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REVIEW ARTICLE

Role of Locoregional and Systemic Approaches for the Treatment of Patients with Metastatic Neuroendocrine Tumors

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Abstract Although gastroenteropancreatic neuroendocrine tumors are often perceived as being indolent tumors, more than half of the patients will harbor liver metastases at the time of diagnosis. Gastroenteropancreatic neuroendocrine tumors have the potential to be aggressive and resistant to therapy, making the integration of both locoregional and systemic therapy even more critical in the treatment of patients with locally advanced or metastatic lesions. Over the last several years, significant advancements have been made in the surgical treatment, liver-directed therapy, and medical management of gastroenteropancreatic neuroendocrine tumors. While surgical resection is the cornerstone of therapy, cytoreductive surgery, orthotopic liver transplantation, local ablation, and intra-arterial therapy all improve the prognosis of patients suffering with locally advanced or metastatic disease. In addition, great strides have been made in the medical management of gastroenteropancreatic neuroendocrine tumors, particularly with the evolution of novel molecular targeted therapy, such as everolimus and sunitinib. Hence, gastroenteropancreatic neuroendocrine tumor is becoming a disease process requiring more of a multi-disciplinary approach with the integration of both locoregional and systemic therapies for improved outcomes.

Keywords Gastroenteropancreatic neuroendocrine tumors · Liver metastases · Intra-arterial therapy · Everolimus · Sunitinib

Introduction

Gastroenteropancreatic neuroendocrine tumors (GEP-NET), comprised of both carcinoid tumors and pancreatic neuroendocrine tumors (PNET), are relatively rare though their incidence has been rising.[1–3] Data from the National Cancer Institute Surveillance, Epidemiology and End Results (SEER) cancer registry demonstrates an increase in incidence of GEP-NET from 1.00 case per 100,000 people between 1973 and 1977 to 3.65 cases per 100,000 people between 2003 and 2007 in the USA.[2] European and Asian studies validate the increasing incidence of GEP-NET as a worldwide trend.[1–5] Some of this noted increase in incidence can be attributed to enhanced awareness among physicians as well as improved imaging techniques, which can lead to incidental identification of NET.[1] Indeed, autopsy series reveal an even higher prevalence of GEP-NET, many of which are asymptomatic and of uncertain clinical significance.[6–8] While the rising incidence is generally thought to be a true phenomenon, determination of the precise epidemiology of GEP-NET is limited by previously inconsistent classification and nomenclature.[1]

GEP-NET are generally perceived to be rare, slow-growing tumors with an indolent course compared to other malignancies arising from the same organ; however, they do have the potential to be aggressive and resistant to therapy.[3] Even patients with resectable tumors may ultimately die of their disease. Acknowledging and accounting for the malignant

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potential of NET, the World Health Organization (WHO) updated its classification system in 2010 to include a proliferation-based grading system in conjunction with the traditional histopathological diagnostic criteria (Table 1).[9]

Poor tumor cell differentiation and pancreatic origin are negative prognostic indicators; however, the greatest prognostic indicator is the presence of metastatic disease.[10,11] More than half of patients with GEP-NET will harbor liver metastases at the time of diagnosis, which are often bilobar in nature.[12] Patients with metastatic disease have a guarded prognosis with 10-year survival ranging from 0 to 30 % depending on the primary site of disease.[3] In this article, we will review the current indications and available interventions for locoregional and systemic control of metastatic GEP-NET, which are often used in conjunction to achieve optimal outcomes.

Locoregional Therapy for Metastatic Disease

Surgical Resection

While operative management is the mainstay of therapy for localized, non-metastatic disease, surgical management of locally advanced or metastatic GEP-NET is controversial.[12] For those patients with locally advanced, recurrent, or metastatic GEP-NET, surgical treatment, including primary tumor resection, regional lymphadenectomy, and/or metastectomy, is the only potential curative therapy. In general, surgical treatment should be undertaken with the goal of a complete resection with microscopically negative margins (R0). When an R0 resection can be achieved (versus R1 where all macroscopic disease is removed but surgical margins are positive for microscopic disease), patients benefit from an improved long-term survival compared with patients who have unresected disease.[13] Several series report 5-year survival of 60–80 % compared with only 30 % among patients with unresected neuroendocrine liver metastases (NELM).[12,14–17] In these series, resection was associated with a low risk of mortality between 0 and 5 % and acceptable morbidity at 30 %. While surgery was associated with prolonged overall survival, disease-free survival was limited with recurrence at a median of 10–20 months after resection and greater than 50 % of patients harboring recurrent disease 5 years after resection.[12,14,18]

In addition, the unfortunate reality is that an R0 resection is achievable in only about 10 % of patients with metastatic GEP-NET.[13] In order to identify patients with metastatic GEP-NET who would likely benefit from surgical resection, the European Neuroendocrine Tumor Society (ENETS) recently established essential criteria for patient selection. Per ENETS, the minimal requirements for resection with "curative intent" of metastatic GEP-NET are resectable, well-differentiated liver disease with an acceptable morbidity and <5 % mortality, the absence of right heart insufficiency, the absence of extra-abdominal metastases, and the absence of diffuse peritoneal carcinomatosis.[18]

The role for cytoreductive surgery (an R2 resection with macroscopically positive margins) for metastatic GEP-NET is even more controversial. Cytoreductive surgery plays a role primarily in those patients with functional tumors but likely requires resection of at least 90 % of the tumor burden to be effective therapy. Tumor debulking not only improves symptomatic control from hormone excess or from mass effect but also may facilitate the effects of nonoperative treatment strategies, such as liver-directed therapies or medical therapy. In a retrospective review of 72 patients with metastatic nonfunctional PNET from the Mayo Clinic, patients undergoing cytoreductive surgery versus patients undergoing R0 resections had no difference in overall survival despite a higher incidence of tumor recurrence in the cytoreductive surgery group.[19] This lack of difference in overall survival between the two groups and the high incidence of recurrence after an R0 resection may actually indicate that persistent subclinical disease is unintentionally being left behind even in the R0 resection group.[14]

In the majority of patients with metastatic GEP-NET, surgical R0 resection or cytoreductive surgery to resect greater than 90 % of tumor burden is often not possible. In these situations, the utility of resection of the primary tumor is debated. A recent systemic review of six studies of metastatic intestinal NET demonstrated a trend towards improved overall survival associated with resection of the primary tumor despite unresectable NELM, with a median survival of 75–139 months versus 50–88 months among those patients who did not undergo resection of the primary lesion.[20] The pooled

Table 1 The World Health Organization (WHO) classification of gastroenteropancreatic neuroendocrine tumors (GEP-NET) and pancreatic neuroendocrine tumors (PNET) was updated in 2010 to include a proliferation-based grading system in conjunction with the traditional histopathological diagnostic criteria. Adapted with permission[9]

Grade	Differentiation	GEP-NET	PNET
Low grade (G1)	Well-differentiated NET	<2 mitoses per 10 hpf AND <3 % Ki67 index	<2 mitoses per 50 hpf AND no necrosis
Intermediate grade (G2)	Well-differentiated NET	2–20 mitoses per 10 hpf OR 3–20 % Ki67 index	2–50 mitoses per 50 hpf OR focal necrosis
High grade (G3)	Poorly differentiated NET	>20 mitoses per 10 hpf OR >20 % Ki67 index	>50 mitoses per 50 hpf

hpf high power field

5-year survival was better among patients who underwent primary tumor resection with unresectable NELM at 74 % versus 36 % for those who did not undergo surgery.[20] Despite the limitations of this study, the trend for possible benefit of resection of primary intestinal NET in those patients with unresectable NELM is intriguing. In patients with PNET harboring unresectable NELM, recent data suggest that resection of the pancreatic primary was associated with improved survival as well.[21–23] Together, these studies suggest a possible benefit for resection of the primary tumor even in globally unresectable NETs.

Orthotopic Liver Transplant (OLT)

Due to the indolent nature of GEP-NET, the high incidence of unresectable disease at presentation, and the perceived benefits of complete resection, surgeons have investigated the possibility of salvaging patients harboring otherwise unresectable NELM with OLT. Early experiences with OLT for NET were disappointing, however, likely due to poor patient selection.[24–26] Mazzaferro et al. recognized the importance of patient selection and proposed patient selection criteria for OLT in the setting of NELM, also known as the NET Milan Criteria. These criteria integrate histologic classification and disease behavior with conventional transplant selection in the hopes of improving outcomes and appropriately allocating scarce donor livers.[27] To meet inclusion criteria, patients must be 55 years of age or younger with confirmed histology of GEP-NET with a Ki67 less than 10 %, a primary tumor drained by the portal system removed with curative resection prior to transplantation, metastatic lesions involving less than or equal to 50 % of the liver parenchyma, and good response to therapy or stable disease for at least 6 months prior to transplantation.[27] Exclusion criteria include small cell carcinoma, high-grade neuroendocrine carcinomas, other medical or surgical conditions contraindicating liver transplantation such as previous tumors, and non-gastrointestinal carcinoids or tumors not drained by the portal system.[27]

Utilizing these selection criteria, the Milan group reported a 96 % patient survival at 5 years and about 80 % recurrence-free survival at 5 years in a prospective series of 30 patients undergoing OLT for NELM.[27,28] Thus, taking into consideration ethical issues related to organ allocation in the setting of donor shortages, OLT is only a reasonable option for those patients with an expected survival of greater than or equal to 70 % at 5 years and a recurrence-free survival greater than 50 % at 5 years. Since the establishment of the Milan Criteria for NET, other groups have validated these outcomes using very stringent patient selection.[29,30]

Local Ablative Therapies

Ablation therapy, including radiofrequency ablation (RFA), microwave ablation, cryotherapy, and ethanol injection, is another well-established modality used in the treatment of NELM. While cryotherapy and ethanol injections have fallen out of favor, RFA radiofrequency ablation (RFA) is the most commonly utilized ablative therapy due to its ability to be performed using either percutaneous or laparoscopic approaches, as well as its low associated morbidity.[31] In situtations where extensive tumor burden, bilobar disease, or anatomically difficult locations can complicate surgical treatment of metastatic disease, RFA can be applied as an adjunct to cytoreductive surgery allowing for a greater number of patients suffering from NELM to benefit from surgical intervention.

RFA can be performed as a percutaneous procedure with interventional radiology or intraoperatively during laparotomy or laparoscopy.[32,33] RFA is most effective in those patients with low tumor volume and best indicated when there are <5 liver metastases, lesions <3.5 cm in diameter, and in the setting of multiple tumors a sum of the diameters <8 cm.[18,34] Large size (>5 cm), hilar location, proximity to major bile ducts increases the risk of complications, and proximity to large vessels (>4 mm) can result in a heat-sink effect limiting the effectiveness of RFA.[18,34] In some of these cases, particularly for tumors in close proximity to large vessels, microwave ablation can be employed, as it is less sensitive to connective tissue cooling and more efficient at tumor destruction.[7,34]

Akyildiz et al. report results from 89 patients who underwent laparoscopic RFA of NELM.[31] Of the 44 % of patients with symptoms related to hormonal oversecretion, 97 % experienced at least partial symptom relief, and 73 % reported significant or complete symptomatic relief lasting a median of 14±5 months. Furthermore, the median disease-free survival after laparoscopic RFA was 15 months and the median overall survival was 6 years after the first RFA.[31] A systemic review of the current literature by Mohan et al. demonstrated similar findings among eight studies that included a total of 301 patients.[35] Fifty-four percent of all patients had symptoms at presentation among whom 92 % reported symptom improvement after RFA lasting a median of 14-27 months. Recurrence was common as well, ranging from 63 to 87 % with 5-year survival rates reaching 57 to 80 %. Overall morbidity was low at less than 10 % and mortality less than 1 %.[35] However, rare complications can be significant, including hepatic abscesses and bleeding.[31,35] Overall, the morbidity and mortality of RFA is low with successful symptom relief making it a reasonable treatment alone or in combination with resection.

Intra-arterial Therapies (IAT)

Hepatic IAT for NELM are based on the major principle that NELM are highly vascular tumors supplied by the hepatic artery while the normal liver parenchyma receives the majority of its blood supply from the portal vein. Vascular occlusion

to induce ischemia and necrosis of metastatic liver lesions can be accomplished percutaneously by bland transarterial embolization (TAE) of the hepatic artery. The co-administration of intra-arterial cytotoxic chemotherapy, such as doxorubicin, cisplatin, mirplatin, gemcitabine, streptozocin, mitomycin C, or 5-fluorouracil, with embolization of the hepatic artery or its branches (transarterial chemoembolization or TACE) can achieve high hepatic concentration of chemotherapeutic agents while limiting systemic exposure to chemotherapy. This technique has been further refined by the development of chemotherapeutic drug eluting beads (TACE-DEB), which achieves embolization with beads that facilitate the slow release of chemotherapeutic agents over time. Yttrium-90 (Y-90) radioembolization is yet another intra-arterial therapeutic option delivering targeted radiation therapy to the liver metastases.[36] Contraindications to these various IAT techniques include portal venous occlusion, significant liver insufficiency, a biliary anastomosis, and left ventricular ejection fraction <50 % when utilizing doxorubicin.[34,37–39] Serial IAT can offer palliation and prolong survival in patients with NELM.

Mayo et al. compared the relative efficacy of surgical management of NELM with IAT in a multicenter international analysis. A total of 753 patients with NELM underwent either surgical intervention (n=339) or IAT (n=414), which included TAE, TACE, TACE-DEB, or Y-90. The median and 5-year survival of patients undergoing surgical intervention was 123 months and 74 %, respectively, versus 34 months and 30 % for IAT, respectively. Of note, asymptomatic disease was strongly associated with a worse outcome on multivariate analysis. While surgical management provided a survival benefit over IAT among symptomatic patients with >25 % hepatic tumor involvement, no difference was noted in long-term outcomes between the surgery versus IAT groups among asymptomatic patients with >25 % liver tumor burden (Fig. 1).[40] Hence, the authors concluded that asymptomatic patients with large >25 % liver tumor burden benefit the least from surgical intervention, making IAT the more appropriate therapy. In turn, the authors suggested that surgery should be reserved for those patients with low-volume disease and those with symptomatic high-volume disease.[40]

In terms of distinguishing one form of IAT over another, the data are currently limited. TAE has most often been compared to TACE, and generally neither therapy has been determined to have a significant benefit over the other.[18,41–43] While TAE-DEB may have high response rates, Baghat et al. reported serious complications such as bilomas and abscess formation in a phase II trial, resulting in premature discontinuation of the trial for serious adverse events.[44] Guiu et al. reported similar results with biloma and liver infarct being independently associated with TACE-DEB.[45] While evidence comparing Y-90 to the effectiveness of the other various forms of IAT is lacking, the advantage of Y-90 is shorter hospital stay with fewer procedures compared to TAE and TACE. Y-90 also has the advantage of being delivered in a "lobar" fashion, which can be helpful for patients with more disseminated disease. Furthermore, repeat radiotherapy treatment of recurrence is possible since the microspheres are smaller, allowing patency of the vascular supply.[39] Ultimately, more clinical trials are required in order to further delineate the benefits versus toxicity ratio of each of these forms of IAT.

Systemic Therapy for Metastatic Disease

While surgical intervention is the cornerstone of therapy for GEP-NET, unfortunately, many patients with metastatic

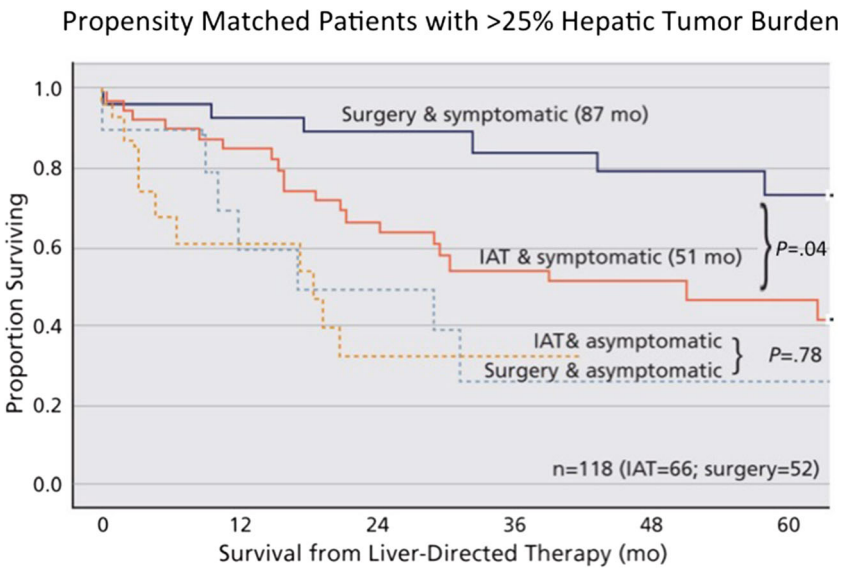

Fig. 1 Kaplan-Meier survival curve for patients with >25 % hepatic tumor burden undergoing either hepatic resection or intra-arterial therapy (IAT) of gastroenteropancreatic neuroendocrine tumor liver metastases. Patients with high-volume, symptomatic disease benefit most from surgical intervention while those with high-volume asymptomatic disease benefit equally from surgical intervention versus intra-arterial theraphy months. Reprinted with permission[40]

disease are not surgical candidates given the significant tumor burden at diagnosis. Thus, systemic therapy for metastatic or advanced GEP-NET remains crucial in controlling tumor growth and managing symptoms. Recently, the medical management of metastatic GEP-NET has evolved. Not only are standard therapies such as somatostatin analogs, interferon, and cytotoxic chemotherapy current options but also novel molecular targeted therapies have come shown great promise in the treatment of metastatic GEP-NET.

Somatostatin Analogs (SSA)

Symptoms of hormone hypersecretion are often common in patients with functional GEP-NET with liver metastases. SSA can provide relief in the majority of symptomatic patients as greater than 70 % of patients' GEP-NET express somatostatin receptors, which can be targeted by SSA.[18,39] Furthermore, octreotide administration periprocedural for those patients with NELM allows for careful symptom control for hormonal hypersecretion with the goal of alleviating carcinoid syndrome and intraprocedural release of serotonin.[18,39]

As demonstrated in the landmark PROMID study, SSA has also been demonstrated to slow the rate of tumor progression by controlling tumor growth in patients with functionally active and inactive midgut NET.[46] In this placebo-controlled, double-blinded, phase IIIB study, 85 treatment naïve patients were assigned to either the placebo (43 patients) or octreotide LAR (42 patients), a specific form of SSA. The primary end point was tumor progression with secondary end points being survival and tumor response. Treatment with octreotide LAR significantly lengthened the time to tumor progression to 14.3 months versus 6 months in the placebo group. Furthermore, 66.7 % of patients in the octreotide LAR group had stable disease compared to 37.2 % of patients in the placebo group. Unfortunately, no significant difference was noted in survival between the two groups with seven deaths in the octreotide LAR group versus nine deaths in the placebo group (Fig. 2).[46] Ultimately, functionally active and inactive tumors responded similarly, and the most favorable outcomes were in patients with low hepatic tumor burden who had the primary tumor resected.[46] Given the lack of survival benefit, octreotide LAR is generally not initiated until tumor progression has been demonstrated.[47]

Since the PROMID study, various studies have been conducted to investigate the efficacy of other SSA, such as lanreotide and pasireotide.[48,49] In the randomized, double-blind, placebo-controlled, multinational CLARINET trial, patients with advanced, well-differentiated or moderately differentiated, nonfunctioning, somatostatin receptor-positive NET were randomized to either the lanreotide group (101 patients) or the placebo group (103 patients). The primary end point was progression-free survival with secondary endpoints being overall survival, quality of life, and safety. The lanreotide group demonstrated a significantly prolonged progression-free survival with the median not reached by the end of the study at 96 weeks versus a median of 18 months for the placebo group. Furthermore, progression-free survival at 24 months was 65.1 % in the lanreotide group and 33.0 % in the placebo group. However, no significant difference was noted in the quality of life or overall survival in either group with the most common treatment-related adverse event being diarrhea.[48]

In the open-label, phase II study, the efficacy of pasireotide in treatment-naïve patients with metastatic grade 1 or 2 NET was investigated. The primary endpoint was progression-free survival with secondary endpoints being overall survival, overall radiographic response rate, and safety. While pasireotide appeared to be efficacious as an antiproliferative agent in the treatment of advanced NET, 79 % of patients in the pasireotide arm developed hyperglycemia raising the concern for its suitability as first-line systemic therapy.[49]

Further expanding upon SSA therapy, SSAs are now being labeled with radionuclides, such as ^{111}indium (^{111}I), ^{90}yttrium (^{90}Y), or ^{177}lutetium (^{177}Lu), and being utilized for peptide receptor radionuclide therapy (PRRT). This potentially allows for targeting cytotoxic radiolabeled compounds to GEP-NET cells in the primary lesion, but also NELM and extra-hepatic sites of disease. Although few studies currently exist, early studies have demonstrated a delay in disease progression and favorable response rates. However, the long-term benefits and adverse effects are yet to be fully determined.[39,50]

Interferon Alpha Therapy

Interferon alpha therapy has also been described as systemic therapy for metastatic GEP-NET given its antiproliferative effects in addition to hormonal control. In a prospective, randomized, multicenter study conducted by Faiss et al., 80 therapy naïve patients with functional and nonfunctional GEP-NET and documented disease progression within the 3 months prior to study entry were randomly assigned to either lanreotide, interferon alpha, or both.[51] All three groups were demonstrated to have comparable antiproliferative effects in metastatic GEP-NET, as well as similar rates of partial remission, stable disease, and tumor progression. The combination arm of lanreotide plus interferon alpha had significant symptom reduction; however, interruption of therapy was more common in the combination group due to side effects, such as increasing liver enzymes, diarrhea, nausea, and other constitutional symptoms. Hence, interferon alpha therapy should primarily be considered in patients with somatostatin negative tumors given the high side-effect profile.[51]

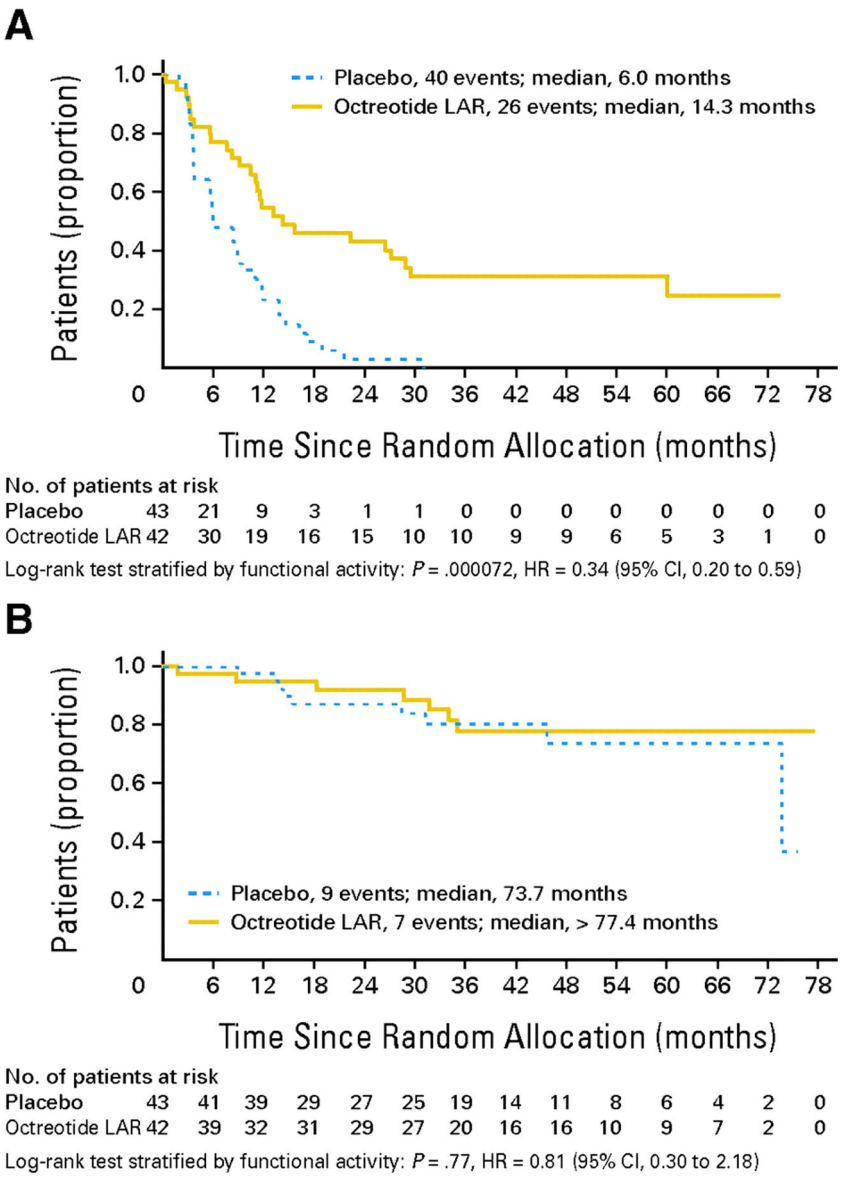

Fig. 2 **a** Conservative intent-to-treat analysis of time to progression or tumor-related death. **b** Intent-to-treat analysis of overall survival. *HR* hazard ratio. Reprinted with permission[46]

Cytotoxic Chemotherapy

Systemic chemotherapy is generally considered first-line therapy for poorly differentiated or rapidly progressing GEP-NET.[52] The specific chemotherapeutic agents administered are primarily determined by the degree of tumor differentiation and location of the primary tumor. Among patients with poorly differentiated or rapidly progressing disease, etoposide used in combination with cisplatin has some benefit with improved response rates but a short duration of response.[53] In general, systemic therapy has a highly variable role in the treatment of GEP-NET outside of this patient population given the variability in tumor biology, regimens used, and endpoints measured, making systemic chemotherapy minimally effective in those with lower grade GEP-NET. PNET may be more chemo-responsive with streptozocin and doxorubicin being the most commonly used regimens demonstrating 69 % tumor regression, roughly 20 months to tumor progression, and a possible survival advantage compared to other combination chemotherapeutic regimens.[54] In another study, Kouvaraki et al. reported on 84 patients with locally advanced or metastatic PNET who received combination streptozocin, 5-fluorouracil, and doxorubicin therapy. In this study, the authors noted a response rate of 39 %, median response duration of 9.3 months, median overall survival of 37 months, 2-year progression-free survival of 41 %, and 2-year overall survival of 74 %. However, 23 % of patients experienced grade 3 or 4 toxicities.[55]

Recently, temozolomide in combination with other chemotherapeutic agents has demonstrated promise in the treatment of locally advanced or metastatic GEP-NET. Strosberg et al. reported on patients with metastatic PNET receiving

temozolomide and capecitabine combination therapy. In this study, the authors reported a 70 % response rate, 18-month progression-free survival, and 92 % overall survival at 2 years with only 12 % of patients experiencing grade 3 or 4 adverse events.[56] In a systemic review by Abdel-Rahman et al., temozolomide-based combination chemotherapy was assessed in patients with advanced NET. In total, 16 trials including 348 patients demonstrated a median progression-free survival ranging from 6 to 31 months, median overall survival ranging from 22 to 83 months, disease control from 65 to 100 %, and grade 3 or 4 toxicities that most frequently included leukopenia, lymphopenia, and elevated transaminases.[57] This systemic review further confirmed the role of temozolomide in combination with other chemotherapeutic agents as a viable treatment option for advanced low to intermediate grade NET.

Molecular Targeted Therapy

Molecular targeted therapy has demonstrated promise in the treatment of metastatic GEP-NET. Our understanding of the molecular biology of PNET improved significantly when Jiao et al. sequenced the exomes of a series of clinically well-characterized PNET. The most frequently mutated genes in these PNET were 44 % *MEN1* (encodes menin) mutation, 25 % *DAXX* (death-domain-associated protein) mutation, 18 % *ATRX* (α thalassemia/mental retardation syndrome X-linked) mutation, and 14 % mutations coding for members of the mTOR (mammalian target of rapamycin) signaling pathway.[58] Using this information, we now hopefully can begin to treat GEP-NET in a more targeted fashion using molecular profiles to guide therapy.

Everolimus and sunitinib are two novel molecular targeted agents approved by the FDA in the treatment of PNET.[59–61] mTOR is a serine/threonine kinase that plays a crucial role in various cell signaling pathways mediating cell growth, proliferation, apoptosis, and angiogenesis; the mTOR pathway has recently been demonstrated to be mutated in a portion of patients with PNET.[58] Everolimus, an orally active mTOR inhibitor, was initially studied in combination with octreotide LAR, in a phase II study that enrolled 60 patients with metastatic, unresectable, low to intermediate grade GEP-NETs. Initial results demonstrated everolimus to have promising antitumor activity with improved response rates and progression-free survival, which led to the RADIANT-1 trial.[62] The RADIANT-1 multinational, phase II trial enrolled 160 patients with progressing, advanced PNET assessing everolimus alone versus combination therapy with both everolimus plus octreotide in chemoresistant patients.[63] Combination therapy significantly improved both tumor stabilization (80 vs. 61.7 %) as well as median progression-free survival (16.7 vs. 9.7 months) when compared to single-agent therapy with everolimus. These encouraging results eventually lead to the RADIANT-3 trial, which was a prospective, randomized, phase III study.[64] Four hundred ten patients with advanced, low grade, or intermediate grade PNET who demonstrated progression of disease within 12 months prior to the study were enrolled. Patients were randomized to everolimus or placebo therapy with the everolimus group exhibiting longer median progression-free survival (11.0 vs. 4.6 months) and greater progression-free survival at 18 months (34 vs. 9 %) with a greater portion of patients living at that time. No significant difference in overall survival was noted at the time of publication, although median overall survival had not yet been reached. The everolimus group also had more adverse events than the placebo group, which were minor and mainly grade 1 or 2.[64]

Sunitinib is another major molecular targeted agent currently used in the treatment of PNET, with its mechanism of action being upstream to the mTOR pathway regulating cell signaling. Sunitinib was initially investigated in a phase II, open-label, multicenter study enrolling 109 patients with advanced, well-differentiated GEP-NET who were randomized to sunitinib therapy or placebo.[65] The endpoints were response, survival, and adverse events. The overall response rate in patients with PNET was 16.7 % with 68 % demonstrating stable disease. Carcinoid patients had a lower overall response rate of 2.4 % with 83 % demonstrating stable disease. Median time to tumor progression was 7.7 and 10.2 months with 1-year survival of 81.1 and 83.4 % in PNET and carcinoid patients, respectively. No difference in quality of life or fatigue was noted between the two therapies. Ultimately, this study demonstrated the antitumor activity in PNET with no definitive antitumor activity against carcinoids.[65] The promising results from this study lead to the multinational, randomized, double-blind, placebo-controlled phase III trial of sunitinib in patients with advanced, well-differentiated PNET.[66] One hundred seventy-one patients, all with documented disease progression within 12 months prior to enrolling, were randomly assigned to the sunitinib or placebo arm. The primary endpoint was progression-free survival with secondary endpoints being objective response rate, overall survival, and safety. The study was terminated early due to more serious adverse events and deaths in the placebo group. Furthermore, the sunitinib group demonstrated significantly improved progression-free survival (11.4 vs. 5.5 months), objective response rate (9.3 vs. 0 %), overall survival (90 vs. 75 %), and decreased death (9 vs. 21) when compared to the placebo group.[66] Despite these promising new molecular targeted therapies, controversy still exists regarding the otimal timing to initiate therapy among patients with unresectable, metastatic, well-differentiated PNET.

Integration of Therapies

While data currently exists for each individual locoregional and systemic therapeutic option in the treatment of metastatic GEP-NET, little evidence-based information is available to guide the integration of these various treatment modalities. In an effort to achieve locoregional control, surgical resection

in combination with liver-directed therapies may be considered. For example, some patients with a PNET and NELM may require both a pancreatic resection as well as some time of liver-directed therapy (e.g., resection, ablation, etc.). However, pancreaticoduodenectomy plus liver-directed therapy can result in significant morbidity (34.1 %) as reported by De Jong et al.[67] For example, undergoing pancreaticoduodenectomy with staged liver-directed therapy (14.5 %) resulted in a significantly greater risk of hepatic abscess compared to simultaneous pancreaticoduodenectomy plus liver-directed therapy (7.0 %).[67] Thus, more clinical trials are necessary to further elucidate the potential risks and benefits of combining different locoregional therapies.

With regard to systemic control, the timing and use of systemic therapy remain controversial. Currently, systemic therapy is often intiated for patients with progressive metastatic GEP-NET, symptom control, or disease progression. Unfortunately, no randomized studies to date assess the role of systemic therapy as neoadjuvant or adjuvant therapy nor do robust data exist to assess the efficacy of these therapies in combination with one another.[68] Thus, many uncertainties remain in the management of metastatic GEP-NET, making prospective, randomized controlled trials even more crucial.

Conclusion

The treatment of metastatic GEP-NET is an evolving field with advancing surgical approaches, liver-directed therapies, and novel medical therapies aimed at improving patient outcomes. Fully integrating locoregional and systemic approaches for the treatment of patients with metastatic GEP-NET, however, requires a multidisciplinary approach to optimize therapy and determine the timing and appropriateness of each individual therapy in a patient's disease course. Given novel molecular targeted therapies, personalized genetic therapy is hopefully the next step in treating metastatic GEP-NET with the potential to stabilize tumor growth, improve survival, and ultimately improve the overall prognosis for patients who suffer from this disease.

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