An Unmet Need in the WHO 2015 Biopsy Classification: Poorly Differentiated NSCCs with Positive Neuroendocrine Markers

To the Editor:

It is with great interest that we read the recent World Health Organization (WHO) Classification 2015 of lung tumors and the state-of-the-art concise review by Travis et al. published in the Journal of Thoracic Oncology.1 The diagnostic criteria for small biopsy specimens are especially interesting and clinically relevant.

The new classification for biopsy specimens to diagnose non–small cell lung carcinoma (NSCLC) without clear morphologic features is driven largely by immunohistochemical (IHC) markers. This classification (Fig. 1) categorizes NSCLC as follows: (1) non–small cell carcinoma (NSCC), favor adenocarcinoma (positive for thyroid transcription factor 1), (2) NSCC, favor squamous cell carcinoma (p63/p40+), or (3) NSCC, not otherwise specified (no morphologic features and negative for IHC markers). Moreover, when neuroendocrine (NE) morphologic features are present, testing for NE markers should be performed, and when the results are positive, the diagnosis “NSCC, favor large cell NE carcinoma (LCNEC)” is preferred. Finally, the diagnostic term for NSCC with morphologic features of NE in the absence of NE IHC markers is NSCC when LCNEC is suspected but stains fail to demonstrate NE differentiation. Following this classification, one category is missing, namely, NSCC without distinct (NE) morphologic features but with positive NE IHC markers, which in this letter is referred as NSCC NE IHC+ (see Fig. 1).

The value of the diagnosis NSCC NE IHC+ has been heavily debated. As many as 10% to 30% of surgically resected NSCLCs have NE differentiation in IHC staining, but no clear association with prognosis has been reported.2,3 These studies were based on NSCLC with morphologic features of squamous cell carcinoma or adenocarcinoma, however, and often only a single NE IHC marker was positive. Moreover, these studies did not report on poorly differentiated NSCC NE IHC+ in the absence of thyroid transcription factor 1 or P63 staining. Therefore, the value of an NSCC NE IHC+ classification on the basis of biopsy specimens is rather unclear and requires further investigation.

Because an NE growth pattern in biopsy specimens is difficult to recognize, the diagnosis LCNEC may be missed and the incorrect diagnosis of NSCC not otherwise specified made. This misdiagnosis is problematic because the prognosis of LCNEC has been shown to be worse than that of squamous cell carcinomas and adenocarcinomas.4 Moreover, we have observed that since 2007, the diagnosis of LCNEC on the basis of biopsies has increased dramatically in the Netherlands and that in approximately 54% of cases, the diagnosis was based on positive NE IHC markers and the pathology reports did not mention morphologic features of NE carcinoma.5 These results indicate that although not advised by the current WHO classification, NE IHC markers have been commonly used in daily practice with undifferentiated carcinomas (NSCCs) in biopsy specimens.

In conclusion, we think that the diagnosis poorly differentiated NSCC NE IHC+ on the basis of biopsy specimens could be of clinical importance and is an unmet need in the current WHO classification. Future studies should provide more insight into this diagnosis on the basis of biopsy specimens.

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Testing for Neuroendocrine Immunohistochemical Markers Should Not Be Performed in Poorly Differentiated NSCCs in the Absence of Neuroendocrine Morphologic Features according to the 2015 WHO Classification

In Response:
In contrast to the recommendations of the 2015 World Health Organization (WHO) classification of tumors, Derks et al. suggest that testing for neuroendocrine (NE) immunohistochemical markers should be performed on all poorly differentiated non–small cell carcinomas (NSCCs) lacking NE morphologic features and reported. We considered this suggestion in our preparation of the WHO classification, and the topic was discussed in detail. For the 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society lung adenocarcinoma classification, we conducted an evidence-based review that addressed this topic specifically. Because there are no consistent evidence-based data in the literature to support any clinical relevance (diagnostic, prognostic, or therapeutic) of a positive NE marker in the absence of NE morphologic features, the 2015 WHO Classification recommends that testing for NE markers not be performed on all poorly differentiated NSCCs in the absence of NE morphologic features. This recommendation is specifically presented on page 20 of the WHO blue book, and this detail could not be included in the short review provided for the Journal of Thoracic Oncology. Only if there is a suggestion of NE morphologic features is testing for NE immunohistochemical markers appropriate. In addition, the problem of NSCC with NE differentiation

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References