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Towards a close computed tomography monitoring approach for screen detected subsolid pulmonary nodules?

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ABSTRACT Pulmonary subsolid nodules (SSNs) have a high likelihood of malignancy, but are often indolent. A conservative treatment approach may therefore be suitable. The aim of the current study was to evaluate whether close follow-up of SSNs with computed tomography may be a safe approach.

The study population consisted of participants of the Dutch-Belgian lung cancer screening trial (Nederlands Leuvens Longkanker Screenings Onderzoek; NELSON). All SSNs detected during the trial were included in this analysis. Retrospectively, all persistent SSNs and SSNs that were resected after first detection were segmented using dedicated software, and maximum diameter, volume and mass were measured. Mass doubling time (MDT) was calculated.

In total 7135 volunteers were included in the current analysis. 264 (3.3%) SSNs in 234 participants were detected during the trial. 147 (63%) of these SSNs in 126 participants disappeared at follow-up, leaving 117 persistent or directly resected SSNs in 108 (1.5%) participants available for analysis. The median follow-up time was 95 months (range 20–110). 33 (28%) SSNs were resected and 28 of those were (pre-) invasive. None of the non-resected SSNs progressed into a clinically relevant malignancy.

Persistent SSNs rarely developed into clinically manifest malignancies unexpectedly. Close follow-up with computed tomography may be a safe option to monitor changes.

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Introduction

Lung cancer screening with computed tomography (CT) has increased the awareness of a specific subtype of pulmonary nodules: the subsolid nodule (SSN). Currently, there are limited data that provide evidence and guidance on how to manage these specific nodules [1, 2]. An SSN is defined as a circumscribed area of increased lung attenuation with preservation of the bronchial and vascular margins and also referred to as a ground glass nodule (GGN). An SSN can be a part-solid GGN (part of the nodule completely obscures the underlying lung parenchyma) or a pure GGN (no completely obscured areas, hence pure ground glass) [3]. While transient SSNs can represent a large range of benign diseases, persistent SSNs have a high likelihood of malignancy, with reported malignancy rates ranging from 19.4% to 75% [4, 5]. These malignancy rates are much higher than the likelihood of malignancy of solid pulmonary nodules: The Early Lung Cancer Action Project (ELCAP) study reported a malignancy rate among their positive findings of 34% for pure GGNs and 63% for part-solid GGNs, while only 7% of the solid nodules were malignant [1].

Despite their high malignancy rates, SSNs usually grow slowly with a low propensity of distant spread and have an excellent prognosis [6, 7]. Data suggest that resected SSNs often represent adenocarcinoma *in situ* (AIS) [8–12] and less aggressive treatment may be suitable for these nodules, especially in patients with severe co-morbidity.

For solid pulmonary nodules, a volume doubling time (VDT) $\geqslant$400 days is often considered to reflect benign histology [13–17]. Diagnosis and treatment of these slow growing solid nodules is usually considered over-diagnosis: diagnosis of ''disease'' that will never cause symptoms or death during a patient's lifetime. Since SSNs usually have a slow growth rate with VDTs $\geqslant$400 days, but with a high likelihood of malignancy, follow-up guidelines for solid pulmonary nodules are not appropriate for SSNs. In 2013, the Fleischner Society published recommendations for management of SSNs, but the committee emphasised that the recommendations were largely based on expert opinion [3]. To confirm persistence of SSNs, a three-month follow-up CT was advised. Persistent pure GGNs >5 mm are recommended to be followed with an annual CT over at least three years. Persistent part-solid GGNs are recommended to be managed more aggressively, regardless of their size. For these nodules, further evaluation and resection was advised for patients without severe co-morbidities.

In the Dutch-Belgian lung cancer screening trial (Nederlands Leuvens Longkanker Screenings Onderzoek (NELSON); International Standard Randomised Controlled Trial Number 63545820) an approach of close follow-up of persistent SSNs was chosen [18]. Only SSNs with a solid component >500 mm^3 at baseline were referred to a pulmonologist immediately. All other SSNs were followed. Further evaluation was only indicated in case of increase in size (either total size or size of the solid component) or density. It was our objective to evaluate our close follow-up protocol for SSNs and relate the results to the new recommendations [3].

Methods

Study participants

This is an ancillary study of NELSON trial, which was approved by the Dutch and Belgian Ministries of Health and by the ethical review boards of the participating hospitals [19]. Written informed consent was obtained from each participant. Details of the study population were described previously [19]. For the present study, we included all participants from the CT screening arm from the participating Dutch screening centres (University Medical Center Groningen, University Medical Center Utrecht and Kennemer Gasthuis, Haarlem, the Netherlands).

CT scanning and reading protocol

CT screening was done at baseline, 1 year and 3.5 years and 5.5 years after baseline plus additional follow-up CT examinations in case indeterminate nodules were detected [18]. All CTs were read for noncalcified nodules and detected nodules were characterised as solid nodule or SSN, either pure GGN or part-solid GGN. Participants who were referred to a pulmonologist underwent diagnostic work-up including a standard-dose CT with intravenous contrast, bronchoscopy and/or biopsy. Positron emission tomography

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was not routinely included in the diagnostic work-up. Based on the results of these exams, the pulmonologist eventually decided with the participant whether resection of the SSN was needed.

Evaluation of SSNs

All participants who had a SSN $\geqslant$5 mm according to trial database on any screening CT were identified. Previous and later exams from these participants were reviewed by two (chest) radiologists with 30 and 10 years of experience, to detect possible unreported SSNs on previous or later CTs and to confirm the subsolid nature of the nodule.

Size measurements

During the trial, volumetry software (LungCare; Siemens Healthcare, Erlangen, Germany) was used to measure nodule dimensions [18]. This software was developed for solid nodules and often failed when applied to SSNs. Therefore, the diameter of SSNs was measured in the trial using electronic callipers. Based on results of these 2-dimensional measurements, volume was calculated by using the following equation:

$$\text{Volume} = 4/3\pi \times (\text{diameter}/2)^3$$

When a solid component was present, the size of the solid component was quantified using the volumetry software. Increase in total volume or volume of the solid component >25% was considered as significant growth in the original NELSON protocol. The radiologist was also allowed to refer a subject to the pulmonologist in case of visual impression of growth not supported by the measurements.

For the current analysis, we retrospectively measured volume and mass of all nodules with dedicated software, based on an established method for solid lesion segmentation, adapted for segmentation and volumetry of SSNs [20]. (CIRRUS Lung; Diagnostic Image Analysis Group, Nijmegen, the Netherlands, and Fraunhofer MEVIS, Bremen, Germany). For the present study, an increase of at least 30% of the mass of the nodule was considered as growth. This cut-off of 30% is based on our phantom study [21] and preliminary unpublished data on the interscan variation in our population.

Follow-up

Patient outcome was retrieved from the NELSON database that contained histological diagnosis, follow up and vital status until November 2012. If needed, hospital information systems were investigated for additional details.

Statistics

Growth was calculated by comparing actual mass to the mass at first detection and expressed as a percentage. Growth rate was expressed as mass doubling time (MDT) in days, using the following equation:

$$\text{MDT} = \Delta t \times (\ln(2))/(\ln(M2/M1))$$

where Δt is the time difference between the two measurements and M1 and M2 is the mass at first detection and sample measurement, respectively.

Data are presented as median and interquartile range (IQR) for non-parametric variables and as mean and standard deviation for normally distributed variables. A t-test was used to compare the subjects with an SSN to the total study population. A p-value <0.05 was considered significant.

Statistical analysis was performed with software (IBM SPSS version 20; SPSS, Chicago, IL, USA)

Results

Study population and nodule characteristics

In total 7135 volunteers (1152 females (16.1%)) received at least a baseline CT. Median age at baseline was 58.0 years (IQR 8.0 years) and median smoking history was 38.0 pack-years (IQR 19.8 yrs); 3194 participants (44.8%) were still smokers at the date of inclusion.

264 SSNs in 234 (3.3%) participants were detected during the trial. 147 (63%) SSNs in 126 participants disappeared at follow-up, leaving 117 persistent SSNs in 108 (1.5%) participants available for analysis, including 11 SSNs in eight participants who were referred after baseline CT and had their SSN resected. In five other participants with five nodules, changes in size could not be assessed because of missing data in three or inadequate segmentation of the nodule in two cases, leaving 101 nodules in 98 participants available for growth-rate analysis. Five participants had two SSNs, two participants had three SSNs. 81 persistent SSNs were visible at baseline and 36 became first visible at follow-up. Baseline demographics are shown in table 1. Median follow-up time since the first appearance of the nodule was 95 months (range 20–110). Median follow-up period after resection was 20 months (range 2–39).

TABLE 1 Baseline demographics

Characteristic	Participants with a persistent SSN n=108
Age at baseline years	62.0 (10.1)
Sex female n (%)	28 (26)
Smoking status n (%)	
Current	57 (52.8)
Former	51 (47.2)
Smoking history pack-years	38 (19.8)
Pure GGN at detection	
Number	69
Size mm	11.1±3.6 (5.1–22.6)
Part-solid GGN at detection	
Number	48
Size mm	12.7±6.2 (4.6–34.3)

Data are presented as median (interquartile range) or mean±SD (range), unless otherwise stated. SSN: sub-solid nodule; GGN: ground glass nodule.

Nodule size and type

Pure GGNs

69 SSNs were pure ground glass at the time of detection, including 37 nodules ⩾10 mm and 32 nodules <10 mm. 20 nodules (in 20 subjects) developed a solid component, resulting in 49 pure GGNs at the last follow-up CT (table 2).

Part-solid nodules

48 nodules were part-solid at detection. 30 part-solid GGNs were ⩾10 mm in diameter and 18 part-solid GGNs were <10 mm. 20 pure GGN's developed a solid component, resulting in 68 part-solid GGNs at the last follow-up CT (table 2).

Clinical course

Non-resected nodules

84 nodules in 75 participants were followed according to the study protocol (table 2). At baseline, 51 were pure GGN and 33 were part-solid. Of the pure GGNs, 13 developed a solid component according to the two radiologists. During follow-up, none of the 84 SSNs developed into a clinical relevant malignancy. Nine (12.0%) subjects died from pulmonary adenocarcinoma presenting as (another) solid nodule (n=6), oesophageal carcinoma (n=1), colon carcinoma (n=1) and lymphoma (1).

Resected nodules

33 SSNs were resected, of which 11 were pure GGNs and 22 were part-solid GGNs (table 2). Five SSNs turned out to be benign, including our only case of atypical adenomatous hyperplasia. Nine SSNs were preinvasive lesions (AIS, originally diagnosed as bronchoalveolar carcinoma) six were pure GGNs (mean size 15.2±3.1 mm) and three were part-solid GGNs (mean size 16.9±3.3 mm). This difference in size was not significant (p=0·21) (table 2). In this group of nine preinvasive lesions, three SSNs had only visual progression according to the trial radiologist.

TABLE 2 Management and histology of all SSNs at the last CT

	Non-resected	Resected	Benign	AIS	Invasive carcinoma	Total
Persistent pure GGN	38	11	1	6	4	49
Persistent part-solid GGN	33	15	4	1	10	48
Pure GGN that developed a solid component	13	7	0	2	5	20
Total	84	33	5	9	19	117

Data are presented as n. SSN: sub-solid nodule; AIS: adenocarcinoma *in situ*; CT: computed tomography; GGN: ground glass nodule.

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19 SSNs were diagnosed as invasive adenocarcinomas, of which six had only visual progression according to the trial radiologist. Among the 19 invasive carcinomas there were four pure GGNs (mean size 12.9±1.2 mm) and 15 part-solid GGNs (mean size 17.5±9.2 mm). This difference in size was not significant (p=0·12).

All but one invasive carcinoma was stage IA (n=16) or IB (n=2). One invasive carcinoma was a stage IV at time of resection, which was delayed because of a competing malignancy. In this group of participants with a resected SSN, four (12.1%) participants died of lung cancer.

Growth rates

Eight participants with 11 SSNs were referred and had their SSN resected after the first detection. These participants consequently had no follow-up CT. In five other participants with five nodules, changes in size could not be assessed because of missing data in three or inadequate segmentation of the nodule in two cases, leaving 101 nodules in 98 participants available for growth-rate analysis (table 3). 22 SSNs were stable or decreased in size and 79 nodules showed growth (table S4 in the online supplementary material).

Relative increase in mass of the nodule as compared to the first appearance is graphically displayed in figure 1. Two of the 13 SSNs that were not resected, showed a minimal increase in size that, in combination with a short follow-up time, resulted in an MDT <400 days. Except for three benign nodules (rapidly increasing infections), all nine fast-growing SSNs (MDT <400days) were invasive or pre-invasive. However, most invasive tumours were slow growing: 16 (84·2%) out of 19 had an MDT ⩾400 days, including one case with a growth <30%. (table 3).

Follow-up protocol

Only nine SSNs showed ⩾30% increase in mass and an MDT <400 days, including three benign cases, three AIS and three invasive carcinomas (table 3). The vast majority of invasive carcinomas had an MDT >400 days, making this cut-off inappropriate to discriminate between benign and malignant subsolid nodules. Table 3 shows the number of nodules that showed ⩾30% increase in size compared with baseline (*i.e.* mass on the first CT on which the nodule could be detected). Note that only one invasive carcinoma showed <30% increase in mass while none of the preinvasive lesions showed <30% increase in mass. The invasive carcinoma that showed <30% increase in mass, however, showed a significant increase in size of the solid component and was therefore referred and resected.

Discussion

In the current analysis, we describe our experience with close follow-up of SSNs and further evaluation of growing SSNs and SSNs with a new or growing solid component (figs 2 and 3). This approach was found to

TABLE 3 Management and histology of persistent decreasing, stable and growing SSNs

	Growth <30%[#]	Growth ⩾30%[¶]		Total
		Slow[+]	Fast[§]	
Non-solid[f]	13	15	1	29
Non-resected	2	1		3
Benign		4	1	5
AIS		2	2	4
Invasive	15	22	4	41
Subtotal				
Part-solid[f]	24	16		40
Non-resected			2	2
Benign		1	2	3
AIS	1	13	1	15
Invasive	25	30	5	60
Subtotal				
Total	40	52	9	101

[#]: including 22 SSNs that were stable or decreased in size. [¶]: increase in mass compared with baseline computed tomography (*i.e.* the first computed tomography on which the nodule could be detected); [+]: mass doubling time ⩾400 days; [§]: mass doubling time <400 days; [f]: nature of the SSN as assessed on the last CT scan.

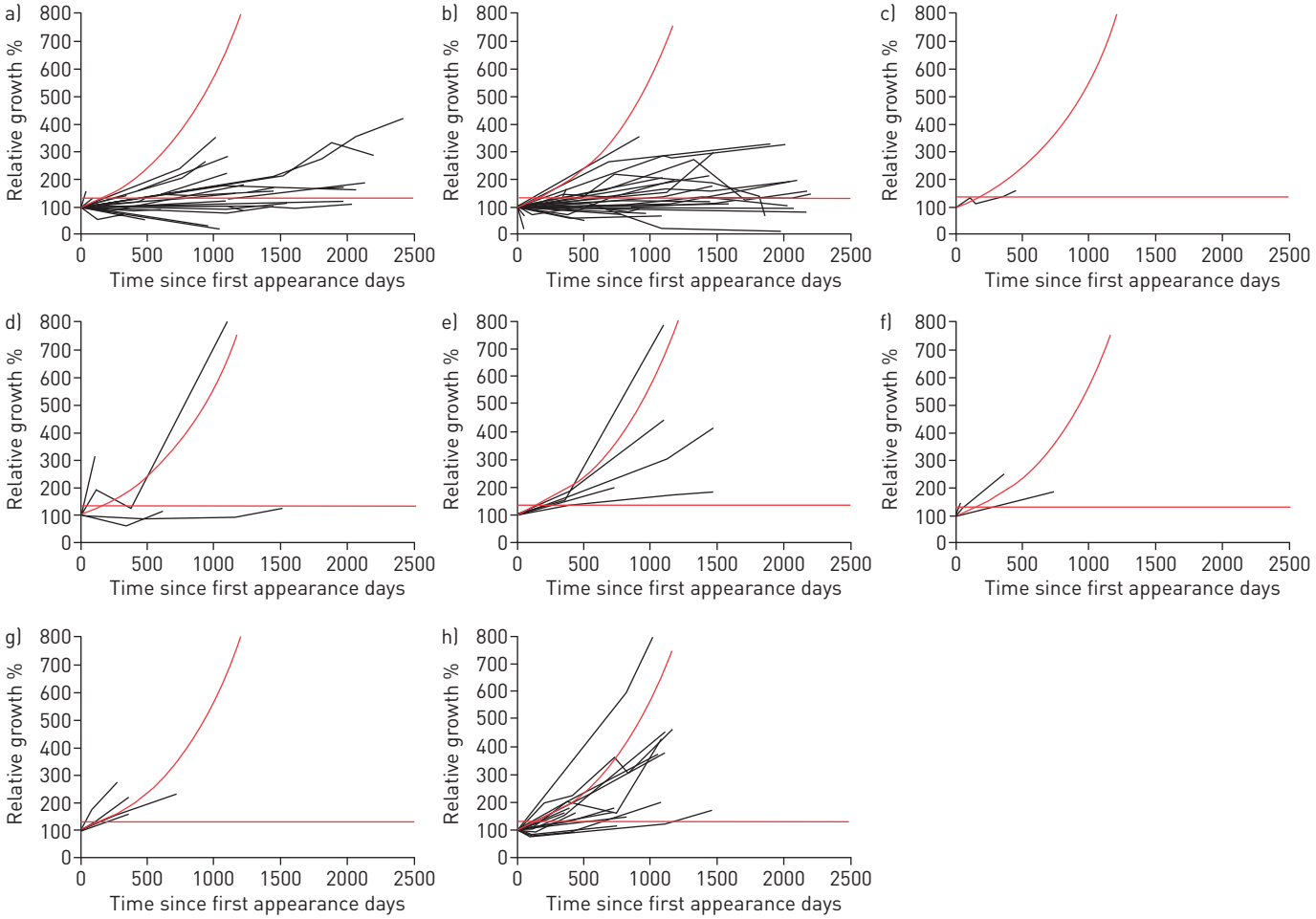

FIGURE 1 Growth patterns on the persistent subsolid nodules in the trial. a) non-resected pure ground glass nodule; b) non-resected part-solid ground glass nodule; c) resected benign pure ground glass nodule; d) resected benign part-solid ground glass nodule; e) resected adenocarcinoma *in situ* pure ground glass nodule; f) resected adenocarcinoma *in situ* part-solid ground glass nodule; g) resected invasive pure ground glass nodule; h) resected invasive part-solid ground glass nodule. On the X-axis, the number of days since the first appearance; on the Y-axis, the relative growth as compared with the first appearance. The horizontal line represents a relative increase of mass of 30%. The curved line represents a mass doubling time of 400 days.

be safe in a large lung cancer screening trial. We also report that, when using a cut-off of 30% increase in mass and/or volume of the solid component, no clinically relevant carcinomas would have been missed during a median follow-up of 95 months.

Recently Kim *et al.* [22] found an interscan variability of -17.7%–18.6% for the mass of SSNs with solid portions $\leqslant$5 mm, which we find supportive of our chosen cut-off value of 30% for significant growth.

For persistent part-solid GGNs with a solid component >5 mm, the new recommendations from the Fleischner Society are fairly aggressive because of their high likelihood of malignancy [1]. We showed, however, that close follow-up may be a safe approach even though it is likely that many of the part-solid GGNs that were followed would have been diagnosed as malignant when resected. None of part-solid GGNs that were not resected developed into clinically relevant lung cancer in our cohort.

For pure GGNs >5 mm, the Fleischner Society recommends further evaluation in case of nodule growth. In the NELSON trial, the decision to refer a SSN to the pulmonologist for further evaluation was based on a 25% increase in volume calculated from the diameter as measured with electronic callipers, irrespective of the baseline character of the nodule. However, in 15 cases, there was visual progression only as assessed by the trial screening radiologist either in size or density of the SSN or size of the solid component. In nine of these cases, the nodule turned out to be either AIS (n=3) or invasive adenocarcinoma (n=6). We therefore retrospectively measured volume and mass of all SSNs and reported that a total increase in mass <30% seems to be a reliable parameter to exclude clinical relevant malignancies, however for an increase $\geqslant$30% there is great overlap between malignant and non-malignant SSNs.

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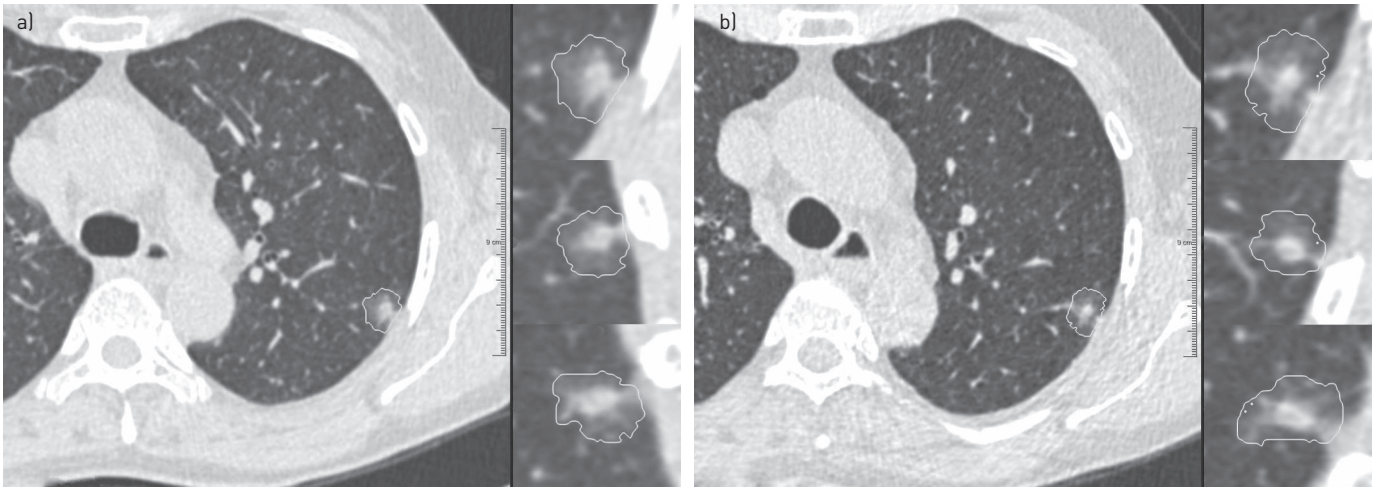

FIGURE 2 Illustration of a stable part-solid ground glass nodule. a) January 2006; b) September 2008. The female trial participant was 57 years of age in 2006 and she was followed up until November 2012. The images show an axial cross-section with magnified axial (top), coronal (middle) and sagittal (bottom) reconstructions. According to the Fleischner recommendations, this nodule would have been resected.

For cancer screening to be effective, a good balance between the benefits and harms is required. One of the potential harms is the extent of overdiagnosis. This issue is still topic of debate in breast cancer screening [23, 24]. Overdiagnosis has been reported to be a problem in lung cancer screening as well [25–27]. In lung cancer screening, detection and treatment of cancers with a VDT $\geqslant$400 days is often considered overdiagnosis [27]. When using this definition, detection and treatment of the vast majority of SSNs can be considered overdiagnosis despite their high likelihood of containing malignant cells.

In the current investigation, we retrospectively used MDT instead of VDT. Mass is a parameter that integrates volume and density, and will therefore not only increase when volume increases, but also when a solid component within a lesion develops or progresses. De Hoop *et al.* [28] showed that mass is a more sensitive parameter to detect progression than volume in SSNs and showed that even in the group of invasive carcinomas, the vast majority had an MDT>400 days [28].

In one case of invasive carcinoma, mass did not increase, even though the solid component increased in size, because total size of the nodule decreased. Therefore, volumetry of the solid component is proposed as an additional indicator of growth of the nodule.

Recently Lee *et al.* [29] described their use of CT features to differentiate between invasive pulmonary adenocarcinomas and preinvasive lesions in SSNs. They observed that in pure GGNs, a cut-off value of 10 mm was optimal for differentiation between a preinvasive lesions and invasive adenocarcinomas with a sensitivity of 55.3% and a specificity of 100%. Lim *et al.* [30] described a cut-off value of 16.4 mm in a series of 46 resected pure GGNs for differentiating invasive adenocarcinomas from preinvasive lesions. We cannot confirm the findings of Lee *et al.* [29] since none of our resected nodules measured less than 10 mm and, in contrast with Lee *et al.* [29] and Lim *et al.* [30], we did not find a significant difference in size between preinvasive and invasive lesions. In the group of part-solid nodules, invasive adenocarcinomas were significantly larger the preinvasive lesions in the series of Lee *et al.* [29]. We also found a larger size of invasive part-sold lesion compared to preinvasive lesions; however, this difference was not significant in our series, which can be attributed to our small number of only three part-solid preinvasive lesions.

Positron emission tomography (PET)-CT was not a routine part of the diagnostic work-up of referred SSNs in our series. The Fleischner Society states that PET is of limited value and even potentially misleading for pure GGNs, and they only recommend considering PET-CT for part-solid nodules >10 mm [3]. PET-CT has been shown to be a significant predictor of surgical outcomes and to be important to determine the appropriateness of sublobar resection in cases of stage 1A adenocarcinoma of the lung [31].

For the management of SSNs one would prefer to be able to predict the lifelong behaviour for SSNs, but that is a challenge that requires larger sample size and longer follow-up. Until this challenge has been addressed, the disadvantages of repeated follow-up must be weighed up with the disadvantages of invasive treatment. Invasive treatment must take into account that enough lung tissue is preserved as subjects often have pulmonary comorbidity and multiple lesions can be present or develop. As limited surgery, stereotactic radiotherapy and percutaneous interventions allow treatment of multiple lesions and preservation of lung

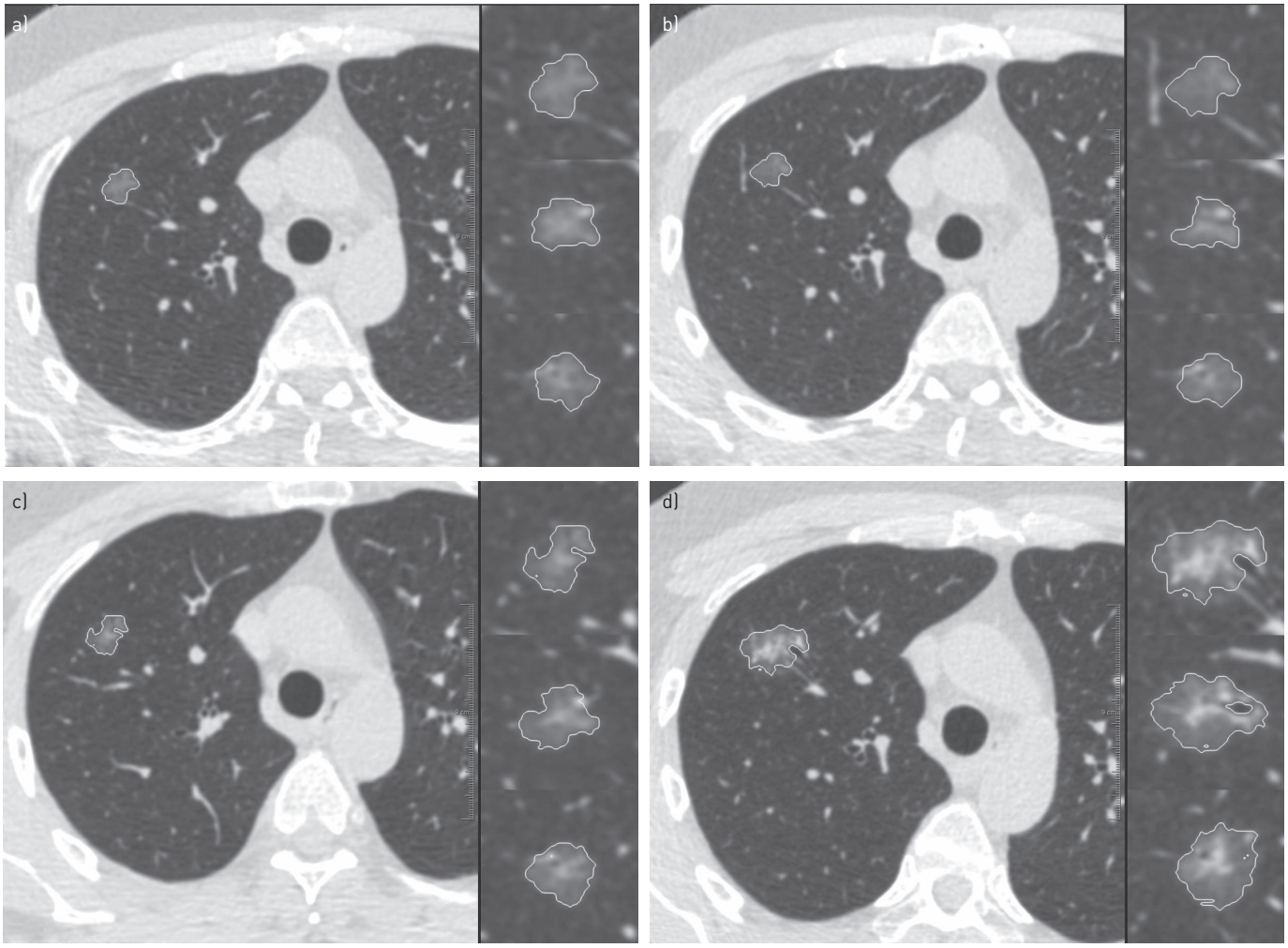

FIGURE 3 Illustration of a pure ground glass nodule which developed a solid component. a) June 2004; b) October 2004; c) June 2005; d) July 2007. The male trial participant was 57 years of age in 2004 and he was followed up until November 2012. The images show an axial cross-section with magnified axial (top), coronal (middle) and sagittal (bottom) reconstructions. The nodule was classified as a pure ground glass nodule from the first three computed tomography images. The histological diagnosis was adenocarcinoma *in situ*.

function, such treatment remains a consideration. In their recent paper on radio frequency ablation for ground glass opacity dominant lung adenocarcinoma, KODAMA *et al.* [32] conclude that this is a feasible, safe and useful therapeutic option to control these carcinomas.

For many participants, low-frequency follow-up with low-dose CT may be preferable for the near future, because these subjects may well be at high risk of developing new solid nodules and SSNs.

The major strengths of the current analysis were the relative large size of the study population of this relatively rare, but important, entity and the relative long follow-up.

The study also suffers from limitations. First, we do not know the exact malignancy rate among the studied SSNs, since the majority of the SSNs were not resected. Secondly, even from those participants, we had stage IA or stage IB at time of resection, three subjects died during follow-up. Thirdly, our results including the cut-off value of 30% mass increase need external validation, preferably in a prospective study.

In conclusion, persistent SSNs have a high malignancy rate according to pathological analysis but rarely develop into clinical manifest malignancies unexpectedly. Our data suggest that long-term follow-up with CT may be a safe option to monitor changes in persistent SSNs. We like to suggest that (minimally) invasive intervention could be considered only in SSNs that show $\geqslant$30% growth or a new appearing or growing solid component.

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