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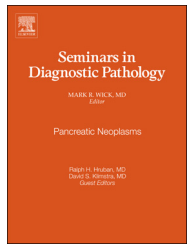

What clinicians are asking pathologists when dealing with lung neuroendocrine neoplasms?

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ABSTRACT

Lung neuroendocrine tumors (NET) are currently classified in resection specimens according to four histological categories, namely typical carcinoid (TC), atypical carcinoid (AC), large-cell neuroendocrine carcinoma (LCNEC) and small cell carcinoma (SCC). Diagnostic criteria have remained unchanged in the 2015 WHO classification, which has ratified the wide acceptance and popularity of such terminology in the pathologists' and clinicians' community. A unifying umbrella of NE morphology and differentiation has been recognized in lung NET, which has pushed to enter an unique box of invasive tumors along with diffuse idiopathic pulmonary NE cell hyperplasia (DIPNECH) as a pre-invasive lesion with a potential toward the development of carcinoids. However, uncertainties remain in the terminology of lung NET upon small samples, where Ki-67 antigen could play some role to avoid misdiagnosing carcinoids as high-grade NE tumors. Epidemiologic, clinical and genetic traits support a biological three-tier over a pathology four-tier model, according to which TC are low malignancy tumors, AC intermediate malignancy tumors and LCNEC/SCC high malignancy tumors with no significant differences in survival among them. Inconsistencies in diagnostic reproducibility, troubles in the therapy of AC and LCNEC, and limitations to histology within the same tumor category argue in favor of a global rethinking of lung NET where a grading system could play a role. This review outlines three main key questions in the field of lung NET: (A) unbiased diagnoses, (B) the role of Ki-67 and tumor grading, and (C) management of predictive markers. Answers are still inconclusive, thus additional research is required to improve our understanding on lung NET.

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Approaching lung NET

The new 2015 WHO classification on lung neuroendocrine tumors (NET)[1] has substantially confirmed the four widely agreed upon histological variants crystallized in the two previous editions of 1999[2] and 2004,[3] namely typical carcinoid (TC), atypical carcinoid (AC), large-cell neuroendocrine carcinoma (LCNEC), and small cell carcinoma (SCC). Remarkably, in this 2015 edition, these tumors have been pushed to enter a unique box of NE proliferations by moving LCNEC from the all-inclusive chapter of large-cell carcinoma, and adding diffuse idiopathic pulmonary NE cell hyperplasia (DIPNECH) as a pre-invasive lesion with a potential toward the development of carcinoids.[1] There are several practical reasons why this traditional terminology of lung NET has been retained in the new 2015 WHO classification, which is the result of widely shared expert opinions according to the current state of the art.[1,4] The term carcinoid, either typical or atypical, has been gaining wide popularity and diagnostic awareness among pathologists and clinicians while valuable alternatives are still lacking.[1,4] Likewise, the other two histological variants, either LCNEC or SCC, are deemed to be full-blown high-grade carcinomas occurring in either pure or combined forms, which are almost relentlessly characterized by aggressive clinical behavior and dismal prognosis.[1,4–8]

There is general agreement that this four-tired histological classification is consistent with an operational three-tier prognostic scheme on the basis of epidemiological (age, sex, and smoking habit), genetic (association with MEN1 syndrome and several other gene pathways), clinical (lymph node and distant metastases, association with paraneoplastic syndromes, type and response to therapy) and behavioral traits, which results in progressive grades of biological aggressiveness.[1,9–14] Accordingly, TC is deemed to be a low malignancy tumor with longer life expectation and time to recurrence, AC an intermediate malignancy tumor with more aggressive clinical course, somewhat unpredictable clinical behavior and shorter time to recurrence, and LCNEC and SCC high malignancy tumors with dismal prognosis, challenging therapy options and, often, difficulties in reliably distinguishing from each others, either pathologically, genetically or clinically.[1,4,8,14–19]

As a function of cell differentiation and in keeping with the recent European Neuroendocrine Tumor Society (ENETS) guidelines[4] and the current WHO classification,[1] TC and AC as a whole are considered well-differentiated NE tumors because of their resemblance to the normal cell counterpart of the NE diffuse system or hyperplastic or pre-invasive lesions, such as neuroendocrine tumorlets and DIPNECH, respectively, as opposed to LCNEC and SCC, which are thought to make up a poorly differentiated tumor group.[1,20,21] As a matter of fact, TC and AC feature organoid growth patterns, typical to slight atypical cytology (even though they may uncommonly exhibit prominent nuclear pleomorphism) (Fig. 1), absent to focal punctate necrosis, up to 10 mitoses per 2 mm^2 and consistent labeling for pan-NE markers, such as chromogranin A and synaptophysin, sometimes less intense and uneven in the setting of AC.[1,4,12,14] Cytological atypias or diverse cyto-histological features, such as clear cells, oncocytic cells, spindle cells even with meningothelioid whorls, melanin or mucus deposition, psammoma bodies, bone metaplasia and pseudoglandular, papillary or follicular configuration, do not help to distinguish TC and AC, whose separation relies on mitotic count and/or necrosis occurrence only.[1] On the contrary, SCC and LCNEC show solid growth patterns, extensive/geographic necrosis, mitotic count higher than 10 mitoses per 2 mm^2, and uneven labeling for pan-NE markers.[1,4,12,14] Cytological criteria are then used to split SCC from LCNEC, although there is a considerable morphologic overlap between them making this separation quite subjective and difficult to carry out, with disappointingly low interobserver diagnostic reproducibility.[12,15,16,22–25]

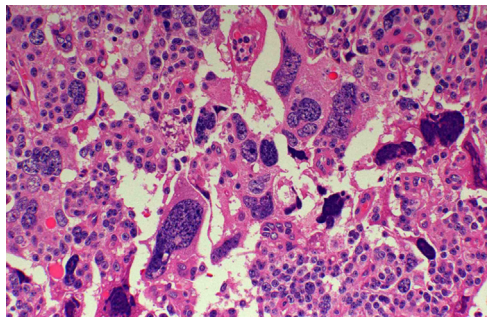

Fig. 1 – Typical carcinoid of the lung (no necrosis; 1 mitosis/2 mm^2) with huge nuclear pleomorphism in tumor cells: this feature is not *per se* diagnostic of atypical carcinoid.

The molecular scenario of lung NET has been pushed to emerge by several studies confirming the assumption that there are two distinct groups in lung NET. As a matter of fact a dichotomous separation between low to intermediate malignancy tumors on the one hand (i.e., TC and AC) and high malignancy tumors on the other hand (i.e., SCC and LCNEC) is solidified by substantial differences in gene pathway alterations, levels of differentiation and cell derivation.[8,12,26–32] Accordingly, it is not surprising that common genetic traits may be shared by each of these two broad tumor categories, with TC/AC on the one hand and LCNEC/SCLC on the other hand exhibiting major differences in the somatic mutation rates and engagement of diverse gene pathways.[8,12,26–33] A further inherent molecular heterogeneity, however, is found within each histological variant on the basis of several functional and genetic biomarkers, which may identify different patient subsets with different prognosis.[31,34–37]

All these assumptions suggest the opportunity to reevaluate lung NET keeping in mind that all lung NET are malignant, that the malignancy rate has to be quantified for clinical purposes of personalized therapy, and that malignancy may be paralleled by several biological and functional factors, among which a grading system specifically devised for the lung could play a pivotal role in the clinical management of the patients.[13] The ultimate and ambitious goal is to improve our understanding in the field of lung NET tumors, placing them into context for the best practice of these patients.

Designing the article

A review of papers reported on the issue of lung NET with special reference to diagnosis, Ki-67, grading and predictive