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Imaging in lung cancer: recent advances in PET-CT and screening

David R Baldwin

Lung cancer is probably the most intensely imaging dependent sub-specialty within respiratory medicine. Historically chest physicians have had close involvement with imaging. The development of mass miniature chest radiographs is attributed to Manuel Dias de Abreu, a Brazilian pulmonologist¹ and in conjunction with providing a tuberculosis service, chest physicians have reported mass miniature chest radiographs, independent of radiologists. Although the latter is now neither appropriate or indeed the case, in lung cancer, chest physicians along with other

clinicians within the cancer multidisciplinary team (MDT) rely heavily on imaging and, aided by the accessibility of images afforded by the Picture Archiving and Communication System (PACS) are becoming increasingly expert. Furthermore, chest physicians are using imaging more for their own diagnostic and therapeutic procedures; in particular transthoracic and endobronchial ultrasound. It is axiomatic therefore that a radiologist who is firmly committed to the cancer MDT makes an enormous contribution to an effective care pathway. Thus any new development in imaging will have a considerable impact on lung cancer clinicians' clinical practice whether they deal principally with diagnosis and staging (chest physicians and radiologists) or treatment (oncologists and thoracic surgeons).

Over the last 10 years there have been important developments in the lung cancer care pathway from early diagnosis through diagnosis and staging and to treatment, many of these driven by improved imaging. It is necessary to have a clear idea about the performance of an imaging test (or any test) to understand how a result should influence management. A self-evident point about imaging tests is that because they do not sample tissue, they tend to yield a greater number of false positive and false negative results and therefore have a lower specificity and negative predictive value compared with minimally invasive tests. Indeed, as imaging tests improve their sensitivity the place of tests that provide biopsy samples is more about excluding benign disease than confirming malignancy.^{2–5}

The central role of multi-detector CT (MDCT) with contrast administration as a test early on in the lung cancer diagnostic and staging pathway is now firmly established and is essential in most patients to guide the next diagnostic test.⁶ Thus most fast-track lung cancer services ask for CT scans prior to the first outpatient

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consultation. CT is a sensitive test to detect lung cancer but not specific, especially if staging information is required.^{7–10} Similarly, the added information provided by FDG-PET scanning has led to universal use in lung cancer pathways, especially where patients are potentially suitable for treatment with curative intent. However, as data accumulate, the limitations of this test are becoming clear. PET-CT is a good example of a test that has a high sensitivity for lung malignancy^{8, 9} and is good at excluding macroscopic disease (except in the brain). However, despite a negative PET-CT, there remain approximately 20% of patients who present with metastatic disease after what was felt to be curative treatment of early stage disease (arguably important to include when classifying patients who are ‘true negatives’).¹⁰ PET-CT is also a sensitive test for lymph node involvement, which is, as we are reminded in this issue of Thorax,¹¹ (*see page 287*) an important and independent prognostic factor. Studies have shown that a negative PET-CT of significantly enlarged nodes on CT (≥ 10 mm short axis) still carries a 15% risk of being a false negative.^{8, 9} A further paper in this issue has confirmed that PET-CT cannot be used to exclude nodal disease where nodes are enlarged on CT. However Fischer *et al*¹² (*see page 294*) also showed that where nodes are not significantly enlarged on CT, the false negative rate of PET-CT was only 4% (only one out of 29 patients). This finding provides strong support for the currently recommended approach that where there are no significantly enlarged lymph nodes on CT and no significant FDG uptake on PET, treatment with curative intent should be offered without further preoperative mediastinal staging but with systematic nodal dissection where treatment is surgical.¹³ When mediastinal nodes are large, further staging is clearly required, irrespective of the findings of PET-CT. A recent randomised trial of combined endobronchial and endoesophageal ultrasound needle aspiration (EBUS and EUS) versus mediastinoscopy has shown that the approaches are equivalent (and when combined better than either alone).¹⁴ The study by Fischer *et al* is supportive of these findings.¹² In the immediate future, decisions about which is offered and whether negative EBUS/EUS results are followed by surgical staging will depend on local expertise and audited test performance.

PET-CT may also provide important help in the vexed area of incidentally identified solitary pulmonary nodules. Small lung nodules are now encountered more frequently since the widespread use of

CTPA for investigation of suspected pulmonary embolism. Help with how to manage these incidentally found nodules is available from the CT screening studies that have published their preliminary findings using different, safer and more efficient follow-up protocols.^{15–17} In all of the published studies, including those with a high prevalence of lung cancer, there are many more benign than malignant nodules detected. PET-CT and measurement of volume doubling time (VDT) may serve to reduce repeat scans and reduce potential harm. The paper by Ashraf *et al*¹⁸ (*see page 315*) shows that, for lung nodules 5–15 mm diameter (non-solid up to 20 mm), PET-CT and VDT yield identical sensitivities and specificities (71% and 91% respectively) and that the combination of the two is better. However, in screening trials, costs and harms are essential considerations and so the authors’ recommendation to use VDT and PET as parallel tools in screening trials needs to be tested in trials capable of defining whether this approach improves cost effectiveness. Until these are available, the suggestion by Gould¹⁹ (*see page 277*) that malignancy should be assumed to be present if VDT is < 365 days and/or FDG uptake on PET-CT is greater than the mediastinal blood pool seems sensible. However, the routine use of PET-CT in very small nodules may add considerable cost for only a small incremental benefit.

The protocol for the first UK randomised controlled trial of the use of CT-screening for lung cancer (UKLS) is published in this issue of Thorax.²⁰ The management algorithm of detected lung nodules heavily relies on VDT but does include PET as part of the work-up once VDT is found to be < 400 days. This is thought to be the most cost-effective approach because PET-CT, expensive in the UK, is used as a downstream investigation for nodules that meet either baseline volume/size criteria or show a VDT of < 400 days. The study will measure the proportion of benign nodules that are evaluated by an invasive approach as part of the harms evaluation. From Ashraf *et al*, when VDT and PET were positive, malignancy was virtually certain but when they differed, the prevalence of malignancy was 57%, with 4 cancers being ‘missed’ by PET-CT and 4 by VDT. UKLS would thus miss some cancers by using VDT only in the screen. However, it is not known how these nodules that show no significant growth influence mortality, the main outcome measure of screening trials. Biologically they may be more likely to be indolent and therefore detected on subse-

quent screens at a stage when still curable. UKLS uses similar criteria to those used in the Dutch-Belgium CT screening study and is designed so that the mortality results of these, the largest of the European screening studies, can be reported together. The interim results of the NELSON study were reported in 2009¹⁵ and show that while most lung cancers were detected by this method, a proportion was detected at subsequent screening rounds. These were either incident nodules or those that were previously too small to characterise. The crucial question will be whether those cancers would be detected more economically by a longer interval between screens without missing potentially curable cancer.

Many centres in the UK use a modification of the Fleischner Society Guidelines on the management of solitary pulmonary nodules and this involves many repeat CT scans, the majority of which (at least 95%) will not detect cancer.²¹ The approach adopted by the use of low dose CT and measuring VDT may reduce the number of repeat scans and radiation dose, and is evidence-based, albeit in high-risk populations. Thus developments in imaging are again suggesting a new pathway—this time for the management of incidentally detected pulmonary nodules. As with other developments, the use of volume measurement software is likely to become widely available and the more straightforward algorithm will diminish confusion among those less familiar with the subject.

Clinicians and commissioners will be reassured that PET-CT improved staging accuracy in the per-protocol population,¹² and will be happy to accept the resultant reduced risk of futile Thoracotomy.³ Could there be additional benefits? One possibility is that the SUV provides independent prognostic information. There is accumulating evidence that it does,²² but the critical SUV level has not been defined nor is it clear how this information should alter management. For example, it may be that patients with complete resections and high SUV should have adjuvant chemotherapy as the potential for metastasis is high. In contrast, patients with low or intermediate SUV should perhaps have more aggressive treatment with curative intent than their lung cancer stage would ordinarily suggest as biologically these cancers may have less metastatic tendency. This additional information is likely to be particularly helpful in otherwise borderline patients being considered for potentially curative treatment with surgery or radical radiotherapy. Although a response in SUV following treatment is considered

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

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Screening for lung cancer has a long and controversial history. Successful screening

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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}