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SPECIAL SECTION: NEUROENDOCRINE NEOPLASMS

Neuroendocrine hepatic metastatic disease: the surgeon's perspective

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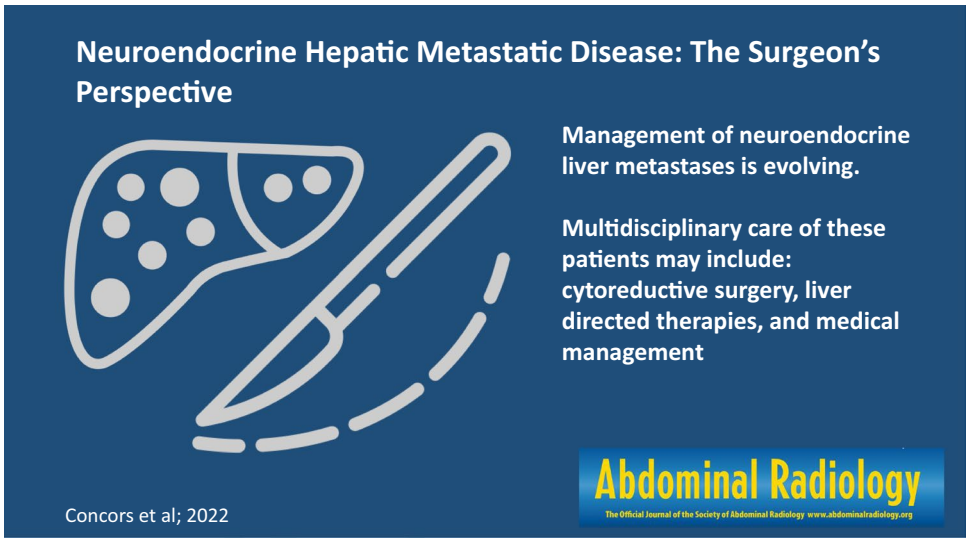
Abstract

Neuroendocrine tumors are a rare subset of tumors that are increasing in incidence over the last 4 decades. These tumors occur along the gastrointestinal tract and bronchopulmonary tree and frequently metastasize. Up to 90% of patients with gastroenteropancreatic neuroendocrine tumors develop liver metastases (NeLM) during their clinical course. The development of NeLM and their appropriate management has a profound impact on patient morbidity and mortality. Workup of NeLM involves biopsy to define tumor grade, cross-sectional imaging to delineate the distribution and number of metastases, and hormonal studies to determine tumor functionality. Depending on these three factors, a combination of cytoreductive surgery, liver-directed therapies, and medical management—with cytostatic and cytotoxic chemotherapies, is utilized. The multidisciplinary management of patients with NeLM should carefully consider all these factors.

Graphical Abstract



Keywords Neuroendocrine tumors · Liver · Metastatic · DOTATATE · Hepatectomy · Cytoreduction

Introduction

Neuroendocrine tumors (NETs) are a group of cancers originating from organs with high density of neuroendocrine cells, with highest frequency in the gastrointestinal tract and bronchopulmonary tree, respectively [1–3]. The overall incidence of NETs has increased over the last 4 decades, from 1.09 per 100,000 persons in 1973 to 6.98 per 100,000

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persons in 2012 [2]. Several large population-based studies have suggested that rather than a true increase in incidence of NET, the increased diagnosis of these rare tumors may be due to increased incidental detection [4]. Tumors of gastroenteropancreatic origin frequently present with liver metastases at the time of diagnosis, between 35 and 95% in large series [2, 5–7]. Primary site of origin impacts the observed rates of these metastases; in retrospective series from specialized centers, approximately 80–90% of patients with small bowel NETs have liver metastases, compared to 60–70% with pancreas NETs [3, 6, 8]. Higher grade, based on KI-67 and/or mitotic count, is associated with risk of metastasis and overall survival [2, 9–12]. T classification, tumor differentiation, and nodal status also influence rates of metastasis [9, 13, 14].

The presence of neuroendocrine liver metastases (NeLM) can be associated with hormonal symptoms and significantly impacts survival. Five-year survival for patients with liver metastases is 13–54% compared to 75–99% without [15, 16]. Appropriate management of NeLM involves consideration of medical therapies (including cytostatic and cytotoxic agents) in combination with liver-directed therapy and/or surgical resection. Surgical resection, for the properly selected patient, represents the only possible cure for patients with NeLM. However, for those patients who do not have a resectable pattern of disease and those with recurrent disease, the optimal treatment paradigm is controversial. Given the complexity of these patients' management, multidisciplinary review at a high-volume center is suggested.

Evaluation of the patient with neuroendocrine liver metastases

There are three key factors in the surgical evaluation of a patient with NeLM: tumor pathology (grade and differentiation), assessment of the anatomic distribution and volume of disease, and determination of tumor hormonal status.

Tumor histopathology, specifically tumor grade and Ki-67, significantly impacts management. The WHO has updated the classification of neuroendocrine neoplasms starting in 2017 to differentiate between neuroendocrine tumors (well differentiated, G1, 2, or 3) and neuroendocrine carcinomas (poorly differentiated G3). Neuroendocrine carcinomas are associated with an aggressive phenotype and early, wide-spread metastases [17]. Suspicion of high-grade NET based on clinical features or imaging characteristics necessitates biopsy and histologic confirmation. Poorly differentiated tumors are initially managed with cytotoxic chemotherapy. Patients with well-differentiated G3 tumors may be candidates for resection of their primaries or metastases, but a period of observation of biology prior to proceeding to the operating room is often employed. In

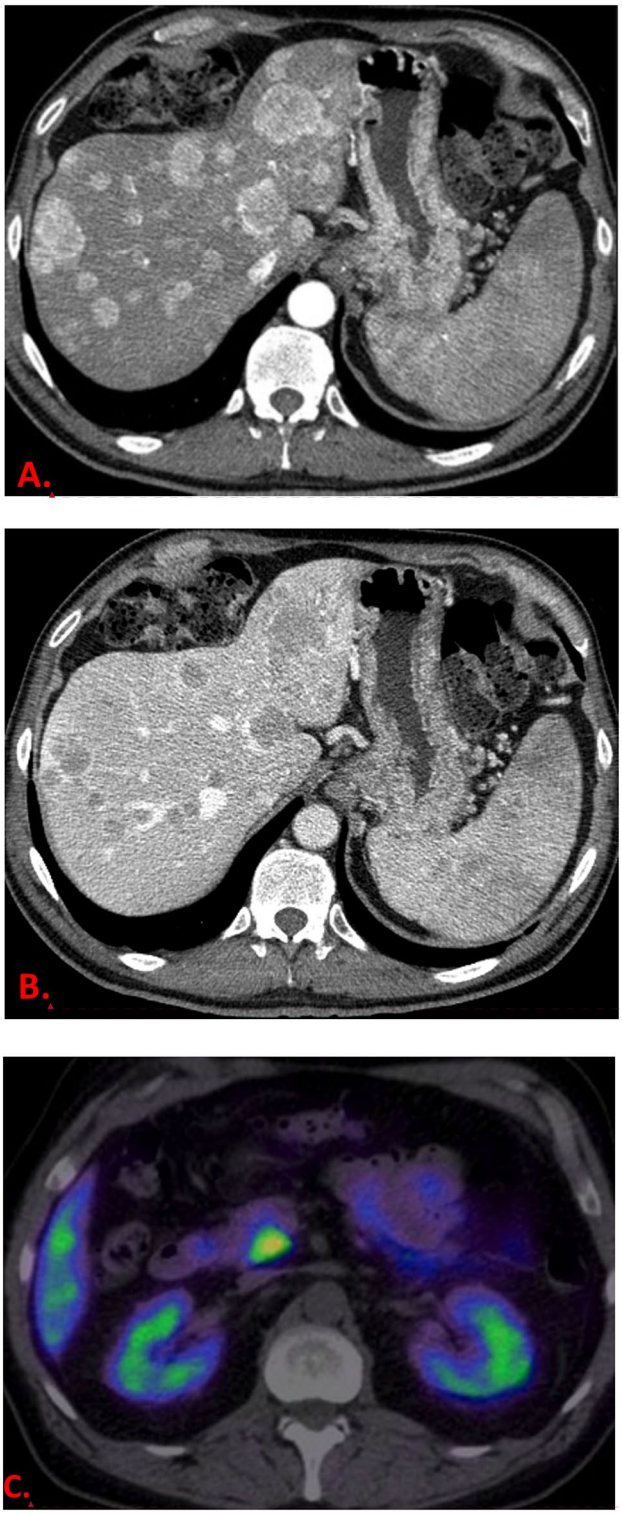

Fig. 1 Representative images of NeLM on CT in Arterial (**A**) and Portal Venous (**B**) phase as well as (C). DOTATATE scan demonstrating avidity in uncinate, which is physiologic

patients with well- or moderately differentiated grade 1 or 2 tumors, NeLM biopsy is controversial. In those patients with previously resected primary tumors, histologic examination of the primary tumor can provide important biologic insight. However, in the setting of synchronous presentation, where the diagnosis is otherwise apparent, biopsy may not be required [5, 15, 18]. If the primary site is unknown or grade is in question, imaging-guided liver biopsy, upper and lower endoscopy to identify the primary tumor, or endoscopic ultrasound guided biopsy may be indicated [18, 19].

Surgical evaluation of NeLM by cross-sectional imaging determines the extent of disease and in turn resectability. Contrast-enhanced CT scan or MRI provides vital information on tumor location, size, proximity to key vascular structures, and volumetry. MRI, particularly with hepatobiliary phase after intravenous gadoxetate disodium contrast injection, is very accurate in identifying NeLM [20, 21]. Somatostatin receptor imaging, specifically, gallium-68 DOTATATE, is highly sensitive and specific for NeLM and can serve as an important adjunct to CT or MRI for preoperative planning if hepatic lesions are indeterminate [22, 23]. It is not used as a stand-alone modality prior to an operation. DOTATATE imaging identifies previously occult hepatic lesions, and assesses somatostatin receptor positivity (which has implications for medical management), in addition to identifying unknown primary tumors [24]. National Comprehensive Cancer Network guidelines recommend combined contrast-enhanced cross-sectional imaging with DOTATATE [19]. Comparative studies between CT, MRI, and DOTATATE imaging exist; however, the choice of imaging modality depends largely on institutional/individual experience, ease of access, and cost [25]. In patients with suspected G2 and G3 NETs, particularly those with KI-67 > 12%, and neuroendocrine carcinomas, 18F-FDG PET/CT offers clinical prognostic ability—with 18F-FDG PET avidity reflecting more aggressive biology[26]. Representative images of NeLM on CT are shown in Fig. 1.

Assessment of liver volumetry—and in turn assessment of future liver remnant after potential resection, is vital. Future liver remnant of 20, 30, and 40% is needed for patients with normal livers, those who are undergone prolonged chemotherapy and cirrhotic patients[27, 28].

Cardiac involvement in metastatic NET predicts poor survival and does not follow a predictable clinical course [1, 29]. Manifesting as right ventricular failure or valvular dysfunction, carcinoid heart disease is thought to be due to progressive deposition of endocardial fibrous tissue [29]. Given this, transthoracic echocardiography and cardiology evaluation for valvular dysfunction are key in preoperative evaluation of these patients [29].

Chromogranin A, pancreastatin, and urinary 5-hydroxyindoleacetic acid (5-HIAA) are helpful biomarkers in metastatic NET and are used for prognostication and surveillance. Chromogranin A is the most commonly utilized test, with serum level correlating with disease burden and overall survival [30, 31]. Its levels can be affected by several common conditions and factors—renal dysfunction, hypertension, proton pump inhibitors, or a recent meal. For these reasons, it is being reconsidered as a standard part of the NET workup and surveillance strategy at numerous centers. Pancreatstatin, a byproduct of chromogranin A cleavage, is not affected by the same factors as CgA and is thus considered a higher yield biomarker in NET. Its levels correlate with tumor burden, and levels may have utility in predicting recurrence, overall, and progression-free survival [32]. Serum serotonin and 5-HIAA are additional markers which may help in the clinical workup of the primary tumor once the diagnosis is confirmed, but have poor correlation with tumor burden and play a more dominant role in monitoring known disease[33]. Urinary 5-HIAA levels are also often obtained in the workup of carcinoid syndrome. For pancreas NET, hormonal evaluation should be guided by clinical symptoms and may include the evaluation of serum

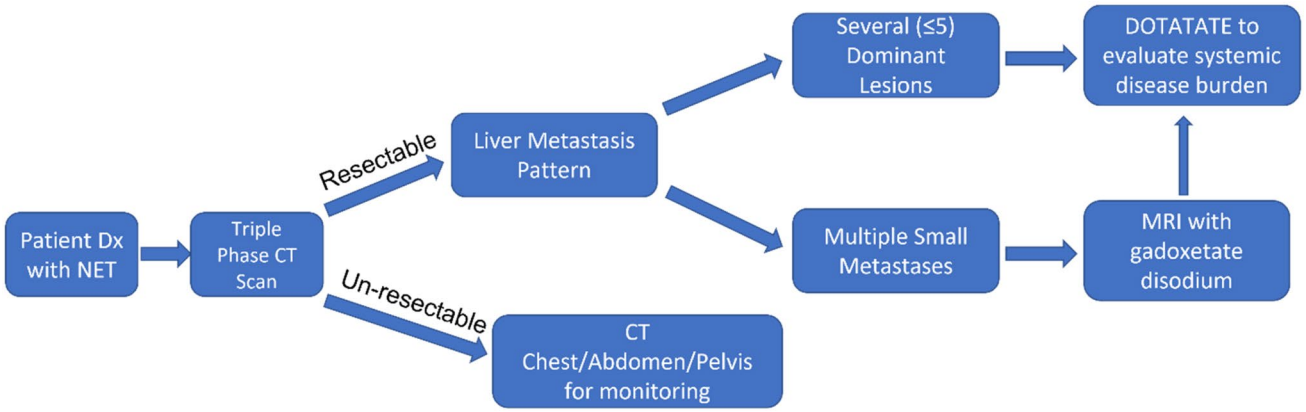

Fig. 2 Proposed imaging algorithm

gastrin, insulin, glucagon, VIP, somatostatin, or pancreatic polypeptide [15, 34, 35].

Our aApproach Careful appraisal of cross-sectional imaging is key to the surgical evaluation of these patients. In our practice, a liver-protocol CT is the imaging study of choice, followed by MRI for better delineation of indeterminant lesions. For both studies, synoptic templated reporting of each NeLM, including degree of steatosis, tumor location, size, and % change of NeLM is extremely useful. Broad terms such as "multiple" or "innumerable" are imprecise, and our preference is to avoid their use, supplanting a more thorough reporting of lesions. Despite the large number of lesions which may be present, a careful accounting of each lesion—particularly in patients who are surgical candidates—is vital to ensure thorough intraoperative evaluation. This approach to reporting may differ from other hepatic malignancies due to the difference in surgical strategy. In NeLM, great emphasis is placed on parenchymal sparing approaches (i.e., individual treatment of each metastasis versus anatomic resection of multiple hepatic segments) and thus an accounting of each lesion is crucial to determining resectability.

We find DOTATATE is particularly helpful in identifying previously unknown NeLM, as well as occult primaries. It is not routinely ordered if the patient's primary tumor has already been resected and preoperative staging prior to liver cytoreduction is of high quality and without suspicious lesions. We scrutinize DOTATATE avidity at the uncinate process and in the tail of the pancreas, as these may represent physiologic findings or accessory spleen, respectively (Fig. 1). Our imaging algorithm is demonstrated in Fig. 2.

Surgical treatment of neuroendocrine liver metastases

Resection of NeLM is the mainstay of treatment for the appropriately selected patient. Surgical resection both decreases tumor-related hormonal burden and improves survival [4, 17]. Retrospective single- and multi-center studies have shown a survival benefit associated with an aggressive surgical approach. In addition, five- and ten-year survival after liver resection for NeLM is 46–86% and 35–79%, respectively [6, 16, 36, 37]. As this evidence is retrospective and limited to highly selected patients, the generalizability of these data remains controversial. Two Cochrane reviews noted no randomized clinical trials exist demonstrating the

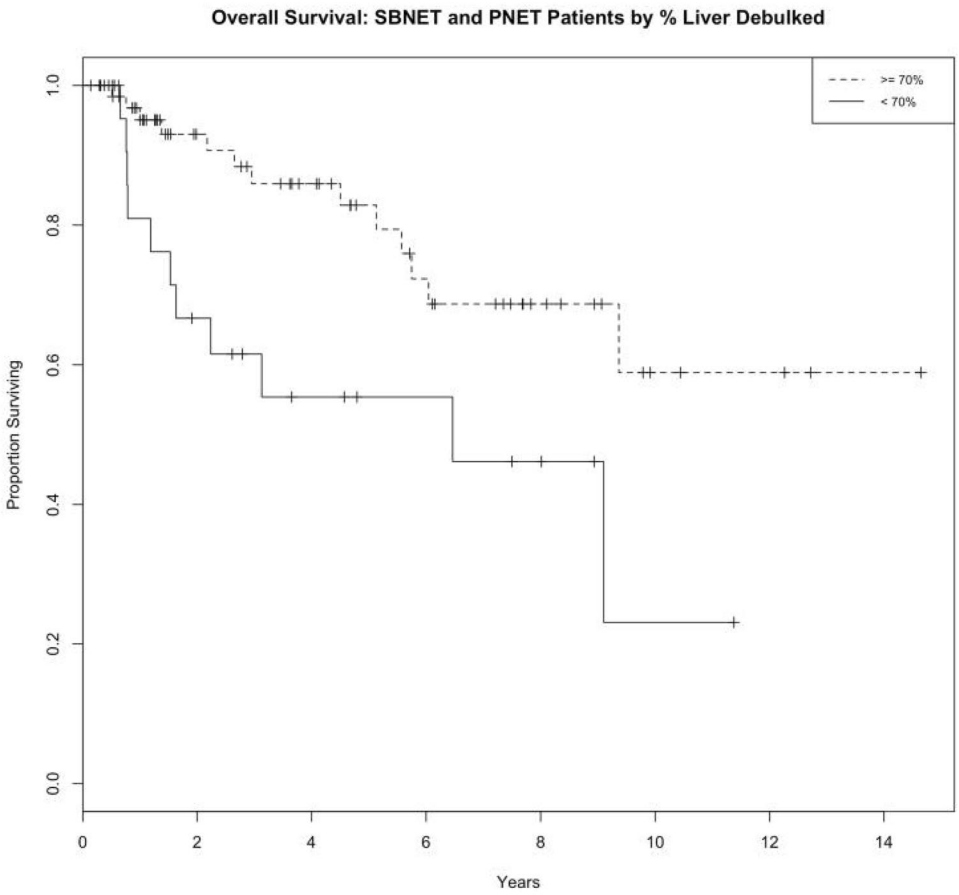

Fig. 3 Improved overall survival with ≥ 70% cytoreduction, relative to < 70%. Adapted from Maxwell et al., 2016

survival benefit of NeLM resection, either in terms of complete resection or debulking [38, 39].

Further controversy exists regarding the benefit of non-complete (i.e., cytoreductive/debulking) surgical resection. Retrospective series demonstrate that cytoreduction of 90% or 70% may lead to improvement in symptoms and survival [6, 16, 36, 40–42]. In one contemporary series, 108 patients underwent liver debulking for metastatic pancreas or small bowel NET, both progression-free survival and overall survival were improved in the overall cohort with ≥ 70% cytoreduction, relative to < 70% (Fig. 3) [43]. Both the North American Neuroendocrine Tumor Society (NANETS) and European Neuroendocrine Tumor Society (ENETS) recommend individualizing treatment, with consideration of cytoreductive surgery [18, 44].

While effective cytoreduction provides the most immediate decrease in tumor burden, it is clear that the majority of patients will recur by 5 years, with a median reported recurrence of 16–20 months [16, 36]. The high rate of recurrence may in part be related to under appreciation of the true burden of disease by preoperative imaging. Elias et al. compared the number of NeLM identified on cross-sectional imaging to those found on final thin-slice pathology and found roughly half were unappreciated preoperatively [45]. Despite near uniform NeLM recurrence, surgical resection improves symptoms and survival and may "reset the clock" in patients' overall disease course.

Liver transplantation has been performed for diffuse NeLM in highly selected patients[46, 47]. Several guidelines exist to define the role of liver transplantation in NeLM and include previous resection of the primary tumor, low grade tumor (G1/G2), and < 50% involvement of the liver parenchyma [48]. In one retrospective analysis, 5-year survival of liver transplant for NeLM was 60–80% [49]. Transplant for NeLM has not been widely adopted, likely due to limited organ supply, and remains relegated to highly specialized centers.

Non-surgical liver-directed therapy with ablation and intra-arterial techniques is also utilized for NeLM. Thermal ablation, most commonly microwave or radiofrequency, is most appropriately utilized for lesions < 2 cm with adequate distance from important vasculature [50, 51]. Ablation can be performed percutaneously or laparoscopically and may also be combined with surgical resection when technically feasible. Small series have reported durable tumor control with laparoscopic ablative techniques alone in selected patients—59% 10-year overall survival in a study of 129 patients with 770 tumors [52].

Trans-arterial bland embolization (TAE), chemoembolization (TACE), and radioembolization (TARE) are also utilized in carefully selected patients. Mayo et al., in a propensity matched analysis, demonstrated improved symptomatic control from surgical resection compared to embolotherapy (combined cohort of TAE, TACE, and TARE) in patients with low volume of disease, or with symptoms related to hormone excess [53]. Intra-arterial therapy is associated with a decrease in tumor burden by approximately 50% and is a good choice for patients with high-volume disease, although the ordering of these therapies among the other choices for metastatic NET and their relative efficacies to one another is unknown. In an attempt to answer the latter question, a multi-center randomized clinical trial (RETNET) is currently ongoing in patients with unresectable NeLM comparing the efficacy of TAE, TACE with conventional injection of lipodiol and TACE utilizing drug-eluting doxorubicin microspheres [54]. The drug-eluting arm of this study has been closed due to 4/10 patients experiencing severe toxicity. Further studies are ongoing combining systemic therapy with TARE in Grade 2 NeLM [55]. Combining or sequencing liver-directed therapy and surgical cytoreduction for NeLM is also frequently performed, though there are no prospective trials examining this approach.

Our approach Surgical resection is offered to those patients for whom we can safely treat 70% or more of the tumor volume. Small, indeterminate lesions or those few situated near vital structures that could require major hepatectomy are often the types of lesions knowingly left behind. In patients with bilateral metastases, this estimation can be challenging. In retrospective surgical series, this level of debulking often correlates with a median overall hepatic replacement by tumor of 10–20%. Although our goal is typically clearance of all gross disease, a 70% clearance rate may be especially appropriate in patients with functional tumors. Resection alone, or resection with ablation (either intraoperative or percutaneous imaging guided), is used to debulk the liver. Importantly, careful consideration is taken to parenchymal sparing approaches, including enucleation when possible, given the high rate of concomitant micrometastatic disease among these patients [56] and the near-inevitability of recurrence in a population that frequently succumbs to liver failure.

Medical management and emerging trends

Cytostatic agents and cytotoxic chemotherapy are the first-line medical therapies in patients with unresectable NeLM. Treatment with somatostatin analogues (SSA) is the cornerstone of medical management for metastatic Grade 1 and 2 NETs. The randomized, placebo-controlled PROMID trial demonstrated prolonged time to tumor progression in patients with midgut metastatic NET after administration of long-acting octreotide (66.7% v. 37.2% stable disease at 6 months) [57]. The CLARINET trial

randomized 204 patients with metastatic grade 1 or 2 midgut NETs, demonstrating similar results; progression-free survival was 65.1% in the long-acting octreotide cohort, versus 33.0% in the placebo cohort at 24 months [58]. Regardless of formulation, SSAs provide cytostatic and hormonal disease control.

Cytotoxic therapy differs based on primary site of origin. In patients with high volume, rapidly progressing, or high-grade pancreatic NET disease, cytotoxic chemotherapy with capecitabine/temozolomide is the preferred regimen based on the ECOG 2211 study [59]. Everolimus, an mTOR inhibitor, has also shown to improve progression-free survival in advanced low- or intermediate-grade pancreatic NET [60]. Combined preoperative treatment with fluorouracil, doxorubicin, and streptozocin prior to hepatic resection in metastatic pancreatic NET has also shown to improve overall survival [61]. Tyrosine kinase inhibitors, including sunitinib, have shown efficacy in metastatic pancreas and small bowel NET, with many currently enrolling clinical trials [62, 63].

177Lu-DOTATATE peptide receptor radionuclide therapy (PRRT) is an emerging therapy, with favorable outcomes particularly in patients with midgut NET who have progressed on SSA therapy. The NETTER-1 trial, evaluating grade 1 and 2 midgut NET with metastatic or locally progressive NET on SSA, demonstrated 18% response rate in the PRRT group compared to 3% with high-dose octreotide. Recent guidelines from NANETS suggest the use of PRRT in progressive small bowel and pancreatic NETs[64]. The NETTER-2 trial is currently enrolling, comparing combined PRRT and long-acting SSA to SSA alone in patients with G2 and G3 advanced gastrointestinal NET.

Conclusion

With increasing frequency and predilection for the development of liver metastasis, more providers will be faced with the management of NeLM. Surgical cytoreduction combined with cytostatic and cytotoxic therapies can provide durable symptom relief and survival benefit. Further research comparing specific liver-directed therapies, and sequencing of medical therapy are ongoing.

Author contributions Seth Concors performed the literature search and data analysis and drafted the work. Jessica Maxwell had the idea for the article and helped draft/critically revise the manuscript.

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Declarations

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Consent to participate Not applicable.

Consent for publication Not applicable.

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