Pulmonary Neuroendocrine Carcinomas: Progress and Pitfalls

This issue of *JNCCN–The Journal of the National Comprehensive Cancer Network* contains the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Small Cell Lung Cancer (SCLC) and other neuroendocrine lung tumors. Overall, these tumors constitute approximately 20% of all lung cancers, with SCLC accounting for 15%, large cell neuroendocrine carcinoma (LCNEC) 2% to 3%, and carcinoid tumors 1% to 2%. Pulmonary neuroendocrine cancers (NECs) are generally categorized by grade: high-grade (SCLC, LCNEC), intermediate-grade (atypical carcinoid), and low-grade (typical carcinoid).

Developing guidelines for pulmonary NECs, including SCLC, is hampered by at least 2 factors. First, the pathologic distinctions between these tumors are not as clear-cut as most clinical oncologists would like to believe. This is particularly problematic in the case of LCNEC, as noted by Glisson and Moran in their article in this issue. Second, the declining incidence of SCLC and the relative rarity of other lung NECs have resulted in a paucity of randomized phase III clinical trials. For LCNEC and bronchial carcinoid tumors, even prospective phase II clinical trials are virtually nonexistent. Therefore, many of our therapeutic recommendations for specific clinical scenarios are based on retrospective analyses or inference from data on more common tumors.

LCNEC presents a particularly difficult area of ongoing debate in thoracic oncology. This controversy is highlighted by the contrary conclusions regarding appropriate management drawn by the NCCN Guidelines Panel for SCLC and by Glisson and Moran in their accompanying article. After reviewing the same data, the NCCN Guidelines Panel recommends that LCNEC should be managed per the NCCN Guidelines for Non–Small Cell Lung Cancer, whereas Glisson and Moran suggest that treatment should follow those for SCLC. Despite being the chair of the NCCN Guidelines Panel for SCLC and reviewing the available data on an annual basis, I must admit that I do not know which of these recommendations is most appropriate. The literature on this topic is frankly inconclusive, consisting almost entirely of relatively small, retrospective series with heterogeneous populations and treatments. Having cared for many patients with LCNEC over the years and using a variety of treatment approaches, I have come to believe that these cancers represent the worst of both worlds: they are nearly as aggressive as SCLC but respond much more like NSCLC, even when treated with an “SCLC regimen,” such as platinum plus etoposide.

Developing guidelines for managing SCLC would seem to pose little challenge since, as my colleagues in other disciplines like to point out, little has really changed over the past couple of decades. Although many rational attempts to develop both empiric and targeted therapeutic strategies have failed to improve patient outcomes, modest advances have been made with the incorporation of PET into the staging algorithm, refinements in combined modality therapy, and the broader use of prophylactic cranial irradiation.

This issue of *JNCCN* takes us “back to the future” with Schneider et al.’s exploration of the data supporting surgery for the treatment of SCLC. Although the NCCN Guidelines for SCLC have always advocated surgical resection as the primary treatment option for patients with true stage I (T1–2,N0,M0) disease, there is a dearth of high-quality studies to support this recommendation. In recent years, despite a resurgence in interest in this topic within the thoracic surgery community, the primary additions to the literature have been retrospective reviews of institutional or registry data. That said,
both Schneider et al. and the NCCN Guidelines Panel for SCLC agree that surgery followed by adjuvant chemotherapy with or without radiotherapy remains the preferred treatment option for the small subgroup of patients with stage I SCLC.

The NCCN Guidelines Panels strive to provide comprehensive recommendations to assist in caring for patients with a wide variety of both common and uncommon malignancies. However, for many less-common tumors, high-quality clinical trials have not been done and probably never will be. NCCN continues to incorporate evidence-based methods into the guidelines development process, but the core of NCCN Guidelines is the consensus opinion of experts in the field. Guidelines organizations that rely solely on high-quality clinical trial data must commonly conclude, especially for less-common cancers, that “available evidence does not allow for a definitive recommendation regarding treatment.” Such comments are not helpful to practicing physicians. By including consensus drawn from both evidence and experience, the NCCN Guidelines present oncologists with reasonable management options for the many clinical situations in which high-quality clinical trials are either not available or have not yielded definitive data. As highlighted by the pulmonary NEC guidelines and accompanying articles in this issue, the results are not always as straight-forward and scientific as we would like. But they do offer educated, practical guidance, which is, after all, the primary goal of a guideline.