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Updates on the management of neuroendocrine liver metastasis

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Abstract

Approximately one-third of patients diagnosed with a neuroendocrine tumor (NET) develop distant metastases, with the liver being the most common site. Therefore, the management of patients with neuroendocrine liver metastasis (NELM) is particularly important, as metastatic disease is often one of the main factors influencing patient prognosis. When patients are amenable to surgery, liver resection is associated with improved long-term outcomes and relief from potential tumor-related symptoms. NELM resection should be considered even when a radical resection is not achievable. Moreover, a tumor burden threshold of 70% for hepatic cytoreductive surgery can be safely adopted with favorable long-term outcomes. For patients with NELM who are not candidates for surgical resection, liver-directed therapies provide a valuable treatment strategy, enabling optimal disease control while preserving liver parenchyma. Furthermore, liver transplantation has emerged as a potential therapy for patients with NELM. Although significant progress has been made in managing NELM, the heterogeneity of NETs poses substantial challenges to research due to the variability in tumor characteristics. Therefore, devising an optimal therapeutic strategy requires a multidisciplinary approach to develop individualized treatment plans and optimize patient outcomes.

Keywords: Neuroendocrine liver metastasis, neuroendocrine tumor, liver resection, tumor debulking



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INTRODUCTION

Neuroendocrine tumors (NETs) are a group of rare neoplasms arising from neuroendocrine cells that can have heterogeneous biological behaviors. Although the incidence of NETs has increased over the last decades, overall survival appears to be improving, possibly as a result of improved imaging and therapeutic strategies^[1]. Overall, NETs are classified as functional or non-functional tumors, with the former secreting bioactive amines such as serotonin, histamine, and kallikrein, possibly leading to diarrhea, flushing, wheezing, and cardiac valvular abnormalities, which characterize carcinoid syndrome^[2]. Similarly, pancreatic NETs (PNETs) can produce other hormones, including: gastrin, which can result in Zollinger-Ellison syndrome; insulin, causing recurrent hypoglycemia; vasoactive intestinal peptide (VIP), which can cause Verner-Morrison syndrome; glucagon, which leads to hyperglycemia, stomatitis, weight loss, and a migratory necrolytic rash; somatostatin, associated with diabetes and diarrhea; adrenocorticotrophic hormone (ACTH), which can cause Cushing syndrome; parathyroid hormone-related peptide (PTHrP), which can result in severe hypercalcemia^[3]. Furthermore, NETs are classified into three different subtypes according to their biological behavior: low grade (G1), with a Ki-67 index < 3%; intermediate grade (G2), with a Ki-67 index of 3 to 20%; and high-grade (G3), with a Ki-67 index > 20%. Poorly differentiated NETs are generally referred to as neuroendocrine carcinoma (NEC), and are considered high-grade by definition with a Ki-67 index > 20% [Table 1]^[4].

The majority of NETs originate from the small intestine, the lungs, and the colon-rectum, followed by PNET, gastric, and appendiceal NETs^[5]. Although NETs are mostly indolent, approximately a third of patients diagnosed with NET develop distant metastasis, with the liver being the most common site^[6,7]. Specifically, the prevalence of liver metastasis ranges from 20-90%, with 12-74% of patients having synchronous neuroendocrine liver metastasis (NELM)^[7-9]. Patients who develop metastatic disease have a markedly reduced survival compared with patients who only have localized disease, with 5-year survival ranging from 13%-54% among patients with NELM compared with 75%-99% for patients with non-metastatic NET^[10,11]. Therefore, the management of patients with NELM is especially important, as liver disease is often one of the main factors influencing patient prognosis regardless of primary tumor location^[12]. Although numerous treatment options have been investigated for NELMs, curative-intent surgical resection is currently the treatment of choice for patients who are amenable to surgical resection, depending on the site of origin, size of the primary tumor and the metastases. However, other treatment strategies such as tumor embolization and ablation are increasingly being used to treat NELMs, especially among patients who are not amenable to surgical resection. Moreover, the use of liver transplant for non-resectable NELM has been increasingly recognized as a viable therapeutic option, particularly for slow-growing tumors with low biological aggressiveness^[13]. As such, the optimal management of patients with NELMs remains a topic of ongoing debate, particularly in light of recent advancements in surgical techniques and therapeutic strategies. A multidisciplinary approach incorporating surgical, interventional, and systemic strategies is often needed to optimize patient care and improve survival. In this framework, the aim of the current study was to review recent advances and provide an overview of current therapeutic approaches for patients with NELM.

Diagnosis of NELM

Although most patients with NET undergo a contrast-enhanced computed tomography (CT) at the time of diagnosis, contrast-enhanced magnetic resonance imaging (MRI) scans have a higher sensitivity to detect hepatic metastases^[14-16]. NELMs typically demonstrate bright enhancement on arterial-phase CT and T2-weighted MRI, while these lesions appear hypointense on unenhanced T1-weighted MRI. On Gadoteric acid-enhanced MRI, NELMs appear as hypointense as the lesions do not take up contrast^[17]. Positron emission tomography (PET) with somatostatin receptor tracers, usually fused with unenhanced CT (PET-CT), has a high sensitivity to detect NET metastases^[18,19]. All patients with high-grade NET and

Table 1. Grade and morphology classification of GEP-NET

	Grade	Morphology	Mitotic count	Ki-67
Low grade	1	Well differentiated	< 2	< 3%
Intermediate grade	2	Well differentiated	2-20	3%-20%
High grade	3	Well differentiated	> 20	> 20%
NEC	3	Poorly differentiated	> 20	> 20%

GEP: Gastro-entero-pancreatic; NET: neuroendocrine tumor; NEC: neuroendocrine carcinoma.

NEC should undergo Fludeoxyglucose (FDG) PET-CT, while patients being considered for liver surgery or liver-directed therapy should undergo a total-body CT scan and an MRI of the liver, with consideration of a PET scan^[14]. The diagnosis is typically confirmed on histopathologic evaluation of the tumor tissue. On pathologic examination of liver specimens, immunohistochemistry (IHC) staining for neuroendocrine markers such as synaptophysin, chromogranin A, keratin, and somatostatin receptors distinguishes NELM from other neoplasms^[20]. The quantification of the Ki-67 proliferative index is needed to determine tumor grade. For NELM with an unknown primary site, extended IHC panels can help distinguish the primary site when no primary tumor can be identified on preoperative imaging^[21,22]. Furthermore, for NELM with no primary tumor seen on preoperative imaging, careful palpation of the small intestine is required during surgical exploration as the primary tumor can often be found in the ileum^[23].

Classification of NELM

The most used classification scheme of NELMs describes three possible distributions of liver metastases: a single metastasis is classified as Type 1 regardless of its size; Type II includes isolated metastatic bulk with smaller deposits that involve both lobes; a disseminated metastatic spread to both lobes or a single lesion with no normal liver parenchyma is classified as Type III^[24]. A more recent approach, suggested by Mahuron and Singh, describes four categories based on the ability to reduce tumor burden through surgical resection. According to this classification, patients classified as Type 1 have only one isolated metastasis that can be surgically removed, patients classified as Type 2 have multiple bilobar lesions that can be cytoreduced for 70% or more of total tumor burden by using parenchyma-sparing techniques, whereas patients classified as Type 3 have extensive bilobar hepatic involvement in which a 70% tumor burden debulking cannot be achieved. Additionally, patients classified as Type 4 cannot achieve the 70% debulking threshold but are significantly symptomatic; therefore, they may benefit from surgical cytoreduction [Figure 1]^[25].

MANAGEMENT OF NELM

Surgical management

Liver resection

Among patients with NELM, liver resection is the only curative option when patients are amenable to surgery, as it is associated with improved long-term outcomes and immediate relief from possible symptoms caused by the tumor^[6,10]. Despite excellent survival following surgical resection of NELM, most patients will experience disease recurrence with long-term recurrence rates approaching 95%. Nonetheless, surgical resection currently represents the best option for patients with NELMs, enabling repeat hepatectomy after disease recurrence with favorable long-term outcomes and optimal palliation of symptoms. A recent meta-analysis of 1,108 patients reported improved survival for patients undergoing liver resection versus systemic therapy alone^[26]. Similar findings were reported in a previous systematic review on patients with pan-NETs who underwent liver resection for NELMs, with longer overall survival (OS) and increased symptom relief among patients who underwent NELM resection^[27]. Liver resection for NELM can be performed either via laparotomy or in a minimally invasive fashion (i.e., via a laparoscopic or

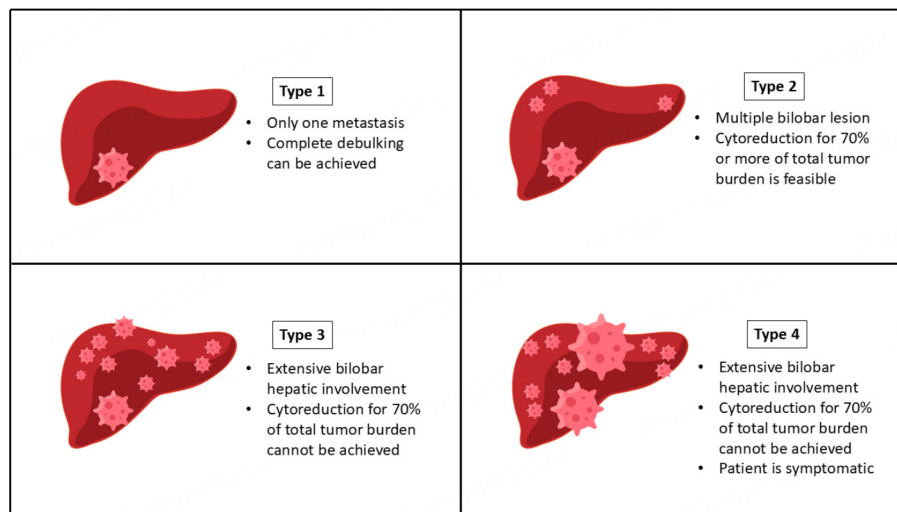


Figure 1. Classification of neuroendocrine tumor liver metastases based on the ability to reduce tumor burden through surgical resection.

robotic approach). Nonetheless, although patients who undergo minimally invasive resection have less postoperative pain, shorter hospital stays, and lower blood loss, minimally invasive surgeries for NETs are often uncommon, given the limited ability to fully evaluate disease extent^[28,29]. In fact, the most recent North American Neuroendocrine Tumor Society (NANETS) guidelines recommend exploratory laparotomy with manual small bowel palpation as the preferred operative approach for small bowel NETs^[30].

Primary tumor resection is overwhelmingly recommended when patients are amenable to curative-intent resection, especially for G1 and G2 NETs, with substantial survival benefits for patients who also undergo concurrent resection of NELM^[31]. Specifically, surgical resection of NELM without resection of the primary lesion has been associated with worse long-term outcomes versus concurrent resection of primary tumor and metastatic lesions^[32-35]. A recent study on 536 PNET patients with liver metastases from the Surveillance, Epidemiology, and End Results Program (SEER) database noted that patients who underwent primary tumor resection had a better 5-year OS compared with patients who did not undergo primary tumor resection (67.9% vs. 22.3%); age <65 years and good or moderate tumor differentiation were associated with longer OS^[36]. Similarly, another study on 1,547 patients with gastro-entero-pancreatic NET (GEP-NET) and liver metastases reported that primary tumor resection was associated with prolonged survival (5-year OS: 57.0% vs. 15.4%); patients with a colorectal NET or with a primary tumor ≥ 4 cm had a higher risk of death^[34]. Surgical resection of NELM is associated with improved OS compared with other treatment modalities, with 5-year OS ranging from 50%-76%^[37-41]. Nonetheless, even after curative-intent surgery, the majority of patients develop disease recurrence. Repeat hepatic resection in selected patients has been associated with good long-term outcomes^[42,43]. Factors associated with disease recurrence include the maximum diameter of the primary tumor, NELM tumor burden score, and the presence of bilateral liver involvement^[44]. In a recent series from the Mayo Clinic Rochester, in a cohort of 546 patients with NELMs from 2000 to 2020, 75% achieved complete resection, whereas 20% achieved tumor debulking greater than 90%; median progression-free survival (PFS) was 17 months and median OS was 122 months. In this series, Ki-67, primary tumor site, number and size of NELM, and presence of distant metastases were associated with OS^[45]. Even when complete resection of the hepatic tumor burden is not technically feasible, optimal cytoresduction (resection of more than 90% of tumor burden in the liver) may improve symptoms and, perhaps, improve survival compared with systemic treatment alone^[14,46]. A recent systematic review by Muttillio *et al.* involving 32 studies on surgery, transplant, and non-surgical treatments for NELM reported

that up-front surgical resection was mainly performed for well-differentiated metastases, whereas systemic therapies were preferred for G3 NETs or NECs. Furthermore, 5-year OS was 67%, with 30.2% of patients achieving 5-year disease free survival (DFS). Recurrence was reported in 24.5% of patients and was mainly intrahepatic (58%). Among patients who underwent transplant, 5-year OS and DFR were 60% and 20%, respectively. The majority of patients who received locoregional treatments had invasive bilateral disease: 5-year OS was 36.2%, while 5-year DFS was 19.0%; all recurrences were intrahepatic. Among patients who received systemic therapy with yttrium-90-DOTA-d-Phe(1)-Tyr(3)-octreotide (Y^{90} -DOTA-TOC), complete remission was noted in only 0.6% of patients, with a mean PFS of 12.7 months and OS of 94.6 months; patients who were treated with ^{177}Lu -Dotate had a PFS of 8.4 months, whereas those receiving traditional chemotherapy alone (Streptozocin) or in combination with other pharmacological regimens had a mean PFS of 11.8 months. Even though patients receiving Lanreotide had a greater PFS (32.9 months), this difference was probably due to the high prevalence of patients with well-differentiated neoplasms (G1-2) in this subgroup of patients^[47].

Early studies on tumor debulking for NELM established a 90% cytoreduction threshold as the optimal goal to maximize both patient survival and symptom control^[46,48]. However, recent evidence has highlighted how even surgical resection of a decreased proportion of tumor burden may be associated with improved symptoms and prolonged survival. Specifically, in a series by Graff-Baker *et al.*, the percentage of gross disease resected (i.e., 70% to 89%, 90% to 99%, and 100%) did not correlate with PFS^[49]. Similarly, in a cohort of patients who underwent NELM debulking, those who had 70% or more of the gross disease resected experienced improved PFS and OS compared to those who underwent cytoreduction of less than 70%^[50]. In a secondary analysis, after stratifying patients according to the number of NELMs resected (i.e., 1-5, 6-10, and > 10), median OS and PFS did not differ between groups, whereas achieving a cytoreduction greater than 70% was associated with a better OS versus a cytoreduction < 70% (134 vs. 38 months, respectively)^[51]. Even among patients with an unknown primary tumor, surgical debulking of NELMs was associated with favorable OS versus patients with small intestine or pancreatic NELMs, according to a retrospective analysis of the National Cancer Database^[52]. More recently, experts have debated the prognostic value of residual tumor volume as opposed to percentage cytoreduction. In fact, assessing only percentage cytoreduction results in a wide range of residual tumor volume depending on the initial extent of disease^[53]. Therefore, recently published studies have advocated that the goal of cytoreductive surgery should be to resect as much tumor as possible, rather than merely achieving a predetermined cytoreduction threshold. Thus, the lower the residual tumor volume after surgery, the better the prognosis. Residual tumor volume has been more strongly linked to survival than percentage cytoreduction^[54]. However, the best threshold for acceptable residual tumor volume above which cytoreductive surgery does not provide a significant survival benefit remains unclear; furthermore, no definitive consensus has been reached on how to account for ablation sites when calculating the volume of residual disease. This topic and the routine application of tumor volumetric measurements in the preoperative evaluation of patients should be the focus of future prospective studies evaluating surgical outcomes of patients with NELMs.

Furthermore, although historically radical/complete (i.e., R0) resection was the aim of liver resection for NELM, more recent series have reported similar outcomes among patients who underwent R0 or R1 resection^[42,46,55,56]. These data likely reflect unrecognized disease that was not resected among patients who are believed to be disease-free after R0 surgical resection^[42,46,55,56]. The NANETS guidelines recommend performing surgical cytoreduction even when a R0 resection cannot be achieved, as removal of the majority of gross disease has been associated with improved symptoms and long-term outcomes^[30,57]. Additionally, resection is recommended when a debulking threshold of at least 70% can be achieved based on preoperative imaging evaluation. Parenchyma-sparing procedures, such as enucleation of superficial

metastases and ablation of deeper lesions, are recommended as possible approaches to achieve optimal cytoreduction without sacrificing large volumes of normal liver^[30,57]. In fact, enucleation of even large NELMs abutting major vascular structures is often preferred over major or extended liver resections. Recently published series have noted how enucleation of NELMs is effective at achieving tumor control while preserving the future liver remnant by avoiding major hepatectomy. This approach is particularly important among patients with NELMs given the high recurrence of this disease in the liver after hepatectomy, potentially allowing the patients to undergo repeat resection or other potential locoregional treatments after disease recurrence^[54,58].

Among patients with extensive liver metastases in which a major liver resection cannot be avoided, possibly leading to post-hepatectomy liver failure (PHLF) as a result of inadequate future liver remnant (FLR), procedures such as portal vein embolization (PVE) can be used to induce parenchymal hypertrophy in the contralateral lobe^[59-61]. Nonetheless, these techniques are rarely considered for NELMs, and parenchyma-sparing procedures such as enucleation are recommended whenever feasible^[58]. Although there is no defined waiting time between PVE and surgery, a meta-analysis reported an average interval between PVE and liver resection of 29 days, with an overall morbidity for PVE of 2.2% and no mortality^[62]. Similarly, associated liver partition and portal vein ligation for staged hepatectomy (ALPPS) can be performed to induce hypertrophy of the FLR, enabling cytoreduction in patients with insufficient baseline liver reserve. The increase in FLR function seems to exceed the increase in FLR volume after both PVE and ALPPS, with the target hypertrophy response reached earlier after ALPPS^[63]. In fact, compared with PVE, ALPPS seems to induce a more rapid FLV hypertrophy, albeit with increased morbidity and mortality^[64].

Liver transplantation

Liver transplantation (LT) has emerged as a potential treatment strategy for patients with neuroendocrine liver metastases, particularly when the tumor burden is greater than the functional liver reserve can support^[13]. Among some patients who would otherwise be deemed unresectable, LT could offer the potential for a cure. Nonetheless, LT is a complex and resource-intensive treatment option reserved for a small subset of patients with extensive, unresectable disease confined to the liver. In fact, NELMs are still an infrequent indication for LT, as only a small percentage of transplants worldwide are performed for NELM. No randomized trial has been carried out comparing LT with other treatment strategies for NELM^[14]. Although several selection criteria for patients with NELM who are suitable for LT have been published, there is no universal agreement upon the best performance criteria [Table 2]. A systematic review by Palaniappan *et al.* reported how indications and selection criteria for NELM patients undergoing LT are still poorly defined. In this study, the median 5-year OS was 65%, whereas the median 10-year OS was 50.0%^[65]. A multi-institutional series comprising 455 undergoing either liver resection (LR) (230) or LT (225) with a median follow-up of 97 months demonstrated that LT outside Milan criteria (HR 2.40, 95%CI: 1.16-4.92, $P = 0.018$) was a negative prognostic factor among transplanted patients. Furthermore, after propensity score match (PSM), patients had a 73.0% and 52.8% 5-year OS after LT and LR, respectively. Nonetheless, no survival benefit was observed after LT among patients transplanted outside Milan criteria^[66].

The Milan NET criteria, initially devised in 2007, consist of 6 characteristics: age < 60 years; low grade on histology (i.e., G1 or G2); primary tumor drained by the portal system; primary tumor and all deposits radically resected before consideration for transplant; metastatic liver involvement of less than 50% of liver volume; stable disease for at least 6 months prior to listing for transplant^[67,68]. According to the most recent European Association for the Study of the Liver (EASL) guidelines, selected patients with G1 or G2 GEP-NETs with non-resectable metastases confined to the liver, with a Ki-67 $\leq 10\%$, portal venous drainage, and with stable disease for > 6 months after resection of the primary tumor may be evaluated for LT^[69]. The

Table 2. Selection criteria for liver transplantation for patients with NELM

	Milan NET criteria	UNOS	EASL	ENETS
Primary tumor drainage	Portal system	Portal system	Portal system	-
Age	< 60 years	< 60 years	-	< 60 years
NET type	-	GEP	GEP	-
Tumor burden	< 50% liver parenchyma	< 50% liver parenchyma	Non-resectable metastases	-
Tumor grade	G1-G2	G1-G2	G1-G2	G1-G2
Ki-67	-	-	-	≤ 10%
Time interval	Stable disease > 6 months after resection of the primary tumor and all extrahepatic metastasis	No evidence of recurrence > 6 months after resection of the primary tumor and all extrahepatic metastasis	Stable disease for >6 months after resection of the primary tumor	-
Other		No other metastases	No other metastases	Early refractory to multiple systemic treatments; No extrahepatic disease; Low bilirubin; Carcinoid syndrome or functional NETs

NET: Neuroendocrine tumor; NELM: neuroendocrine liver metastasis; UNOS: united network for organ sharing; EASL: European Association for the Study of the Liver; ENETS: European Neuroendocrine Tumor Society; GEP: gastro-entero-pancreatic.

United Network for Organ Sharing (UNOS) guidelines for LT in patients with NELM are based on the Milan criteria, with the aim to reduce the risk of transplantation waiting list dropout while achieving good outcomes^[70]. The guidelines recommend complete resection of primary and extrahepatic disease without any evidence of recurrence for at least 6 months, as opposed to the Milan criteria that require stable disease for at least 6 months^[71]. The series published by Nobel & Goldberg based on the UNOS database reported 1-, 3-, and 5-year OS of 87%, 69%, and 63%, respectively^[72]. Some studies suggested that the application of the Milan NET criteria can lead to improved long-term outcomes, with a 5-year survival of 79%-97%^[68,73]. Among the Milan NET criteria, the time interval of at least 6 months between surgical resection and transplantation is thought to play a crucial role, as this subset of patients with indolent disease seems to benefit the most from LT compared with patients who have medically refractory disease^[13]. Additionally, the nature of the primary tumor seems to be associated with varying long-term outcomes after LT for NELM. Specifically, non-gastrointestinal NETs have been associated with an increased risk of extrahepatic metastasis and systemic recurrence; patients whose primary tumor cannot be found represent a controversial cohort for transplant, although some studies suggest favorable outcomes in this subset^[74,75]. After LT for NELM, recurrence rates range from 31.3%-56.8%, which are higher than those observed after transplant for other tumor types^[76]. Nonetheless, 5-year OS seems to be comparable, according to a propensity score-matched study comparing patients who underwent LT for NELM, hepatocellular carcinoma, and cholangiocarcinoma^[77]. When approaching a patient with NELM, the decision between resection and transplantation depends on a strict evaluation of tumor extent (intra- and extrahepatic), biology, patient performance status, and liver function [Table 3]. Even though resection remains the primary approach for resectable disease, LT represents a valid approach that could lead to improved outcomes in a highly selected cohort of patients with unresectable liver-confined NELM.

Liver-directed therapies

Ablation

Tumor ablation using radiofrequencies, microwaves, cryotherapy, or electroporation is an alternative strategy to surgical resection when liver lesions are not amenable to surgical resection. Ablation can be

Table 3. Comparison of liver resection and transplantation for neuroendocrine liver metastases

	Liver resection	Liver transplantation
Indications	Surgical removal of liver lesions	Unresectable, diffuse NELM confined primarily to the liver
Liver tumor burden	Localized or multifocal disease if resection or optimal debulking (> 70%-90%) is achievable with adequate FRLV	Extensive, bilobar disease not amenable to resection due to tumor volume or distribution
Primary tumor	Resected or stable, or concurrently resectable	Primary tumor must be resected prior to LT, with no evidence of active primary disease
Extrahepatic disease	Generally contraindicated if extensive or unresectable	Strict contraindication
Patient status	Good PS, limited EHD, capable of tolerating a major hepatectomy	Young patients (< 60-65 years), good PS, liver-limited disease, favorable tumor biology, no significant comorbidities
Outcomes	5-year OS 50.0%-76.0%	5-year OS 60.0%-73.0% (only in highly selected patients)

NELM: neuroendocrine liver metastasis; FRLV: functional residual liver volume; LT: liver transplantation; PS: performance status; EHD: extrahepatic disease; OS: overall survival.

performed either percutaneously or during laparotomy or minimally invasive surgery. Additionally, ablation techniques can be used as an adjunct to surgical resection to achieve greater cytoreduction while minimizing the loss of normal liver tissue in a parenchyma-sparing fashion. Smaller lesions (< 3 cm in diameter) are usually more amenable to ablation, whereas tumors near vascular structures or tumors greater than 5 cm in diameter have a higher risk of complication and recurrence^[78,79]. Additionally, injury to major bile ducts is another major concern after tumor ablation; in particular, bulky tumors located in liver segments 4b and 5 are at risk of bilateral bile duct injury and subsequent liver failure. Complication rates for NELM ablation include hemorrhage, pneumothorax, and local symptoms, with morbidity rates ranging around 6%-52% and with negligible mortality^[80,81].

Radiofrequency ablation (RFA) heats the target tissue at temperatures exceeding 60 °C via either percutaneous or intraoperative needle placement. In a series by Huang *et al.* on patients with NELMs who underwent RFA, the technical efficacy rate was 91.3% without major complications, although new liver lesions were noted in up to 50% of patients after treatment with a median PFS of 15 months, which was longer among patients with Ki-67 < 5%^[82]. In another study on 129 NELM patients undergoing laparoscopic ablation, the incidence of local recurrence and extrahepatic recurrence was 22% and 33%, respectively, after a median follow-up of 73 months; tumor size, grade, and resection status of the primary tumor were associated with OS^[32].

Microwave ablation (MWA) is now more often used for liver metastases with both curative and cytoreductive intents. In a retrospective analysis of 50 patients, Pickens *et al.* reported a 5-year OS of 70% for patients who underwent curative-intent MWA, whereas patients who underwent cytoreductive MWA had a 5-year OS of 69%^[83]. In a recently published single-center retrospective series of 94 patients who underwent surgical MWA between 2007 and 2022, the rate of incomplete ablation was 0.3% per tumor; 2.8% of tumors developed local recurrence, with a 5-year survival probability of 70.2%^[84].

Embolization

Transarterial embolization (TAE) achieves tumor reduction by inducing ischemia through intravascular administration of embolic beads, thus obstructing the arterial blood flow to the tumor, whereas transarterial chemoembolization (TACE) is based on the administration of cytotoxic chemotherapy into the tumor's vascular supply^[26]. In patients with NELM, tumor embolization is associated with symptom improvement and prolonged long-term survival. In a cohort of 91 NELM patients undergoing TACE, 5-year OS and PFS were 40.8% and 20.3%, respectively, whereas 54% of patients with carcinoid syndrome experienced

symptom relief^[31,85]. A meta-analysis comparing 504 patients who underwent TACE or TAE for NELM reported no differences in OS and PFS between the two treatment strategies^[86]. Similarly, a recent retrospective series by Ruff *et al.* noted that among 412 patients with NELM, TACE was associated with similar short-term outcomes (23.3% vs. 29.3%) and improved PFS (21.8 vs. 10.7 months), but no difference in OS compared with TAE after matching^[87]. The RETNET multi-institutional trial (Randomized Embolization Trial for NeuroEndocrine Tumor Metastases to the Liver) recently released its first preliminary data. The study randomized patients with liver-dominant NET 1:1:1 to TAE with 40-500µm microspheres, TACE with lipiodol-docorubicin 40-500µm microspheres, and drug-eluting bead doxorubicin (DEBDOX) delivery. Notably, the DEBDOX arm was halted early due to a 40% treatment-related serious adverse event rate. In the early results, no difference in hepatic PFS was observed between patients undergoing TAE and TACE, even after adjusting for tumor grade, tumor burden, performance status, and histology. The TACE arm achieved a 40% 3-month response rate, which was sustained at two years, whereas the TAE arm achieved a 60% 3-month response rate that declined to 20% at 2 years. A total of 101 severe adverse events were reported in the TAE arm versus 39 in the TACE arm^[88].

Transarterial radioembolization (TARE) has been widely used for the treatment of NELMs to debulk large tumor burdens while preserving normal liver parenchyma. Through TARE, the vascular supply of the tumor is embolized using Yttrium-90-coated microspheres^[89]. In a series of 91 patients undergoing either TARE or TACE for NELMs, the number of patients who experienced intrahepatic progression of disease was higher among patients undergoing TACE versus patients undergoing TARE (75% vs. 43%, respectively)^[90]. Similarly, in a recent meta-analysis that included a total of 643 patients with NELMs, OS ranged from 16.8-81.9 months after TACE and from 14.5-66.8 months after TARE, with patients treated with TACE having improved OS (OR 1.92, 95%CI 1.14-3.22). Furthermore, morbidity was comparable between the two groups, with only 6.9% and 8.5% of patients developing major complications after TACE and TARE, respectively^[91]. A recent systematic review by Garrou *et al.* on the use of TARE for NELM patients demonstrated that 28.6% of patients had a complete or partial response on imaging, while 13.6% had disease progression; median OS was 33 months, whereas median hepatic PFS was 24 months, supporting TARE as a viable treatment option in selected patients^[92]. Overall complication rates for embolization procedures range from 15-90%, with the most common complication being post-embolization syndrome (PES), an inflammatory clinical syndrome characterized by fever and right upper quadrant abdominal pain, often with nausea, vomiting, leukocytosis, thrombopenia, and elevation of transaminases and lactate dehydrogenase. Such symptoms can often limit the use of these techniques as a long-term strategy to achieve disease control^[31,93,94].

Peptide receptor radionuclide therapy

Peptide receptor radionuclide therapy (PRRT) is a technique based on the intravascular administration of a somatostatin receptor (SSTR) ligand (usually DOTATATE) attached to a chelator and a radionuclide such as Yttrium-90 or Lutetium-177, which bind to somatostatin receptors on the tumor surface, inducing tumor necrosis^[26,31]. Currently, low-grade NELMs and extrahepatic metastases with ample SSTR expression represent the main indication for PRRT^[23]. In the NETTER-1 trial, undergoing PRRT was associated with increased PFS compared with somatostatin analog (SSA) therapy alone, although no patients with NELM were included in the study^[95]. In a series assessing long-term outcomes among NELM patients undergoing PRRT, OS and PFS were 33.5 and 28.5 months, respectively, with patients who underwent liver resection prior to PRRT showing improved PFS^[96]. PRRT can also be used in conjunction with systemic therapies to improve its efficacy, as well as after other treatment strategies, such as liver embolization, with adequate safety and efficacy^[97,98]. Similarly, in the NETTER-2 randomized trial on 230 treatment-naïve patients with SSTR-positive G2 or G3 NET, the association of PRRT with Lu-177 DOTATATE and octreotide was found

to improve PFS compared to high-dose octreotide (23 vs. 9 months, respectively), with an acceptable toxicity profile, suggesting that this combination could represent an appropriate treatment strategy for carefully selected patients^[99]. Moreover, PRRT has demonstrated promising results in reducing hepatic tumor burden prior to liver resection in patients who present with advanced disease^[100]. The most common complications of PRRT are kidney, bone marrow, and liver toxicity^[31,98].

Medical management

Systemic medical therapy is used in patients with NELM to both control symptoms and manage tumor burden. Furthermore, patients with poor performance status, significant comorbidities, or high-grade NELMs with extensive liver involvement may not be candidates for surgical management and may instead be managed with systemic approaches^[30,101]. Commonly used treatments include SSA, targeted therapy, and cytotoxic chemotherapy.

SSAs are currently the primary treatment for symptom control in patients with carcinoid syndrome and also act as antiproliferative agents. SSAs such as octreotide and lanreotide bind to SSTRs on the cell surface of most gastro-entero-pancreatic NETs, thus inhibiting peptide secretion^[31]. A PET-CT scan using gallium Ga-68 DOTATATE, Ga-68 DOTATOC, or copper Cu-64 DOTATATE is often needed to detect SSTR expression, as SSTR-positive tumors are most likely to benefit from SSA therapy^[102]. In patients with locally advanced or metastatic NETs with high tumor burden or significant symptoms, therapy with a long-acting SSA has been demonstrated to halt tumor growth and reduce symptom intensity. Specifically, in the PROMID trial, Octreotide long-acting release was associated with improved PFS among patients with metastatic NET compared with a placebo control group (HR 0.34, 95%CI 0.20-0.59)^[103]. Similarly, in the CLARINET trial, patients receiving lanreotide had a markedly prolonged PFS versus a placebo group, with a reduced risk of death (HR 0.47, 95%CI 0.30-0.73), although with a higher rate of adverse events^[104]. Although limited data are available on the effect of SSAs on OS, longer PFS seems to be associated with an improved OS among patients with advanced NET treated with SSAs^[105].

For high-grade NETs and NECs, systemic cytotoxic chemotherapies are generally indicated^[6,57]. Poorly differentiated NETs with a Ki-67 > 20% are usually treated with platinum-based regimens in combination with etoposide, albeit with a response rate of about 30% and a median PFS of 4 months^[106]. Streptozocin-based regimens with 5-fluorouracil or doxorubicin have been used in patients with PNETs, with response rates of around 40%^[107]. A recent study comparing the efficacy of cisplatin versus etoposide or irinotecan noted that overall response was comparable to previous studies reporting overall response rates of 28%-52% for platinum/etoposide or platinum/irinotecan combinations^[9]. In the ECOG-ACRIN-E2211 trial, the combination of temozolomide with capecitabine (CAPTEM) versus single-agent temozolomide was reported to increase PFS (22.7 vs. 14.4 months, respectively) among patients with advanced PNETs, with potential applications for patients in whom cytoreduction is the primary goal of treatment^[108]. Although the CAPTEM regimen has lower efficacy in gastrointestinal NETs, with response rates of around 15%, it can be used in patients with progressive intestinal NETs who have failed other treatments^[6,109]. More recently, novel targeted therapies inhibiting specific molecular pathways are being extensively investigated. Studies analyzing tumor samples to identify actionable somatic mutations in NETs have reported good preliminary results^[110,111]. Specifically, the RADIANT-3 trial assessed the efficacy of everolimus, an inhibitor of the mammalian target of rapamycin (mTOR), in patients with advanced PNET, demonstrating improved PFS for patients who received everolimus versus patients who only received placebo (11.0 vs. 4.6 months, respectively)^[112]. The RADIANT-4 trial compared everolimus with placebo plus best supportive care for advanced NETs, including patients with hepatic metastases, and the results demonstrated longer PFS among patients receiving everolimus (11.0 vs. 3.9 months)^[113]. Similarly, the RADIANT-1 and RADIANT-2 trials compared everolimus with the combination of everolimus and octreotide, and the combination of

everolimus and octreotide with octreotide single-agent therapy, respectively. Both studies reported promising results for the use of everolimus with and without octreotide in the management of advanced NETs, with limited toxicity and improved disease and symptom control^[114,115]. Other systemic therapies such as immune checkpoint inhibitors have demonstrated only minimal anti-tumor activity among patients with advanced NET in recent clinical trials, with only limited efficacy and manageable adverse events^[116-118]. Additionally, antiangiogenic therapies have demonstrated evidence of objective response with disease stabilization, although published studies are still limited^[119,120]. Emerging findings in basic and translational research are beginning to reshape the approach to NET management, revealing molecular subtypes and key drivers of tumor progression. Further studies on the PI3K/AKT/mTOR signaling pathways and alterations in the chromatin remodeling genes such as MEN1, DAXX, and ATRX may provide further insight into new therapeutic targets^[47]. Moreover, basic research into the tumor immune microenvironment could identify potential strategies to overcome resistance to systemic therapies, ultimately improving the treatment and prognosis of patients with NELM.

CONCLUSIONS

About one-half of patients with GEP-NET will develop NELM during follow-up. While the characteristics of the primary tumor are key prognostic factors, the presence and extent of NELM are important determinants of prognosis, as the primary tumor is often indolent in behavior. Primary tumor resection and resection of NELM should always be considered, even when a R0 resection cannot be achieved. Furthermore, in light of recent evidence, a 70% tumor burden threshold for liver cytoreductive surgery should be considered for surgical management. For patients with NELM who are not amenable to surgical resection, liver-directed therapies offer a valid treatment strategy, achieving optimal disease control in a parenchyma-sparing fashion. Although significant progress has been made in the management of NELMs, the heterogeneity of NETs poses significant challenges due to variability in tumor characteristics. Therefore, a multidisciplinary approach is required to develop individualized treatment strategies to improve patient outcomes.

DECLARATIONS

Authors' contributions

Contributed to the conception and design of the study: Catalano G, Alaimo L, Ruzzenente A, Pawlik TM

Conducted the literature review: Catalano G, Alaimo L

Drafted the manuscript: Catalano G, Alaimo L, Ruzzenente A, Pawlik TM

All authors critically revised the manuscript for important intellectual content and approved the final version for submission.

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Conflicts of interest

Pawlik TM is an Advisory Editor of *Journal of Cancer Metastasis and Treatment*. Pawlik TM was not involved in any steps of editorial processing, notably including reviewer selection, manuscript handling, or decision making. The other authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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