Should we continue to use the term non-small-cell lung cancer?

A. F. Gazdar*

Hamon Center for Therapeutic Oncology Research and Department of Pathology, University of Texas Southwestern Medical Center, Dallas, TX, USA

Until recently the major clinical question was ’Is it small-cell or non small-cell cancer’. However, advances in conventional and targeted therapy have completely changed the landscape. Identification of the major non-small-cell lung cancer (NSCLC) types (adenocarcinoma and squamous carcinoma) are important for a number of predictive and prognostic reasons, including pemetrexed treatment, anti-angiogenic therapy and administration of tyrosine kinase inhibitors. Fortunately, advances in pathology of lung cancer have kept abreast, with newer, simplified methods to identify the major NSCLC types in small diagnostic samples, and modifications of the pathological classification of adenocarcinomas reflecting changing clinical and molecular concepts. For the patient to obtain maximum benefit from the recent developments in therapeutics, a multidisciplinary approach is required with co-operation between oncologists, surgeons, radiologists and pathologists.

what is non-small-cell lung cancer?

Non-small-cell lung cancer (NSCLC) may be defined as ‘Cancer of the lung which is not of the small cell carcinoma (oat cell carcinoma) type’. The term NSCLC is generally applied to the ‘various types of bronchogenic carcinomas (those arising from the lining of the bronchi), which include adenocarcinoma, squamous cell carcinoma, and large cell undifferentiated carcinoma’ [1].

The distinction between small-cell lung cancer (SCLC) and NSCLC came into prominence during the 1970s, when it was realized that SCLC was characterized by widespread metastatic spread at diagnosis and often displayed partial or complete response to conventional cytotoxic therapies [2]. By contrast, NSCLC was less likely to have spread at diagnosis, and usually failed to demonstrate objective responses to cytotoxic therapies. Because of major differences between the etiology, pathology, clinical features and prognosis of these forms of lung cancer, the principles of their clinical management diverged greatly. By contrast, the clinical management of all the major forms of NSCLC was similar, and the major question required by clinicians of the pathologist was ’Is it SCLC or NSCLC?’ If the pathologist responded ‘NSCLC’ there was no major therapeutic decision based on the NSCLC subtypes. For about three decades there remained no pressing clinical necessity for further classification of NSCLC. However, during the past decade advances in pathology, molecular biology, clinical therapeutics and the advent of individualized therapy have led to a re-evaluation of NSCLC, with major therapeutic and prognostic differences being based on its accurate typing.

the pathological basis of NSCLC

The lung may be divided into central and peripheral compartments, with the major conducting pathway (bronchi and larger bronchioles) forming the central airways and the respiratory bronchioles and the alveoli forming the peripheral airways, whose major function is gaseous exchange [3]. The term lung cancer or pulmonary carcinoma usually refers to the epithelial tumors arising in the lung and excludes sarcomas, mesothelial tumors and lymphomas. The World Health Organization (WHO) identifies multiple forms of NSCLC, but the major forms are squamous cell carcinomas (SCCs), adenocarcinoma (ADC) and large-cell (undifferentiated) carcinoma [4]. The latter is a waste bag term, used when evidence of differentiation is not apparent and may consist of relatively undifferentiated forms of the other lung cancers. Some may represent true undifferentiated cancers.

SCCs (along with SCLC) usually arise from the central compartment. While there are no squamous cells in the normal respiratory epithelium, we presume that SCCs arise from stem cells of the central compartment (believed to be the basal cells) that have undergone conversion to metaplastic squamous cell precursors. SCC used to be the commonest form of lung cancer in many parts of the world including Europe and the USA. However, over the past four decades its relative and absolute incidence has decreased dramatically. ADCs may arise from either compartment, although most are peripheral tumors arising from what is believed to be a common stem cell of the respiratory bronchioles and alveoli. It has always been the commonest form of cancer in never-smokers, women, young persons and East Asians. However, its relative incidence worldwide has increased dramatically and it is the commonest form of lung cancer in most parts of the world today. The
reasons for these dramatic shifts in lung cancer patterns are not apparent although in part they may be attributed to a shift towards filtered, low-tar cigarettes.

ADC and its subtypes

From a morphological and molecular basis, lung ADC is a highly complex form of cancer with several subtypes. The latest WHO classification of lung cancer [4], now over a decade old, recognized four subtypes—a non-invasive form known as bronchioloalveolar carcinoma (BAC) and three invasive patterns—acinar (gland forming), papillary and solid with mucin. Also, these subtypes could be mucinous or non-mucinous. In addition, mixtures of these subtypes were common. The BAC subtype was characterized by scale-like (lepidic) growth over the alveoli and bronchioles, and lack of invasion. The pattern recapitulated the presumed origin of most ADCs from the peripheral airways. Using the WHO classification, the vast majority of ADCs fell into the mixed subtype group [5]. Thus, it was recognized that simply calling >80% of ADCs as ‘mixed subtype’ was of little or no benefit.

new concepts about ADCs

It gradually became apparent to pathologists (and clinicians) that modifications to the revised WHO classification had to be made. An international group of pathologists, with major input from clinicians and radiologists, re-evaluated ADCs. These studies were sponsored by the International Association for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS) and the European Respiratory Society (ERS). Their consensus views were presented at the last IASLC World Congress (November 2009) and are now in press [5].

Important new features of the new classification include identifying the major ADC subtype present in mixed tumors. This will greatly aid clinical-pathological correlations. In addition a micropapillary subtype is recognized as distinct from the papillary subtype, because of its association with epidermal growth factor receptor (EGFR) mutations (see below). The most important clinical impact of the new proposed classification is the replacement of the term BAC with adenocarcinoma in situ (see below).

the turbulent life and untimely death of BAC

The term BAC is one of the most beloved terms to pathologists and clinicians, and, at the same time one of the most misused, misspelled and misunderstood terms in medicine. It was coined in 1960 by Averill Liebow, a pioneering lung cancer pathologist, who wrote that with extensive BAC, foci with invasion and destruction of the pulmonary architecture were to be expected [6, 7]. In other words what Liebow originally described is what we now recognize as a mixed histology ADC, predominantly BAC, with an invasive component. However, in the mid-1990s Noguchi and colleagues [8, 9] demonstrated that small (<2 cm) peripherally located non-invasive ADCs had an excellent (~100%) survival if resected. Thus, the presence or absence of invasion became a critical factor in determining prognosis. However, no one knew for sure whether minor degrees of invasion altered the prognosis. The revised WHO classification defined BAC as a truly non-invasive cancer, and those with an invasive component were placed in the mixed subtype category [4]. However, many pathologists and clinicians failed to follow the revised definition, with the result that there was no uniformity of diagnostic criteria, leading to considerable confusion and discrepancies about prognosis in the literature. For instance, one article describing the correlation between BAC subtype and response to tyrosine kinase inhibitors (TKIs) included mixed subtype ADCs containing a BAC component [10]. The authors did not state whether the BAC component had to be the major component or simply be recognizable irrespective of percentage. Correlation of response with pathological evidence of peripherally arising ADCs might have been a more accurate description of their correlation.

After struggling with the issue for a long time, the consensus recommendation of the Adenocarcinoma Panel was to replace the term BAC with adenocarcinoma in situ [5]. If the pattern was predominantly in situ with focal or modest invasion, the extent of invasion should be documented, permitting future prognostic studies. Because the term BAC is so well entrenched, it will take some considerable time for this change to be widely accepted and followed.

the molecular classification of lung cancers

In addition to multiple pathological subtypes, ADC of the lung demonstrates considerable molecular heterogeneity as demonstrated by genome-wide expression and copy number studies [11]. As reviewed by Yatabe [12] multiple clustering studies have demonstrated that ADCs can be divided into three or four subgroups. One subgroup is characterized by expression of products characteristic of the peripheral airways including surfactant proteins and the master transcription factor TITF1, which controls peripheral airway differentiation. Most EGFR mutant tumors fall into this category and arise from peripheral airway cells that constitute the ‘terminal respiratory unit’ [12]. Because oncogenic mutations target specific signaling pathways at specific nodal points, such mutations in tumor cells are characterized by highly specific molecular signatures [13]. Thus, the molecular signatures of KRAS and EGFR mutations are very different. These findings not only have biological significance, but may be of considerable therapeutic importance.

mutations have characteristic histological features

Oncogenic mutations target specific lung cancer cell types and disrupt crucial signaling pathways at nodal points. Thus it is not surprising that specific mutations are associated with specific tumor subtypes. While some mutations such as TP53 are present in all forms of lung cancer, many others target ADCs. EGFR mutations target the peripheral airways, and are associated with well-differentiated carcinomas expressing...
therapy both clinically and parametrically. KRAS mutations have been associated with resistance to TKI toxicities, limiting their use and making NSCLC typing of pathological types often show pathological type bias. Other targeted therapies often show pathological type bias. Other targeted therapies that attack a range of tumor types, such as antiangiogenic therapies, may demonstrate tumor type-specific toxities, limiting their use and making NSCLC typing of paramount importance. The current role of the pathologist or molecular pathologist in aiding clinically relevant decision-making about patient therapy or management is summarized in

**NSCLC histology and chemotherapy**

As reviewed recently [18], histology has not been a consistent predictor of response to conventional chemotherapy. Although some reports indicated that ADC histology predicted a better response to pemetrexed, a larger study failed to identify a major role of histology in the overall survival or time to progression after treatment with common first-line doublet regimens [18]. However, histology was prognostic for survival, with better outcomes associated with SCC.

**histology and angiogenic therapy**

Angiogenesis is an integral part of all tumors and inhibitors of angiogenesis have elucidated much interest in NSCLC. Bevacizumab, a monoclonal antibody against vascular endothelial growth factor, has been shown to benefit patients with NSCLC of non-squamous histology when combined with standard doublet therapy [19]. Because bevacizumab therapy may be associated with serious hemorrhagic events, apparently more common among patients with predominantly SCC, drug administration is usually limited to NSCLC of non-squamous histology [20].

**ADC and response to TKIs**

The widespread use of TKIs gefitinib and erlotinib identified certain subsets of NSCLC as being more likely to respond—ADC histology, never-smoker status, female gender and East Asian ethnicity. After the discovery of EGFR mutations in 2004, it was noted that mutations targeted the same subtypes, and numerous studies have demonstrated that mutations predict response [21, 22]. Whether ADC histology predicts response in the absence of mutations is more controversial, as is the role of increased gene copy number. However, ADC histology remains one of the main clinicopathological factors in the decision to treat with TKIs in the absence of the mutational status, or in the decision as to whether to perform mutation testing. At some institutions the diagnosis of lung ADC initiates automatic testing for EGFR (and possibly other gene) mutations (so called ‘reflex testing’). KRAS mutations have been associated with resistance to TKI therapy both clinically and in vitro [23, 24].

---

**pathological identification of NSCLC histological types**

In resected specimens, pathological typing of NSCLC should always be possible, leaving no reason for a diagnosis of ‘NSCLC, not otherwise specified (NOS)’. However, most NSCLCs are unresectable. Thus the diagnostic material is often small biopsies or cytologic specimens. The combination of tumor heterogeneity, poor differentiation and scant diagnostic material results in pathological uncertainty and the NSCLC-NOS diagnosis. However, application of a simple panel of tests results in accurate subtyping of most poorly differentiated NSCLCs, even in small biopsies and cytologic specimens [25, 26]. The panel consists of a mucin stain and immunostaining for TTF1 (also called TFF1), the master transcription factor for squamous cells present in bronchial epithelial cells (for SCCs). Additional stains, such as for high molecular weight keratins, may also be employed. Commercial companies offer microRNA-based diagnostic tests for the subtyping of NSCLC [27]. However, the cost (>$2000) is hard to justify when a simple marker panel, which most pathology labs can perform and which is accurate, is available at a substantially lower cost.

**concluding remarks**

Until recently pathology of lung cancer was a relatively stagnant field. The importance of differentiating SCLC from NSCLC had been identified nearly four decades ago. This distinction can be made reliably by pathologists. However, the same impetus to identify the NSCLC types was lacking because of lack of availability of effective therapies for these types. The advent of targeted therapies and the widespread use of newer cytotoxic drugs such as pemetrexed has completely rejuvenated the importance of typing NSCLC. Current anti-angiogenic therapies require exclusion of tumors with squamous differentiation. However, ADC is a highly heterogeneous tumor, with at least three molecularly defined subtypes. Pathologically it currently consists of five subtypes. However, because most ADCs are mixtures of two or more of these subtypes, the dominant component needs to be identified for future correlative studies. Molecular changes targeting ADCs, including EGFR, KRAS and ALK mutations, are associated with specific subtypes. Because of the association of ADCs with micropapillary (and other) subtypes, this has been added to the list of recognized subtypes. Because of widespread misuse and misunderstanding of the term BAC, it has been recommended that it be replaced with the term ‘adenocarcinoma in situ’.

Unlike conventional therapies, targeted therapies are directed at specific changes especially those that result in oncogene addiction. As these changes often show strong associations with specific NSCLC types, the efficacies of specific targeted therapies often show pathological type bias. Other targeted therapies that attack a range of tumor types, such as antiangiogenic therapies, may demonstrate tumor type-specific toxities, limiting their use and making NSCLC typing of paramount importance. The current role of the pathologist or molecular pathologist in aiding clinically relevant decision-making about patient therapy or management is summarized in

TITF1. Not surprisingly these tumors have features of peripheral airways including an extensive in situ component. In some cases they may be truly in situ (i.e. BAC). Mucin secretion is absent. Other EGFR mutant ADCs may have a papillary or micropapillary growth pattern [14]. EGFR mutations have also been described in pleomorphic carcinomas, a rare form of lung cancer having sarcomatoid features [15]. By contrast, KRAS mutant tumors tend to be poorly differentiated or are mucinous [16]. Our unpublished studies demonstrate that KRAS lung cancer cells often demonstrate epithelial–mesenchymal differentiation, a characteristic of poorly differentiated tumors, and may or may not express TITF1. While only small numbers have been analyzed, the association of ALK-positive tumors and specific subtypes is not clear [17].

**Annals of Oncology symposium article**

Table 1. While relatively small in number, we fully expect the list to lengthen considerably in the not too distant future.

Improvements in pathological diagnosis permit the typing of all resected specimens and others that provide adequate amounts of tumor tissue. While more sophisticated (and expensive) molecular characterization is available, simple to perform immunostains combined with standard tests for mucin secretion provide the ability to separate SCC from ADC tumors. Absence of these forms of differentiation result in a diagnosis of large-cell undifferentiated carcinoma. However, tumor heterogeneity and small biopsies or scant cytological material (which form the majority of diagnostic specimens) remain a problem. While special techniques for diagnosis (already discussed) can be applied to them in many cases, in some instances another biopsy is required for definite typing. The Update Committee of the America Society of Clinical Oncology recently stated that ‘in order to obtain tissue for more accurate histologic classification or for investigational purposes, [it] supports reasonable efforts to obtain more tissue than what is contained in a routine cytology specimen.’ In other words, it appears justifiable to obtain additional diagnostic materials via an invasive procedure for pathological typing under certain circumstances. Most patients will consent to an additional invasive procedure if it is explained to them that it may result in optimized therapy selection.

It is obvious that the past decade has seen many improvements in therapeutic applications that necessitate accurate typing of NSCLC. Pathological advances, which are often driven by clinical necessity, have kept pace with the ability to accurately type most diagnostic specimens including scant ones. Currently, the term ‘NSCLC-NOS’ should be limited to specimens with scant or necrotic material, and require a further typing under certain circumstances. Most patients will consent to an additional invasive procedure if it is explained to them that it may result in optimized therapy selection.

Inter-disciplinary approaches are required in order for the patient to obtain maximum benefit from the recent developments in therapeutics. Communication between the pathologist, oncologist, surgeon and radiologist are required in order to obtain the required diagnostic material, to make the appropriate diagnosis and identify the stage, and to have the knowledge to correctly interpret the pathology findings and select the optimal therapy.

disclosure

The author serves as a consultant/lecturer to AstraZeneca Plc.

references

17. Wong DW, Leung EL, So KK et al. The EML4-ALK fusion gene is involved in various histologic types of lung cancers from nonsmokers with wild-type EGFR and KRAS. Cancer 2009, 115: 1723–1733.

Table 1. The role of the pathologist and molecular pathologist in therapy selection

<table>
<thead>
<tr>
<th>Application</th>
<th>Purpose</th>
<th>Test(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis of NSCLC subtype</td>
<td>Selection/exclusion of personalized therapy</td>
<td>Immunostaining for TTF1, p63, other markers</td>
</tr>
<tr>
<td>Bevacizumab therapy</td>
<td>Avoidance of toxicity</td>
<td>Identification of non-squamous non-small-cell lung cancer cases</td>
</tr>
<tr>
<td>Pemetrexed therapy</td>
<td>Selection of potential responders</td>
<td>Identification of non-squamous NSCLC cases</td>
</tr>
<tr>
<td>Tyrosine kinase inhibitor therapy</td>
<td>Targeting EGFR signaling</td>
<td>EGFR gene mutation or copy number determination</td>
</tr>
<tr>
<td>ALK fusion protein inhibition</td>
<td>Personalized therapy</td>
<td>ALK gene rearrangement</td>
</tr>
<tr>
<td>Tyrosine kinase inhibitor therapy</td>
<td>Exclusion of therapy</td>
<td>KRAS gene mutation</td>
</tr>
</tbody>
</table>

EGFR, epidermal growth factor receptor.