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EDITORIAL – ENDOCRINE TUMORS

First Differentiate and Then Operate (Or Not)

Editorial on "Surgical Treatment of Patients with Poorly Differentiated Pancreatic Neuroendocrine Carcinoma: An NCDB Analysis"

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In their article, Kaslow et al.[1] use the National Cancer Database (NCDB) to study the impact of surgical resection in patients with poorly differentiated pancreatic neuroendocrine carcinoma (PanNEC). They identified 1473 patients with poorly differentiated grade (defined herein as Grade 3 (G3) 'poorly differentiated' or Grade 4 (G4) 'undifferentiated; anaplastic') and observed that patients with PanNEC underwent surgical resection in 31% of cases (when compared with 83% of patients with well-differentiated pancreatic neuroendocrine tumors [PanNETs]). They furthermore used propensity score matching in an attempt to correct for bias in patient selection for surgical resection and noted that surgery remained associated with longer overall survival when stratified by differentiation (36 vs. 8 months for PanNEC). The authors conclude that patients with PanNEC should be considered for surgical resection.

High-grade pancreatic neuroendocrine neoplasms (PanNENs) are a heterogeneous entity with varying biological behavior and prognosis. The 2010 WHO classification for PanNENs limited the term 'carcinoma' to G3 neoplasms (defined as a Ki-67 >20%), which reflected the idea that tumor grade was the only determinant of prognosis.[2] However, recent studies have shown that tumor morphology is an important predictor of tumor biology in high-grade NENs. A poorly differentiated morphology, defined as small cell and large cell carcinomas with pleomorphic and highly atypical nuclei, solid growth pattern, and abundant non-ischemic necrosis is associated with a significantly worse prognosis than a well-differentiated morphology, regardless of grade. This led to a reclassification of high-grade PanNENs by the WHO in 2017, which took both tumor morphology and grade into account.[2,3] High-grade PanNENs are now subclassified as well-differentiated G3 (Ki-67 >20%) PanNETs and poorly differentiated PanNECs.

Some clinicians have observed different response rates to radiolabeled therapies such as ^{177}Lu DOTATATE and chemotherapy regimens in poorly differentiated NECs (PDNECs), and have proposed to further subclassify them as NECs with Ki-67 ≤55% and Ki-67 >55%.[2,4,5]

A recent study has analyzed the molecular differences in high-grade gastroenteropancreatic NENs and found distinct differences in driver mutations between PDNECs (TP53 [64%], APC [28%], KRAS [22%], and BRAF [20%]) and well-differentiated, high-grade NETs (MEN1 [21%], ATRX [17%], DAXX, SETD2 and TP53 [each 14%]), potentially explaining the heterogeneous biology and treatment response within this group.[6]

As surgeons, understanding the intricate differences in classifying high-grade NENs is crucial to a sound approach when considering which patients we should operate on. It certainly makes sense, for example, to operate on a patient with a localized, well-differentiated G3 PanNET. It might even make sense to operate on such a patient in the presence of limited liver metastases if the tumor expresses somatostatin receptors (SSTR2), as seen on DOTATATE imaging, and if tumor growth can be controlled on somatostatin analogs for several months prior to surgery. These factors would be indicative of a favorable long-term prognosis (biology is king!) and make aggressive surgical debulking a reasonable option in addition to other local and systemic therapies.

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However, I would suggest interpreting the findings from this NCDB analysis with caution. Beyond the usual limitations that are intrinsic to NCDB analyses (selection bias, incomplete or erroneous data collection, retrospective design, etc.), in my opinion this study suffers most from the inability to differentiate between subgroups of high-grade NENs.

It is quite probable that the favorable overall survival reported in the PanNEC group in this study is due to the inclusion of a sizeable group of well-differentiated grade 3 NETs or even misclassified lower-grade tumors. For example, the authors rightfully state, "PanNEC account for 2–3% and are thought to have uniformly poor prognosis regardless of treatment" in their introduction. However, approximately 17% of their NCDB PanNEN cohort qualified as high grade/poorly differentiated or anaplastic and the reported median overall survival for PanNECs undergoing surgical resection was an astounding 36 months (similar to that of well-differentiated NETs without surgery). In our experience, patients with high-grade, poorly differentiated, small or large cell morphology have low 1- to 2-year survival rates, despite cytotoxic platinum-based chemotherapy, and do not benefit from surgical intervention. This is in line with previous studies reporting a median overall survival of 5.8–14.8 months in PDNEC, despite chemotherapy.[7,8]

It is also not clear how many PanNEC patients in the propensity-matched group had distant metastases, but due to their aggressive behavior it remains exceedingly rare in our experience to see a patient with a poorly differentiated small or large cell PanNEC that has not metastasized at presentation. Here, it is also worth noticing that since most PDNECs (unlike their well-differentiated G3 counterparts) do not express SSTR2, evaluation for distant metastatic spread should include F-fluorodeoxyglucose (FDG) positron emission tomography (PET) and not DOTATATE PET.[2,3]

In order to make appropriate treatment recommendations for high-grade NENs, one should first determine in which category the patients fall (well-differentiated G3 vs. poorly differentiated NEC with Ki67 $\leq$55% or >55%), stage them with the appropriate modality, and finally, carefully examine, in a multidisciplinary manner, which patients may benefit from surgical intervention.

DISCLOSURE Xavier M. Keutgen declares no potential conflicts of interest.

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