Surveillance of subsolid nodules avoids unnecessary resections in lung cancer screening: long-term results of the prospective BioMILD trial

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Surveillance is a safe option for monitoring subsolid nodules in lung cancer screening, preventing unnecessary treatments without compromising stage or survival and ensuring the resection of more aggressive lung cancers detected away from subsolid nodules https://bit.ly/3WbCVy0

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Abstract

Background The management of subsolid nodules (SSNs) in lung cancer screening (LCS) is still a topic of debate, with no current uniform strategy to deal with these lesions at risk of overdiagnosis and overtreatment. The BioMILD LCS trial has implemented a prospective conservative approach for SSNs, managing with annual low-dose computed tomography nonsolid nodules (NSNs) and part-solid nodules (PSNs) with a solid component <5 mm, regardless of the size of the nonsolid component. The present study aims to determine the lung cancer (LC) detection and survival in BioMILD volunteers with SSNs.

Materials and methods Eligible participants were 758 out of 4071 (18.6%) BioMILD volunteers without baseline LC and at least one SSN detected at the baseline or further low-dose computed tomography rounds. The outcomes of the study were LC detection and long-term survival.

Results A total of 844 NSNs and 241 PSNs were included. LC detection was 3.7% (31 out of 844) in NSNs and 7.1% (17 out of 241) in PSNs, being significantly greater in prevalent than incident nodules (8.4% *versus* 1.3% in NSNs; 14.1% *versus* 2.1% in PSNs; p-value for both nodule types p<0.01). Most LCs from SSNs were stage I (42/48, 87.5%), resectable (47/48, 97.9%), and caused no deaths. The 8-year cumulative survival of volunteers with LC derived from SSNs and not derived from SSNs was 93.8% and 74.9%, respectively.

Conclusion Conservative management of SSNs in LCS enables timely diagnosis and treatment of LCs arising from SSNs while ensuring the resection of more aggressive LCs detected away from SSNs.

Introduction

Lung cancer screening (LCS) with low-dose computed tomography (LDCT) reduces mortality in heavy smokers by enabling early identification of lung cancers (LCs) otherwise diagnosed as symptomatic advanced disease [1–6]. Nevertheless, LCS might lead to the diagnosis and treatment of lesions that would not affect prognosis, thus exposing volunteers to unnecessary risks of intervention, such as those related to biopsy procedures or excision [7–10].

Nonsolid nodules (NSNs, also referred to as ground-glass nodules) and part-solid nodules (PSNs), collectively referred to as subsolid nodules (SSNs), may contribute to overdiagnosis and overtreatment in LCS [7, 11, 12]. Found in ∼9% of LCS participants [13, 14], SSNs are associated with a higher rate of malignancy than solid nodules but, when malignant, tend to demonstrate a slower growth rate and lower risk for recurrence or metastatic disease than solid tumours [15–17]. This indolent behaviour challenges

radiologists and clinicians in determining the risk of clinically significant malignancy of SSNs, whose prognostic weight may be overcome by competing causes of death, including non-neoplastic comorbidities and extrapulmonary cancer [18, 19].

Emerging data from LCS trials indicate that conservative management may be suitable for SSNs. In the NELSON trial (NELSON is a Dutch acronym for 'Nederlands-Leuvens Longkanker Screenings Onderzoek'), only SSNs with a solid component >500 mm^3 at baseline prompted immediate clinical referral, while all other SSNs were followed and deemed worthy of further evaluation if increased in size or density [20]. Through this close follow-up strategy, no clinically relevant carcinomas were missed during a median follow-up of 95 months [20]. In the Multicentric Italian Lung Detection (MILD) trial, Silva *et al*. [21] demonstrated the safety and efficacy of long-term active surveillance for SSNs. The authors found that volunteers with SSNs showed a high risk of developing LC elsewhere in the lung, with only a minority of cases arising from SSNs and never representing the cause of death [21]. In keeping with these studies, a joint task force with members of the European Society of Radiology (ESR) and European Respiratory Society (ERS) recently stated that follow-up of persistent SSNs potentially reduces overdiagnosis in LCS [22]. That said, current strategies for SSNs are still mainly based on expert opinion, and the best approach for these nodules in LCS remains to be determined, pending prospective data.

The BioMILD trial, an ongoing prospective study evaluating the combined use of plasma microRNA (miRNA) and LDCT for improving the efficacy of LCS through individual risk profiling and personalised screening intervals (clinicaltrials.gov ID: NCT02247453), has implemented a conservative approach to managing SSNs [23]. The present study aimed to detail the LC detection in BioMILD trial volunteers with SSNs over a 10-year follow-up period, stratifying SSNs by type, size and time of appearance. The overall survival of the same group of participants was also explored.

Materials and methods

Study population

Data for the present analysis were extracted from the BioMILD trial, in which a total of 4119 volunteers were enrolled at the Istituto Nazionale dei Tumori of Milan from 2013 to 2016 [23]. Eligible participants were 1) aged 50–75 years and current heavy smokers of ⩾30 pack-years or former smokers with the same smoking habits who stopped ⩽10 years ago; 2) aged 50–75 years and current or former smokers of ⩾20 pack-years with a family history of LC or a prior diagnosis of COPD or pneumonia. The exclusion criteria were the presence of neoplasms within the previous 5 years and suspected lung nodules under investigation. The original Institutional Review Board approval and written informed consent allowed the use of the study data for future research.

Among the volunteers in the original BioMILD trial, those without baseline LC (*i.e.* LC cases detected within the planned 3/6 months recall from the baseline LDCT scan) and with at least one SSN, either NSN or PSN, detected at baseline or further LDCT rounds, were included in the present study.

LDCT evaluation and SSN management

LDCTs underwent prospective double reading by one radiologist (first reading) using computer-aided detection (CAD) software (MM Oncology, syngo.via; Siemens Healthcare) and another radiologist (second reading) with the aid of the maximum intensity projection (MIP) images. In the case of discordant evaluations, consensus was reached through discussion.

The maximum diameter was recorded for NSNs measuring >5 mm. All the NSNs were followed with annual LDCT. PSNs were managed according to the maximum diameter of the solid component. In particular, PSNs with a solid component <5 mm were followed with annual LDCT, regardless of the size of the nonsolid component; PSNs with a solid component measuring ⩾5 mm at baseline were evaluated by 3-month interval LDCT and, whenever persistent, assessed by the multidisciplinary team (MDT); PSNs with a new or growing solid component measuring ⩾5 mm were assessed by the MDT as follows: calculation of the volume-doubling time of the solid component (threshold <400 days), ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) and computed tomography (CT)-guided transthoracic biopsy. The MDT was tasked with providing recommendations for treating suspicious PSNs. Given the low sensitivity and high positive predictive value of ^{18}F-FDG-PET in distinguishing malignant from benign SSNs, a negative ^{18}F-FDG-PET uptake did not necessarily rule out intervention, while a positive ^{18}F-FDG-PET outcome, as well as a positive biopsy, prompted surgery. Moreover, volunteers with PSNs showing a growing solid component were considered for direct surgical referral if a limited resection of the lesion was deemed feasible. A negative workup led to continuous active surveillance by annual LDCT until evidence of solid component growth.

The time elapsed between the first LDCT that detected SSNs and surgical resection was prospectively recorded along with the histology and LC pathological stage. The vital status of the volunteers was obtained through the Istituto Nazionale di Statistica (ISTAT, SIATEL 2.0 platform), which provides the exact date of death within 3 months of occurrence. Person-years of follow-up were calculated for each participant from baseline until the date of death or the date of the last follow-up as of June 2023.

Study objectives

The primary outcome was the detection of LC, by means of biopsy or surgery, in SSNs (either NSNs or PSNs) detected at baseline (*i.e.*, prevalent nodules) or further LDCT rounds (*i.e.*, incident nodules). LC detection was further stratified by nodule size. The maximum diameter of the NSNs was retrospectively binarised into two categories, <10 mm and ⩾10 mm, in accordance with previous evidence suggesting this threshold to stratify NSNs based on malignancy risk [24]. The diameter of the solid component of the PSNs was classified as <5 mm or ⩾5 mm following the prospective LDCT reading. Characteristics of SSNs were referred to at the time of their detection. The secondary outcome was 8-year overall survival.

Statistical analysis

Categorical data were reported as numbers and percentages, whereas continuous data were reported as the median and interquartile range (IQR). The chi-square test or Fisher's exact test was used to compare categorical data, and the Mann–Whitney U-test was used to compare continuous variables. The 8-year detection of LC derived from the SSNs was estimated by cumulative incidence curves, and the selected strata were compared by the log-rank test. 8-year overall survival was estimated by Kaplan–Meier curves, and the selected strata were compared by using the log-rank test. A p-value <0.05 was considered as the threshold for the statistical significance.

The statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

Study sample

A total of 1085 SSNs (844 NSNs and 241 PSNs) were detected in 758 out of 4071 (18.6%) BioMILD volunteers without baseline LC. 584 (77.0%) volunteers had only NSNs, 130 (17.2%) had only PSNs and 44 (5.8%) had both types of nodules; the demographic characteristics of these subgroups were similar (table 1). Overall, 52.6% (399 out of 758) of the enrolled volunteers were male, the median age at baseline LDCT was 60 years (IQR 56–65) and 79.4% (602 out of 758) were current smokers. A total of 4008 LDCT scans (mean number of LDCT scans per participant, 5.3) were performed during the study period. Volunteers with only NSNs, with only PSNs and with both types of nodules underwent a mean of 5.2, 5.0 and 7.1 LDCT scans, respectively.

SSN characteristics

SSNs were more likely to be incident (558 out of 844, 66.1% NSNs; 142 out of 241, 58.9% PSNs), but the differences in location and dimensions between incident and prevalent SSNs were not significant (supplementary table S1). Most NSNs measured <10 mm, while PSNs were almost equally likely to have a <5 mm solid component and a ⩾5 mm solid component (supplementary table S1). Of the 718 NSNs and 219 PSNs that were subjected to at least one follow-up LDCT, 216 (30.1%) and 139 (63.5%) resolved over time, respectively (table 2). Incident nodules resolved more frequently than prevalent nodules for both NSNs (34.8% *versus* 22.3%, p<0.001) and PSNs (69.8% *versus* 54.8%, p=0.0227). As expected, the median CT screening duration was longer for prevalent nodules (NSNs, 6.9 years (IQR 3.1–8.1); PSNs, 5.3 years (IQR 2.2–7.5)) than for incident nodules (NSNs, 1.5 years (IQR 1.0–4.4); PSNs, 3.6 years (IQR 0.4–5.6)) (p<0.001 for both NSNs and PSNs).

LC derived from SSNs

The LC detection was 3.7% (31 out of 844) for NSNs and 7.1% (17 out of 241) for PSNs; in both groups, LC was significantly more common for prevalent than for incident nodules (8.4% *versus* 1.3% for NSNs, p<0.001; 14.4% *versus* 2.1% for PSNs, p<0.001). For both NSNs and PSNs, the median interval from nodule detection to LC diagnosis was greater for prevalent nodules than for incident nodules (NSNs, 4.3 years (IQR 3.7–6.3) *versus* 2.4 years (IQR 1.5–5.6), p=0.0422; PSNs, 3.2 years (IQR 2.3–4.3) *versus* 0.4 years (IQR 0.2–2.9), p=0.0588). At the time of LC detection, all the SSNs showed a solid component, and the majority were found with a positive ^{18}F-FDG-PET uptake (35 out of 45 who underwent ^{18}F-FDG-PET, 78%); the LC diagnosis was made with CT-guided transthoracic biopsy (11 out of 48, 23%) or surgery (37 out of 48, 77%), the latter with (29 out of 37, 78%) or without (8 out of 37, 22%) intra-operative frozen section examination (supplementary table S2).

TABLE 1 Characteristics of volunteers with subsolid nodules detected at baseline and further screening rounds

	Total	Only NSNs	Only PSNs	NSNs and PSNs	p-value
Total, n (%)	758	584 (77.0)	130 (17.2)	44 (5.8)	
Sex, n (%)					
Female	359 (47.4)	281 (48.1)	57 (43.9)	21 (47.7)	0.6770
Male	399 (52.6)	303 (51.9)	73 (56.2)	23 (52.3)	
Age years, n (%)					
<55	152 (20.0)	122 (20.9)	23 (17.7)	7 (15.9)	0.5881
55–64	388 (51.2)	300 (51.4)	63 (48.5)	25 (56.8)	
⩾65	218 (28.8)	162 (27.7)	44 (33.9)	12 (27.3)	
Median (IQR)	60 (56–65)	60 (56–65)	61 (56–65)	61 (56–65)	0.5432
Pack-years, n (%)					
<30	48 (6.3)	37 (6.3)	8 (6.2)	3 (6.85)	0.9878
⩾30	710 (93.7)	547 (93.7)	122 (93.9)	41 (93.2)	
Median (IQR)	41 (35–52)	41 (35–52)	42 (35–54)	41.5 (35.5–48.5)	0.6025
Smoking status, n (%)					
Current smokers	602 (79.4)	462 (79.1)	103 (79.2)	37 (84.1)	0.7318
Former smokers	156 (20.6)	122 (20.9)	27 (20.8)	7 (15.9)	
BMI $kg \cdot m^{-2}$, median (IQR)	24.6 (22.2–27.3)	24.6 (22.3–27.4)	24.8 (21.8–27.3)	24.4 (22.0–26.3)	0.5619
CRP $mg \cdot L^{-1}$, median (IQR)	1.4 (0.7–2.7)	1.4 (0.7–2.7)	1.5 (0.8–3.3)	1.9 (0.9–3.1)	0.4468
Median person-years	8.6	8.6	8.7	9.2	
Total n of LDCT scans	4008	3051	645	312	
Mean LDCT scans per participant	5.3	5.2	5.0	7.1	

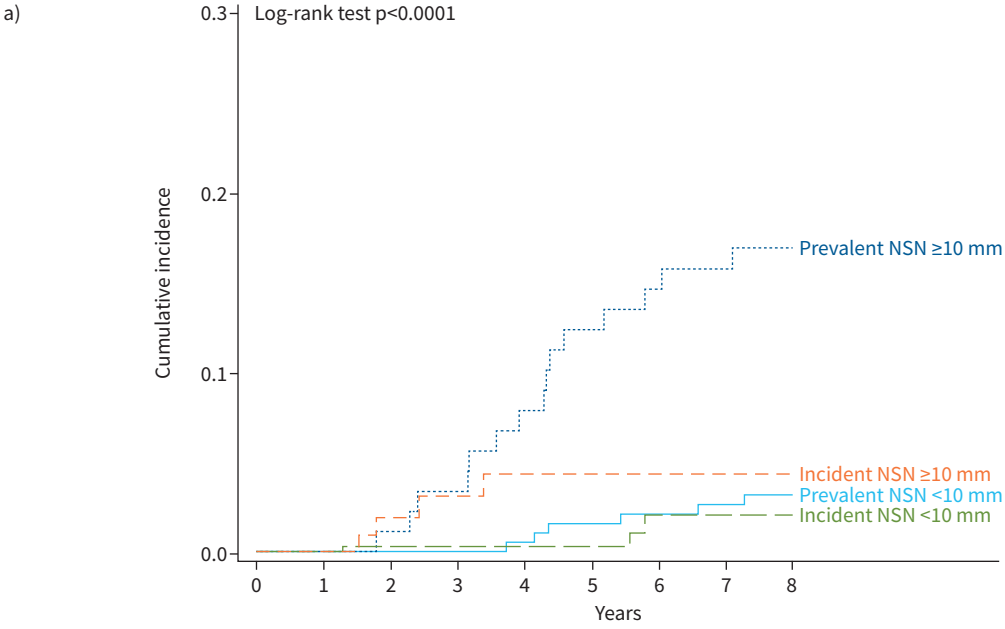
NSNs: nonsolid nodules; PSNs: part-solid nodules; BMI: body mass index; IQR: interquartile range; CRP: C-reactive protein; LDCT: low-dose computed tomography.

TABLE 2 Clinical course of subsolid nodules detected at baseline and further screening rounds

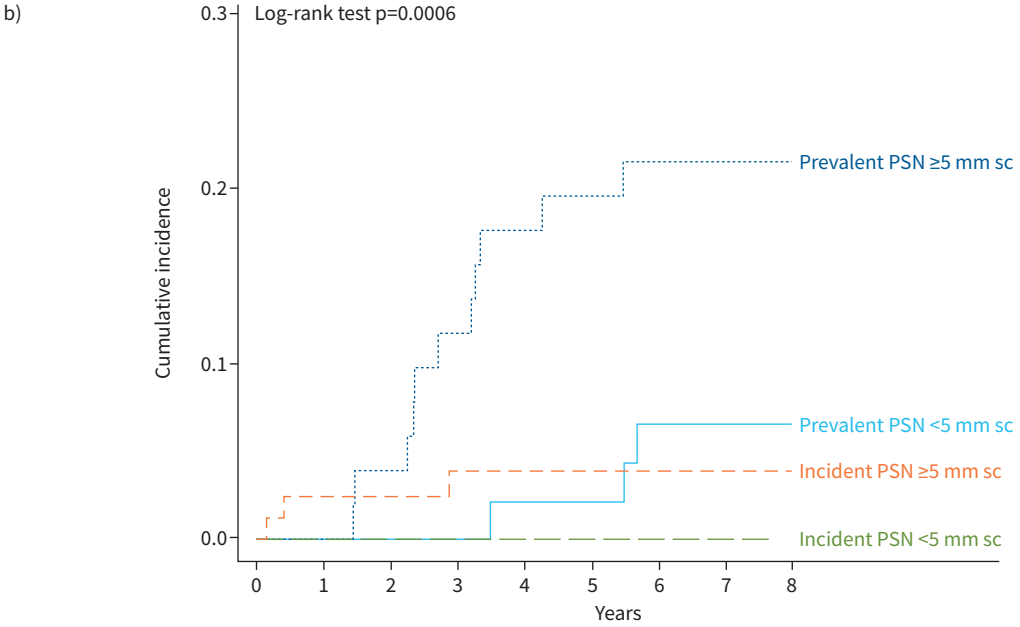
	Total	Prevalent	Incident	p-value
NSNs present, n (%)	844	286 (33.9)	558 (66.1)	
Incident lung cancer derived from NSNs, n (%)	31 (3.7)	24 (8.4)	7 (1.3)	<0.0001
Stage I, n (%)	26 (83.9)	19 (79.2)	7 (100)	0.5622
Interval from NSN detection to incident LC, years, median (IQR)	4.3 (3.1–5.8)	4.3 (3.7–6.3)	2.4 (1.5–5.6)	0.0422
LC deaths, n	0	0	0	
Resolution/NSNs with at least one follow-up LDCT, n/N (%)	216/718 (30.1)	61/273 (22.3)	155/445 (34.8)	0.0004
Duration from first detection of nodules to the last LDCT scan, years, median (IQR)	3.4 (1.1–6.0)	6.9 (3.1–8.1)	1.5 (1.0–4.4)	<0.0001
PSNs present, n (%)	241	99 (41.1)	142 (58.9)	
Incident lung cancer derived from PSNs, n (%)	17 (7.1)	14 (14.1)	3 (2.1)	0.0005
Stage I, n (%)	16 (94.1)	14 (100)	2 (66.7)	0.1765
Interval from PSN detection to incident LC, years, median (IQR)	2.9 (2.3–3.5)	3.2 (2.3–4.3)	0.4 (0.2–2.9)	0.0588
LC deaths, n	0	0	0	
Resolution/PSNs with at least one follow-up LDCT, n/N (%)	139/219 (63.5)	51/93 (54.8)	88/126 (69.8)	0.0227
Duration from first detection of nodules to the last LDCT scan, years, median (IQR)	3.9 (1.2–6.5)	5.3 (2.2–7.5)	3.6 (0.4–5.6)	<0.0001
Incident lung cancer not derived from SSNs, n	32	18	14	
Stage I, n (%)	15 (46.9)	7 (38.9)	8 (57.1)	
LC deaths, n	6	5	1	

NSN: nonsolid nodule; LC: lung cancer; IQR: interquartile range; PSN: part-solid nodule; LDCT: low-dose computed tomography; SSN: subsolid nodule.

Most LCs derived from SSNs were diagnosed at stage I (42 out of 48, 87.5%), irrespective of the nodule type (26 out of 31, 83.9% in NSNs; 16 out of 17, 94.1% in PSNs) or time of appearance (79.2% for prevalent *versus* 100% for incident NSNs; p=0.5622; 100% in prevalent *versus* 66.7% in incident PSNs; p=0.1765) (table 2). Most stage I LCs were diagnosed at stage IA in both NSNs (23 out of 26, 88.5%) and



Prevalent NSN <10 mm	196	196	196	194	193	187	185	181	150
Prevalent NSN ≥10 mm	90	90	89	86	82	78	76	72	50
Incident NSN <10 mm	417	398	283	237	232	182	90	36	12
Incident NSN ≥10 mm	141	137	94	80	76	60	32	9	2



Prevalent PSN <5 mm sc	48	48	47	47	46	45	42	40	33
Prevalent PSN ≥5 mm sc	51	51	49	45	42	41	39	38	34
Incident PSN <5 mm sc	60	59	41	39	38	33	16	9	0
Incident PSN ≥5 mm sc	82	79	71	66	65	52	41	25	9

FIGURE 1 8-year incidence of lung cancer derived from a) nonsolid nodules (NSNs) and b) part-solid nodules (PSNs) stratified by type, prevalence or incidence, and size. sc: solid component.

PSNs (10 out of 16, 62.5%) (supplementary table S3). No LC deaths were recorded in subjects with LC derived from SSNs, and no recurrence of LCs from SSNs was observed during follow-up.

The 8-year LC detection curves for SSNs stratified by nodule type and solid component size were significantly different; specifically, volunteers with prevalent NSNs ⩾10 mm (figure 1a) and prevalent PSNs with a solid component ⩾5 mm (figure 1b) had higher rates of LC (16.9% and 21.6%, respectively) than volunteers with other nodule subcategories (log-rank test p<0.0001).

No LC was found within 1 year of NSN detection, and only 0.5% (four out of 844) of the NSNs were diagnosed as LC in the second year after detection (one prevalent NSN ⩾10 mm, one incident NSN <10 mm and two incident NSNs ⩾10 mm) (supplementary figure S1A). Of the 241 PSNs, two (0.8%) were diagnosed as cancer within 1 year after detection (both incident PSNs with a solid component ⩾5 mm), and 4 (1.6%) within 2 years after detection (two prevalent and two incident PSNs with a solid component ⩾5 mm) (supplementary figure S1B). LC cases arising from prevalent SSNs were essentially diagnosed over the entire screening period, while those derived from incident SSNs were diagnosed from the 4th year onwards (figure 2).

LC not derived from SSNs

32 out of 80 (40.0%) LCs were not SSNs. These LCs, mostly located in a different lobe from SSNs (28 out of 32, 87.5%), were deemed resectable in most cases. However, compared to those derived from SSNs, LCs not derived from SSNs were more frequently diagnosed at stages II–IV (50.0% of LCs not derived from SSNs *versus* 10.4% of LCs derived from SSNs, p<0.0001) and were associated with relatively lower 5-year survival from LC diagnosis (71.9% *versus* 93.8%, p=0.01) (table 3).

Overall survival

37 out of 758 (4.9%) participants died during a median follow-up period of 8.6 years. The 8-year cumulative survival in volunteers with LC derived from SSNs and not derived from SSNs was 93.8% and 74.9%, respectively, with the former being remarkably similar to that of volunteers with other cancers (95.7%) or free from malignancies (97.6%) (log-rank test p<0.01) (figure 3).

Discussion

The management of SSNs remains an open question in LCS, and the most effective strategy to manage indolent lesions and reduce overdiagnosis and overtreatment has still to be defined. The findings of this study support the hypothesis that conservative management of SSNs in LCS is safe and effective because it prevents futile resections, enables timely diagnosis and treatment of the few invasive LCs arising from SSNs with excellent survival, and, in the meantime, ensures resection of the more aggressive LCs detected away from SSNs [20, 21]. Moreover, we provided information on the LC risk of SSNs detected in LCS,

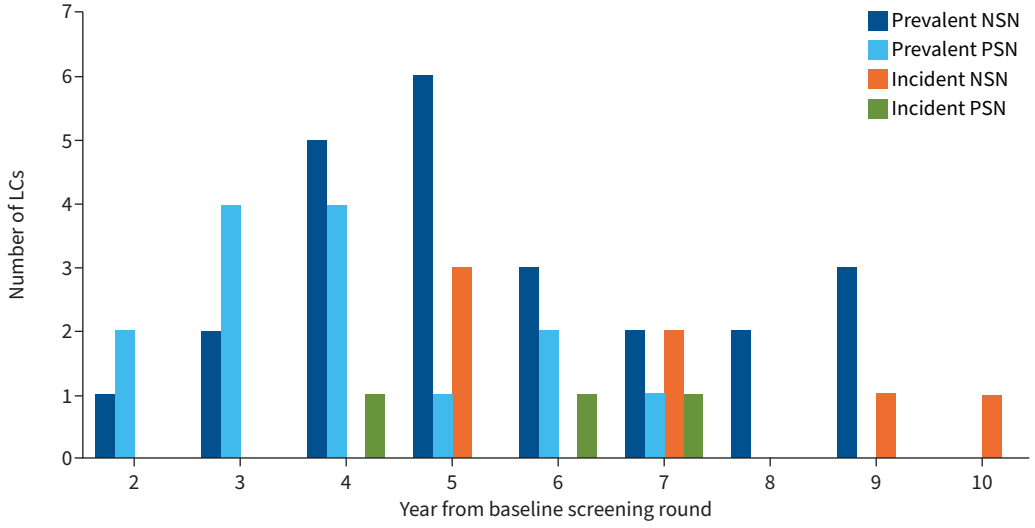


FIGURE 2 Timeline of lung cancer (LC) diagnosis derived from subsolid nodules following the baseline screening round. NSN: nonsolid nodule; PSN: part-solid nodule.

TABLE 3 Clinical outcomes of volunteers diagnosed with incident lung cancer (LC)

	Total incident LC	Incident LC derived from SSNs	Incident LC not derived from SSNs	p-value
Volunteers, n	80	48	32	
Resectability, n (%)	72 (90.0)	47 (97.9)	25 (78.1)	0.0059
Stage distribution, n (%)				0.0003
Stage 0	2 (2.5)	1 (2.1)	1 (3.1)	
Stage I	57 (71.3)	42 (87.5)	15 (46.9)	
Stage II	9 (11.3)	2 (4.2)	7 (21.9)	
Stage III	8 (10.0)	3 (6.3)	5 (15.6)	
Stage IV	4 (5.0)	0	4 (12.5)	
5-year survival from LC diagnosis, n (%)	68 (85.0)	45 (93.8)	23 (71.9)	0.0105

SSNs: subsolid nodules.

suggesting that small NSNs may be monitored with a prolonged LDCT interval and that an overcautious approach for incident SSNs, which did not exhibit more aggressive behaviour than prevalent SSNs, seems unjustified.

Retrospective analyses of the data from the National Lung Screening Trial (NLST) revealed that SSNs classified as Lung-RADS categories 2 and 3 had a malignancy risk of ~3% and 13%, respectively, according to baseline CT, exceeding those reported in the Lung-RADS 1.1 document (*i.e.*, up to 2%) and approaching the rates found in the present cohort [24]. Consistent with our findings, the risk of malignancy was greater for PSNs and NSNs >10 mm [24]. These results indicate the potential for safely managing smaller NSNs with an increased screening interval. In fact, in the BioMILD trial, only one out of 613 (0.2%) incident and prevalent NSNs <10 mm was resected and proven to be cancer within 24 months of detection, suggesting that biennial scanning may be considered for these volunteers with no impact on survival while reducing costs and cumulative radiation burden. These results echo previous analyses encouraging biennial follow-up for negative LDCTs in LCS [25, 26] and provide evidence for further stratification of NSNs within the Lung-RADS 2 category based on a 10-year active surveillance strategy.

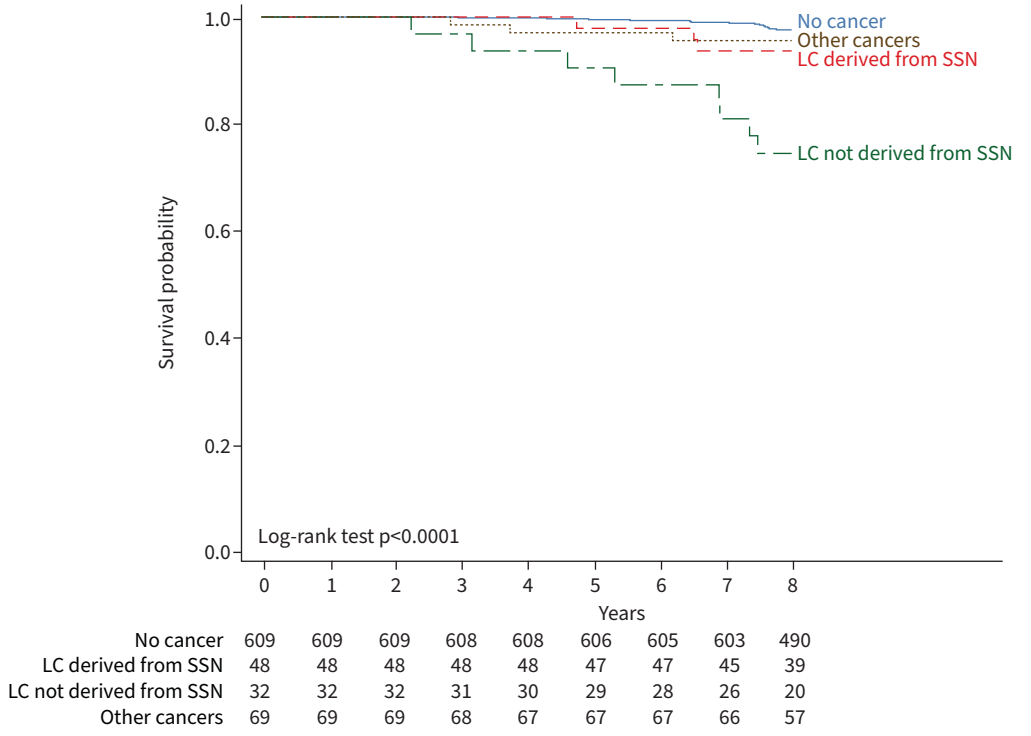


FIGURE 3 Kaplan–Meier survival curves of screened volunteers with subsolid nodules (SSNs) according to disease diagnosis. LC: lung cancer.

There are scarce data on the incidence and LC probability of new SSNs in LCS. In the I-ELCAP trial, nearly 70% of new SSNs resolved or decreased in size at follow-up, and 3.8% were ultimately diagnosed as LC *versus* 2.9% of those detected at baseline [13, 27]. The NELSON trial reported a similar likelihood of resolution yet a higher malignancy rate (*i.e.*, 6%) for new SSNs [28]. According to a more recent analysis of SSNs detected *via* LDCT screening in Korea, 78.9% of new SSNs disappeared or decreased in size, while 1.1% were diagnosed as cancer [29]. Of the 700 incident SSNs in the BioMILD trial, only 10 were malignant (1.4%), and 243 of the 571 incident SSNs that underwent follow-up (42%) resolved over time. Moreover, most incident SSNs that were revealed to be malignant led to a cancer diagnosis >12 months after detection (eight out of 10, 80%), all of which were diagnosed with favourable staging. Our findings reveal that the malignancy risk of new SSNs is similar to or lower than that reported in previous studies and corroborate the hypothesis that a more aggressive follow-up for new than for baseline SSNs seems unwarranted.

The evidence from the BioMILD trial discourages early aggressive management of SSNs, an approach that led to the resection of benign lesions and a greater proportion of noninvasive LCs in the early era of LCS (*e.g.*, 5–18% [7, 30–32]), but rather supports a more conservative strategy capable of ensuring timely intervention and the avoidance of unnecessary surgery [13, 20, 33]. Indeed, in the BioMILD cohort, no SSNs were diagnosed as benign disease or atypical adenomatous hyperplasia, and only one case of adenocarcinoma was found at stage 0. This result, along with the lack of increased mortality risk related to surveillance, arguably suggests that the early resection of SSNs should be considered overtreatment rather than timely diagnosis. Notably, 32 of the 80 LCs (40.0%) found in the BioMILD volunteers under surveillance for SSNs arose from lesions other than SSNs, most of which were located in the lung parenchyma far from concomitant SSNs. Volunteers with these LCs had lower survival than those diagnosed with SSNs, in accordance with previous data [21]. Therefore, in these cases, early SSN resection could have potentially hampered the surgical approach to treat more aggressive pulmonary lesions, which, instead, was ensured by SSN conservative management.

In the BioMILD trial, the median time interval from detection to LC diagnosis was up to 6 years, and LCs from SSNs were encountered over the entire 10-year follow-up period. New SSNs were detected up to 9 years after baseline, and there was no clear safety point at which to discontinue screening to avoid missing their detection. These findings suggest that SSNs should be followed up until the volunteers may benefit from intervention, in line with findings from the literature that favour long-term monitoring of SSNs to prevent misdiagnosis or missed diagnosis of clinically significant LC [34, 35]. Since a lower incidence of growth has been suggested for stable SSNs (*e.g.*, after 2 or more years of stability [35–38]), further analyses may help optimise SSN management by evaluating individual nodule trajectories to personalise LDCT screening intervals [39].

The major strengths of the current analysis were the relatively large size of the study population, the prospective nodule management and long-term follow-up.

The study also suffers from limitations. First, the conservative approach of the BioMILD protocol prevented histological assessment of most SSNs because only suspicious lesions were considered for resection. Moreover, the dimensional evaluation of the SSNs was based on the maximal diameter rather than the volume or mean diameter, as now recommended by Lung-RADS [40], potentially affecting comparisons with the Lung-RADS categories.

In conclusion, a surveillance strategy has proven to be a safe option for monitoring SSNs in LCS, preventing unnecessary treatments without compromising the overall LC stage or survival, while ensuring the resection of more aggressive LCs detected away from SSNs. The results also reveal the potential for increasing LDCT intervals for volunteers with small NSNs and suggest that incident SSNs do not carry a greater risk of LC than prevalent SSNs, as otherwise indicated by current recommendations.

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Conflict of interest: R.E. Ledda reports consulting fees from Brainomix Limited and lecture honoraria from Boehringer Ingelheim outside the submitted work. N. Sverzellati reports consulting fees from Chiesi, AstraZeneca and Coreline; lecture honoraria from Boehringer Ingelheim, Chiesi and AstraZeneca; travel support from Bracco; and advisory board participation from AstraZeneca and Boehringer Ingelheim, all outside the submitted work. All other authors have nothing to disclose.

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