



Neuroendocrine liver metastasis

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Predicting the natural history of neuroendocrine neoplasms (NEN) is most difficult for medical providers to prognosticate due to the wide range of tumor origin, disease differentiation, and timing of diagnosis. One of the most challenging features of NEN is that the majority of patients present with metastatic disease at the time of diagnosis (1), which is why it is paramount for surgeons to understand the variety of treatment strategies available. Liver metastases (LMs), in particular, are the most critical prognostic factor for survival for NEN (2,3). Left untreated, the 5-year survival of neuroendocrine liver metastases (NELM) are 30–32% (1). Unfortunately, less than 20% of patients are eligible for curative resection of NELM at the time of presentation (4). It has been cited that local recurrence rates after resection of LMs are as high as 94% in 5 years (4). While surgical resection is the preferred first-line therapy, other modalities have become significant in treating unresectable disease. These include somatostatin analogues (SSA), chemotherapy, chemoembolization, peptide receptor radionuclide therapy (PRRT), radiofrequency ablation, immunotherapy, and even transplant in highly selected patients. Those with resectable disease who are able to undergo an R0 resection have an estimated 5-year survival rate of about 70%. Additionally, 95% of these patients achieve symptom relief from resection of NELM. Debulking of NELM remains controversial, yet some studies have demonstrated an improved survival with even a 70% reduction in disease burden (5). Because NELM

have a rich arterial blood supply, transarterial embolization and chemoembolization are valid treatment options that are generally employed for multiple unresectable NELM. Radiofrequency ablation is indicated for NELM that are less than 5 centimeters and are otherwise inoperable or in combination with hepatectomy to limit the extent of resection. PRRT consists of a radionuclide attached to a somatostatin receptor analogue and has been used for the treatment of NELM and metastases outside of the liver, especially after resection of the primary lesion. In regards to liver transplantation, requirements for consideration have been proposed by different groups including the Milan group, the European Neuroendocrine Tumor Society (ENETS), and the United Network for Organ Sharing, the Milan criteria are defined as age less than 55 years, G1 or G2 histology, primary tumor drained by the portal system and already resected, involvement of less than 50% of hepatic parenchyma, and stable disease for at least 6 months. The Milan group found that those undergoing transplant who fulfilled these criteria had a 5-year survival of 97.2% compared to 50.9% in those who received traditional treatment options. It is important to note that in a separate study, those patients who fulfilled the Milan criteria and underwent multimodal therapy that did not include transplant also demonstrated a 5-year survival of 97% (5). Furthermore, recurrence rates after liver transplant have been reported as high as 56.8% in one systematic review (6), which begs the question of resource utilization

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in this particular disease process. Many attempts have been made to create a set of guidelines for approaching NELM treatment, but more data are required about the integration of medical, interventional, and surgical approaches towards the yield with the highest survival.

Notably, “Trends in the Management and Outcomes of Neuroendocrine Liver Metastases: A Three-decade, Multi-centre Observational Cohort Study” (7) was written and published in *Annals of Surgery* in December 2024 by Professor Andrea Frilling *et al.* This unique and impressive retrospective review of prospectively collected data reported 551 patients with NELM treated at four different European hospitals between January 1st, 1990, to December 31st, 2020. The authors sought to document the changing paradigms of treatment options for the management of NELM in a uniquely heterogeneous tumor type such as NEN. The authors used their collective data to examine practice patterns and patient outcomes over the course of three decades. The comparison groups were divided into three overarching treatment categories: surgical, interventional, and medical. The primary endpoint was overall survival. Secondary endpoints included recurrence-free survival and progression-free survival. The majority of primary tumors were in the small bowel and pancreas, and most tumors were well differentiated. The authors found that 73% of patients received multimodal therapy, defined as treatment from more than one of the three categories. They examined how these treatments changed throughout the course of the three decades and found that while the number of surgical cases performed remained the same, the extent of resection decreased over time. Somatostatin receptor analogues (SSA) and transarterial radioembolization increased over time, yet peptide receptor radiotherapy and chemotherapy did not vary significantly. Radiofrequency ablation use steadily decreased over the study time period. There was no significant difference in patients who received multimodal therapy in each decade. In regard to 5- and 10-year survival, each notably improved by the third decade of the study. The authors posited that overall, the improvement in outcomes could be attributed to advancements in imaging technology in addition to increased use of SSAs. This was in the setting of consistent application of hepatectomy, which had been established by other studies to be an imperative component of NELM treatment.

This study impressively organized and collated data across four centers over 30 years’ worth of patient management. One wild-card to the interpretation of the

dataset was the introduction of the 2004 ENETS guidelines. Although guidelines implementation in the latter half of the study was described as being followed, this introduced a potential for randomness into the data simply by the abrupt introduction of guidelines when previously there were none and the notion of compliance to guidelines by each center. The authors very nicely described which procedures were performed but indication for surgery was not reported in this series. The decision to operate has changed substantially over 30 years in light of a better understanding of the natural history of NEN based on grade. The other lingering question revolved around the role of surgery in patients with symptomatic primary disease and incidental LM without carcinoid syndrome. This is likely the most common type of patient seen in all centers.

This article very clearly delineated the trends of treatment strategies over the course of three decades. Particularly evident was the increased sample size in each decade [I (n=81), II (n=137), and III (n=333)]; this trend suggested an increased diagnosis and subsequent management, not necessarily increased incidence. Parallel to these changes was the most important finding that survival for patients with NELM had improved as well. Clearly, there had been advancements in technology relative to diagnostic imaging, improved surgical techniques, and the specificity of medical therapies for NEN that had contributed to these improvements over time. The biggest question that remained was which treatment trend specifically correlated with the observed improvement in survival. For instance, while we know that surgical resection has been shown in many studies to be the single most important factor in survival outcomes for those with NELM, how do we account for the observed increase in SSA use over time, superimposed on the trend toward less aggressive surgical resection? Similarly, can we solely attribute survival improvements to treatment strategy? How much has the advancement in technology improved our ability to diagnose NELM? One could surmise that NELM were being detected earlier due to improved access and specificity of radiologic techniques, and thus, increased survival may reflect lead time bias as a result of earlier diagnosis. Another aspect that could allow for better perceived survival is that the tumor biology of NEN reported in this series was favorable, with a low percentage of patients with poorly differentiated tumors. The presumption was that the increased use of SSA altered the landscape of indication for surgery, as symptoms in many cases had been the primary factor for proceeding with

surgery. What was most interesting was that the number of resections performed stayed consistent by decade in spite of the decreased extent of resection and with an increased diagnosis of the NEN with associated NELM over time. Thus, one (controversial) interpretation could be that hepatectomy in isolation may not be the key component to improved survival.

Finally, perhaps future research could focus on the effectiveness of different treatments themselves. For example, case-controlled studies comparing the various interventional techniques when compared to each other or when compared to medical and surgical therapy focused on survival. Further delineating which changes in treatment strategies are most effective will improve treatment algorithms and define best practice. NELM is a complex clinical pathology with a variety of treatment options available. Multimodal therapies elicit the best disease response, but there is further work to be done to understand which are most effective. This manuscript is an important contribution to the literature and the authors are to be commended, as this has always been a difficult topic to coordinate the collection of data and communicate effectively. This study clearly documented the change in treatment paradigm over the decades as other therapeutic options arose and were implemented into true clinical practice with a real patient benefit.

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Footnote

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