New staging system for pulmonary neuroendocrine tumors: A clinical and pathologic necessity

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Although neuroendocrine tumors are rare, their incidence has been increasing in recent years.¹ Pulmonary neuroendocrine tumors (PNETs) consist of a heterogeneous group of tumors—typical carcinoid (TC), atypical carcinoid, large cell neuroendocrine carcinoma, and small cell carcinoma—that share morphologic, molecular, and immunohistochemical characteristics.² These tumors are graded according to mitotic activity, presence of necrosis, and Ki-67 proliferation index. Survival analysis has shown that large cell neuroendocrine carcinoma and small cell carcinoma exhibit the worst survival, whereas TC has the best.³ The importance of PNET grading is highlighted by its inclusion in the National Comprehensive Cancer Network guidelines for patient management.⁴ The TNM staging system used for PNETs is the same as for non-small cell lung cancer (NSCLC).⁵ Although this approach is convenient, the staging of PNETs may benefit from more specific criteria because their pathologic and clinical outcomes are highly variable among different subtypes when compared with NSCLC.³

To this end, Cattoni and colleagues⁶ analyzed clinical and pathologic data from 510 cases of resected primary grade 1 (G1) TC, grade 2 (G2) atypical carcinoid, and grade 3 (G3) large cell neuroendocrine carcinoma from 8 centers and their results are presented in this issue of the *Journal*. Cattoni and colleagues⁶ compared disease-free survival (DFS) with either a modified staging system or the seventh edition TNM staging system for NSCLC. In applying their proposed staging system—IA (pT1-2G1), IB (pT3G1, pT1G2), IIA (pT4G1, pT2-3G2, pT1G3), IIB (pT4G2, pT2-3G3), and III (pT4G3)—Cattoni and colleagues⁶ found a clear difference in 5-year DFS (98%, 81%, 69%, 52%, and 0%, respectively) compared with stratification according to the seventh edition TNM staging system (5-year DFS

Hematoxylin and eosin staining (×400) of atypical carcinoid demonstrating mitoses (arrow).

Central Message

A modified staging system that incorporates tumor grades may be beneficial for pulmonary neuroendocrine tumors.

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95%, 92%, 68%, 71%, and 65% for stages IA, IB, IIA, IIB, and III, respectively).

This study by Cattoni and colleagues⁶ is relevant and important because it includes a large, multi-institutional cohort. They evaluated DFS, which is a better statistical metric for cancer-related deaths than overall survival and reflects tumor biology.⁷ Furthermore, the proposed staging system is practical and simpler to reproduce.

However, this study does have several limitations. The study design was retrospective, the inclusion criteria may hamper generalizability, and, despite the large cohort, 67% of the cases were TC, which already have a good prognosis.^{8,9} Furthermore, the inclusion of cases without lymph node sampling or dissection may explain why lymph node metastasis was not found to be a statistically significant contributing factor. Additionally, the distribution of surgical procedures (wedge 15% vs anatomic 77%) indicates that procedure choice may also be a relevant factor. The absence of a central pathologist and the lack of a second review of histologic slides limit the validity of the pathologic data.

Despite these limitations, Cattoni and colleagues⁶ should be commended for their multi-institutional efforts to address this clinical necessity. The proposed staging system provides a platform for future studies, with a study design that incorporates clinical and pathologic variables, including predetermined pathologic criteria, and a comparison of outcomes with the eighth edition of the TNM classification system.

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