Individualised treatment in non-small cell lung cancer: precise tissue diagnosis for all?

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A number of key advances in the therapeutic management of lung cancer have signposted the need for substantial changes in the diagnostic pathway and techniques for patients with suspected lung cancer. Cell-type-specific agents are available to treat lung cancer and, together with new molecular markers, they can improve outcomes through individualised treatment regimens. For example, a prospective phase III trial of platinum-based chemotherapy in advanced non-small cell lung cancer (NSCLC) demonstrated that the combination of cisplatin/pemetrexed improved outcomes for patients with non-squamous tumours, but that cisplatin/gemcitabine was better in patients with squamous histology.[1] Bevacizumab, a monoclonal antibody to vascular endothelial growth factor, plus chemotherapy is a standard of care in advanced NSCLC but is contraindicated in squamous cell subtypes due to the association with life-threatening haemoptysis.[2] Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) are indicated in first and second-line treatment of advanced NSCLC but are more effective in female, non-smokers with adenocarcinoma, an effect most likely mediated by the presence of sensitising EGFR gene mutations.[3 4] Most recently, the National Institute for Health and Clinical Excellence (NICE) has approved the use of gefitinib (an EGFR TKI) in advanced NSCLC for patients demonstrating EGFR mutation positivity.[5] In addition, EGFR gene copy number by fluorescence in-situ hybridisation may also help to predict favourable outcomes with EGFR TKI or cetuximab-containing therapy.[6] EGFR mutation positivity may 'trump' the clinical phenotype as a predictor of response and improved survival following EGFR TKI, even in patients with a low performance score (PS 3, 4). A recent report describing first-line treatment with gefitinib in EGFR mutation-positive patients (50% with metastatic brain disease) demonstrated a response rate of 90% and a startling improvement in PS from 3, 4 to 0, 1 of 68% and 1-year survival of 63%.[7] Taken together with the recent NICE appraisal, it is clear that greater rates of tissue acquisition are required, even in some patients with poorer performance status, to facilitate both pathological and molecular characterisation.

Consequently, a nihilistic approach to obtaining a detailed pathological and molecular diagnosis is no longer justified. The relative inaccessibility of thoracic tumours coupled with high rates of comorbidity is often quoted as a barrier to obtaining lung cancer tissue for diagnosis. In the UK in 2008, the average rate of histological confirmation was 73%, ranging from 25% to 88% in different cancer networks. Fifty-five per cent of cancer networks (representing 64% of patients) did not achieve the proposed standard of 75% histological confirmation, with 15% of networks (~20% of patients) attaining less than 65% confirmation.[8] This huge variation in quality of care for patients with lung cancer is unacceptable. Indeed, the currently available therapeutic modalities argue for an increase in the proposed standard because clinically meaningful benefit can be derived for patients with poorer PS by well tolerated molecularly targeted agents.

How should respiratory physicians respond to the challenge of attaining a tissue diagnosis given the difficulties that comorbidity, poor PS and inaccessibility pose? A diagnosis of lung cancer is most commonly made by biopsy and lavage at fibreoptic bronchoscopy, a safe, well tolerated outpatient procedure carried out under conscious sedation.[9] Endobronchial disease will, however, be evident in only 30% of cases. Improved targeting of disease can be achieved by ensuring patients undergo CT before bronchoscopy[8] to facilitate distal blind biopsy of parenchymal lesions and transbronchial needle aspiration (TBNA) of accessible nodes, each avoiding further invasive tests when positive and possibly obtaining important pathological staging information. However, in the UK, this optimal diagnostic sequence does not occur in a quarter of patients,[8] further limiting diagnostic opportunities. In addition, small biopsy samples introduce inaccuracies in the assessment of histological subtypes,[10] and may be ameliorated in some cases by the use of endobronchial diathermy/ electrocautery, a simple, cheap and underused modality that facilitates the biopsy of bulky endobronchial disease while minimising the risk of significant haemorrhage.[11] All respiratory physicians performing bronchoscopy should be skilled and competent in these techniques.

Advances in bronchoscopic techniques have also facilitated the improved acquisition of tissue by extending the reach of the bronchoscope beyond the limits of conventional visibility. Linear endobronchial ultrasound (EBUS) TBNA provides accurate access to mediastinal and hilar lymph nodes providing both diagnostic and staging information.[12] In addition, EBUS TBNA can confirm the diagnosis of lung cancer in 77% of cases, with a diagnostic sensitivity of 82% (95% CI 69% to 91%) in central parenchymal lung lesions where previous bronchoscopy has been non-diagnostic.[13] Importantly, the procedure can be performed as an outpatient and without serious procedure-related complications. Radial EBUS transbronchial biopsy (TBB), which uses an ultrasound probe through the working channel of a normal 5 mm bronchoscope, can be used effectively in the diagnosis of peripheral pulmonary nodules. In a prospective randomised trial of 799 patients EBUS TBB demonstrated greater sensitivity (0.79 vs 0.55, p=0.0004) and accuracy (0.85 vs 0.69, p=0.0007) compared with conventional TBB for nodule lesions of less than 3 cm.[14] Furthermore, the use of guide sheaths, multiple biopsies and thinner bronchoscopes with EBUS TBB facilitates the successful biopsy of lesions smaller than 2 cm.[15–18] NICE approved EBUS TBNA in February 2008[19] and EBUS TBB in March 2010.[20] These safe outpatient techniques require an investment in technology and lead respiratory physicians in cancer

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centres should have access at least to EBUS and be competent in its uses. Whether they should routinely be applied to patients of poor performance status will depend heavily upon the efficacy of any proposed molecularly targeted therapy that predicates tissue biopsy. These advanced bronchoscopic procedures can be applied serially, if necessary, to patients with significant comorbidity and respiratory compromise, to facilitate small biopsy or cytological sampling, where no sample previously existed. The challenge for pathologists is to provide a robust morphological diagnosis on such material and to ensure sufficient residual sample for molecular typing if necessary.

The differential efficacy of the new targeted, biological agents highlights the practical importance of distinguishing adenocarcinoma from squamous cell carcinoma. The WHO classification (that does not incorporate immunohistochemistry) is unsuited to small bronchoscopic biopsies, or TBNA and cytology samples on which almost all patients are diagnosed and managed.[10] Unfortunately, the frequent heterogeneity and presence of undifferentiated areas in most lung cancers means that an accurate subtype is not always possible in small biopsy or cytology samples that may not be representative of the tumour as a whole. Of the NSCLC subtypes, only squamous cell, adenocarcinoma and occasional rare subtypes, can be reliably diagnosed in most but not all cases. Many of the categories cannot, including large cell carcinoma. The potential inaccuracy incumbent from small biopsy specimens is diminished by using a less specific 'non-small cell carcinoma' category, but this is not now appropriate. Where clear differentiation is not morphologically visible, tumours have been assigned a 'not otherwise specified' (NOS) category. In a recent US study reviewing lung cancers diagnosed over a 16-year period, the NOS rate appears to be increasing over the period, averaging 22%. For cytological diagnoses, the rate approaches 40%.[21] In a large UK region, NOS accounted for 40% of histological types in patients less than 75 years of age, increasing to 60% in patients over 75 years. Of particular concern is the association of NOS with no active treatment in 50–70% of patients receiving this histological classification.[22] The acceptance of less specific subtypes or high rates of NOS disadvantages lung cancer patients and exposes them to suboptimal treatments and ultimately inferior response rates and survival when compared with patients with specific histologies.

In an attempt to attain greater specificity, pathologists often resort to immunohistochemistry to refine a diagnosis and lung cancer multidisciplinary teams are familiar with the utility of TTF-1 in the differentiation of pulmonary and metastatic adenocarcinoma. The true morphological identity of NSCLC NOS can be approximated by a panel of immunohistochemistry markers (PAS-D, TTF-1, p63 and CK5/6) with an accuracy of approximately 80%.[23] This approach can reduce from 25% to approximately 7% the number of NSCLC NOS reports issued without a prediction of NSCLC subtype. The Royal College of Pathologists is currently reviewing its recommendations for the histological diagnosis of lung cancer, including the role of immunohistochemistry, and is due to report in 2010.

Exfoliative cytopathology is a well established pathological tool in lung cancer diagnosis, and is capable of increasing diagnostic accuracy, particularly for squamous cell and small cell carcinoma. Many centres utilise the direct manual smear, performed at the time of needle aspiration or brushing, but this method does limit the routine performance of immunohistochemistry and downstream molecular testing. Liquid-based cytology has the potential to reduce the amount of laboratory processing, preserve or increase the quality of cytological slides for morphological assessment and provide cell pellets for immunohistochemistry without compromising sample quality.[24] However, there is currently no standard operating procedure widely adopted in national or international practice. Cytological fine needle aspirates are increasing in frequency and attract greater significance in the diagnostic pathway (as minimally invasive procedures become established) and in serial sampling for molecular profiling. The ease of obtaining these samples will need to be balanced against the sufficiency of the sample provided by the technique—this is a new challenge with significant difficulties, and further research is needed to optimise the preservation and processing of cytological samples for diagnostic and molecular typing. This difficulty has been starkly highlighted by the demonstration of sensitising mutations in exons 18–21 of the EGFR tyrosine kinase domain and the current clinical need to genotype adenocarcinomas to ensure improved outcomes when receiving EGFR TKI.[25] Molecular profiling encompasses many different techniques with different sensitivities and specificities from differing source materials,[26 27] and these are being refined as genetic testing becomes commonplace in the clinic.

However, the suitability of a sample for molecular analysis should be assessed on a case-by-case basis and the availability of a cytological sample only should not preclude the need to obtain a tissue confirmation for more precise diagnosis, when there is clinical or therapeutic justification.

The era of molecularly targeted, personalised oncology has arrived. Patients with lung cancer deserve the improved outcomes that will follow precise molecular typing, but this will require patients to have adequate amounts of diagnostic tissue for these different techniques. It will require a sea-change in attitude among respiratory physicians, access to new diagnostic and staging techniques for many, and a possible revision to the diagnostic pathway that aims to confirm tissue diagnosis and stage in one procedure. It will require significant service planning and investment. Close collaboration is required between histopathologists, cytopathologists and geneticists, and increased numbers of appropriately trained pathologists and technicians may be needed. It is time to scan the horizon—advances in molecular typing and the likely need to perform serial lung cancer biopsies (that current techniques facilitate) should encourage widespread tissue banking to facilitate a correlation of clinicopathological data with the molecular natural history of treated lung cancer. It is time to abandon the 'NSCLC' category, to start making an increasingly precise diagnosis that enables our oncologists to provide targeted treatment for an improved prognosis to all patients—even those with metastatic disease and poor performance status. The central review of lung cancers, with reorganisation of existing services, may offer one solution.

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