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EDITORIAL

Are Neuroendocrine Tumors Going Mainstream?

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Neuroendocrine tumors were thrust to the forefront of the oncology world last year with the much-heralded approval of two drugs, everolimus and sunitinib, for the treatment of advanced pancreatic neuroendocrine tumors.[1,2] The large, prospective randomized trials leading to these approvals were a clear break from the recent past, when clinical practice was based, in large part, on small institutional series and anecdotal experience. Less well publicized have been parallel advances in the development of methods to increase understanding of the clinical behavior of this diverse group of malignancies. The American Joint Committee on Cancer (AJCC) and similar organizations recently adopted formal pathologic staging and histologic classification schemes for neuroendocrine tumors. In the article that accompanies this editorial, Strosberg et al[3] report on a large series of more than 600 small bowel carcinoid tumors and evaluate how well these new systems work.

Remarkably, formal TNM staging systems were first adopted for neuroendocrine tumors only in the last decade. The first of these systems was developed by the European Neuroendocrine Tumor Society (ENETS) during a consensus conference held in 2006.[4,5] The AJCC formally adopted a TNM staging system for neuroendocrine tumors in 2010. Although broadly similar to the system used by ENETS, the AJCC system differs in some respects with its classification of pancreatic neuroendocrine tumors and appendiceal carcinoids.[6] Several investigators have now performed validation studies of these staging systems in large institutional series.

Although both the ENETS and the AJCC systems have been broadly validated for pancreatic neuroendocrine tumors, recent studies have also suggested that that the systems are not completely interchangeable. A European study of more than 1,000 patients with pancreatic neuroendocrine tumors, for example, found that the ENETS system provides more definitive and detailed prognostic information than AJCC system in this setting.[7,8] Differences between the AJCC and ENETS staging systems for small bowel carcinoid are minimal, and both European investigators as well as the current North American–based study by Strosberg et al[3] have now confirmed their general prognostic validity.[9] However, as with pancreatic neuroendocrine tumors, several observations suggest that future revisions may be warranted. For example, there seem to be minimal differences in outcome in node-negative (stage I and II) resected small bowel carcinoid tumors, which suggests that tumor size and depth of invasion have little independent impact on outcome. Strosberg et al additionally point out that lymph node status alone seems to have less of an impact on prognosis than whether lymph nodes and associated mesenteric disease have been resected. These findings are consistent with clinical experience. It is often the associated mesenteric disease rather than the primary tumor itself that is the main contributor to patient morbidity.

The optimal histologic classification of neuroendocrine tumors remains controversial. The importance of histologic grade in determining outcomes for neuroendocrine tumors is broadly accepted and has been recognized by WHO for years.[10] Conversely, defining the boundaries between histologic categories has proved challenging. A current classification scheme, first recommended by ENETS and subsequently adopted by the AJCC, uses a mitotic count cutoff of less than two per 10 high-powered fields (hpf) and a Ki-67 proliferative index of no more than 2% to define the boundary between the most indolent low-grade tumors and the somewhat more aggressive intermediate-grade group.[11] Strosberg et al[3] suggest that, at least for small bowel carcinoid tumors, a mitotic count cutoff value of less than five per 10 hpf more reliably distinguishes between truly indolent low-grade tumors and their intermediate-grade counterparts. Recent data from studies in pancreatic neuroendocrine tumors similarly suggest that the Ki-67 proliferative rate index cutoff distinguishing low- and intermediate-grade tumors could potentially be raised from 2% to 5%.[8,12]

Parallel questions surround the histologic definition of high-grade tumors. According to current classification systems, tumors with a mitotic rate of more than 10 mitoses per 10 hpf or a Ki-67 proliferative index of more than 20% are classified as high grade.[11] The distinction between low-, intermediate-, and high-grade tumors is of more than academic interest, given that it has potentially significant clinical implications. In general, high-grade tumors are treated with platinum-based chemotherapy regimens. In contrast, patients with more slowly growing low- or intermediate-grade tumors are more likely to benefit from treatment with somatostatin analogs or targeted therapies.[1,2,13] A recent retrospective study of 252 patients with high-grade tumors suggests that the Ki-67 cutoff value of 20% may be too low to effectively distinguish between these groups. In this study, platinum-based therapy was beneficial primarily in the group of patients with a proliferative index of more than 55%, and seemed to offer little benefit to the group of patients with lower Ki-67 indices.[14] Additional studies that correlate tumor histology not only with prognosis but also with treatment outcomes are likely to be helpful in further refining histologic classifications.

Although not a primary focus of the article, the findings by Strosberg et al[3] highlight a persistent and vexing question regarding survival durations for patients with neuroendocrine tumors. There is surprisingly limited data regarding median disease-free and overall

survival. Studies using the population-based SEER database have suggested a median survival duration of 2 years for patients with advanced pancreatic neuroendocrine tumors and 4.7 years for patients with advanced small bowel carcinoid.[15] The single-institution data from Strosberg et al suggest that the median overall survival for patients with metastatic small bowel carcinoid tumors is 8.6 years. Clearly, selection bias may be contributing to these results. A second potential explanation for this discrepancy, although one which seems to play a lesser role in the current series, is the problem of so-called immortal time bias, in which patients who live longer are more likely to be seen at a tertiary referral center and included in that institution's database.

Nevertheless, the possibility that some patients with advanced neuroendocrine tumors may experience prolonged survival raises a number of questions regarding treatment strategies. Recent positive randomized studies of octreotide, everolimus, and sunitinib in patients with advanced neuroendocrine tumors have understandably used time to tumor progression or progression-free survival, rather than overall survival, as their primary end point.[1,2,13] Initiation of these therapies clearly has some urgency in patients with only a few years to live. Conversely, in an asymptomatic patient who may continue to feel well for 5 or more years, waiting to initiate treatment might be the more prudent option.

Just how to determine where patients fall within this spectrum, and how best to treat them, is likely to require not only improvement in the definitions of stage and grade, but also advances in our fundamental understanding of neuroendocrine tumor biology. The positive results that have been observed with sunitinib and everolimus have led to a number of ongoing clinical trials of drugs and drug combinations targeting the vascular endothelial growth factor and mammalian target of rapamycin pathways. Looking beyond these pathways, a recent study reported previously unsuspected mutations in *DAXX* and *ATRX*, genes implicated in the maintenance of chromatin structure and telomere stability, in pancreatic neuroendocrine tumors.[16,17] One can hope that that these and similar discoveries will begin to shed light on additional targets and treatment strategies.

Neuroendocrine tumors have spent several decades perceived as a rarely seen, eccentric relative in the oncology family. Although they are certainly unusual, it has become increasingly clear that they can and should be evaluated with the same critical attention previously reserved for their better known oncologic counterparts. Such rigor will be essential as we build on the encouraging successes of the last few years.

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REFERENCES

1. Raymond E, Dahan L, Raoul JL, et al: Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med 364:501-513, 2011
2. Yao JC, Shah MH, Ito T, et al: Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med 364:514-523, 2011
3. Strosberg JR, Weber JM, Feldman M, et al: Prognostic validity of the American Joint Committee on Cancer staging classification for midgut neuroendocrine tumors. J Clin Oncol 31:420-425, 2013
4. Rindi G, Klöppel G, Alhman H, et al: TNM staging of foregut (neuro)endocrine tumors: A consensus proposal including a grading system. Virchows Arch 449:395-401, 2006
5. Rindi G, Klöppel G, Couvelard A, et al: TNM staging of midgut and hindgut (neuro) endocrine tumors: A consensus proposal including a grading system. Virchows Arch 451:757-762, 2007
6. Edge SB, Byrd DR, Compton CC, et al: AJCC Cancer Staging Manual (ed 7). New York, NY, Springer, 2010
7. Strosberg JR, Cheema A, Weber J, et al: Prognostic validity of a novel American Joint Committee on Cancer Staging Classification for pancreatic neuroendocrine tumors. J Clin Oncol 29:3044-3049, 2011
8. Rindi G, Falconi M, Klersy C, et al: TNM staging of neoplasms of the endocrine pancreas: Results from a large international cohort study. J Natl Cancer Inst 104:764-777, 2012
9. Jann H, Roll S, Couvelard A, et al: Neuroendocrine tumors of midgut and hindgut origin: Tumor-node-metastasis classification determines clinical outcome. Cancer 117:3332-3341, 2011
10. Solcia E, Klöppel G, Sobin LH: Histological Typing of Endocrine Tumours (ed 2). Berlin, Germany, Springer, 2000
11. Klimstra DS, Modlin IR, Coppola D, et al: The pathologic classification of neuroendocrine tumors: A review of nomenclature, grading, and staging systems. Pancreas 39:707-712, 2010
12. Scarpa A, Mantovani W, Capelli P, et al: Pancreatic endocrine tumors: Improved TNM staging and histopathological grading permit a clinically efficient prognostic stratification of patients. Mod Pathol 23:824-833, 2010
13. Rinke A, Müller H, Schade-Brittinger C, et al: Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: A report from the PROMID Study Group. J Clin Oncol 27:4656-4663, 2009
14. Sorbye H, Welin S, Langer SW, et al: Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): The NORDIC NEC study. Ann Oncol [epub ahead of print on September 11, 2012]
15. Yao JC, Hassan M, Phan A, et al: One hundred years after "carcinoid": Epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 26:3063-3072, 2008
16. Jiao Y, Shi C, Edil BH, et al: DAXX/ATRX, MEN1, and mTOR pathway genes are frequently altered in pancreatic neuroendocrine tumors. Science 331:1199-1203, 2011
17. Heaphy CM, de Wilde RF, Jiao Y, et al: Altered telomeres in tumors with ATRX and DAXX mutations. Science 333:425, 2011

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