Pathology of lung tumours

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Abstract

The pathological spectrum of lung tumours is broad; however it is dominated by primary lung carcinoma (cancer). The WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart, published in 2015, has significantly altered the landscape of lung cancer reporting, particularly with respect to lung adenocarcinoma.

In this review article, the aim is to provide insight into lung pathology reporting and its implications. Lung tumours can be diagnosed on biopsy tissue, cytology material or resected specimens. Conservation of tissue for molecular characterization is paramount, particularly when small amounts of tissue are received. Histological and molecular diagnostics of lung cancer specimens guides personalized targeted therapy. A multidisciplinary approach to primary lung carcinoma management is imperative so as to achieve the best possible patient outcomes.

Keywords Classification; diagnosis; lung carcinoma; molecular diagnostics; multidisciplinary team; staging; terminology

Introduction

The pathological spectrum of lung tumours includes many benign and malignant entities; however, any discussion on this topic will inevitably be dominated by primary lung carcinoma (lung carcinoma/cancer throughout this document). Lung carcinoma is the leading cause of cancer death worldwide accounting for more than 1.5 million deaths annually.[1] Amongst men, lung is the most common site for cancer while it is the third most common site in females.

Over the last few years, and as further detailed in the revised WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart, 2015,[1] the pathology of and subsequent management of primary lung carcinoma has changed considerably. We are all well aware that definitive surgical options are only possible in a small subpopulation of these cases, given that approximately 70% of patients with primary lung cancer present at an advanced stage requiring systemic therapeutic options rather than surgical resection.[2] Advances in our knowledge of tumour response to different chemotherapeutic agents as well as our increased understanding of tumour genetics gained through molecular biological techniques has led to our ability to develop a more 'personalized' approach to primary lung cancer patient management in this large non-surgical cohort in an attempt to improve survival outcomes.[2] 'Targeted' therapies and immunotherapies specifically directed towards the pathological subtype of lung cancer have been developed with significantly improved disease-free survival outcomes.[3] This paradigm shift in patient management therefore underlies the increased importance for all clinicians dealing with primary lung carcinoma patients to understand the pathology of and terminology utilized by pathologists when reporting lung cancer pathology.

As now clearly evident at multidisciplinary team meetings (MDTs), a detailed care pathway for all patients with lung carcinoma is chosen where decisions regarding surgical options, chemotherapy, radiotherapy, palliative care etc are taken. The understanding of the pathology of lung carcinoma is paramount to this decision process and as a result the role of the pathologist has changed considerably in parallel with the aforementioned advances. There is now an increased requirement on pathologists to accurately sub-classify lung carcinoma in small biopsies/cytological samples (Figure 1) (in the non-surgical cohort these small samples are generally all that is available), judiciously using tissue samples during this diagnostic process so as to ensure that enough tumour tissue remains for predictive marker testing to guide appropriate chemotherapeutic management.

For all involved in the management of patients with lung cancer, an understanding of the revised World Health Organization (WHO) pathological classification of lung carcinoma and of the associated molecular pathological advances is imperative so as to enable all disciplines to fully understand why specific care pathways are chosen for each of the patients presenting with this disease. This article will help facilitate this understanding and endow surgeons with increased knowledge that will be helpful when explaining to individual patients why a specific care pathway has been chosen for them.

Molecular pathology of primary lung carcinoma

For many years the main pathological distinction for a primary lung carcinoma was between that of a Small Cell Carcinoma (SCC) or a Non-Small Cell Carcinoma (NSCC), given the significant differing first-line therapeutic options available for these patients. Patients with small cell carcinoma generally are not amenable to surgical options as they present in advanced stages and therefore progress to chemotherapeutic options as first line therapy.[4] Within the larger heterogeneous NSCC group, surgical resection is carried out as a first-line therapeutic option where possible, although this is typically only in approximately 30% of cases.[2] For many years the need to further sub-classify NSCC was no more than of a pathological interest as there were no differing chemotherapeutic strategies for the numerous tumour sub-classifications that existed within this group. The major pathological subtypes in this group include adenocarcinoma and Squamous Cell Carcinoma.[1]

The need to sub-classify within the NSCC category became more apparent when it became evident that differentiating adenocarcinoma from squamous cell carcinoma had implications for chemotherapeutic regimens.[2] Some agents, such as pemetrexed, are preferentially effective in non-squamous histologies while other agents such as the anti-vascular endothelial growth factor (anti-VEGF) inhibitor bevacizumab can lead to

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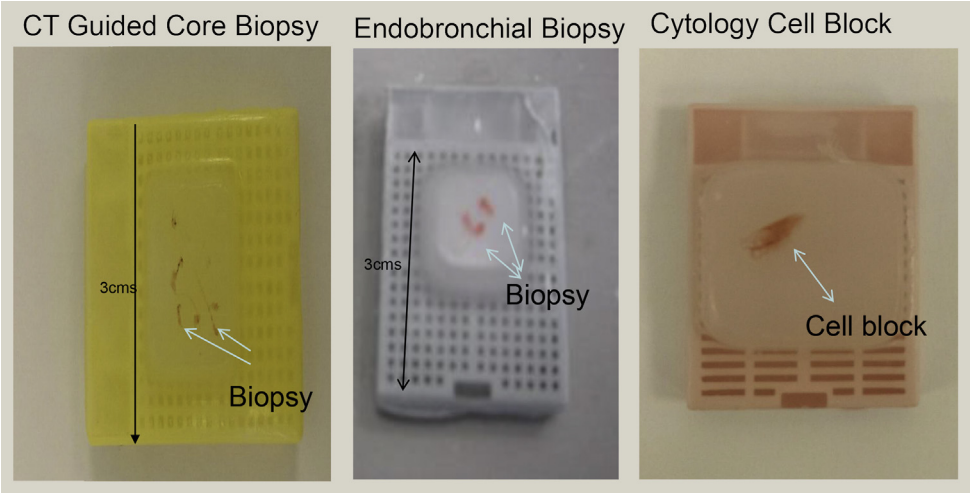

Figure 1 Paraffin embedded blocks demonstrating the size of the small tissue samples/cytology cell blocks utilized for diagnosis and predictive marker testing in the non-surgical cohort of lung cancer patients.

life-threatening haemorrhage when administered to patients with squamous cell carcinoma.[2] This requirement to clearly identify adenocarcinomatous differentiation became even more relevant in the advent of increased understanding of tumour genetics in primary lung carcinoma and the development of targeted therapies particularly effective against mutations in the epidermal growth factor receptor (EGFR) gene, EML-4/ALK translocation, Ros-1 etc, again more applicable to this category of non-squamous cell carcinomas.[5] For these reasons, several pathological algorithms and specimen pathways have been devised for this NSCC cohort so as to ensure optimal pathological utilization of tissue for both conventional diagnostics and molecular testing.[6]

As detailed in the RCPath algorithm,[6] the core genetic analysis to date advizes analysis of non-squamous histology (adenocarcinoma, NSCC, NOS, etc) for EGFR mutations and EML-4/ALK translocations. More recently, ROS 1 analysis is now being requested. As more drugs to specific genetic alterations become available, this list will no doubt continue to expand, giving increased hope for potential increased survival in this cohort of patients.

In the Western world, EGFR mutations are seen in about 10−20% of lung adenocarcinoma;[5] however the rate of EGFR mutation is substantially higher in Asian populations where it was reported in 51.4% of lung adenocarcinomas in the PIONEER study. Mutations in EGFR are most often associated with never smokers with a non-mucinous tumour morphology.[7] EGFR mutations are responsible for the constitutive activation of the tyrosine kinase. The most frequent mutations are present in exons 18−21 of the EGFR gene. Detecting EGFR genotype is the most useful method to select patients for consideration of first-line therapy with EGFR tyrosine kinase inhibitors (TKIs) as the presence of a mutation strongly predicts for sensitivity to TKIs such as erlotinib, gefitinib and afatinib. Several studies have demonstrated that lung adenocarcinomas that harbour EGFR mutations that were treated with TKIs had significantly higher response rates and longer progression-free survival than patients lacking mutations.[5] The presence of EFGR thus confers a more favourable prognosis in patients with advanced lung adenocarcinoma. It must be noted, however, that resistance to EGFR TKIs can occur in patients who previously responded to these drugs. The T790M mutation in exon 20 is associated with more than half of these patients with acquired resistance along with a small proportion of patients with primary resistance.[5]

Translocations involving the anaplastic lymphoma kinase (ALK) tyrosine kinase are most frequently EML4-ALK fusions and are reported to occur in between 3% and 13% of patients with lung adenocarcinoma.[5] Their frequency is higher in Asians, never smokers and younger patients who present at an advanced clinical stage. The presence of an ALK translocation strongly predicts sensitivity to ALK TKIs such as crizotinib and ceritinib which have recently been approved by the US Food and Drug Administration (FDA) for the treatment of advanced lung adenocarcinoma.[2] Treatment with these agents significantly prolongs progression-free survival in patients harbouring this translocation; however, the development of resistance to these drugs is problematic.[7]

ROS1 is a receptor tyrosine kinase of the insulin receptor family that is responsible for driving 1−2% of NSCC via genetic translocations with other genes. Those patients harbouring this translocation have adenocarcinoma histology and are young never smokers. *ROS1* translocations are important because they are indicative of response to treatment with crizotinib.[8]

Other genetic changes including Her2 − Her2 (ERBB2), BRAF mutations, *MET* and *RET* abnormalities have also been described in patients with NSCC of the lung and the list is continuing to grow.[5,7]

Given the therapeutic importance for individual patients in identifying these mutations, clear testing guidelines of appropriate and optimal samples is imperative. An algorithmic approach as recommended by The Royal College of Pathologists (RCPath), UK can be utilized.[6] As indicated, and given the frequency of mutations identified, commencement with analysis for EGFR mutations is preferred followed by reflex testing for ALK abnormalities in the absence of an EGFR mutation.

Therapeutic options for adenocarcinoma subtypes have become more clearly defined, however work on squamous cell carcinoma is on-going. One of the main needs to identify squamous cell carcinoma as a distinct type of NSCC in the lung is with

