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## Invited Commentary

### Is radical ever too radical?



Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) are heterogeneous lesions with varied presentations, clinical courses, and prognoses. Some of these neoplasms display a very benign behavior, while others are extremely aggressive. Appropriately determining which patients will benefit from curative resection attempts is often difficult. While indications for resection of metastatic GEP-NENs continues to evolve, those with high grade (G3) lesions have not traditionally thought to benefit from curative intent surgery.<sup>1,2</sup> The authors of this paper question this paradigm and suggest an intent-to-cure resection is beneficial to highly selected patients with stage IV G3 GEP-NENs.<sup>3</sup> Their retrospective multi-site review of 15 patients reports an increase in expected median overall survival (OS) for resected patients when compared to historical controls treated with systemic treatment only. They astutely recognize the studies' limitations in that it is a highly selected cohort in which an intent-to-treat analysis is not possible to perform. Despite these shortcomings, a few key findings are very enlightening.

While 11 (73%) patients had a margin negative resection, all had disease recurrence with a median recurrence free survival (RFS) of 8 months. The authors argue that while the RFS is short, the median OS of 59 months would suggest a benefit compared to historical reports of patients receiving only systemic treatment. However, with a median recurrence at 8 months and a survival of 59 months we can see that these patients had a median survival after recurrence of 51 months. This is despite the fact that only 4 of these patients received any post-operative systemic treatment. To me this suggests very indolent disease in these selected patients, and one wonders how well they would have done without the resection? This question becomes particularly difficult to answer in this patient cohort as two-thirds of these patients would probably have had a resection regardless of their tumor grade.

In this study, 5 patients presented with incidental disease and 10 were symptomatic. While the data is limited about the 10 symptomatic patients, many of their diagnoses suggest a palliative operation was appropriate regardless of tumor grade. When we look further at the 5 patients who were incidentally discovered, 3 of them went on to receive pre-operative systemic therapy. Presumably these 3 patients only would have been offered resection if their GEP-NENs had not progressed, thereby favorably selecting them as having more indolent disease. Importantly, we do not know the denominator regarding how many incidentally discovered high grade GEP-NENs were started on systemic treatment and subsequently not offered resection, thereby significantly skewing the final survival data. When we look at the 2 patients in the study who did not have another surgical indication for resection (i.e. symptomatic) or biologic selection (i.e. pre-operative systemic therapy), we find 1 patient with a poorly differentiated neuroendocrine carcinoma (NEC)

and 1 with a well-differentiated G3 neuroendocrine tumor (NET).

The patient with the ileal NEC had a resection of their primary tumor, liver metastases, and omental implant. The pathologic margins were positive, they underwent post-operative systemic treatment, had a recurrence 8 months post-resection, and died after 18 months. Limited resection of peritoneal implants is generally considered cytoreductive and therefore this patient's early recurrence is not unexpected. This outcome is in line with other surgical series of patients with stage IV poorly differentiated GEP-NENs resected from their liver that reported median overall survivals 6 and 15 months.<sup>4,5</sup> The patient with the G3 pancreatic NET and liver metastasis had a similar time to recurrence (7 months), but was still alive at 32 months. Again, not unexpected that this patient fared better as we know that patients with well-differentiated G3 tumors have improved survival over patients with poorly-differentiated tumors.<sup>6,7</sup> Of note, in each of these previous series, the primary tumor may not have been resected and the operation was not necessarily performed with a curative intent. Despite those caveats, the outcomes are similar to the 2 unselected patients in this report.

When considering an operation for a patient, the surgeon must weigh the chance of cure against the impact on the patient's quality of life. For patients who are symptomatic, surgery may impart a significant palliative improvement. However, for patients with incidentally discovered tumors this is not the case and the extent of the proposed resection must balance the associated morbidity with the expected outcome. The rubric for a patient with asymptomatic, oligometastatic G3 disease will be different depending on whether the primary tumor is in the pancreatic head requiring a Whipple procedure or is a small bowel tumor requiring a comparatively limited resection. Keeping in mind that neither of these hypothetical patients are likely cured of their disease, we must carefully assess the risk of significant life-altering complications against the questionable benefit of a limited disease free interval.

I applaud the author's work to shine more light on this difficult clinical question. I think that the key takeaway from this study is that we need to select the right patients for the right treatment. For patients with symptomatic, oligometastatic G3 GEP-NENs it likely makes sense to offer resection for palliation, understanding that disease control is unlikely. For patients with incidentally discovered disease the case is less clear and a test of biology with systemic treatment may allow for the selection of a subset of these patients with more indolent disease. However, it continues to be unproven if offering a resection to these patients provides benefit.

#### Declaration of competing interest

I have no conflicts of interest

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