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Growing small solid nodules in lung cancer screening: safety and efficacy of a 200 mm^3 minimum size threshold for multidisciplinary team referral

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ABSTRACT

The optimal management of small but growing nodules remains unclear. The SUMMIT study nodule management algorithm uses a specific threshold volume of 200 mm^3 before referral of growing solid nodules to the multidisciplinary team for further investigation is advised, with growing nodules below this threshold kept under observation within the screening programme. Malignancy risk of growing solid nodules of size >200 mm^3 at initial 3-month interval scan was 58.3% at a per-nodule level, compared with 13.3% in growing nodules of size ≤200 mm^3 (relative risk 4.4, 95% CI 2.17 to 8.83). The positive predictive value of a combination of nodule growth (defined as percentage volume change of ≥25%), and size >200 mm^3 was 65.9% (29/44) at a cancer-per-nodule basis, or 60.5% (23/38) on a cancer-per-participant basis. False negative rate of the protocol was 1.9% (95% CI 0.33% to 9.94%). These findings support the use of a 200 mm^3 minimum volume threshold for referral as effective at reducing unnecessary multidisciplinary team referrals for small growing nodules, while maintaining early-stage lung cancer diagnosis.

INTRODUCTION

Indeterminate pulmonary nodules are common in lung cancer screening, with only a small proportion ultimately confirmed as malignant. On baseline scans, malignancy risk and thus nodule management in solid nodules is primarily driven by size[1–3] whereas at follow-up CT scan, growth indicates an elevated risk of malignancy.[3 4] The question of how to optimally manage growing solid nodules which remain below a size threshold for subsequent investigations is an area of uncertainty.

In LungRads 1.1,[1] participants with growing nodules that remain <8 mm are recommended for either CT surveillance or positron-emission tomography (PET)/CT scanning. The British Thoracic Society (BTS) guidelines and the European Position Statement[5] stipulate that all nodules initially between 80 or 100 mm^3 (respectively) and 300 mm3 (or ≥5 to <10 mm in diameter when volumetry is not possible) which subsequently demonstrate growth with volume doubling time (VDT) <400 days are referred for further definitive management, regardless of size.

The SUMMIT study (NCT03934866) is an observational study in high-risk participants using low-dose CT (LDCT) screening in London. The nodule management protocol used in SUMMIT is based on the BTS guidelines but includes a specific threshold volume of 200 mm^3 before referral for growing solid nodules to the multidisciplinary team (MDT) for further investigation is advised. The rationale for this was twofold: first, data from the NELSON study[6] found that the development of new solid pulmonary nodules was associated with a higher cancer risk, but only above a threshold volume of 206 mm^3[6]. The implication is that nodules below this size, even if growing, have a lower risk of malignancy and do not require definitive investigation at this stage. Second, there are particular challenges when performing further investigations on nodules smaller than 8 mm/200 mm^3 as they are typically below the resolution limits of positron-emission tomography (PET)/CT and technically more difficult to biopsy.

There is little previous data from studies that have prospectively managed small growing nodules in this way. The aim of this study was to assess the safety and efficacy of this approach.

METHODS

The SUMMIT study is a prospective observational cohort study to examine the performance of delivering a LDCT screening service to a high-risk population in London and to validate a multicancer early detection blood test (ClinicalTrials.gov NCT03934866). Eligible participants were 55–77 years old, met the US Preventive Services Task Force 2013 screening criteria,[7] or had a $PLCO_{m2012}$ risk of ≥ 1.3%[8] and attended three annual lung health checks (baseline (Y0), year 1 (Y1) and year 2 (Y2)) with LDCT. Study scans were performed without contrast at maximal inspiration in one continuous craniocaudal acquisition with radiation dose optimised based on body weight. Images were read by thoracic radiologists using computer aided detection (CADe) software (Veolity V.1.4, MeVIS Medical Solutions, Germany) and semiautomated volumetry.

The SUMMIT nodule management protocol has been published.[9] In brief, solid nodules of ≥80 mm^3 and <300 mm^3 on baseline scan undergo interval

scan at 3 months. Nodule growth was defined as percentage volume change (PVC) of ≥25%, or on visual assessment if baseline volumetry was unreliable. At follow-up, scan nodule stability was defined as PVC of between −24 and+24%, or stable diameter in cases of unreliable segmentation. Nodules stable at 3-month interval scan undergo further scans at Y1 and Y2. Nodules demonstrating growth with volume >200 mm^3 are referred to the MDT for definitive assessment. Growing nodules which remain ≤200 mm^3 are scheduled to undergo a further surveillance scan after another 3-month interval and are only referred for MDT assessment when volume exceeds 200 mm^3. At all time points, protocol deviation was permissible based on radiologists' assessment in individual cases.

This study analyses outcomes from all participants who had a baseline scan between study commencement (4 April 2019) and temporary closure for the Sars-CoV-2 pandemic on 18 March 2020 (N=11 566), with solid nodules between 30 and 300 mm^3 at baseline CT, showing growth at a 3-month interval scan. Nodules interpreted as benign intrapulmonary lymph nodes at baseline did not undergo surveillance and are excluded from this analysis.

Solid nodules present on baseline scan but not marked on initial review, and subsequently noted to be growing on 3-month interval scan (referred to as 'retronodules') were included in this analysis. Growing nodules which had unreliable volumetry at follow-up scan were excluded from this analysis. Participants who had their scheduled 3-month interval scan delayed beyond 6 months from baseline (primarily due to the SARS-CoV2 pandemic) were also excluded from this analysis.

Cancer was confirmed by histology or diagnosed clinico-radiologically by MDT assessment. Nodules were recorded as benign based on any of the following criteria: (1) benign histology following MDT referral; (2) volume stability or decrease in volume over at least 12 months (PVC<25% and/or volume-doubling time (VDT)>600 days[2]); (3) stability on 2D measurements over 2 years where volumetry was unreliable or (4) resolution of nodules.

Measured outcomes were (1) false-negative rate, defined as the proportion of all growing nodules managed initially by surveillance and subsequently diagnosed as lung cancer at greater than stage 1[10]; (2) positive predictive value (PPV) of our protocol, defined as [(all cancers diagnosed) ÷ (all growing nodules >200 mm^3)] and (3) Relative risk of malignancy at 2 years, defined as the percentage of nodules proved malignant within 2 years in those that demonstrated growth and had volume >200 mm^3 at initial 3-month interval divided by the percentage of nodules proved malignant within 2 years in those that demonstrated growth but remained ≤200 mm^3 at initial 3-month interval scan. Fishers' exact test was used to assess proportional differences with statistical significance defined as p value of less than 0.05.

Analysis was performed using R Studio (V.4.0).

RESULTS

Of the 11 566 participants who underwent a baseline scan in this analysis, 3621 solid nodules with volume 30–300 mm^3 were identified in 2344 participants (figure 1). Of these, 1620 nodules in 953 participants underwent a 3-month interval scan (nodules 30–80 mm^3 do not undergo interval scanning in BTS/SUMMIT protocol so these scans were performed for a coexisting finding (larger nodule or consolidation)). At initial interval scan, 1424/1620 (88%) nodules persisted, while the remaining 196 (12%) resolved. Seventy-nine nodules in 70 participants demonstrated growth at 3-month scan, with an additional two nodules in two participants showing clear growth on visual assessment but with unreliable segmentation at follow-up CT; these were excluded from further analysis. A further 17 nodules in 17 participants were noted to be growing on 3-month interval scan having been initially missed or disregarded on baseline scan giving a total of 96 solid nodules in 87 participants with clear evidence of growth at the 3-month scan. Of the 96 growing solid nodules, 36 nodules in 30 participants had volume >200 mm^3 (management and outcomes shown in figure 2); and 60 nodules in 59 participants had volume ≤200 mm^3 (management and outcomes shown in figure 3).

On a per-nodule level, of the 96 growing solid nodules included in this analysis, 29 nodules (30.2%) were ultimately identified as malignant. Of these, 22/29 (75.9%) nodules were bronchogenic carcinomas in 22 participants, comprising 18 lung cancers diagnosed on histology and four lung cancers diagnosed clinicoradiologically by the MDT (based on CT and PET/CT findings due to patient preference or fitness). The remaining 7/29 nodules in one patient were clinicoradiologically diagnosed lung metastases from a subsequently diagnosed primary oesophageal cancer.

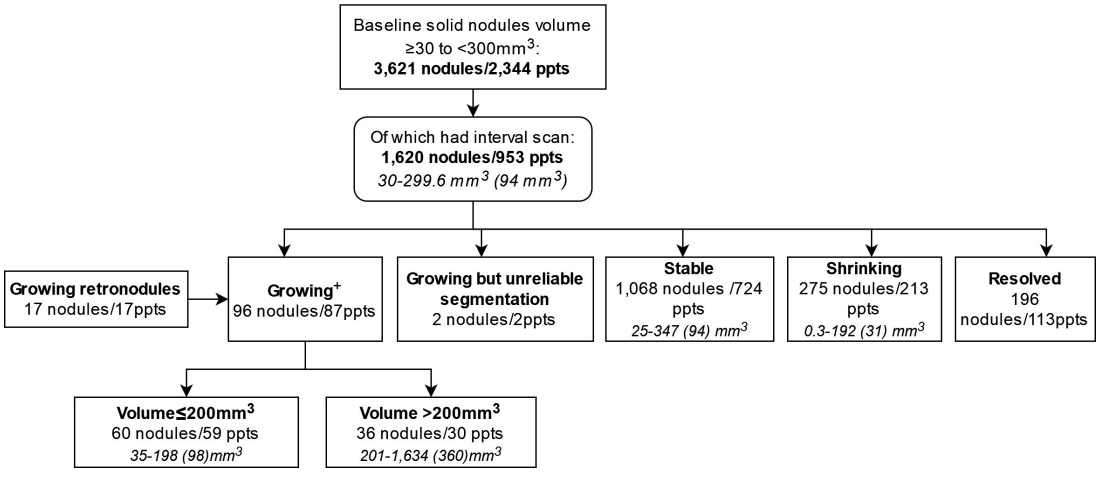

Figure 1 CONSORT diagram for participants in this analysis. Numbers in italics are nodule volume range (median) in mm^3. Participant numbers add up to greater than total due to participants having multiple nodules in different categories +96 growing nodules includes 79 nodules noted at baseline and 17 nodules present but not marked on initial scan and subsequently seen to be growing ('retronodules') Ppt, participant.

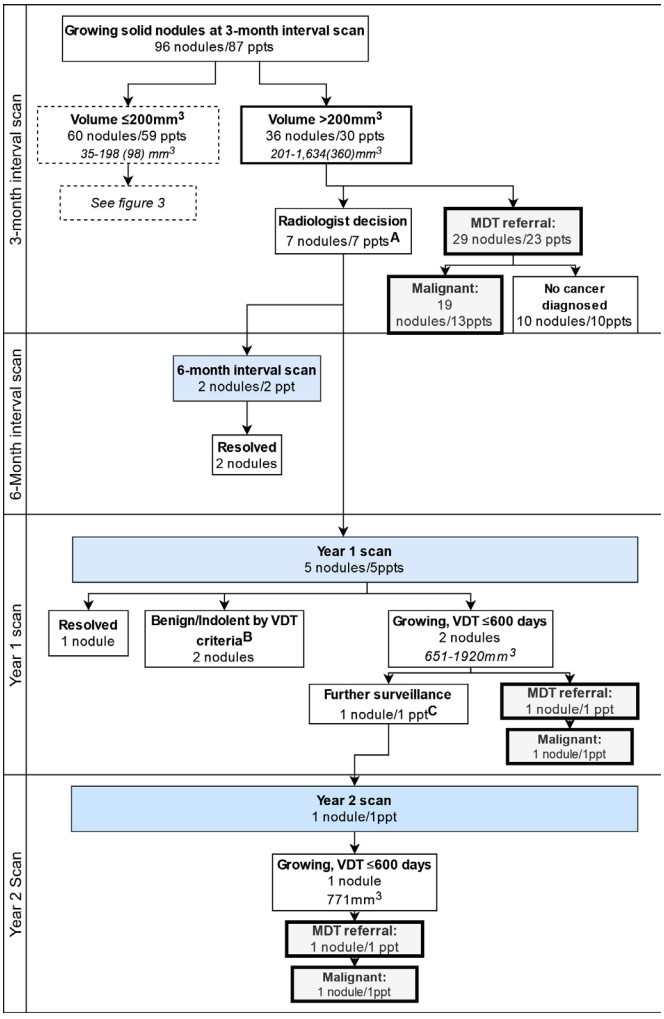

Figure 2 Outcomes of growing solid nodules >200 mm^3 at first interval scan. Numbers given at per-nodule and per-participant level. Numbers in italics are nodule volume range and (median), mm^3. [A]Protocol deviation due to radiologist assessment: interpreted as intrapulmonary lymph nodes (n=2) or likely inflammatory (n=5). [B]Defined as VDT >600 days. [C]Radiologists' decision based on morphology. MDT, multidisciplinary team; ppt, participant; VDT, volume doubling time.

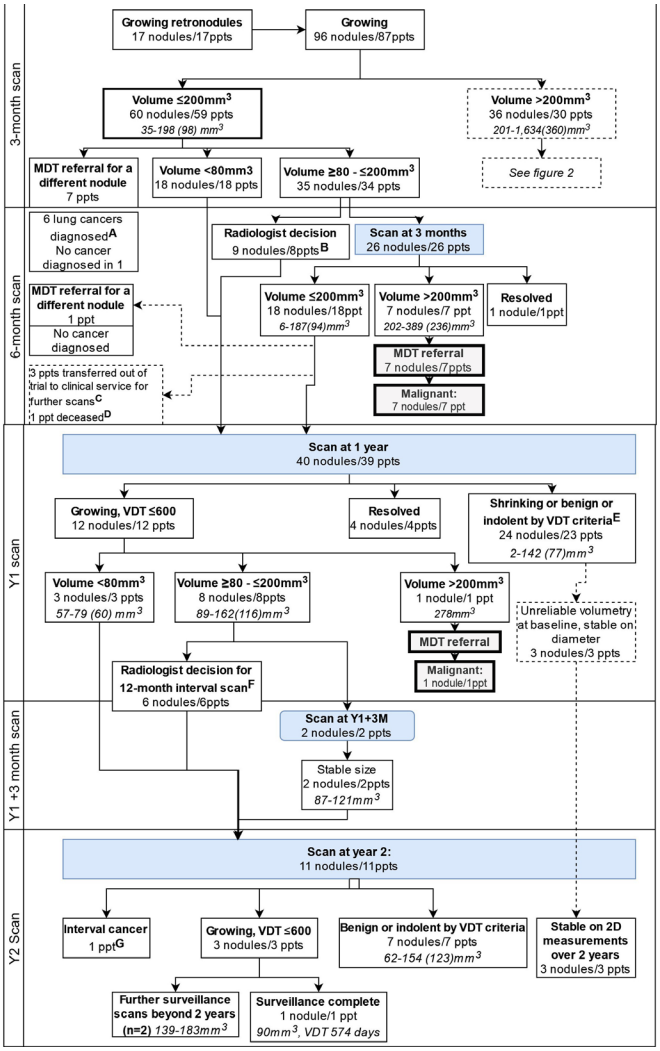

Figure 3 Outcomes of growing solid nodules ≤200 mm^3 at first interval scan. Numbers given at per-nodule and per-participant level. [A]n=2 growing solid nodule >200 mm^3 covered in figure 2, n=1 lymph node mass, n=3 growing part-solid nodules. [B]Protocol deviation due to radiologist interpretation: (likely inflammatory n=2, IPLNs n=7). [C]No thoracic cancer diagnosis. [D]Non-lung cancer cause of mortality. [E]VDT >600 days. [F]Protocol deviation due to radiologist interpretation (benign morphological appearances n=2, No growth since 3-month scan n=4). [G]Small cell lung cancer separate to nodule under surveillance. IPLN, intrapulmonary lymph node; MPT, multidisciplinary team; ppt, participant; VDT, volume doubling time.

Of the 36 nodules showing growth with volume>200 mm^3 at first interval scan (figure 2), 21/36 (58.3%) were malignant in 15/30 (50%) participants (table 1). In the 60 nodules ≤200 mm^3 at initial 3-month interval scan (figure 3), the risk of a growing nodule being diagnosed as cancer within 2 years was 13.3% on a per-nodule (8/60) and 13.6% on per-participant (8/59) basis (relative risk of nodule malignancy 4.4, (95% CI 2.17 to 8.83), two nodules (two participants) ≤200 mm^3 at initial 3-month interval scan underwent further surveillance beyond 2 years).

The PPV of a growing nodule that reached size >200 mm^3 being malignant was 65.9% (29/44), constituting 21 cancers in 36 nodules >200 mm^3 at first interval scan (figure 2) plus 8 cancers in 8 nodules which grew to >200 mm^3 at subsequent scans (figure 3). PPV was 60.5% (23/38) on a per-participant basis.

In this study, 53 growing nodules of ≤200 mm^3 at 3 months were managed by further surveillance (figure 3). Of these, eight were diagnosed as lung cancer within 2 years. Of these, seven were stage 1 and one was stage 3 (pN2 nodal involvement at surgical resection, not demonstrable on preoperative CT imaging). The false negative rate of the protocol was therefore 1.9% (95% CI 0.33% to 9.94%) (1/53).

At first interval scan, median VDT was shorter in nodules subsequently confirmed to be malignant compared with those where malignancy was ultimately excluded (median 98 (range 42–389) days vs median 202 (range 27–440) days). At first interval scan, a nodule management protocol based on evidence of growth alone would have resulted in all 87 participants being referred for definitive assessment[2]; a combination of growth and minimum volume threshold reduced this by 62% to 33/87 (figures 2 and 3). Example images are shown in figure 4.

Table 1 Volume at first interval scan and probability of malignancy of growing solid nodules

	Nodule volume ≤200 mm^3 (cancers/total no of nodules)	Nodule volume >200 mm^3 (cancers/total no of nodules)	
Growing solid nodules	8/60*	21/36	RR 4.4 (95% CI 2.17 to 8.83)

Data presented at a per-nodule level.
*8 nodules ≤200 mm^3 at first interval scan subsequently grew to >200 and were diagnosed as cancer.

DISCUSSION

In the NELSON study, the malignancy risk of new nodules at interval scan<206 mm^3 was 3.1%.[6] Our data show the malignancy risk in nodules which grow on first interval scan (performed at 3–6 months after baseline) but remain ≤200 mm^3 was over fourfold higher, at 13.3%.

However, our results provide support for a conservative approach involving close CT observation in growing nodules ≤200 mm^3. Of the nodules in this category that were malignant, all but one remained at stage I, with an overall false-negative rate of 1.9%.

Importantly, this approach avoids unnecessary MDT referral and further investigation for a finding which is benign or indolent in 86% of cases. By contrast, our results indicate that growing nodules >200 mm^3 require further investigation for lung cancer, with a PPV for malignancy of 65.9% on a per-nodule or 60.5% on a per-participant basis. This approach has two potential benefits: it focuses MDT discussion on cases that are more likely to represent lung cancer and which have reached a size for meaningful intervention, while ensuring that smaller nodules can remain within the protocol-driven, streamlined management and safety netting provided by a screening programme. We anticipate that this strategy would reduce both variability in and overall rates of PET-CT referral at a stage when such nodules would be too small to evaluate.

Key strengths of our study include our large cohort size and that our management approach to nodules ≤200 mm^3 was implemented prospectively. Furthermore, all studies were read by experienced thoracic radiologists with standardised scanners and CADe software ensuring consistency.

A limitation of our study is that as our protocol used a 200 mm^3 volume threshold, only nodules with reliable segmentation at follow-up scan were included in this analysis. While this allows us to validate this approach (and volumetric assessment is currently recommended by national[2] and European[5] guidelines), it means a small number of nodules where reliable volumetric analysis could not be achieved were excluded. This may limit generalisability in contexts where nodule volumetry is not routinely available or for nodules where volume cannot be accurately assessed. Furthermore, although the SUMMIT study includes a large number of participants, as growing solid nodules comprise only a small proportion of total screen-detected nodules, focusing specifically on this group limits the number of nodules and cancers in this final analysis. Our findings should therefore be taken cautiously, and this approach would benefit from prospective validation in further cohorts. Finally, it is important to recognise that this approach was used within a screening context, where participants would return for further annual or biennial scans to identify more slowly growing nodules. Nevertheless, there is precedent for nodule management approaches derived from screening programmes to be used in guidelines for the management of incidentally detected nodules, including the Brock score and volume-doubling time.

In conclusion, we provide unique, prospective evidence that

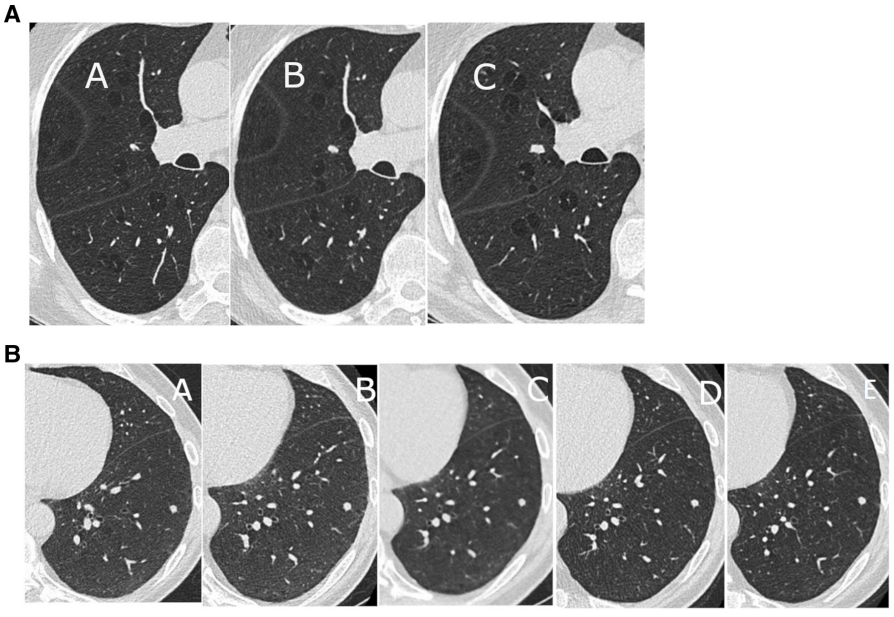

Figure 4 Panel A: Growing nodule subsequently diagnosed as lung cancer. (A) Baseline scan, volume 42 mm^3 (B) 3 months, volume 92 mm^3, PVC +117%, VDT 98 days. (C) 6-month scan (performed at 8 months), volume 246 mm^3, PVC +168%, VDT 109 days (referred at this time). Panel B: Growth seen at first interval scan, subsequently stable over 2 years. (A) Baseline, volume 82 mm^3 (B) 3 months, volume 126 mm^3, PVC+53%, VDT 153 days. (C) 6-month scan (performed at 8 months), volume 74 mm^3, PVC −41%. (D) 12 months, volume 53 mm^3, PVC -28% (E) 24 months, volume 58 mm^3. PVC, percentage volume change; VDT, volume doubling time.

a solid nodule management protocol encompassing a combination of growth and minimum size threshold is safe and reduces unnecessary MDT referrals for benign lesions, while maintaining early-stage lung cancer diagnosis.

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Ethics approval This study involves human participants and was approved by London—City and East Research Ethics Committe17/LO/2004. Participants gave informed consent to participate in the study before taking part.

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