Classification of Lung Cancer: Proposals for Change?

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- Clinical need and developments in pathology and molecular biology require our cancer classifications to be constantly updated to keep them relevant and useful. A review of lung cancer classification is due and has been initiated with new proposals on classification of lung adenocarcinoma. Other major lung cancer types also deserve a similar consideration. As well as addressing the categories of tumor, as signed out in surgical resection specimens, recent proposals on small diagnostic-sample reporting would be an important addition to any new classification. The huge increase in data on the molecular biology of lung cancer has improved our understanding of these diseases, has driven improved therapy for some patients, and must be reflected in the way lung cancer is classified.


The World Health Organization (WHO; Geneva, Switzerland), in conjunction with the International Association for the Study of Lung Cancer (Aurora, Colorado), published its last official classification in 2004, and this book has served well as a benchmark for classification of lung tumors since then. The world of lung cancer pathology moves on, however, reacting as it must, to developments in other fields of lung cancer medicine and innovating changes where it has the data and tools to do so. Since 2004, lung cancer pathology has seen an enormous growth in data on the molecular pathology of lung cancer and the way that influences both the development of the disease and how it should be treated. These advances have had major repercussions for pathologists dealing with lung cancer, not only on our core morphologic diagnoses but also on the need for molecular data to inform therapeutic decisions.

Around the time of publication of the last WHO lung cancer classification a large amount of important new data appeared on many aspects of pulmonary adenocarcinoma and its development. This occurred as emerging data on molecular aspects of adenocarcinoma, particularly the epidermal growth factor receptor (EGFR) mutation story, stimulated many meetings and publications and culminated in proposals for a revised classification of adenocarcinoma, driven by William D. Travis, MD; Elisabeth Brambilla, MD; and Masayuki Noguchi, MD, and sponsored by the International Association for the Study of Lung Cancer, the European Respiratory Society, and the American Thoracic Society. These and other emerging concepts and discussions form the basis for this article. I would like to pay tribute to my fellow members of the International Association for the Study of Lung Cancer Pathology panel (William D. Travis, MD; Elisabeth Brambilla, MD; Masayuki Noguchi, MD; Yasushi Yatabe, MD, PhD; Ming Tsao, MD; Erik Thunnissen, MD; Andrew G. Nicholson, DM; Lucian Chireac, MD; Kim R. Geisinger, MD; Ignacio Wistuba, MD; Iver Petersen, MD; Yuichi Ishikawa, MD, PhD; Victor Roggli, MD; and Seena Aisner, MD) for their contributions to many stimulating discussions on some of these topics.

MOLECULAR CLASSIFICATION OF LUNG CANCER

Individual molecular characteristics and more-global molecular or genetic profiles of lung cancer have been known for many years but have failed to make much impact on clinical or pathologic practice because of a lack of clinical relevance, until recently. The increasing availability of accessible technology to characterize molecular profiles of lung cancer in many different ways and the integration of morphologic and molecular data into classifications of malignant tumors in other organs has increased the appetite for a molecular classification of lung cancer. The main impetus, however, has been through the identification of important molecular drivers, to which subsets of lung cancers, mainly adenocarcinomas, are “addicted.” Many of these drivers are tyrosine kinases that become constitutively activated by a mutation in the corresponding gene and have strategic importance in one or more intracellular signaling pathways. Mutations, translocations, or other upregulation of keys genes, such as EGFR, KRAS, ALK, ERBB2 (HER2), BRAF, or MET, are now becoming part of the landscape of lung cancer classification because there are drugs available that target these key molecular drivers, leading to dramatic clinical benefits. Oncologists increasingly think of individual lung cancer cases by the targetable molecular abnormalities that may be present in each—a molecular classification of sorts—but this should not replace...
the morphologic classification of the disease, but instead, complement it (see below).

Lung adenocarcinoma, in particular, has been the focus of attempts to subdivide and classify the disease according to profiles of expression of the many thousands of genes. Not surprisingly, these tools are capable of identifying separate groups of lung cancers or subgroups within histologic subtypes such as adenocarcinoma. The idea that we may usefully classify lung cancer in this way, however, has been something of a “false dawn.” The enormous amount of data generated by these profiling experiments, at a not insignificant cost, and the need for extensive bioinformatic analyses have led to substantial inconsistency in outcomes. One consistent message from these studies has been that tumors differ in their degree of differentiation and their proliferative (cell cycle) activity. They also support many of the concepts of the origins of adenocarcinomas (see below).

The amount of data available on molecular aspects of lung cancer is vast, and it is a considerable challenge to assimilate that information and use it in a way that is clinically useful and relevant and that advances our classification of this disease. Molecular information, for its own sake, has no importance.

**CLASSIFICATION OF LUNG CANCER IN SMALL DIAGNOSTIC SAMPLES**

The WHO classification is designed for the diagnosis of whole, surgically resected tumors and many aspects of the classification are simply not applicable to diagnosis of these tumors in small diagnostic biopsy samples, including cytology specimens. Attempts to “force” cases into one of those WHO categories that may only be reliably assigned on surgically resected specimens (large cell and sarcomatoid carcinomas, adenosquamous carcinoma, some carcinoid tumors) led to many publications describing the inaccuracy of pathologic classification of lung cancer in small samples. Small cell lung carcinoma (SCLC) diagnosis is generally reliable in small samples. For those cases that were not SCLC, there emerged a perfectly reasonable recommendation that, in the absence of definite evidence of differentiation (de facto a diagnosis of squamous cell or adenocarcinoma), a more honest approach was to sign out these case as non-small cell lung cancer, not otherwise specified. For many years, this was perfectly acceptable to oncologists because all non–small cell lung cancer was effectively treated in the same way. The more recent emergence of molecular-targeted therapies associated with mutations that are themselves associated with adenocarcinomas, rather than squamous carcinoma, for example, and the recognition that some therapeutics are more effective against adenocarcinomas (pemetrexed, Eli Lilly and Company, Indianapolis, Indiana) or show greater toxicity in squamous carcinomas (bevacizumab, Genentech, Inc, South San Francisco, California, and Roche, Basel, Switzerland) has emphasized the need to reduce the usage of the non–small cell lung cancer, not otherwise specified diagnosis as much as possible.

The association of particular proteins with either squamous cell or adenocarcinomas in the lung—so-called lineage markers—has led to the frequent use, but also abuse, of immunohistochemistry to identify markers, such as thyroid transcription factor 1 (TTF1) and cytokeratin 7 (CK7) (for adenocarcinoma), and CK5/6, p63, and p40 (for squamous cell carcinoma) in non–small cell lung cancers. This simple molecular classification is extremely useful in helping to predict the likely histology of cases of non–small cell lung cancer, not otherwise specified, and can reduce the reporting rates of this category from 30% to 40% of cases to less than 10%, a level that is not possible to better. These lineage markers are not unique to any particular cancer type and do not define any of the non–small cell lung cancer subtypes. Although they are extremely useful in difficult, undifferentiated, small tumor samples to predict a likely or probable non–small cell lung cancer subtype, this strategy is not, and cannot be, 100% accurate, and these markers are not necessary if definite morphologic evidence of squamous cell or adenocarcinomatous differentiation is present.

The International Association for the Study of Lung Cancer/European Respiratory Society/American Thoracic Society recommendations provide a nomenclature for predictive diagnosis on small samples, which addresses the lack of guidance in the existing WHO classification. This useful approach should be adopted, not only by pathologists reporting such samples but also by those gathering histologic data in the context of therapeutic trials in advanced lung cancer.

**ADENOCARCINOMA: NEW RECOMMENDATIONS**

Published in early 2011, these proposals are based on an extensive review of contemporary literature, a recognition that lung adenocarcinoma classification needed to integrate molecular and radiologic data into the classic morphologic descriptions of this most heterogeneous non–small cell lung cancer subtype, and extensive discussion and debate. Apart from the issues around small-sample diagnosis and the need to correlate morphology with molecular data and radiology, as already mentioned above, there were 2 major pitfalls in the 2004 WHO classification of adenocarcinoma: (1) the term bronchioleodular carcinoma (BAC) was widely misunderstood and misused, and (2) the mixed adenocarcinoma category accounted for most surgically resected cases.

In the 2004 WHO classification, as in its predecessor from 1999, the term BAC was reserved for a small, localized, peripheral lesion of glandular neoplasia that showed no evidence of invasion. Despite that, the term BAC continued to be used in a wide range of situations, including advanced, multifocal, and even metastatic disease settings, all inconsistent with the definition of BAC. The seminal work of Masayuki Noguchi, MD, and many other Japanese pathologists, informed discussion about the nature of those lesions that fulfilled criteria of BAC and reinforced the conclusion that this lesion represented adenocarcinoma in situ (AIS). The term BAC should be discontinued. In defining some lesions as AIS, there would inevitably be others with only minor evidence of invasion, and from that came the concept of minimally invasive adenocarcinoma, a lesion of less than 3 cm with invasion or non-AIS adenocarcinoma morphology of any focus less than 5 mm in diameter. Crucially, these proposals are again based on evidence from many studies that indicated such minimal evidence of invasive disease does not, as with AIS, pose any metastatic risk.

Adenocarcinoma in situ is a lesion in which the only growth pattern present is the spread of tumor cells around the alveolar walls—the so-called lepidic spread. The 2004 WHO classification recognizes 3 other patterns of invasive adenocarcinoma—acinar, papillary, and solid (with mucin). Emerging evidence of the particularly aggressive nature of a
micropapillary pattern of adenocarcinoma\textsuperscript{7,8} justified the addition of this fifth pattern. Most resected adenocarcinomas show a mixture of at least 2 of these patterns. Numerous studies have shown that assessment of the predominant pattern of disease can separate cases into good, intermediate, and poor prognostic groups for the risk of disease recurrence and postoperative survival. Tumors with the lepidic pattern predominant do relatively well, whereas those that are predominantly solid or micropapillary do relatively badly. Assessing the 2 most prevalent patterns may improve case separation. There is emerging evidence that these patterns may, in most instances, be reliably recognized, but these proposals still pose questions, not least around the biologic nature of tumor that grows around the alveolar structures without destroying them, where there is invasive disease in the central part of the lesion. Should all lepidic-pattern disease be labeled AIS biologically speaking? Micropapillary disease often grows in this fashion, yet it is biologically more advanced than preinvasive in situ disease.\textsuperscript{7}

Other recommendations included in the document are recognition of the enteric pattern of adenocarcinoma as a variant, and assimilation of what once was referred to as mucinous BAC into the variant category of invasive mucinous adenocarcinoma. The former needs to be distinguished from metastatic colorectal cancer, whereas the latter frequently bears KRAS mutation. Clear cell and signet ring cell variants have been removed but are still recognized as legitimate descriptions; signet ring cell adenocarcinoma is especially important given its association with ALK fusion gene alterations.

**SQUAMOUS CELL CARCINOMA: A FORGOTTEN DISEASE?**

In comparison to adenocarcinoma, there have been rather fewer developments in squamous cell carcinoma. Mention has already been made of the use of lineage markers identified by immunohistochemistry (IHC) for a predictive diagnosis of squamous cell carcinoma in the context of a small, diagnostic sample. Several markers have a tendency to stain squamous cell carcinomas, but CK5/6 and p63 have gained greatest popularity based on their good sensitivity and specificity. The p63 stain has received some “bad press,” suggesting lack of specificity, with a recommendation to use instead p40, an isoform of p63 protein more specific to the lung. p63 does stain some adenocarcinomas, but, if used correctly with an appropriate predictive staining threshold applied, p63 is a perfectly adequate predictor of squamous histology. In my opinion, squamous cell carcinoma may be “overdiagnosed” by morphology in many small samples based on various morphologic features that may confer “squamoid” appearances to a tumor that lacks defining squamous features, namely keratin formation and intercellular bridges. The often-recounted anecdotes of TTF1\textsuperscript{+} and EGFR-mutated squamous cell carcinomas may support this impression. That may argue in favor of more, rather than less, IHC in small biopsy diagnosis.

There have been some exciting developments in the molecular biology of lung squamous cell carcinoma with the identification of important molecular drivers that are potentially targetable by drugs.\textsuperscript{14,15} Amplification of the FGFR1 and PI3k genes is found in about 20% and 8% of cases, respectively; mutations of DDR2 and FGFR3 are found in 3% and 1% of cases, respectively. These data and the clinical story that follows are much less mature than the equivalent with adenocarcinoma, but it certainly provides some hope for the future. This potential molecular classification and the differential responsiveness and toxicity with some other agents in squamous cell carcinoma already mentioned emphasize the importance of precise diagnosis.

The surgically resected squamous cell carcinoma is usually a straightforward diagnosis. Four relatively uncommon variants are, however, described in the 2004 WHO classification (papillary, clear cell, small cell, and basaloid). Of these, the clear cell variant is difficult to justify because almost any lung cancer can show clear cells, and it may be better used as a descriptive term only. Many pathologists struggle with the concept of the small cell variant of squamous cell carcinoma, and it may be better deleted. Papillary patterns of squamous cell carcinoma clearly occur, but its significance is not clear. Evidence that it is related to human papillomavirus infection is conflicting, and the papillary architecture may, at least in part, be a function of some tumors growing within a large space (for example an airway or cyst). The basaloid variant of squamous cell carcinoma has a stronger argument for retention because there is evidence that it carries a poorer prognosis,\textsuperscript{16} although the relationship between this lesion and basaloid carcinoma (currently a large cell variant) is open to question. Other patterns of squamous cell carcinoma have been described, but their clinical relevance is less certain, making their place in any new classification questionable. Microcystic squamous cell carcinoma, cancers arising in squamous papillomas, and rare pediatric cases associated with the NUT mutation are described. Early endobronchial squamous cell carcinomas with variable growth patterns—“creeping carcinoma”—appear to carry a good prognosis. An “alveolar filling” pattern of squamous carcinoma growing within the parenchymal lung has also been associated with a good prognosis.\textsuperscript{17} Whether this is because of different biology or simply because of the cancer growing in a different tissue is not clear. There is good evidence, however, that relatively peripherally arising squamous cell carcinoma appears to be increasing in prevalence. It remains to be seen whether these tumors are biologically different from their central bronchial counterparts and deserve a classification niche.

**NEUROENDOCRINE LUNG TUMORS**

In the 2004 WHO classification, some neuroendocrine tumors have categories to themselves (small cell carcinoma [SCLC], carcinoid tumors), whereas another is a variant of large cell carcinoma (large cell neuroendocrine carcinoma [LCNEC]). Some perfectly straightforward squamous or adenocarcinomas express neuroendocrine (NE) markers on IHC, whereas some tumors have NE morphology but fail to express NE markers on IHC. A more unified approach in the classification is justified, but that approach should not be at the expense of clarity, should be biologically appropriate, and needs to be practical. Some have suggested a complete amalgamation along the lines of gastrointestinal NE tumor classification (3 grades of NE malignancy), but disposal of the well-known terms currently in use would be a mistake and would likely be unacceptable to the oncologic community. Instead, under a broad category of NE tumors might reside carcinoid tumors in a low-grade category, and both SCLC and LCNEC would be 2 distinct entities under a high-grade category. Morphologic, epidemiologic, and
molecular and genetic data all suggest that carcinoid tumors are quite separate entities from the high-grade lesions, and any inference of a closer relationship, or even a biologic continuum between carcinoids and SCLC and LCNEC, would be quite wrong. There are epidemiologic and molecular similarities between SCLC and LCNEC, however, and a debate around their amalgamation is at least justified; I would keep them as separate entities based on morphologic differences. Do we need a category for those rare, resected, high-grade NE tumors that don’t quite fit into either SCLC or LCNEC classification? That is another question for debate, although tumor classifications cannot account for every problem area or rare issue that may be encountered.

**LARGE CELL AND SARCOMATOID CARCINOMAS**

Large cell neuroendocrine carcinoma would be better placed in a NE category. Lymphoepithelioma-like carcinoma is a rare, but relatively distinct, entity, at least in those with ethnic and Epstein-Barr virus associations. It is a harder issue to justify in the absence of Epstein-Barr virus because the distinction between lymphoepithelioma-like carcinoma and an undifferentiated carcinoma with a heavy lymphoid infiltrate may be difficult. Basaloid carcinoma has many distinctive morphologic features and has clinical correlates; it is an aggressive tumor. Basaloid carcinomas may occasionally demonstrate a peculiar form of nested, cellular keratinization, but they lack the intercellular bridges of squamous cell carcinomas. Basaloid carcinomas almost universally share an expression of squamous-type lineage IHC markers with squamous cell carcinomas, and this has supported suggestions that these tumors should reside with basaloid variant of squamous cell carcinoma. This argument has some validity but also has issues, such as accepting into this category cases that lack defining morphologic criteria of squamous cell carcinoma and implying that IHC findings can become the defining criteria of squamous cell carcinoma. This brings the discussion to large cell carcinoma, not otherwise specified. It is perfectly legitimate to have a category for undifferentiated tumors in a morphologic tumor classification. Because a proportion of large cell not otherwise specified carcinomas express IHC lineage markers for either squamous cell or adenocarcinoma does not, by definition, mandate a diagnosis of a differentiated tumor. The undifferentiated large cell carcinoma may be due to dedifferentiation of a previously differentiated tumor. That does not change how the tumor looks, in our morphologic classification. The potential therapeutic issues and the need for molecular analysis do argue for an acknowledgement that an undifferentiated large cell carcinoma may have a squamous cell or adenosquamous carcinoma immunophenotype, and such a qualification would be perfectly reasonable as part of a classification, within the large cell category. A similar situation could apply to sarcomatoid carcinomas when there is no associated, differentiated element of squamous cell or adenosquamous carcinoma present. Sarcomatoid areas of the tumor may have a squamous cell or adenosquamous carcinoma immunophenotype, and sarcomatoid carcinomas, in general, are recognized as aggressive tumors worthy of distinction. The frequent presence of squamous cell carcinoma or adenosquamous carcinoma in association with undifferentiated sarcomatoid carcinoma also supports the hypothesis of tumor progression/dedifferentiation in these cases. A significant proportion of large cell and sarcomatoid carcinomas do not express lineage IHC markers. These diagnoses remain an issue for surgical resection specimens alone; neither is reliably diagnosable on small, diagnostic samples.

**CONCLUSION**

This article has combined some existing proposals with some speculation about the shape of a future lung cancer classification. It has not addressed all possible issues that would likely have to be reconsidered (adenosquamous and other combined tumors, salivary-type carcinomas, preinvasive lesions, among others). There is both a clinical need and an academic desire to integrate molecular data into the classification of lung cancer. There is already good evidence that doing so enhances the clinical relevance of the classification, makes it more biologically meaningful, and, in some circumstances, makes it more accurate. Fundamentally, the classification remains a morphologic one, which may, when appropriate, be enhanced or qualified by IHC and/or molecular pathologic findings. There is no need, sense, or indication to replace our morphologic classification with a molecular classification, even if such a thing existed. In today’s lung cancer clinic, neither the morphologic nor the molecular approach, in isolation, serves patients adequately; in combination, they provide significant improvements in the way patients with lung cancer can be treated.

**References**