favourable, we do not know if this is a valid method of predicting outcome and response in SUV is not yet a competitor to the established RECIST criteria for tumour response.[23 24]

A key development in lung cancer imaging occurred in November 2010 when the US National Cancer Institute announced that the National Lung Screening Trial, a randomised trial of low-dose CT versus chest radiography, had achieved its primary end point of a reduction in mortality of 20% in the CT arm and has therefore been stopped.[25] The trial, that enrolled 53 456 people, is the only screening trial to show a mortality benefit. The full publication will appear in the next few months and report important secondary outcomes including cost-effectiveness and harms. The other ongoing studies with different designs and in different healthcare systems, and may be important in determining the best approach to screening.[16–18] With this important development it seems that unprecedented major improvements in mortality from lung cancer are achievable and with this comes the certainty that the problem of the small pulmonary nodule will become increasingly common.

Competing interests I am lead physician on the UKLS trial.

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REFERENCES

1. **Alves Fliho M.** Manoel de ABREU, M.D., 1892–1962. *Am J Roentgenol Radium Ther Nuclear Med* 1962;**87**:1167–9. ISSN 0002–9580.
2. **Baldwin DR,** Eaton T, Kolbe J, *et al*. Management of solitary pulmonary nodules: how do thoracic computed tomography and guided fine needle biopsy influence clinical decisions? *Thorax* 2002;**57**:817–22.
3. **Chang CY,** Tzao C, Lee SC, *et al*. Incremental value of integrated FDG-PET/CT in evaluating indeterminate solitary pulmonary nodule for malignancy. *Mol Imag Biol* 2010;**12**:204–9.
4. **Herder GJ,** van Tinteren H, Golding RP, *et al*. Clinical prediction model to characterize pulmonary nodules: validation and added value of 18Ffluorodeoxyglucose positron emission tomography. *Chest* 2005;**128**:2490–6.
5. **Sortini D,** Maravegias K, Feo CV, *et al*. Repeat needle biopsies combined with clinical observation are safe and accurate in the management of a solitary pulmonary nodule. *Cancer* 2005;**104**:664–5.
6. **Laroche C,** Fairbairn I, Moss H, *et al*. Role of computed tomographic scanning of the thorax prior to bronchoscopy in the investigation of suspected lung cancer. *Thorax* 2000;**55**:359–63.
7. **Kramer H,** Groen HJ, Kramer H, *et al*. Current concepts in the mediastinal lymph node staging of non small cell lung cancer. [Review] [97 refs]. *Ann Surg* 2003;**238**:180–8.
8. **Gould MK,** Kuschner WG, Rydzak CE, *et al*. Test performance of positron emission tomography and computed tomography for mediastinal staging in patients with non-small-cell lung cancer: a meta-analysis. [Review] [109 refs]. *Ann Intern Med* 2003;**139**:879–92.
9. **De Wever W,** Meylaerts L, De Ceuninck L, *et al*. Additional value of integrated PET-CT in the detection and characterization of lung metastases: correlation with CT alone and PET alone. *Eur Radiol* 2007;**17**:467–73.
10. **Kelsey CR,** Marks LB, Hollis D, *et al*. Local recurrence after surgery for early stage lung cancer: an 11-year experience with 975 patients. *Cancer* 2009;**115**:5218–27.
11. **Wisnivesky JP,** Arciniega J, Mhango G, *et al*. Lymph node ratio as a prognostic factor in elderly patients with pathological N1 non-small cell lung cancer. *Thorax* 2011;**66**:287–93.
12. **Fischer BM,** Mortensen J, Hansen H, *et al*. Multimodality approach to mediastinal staging in non-small cell lung cancer. Faults and benefits of PET-CT—a randomised trial. *Thorax* 2011;**66**:294–300.
13. **Lim E,** Baldwin D, Beckles M, *et al*. Guideline on the radical management of patients with lung cancer. *Thorax* 2010;**65**(Suppl III):iii1–27.
14. **Annema JT,** van Meerbeeck JP, Rintoul R, *et al*. Mediastinoscopy vs Endosonography for mediastinal node staging of lung cancer: a randomised trial. *JAMA* 2010;**304**:2245–52.
15. **van Klaveren RJ,** Oudkerk M, Prokop M, *et al*. Management of lung nodules detected by volume CT scanning. *N Engl J Med* 2009;**361**:2221–9.
16. **Pedersen JH,** Ashraf H, Dirksen A, *et al*. The Danish Randomized Lung Cancer CT Screening Trial—Overall Design and Results of the Prevalence Round. *J Thorac Oncol* 2009;**4**:608–14.
17. **Infante M,** Cavuto S, Lutman F, *et al*. A Randomized Study Of Lung Cancer Screening With Spiral Computed Tomography: three-year results from the DANTE trial. *Am J Respir Crit Care Med* 2009; **180**:445–53.
18. **Ashraf H,** Dirksen A, Loft A, *et al*. Combined use of PET and volume doubling time in lung cancer screening with low dose CT. *Thorax* 2011;**66**:315–19.
19. **Gould MK.** Evaluation of screening-detected lung nodules: minimising the risk of unnecessary biopsy and surgery. *Thorax* 2011;**66**:277–79.
20. **Baldwin DR,** Duffy SW, Wald NJ, *et al*. *United Kingdom Lung Screen (UKLS) Nodule Management Protocol: Modelling of a Single Screenin Randomised Controlled Trial of Low-Does CT Screening for Lung Cancer*.
21. **MacMahon H,** Austin JH, Gamsu G, *et al*; Fleischner Society. Guidelines for management of small pulmonary nodules detected on CT scans: a statement from the Fleischner Society. *Radiology* 2005;**237**:395–400.
22. **Berghmans T,** Dusart M, Paesmans M, *et al*. Primary tumor standardized uptake value (SUVmax) measured on fluorodeoxyglucose positron emission tomography (FDG-PET) is of prognostic value for survival in non-small cell lung cancer (NSCLC): a systematic review and meta-analysis (MA) by the European Lung Cancer Working Party for the IASLC Lung Cancer Staging Project. [Review] [46 refs]. *J Thorac Oncol* 2008;**3**:6–12.
23. **Therasse P,** Arbuck SG, Eisenhauer EA, *et al*. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;**92**:205–16.
24. **Wong CY,** Schmidt J, Bong JS, *et al*. Correlating metabolic and anatomic responses of primary lung cancers to radiotherapy by combined F-18 FDG PET-CT imaging. *Radiat Oncol* 2007;**2**:18.
25. http://www.cancer.gov/newscenter/pressreleases/NLSTresultsRelease.

Evaluation of screening-detected lung nodules: minimising the risk of unnecessary biopsy and surgery

Michael K Gould

Screening for lung cancer has a long and controversial history. Successful screening is predicated on two fundamental principles.[1] First, the screening test should be able to detect disease in an early preclinical phase before symptoms develop. Second, treatment should be available and more effective when provided during the preclinical phase. On the surface it would appear that screening for lung cancer passes both of these tests, given our experience with treating 'early' versus 'late' stage lung cancer that is clinically detected. However, if we acknowledge that at least some cases of clinically detected stage I and II lung cancer might represent disease that is relatively indolent biologically as opposed to 'early', then the possibility exists that early detection will not alter the natural history of lung cancer and result in more frequent cure. Fortunately, the hypothesis that lung cancer screening with CT scanning reduces mortality is currently being evaluated in several large randomised controlled trials in both the USA and Europe.[2–6]

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Another set of prerequisites for any screening programme is that both the screening test and any downstream testing should be convenient for patients, relatively inexpensive and without a high risk of complications. Recent attention has focused on previously discounted risks from the radiation exposure that are associated with undergoing CT screening and follow-up.[7] Smith-Bindman *et al* estimated that the median effective radiation dose associated with a single non-contrast CT examination of the chest (8 mSV) was approximately equal to that of 117 chest x-rays and that, in 40-year-old women, one radiation-induced cancer would ultimately develop for every 720 who underwent CT.[8] In a population-based analysis, Berrington de Gonzalez *et al* calculated that the approximately 72 million CT scans performed in the USA in 2007 would ultimately be responsible for 29 000 future radiation-induced cancers including 4100 related to CT scans of the chest.[9]

Other downstream risks associated with CT screening for lung cancer include complications of surgery and non-surgical biopsy. CT-guided needle biopsy is generally regarded as safe, but pneumothorax requiring chest tube placement occurs in about 5% of cases.[10] Likewise, while fatal complications of video-assisted thoracoscopic wedge resection are infrequent (<1%), persistent air leaks and postoperative pneumonia can complicate 5–10% of cases.[11]

In this context, anything that can be done to minimise complications associated with screening or downstream testing will help tilt the balance in favour of benefits over harms. For over 10 years, beginning with the Early Lung Cancer Action Project,[2] studies of lung cancer screening have implemented follow-up protocols that attempt to minimise downstream testing and its potential complications. However, practices for follow-up of incidentally-detected or screening-detected nodules have not been standardised for use in clinical settings or prospectively validated. The objective of follow-up is to identify malignant nodules promptly to permit timely surgical resection while minimising the frequency of unnecessary surgery (or biopsy) in the overwhelming majority of patients who have benign nodules or the smaller group of patients with relatively indolent malignant nodules that may represent cases of overdiagnosis.

In the absence of evidence-based recommendations for follow-up, the current standard of care is to use the expert consensus-based recommendations of the Fleischner Society[12] which specify the frequency and duration of CT follow-up depending on the presence of risk factors for lung cancer and the size of the nodule. In general, the recommended follow-up is more aggressive for patients with risk factors and larger nodules because the prevalence of malignancy is higher in these groups and because it is more difficult to detect growth in smaller lesions over shorter time intervals. This difficulty is related to both technical and human factors. Because one doubling in volume corresponds to a 26% increase in diameter, it is nearly impossible in most clinical practice settings reliably to identify growth corresponding to one doubling in volume in a nodule that initially measures 4 mm in diameter, which would measure 5 mm in diameter after one doubling time.

The concept of volume doubling time (VDT) was introduced first by Collins *et al*[13] in a study of pulmonary metastases and later studied empirically in patients with lung nodules by Nathan *et al*,[14] Weiss *et al*,[15] Steele and Buell[16] and Geddes.[17] Importantly, the concept of VDT assumes that the tumour grows exponentially, which is to say that the tumour doubles in volume at a constant rate. While there is some empirical evidence to support the exponential growth hypothesis for nodules when they measure between 10 mm and 30 mm in diameter, it is likely that growth is even faster for tumours earlier in their natural history, while growth is probably slower than exponential when tumours become very large and outgrow their blood supply. Computer-assisted methods of volumetric analysis were initially described and applied to the problem of characterising small pulmonary nodules over 10 years ago,[18 19] but have not been widely adopted in clinical practice.

More recently, functional or molecular imaging with positron emission tomography (PET) has gained favour in thoracic oncology for characterisation of (primarily) incidentally detected lung nodules, initial staging of patients with non-small cell carcinoma and prognostication. Interestingly, greater uptake of fluorodeoxyglucose (FDG) in a malignant nodule has been shown be associated with faster growth rates[20] and worse survival.[21] The association between FDG uptake and growth suggests that PET might be used to distinguish between malignant and benign nodules. An important limitation of this approach is that PET is thought to be less sensitive for identifying malignancy in nodules measuring <8–10 mm in diameter.

Ashraf *et al* have attempted to capitalise on technological advances in computer-assisted measurement and molecular imaging to improve the characterisation of screening-detected lung nodules,[22] presumably in an effort to reduce the rate of false positive screening evaluations and thereby reduce the risk of unnecessary biopsy or surgery **(*see page 315*)**. In this retrospective analysis of data from the Danish Lung Cancer Screening Trial, they used semiautomated computer software (accompanied by manual measurements in a small number of nodules) that enabled them to estimate growth rates based on measurements performed on the initial scan in comparison with a follow-up scan 3 months later. In addition, they reviewed the results of PET imaging performed within 3 months of nodule detection. Subjects included 53 participants with 54 indeterminate pulmonary nodules measuring up to 20 mm in diameter, including 35 solid nodules, 9 semi-solid nodules and 10 ground glass opacities. In this sample the prevalence of malignancy was 37%. Almost 60% of the nodules were identified during the baseline (prevalence) round of screening.

The authors found that both greater FDG uptake and shorter VDT were significantly associated with malignancy. Using thresholds of equal to or greater than the mediastinal blood pool for FDG uptake and less than 365 days for VDT, they found that either technique, when evaluated in isolation, identified malignancy with a sensitivity of 70% (95% CI 48% to 85%) and a specificity of 91% (95% CI 77% to 97%). In a multivariable analysis, both FDG uptake and VDT were independently associated with malignancy. Furthermore, all 10 nodules with high FDG uptake and short VDT were malignant, while only 2 of 30 nodules (7%) with low FDG uptake and long VDT were malignant.

Although larger confirmatory studies are needed, these data suggest that patients with rapidly growing hypermetabolic nodules should be referred immediately for surgical resection, provided that three additional conditions are met: (1) the nodule is located in the periphery and accessible via video-assisted thoracoscopy (VATS); (2) there is no medical contraindication to VATS wedge resection; and (3) the suspicion of endemic mycosis or tuberculosis is not high. In such cases, many surgeons are correct to argue that needle biopsy adds little to the evaluation.

For patients with nodules that are not hypermetabolic and have a long VDT, I agree with Afshar *et al* that a follow-up scan in 1 year is probably sufficient provided that the patient understands and

accepts the uncertain risks associated with delayed diagnosis and treatment of malignancy that will occur in as many as 21% of cases (the upper limit of the 95% CI around the false negative rate of 7%). Recent results from the Dutch-Belgian randomised trial of lung cancer screening, although not directly comparable, support this approach because <0.3% of participants with a negative evaluation that included volumetric measurement were eventually found to have lung cancer in this study.[23] In patients with larger nodules or equivocal findings, a follow-up scan in 3–6 months should still be considered. In order to minimise radiation exposure and the attendant risks highlighted by Smith-Bindman and Berrington de Gonzalez, a low-dose thin-section unenhanced protocol with limited longitudinal coverage should be employed, as suggested by the Fleischner Society.[12] Why this important and sensible recommendation has not been widely implemented in clinical practice is a worthy, indeed urgent, topic for quality improvement committees.

Lastly, for patients with discordant findings on FDG-PET and volumetric analysis, the likelihood of cancer is intermediate to high (57%, 95% CI 33% to 79%). Ashraf *et al* recommend repeating the CT scan in 3 months, but this seems redundant and unnecessary if rapid growth has already been identified. Likewise, increased FDG uptake on PET suggests that one is likely to be dealing with an active infectious or inflammatory process that requires further investigation, even if the finding is technically a false positive one for malignancy. I would therefore recommend tissue sampling by needle biopsy or bronchoscopy in this group, although it would not be wrong to perform VATS wedge resection in patients with larger nodules or borderline FDG uptake or VDT.

A remaining question is to what extent these findings apply to patients in current practice with incidentally detected lung nodules. It is not unreasonable to consider these patients as being similar to those with nodules that are detected during the prevalence round of CT screening. Not surprisingly, malignancy was significantly more likely in prevalent nodules than in incident nodules in the study by Ashraf *et al*, although the difference was not significant after adjustment for FDG uptake and VDT. Nevertheless, the lower prevalence of malignancy among nodules detected during baseline screening suggests that the combined criteria of FDG uptake and VDT will have a better negative predictive value and worse positive predictive value when applied to patients with incidentally detected nodules.

Going forward, practices for characterising small pulmonary nodules should be evaluated in randomised controlled trials in which the intervention is compared with the current standard of care (Fleischner Society guidelines), so trade-offs between benefits and harms can be quantified for the benefit of patients and the clinicians who counsel and care for them. Such information is of immediate importance for managing patients with incidentally detected pulmonary nodules, but it will take on additional urgency if CT screening for lung cancer is ultimately found to be effective in reducing mortality.

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REFERENCES

1. **Obuchowski NA,** Graham RJ, Baker ME, *et al*. Ten criteria for effective screening: their application to multislice CT screening for pulmonary and colorectal cancers. *Am J Roentgenol* 2001;**176**:1357–62.
2. **Henschke CI,** McCauley DI, Yankelevitz DF, *et al*. Early lung cancer action project: overall design and findings from baseline screening. *Lancet* 1999;**354**:99–105.
3. **Swensen SJ,** Jett JR, Sloan JA, *et al*. Screening for lung cancer with low-dose spiral computed tomography. *Am J Respir Crit Care Med* 2002;**165**:508–13.
4. **Van Israel CA,** de Koning HJ, Draisma G, *et al*. Risk-based selection from the general population in a screening trial: selection criteria, recruitment and power for the Dutch-Belgian randomized lung cancer multi-slice CT screening trial (NELSON). *Int J Cancer* 2007;**120**:868–74.
5. **Infante M,** Lutman FR, Cavuto S, *et al*. Lung cancer screening with spiral CT baseline results of the randomized DANTE trial. *Lung Cancer* 2008;**59**:355–63.
6. **Pedersen JH,** Ashraf H, Dirksen A, *et al*. The Danish randomized lung cancer CT screening trial—overall design and results of the prevalence round. *J Thorac Oncol* 2009;**4**:608.
7. **Smith-Bindman R.** Is computed tomography safe? *N Engl J Med* 2010;**363**:1–4.
8. **Smith-Bindman R,** Lipson J, Marcus R, *et al*. Radiation dose associated with common computed tomography examinations and the associated lifetime attributable risk of cancer. *Arch Intern Med* 2009;**169**:2078–86.
9. **Berrington de Gonza lez A,** Mahesh M, Kim K-P, *et al*. Projected cancer risks from computed tomographic scans performed in the United States in 2007. *Arch Intern Med* 2009;**169**:2071–7.
10. **Wahidi MM,** Gover JA, Goudar RK, *et al*. Evidence for the treatment of patients with pulmonary nodules: when is it lung cancer? An ACCP evidence-based clinical practice guideline (2nd edition). *Chest* 2007;**132**:94–107S.
11. **Gould MK,** Wiener RS. Shared decision making in patients with pulmonary nodules. pulmonary, critical care, *Sleep Update (PCCSU)* 2009;**23**(Lesson 19). http://www.chestnet.org/accp/pccsu (accessed 17 Aug 2010).
12. **MacMahon H,** Austin JH, Gamsu G, *et al*. Guidelines for management of small pulmonary nodules detected on CT scans: a statement from the Fleischner Society. *Radiology* 2005;**237**:395–400.
13. **Collins VP,** Loefler RK, Tivey H. Observations on growth rates of human tumors. *Am J Roentgenol* 1956;**76**:988–1000.
14. **Nathan MH,** Collins VP, Adams RA. Differentiation of benign and malignant pulmonary nodules by growth rate. *Radiology* 1962;**79**:221–31.
15. **Weiss W,** Boucot KR, Cooper DA. Growth rate in the detection and prognosis of bronchogenic carcinoma. *JAMA* 1966;**198**:1246–52.
16. **Steele JD,** Buell P. Asymptomatic solitary pulmonary nodules: host survival, tumor size, and growth rate. *J Thorac Cardiovasc Surg* 1973;**65**:140–51.
17. **Geddes DM.** The natural history of lung cancer: a review based on rates of tumor growth. *Br J Dis Chest* 1979;**73**:1–17.
18. **Yankelevitz DF,** Reeves AP, Kostis WJ, *et al*. Small pulmonary nodules: volumetrically determined growth rates based on CT evaluation. *Radiology* 2000;**217**:251–6.
19. **Winer-Muram HT,** Jennings SG, Tarver RD, *et al*. Volumetric growth rate of stage I lung cancer prior to treatment: serial CT scanning. *Radiology* 2002;**223**:798–805.
20. **Higashi K,** Ueda Y, Yagishita M, *et al*. FDG PET measurement of the proliferative potential of non-small cell lung cancer. *J Nucl Med* 2000;**41**:85–92.
21. **Berghmans T,** Dusart M, Paesmans M, *et al*. Primary tumor standardized uptake value (SUVmax) measured on fluorodeoxyglucose positron emission tomography (FDG-PET) is of prognostic value for survival in non-small cell lung cancer (NSCLC): a systematic review and meta-analysis (MA) by the European Lung Cancer Working Party for the IASLC Lung Cancer Staging Project. *J Thorac Oncol* 2008;**3**:6–12.
22. **Ashraf H,** Mortensend J, Dirksen A, *et al*. Combined use of PET and volume doubling time in lung cancer screening with low dose CT. *Thorax* 2011;**66**:315–19.
23. **Van Klaveren RJ,** Oudkerk M, Prokop M, *et al*. Management of lung nodules detected by volume CT scanning. *N Engl J Med* 2009;**361**:2221–9.