

Changing roles for histology and cytology in the management of patients with lung carcinoma

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Published online October 2008

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ABSTRACT The examination of histological and cytological specimens plays a pivotal role in the diagnosis and staging of lung cancer. This review aims to describe why the correct choice of specimen type may be important in optimising patient management. Tissue biopsies obtained for diagnosis provide specimens that are the most highly sensitive for the diagnosis of malignancy and cell typing. In addition, they provide sufficient material for further detailed studies, either at the time of diagnosis or subsequently during the patient's management. Cytology specimens, in contrast, have generally lower sensitivities, are recognised to be prone to false positive errors and in many instances provide very limited material for detailed immunohistochemical studies. Cytology specimens will, however, have an increasingly important role in lung cancer staging with the development of minimally invasive endoscopic techniques for sampling mediastinal lymph nodes. Lymph node aspiration, either via the oesophagus or the bronchus, provides a highly sensitive method for the detection of metastatic carcinoma. Furthermore, this allows access to nodal groups not assessable by mediastinoscopy. In future, tissue biopsy for histological assessment should be seen as the 'gold standard' for primary diagnosis in lung cancer patients.

KEYWORDS Cytology, diagnosis, histology, lung cancer, staging

DECLARATION OF INTERESTS The author has spoken at meetings on respiratory cytology organised by Cytoc UK Ltd and KeyMed (Medical and Industrial Equipment) Ltd, but has received no remuneration or benefits in kind from this.

INTRODUCTION

Carcinoma of the lung presents a continuing problem in respiratory medicine and oncology, with little improvement in outcome for patients over the past few decades.^{1–3} The reasons for this are multifactorial and include delayed presentation, age and existing co-morbidities.^{4–6} It is vital that when patients do present with lung cancer they are diagnosed and staged so that rational management decisions can be made. Imaging techniques such as computed tomography (CT)^{7,8} and, more recently, CT combined with fludeoxyglucose positron emission tomography (FDG-PET)^{9–11} give valuable information regarding the diagnosis and stage of lung cancer, but it is widely accepted that tissue sampling from the primary lesion and/or sites of possible metastases is highly desirable in order to confirm the diagnosis and establish the cell type.^{12,13}

A wide range of specimens may be submitted to a pathology department for examination, depending on the site of the primary tumour in the lung or potential sites of metastases. The object of this paper is to review changing usage of histological and cytological specimens in the diagnosis and staging of lung cancer. The reasons behind this will be discussed, and potentially new important roles for cytology will be highlighted. The ultimate aim is to encourage critical thinking at early stages in the patient pathway about how different types of samples can best be used to address specific clinical questions.

DIAGNOSIS OF LUNG CARCINOMA

Fibreoptic bronchoscopy has for many years been the principal method of investigating and establishing the diagnosis of bronchial carcinoma. Using this approach, endobronchial and transbronchial biopsies can be obtained for histology and bronchial brushings and washings obtained for cytological examination (see Figure 1). For central endobronchially visible tumours, systematic literature reviews have shown that bronchial biopsy has the highest diagnostic sensitivity (70–80%) and that the use of additional cytological sampling techniques increases the overall diagnostic yield to approaching 90%.^{14,15} It is, however, in the context of more peripheral lesions that cannot be visualised that cytology has historically played a more crucial role, with bronchial brushing and washing samples being obtained from the relevant lobar segments. Inevitably, this has a lower diagnostic sensitivity, with systematic reviews of the literature suggesting this is between 48–52% for brushings and 37–43% for washings.^{14,15} Even when combined with directed endobronchial or transbronchial biopsies, the overall sensitivity is still under 70%.^{14,15} This figure compares poorly with a diagnostic sensitivity for radiologically guided percutaneous fine needle aspiration (FNA)/core biopsy of around 90% for similar peripheral tumours.^{14,15}

Logically, this comparison is leading to an increasing use of percutaneous rather than bronchoscopic procedures for peripheral lesions demonstrated on CT scans,¹⁶ and a

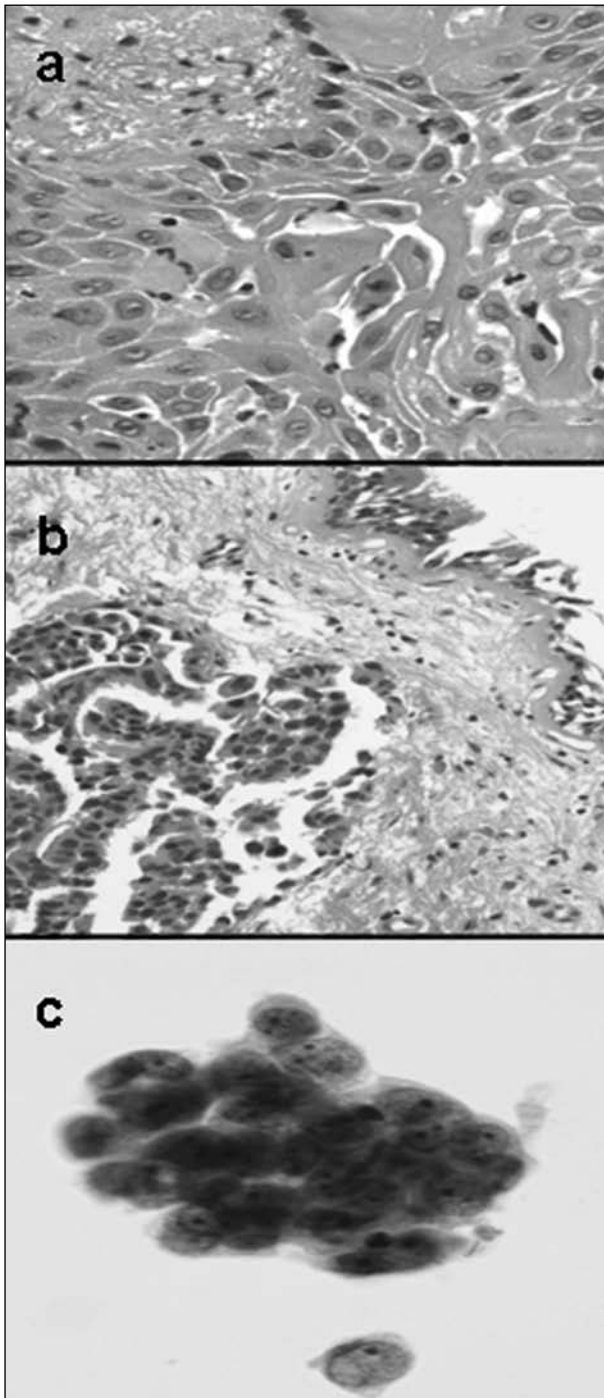


FIGURE 1 The primary diagnosis of lung carcinoma can be made on histological sections obtained from biopsies or on cytological specimens. Panel (a) illustrates the histological features of a squamous carcinoma in a CT-guided core biopsy, while (b) demonstrates submucosal infiltration of the bronchus by adenocarcinoma in a bronchial biopsy. Panel (c) shows the cytological appearances of malignant cells in a bronchial brushing sample from the same patient as panel (b). While the cells are clearly malignant, the architecture of the tumour is less obvious. (a) H&E stain x 200, (b) H&E stain x 100, (c) PAP stain x 600.

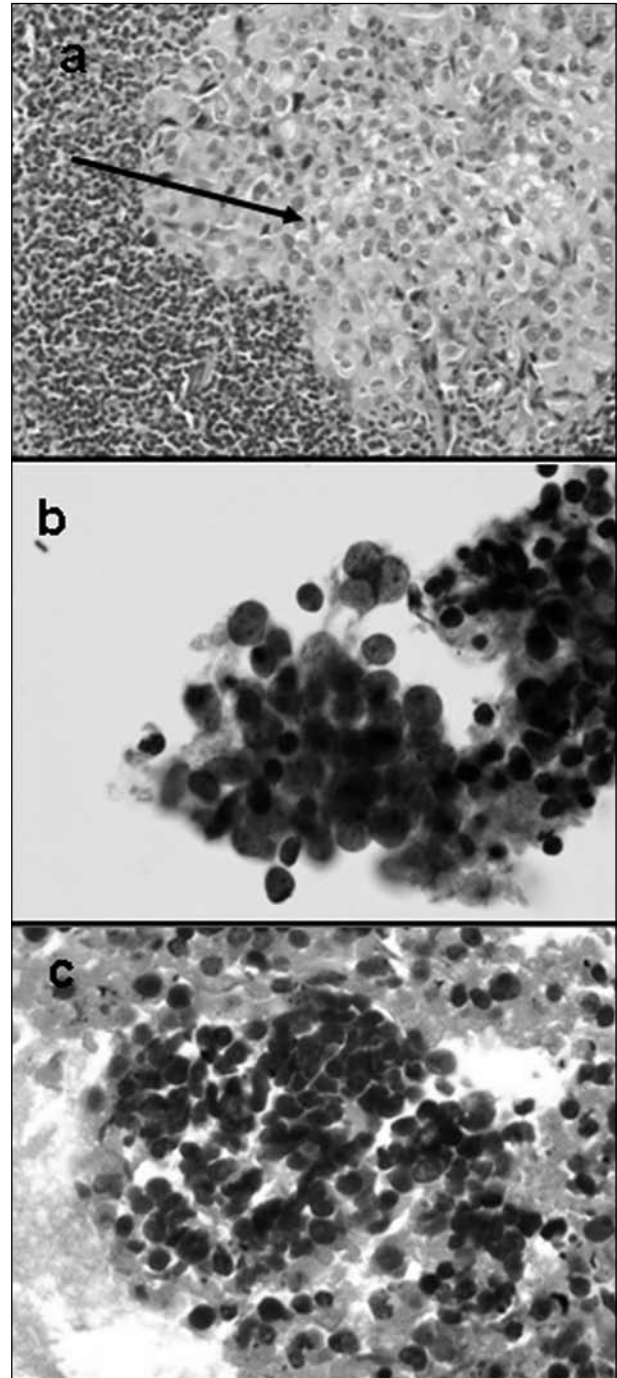


FIGURE 2 Assessment of mediastinal nodal involvement can be made by histological assessment of node biopsies or cytological examination of endoscopically derived aspirates. Panel (a) shows a lymph node biopsy obtained at mediastinoscopy with a focus of metastatic non-small cell carcinoma (arrow). Panel (b) shows an endobronchial ultrasound transbronchial needle aspiration sample containing groups of malignant cells with features consistent with small cell carcinoma. A cell block produced from this aspirate (c) shows small fragments of tumour admixed with necrotic debris. (a) H&E stain x 100, (b) PAP stain x 200, (c) H&E x 200.

consequent reduction in the use of endobronchially derived cytology specimens from patients with more peripheral lesions. Percutaneous procedures can be carried out as FNAs for cytological examination¹⁷ or with cutting needles

that generate cores of tissue for histological assessment.¹⁸ A review of current practice is difficult to assess from the literature as the terms 'FNA' and 'biopsy' are often loosely applied and in some instances it is even unclear whether

samples obtained were for cytological or histological assessment. While there is no consensus that core biopsies have a higher diagnostic sensitivity for malignancy than FNAs, some groups have suggested that this may be the case.¹⁹ Core biopsies are recognised, however, to have the clear advantage over FNAs in allowing the definitive histological diagnosis of benign lesions.²⁰ This approach may obviate the need for more invasive procedures, including thoracotomy, without a significant increase in overall morbidity, although some studies have identified a trend towards an increased risk of haemorrhage.^{19–22}

Sputum samples have generally been seen as easy non-invasive specimens that may be obtained in patients with suspected lung cancer. Systematic reviews of published series have suggested a diagnostic sensitivity of around 60% for sputum cytology,^{14,15} but this appears to be obtainable only in very controlled and optimised settings and in general use the sensitivity is very low – around 5%.²³ In the UK, the Royal College of Pathologists has suggested that sputum cytology should be regarded as a specimen with ‘limited or no clinical value’,²⁴ and both the recent Scottish Intercollegiate Guidelines Network (SIGN) and National Institute for Health and Clinical Excellence (NICE) guidelines have suggested that its use should be restricted to patients who are unfit for more invasive investigations.^{12,13} Experience in Edinburgh, following local audits of sputum cytology and its often inappropriate use, has resulted in a decrease from around 1,200 requests per year in 2001 to 116 in 2005 without any effect on the overall lung cancer service (personal observation).

Thus while cytology specimens continue to play a part in the diagnosis of lung cancer, this is changing. There is a movement towards greater use of tissue biopsies for primary diagnosis of lung carcinomas, the reasons for which are multifactorial. It is recognised that, in general, interpretation of cytology specimens is more difficult than biopsies. Much is made of the difficulties in accurately cell-typing tumours in cytology samples, but in fact the critical distinction between small cell carcinoma and non-small cell carcinoma in cytology specimens is remarkably robust and similar to that seen with small biopsies.^{14,25,26}

False positive diagnoses of malignancy can occur with histology, and although data on the frequency of this is not available, these are likely to be very rare. In contrast, systematic reviews of published series for respiratory cytology samples (bronchoscopic, percutaneous FNA and sputum) have shown false positive rates of 1–2%.¹⁴ While this may be low, it still presents a potentially significant problem. Part of the problem may be attributable to the quality of the specimens available for reporting, which can be spread poorly, blood-stained and show drying and smearing artefacts.^{25,27} Specimen quality might be improved by cyto-technicians being present when samples are collected in bronchoscopy suites and radiology departments, but given the current financial pressures in

healthcare and moves towards centralised pathology services this support is unlikely to be widely available.

The application of new methodologies in collecting and processing cytology samples may help in optimising the quality of samples available for reporting.²⁸ Nevertheless, the basis of a cytological diagnosis of malignancy relies purely on the appearances of the cells, with little or none of the architectural clues available in a biopsy, and there are well-recognised situations where a reactive proliferation of epithelial cells can very closely mimic malignancy.²⁹ In addition, cytology specimens cannot be used to distinguish invasive from *in situ* malignancy. This is clearly a major issue in the lung where squamous metaplasia, dysplasia and carcinoma *in situ* are frequent findings in smokers,^{30,31} and this leads inevitably to a degree of caution in the interpretation of cytology samples and the reporting of cases as being ‘suspicious’ or ‘highly suspicious’ of malignancy. In some cases this may prompt the need for further investigation and a potentially avoidable delay in treatment if a tissue biopsy could have been obtained in the first instance.

There is a clear and increasing demand for more information on tumours in the lung beyond the fact of their being a malignant neoplasm of ‘small cell’ or ‘non-small cell’ type. It is widely recognised that classifying primary non-small cell carcinomas of the lung on small biopsy specimens is poorly reproducible, due to the absence of specific diagnostic features and the well-documented heterogeneity that these tumours show.^{26,32,33} It is, however, clear that the architectural features of a tumour present in a biopsy may provide more clues as to the cell type than the individual cells in a cytology specimen. In addition, an increasing number of patients who have had previous carcinomas at other sites are presenting with lung masses, and future management will often be different for a metastasis as opposed to a primary lesion. Such issues will also be more easily addressed, although not always answered, with tissue for histological assessment, where again the architecture of the tumour may be helpful and there is greater scope for immunohistochemical studies.

Biopsy tissue present in pathology departments’ archives also represents a good ‘bank’ of material that is available for biomarker expression studies, such as epidermal growth factor receptor (EGFR), and is something that is likely to become important as new targeted therapies emerge. While in some instances cytology samples can be processed to cell blocks, and archived in many situations, the material available is limited and used up in the diagnostic process.

STAGING OF LUNG CARCINOMA

Hilar and mediastinal nodes

National guidelines have stressed that accurate staging of lung cancer is crucially important in dictating treatment options.^{12,13} One of the more difficult areas is that of

mediastinal nodal staging. While CT scanning will allow the assessment of nodal size, it is recognised to correlate poorly with involvement by metastatic carcinoma.³⁴ Even the use of CT-PET, which is better than CT alone, is recognised to show a significant false positive and negative rate.¹¹ Confirmation of mediastinal nodal stage prior to thoracotomy has relied heavily on mediastinoscopy with nodal biopsy (see Figure 2a). This has the disadvantages that it is a surgical procedure and access is limited to nodal stations around the trachea (stations 2R, 3, 4R, 4L and 7). Nodal stations at the pulmonary hila (stations 10 and 11), the mediastinum below the subcarina, in the aorto-pulmonary window and in the para-aortic and para-oesophageal areas (stations 5, 6, 8 and 9) cannot be reached by this approach.

Anatomically, these latter nodal groups, with the exception of those in the aorto-pulmonary window, lie adjacent to either the airway or the oesophagus and therefore endoscopic nodal sampling by FNA has been proposed as a way of allowing minimally invasive nodal staging with the added advantage of increasing the number of nodal groups that can be assessed. This approach led to the development of transbronchial needle aspiration (TBNA) techniques using a Wang needle.³⁵ While TBNA has been found by some groups to be highly sensitive, it has failed to be widely adopted.³⁶ The more recent development of endoscopes with ultrasound probes at the tip, first for use in the oesophagus and more recently in the bronchus, has resulted in the ability to assess nodes in the mediastinum and masses or nodes at the hila with aspiration being performed under real-time ultrasound control.^{37,38}

Both endoscopic ultrasound FNA (EUS-FNA) from the oesophagus and endobronchial ultrasound TBNA (EBUS-TBNA) have been shown by several groups to be a safe and sensitive method for obtaining material from hilar and mediastinal nodes for confirmation of stage and, in some cases, providing simultaneous diagnosis and stage.³⁹⁻⁴² We have shown that thin layer methods of processing cytology specimens work well and produce high quality specimens for reporting without the requirement for on-site technical support in the bronchoscopy theatre.⁴³ We have found that these specimens also often produce 'micro-biopsy' cores that can be processed as cell blocks (see Figures 2b and 2c). When available, this material may be used for immunohistochemical studies where these are required.⁴³ It is likely that EUS-FNA and EBUS-TBNA will play an increasingly important role in the staging of lung cancer, particularly in conjunction with new imaging modalities such as CT-PET, prior to patients being considered for radical therapy. In the longer term this may result in a decreased requirement for mediastinoscopy and histological assessment of node biopsies prior to surgery.⁴⁴

Metastatic spread beyond the mediastinum

Sampling of clinically or radiologically detected/suspected more distant metastatic lesions is often performed to confirm advanced stage in lung cancer or to obtain a

primary diagnosis in patients presenting with advanced disease when these metastatic lesions are more easily accessible than the primary. This can be performed by either core biopsy or FNA and practice varies widely. In principle, if the specimen is being obtained to confirm primary diagnosis rather than as a staging procedure, biopsy for histological assessment may be preferable for the reasons discussed above.

Pleural effusion is a common clinical or radiological feature in patients presenting with lung carcinoma.¹⁴ Aspiration is frequently carried out to ascertain whether the effusion is reactive or due to malignant involvement of the pleura. The sensitivity of pleural aspiration cytology in this context is difficult to ascertain. While there are published reports detailing the incidence of positive cytology in patients presenting with pleural effusions,⁴⁵ and suggestions of an overall sensitivity of around 60%,⁴⁶ the overall reliability of a negative result, in any given case, is not clear. This is further complicated by the fact that cytological examination of pleural fluid usually demonstrates adenocarcinoma or small cell carcinoma, but squamous carcinoma is rarely seen. The reasons for this are unclear but may reflect the fact that cells in squamous carcinoma are more cohesive and do not shed into the fluid in the same manner as other tumour types. Consequently, recent clinical guidelines suggest that pleural biopsy or thoracoscopic assessment should be considered in patients with unexplained pleural effusion following a negative aspirate, where radical therapy is being considered.¹²

One new area, where there has been increasing use of cytology, is in the assessment of supraclavicular lymph nodes for metastatic disease. Recent reports have demonstrated that aspiration of identifiable nodes on ultrasound will result in a positive result for malignant cells in around 75% of cases.^{47,48}

CONCLUSION

While cytology remains an important diagnostic tool in the management of patients with lung cancer, there is a clear drift towards obtaining tissue for primary histological diagnosis, where possible. In contrast, cytology is increasing in importance in the area of nodal staging, which in the past has largely been dominated by histological assessment of lymph node biopsies. The advent of minimally invasive mediastinal staging procedures represents an important development, and one where cytology will play a critical role in conjunction with modern imaging modalities such as CT-PET.

With choices in the types of specimens that may be obtained for cancer diagnosis and staging, it is important that requesting clinicians take into account the questions that they wish to have answered in an individual case. Cytology is a powerful tool for confirming the presence

of malignant cells in a tissue, but can be less useful than histology in answering related questions that may be important in formulating management plans. While recognising that a cytological confirmation of malignancy may be adequate in many instances, a strategy of favouring tissue biopsy for diagnosis, coupled with cytology for

staging, may represent the optimal approach. Close co-operation and discussion between physicians, radiologists and pathologists should have the aim of ensuring, in any given clinical situation, that the type of specimen obtained is that which is most likely to answer the specific questions raised.

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