



Surgical treatment for neuroendocrine liver metastasis: moving ahead in controversy

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Despite the indolent nature of neuroendocrine tumors (NETs), 45–90% of patients experience neuroendocrine liver metastasis (NELM) during the disease course (1). These patients will develop systemic symptoms secondary to the liver lesions, decreasing both quality of life and prognosis (2). Frilling *et al.* reported a 5-year overall survival (OS) of 13–54% in NELM patients, which was significantly lower than the 75–99% OS for patients without hepatic metastases (3). Surgical treatment plays an important role and has been accepted as the only potential curative option for appropriately selected patients with NELM. However, controversy continues to exist regarding indications for surgery and effectiveness. Over the past few years, a variety of treatment options have improved the outcomes of NELM patients, including surgery, non-operative hepato-directed treatment, and systemic therapy. As Cloyd *et al.* stated in a current review of NELM management (4), a multidisciplinary and comprehensive evaluation is important when selecting patients for appropriate treatment approaches. Herein, we summarize some key issues related to surgical treatment for NELM that need to be resolved in future research.

Several studies have reported therapeutic benefits of surgery for NELM, and surgical resection is widely employed when feasible. An international multicenter review of over 300 NELM patients undergoing hepatectomy reported a 5-year survival of 74%, which was superior to the OS of 30% in patients treated with intra-arterial therapies (1). In contrast, a systematic review found no evidence for long-term

survival benefit of liver resection compared with any other liver-directed therapies (5). Since prospective randomized controlled trials are unlikely to be conducted, the dispute will continue. The fundamental reason behind the controversy is the range of surgical indications. The impact of hepatectomy on long-term prognosis is still difficult to assess due to potential selection bias for different treatments. For example, patients with heavier disease burden, worse performance status, and severe comorbidities tend to receive conservative treatment and are more likely to have poor outcomes. The European Neuroendocrine Tumor Society (ENETS) guidelines recommend hepatic resection for NELM patients as long as R0 resection is feasible, tumors are classified as grade 1 or 2, there are no extrahepatic metastases, and perioperative morbidity is <30% and mortality <5% (5). However, due to the heterogeneity of NETs, “off-label” indications for hepatectomy are not uncommon.

Debulking is gradually being an accepted treatment strategy for patients who cannot undergo complete resection of all lesions. Previous studies have reported comparable OS in patients receiving cytoreductive surgery in which 70–90% of lesions were resected (6). Specifically, there is ongoing debate over resection of the primary tumor in the setting of unresectable metastasis. While improvement of long-term survival was observed in a systematic review of primary tumor resection for unresectable NELM, other research has reported limited benefit for symptomatic patients (7). The proposed rationale behind the approach is to relieve symptoms caused by the primary tumor, prevent

the future possibility of obstruction and bleeding, obtain histological diagnosis, and potentially improve outcomes. However, there are no randomized controlled trials and only 1 prospective observational study currently registered on Clinicaltrials.gov (NCT03442959) to identify the specific issue of survival benefits of primary resection in the case of unresectable metastasis, and therefore the findings need to be interpreted cautiously. Taken together, rather than routine primary resection for patients with asymptomatic NELM, it would be more appropriate to conduct a multidisciplinary discussion involving careful consideration of the patient's physical status and comorbidities.

There is also controversy over whether hepatectomy should be performed in NELM patients with unresectable primary tumor and in the case of extrahepatic metastasis. Our previous study revealed similar long-term outcomes in NELM patients with primary tumor resection versus those without resection (8). In contrast, compared to patients with intrahepatic-only disease, patients with extrahepatic metastases had a risk of death that was 2.5 times higher (8). However, a median OS of 87 months was observed in patients with extrahepatic disease who received liver-directed therapies for NELM (9). In addition, the survival of patients with extrahepatic metastasis undergoing surgical resection was significantly higher than that of patients receiving other treatments (10). Given that the majority of NELM patients eventually die from hepatic dysfunction, aggressive treatment may be required, even in cases of extrahepatic lesions or unresectable primary disease. Further studies are needed to investigate the benefits of surgical resection and minimally invasive treatment such as intra-arterial therapy and concomitant ablation for patients with a heavy burden of disease.

Although NETs are often considered a low-grade malignancy, some NELM patients will relapse, and thus aggressive resection cannot be considered long-term curative. Recurrent disease prediction and management are key issues for NELM patients after initial resection. Some studies have found recurrence rates of 70–95% in patients undergoing initial resection for NELM (4). Among patients who experienced recurrence, almost 40% relapsed within 1 year and 40% within 3 years (4). Collectively, postoperative recurrence was significantly associated with morphological (tumor size, number, lymph metastasis, extrahepatic disease) and biological (differentiation, ki-67 index, synchronous disease, nonfunctional status, primary location) features of disease and treatment modality (major hepatectomy, margin, adjuvant therapy) (10). After recurrence, repeat

resection is safe and feasible and may achieve good long-term prognosis in carefully selected patients (2,11). Non-surgical treatments such as octreotide, chemotherapy, molecular-targeting therapy, and liver-directed treatments are alternative options, and these have been investigated in different cohorts (11). Therefore, the treatment strategy for recurrent NELM should be individually tailored and involve discussion among oncologists, gastroenterologists, and surgeons.

Liver transplantation is a definitive treatment for unresectable NELM in the setting of resected primary NET and absence of extrahepatic disease (4). Under strict selection criteria, one previous study presented 5-year OS and disease-free survival (DFS) rates of 97% and 89%, respectively, in patients undergoing liver transplantation for recurrent NELM (12). Similarly, the European Liver Transplant Registry study presented a 5-year OS of 59% post-transplantation for recurrent NELM (13). When researchers applied the Milan criteria retrospectively, the calculated OS improved to 79% but came at the expense of excluding 64% of patients. The need for such a rigorous selection process is debatable and expansion of the Milan criteria was recently suggested. In addition to standardization of patient selection, future studies on multidisciplinary approaches, posttransplant immunosuppressants, and perioperative medical therapies for NELM are needed.

Over the last few years, the rapid development of systemic therapies has significantly improved the long-term survival and quality of life for NELM patients. Adjuvant and neoadjuvant therapies highlighted possible changes of surgical indications, timing, and management of advanced and/or recurrent disease. In addition to chemotherapy, current options for systemic therapy include local interventional treatment [conventional transarterial chemoembolization (TACE), transarterial embolization (TAE), transarterial radioembolization (TARE), radiofrequency ablation (RFA), and microwave ablation (MWA)], inhibition of mammalian target of rapamycin (mTOR) and tyrosine kinases to limit tumor growth and malignant transformation, somatostatin analogs (SSA) that can reduce functional output and have an antiproliferative effect, and immunotherapy that regulates the response of the immune system to antineoplastic drugs (14). Despite the variety of armamentarium available, the optimal treatment regimen remains uncertain. An obvious question involves the combination, timing, and sequence of treatments available. Moreover, effective biomarkers are needed to aid

in individualizing treatment decisions in NELM. Thus, the appropriate selection and sequencing of treatment approaches relies mostly on clinical judgment while investigations of combined therapy are still underway (15).

Although abundant knowledge of NELM is currently available, many questions and debates remain regarding surgical treatment for NELM, especially for advanced tumors. The optimal therapy should be personalized and consider a variety of factors, including biological tumor features, liver metastasis patterns, extrahepatic disease, patient characteristics, as well as outcome perspective.

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