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Original Research

Ten-year results of the Multicentric Italian Lung Detection trial demonstrate the safety and efficacy of biennial lung cancer screening

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Abstract ***Background:*** The Multicentric Italian Lung Detection (MILD) trial demonstrated that prolonged low-dose computed tomography (LDCT) screening could achieve a 39% reduction in lung cancer (LC) mortality. We have here evaluated the long-term results of annual vs. biennial LDCT and the impact of screening intensity on overall and LC-specific mortality at 10 years.

Patients and methods: Between 2005 and 2018, the MILD trial prospectively randomised the 2376 screening arm participants to annual (n = 1190) or biennial (n = 1186) LDCT, for a median screening period of 6.2 years and 23,083 person-years of follow-up. The primary outcomes were 10-year overall and LC-specific mortality, and the secondary end-points were the frequency of advanced-stage and interval LCs.

Results: The biennial LDCT arm showed a similar overall mortality (hazard ratio [HR] 0.80, 95% confidence interval [CI] 0.57–1.12) and LC-specific mortality at 10 years (HR 1.10, 95% CI 0.59–2.05), as compared with the annual LDCT arm. Biennial screening saved 44% of follow-up LDCTs in subjects with negative baseline LDCT, and 38% of LDCTs in all participants, with no increase in the occurrence of stage II-IV or interval LCs.

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Conclusions: The MILD trial provides original evidence that prolonged screening beyond five years with biennial LDCT can achieve an LC mortality reduction comparable to annual LDCT, in subjects with a negative baseline examination.

1. Introduction

In 2011, the National Lung Screening Trial (NLST) proved the benefit of two-year LC screening with low-dose computed tomography (LDCT) on a population of 53,454 current and former smokers of ≥30 pack-years, aged 55–74 years, by achieving a 20% decrease in LC mortality as compared with annual chest radiography [1]. Other European randomised trials testing annual LDCT versus observation on younger populations, with lower LC risk than NLST and a total screening period of 4–5 years, showed no mortality reductions, possibly due to a small number of participants and short follow-up [2–4].

The 10-year results of prolonged LDCT screening in the Multicentric Italian Lung Detection (MILD) study showed a significant 39% reduction in lung cancer (LC) mortality (hazard ratio [HR] 0.61; 95% confidence interval [CI] 0.39–0.95; P = 0.017), as well as a non-significant 20% decrease in all-cause mortality, in a population of 4099 current and former smokers of ≥20 pack-years, aged 49–75 years, randomised to LDCT screening for a median period of 6.2 years or control without intervention [5]. A recent meta-analysis of randomised LDCT screening trials, including preliminary report of the Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON) trial [6], has confirmed an overall LC mortality reduction of 20% [7].

According to the initial protocol, the screening arm of the MILD trial was further randomised to an annual or biennial LDCT, and a preliminary analysis reported similar LC detection rates and interval cancers in the two LDCT interval arms at 7 years [8]. We present here the 10-year results of the two MILD screening intensity arms, with a focus on overall and LC mortality.

2. Material and methods

2.1. Study population

The MILD project is a prospective randomised controlled screening trial launched in 2005 at the National Cancer Institute of Milan (ClinicalTrials.gov Identifier: NCT02837809). Details of this program have been reported elsewhere [4]. Briefly, the MILD project included 4099 current or former smokers (within 10 years of recruitment) of ≥20 pack-years, aged from 49 to 75 years, without history of cancer in ≤5 years. The study was approved by our institutional review board and ethics Committee, and all eligible subjects provided written informed consent. Details about ethics committee approval, LDCT technique, diagnostic workup and baseline and early outcome of the MILD study were published elsewhere [4, 5].

Among the 2376 participants randomised to the screening arm, 1190 were further randomised to annual (LDCT every 12 months) and 1186 to biennial (LDCT every 24 months) screening (Table 1). Baseline LDCT was evaluated as negative for subjects without non-calcified nodules (NCNs) or with NCN with volume <60 mm^3, indeterminate for NCN 60–250 mm^3, and positive for NCN>250 mm^3. In the biennial screening arm, subjects with positive or undetermined pulmonary nodules underwent diagnostic workup according to the general study protocol, with three-month and/or annual LDCT repeats, likewise the annual screening arm. Non-solid or partly solid nodules were kept under active surveillance, by annual LDCT repeats in both interval arms, until development of a solid component >60 mm^3 in volume [9].

Comparison between the control arm and the screening arm at 10-year of follow-up has been reported [4]. In the present study, we restricted the analysis on the 2376 participants of the screening arms, with the aim of testing the performance of low-intensity biennial rounds.

Table 1
Selected characteristics of 2376 MILD participants by the randomisation arm.

Subjects' characteristics	Total	Group (N [%])	
	(N = 2376)	Annual (N = 1190)	Biennial (N = 1186)
Age (years)			
<55	773 (32.5%)	394 (33.1%)	379 (32.0%)
55-64	1235 (52.0%)	611 (51.3%)	624 (52.6%)
≥65	368 (15.5%)	185 (15.5%)	183 (15.4%)
Females	750 (31.6%)	376 (31.6%)	374 (31.5%)
Pack-years			
<30	521 (21.9%)	251 (21.1%)	270 (22.8%)
≥30	1855 (78.1%)	939 (78.9%)	916 (77.2%)
Smoking status at randomisation			
Former	747 (31.4%)	370 (31.1%)	377 (31.8%)
Current	1629 (68.6%)	820 (68.9%)	809 (68.2%)
Quitters on screening	464 (19.5%)	236 (19.8%)	228 (19.2%)

MILD, Multicentric Italian Lung Detection.

2.2. Data collection and follow-up

All participants underwent an LDCT scan and a program of primary prevention (smoking cessation) with pulmonary function test evaluation and blood sample collection. Furthermore, outcome information on stage, resectability and histology of disease was collected during follow-up. Each member of the study cohort accumulated person-years of follow-up from baseline (i.e., at the date of the randomisation) until the date of death or the date of the last follow-up (June 2018). The vital status of participants was collected through the platform SIATEL 2.0, and the causes of death were retrieved from the Istituto Nazionale di Statistica. Cause of death was missing in 3 cases, 1 in the annual arm and 2 in the biennial arm.

Of the 2376 randomised participants, 216 (9%) withdrew from the study (94 in the annual arm and 122 in the biennial arm), among them 20 within two years from the baseline and 100 within 5 years, for different reasons, including health problems, distance problems or loss of interest in the study. A total of 23,083 person-years were accumulated, 11,521 in the annual arm and 11,562 in the biennial arm.

2.3. Statistical analysis

According to the intention-to-treat principle, we considered each subject in the study arm at which he/she was initially assigned. Primary analysis included all the 2376 subjects, as follows: 1190 of the annual arm and 1186 of the biennial arm. The analysis was also restricted to 1924 subjects with negative baseline LDCT, 981 in the annual arm and 993 in the biennial arm, respectively. Descriptive statistics were reported as numbers and percentages comparing the annual LDCT arm and the biennial LDCT arm. Comparisons were made by the chi-square test or Fisher's exact test, as appropriate.

Primary outcomes were LC incidence at 10 years, overall 10-year mortality, LC 10-year specific mortality and other causes of mortality at 10 years, other cancers mortality and non-neoplastic mortality.

Cumulative incidence and cumulative mortality were evaluated using Kaplan–Meier estimator, and differences among groups were tested using the log-rank test. The diagnostic and prognostic value of the assigned arm was investigated by HR and 95% CI estimated by Cox's proportional hazard regression models with the annual arm as reference. Analyses were obtained using Statistical Analysis System Software (version 9.4; SAS Institute, Cary, North Carolina, USA).

3. Results

Patients' characteristics stratified by the intensity arm are summarised in Table 1. The two LDCT arms were similar for age, sex, smoking status and number of pack-years. The smoking quit rate during the whole screening period was 19.8% in the annual arm and 19.2% in the biennial arm, with the same proportion of permanent smokers (49.1%). The frequency of positive or indeterminate baseline LCDT was 14.4% in the annual arm and 13.3% in the biennial arm. Participants underwent a total of 12,375 chest LDCT scans, 7369 in the annual arm and 5006 in the biennial arm, respectively. A median of 7 LDCT scans was recorded in the annual arm and a median of 4 LDCT scans in the biennial arm. A total of 73 participants (3.1%) did not receive any LDCT (38 and 35, respectively). Baseline LDCT results were positive or indeterminate for 329 participants (171 and 158, respectively), while 1974 were negative (981 and

Table 2
Lung cancer and mortality at 10 years by the randomisation arm.

Outcomes	Total (N = 2376)	Annual (N = 1190)	Biennial (N = 1186)	P-values
Lung cancer incidence	98 (4.1%)	58 (4.9%)	40 (3.4%)	0.0658
Stage I	49 (50.0%)	31 (53.4%)	18 (45%)	0.4110
Resected cancers	64 (65.3%)	43 (74.1%)	21 (52.5%)	0.0004
Adenocarcinoma	55 (56.1%)	33 (56.9%)	22 (55.0%)	0.8525
Interval cancers	27 (27.6%)	14 (24.1%)	13 (32.5%)	0.3625
Lung cancers beyond 5 years	39 (39.8%)	23 (39.7%)	16 (40.0%)	0.9727
Total deaths [a]	137 (5.8%)	76	61	0.1936
Overall mortality rate (per 100,000)	593.5	659.7	527.6	
Lung cancer deaths	40 (1.7%)	19	21	0.7417
Lung cancer mortality rate (per 100,000)	173.3	164.9	181.6	
Other causes of deaths	94	56	38	0.0604
Other causes of mortality (per 100,000)	407.2	486.1	328.7	
Number of LDCTs performed	12,375	7369	5006	
Number of LDCTs performed after baseline	10,072	6217	3855	
Number of PETs performed	51	37	14	
Benign lung resection	3	0	3	

LDCT, low-dose computed tomography; PET, positron-emission tomography.
[a] 3 missing causes of death (1 annual arm and 2 biennial arm).

993, respectively). Subjects who returned within 3 months from the date of baseline evaluation were 308 (158 and 150, respectively), at 1 year from the baseline 1235 (1082 and 153, respectively) and at 2 years from the baseline 2149 (1087 and 1062, respectively). Extended screening interval prevented 86% of first-year LDCT repeats and 38% of all repeats in the biennial arm, allowing a 32% reduction in the total number of LDCT, and 37% reduction among subjects with negative baseline LDCT.

3.1. LC detection

LC was diagnosed in 58 participants (514/100,000 person-years) of the annual arm and 40 (350/100,000 person-years) of the biennial arm (Table 2), but the difference did not reach statistical significance (HR = 0.68, 95% CI 0.46 to 1.02, Fig. 1a). There were no differences between the two arms in the LC stage frequency (p = 0.4110), LC histology (p = 0.0998) or proportion of interval LC (not screen detected, p = 0.3625). Interestingly, the number of LC detected in stage II-IV was higher in the annual arm (27 vs. 22 cases). Furthermore, the prevalence of LC resections was significantly higher in the annual arm compared with the biennial arm (74% vs. 53%, p = 0.0004). The absolute excess of LC resections in the annual arm (22 cases) was consistent with the excess of LC diagnoses (18 cases). The frequency of subsolid nodules was 17% in the annual arm and 15,8% in the biennial arm (Table 3), with a non-significant excess of LC in the annual arm (22 vs. 11 cases, p = 0.0765).

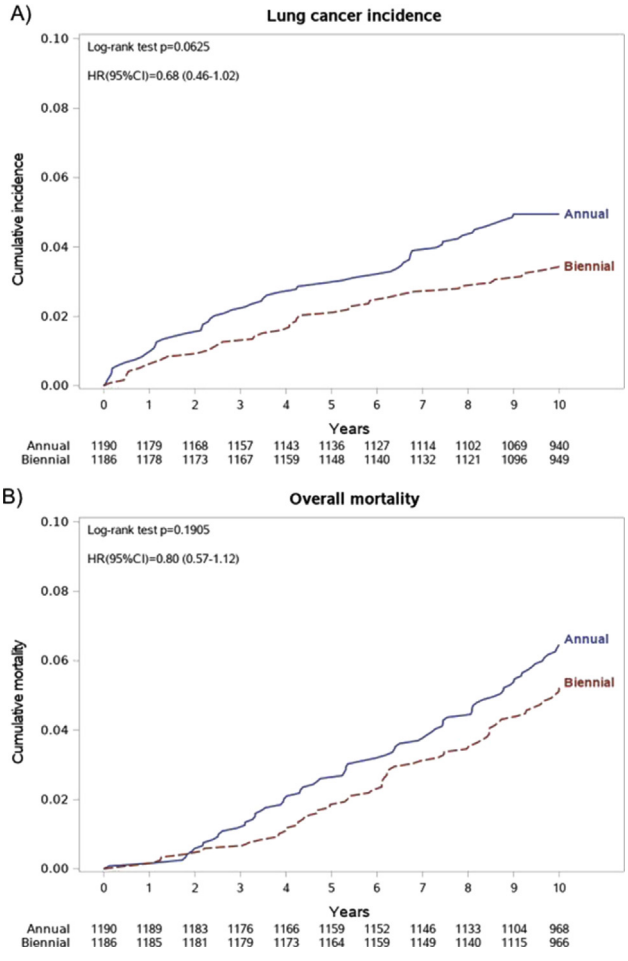

Fig. 1. (A) Lung cancer incidence at 10 years by the randomisation arm. (B) Overall mortality at 10 years by the randomisation arm. HR, hazard ratio; CI, confidence interval.

3.2. Ten-year mortality

At 10-year follow-up, a total of 137 deaths were recorded, 76 in the annual arm (660/100,000 person-years) and 61 in the biennial arm (528/100,000 person-years), with a non-significant decrease of the overall 10-year mortality in the biennial arm (HR 0.80, 95% CI 0.57–1.12, Fig. 1b). LC-specific mortality was 165/100,000 person-years (19 deaths) in the annual arm and 182/100,000 (21 deaths) in the biennial arm, and cumulative LC mortality curves showed no difference among the annual and the biennial arms (HR 1.10, 95% CI 0.59–2.05, Fig. 2a). Of interest, in the subset of individuals kept on active surveillance for subsolid nodules, we observed a similar overall mortality and the same number of LC deaths (5 in each arm, Table 3). Deaths for other causes were 56 in the annual arm (486/100,000 person-years) and 38 in the biennial arm (329/100,000 person-years), showing a non-significant difference between the two arms (HR 0.72, 95% CI 0.46 to 1.13, Fig. 2b).

3.3. Negative baseline LDCT

When the analysis was restricted to the 1974 participants with negative baseline LDCT, biennial screening prevented 44% of all repeats, allowing a 37% reduction in the total number of LDCT scans (Table S1). The LC incidence was higher in the annual arm (Fig. S1a), with an excess of LC diagnosis in the annual arm of 15 cases (37 LC, 3.8% in the annual arm vs. 22 LC, 2.2%, in the biennial arm, HR 0.58, 95% CI 0.34–0.98). Nonetheless, the stage and histology distribution, as well as the resection rate, were not significantly different in the two arms. In particular, the number of LC detected in stage

Table 3
Active surveillance of subsolid nodules by the randomisation arm.

Subsolid nodules and outcomes	Total (N = 2376)	Annual (N = 1190)	Biennial (N = 1186)	P-values
Subsolid nodules	389 (16.4%)	202 (17.0%)	187 (15.8%)	0.4264
Lung cancer incidence	33 (8.5%)	22 (10.9%)	11 (5.9%)	0.0765
Total deaths	29 (7.5%)	16 (7.9%)	13 (7.0%)	0.7162
Lung cancer deaths	10 (2.6%)	5 (2.5%)	5 (2.7%)	0.9016
Other causes of deaths	19 (4.9%)	11 (5.4%)	8 (4.3%)	0.5935

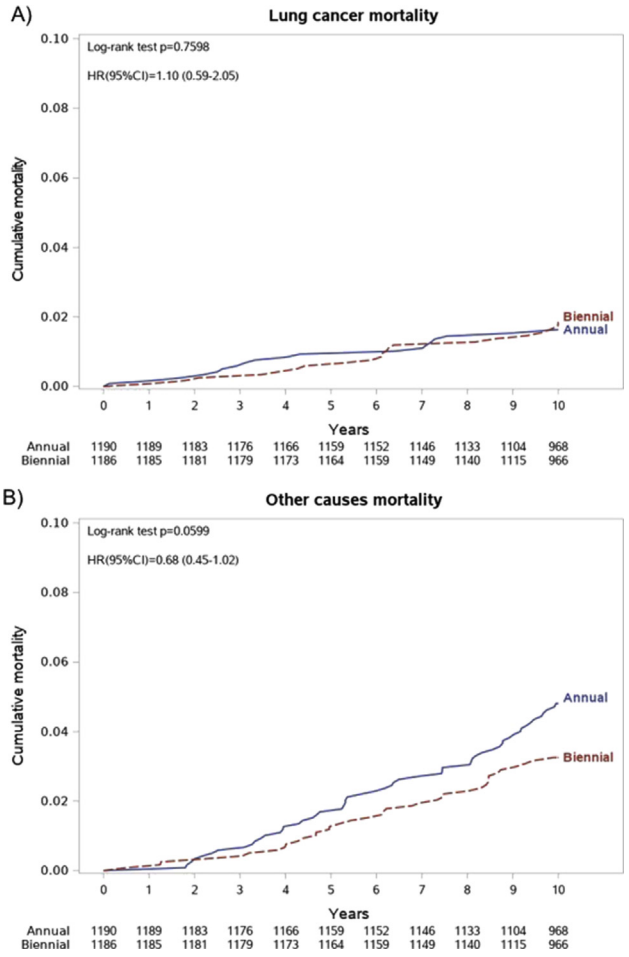

Fig. 2. (A) Lung cancer mortality at 10 years by the randomisation arm. (B) Other causes of mortality at 10 years by the randomisation arm. HR, hazard ratio; CI, confidence interval.

II-IV and of interval cancers were similar (16 vs. 12, and 13 vs. 8 cases respectively). Indeed, no difference was observed in 10-year overall mortality (HR 0.84, 95% CI 0.57−1.24, Fig. S1b), LC mortality (HR 1.16, 95% CI 0.52−2.59, Fig. S2a) or other causes of death (HR 0.72, 95% CI 0.46−1.13, Fig. S2b).

4. Discussion

MILD is the only randomised LC screening trial designed to compare the performance of two different LDCT intervals. After a median active LDCT screening period of 6.2 years, MILD trial results showed a statistically significant 39% reduction of LC mortality at 10 years in the LDCT arm [5], providing a strong confirmation of the 20% LC mortality reduction shown by NLST with 2 years of annual LDCT screening [10].

The novel results of the present study indicate that biennial intensity of LC screening can achieve a clinical outcome similar to annual intensity, in subjects with negative baseline LDCT, that represent the vast majority (83%) of MILD screening population. In particular, the low-intensity screening algorithm allowed a 38% reduction of LDCT burden and did not incur in detrimental effect on survival.

A study from the U.S. Preventive Service Task Force modelled several scenarios for LC screening and reported that annual intensity is expected to outperform biennial and triennial approach [11]. Nonetheless, several post hoc analyses of NLST data showed that biennial intensity could be pursued by post-test risk stratification, namely by stratification of LC risk by nodule categories, suggesting that biennial repeats could be safe in case of negative baseline LDCT [12−14]. Indeed, personalised stratification of LC risk by nodule size seems to be the most accurate option, especially when volumetric assessment is applied [15,16].

Noteworthy, a prospective evaluation of longer-than-annual approach comes from the two positive European trials—NELSON and MILD—where long-term survival was maintained by screening algorithms with lower intensity in subjects with nodule volume below predefined thresholds [5, 17]. Only the MILD trial prospectively randomised screening participants in two arms with different LDCT intensity, namely annual or biennial round. Such differentiation was adopted to assess the best screening strategy in terms of health care resources and radiation exposure that were uncertain when randomised trials were initiated. Biennial screening saved about one-third of LDCTs, maintaining similar performance and mortality rates [4,8]. In fact, while the 2.5-year timeframe in the fourth round of the NELSON trial resulted in a significant increase in interval cancers and more cancers detected at a later stage [18], the individually selective design of MILD randomisation granted a similar proportion of stage II-IV, and interval cancers in the two arms, with lower costs and radiation exposure in the biennial arm.

Recently, Robbins *et al.* [14] showed that many, but not all, screen-negatives (e.g. 57.8% of the NLST screen-negatives) might reasonably lengthen their CT screening interval by using a risk-based approach. Cost-effectiveness analyses currently support biennial screening [19], reflecting an increasing attention of North American stakeholders towards this approach for LC screening [10]. Such low-intensity approach is also convenient to minimise medical risk (e.g. procedure-related morbidity and mortality) [20], psychological stress [21], economic burden [22] and added oncologic risk from radiation exposure [23], while granting prolonged screening [5], which outstands as a pivotal strategy for continuous and incremental control of LC and overall mortality [7].

Even though the screening intensity issue will require further validation by a multicentric randomised trial with larger sample size [24,25], MILD results at 10 years provide substantial evidence that tailored biennial LDCT did not hamper the efficacy of prolonged screening [5], notwithstanding the implementation of an active surveillance program to reduce the frequency of

unnecessary resection for subsolid pulmonary lesion [26]. In this respect, even the absolute excess of LC cases and resections, without favourable stage shift or decrease of LC mortality in the annual arm, may be the effect of overdiagnosis. We recognise that MILD trial sample size is clearly insufficient for a proper non-inferiority efficacy assessment, that may require ten times more subjects. Nonetheless, the randomised design with two very balanced populations, total length of intervention, quality of follow-up (93% at 9 years), and the non-significant mortality trend in favour of the biennial arm provides a reliable estimate of long-term safety and efficacy, to be confirmed by a new randomised trial with adequate sample size.

Individual risk stratification by radiomic and artificial intelligence analysis of baseline LDCT findings represents a promising development for future screening programs, to improve the efficacy of limited health care resources and reduce costs [25].

Furthermore, circulating biomarkers could help the individual risk stratification and optimise LDCT intensity. We are currently testing the value of blood microRNAs [26] in the prospective bioMILD trial, which scheduled triennial rounds for subjects with double negative baseline LDCT and microRNAs [27, 28].

5. Conclusions

The MILD trial provides new evidence that prolonged biennial LDCT screening is safe and effective when compared to annual screening, in subjects with negative baseline LDCT. Biennial LDCT has achieved a similar mortality reduction at 10 years, notwithstanding the active surveillance protocol for subsolid pulmonary nodules.

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Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.06.009.

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