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EDITORIAL – GASTROINTESTINAL ONCOLOGY

Liver Resection for Neuroendocrine Metastases and the Obligation to Individualize Care

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Neuroendocrine tumors (NETs) are a unique entity, posing particular challenges for the clinician. Once considered rare, the incidence of NETs is now known to be approximately 7 per 100,000.[1] Their clinical behavior often runs an indolent course even when metastases are present, although most patients with metastases ultimately die as a result of liver replacement by tumor.[2]

Because of their peculiar nature, the role of surgery for neuroendocrine liver metastases (NELMs) differs from that for other solid tumors. Cytoreductive surgery is used to achieve palliation through reduction of tumor mass, symptom control, and biochemical regulation, all of which can provide longer survival and better quality of life. Furthermore, cytoreduction can be therapy-sparing, reserving other treatment methods for a later phase of the disease course. Because R0 resection is not mandated, the ideal threshold for debulking is unknown. It is not clear to what extent the tumor (primary or metastatic) must be resected to provide benefit and whether the location and behavior of the cancer left in situ matters.

The volume threshold for debulking in the liver is the subject of ongoing debate.[3,4] In 2003, Sarmiento et al.[3] suggested a debulking goal of 90% of liver metastases. However, most patients in their study had functional disease (70 vs. 10% nonfunctioning disease), and the benefits were primarily measured by decreasing hormonal symptoms and urinary 5-hydroxyindoleacetic acid (5-HIAA) levels. Although subsequent studies have confirmed that the greatest benefit is seen for patients with functional tumors, major liver resection currently is commonly used for nonfunctional (NF) NELM, with a much lower volume of debulking. Many groups suggest that a lower tumor debulking threshold of 70% provides survival benefit for a greater proportion of patients with both functional and nonfunctional NELMs.[4–6] Regardless of the debulking threshold, recurrence is nearly universal, so the procedure is largely palliative in nature.

Where significant disease is left in situ, clinicians naturally wonder whether the location of the disease is important. We therefore read with interest the article by Xiang et al.[7] in this month's journal that evaluates the oncologic outcomes of liver debulking for NF-NELM.[7] In this study, liver resection was performed for a multi-national multi-center cohort with NF-NELM. The authors report that survival after liver resection was not significantly affected by resection of the primary tumor, with a 10-year survival rate of 60% when the primary tumor remains in place versus 76% ($p = 0.271$) when the primary tumor is resected. They also confirmed previous data from their own group showing that extra-hepatic metastases portended worse outcomes, with 38% survival at 10 years.[8]

Can these results help us to manage this group of patients? The data suggest that we might further expand surgical indications for NF-NELM. But this conclusion should be advanced with caution. Although this study had one of the largest cohorts assembled with NF-NELM, it still was relatively small, involving nine centers and 35 years of data, with only 332 patients undergoing surgery. The groups with variables of interest (unresected primary tumor and extra-hepatic metastases) contained only 51 and 37 patients, respectively. Our ability to answer

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the question of interest was therefore limited by small numbers. Although we appreciate that no statistically significant difference was found, the magnitude of the observed difference in the 10-year survival rate (15.3%) between the patients with resected and unresected primary tumors was difficult to ignore. Thus, the conclusion that patients with resected versus unresected primary cancers have comparable outcomes probably is overly generous given the potential for a statistical type 1 false-negative error due to low sample size/event rates.

Perhaps an equally valid question to ask after reading this paper is whether surgery alters outcomes at all. The availability of several new systemic treatment options should temper our enthusiasm for further expanding the indications for metastastectomy. Systemic approaches for gastroenteropancreatic NETs currently include long-acting somatostatin analogs, everolimus, suninitub, and most recently, peptide receptor radionucleotide treatment with lutetium-177 (^{177}Lu)-dotatate.[9–12] No studies to date have compared the outcome of these treatment methods with cytoreductive surgery for advanced disease.

It also is important to keep in mind that other liver-directed therapies, such as intra-arterial treatment (IAT), including trans-arterial bland- or chemo-embolization, DEB, and Y-90, are viable therapeutic options. A previously reported comparison of outcomes for resection versus IAT in a multinational cohort using propensity score-matching has shown that resection for patients with high liver burden and asymptomatic disease holds no benefit compared with IAT. Surgery and IAT have comparable survival times (median survival: surgery, 16.7 months vs. IAT, 18.5 months; $p = 0.78$) in a propensity score-matched group.[13] This suggests that when the primary tumor is unresectable, avoiding surgery entirely and considering IAT as an alternative treatment strategy may be reasonable. The evidence shows that "you could operate" but stops well short of "you should operate."

Therefore, how should surgeons decide when to offer surgery? Modern management sees the combination of different methods used sequentially during the long disease course. Because treatment goals for metastatic NETs are palliative in principle, an individualized approach to care is best. For each patient, the impact of surgery depends on his or her fitness or desire for surgery, the extent of surgery, the presence of symptoms, and the like. The potential for surgery to affect the patient's clinical situation should guide the decision regarding the appropriateness and extent of metastastectomy. This breaks down into a number of more specific issues that must be considered.

The first issue to consider is whether the tumors are hormonally active or not. For patients with functional tumors, the advantages of liver debulking are more readily apparent. Hormonal symptoms can be palliated, and additional therapies may be spared until symptoms recur. Furthermore, the overall survival after liver resection for functional NELM is better than for NF-NELM.[13] In the current study, the target population comprised patients with NF-NELM, which made the benefit of liver resection more difficult to demonstrate. In this situation, debulking may be considered for R2 disease if 70–90% of the tumor can be removed with intent to prevent liver replacement by tumor, which can precipitate liver failure.

The second issue to consider is the site of the primary tumor. Small bowel primary tumors are frequently symptomatic due to the bulky lymphadenopathy and the surrounding desmoplastic reaction that occurs at the root of the mesentery. Bowel obstruction or mesenteric angina may limit quality of life, ability to tolerate further therapies, and/or survival. If liver resection is proposed, resection of small bowel primary tumors to palliate symptoms should strongly be considered if anatomically feasible. On the other hand, locoregional symptoms are less common for pancreatic primary tumors, and pancreatectomy is associated with higher perioperative risk. In this scenario, liver resection without primary resection may be a reasonable option. Based on the results of the study by Xiang et al.[7] survival appears comparable between the two groups, although the study did not distinguish between outcomes by site of primary disease.

The third issue to consider is the presence of extra-hepatic metastases. With the availability of new imaging methods, including gallium 68-dotatate, positron emission tomography/computed tomography (PET/CT), and PET/magnetic resonance imaging (MRI), we currently can detect up to 95% of lesions.[14,15] This has led to stage migration in which occult metastases are now routinely identified. Because extra-hepatic metastases are correlated with poorly differentiated disease and because the biology of disease is a powerful determinant of outcomes, it is not clear that surgery will benefit these patients beyond the reduction of uncontrolled symptoms.

The fourth issue to consider, and probably the most important, is what other treatments are available for the patient and when is liver resection being considered in the overall trajectory of care? We believe that liver resection should be used primarily for therapy-sparing purposes. It has only a limited role in late-stage disease, when liver replacement with tumor is imminent or liver failure has occurred. If debulking with or without locoregional control can control disease for a time, other methods, such as peptide receptor radionucleotide therapy, can be reserved for later stages, thereby minimizing the side effects of ongoing therapy and maximizing quality of life.

Individualizing the care offered to each patient requires consideration of these factors at the very least. We recognize that many unanswered questions remain about the

optimal management of NELM. The study by Xiang et al.[7] does not offer a definitive answer to any of the pressing clinical questions. On the contrary, it raises a number of additional, and in some ways more difficult, questions. Current management of these complex clinical situations requires choosing from a range of very different therapeutic methods. This requires multidisciplinary knowledge and a flexible approach that can match the best method for each patient and for each phase of his or her disease to achieve the most satisfactory outcome.

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