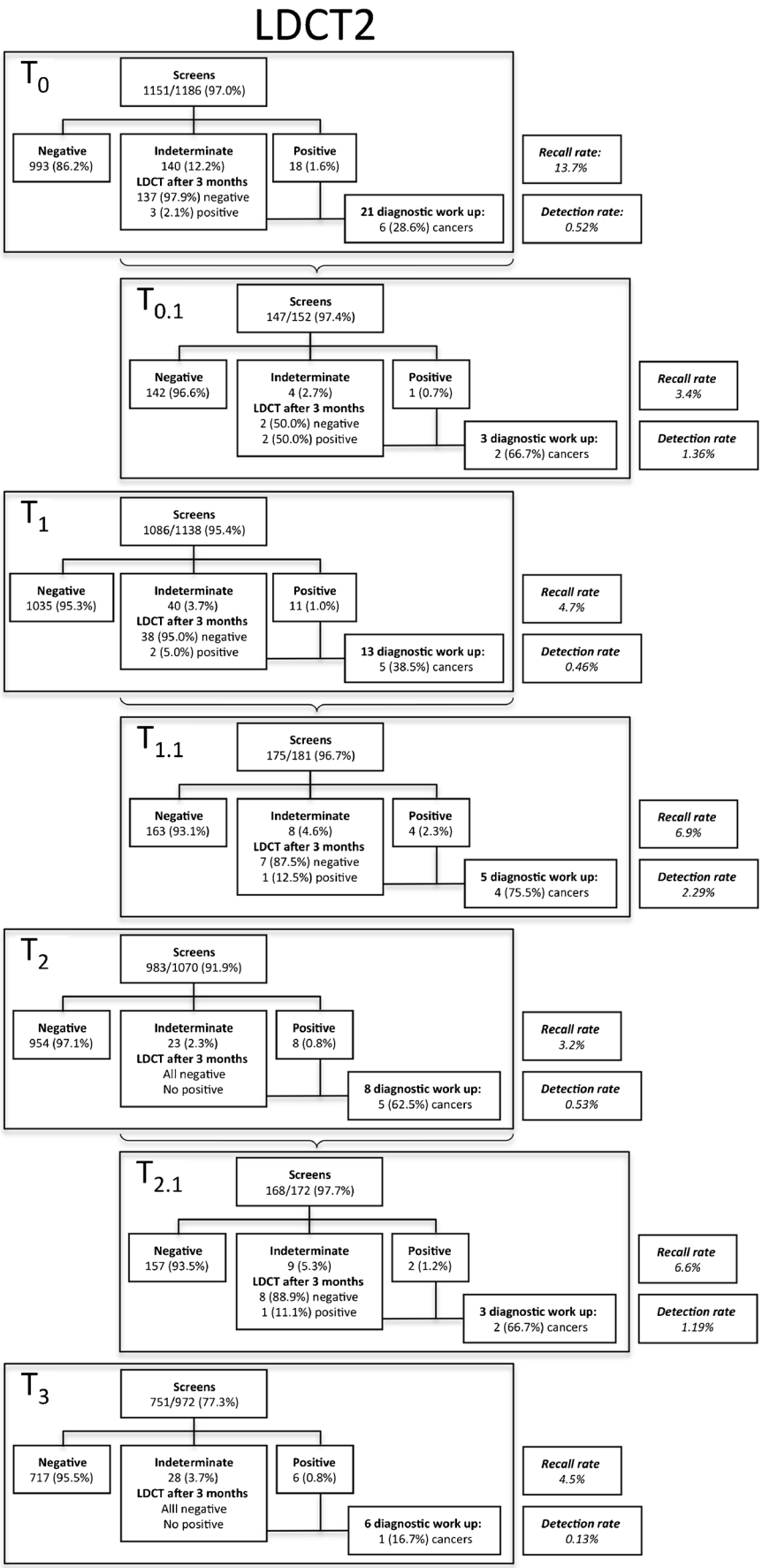

Fig. 2 Results of the first four rounds of biennial low-dose computed tomography screening. T0.1, T1.1., T2.1 are rounds of subjects shifted to the annual follow-up

Table 2 Stage and histology data of screen-detected and interval cancers

	LDCT1		LDCT2		*p* value*
	Screen-detected (29/42)	Interval cancers (13/42)	Screen-detected (21/31)	Interval cancers (10/31)	
Stage					
Ia	15	4	9	4	0.42
Ib	1	2	3	0	
IIa	1	0	0	0	
IIb	2	0	1	0	
IIIa	4	1	0	2	
IIIb	0	0	2	0	
IV	6	5	3	3	
Indeterminate	0	1	3	1	
Histology					
Adenocarcinoma	14	9	14	5	0.09
Squamous cell carcinoma	12	0	1	1	
Large cell carcinoma	0	1	0	3	
Small cell carcinoma	1	0	2	0	
Indterminate	2	3	4	1	

* Comparison between LDCT arms (both screen-detected and interval types)

two-thirds of scans performed in the LDCT1 arm. However, we also showed that the recall rate for invasive procedures was similar.

Reducing the number of LDCT screens is a less harmful as well as more cost-effective strategy. In a recent retrospective analysis of the NLST and PLCO trial data, De Koning et al. suggested that biennial screening is less effective in absolute terms, but induces substantially fewer harms (e.g, overdiagnosis, radiation-related deaths from lung cancer, false-positive results, and number of screening examinations per individual) compared to annual screening; thus, it might be similarly cost-effective [9].

Table 3 LDCT arms performance

	LDCT1	LDCT2	*p* value for comparison between arm*
Screened participants	1152	1151	
Median follow-up time (Interquartile Range) – years	7.3 (0.9)	7.3 (0.9)	
Negative screen result	6530	4402	
True negative	6513	4393	0.56
False negative†	17†	9†	
Positive screen result	91	59	
True positive	37	25	0.84
False positive	54	34	
Participants with interval cancers	13 (1.1)	10 (0.9)	0.68
1a	5 (38.5)	3 (30)	0.37
1b	6 (46.1)	3 (30)	
2	2 (15.4)	2 (20)	
3	0	2 (20)	
Sensitivity % (95 % CI)	68.5 (52.8–87.0)	73.5 (55.2–89.9)	0.62
Specificity % (95 % CI)	99.2 (99.0–99.3)	99.2 (99.1—9.4)	1.00
Positive predictive value % (95 % CI)	40.6 (34.1–46.2)	42.4 (35.9–49.3)	0.83
Negative predictive value % (95 % CI)	99.7 (99.6–99.9)	99.8 (99.5–100)	0.71

* Comparisons between LDCT arms (both screen-detected and interval types) were performed using Wilcoxon test for continuous variable and Chi-square or Fisher's exact test, as appropriate, otherwise, † false negative screens account to the number of false negative LDCTs

One of the major concerns about increasing the interval time between screens is the potential increase in interval cancers, in particular those in advanced stage. In the NELSON study, different screen intervals (1, 2, and 2.5 y) were used to assess the optimal screen interval [11]. It was found that the number of interval cancers increased by prolonged screen intervals. The 5-year results of MILD trial were published in 2012, no difference in the number of interval cancers was found between the LDCT arms [2]. In the present study, by considering a broader definition of interval lung cancer (in keeping with the NELSON'study [11]), we found a higher rate of interval cancers in the LDCT1 arm. Notably, the LDCT arms were similar for advanced stage interval and also screen detected lung cancers porportions. In line with the study by Hoereweg et al., about two-thirds of the interval cancers were retrospectively visible on both LDCT arms, but were not diagnosed [11]. Importantly, the type 1a interval cancers rate was similar between the two LDCT arms. Two out of three type 1a interval cancers in the LDCT2 arm were recorded in participants shifted into annual follow-up, suggesting that a longer follow-up may be equally safe.

The LDCT2 (73.5 %) sensitivity was slightly but not significantly higher than in LDCT1 (68.5 %). The overall sensitivity in both LDCT arms was slightly lower than that reported in the NELSON (84.6 %) and in the NLST trial (93.8 %) [11, 14]. Aside from other factors (e.g., different workup protocols), our longer term follow-up study may account for the lower sensitivity, which may decrease over follow-up LDCTs, likely due to the increase of the interval cancers rate [11]. The specificity in both LDCT arms was very high (99.2 % in both LDCT arms), similar to that reported by the NELSON trial (98.6 % in the NELSON) and substantially higher than in the NLST (73.4 %) [11, 14]. The lower NLST specificity is likely due to the definition of positive screen (i.e. NCN > 4 mm in the longest diameter) that increased the FP rate as compared to both NELSON and MILD. Indeed, the latter trials used volumetric evaluation of NCN with higher corresponding diameter to define positive screens. The NPV of MILD LDCT arms (99.7 % and 99.8 % in LDCT1 and LDCT2, respectively) was as high as those of both NELSON (99.8 %) and NLST (99.9 %) studies. The PPV of LDCT1 (40.6 %) and LDCT2 (42.4 %) arms were similar to those reported in the NELSON study, and substantially higher than those reported by the NLST (again, due to their higher rate of FP) and the LUSI trials [15, 16]. Therefore, it seems that both MILD LDCT arm protocols may be as efficient as those of the two largest screening trials.

The LDCT arms were similar in terms of global detection rate. However, the initial detection rate in LDCT2 (0.52) was lower than those reported by other trials (0.8–2.2 %), and increased among participants shifted into the LDCT2 arm with annual follow-up, as compared to those who remained in the arm with biennial follow-up. [17, 18]. This finding suggests that a tighter follow-up would be more appropriate for participants with indeterminate or positive findings, despite negative initial diagnostic workup. Importantly, we found that the detection rate of early stage lung cancers was similar between the LDCT arms. This is important, as the proportion of early stage cancers is considered a surrogate measure for the effectiveness of screening, since effective screening should detect and eradicate cancers in an early state before they can grow into advanced stage [18].

The higher recall rate at T0 in both LDCT arms was also observed by other European studies and NLST [15, 17, 18]. However, the recall rates across the screening rounds of MILD (1–15 % in LDCT1 and 3.1–14 % in LDCT2) were lower than those reported by the other studies (3.8–27.9 %) [15, 17, 18].

This study has some limtiations. The MILD double LDCT randomization protocol may be concerning due to the small screening population size and the number of LDCT2 subjects with either indeterminate or positive results shfting to annual follow-up. However, the LDCT2 arm aimed primarily to establish whether biennial screen is as safe as annual screen in participants with no or smaller nodules. Future investigations are needed to verify how prologation of interval time between screens will influence mortality and overdiagnosis, and to define the optimal interval.

In conclusion, our prospective and unique data show that biennial screening by LDCT may save about one-third of scans with performance similar to annual screening.

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Methodology: Prospective, Randomized controlled trial, Performed at one Institution.

References

1. Saghir Z, Dirksen A, Ashraf H et al (2012) CT screening for lung cancer brings forward early disease. The randomised Danish Lung Cancer Screening Trial: status after five annual screening rounds with low-dose CT. Thorax 67:296–301
2. Pastorino U, Rossi M, Rosato V et al (2012) Annual or biennial CT screening versus observation in heavy smokers: 5-year results of the MILD trial. Eur J Cancer Prev 21:308–315
3. National Lung Screening Trial Research T, Aberle DR, Adams AM et al (2011) Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 365:395–409
4. Infante M, Cavuto S, Lutman FR, et al (2015) Long-term Follow-up Results of the DANTE Trial, a Randomized Study of Lung

Cancer Screening with Spiral Computed Tomography. Am J Respir Crit Care Med
5. Heuvelmans MA, Vliegenthart R, Oudkerk M (2015) Contributions of the European trials (European randomized screening group) in computed tomography lung cancer screening. J Thorac Imaging 30: 101–107
6. Field JK, Hansell DM, Duffy SW, Baldwin DR (2013) CT screening for lung cancer: countdown to implementation. Lancet Oncol 14:e591–e600
7. Moyer VA, Force USPST (2014) Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 160:330–338
8. (2014) Lung-RADS™ Version 1.0 Assessment Categories. Available via http://www.acr.org/~/media/ACR/Documents/PDF/QualitySafety/Resources/LungRADS/AssessmentCategories.pdf
9. de Koning HJ, Meza R, Plevritis SK et al (2014) 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 160:311–320
10. Marchiano A, Calabro E, Civelli E et al (2009) Pulmonary nodules: volume repeatability at multidetector CT lung cancer screening. Radiology 251:919–925
11. Horeweg N, Scholten ET, de Jong PA et al (2014) Detection of lung cancer through low-dose CT screening (NELSON): a prespecified analysis of screening test performance and interval cancers. Lancet Oncol 15:1342–1350
12. Goldstraw P, Crowley J, Chansky K et al (2007) The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. J Thorac Oncol 2:706–714
13. Seigneurin A, Field JK, Gachet A, Duffy SW (2014) A systematic review of the characteristics associated with recall rates, detection rates and positive predictive values of computed tomography screening for lung cancer. Ann Oncol 25:781–791
14. National Lung Screening Trial Research T, Church TR, Black WC et al (2013) Results of initial low-dose computed tomographic screening for lung cancer. N Engl J Med 368:1980–1991
15. Aberle DR, DeMello S, Berg CD et al (2013) Results of the two incidence screenings in the National Lung Screening Trial. N Engl J Med 369:920–931
16. Becker N, Motsch E, Gross ML et al (2012) Randomized study on early detection of lung cancer with MSCT in Germany: study design and results of the first screening round. J Cancer Res Clin Oncol 138:1475–1486
17. Field JK, van Klaveren R, Pedersen JH et al (2013) European randomized lung cancer screening trials: Post NLST. J Surg Oncol 108: 280–286
18. Becker N, Motsch E, Gross ML, et al. (2015) Randomised study on early detection of lung cancer with MSCT in Germany: results of the first 3 years of follow-up after randomisation. J Thorac Oncol