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EDITORIAL – GASTROINTESTINAL ONCOLOGY

It May Not Be Too Little or Too Late: Resecting Primary Small Bowel Neuroendocrine Tumors in the Presence of Metastatic Disease

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In 2000, neuroendocrine tumors (NETs) surpassed adenocarcinoma as the most common type of small bowel tumor[1] and 2006 had an annual incidence of 12 cases per million.[2] In national databases, 34% of neuroendocrine tumors present with metastatic disease,[3] and this may rise to as high as 80% in select tertiary referral centers.[4]

For patients with metastatic disease, resection of the primary tumor and cytoreduction of liver metastases are the preferred approach where possible to improve long-term survival.[5] In series requiring that 90% cytoreduction be achieved, only about 20% of all patients may undergo surgical treatment,[6] whereas if the cytoreduction threshold is lowered to 70%, then up to three-fourths of patients may have cytoreduction attempted.[7] Similar improvements in overall survival have been seen for patients, achieving 70–90% and more than 90% cytoreduction.[5]

In cases for which this level of cytoreduction cannot be achieved or would not be attempted, a strong argument can be made for resecting primary small bowel neuroendocrine tumors (SBNETs) causing symptoms for patients. Another very important and still unanswered question is whether resection of the primary SBNET without cytoreduction of metastatic disease leads to improved survival. Many possible reasons why this could be true can be given. Small bowel tumors may cause obstruction, bleeding, or bowel ischemia, all of which may shorten a patient's lifespan. This also will lead to more emergency operations with poorer outcomes and less complete removal of multifocal tumors or enlarged nodes, potentially leading to future problems. As these tumors slowly enlarge, they may grow through the bowel wall and lead to carcinomatosis, which puts the patient at further risk for bowel obstruction. Finally, if the primary tumors and their nodal metastases are left in place, they may continue to metastasize to the liver, and because patients ultimately die of liver replacement, removal of the primary tumor may slow this progression.

Multiple single and multi-institutional studies have retrospectively examined whether removing the primary SBNET improves survival when metastatic disease is present, and most have shown benefit. Hellman et al.[8] found a median overall survival (OS) of 7.4 years for 249 patients with SBNETs (80.6% with liver metastases) who had their primary tumor resected, in contrast to 4 years for 63 patients who did not undergo resection, which remained significant when the patients without liver metastases were excluded. Ahmed et al.[9] found significantly improved OS for 209 patients with SBNETs and liver metastases who had primary tumor resection compared with 151 patients who had no resection performed (median OS, 9.9 vs 4.7–6.7 years, respectively; relative risk, 0.26). A smaller study by Givi et al.[10] examined outcomes for 84 patients with SBNETs and unresectable liver metastases, where the primary tumor was resected for 60 of the patients and not resected for 24 of the patients. Both groups were similar in terms of Karnofsky scores and chromogranin A levels. The median OS was 159 months for the resected group and 47 months for the no-resection group ($p < 0.001$).

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Similar conclusions have been reached through retrospective reviews of large, national databases. Tierney et al.[11] reviewed the National Cancer Database (NCDB) for stage 4 gastroenteropancreatic NETs to compare whether patients had better survival with resection of the primary tumor than with no resection. They found 2426 patients with SBNETs who had resection of the primary tumor and 1726 who did not. The median OS was 91.3 months for the resection group versus 44.2 for the no-resection group ($p = 0.002$). The authors concluded that resection of the primary tumor conferred a survival benefit for patients with metastatic disease. However, the resection group likely was favored by a significant selection bias, with patients who had a higher degree of liver replacement, more comorbidities, and worse mesenteric adenopathy not having resection. Conversely, the resected group also might have included patients requiring emergency surgery for bowel obstructions and fewer patients who were asymptomatic from their tumors.

The current study by Polcz et al.[12] reviewed the NCDB during the same years as Tierney et al.[11] but focused on midgut tumors (76% jejunoileal and 24% right colon or appendiceal tumors). They compared clinicopathologic factors and survival between patients who had resection of their primary tumor (PTR group) and those who did not, but specifically excluded patients with resection of liver metastases and those who died within 30 days after surgery. In their study, 2520 of the patients had PTR, and 1556 did not. The median OS was significantly better for the PTR group than for the non-PTR group (78.6 vs 28.6 months; $p < 0.01$), and the benefit of PTR was observed for both jejunoileal and right colon/appendiceal primary sites.

In the multivariable analysis, increasing age, lower income, comorbidities, non-academic hospitals, lack of insurance, poorly differentiated tumors, colon and appendiceal primaries, extrahepatic metastases, and non-resection of primary tumors were negatively associated with survival. Although this represents yet another study showing the survival benefit of PTR, it had bias in that the PTR group was younger and had less poorly differentiated tumors, fewer comorbidities, smaller tumors, and more small bowel tumors (vs right colon/appendiceal tumors).

A recent study from the group in Uppsala questioned the value of PTR. Daskalakis et al.[13] reviewed 363 patients with asymptomatic stage 4 SBNETs presenting to their hospital between 1985 and 2015. They found significantly better OS for 161 patients who underwent locoregional resection than for 202 patients who had no surgery or delayed surgery (> 6 months after diagnosis). The median OS periods for these groups were 9.5 versus 5.3 years, respectively ($p = 0.01$). Liver-directed surgery was more frequently applied to the former group (24% vs 11% for the delayed or no-resection group), which may have factored into the improved survival. However, when they performed nearest-neighbor propensity-matching by selecting 91 patients from each group, locoregional tumor resection no longer showed a survival benefit (median OS, 7.9 vs 7.6 years; $p = 0.93$). The authors concluded that locoregional tumor resection did not improve survival for asymptomatic patients with metastatic SBNETs. Because propensity-matching can reduce the bias inherent in retrospective reviews, this conclusion would seem convincing. However, 58% of the patients in the delayed surgery or no-resection group had surgery after 6 months. Because most of these patients actually did have their primary tumors resected, it is difficult to be sure that removing primary tumors did not affect survival.

Therefore, is resecting the primary tumor after it has metastasized too little too late?

Due to the problem of selection bias inherent in all the studies addressing this issue, it is clear that a randomized clinical trial is needed to answer this question conclusively. This has not been done and possibly never will be done because patients generally feel strongly about whether they want to have surgery or not, and a significant portion of patients randomized to not have surgery may end up having surgery anyway. Until we can study this more definitively, the surgeon or medical oncologist will decide based on his or her experience and opinions. Perhaps the best we can do at this point is to recommend a measured approach, as suggested in the SBNET guidelines of the North American Neuroendocrine Tumor Society, which state: "Resection of primary SBNETs in selected patients with metastatic disease should be considered when feasible to relieve existing symptoms and avoid future symptoms, and for its potential survival advantage. However, other factors need to be carefully considered, such as the patient's performance status and degree of liver replacement, with higher levels (> 50–70%) being associated with shorter survival and higher risk of significant postoperative liver dysfunction. The fact that asymptomatic patients generally will have a long survival without intervention, with or without somatostatin analogues or additional medical therapies, means that surgical procedures must be performed with minimal mortality and morbidity."[6]

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