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European and North American lung cancer screening experience and implications for pulmonary nodule management

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Abstract The potential for low dose computed tomography (LDCT) to act as an effective tool in screening for lung cancer is currently the subject of several randomised control trials. It has recently been given prominence by interim results released by the North American National Lung Screening Trial (NLST). Several other trials assessing LDCT as a screening tool are currently underway in Europe, and are due to report their final results in the next few years. These include the NELSON, DLSCT, DANTE, ITALUNG, MILD and LUSI trials. Although slow to instigate a trial of its own, the UK Lung Screen (UKLS) trial will shortly commence. The knowledge gained from the newer trials has mostly reinforced and refined previous concepts that have formed the basis of existing nodule management guidelines. This article takes the opportunity to summarise the main aspects and initial results of the trials presently underway, assess the status of current collaborative efforts and the scope for future collaboration, and analyse observations from these studies that may usefully inform the management of the indeterminate pulmonary nodule.

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Key Points
- *Low dose CT screening for lung cancer is promising.*
- *The effect of LDCT screening on mortality is still uncertain.*
- *Several European randomised controlled trials for LDCT are underway.*
- *The trials vary in methodology but most compare LDCT to no screening.*
- *Preliminary results have reinforced existing nodule management concepts.*

Keywords Screening · Lung cancer · Clinical trials · Randomized · Helical computed tomography · Solitary pulmonary nodules

Introduction

Lung cancer remains a leading cause of death in Europe and the UK [1] and in recent years, low dose computed tomography (LDCT) has been proposed as an effective screening tool [2]. Early studies demonstrated the ability of LDCT to detect early stage cancers, but definitive conclusions have been lacking because of the lack of a control group [3–7], or by the use of 5-year survival rate (5YSR) as an outcome measure [8, 9]. With its susceptibility to the combined effects of lead-time, length and overdiagnosis biases, improved 5YSR is not a satisfactory surrogate for reduced disease-specific mortality, the most important outcome measure [10]. The effect of LDCT screening on mortality is still uncertain [11], but is the subject of several randomised controlled trials (RCTs) that are underway or nearing completion. The North American National Lung Screening Trial (NLST) is such a trial. The NLST

investigators made headlines in October 2010 with their announcement that an interim analysis had demonstrated a significant mortality reduction [12]. This article reviews the status of the trials currently underway, assesses the scope for international collaborative efforts, and extracts observations from these studies that may inform the management of the indeterminate pulmonary nodule.

Summary of current trials

The study design, target population and other characteristics of the trials discussed below are summarised in Table 1; the yield of lung cancers from some of the trials is provided in Table 2.

The NLST

The NLST, launched in 2002, is a 33-centre prospective RCT in the United States, designed to establish whether screening using LDCT compared to single-view chest radiography, can reduce lung cancer-specific mortality in high-risk participants [13]. Three rounds of annual screening were performed on participants who were followed for a maximum period of 8 years. Annual interim analyses were conducted from April 2006 through to 2009, with semi-annual analysis in 2010. The study was designed to have 90% power to detect a 21% reduction in mortality, independent of the number of rounds of screening [13].

A positive result in the NLST constituted a finding suspicious for lung cancer, defined on LDCT as non-calcified nodule(s) (NCNs) ≥4 mm in greatest transverse dimension, or suspicious morphology. The NLST management protocol was not prescriptive—general guidance was issued, but diagnostic and follow-up work-up was devolved to usual clinical practice at a local level [14]. The issued guidance predated, but did not differ substantially, from the Fleischner Society guidelines for management of small pulmonary nodules [15] (Table 3).

The NLST accomplished the fast accrual of 53,454 individuals between August 2002 and April 2004 [16]. The interim analysis performed in October 2010 revealed 356 deaths in the LDCT arm of the trial, compared to 443 in the CXR arm, corresponding to cumulative lung cancer mortality rates of 247 and 309 per 100,000 person-years, respectively [17]. This 20.3% reduction in lung cancer-specific mortality was statistically significant, far exceeding that expected by chance. A lower but still statistically significant decrease in all-cause mortality of 6.7% was also observed in the LDCT cohort. However, the false-positive rate of screens varied between 95% and 98% on LDCT, compared to between 93% and 96% on CXR. The analysis of patients undergoing further work-up and associated adverse events has just been reported, but the sensitivity, specificity, positive and negative predictive values are not yet forthcoming [17].

A recurrent question in designing screening trials is whether the control arm of such a trial should include some method of detection or none at all. Two reasons have been given for the decision to include chest radiography in the non-LDCT (screening) arm of the NLST. First, the lung component of the National Cancer Institute's Prostate, Lung, Colorectal and Ovarian screening trial (PLCO), to which the NLST is allied, assesses the use of chest radiography versus no screening, and can already provide one comparison to usual care, i.e. no screening [18]. As such, integrating the NLST and PLCO data may possibly offer a three-way (albeit indirect) comparison between LDCT, chest radiography and no screening. Second, chest radiography as a form of 'usual care' is already offered to many individuals at risk of lung cancer as a method of screening, for example in Japan [19], although this is not the case in all countries. The decision to use chest radiography in the control arm of the NLST makes it unable to answer directly the question of whether LDCT confers a mortality benefit over no screening.

The NELSON study

The largest RCT LDCT screening trial in Europe has the acronym NELSON (Nederlands-Leuvens Longkanker Screenings Onderzoek) and has been in progress in the Netherlands and Belgium since 2003 [20]. Compared with the NLST, NELSON randomised participants to screening with LDCT or 'usual care', that is, no screening of any form.

NELSON differs from the NLST in several other respects. Rather than the pre-defined eligibility criteria adopted by the NLST, NELSON used a population-based questionnaire to determine what the optimum risk-based selection criteria would need to be to achieve a balance between risk profile, sample size and required rates of participation and retention [20]. NELSON also offers three rounds of screening, but in years 1, 2 and 4 (compared to years 1, 2 and 3 in the NLST). Further, NELSON participants are followed up over a longer period of 10 years.

NELSON was the first study to incorporate software-calculated volume doubling time (VDT) of nodules (with the exception of pleural-based nodules, which are followed up based on their measurable diameter) into a management algorithm (Table 4) [21]. Volumetric analysis is semi-automated, with the option of manual measurement if nodule segmentation is suboptimal or impossible. Growth was defined as a percentage volume change of 25% or

Table 1 Characteristics of ongoing trials of low-dose computed tomography in lung cancer screening. *LDCT = Low dose computed tomography. CXR = chest radiograph; NR = Not reported*

Trial	Design	Recruitment Period	Screening Strategy				Year Final Results Expected	Main characteristic(s) assessed	CT Reconstructed Slice width (mm)	Target Population			
			Arms	No. of screening rounds	Screening times[a] (years from randomisation)	Total follow-up period (years from randomisation)				Age	Sex	Smoking status	
												History (pack-years)	Ex-smoker, quit(years)
NLST [16]	RCT	2002–2004	LDCT vs CXR	3	1,2,3	8	2011	Diameter	2–3.2	55–74	Male and Female	≥30	<15
NELSON [20]	RCT	2003–2006	LDCT vs usual care	3[b]	1,2,4	10	2016	Volume and diameter	1	50–75	Male and Female	>15–18.75	<10
DLCST [30]	RCT	2004–2006	LDCT vs usual care	5	1,2,3,4,5	10	2016	Volume and diameter	1–3	50–70	Male and Female	≥20	<10 (after age >50)
DANTE [31]	RCT	2001–2006	LDCT vs usual care; CXR at baseline in both arms	5	1,2,3,4,5	NR	NR	Diameter	5	60–74	Male only	≥20	<10
ITALUNG [32]	RCT	2004–2006	LDCT vs usual care	4	1,2,3,4	NR	NR	Diameter	1–3	55–69	Male and female	≥20	<10
MILD [37]	RCT	2005–current	LDCT vs usual care	NR	CT group randomised: either annual or every 2 years	NR	NR	Volume	1	50–75	Male and female	≥20	<10
LUSI [38]	RCT	2007–current	LDCT vs usual care	5	1,2,3,4,5	NR	2015–2017	NR	NR	50–69	Male and female	"heavy"	NR
Depiscan [29]	RCT	2002–2004	LDCT vs CXR	3	1,2,3	None	2007	Diameter	1.25–3	50–75	Male and female	≥15	<15
COSMOS [52]	Observational	2004–2005	LDCT	5	1,2,3,4,5	NR	2011	Diameter and volume	2.5 mm	50–85	Male and female	≥20	<10
UKLS [39]	RCT	2011–current	LDCT	1 (Wald single screen design)	1	1.5	2013	Volume and diameter	1	50–75	Male and female	Target population with 5% risk of developing lung cancer in 5 years selected using Liverpool Lung Project risk prediction model (multiple variables)	

[a] The baseline screening year has been designated year 1

[b] The NELSON trial has since included a fourth round at year 5 of screening with LDCT (R Vliegenthart, oral communication, January 2011)

Table 2 Published results from current lung cancer screening trials using low-dose computed tomography. *NR = Not reported*

Trials	NLST [17]			NELSON [23]		DLCST [30]	DANTE [31, 33]		ITALUNG [32]	Depiscan [29]
Screening round	1	2	3	1	2	1	1	3	1	1
No. recruited	53454			15822		4104	2472		3206	765
No. screened in LDCT arm	26309	24715	24102	7557	7289	2052	1276	1276	1406	336
Positivity rate (%)[a]	27.3	27.9	16.8[c]	2.6	1.8	8.7	15.6	27.5	30.3	24.1
No. of lung cancers in LDCT arm	270	168	211	70	54	17	28	60	21	8
Lung cancer detection rate (%)	1.0	0.7	0.9	0.9	0.5	0.8	2.2	4.7	1.5	2.4
Stage I cancer(%)	63.0[d]			63.9	73.7	53	57[f]	2.6	0.7	0.9
Invasive procedures (%)[b]	1.7	1.1	1.3	1.2	0.8	1.2	4.2	7.5	2.3	NR
% with no lung cancer	29.8[d]			27.2	21.3	32	18.9	NR	NR	NR
Positive predictive value (%)	NR	NR	NR	35.7	42.2	9.5	NR	NR	23.5	NR
Negative predictive value (%)	NR	NR	NR	99.7[e]	99.9	NR	NR	NR	NR	NR
Interval cancers	NR	NR	NR	3	NR	NR	NR	NR	1	NR

[a] Positivity rate has been calculated as the number of positive results over the total number screened in the LDCT arm, expressed as a percentage

[b] The ways in which invasive procedures have been defined and reported varied between trials; as such, exact comparison of the rates of invasive procedures is difficult, and the figures provided are intended as an illustrative comparison

[c] An abnormality that was stable over 3 rounds could be considered negative by the NLST protocol

[d] These results reflect the cumulative rates of stage I lung cancer, and percentage of patients who underwent invasive procedures in whom lung cancer was not confirmed, respectively

[e] Negative predictive value takes into account 20 lung cancers found on subsequent 2-year follow-up

[f] The rate of stage I detected cancers increased to 71.4% for cases diagnosed by LDCT only

more. In cases demonstrating serial change, significant growth requiring action was defined as a VDT of <400 days. The choice of this VDT threshold was based on the observation that nodules with a VDT ≥400 days may represent overdiagnosed lung cancers, i.e. slower-growing lung cancers that would not have been detected in the

Table 3 Comparison of recommendations for follow-up of non-calcified solid nodules from the Fleischner guidelines 2005, the NLST protocol, and NELSON

Non-calcified solid nodule		Follow-up recommendations		
Diameter (mm)	Volume (mm^3)[a]	Fleischner guidelines 2005[b] [15]	NLST [14]	NELSON [21]
<4	<50	CT at 12 months; if unchanged, no further follow-up	None	LDCT at 12 months
4 5 6	50–500	CT at 6–12 months, then 18–24 months if unchanged	LDCT at 3,6,12 or 24 months, depending on lesion size and level of suspicion of malignancy	LDCT at 3 months
7 8		CT at 3–6 months, then 9–12 months, and 24 months if unchanged		
9 10		CT at 3,9 and 24 months if unchanged, PET, dynamic contrast-enhanced CT, and/or biopsy		
>10	>500		LDCT at 3,6,12 or 24 months, depending on lesion size and level of suspicion of malignancy; PET, dynamic contrast-enhanced CT, and/or biopsy	Referral to pulmonologist for work-up

[a] The positioning of the volume-ranges in this column in relation to the nodule diameters is meant to provide an approximate estimate of the corresponding volumes for the diameters for illustration only, calculated assuming a perfectly spherical nodule

[b] For the high-risk individual ≥35 years of age

Table 4 Nodule management protocol of the NELSON study [21]. *VDT = Volume Doubling Time*

Category	Definition	Management strategy			
Nodule size		Baseline Screening (Year 1)		Incidence screening (Years 2 and 4)	
		Definition of result	Action	Definition of result	Action
I	Benign characteristics	Negative	Screening CT in 1 year	Negative	Screening CT in 2 years
II	No characteristics of Category I or III	Negative	Screening CT in 1 year	Indeterminate	Follow-up CT in 1 year
III					
Solid	50–500 mm^3	Indeterminate	Follow-up CT in 3 months[d]	Indeterminate	Follow-up CT in 6–8 weeks[d]
Solid, pleural-based	Minimum diameter[b] 5–10 mm				
Partial solid	Solid component: 50–500 mm^3				
	Non-solid component: mean diameter ≥ 8 mm				
Non-solid	Mean diameter[c] ≥ 8 mm				
IV					
Solid	>500 mm^3	Positive	Work-up required	Positive	Work-up required
Solid, pleural-based	Minimum diameter[b] > 10 mm				
Partial solid	Solid component: >500 mm^3				
Growth[a]					
A	VDT>600 days	Negative	Screening CT in 1 year	Negative	Screening CT in 2 years
B	VDT 400–600 days	Indeterminate	Screening CT in 1 year	Indeterminate	Follow-up CT in 1 year[d]
C	VDT<400 days	Positive	Work-up required	Positive	Work-up required

[a] Growth was defined as a percentage volume change (PVC) ≥25%

[b] The minimum diameter was defined as the diameter perpendicular to the costal pleura

[c] The mean diameter was defined as the average of length and width

[d] At follow-up, if growth had occurred, the appropriate growth category (A, B or C) was assigned and the corresponding action taken

absence of screening, and hence would not be expected to contribute to lung-cancer specific mortality [22–24].

NELSON initially employed two independent readers for LDCT interpretation during the first and second rounds of screening, unlike the single reader in the NLST. However, subsequent analysis has suggested that an extra reader does not contribute to improved accuracy, and as such a switch to single reading in subsequent screening rounds was made [25].

Initial results from the NELSON trial have been encouraging: on baseline screening, the initial rates of negative and positive scans in the 7557 participants were 79.2% and 1.6% respectively, with 19.2% of participants having an indeterminate result. The strategy of follow-up and re-classification of these indeterminate nodules using volumetric assessment at 3 months significantly increased the rates of negative and positive scans to 97.4% and 2.6% respectively. Twenty lung cancers were detected in the 7361 negative subjects over 2 years of follow-up, while 70 lung cancers were detected in 196 participants with a positive result [23]. These results corresponded to negative and positive predictive values of 99.7% and 35.7% respectively.

The baseline screening lung cancer detection rate of 0.9% in NELSON is lower than that of other published trials [3, 7, 26–28], but the proportion of Stage I disease in both the baseline and second (i.e. first incidence) screening rounds was similar to that of other trials (63.9% and 73.7% respectively). Unlike the NLST, a conclusive mortality analysis for NELSON will probably not be released before 2012.

Other trials

Several European trials have published or presented an initial design, and/or baseline results, with the promise of results from further screening rounds in the future (Table 1).

The Depiscan study, performed in France, has been the sole European trial to date to adopt the NLST design of comparing LDCT to chest radiography screening, and was intended as a pilot on which a larger trial (Grandepiscan) could be based [29].

Two other RCTS besides NELSON, namely the Danish Lung Cancer Screening Trial (DLCST) and the Italian Lung Cancer Computer Tomography screening trial (ITALUNG), are also comparing LDCT against usual care with no other form of screening. The DLCST, initiated in 2004, has already revealed a lung cancer prevalence rate similar to the NELSON study, albeit with a lower percentage of Stage I disease [30].

The DLSCT and NELSON intend to amalgamate data, but a few differences between the two studies [20, 30] probably necessitate an individual, as well as a composite approach in the analysis of the data from these trials. A fourth RCT, the DANTE study, has adopted a 'hybrid' strategy of a baseline chest radiograph for all participants, who then underwent either CT screening or "usual care".

The DANTE and ITALUNG studies have reported lower percentages of stage I cancers at baseline analysis compared to earlier observational studies [31, 32]. A 3-year analysis of the DANTE trial revealed no significant difference in either all-cause or lung cancer-specific mortality between screened and control cohorts (2.0 versus 2.1%, and 1.6 versus 1.7%, respectively) [33]. The exclusive targeting of a male population in the DANTE trial, and its offer of a baseline CXR screen to both study arms, potentially limits extrapolation of its results to the general population. Although women do not appear to be more susceptible than men to the carcinogenic effects of smoking [34], their exclusion from this study may be poignant in the context of the rising female incidence of non-small cell lung cancer (NSCLC) [35], and the better prognosis of NSCLC independent of tumour stage in women [36].

The Multi-centric Italian Lung Detection trial (MILD) [37] and the Lung Cancer Screening Intervention study (LUSI) in Germany [38] are still in progress. The UK has been slow to instigate a national screening trial of its own. The pilot study of a proposed nationwide multicentre trial comparing LDCT to usual care is currently finally underway, based on the NELSON approach. However, a higher risk cohort will be targeted, and randomised to a single baseline LDCT examination (unless follow-up is required based on protocol recommendations) or no intervention, and followed for a total of 10 years [39].

The initiation of these other trials across Europe is indicative of a more or less concerted and collaborative effort to prove the effectiveness of LDCT-based lung cancer screening beyond reasonable doubt. Such collaboration, whether national or international, can facilitate the formidable and expensive task of determining the effectiveness and desirability of population-based screening in several ways, as outlined in Box 1. However, differences in healthcare systems, distribution and costs of health provision, risk profile and current lung cancer survival mean that results from one nation are not necessarily transferable to another.

Box 1 Potential benefits of collaborative efforts in cancer screening

1. Pooled dataset can be accumulated
   → large numbers of participants required to demonstrate a statistically significant benefit achieved more quickly
2. Countries with limited financial resources or small populations can still gain screening expertise
3. Easier comparison of trials with agreed shared characteristics e.g. quality assurance, minimum consensus datasets.

The future of lung cancer screening

Molecular and genetic biomarkers that can aid the detection of early lung cancers are possible future screening modalities that are as yet unrealised. However, this field is rapidly advancing with progress being made with DNA-methylation-based markers in NSCLC [40], proteomic analysis [41], and breath analysis of volatile compounds and exhaled breath condensate [42]; these offer some hope for non-invasive testing methods, that could obviate the need for LDCT and its attendant radiation in the future. For now, however, the multiple serum and sputum samples being opportunistically collected from subjects in the multiple LDCT trials will provide a rich source of material for future analysis.

Reinforced observations in the management of the indeterminate nodule

Data from some of the current screening trials can, with important caveats, inform practical non-invasive strategies for the management and follow up of indeterminate NCNs found in everyday radiological practice. The Fleischner Society has already used data from cohort trials such as the Early Lung Cancer Action Project (ELCAP) to construct their recommendations for the management of such nodules in 2005 (Table 3) [15]. However, such screening-derived information is inevitably more applicable to a high-risk population, where the approach to a suspicious nodule may be appropriately more aggressive than warranted in a low-risk individual (e.g. a 20-year old non-smoker). In clinical practice, such an approach would lead to an unacceptably large number of benign lesions being surgically resected. Strategies that maximise malignant nodule detection while minimising unnecessary invasive diagnostic procedures, and so avoid undesirable negative effects on patient morbidity, emotional anxiety and cost, are therefore welcome.

For the most part, the newer trials have reinforced current thinking with respect to four interdependent questions that are key to a nodule management strategy. These are:

1. What characteristics reliably distinguish a benign from a malignant nodule?
2. What factors influence variability in nodule measurement?
3. How variable is the detection of nodule growth?
4. What is the likelihood that an invasive procedure will be necessary?

Another question, regarding cost-effectiveness, is also important but difficult to extrapolate from the screening trial costings to the clinical situation of an individual with a lung nodule.

1. What characteristics reliably distinguish a benign from malignant nodule?

Size-based characteristics

Size at baseline screening

All the trials currently running have incorporated ELCAP-like strategies to manage NCNs based on the size of nodules at the baseline CT; this is logical because good evidence exists for a strong correlation between size and risk of malignancy [43]. These trials have therefore made size an important discriminator. The diameter threshold beyond which more aggressive work-up is recommended varies between 10 mm in the NLST [14] and NELSON [21], to 20 mm in the DANTE trial [31], and a volume >500 mm^3 in NELSON triggered further work-up.

Growth at subsequent follow-up

- Measuring growth using diameter

  The NLST, DLCST, DANTE and ITALUNG have used nodule diameter as the main (but not only) discriminator in nodule categorisation, as diameter remains a convenient, universally accessible way of assessing size [14, 30–32]. There are two limited inferences from results published thus far: (a) the majority of nodules under 10 mm are benign, reaffirming previous observations [5], and (b) the probability that a nodule will demonstrate growth on diameter alone is small. The high rate of false positive results in the NLST so far (between 95% and 98%), and the small proportion (1.6%) of participants with growing nodules that proved to be lung cancer at baseline screening in the ITALUNG trial, underscore these conclusions. The correlation between the exact sizes of nodules and those that ultimately proved to be lung cancer in the NLST, DANTE and ITALUNG has not yet been published.
- Measuring growth using volume

  It is possible that volumetric surveillance of nodules could allow less frequent CT examinations than currently recommended by the Fleischner guidelines, based on some of the screening trial data. Such surveillance is the main method of growth assessment in the NELSON, DLCST and MILD trials, where growth is defined as a percentage volume change of ≥25%. A prerequisite of this method is the availability of multidetector CT. The NELSON study, for instance, has so far demonstrated that following up nodules 50–500 mm^3 (corresponding to diameters of 4.6–9.8 mm, assuming a spherical shape) with a CT in 3 months resulted in 91.8% of these indeterminate nodules being reclassified as negative [23]. Furthermore, the NELSON study has confirmed that significant growth may also occur in benign lesions; 58/68 (85%) nodules with a positive VDT of <400 days after 3 months were benign in a sub-analysis [44].

Non-size based characteristics

Morphology and location

Analyses of the screening data have reinforced previous notions of malignant and benign differentiation using morphological criteria [45]. In a subgroup evaluation of the NELSON study, Xu et al. have found that in 469 solid intraparenchymal NCNs, a lobulated or spiculated margin, and an irregular (as opposed to a polygonal) shape increased the likelihood of malignancy in the 141(30%) nodules >50 mm^3 [46]. The same group have also described a new observation: the complete absence of malignancy in nodules that are either smooth, or pleural-based, juxtavascular or fissure-attached [44]. On this basis, they recommend that such nodules require further follow-up at 1 year only.

Density

Subsolid and non-solid nodules constitute the minority of nodules detected in the newer screening trials. The frequency of malignancy in such nodules is higher [47], but their growth rate is slower [48]. Until recently, neoplasia in such nodules corresponded to a spectrum of pathological lesions encompassing atypical adenomatous hyperplasia (AAH), bronchioloalveolar carcinoma (BAC) and mixed subtype adenocarcinoma [49]. This pathological classification has just been revised [50]. As such, further work on the methods of measurement and follow-up for these lesions on CT will probably be needed to better reflect the updated classification. Ultimately, separate guidelines for subsolid nodule management, such as that already proposed by Godoy et al. in 2009 [51], will need to be agreed, and will require validation.

Biological activity

The current trials have reinforced the presently limited role of positron emission tomography (PET) and PET-CT with

F-18 fluoro- 2-deoxyglucose (FDG) in the work-up of non-solid NCNs and solid NCNs <10 mm. Both the ITALUNG and COSMOS studies, for instance, mandated PET and PET-CT respectively in solid NCNs >8 mm. Veronesi and colleagues found that the diagnostic sensitivity of PET-CT in such cases was 88%, but increased to 100% for solid NCNs >10 mm, in an analysis of the COSMOS study [52].

2. What factors influence variability in nodule measurement?

There is substantial inter- and intraobserver variation in single and two-dimensional measurements, particularly for nodules <10 mm [53, 54]. Volumetric software-derived measurements demonstrate less variation [55, 56], although this can still occur for a variety of reasons [57–61]. Segmentation of a nodule attached to the pleura or vessels is also difficult with current software packages. Analysis of selected NELSON data has suggested that interobserver variability of semiautomated volumetric measurements of solid nodules completely surrounded by lung also occurs, most frequently due to irregular shape or margins [62]. Variability is further affected by CT reconstruction parameters, with a more recent NELSON-based analysis demonstrating that the most repeatable measurements are obtained with 1 mm section thickness and a soft reconstruction kernel [63].

3. How variable is the detection of nodule growth?

The current screening data suggests that nodule growth can be detected with high consistency [64, 65]. In an analysis of 100 nodules selected at random from the NLST, Singh et al. have found that nine test readers detected the presence of growth, or any type of change, 90% and 97% of the time respectively within 1 year, in the 11 NCNs that proved to be lung cancer. However, there was only moderate overall agreement between readers in the assessment of growth in all nodules (i.e. including those that proved to be non-malignant) [64].

4. What is the likelihood that an invasive procedure will be necessary?

Based on the published results of the trials so far (Table 2), the rate of invasive procedures employed as part of various nodule management protocols is between 0.8% and 7.5%. This is lower than the previously reported rate of 28 of 233 (12.1%) patients undergoing biopsy in ELCAP, using their original protocol recommending invasive investigation of NCNs over 11 mm, with possible invasive investigation considered for nodules 6–10 mm in size [66].

Over a quarter of these procedures may reveal benign disease. In a recent meta-analysis of the trial literature, including results from the Depiscan, DANTE, ITALUNG, DLCST, and LSS studies, among others, Gopal et al. concluded that one unnecessary thoracotomy would be performed for every 250 subjects screened for lung cancer with LDCT [67].

Thus, the knowledge gleaned from the screening trials at present serves to reinforce and refine, rather than replace, existing nodule management guidelines.

Conclusion

Screening for lung cancer using low dose computed-tomography remains the focus of several randomised control trials. Preliminary results from these trials, in particular the NLST, have been encouraging. The release of cumulative, and more definitive, results over the next 5 years should answer the question of whether the introduction of lung cancer screening using LDCT is a desirable public health imperative in a particular country and, as a spin-off, provide further practical insights into the management of the indeterminate pulmonary nodule.

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