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REVIEW ARTICLE – ENDOCRINE TUMORS

The Landmark Series: Management of Small Bowel Neuroendocrine Tumors

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ABSTRACT Surgical resection is the foundation for treatment of small bowel neuroendocrine tumors (SBNETs). Guidelines for surgical management of SBNETs rely on retrospective data, which suggest that primary tumor resection and cytoreduction improve symptoms, prevent future complications, and lengthen survival. In advanced NETs, improvement in progression-free survival has been reported in large, randomized, controlled trials of various medical treatments, including somatostatin analogues, targeted therapy, and peptide receptor radionuclide therapy. This review discusses important studies influencing the management of SBNETs and the limitations of current evidence regarding surgical interventions for SBNETs.

Small bowel neuroendocrine tumors (SBNETs) are epithelial neoplasms of the small intestine characterized by neuroendocrine differentiation and the ability to secrete functional hormones or amines. The term SBNETs refers primarily to jejunoileal NETs, which are of midgut origin and have a distinct presentation compared to duodenal NETs, which are considered to be of foregut origin. Recapitulating enterochromaffin cells of the small bowel, SBNETs give rise to submucosal tumors, which are multifocal in 20–56% of patients.[1–6] It can be difficult to distinguish between jejunal and ileal NETs, because there is not a clear anatomic delineation between the two sites, but 72% of SBNETs occur within 100 cm of the ileocecal valve.[6]

The incidence of SBNETs has increased steadily, surpassing adenocarcinoma as the most common tumor of the small bowel in 2000.[7,8] Surgical resection of the primary tumor, nodal metastases, and mesenteric masses remains the most important initial treatment for these tumors, which has been advocated even for patients with metastatic disease.[9,10] No randomized, controlled studies of surgical management in SBNETs exist due to their low incidence (12 cases per 100,000), variable presentation, and indolent nature.[8] Therefore, unlike in other areas of surgical oncology, such as breast cancer, where large, high-quality, randomized trials inform all aspects of surgical and medical care, consensus guidelines in SBNETs rely primarily on retrospective data and expert opinion. These data suggest that resection of the primary tumor with or without cytoreduction of metastases alleviates symptoms and improves survival, although selection bias and treatment group heterogeneity affect these conclusions. In contrast to surgery, medical therapies available to treat SBNETs, such as somatostatin analogues (SSAs), molecularly targeted therapies, and peptide receptor radionuclide therapy (PRRT), have been evaluated in randomized, controlled trials. This review addresses studies, both randomized and not, that have changed the landscape of SBNET management.

SURGICAL MANAGEMENT

Resection represents the preferred first-line treatment of SBNETs and their associated mesenteric nodes and masses, as surgical management can improve survival and may reduce the risk of developing metastasis and carcinomatosis.[11–14] Resection and cytoreduction can alleviate

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tumor symptoms, including obstruction, gastrointestinal bleeding, and abdominal pain, as well as symptoms related to hormone production.[15] Furthermore, an elective oncologic operation will likely result in improved disease clearance and patient outcomes compared with one performed urgently for obstruction.[16] This latter scenario is increasingly common and one for which general surgeons should be prepared, because patients can present with obstruction without a prior diagnosis of an SBNET. In these urgent operations, the surgeon should still perform resection of the primary tumor and mesenteric nodes when feasible to relieve symptoms of obstruction and ischemia.[17,18] These patients should then be referred to centers with expertise in caring for patients with NETs.[19,20]

RESECTION OF PRIMARY TUMORS WITH UNRESECTABLE METASTASES

Unlike many other malignancies, the presence of unresectable metastases does not preclude resection of the primary SBNET. Retrospective studies report that resection of the primary SBNET can improve survival and symptoms compared to historical or nonrandomized controls when there are metastases.[12,14,21,22] The caveat to these studies is that historical controls do not reflect improvements in survival outcomes that have accompanied recent improvements in medical treatment options, such as with peptide receptor radiotherapy (PRRT).

To address limitations of single-institution series, Capurso et al. reviewed 2,399 papers and identified 6 studies that reported outcomes of patients with SBNETs and liver metastases who underwent resection of the primary tumor (Table 1).[23] No randomized, controlled trials were identified, so a meta-analysis was not possible, but six retrospective cohort studies were included for pooled analysis. The authors found a trend towards improved overall survival (OS) in the resection group compared with the nonresection group (median OS 75–139 vs. 50–88 months); however, the qualitative review was limited by heterogeneity of characteristics between the groups and inadequate information to account for clinicopathologic variables, such as Ki-67.

Daskalakis et al. performed a more sophisticated retrospective cohort study in 363 patients with "asymptomatic" SBNETs and distant metastases. Patients were divided into two groups: those having prophylactic locoregional surgery versus those who underwent either delayed surgery (> 6 months after diagnosis) or nonsurgical treatment.[24] The prophylactic surgery group had improved survival (median OS 9.5 vs. 5.3 years), but the delayed or nonsurgical group was older, had larger liver tumor burden and higher 5-HIAA levels, and was more likely to have extrahepatic metastases and carcinoid heart disease. The heterogeneity of the two groups highlights the bias that hampers interpretation of retrospective cohort studies, and therefore propensity score-matching was performed in 91 patients from each group. This revealed similar outcomes in both groups for both OS (median 7.9 vs. 7.6 years; hazard ratio [HR] 0.98, log-rank $P = 0.93$) and cancer-specific survival (median 7.7 vs. 7.6 years; HR 0.99, log-rank $P = 0.99$).

The authors suggested these findings indicated that initial surgical treatment offers no survival benefit over nonsurgical management. However, the majority of

TABLE 1 Summary of studies included in a qualitative review by Capurso et al.[23] which compared survival in patients with SBNETs and liver metastases who did and did not have resection of their primary tumor

References	No. of patients	Median OS, months (95% CI)	5-year survival (%)	Median PFS, months
Givi et al.[12]	Resected 66	108	81	54
	Unresected 18	50	21	27
Strosberg et al.[75]	Resected 100	110	NR	NR
	Unresected 35	88	NR	NR
Ahmed et al.[22]	Resected 209	119 (89, 149)	74	NR
	Unresected 76	57 (32, 81)	46	NR
Søreide et al.[21]	Resected 53	139	NR	NR
	Unresected 12	69	NR	NR
Norlén et al.[25]	Resected 493	NR	75	NR
	Unresected 86	NR	28	NR
van der Horst-Schrivers et al.[76]	Resected 27	75 (44, 107)	57	NR
	Unresected 49	52 (37, 68)	44	NR

There was a trend toward improved OS in in the resection group compared with the nonresection group (median OS 75–139 vs. 50–88 months)

CI Confidence interval, *PFS* Progression-free survival, *OS* Overall survival, *SBNET* Small bowel neuroendocrine tumor, *NR* Not reported

patients in the propensity-matched delayed or nonsurgical group had surgery performed at some point (53/91 patients, 58%). Furthermore, 20 patients in the delayed surgery group later developed symptoms requiring surgery, and these patients may have benefited from prophylactic operations. Because the majority of patients in both groups had surgery for their primary tumor, it is difficult to conclude that surgical resection of the primary does not improve survival in patients with asymptomatic stage IV SBNETs. A study of 121 patients from the same institution reported in 1996 argued that few patients were truly asymptomatic, as 48% of patients had carcinoid syndrome, and of those without, 81% had abdominal pain, 68% had diarrhea, 59% had weight loss, and 62% had nausea/distention.[16]

Because there are no randomized, clinical trials and a dearth of high-quality data, consensus guidelines rely on the existing observational studies. The North American Neuroendocrine Tumor Society (NANETS) and the European Neuroendocrine Tumor Society (ENETS) recommend patients with metastatic SBNETs be carefully evaluated and considered for resection of the primary tumor to alleviate current symptoms, minimize future symptoms, and possibly to prolong progression-free survival (PFS) or OS.[9,10] Patients with negative prognostic factors, such as poor performance status or very high liver tumor burden, may not benefit from surgical resection if truly asymptomatic.

MANAGEMENT OF REGIONAL LYMPH NODES

In addition to primary tumor resection, resection of mesenteric nodes and masses can improve symptoms and survival outcomes.[25,26] Up to 88% of patients with SBNETs will present with mesenteric metastases, which can be accompanied by marked fibrosis causing mesenteric ischemia, obstruction, and abdominal pain.[25,27,28] In addition to facilitating accurate staging, clearance of mesenteric lymph nodes and masses can improve these symptoms and those related to carcinoid syndrome.[16,29]

The largest retrospective study from the Surveillance, Epidemiology and End Results (SEER) database addressing the management of mesenteric lymph nodes in SBNETs found that removal of at least one lymph node was associated with improved survival compared to no lymph nodes (HR 0.64, $P = 0.0027$).[26] However, this association dropped out on multivariate analysis after adjusting for age, histology, tumor size, and overall stage (HR 0.93, $P = 0.14$).[26] In patients who did have resection of regional nodal metastases, removal of at least eight nodes (HR 0.73, $P = 0.05$) or a lymph node ratio (LNR; positive to negative node ratio) of < 0.29 was associated with improved OS (HR 1.65 for LNR > 0.29, $P = 0.0019$). Based on several similar studies and the complications associated with residual nodal disease, guidelines recommend routine lymph node clearance during resection of SBNETs.[9,10]

Regarding surgical technique, Öhrvall et al. and others have described wedge resection of the affected bowel and associated mesentery down to the branching of segmental vessels from the superior mesenteric artery (SMA) and vein (SMV).[30–32] Mobilization of the cecum, terminal ileum, and mesenteric root may allow for dissection of the mesenteric nodes and mass from the posterior aspect. However, if the mesenteric root is extensively involved with encasement of the SMA and SMV, resection of a proximal mesenteric mass may not be possible without injury to mesenteric vessels and vascular compromise to the remaining bowel. Although there are concerns that these mesenteric root masses may cause SMV thrombosis, patients can develop collateral vessels, which reduce the risk of mesenteric ischemia symptoms.[10,31] The potential for complications with extensive nodal dissections needs to be weighed carefully against the fact that patients can live for years without resection.

In contrast, optimal management of distant lymph nodes, such as para-aortic or retroperitoneal nodes, is not clear. Although extended nodal dissections have been studied in randomized trials for other abdominal cancers, no such studies exist in SBNETs.[33,34] As such, guidelines recommend against routine resection of distant abdominal nodes beyond the mesenteric vessels unless imaging suggests these metastases may threaten neighboring structures.[10]

ROLE OF LAPAROSCOPY

The "gold standard" for resection and cytoreduction in SBNETs is open surgery with resection of the primary tumors, regional lymph nodes, mesenteric masses, and peritoneal metastases, which also may include resection or ablation of hepatic metastases. The surgeon must manually palpate the entire length of small bowel to identify all tumors, which can be small and multifocal. Some authors have found a rate of multifocality as low as 20%.[1–4] In a comprehensive study of tumor location in 123 patients, Keck et al. found that 56% of patients with SBNETs undergoing resection at a tertiary care center had multifocal tumors. The mean tumor size was 2 cm, although tumors could be as small as a few millimeters in diameter.[6] Laparoscopy may successfully be used to identify SBNETs, but graspers are inadequate to find additional lesions that would be found by palpation. Surgeons also should carefully examine the diaphragm, mesentery, and

pelvis; 17% and 4% of patients will present with peritoneal and ovarian metastases, respectively.[25] Performing adequate examination and cytoreduction laparoscopically can be challenging, and the role of laparoscopy in resection of SBNETs remains controversial.

Small studies have reported successful laparoscopic resection of SBNETs, primarily in the setting of NETs of unknown primary or for SBNETs with limited nodal metastases.[5,35–37] Wang et al. emphasized that even if resection is performed laparoscopically, the authors routinely exteriorize the small bowel via a soft-tissue wound retractor or hand-assisted laparoscopic device for manual palpation of the bowel.[5] Massimino et al. reported that of 46 patients undergoing laparoscopic resection for SBNETs, 14 patients (30%) required conversion to an open procedure for palpation of the bowel or to facilitate hepatic cytoreduction.[35] In the largest series of patients with SBNETs undergoing laparoscopic resection ($n = 83$), Kasai et al. demonstrated that minimally invasive techniques often were successful with mesenteric masses > 2 cm from the origins of the ileocolic artery and vein, with only 9% of these patients requiring conversion to an open procedure.[38] The conversion rate was 39% for patients with mesenteric masses ≤ 2 cm from the ileocolic artery and vein and 80% for patients with mesenteric masses involving the SMA/SMV or proximal to the origin of the ileocolic artery and vein. Expert guidelines thus recommend an open approach to resection of SBNETs, although hand-assisted laparoscopic techniques also may be reasonable if the entire small bowel can be assessed.[9,10] Patients requiring extensive nodal dissection, hepatic cytoreduction, or peritoneal debulking may be better served by open operations.

MANAGEMENT OF PERITONEAL CARCINOMATOSIS

Peritoneal carcinomatosis occurs in almost 20% of patients with SBNETs and is a negative prognostic factor for survival.[11,13,25,39,40] Peritoneal metastases can cause local fibrosis and adhesions, and resection of these metastases may reduce the risk of developing future pain and obstruction.[10] Cytoreductive surgery with heated intraperitoneal chemotherapy (HIPEC) is used for the management of peritoneal carcinomatosis due to other malignancies but has not been well-studied in SBNETs.[41–43]

Elias et al. reviewed 41 patients with well-differentiated NET peritoneal carcinomatosis who underwent cytoreductive surgery with or without HIPEC (Fig. 1).[44] Disease-free survival (DFS) was longer in the HIPEC group (2-year DFS 49% vs. 16.7%, $P = 0.018$). Despite this, there was no

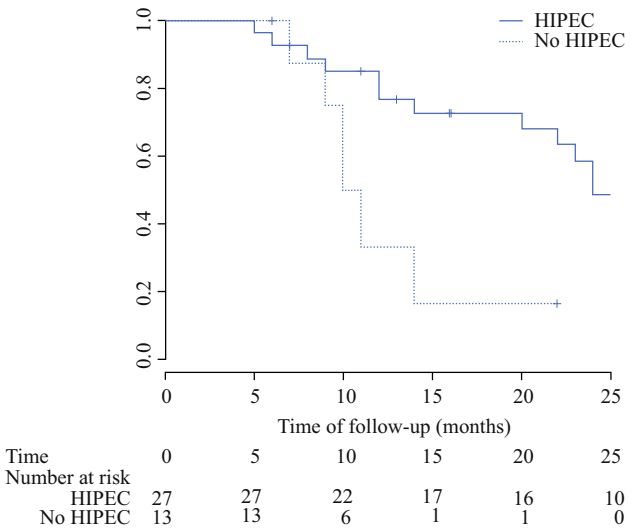

FIG. 1 Disease-free survival of patients with NET peritoneal carcinomatosis undergoing cytoreduction and HIPEC versus cytoreduction alone in Elias et al.[44] Disease-free survival (DFS) was longer in the HIPEC group compared with the non-HIPEC group (2-year DFS 49% vs. 16.7%, $P = 0.018$), although there were no differences in OS, peritoneal recurrence rates, or liver recurrence rates. HIPEC is not currently recommended for NET treatment. *HIPEC* Heated intraperitoneal chemotherapy, *NET* Neuroendocrine tumor, *OS* Overall survival

difference in OS or peritoneal or liver recurrence rates. Limitations of this study included heterogeneity between the groups, short follow-up, and different time periods during which the groups were treated. The authors stopped performing HIPEC on patients with NET peritoneal carcinomatosis after 2007 due to high rates of recurrence, procedure complexity, and morbidity associated with the procedure. As a result of these limited data, expert guidelines do not recommend HIPEC in the management of SBNET carcinomatosis.[10,45] Instead, larger peritoneal metastases can be resected with the underlying peritoneum and smaller lesions ablated with electrocautery or argon beam. Patients with extensive disease also may develop disease affecting the ureters, particularly the right ureter, which surgeons should keep in mind during surgical planning.[46,47]

CYTOREDUCTION OF LIVER METASTASES

Liver metastases negatively impact survival and can cause hormonal symptoms, as the biogenic amines secreted by liver metastases may be released into the systemic circulation and bypass hepatic inactivation.[18,25,48,49] Unfortunately, more than 60% of patients with SBNETs will present with liver metastases.[25] Again, high-quality data are lacking, but based on retrospective studies, cytoreduction of hepatic metastases improves symptoms due to hormonal overproduction and may improve

survival.[11,13,39] In early series, hepatic cytoreduction was only recommended when > 90% of grossly visible hepatic metastases could be removed.[50,51] However, this threshold is achievable in less than 20% of patients with SBNETs and hepatic metastases.[18] More recent studies have demonstrated that cytoreduction can still provide survival benefit if > 70% of liver tumor burden is resected (Fig. 2).[40,52] These series also demonstrate that parenchymal-sparing procedures, such as enucleation and ablation, are safe and effective for hepatic cytoreduction. An in-depth discussion of the management of NET liver metastases is the topic of another Landmark Series article in *Annals of Surgical Oncology*.[53]

MEDICAL MANAGEMENT

In contrast to the absence of trials studying surgery in SBNETs, there exist several, randomized controlled trials for medical treatment of advanced SBNETs. This section will briefly discuss these clinical trials.

PROMID AND CLARINET TRIALS

Somatostatin analogues have been used since the 1980s to treat hormonal symptoms and carcinoid syndrome in NETs.[54] Neuroendocrine tumors express a high density of somatostatin receptors (SSTRs), and SSAs like octreotide and lanreotide bind to these receptors, inhibiting secretion of vasoactive substances responsible for symptoms, such as diarrhea and flushing.[55–57] The PROMID study sought to determine the effect of octreotide on locally inoperable or metastatic well-differentiated midgut NETs. This phase III

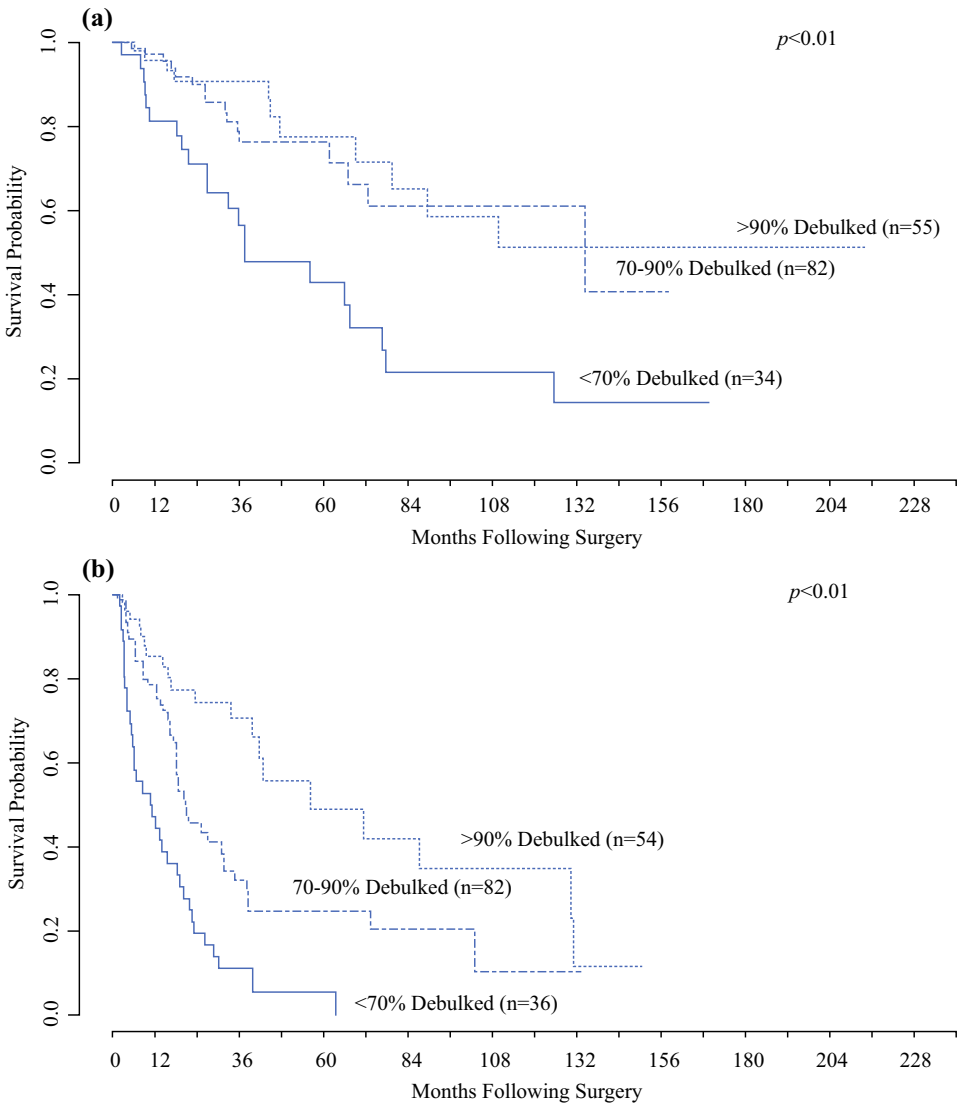

FIG. 2 Kaplan–Meier curves of **a** OS and **b** PFS in patients with small bowel (SBNETs) or pancreatic (PNETs) neuroendocrine tumors who underwent hepatic cytoreduction in Scott et al.[52] Patients with cytoreduction of at least 70% of their hepatic tumor burden had improved OS and PFS compared with patients with < 70% cytoreduction. *OS* Overall survival, *PFS* Progression-free survival

randomized, double-blind, placebo-controlled trial assigned patients to 30 mg/month octreotide long-acting repeatable (LAR; $n = 42$) or placebo ($n = 43$).[58] Progression-free survival was improved in the treatment group (median PFS 14.3 vs. 6.0 months; HR 0.34, $P < 0.001$). Subsequent long-term follow-up found no difference in OS between the groups (median OS 84.7 vs. 83.7 months; HR 0.83, $P = 0.51$), but the majority of patients in the placebo group (38/43) crossed over to receive octreotide upon progression, potentially underestimating the impact of octreotide on OS.[59] PROMID showed that octreotide LAR prolongs PFS in patients with advanced midgut NETs, providing level-I evidence confirming the antiproliferative effects of this SSA (Fig. 3).

The CLARINET trial sought to test another long-acting SSA, lanreotide, in a broader population.[60] Compared with octreotide, lanreotide displays relatively greater affinity for type-5 SSTRs,[61] and the CLARINET trial studied a slightly different patient population than PROMID. This multicenter, phase III, randomized, placebo-controlled study included patients with advanced, well- or moderately differentiated, nonfunctional gastroenteropancreatic (GEP) NETs. The study randomized patients to treatment with 120 mg/28 days of lanreotide ($n = 101$) or placebo ($n = 103$). The treatment group realized improved PFS compared with placebo (median PFS not reached vs. 18.0 months; HR 0.47, $P < 0.001$).[60] At 24 months, PFS was 65.1% in the lanreotide group compared to 33.0% in the placebo group. Similar to the PROMID trial, OS did not differ between the groups, and crossover from placebo to lanreotide was common (47/88 patients). The CLARINET trial provided further high-quality evidence of the antiproliferative effects of SSAs in GEP NETs.

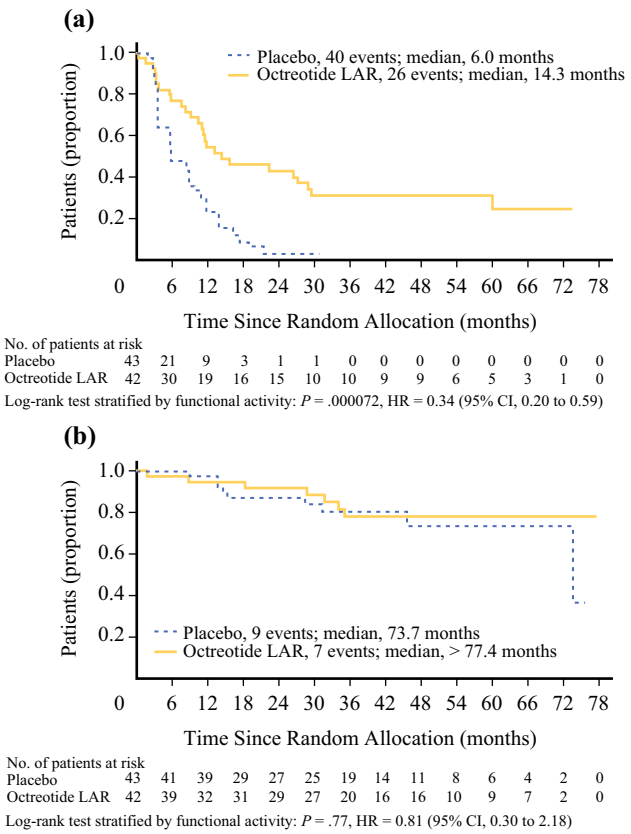

FIG. 3 Survival outcomes from the PROMID trial.[58] Kaplan–Meier analysis of **a** PFS and **b** OS in patients with advanced midgut NETs receiving octreotide long-acting repeatable (LAR) or placebo. The octreotide LAR group had longer PFS (14.3 vs. 5 months; HR 0.34, $P = 0.000072$). The two groups had similar OS, although the majority of patients in the placebo group (38/43) received octreotide upon progression. *HR* Hazard ratio, *NET* Neuroendocrine tumor, *OS* Overall survival, *PFS* Progression-free survival

While SSAs have not been directly compared to everolimus or sunitinib, based on PROMID and CLARINET and the drugs' relative safety, NANETS and ENETS recommend SSAs as first-line treatment for patients with GEP NETs with carcinoid symptoms, high-volume disease, or signs of progression.[62, 63] No direct randomized comparisons exist to inform the choice of octreotide versus lanreotide for SBNETs. Existing evidence shows clear efficacy for both in terms of PFS-prolongation, and the importance of their slightly different receptor specificities remains unclear. Most clinicians consider the two drugs equivalent, and guidelines do not recommend one SSA over the other.[63]

NETTER-1

Peptide receptor radionuclide therapy administers a radioisotope conjugated to an SSA, which is taken up by SSTRs on the surface of NET cells, then internalized, where it exerts its cytotoxic effects.[57,64] The NETTER-1 trial was a phase III, randomized, open-label study investigating the efficacy of ^{177}Lu-Dotatate PRRT for treatment of midgut NETs. Eligible patients had advanced, well-differentiated midgut NETs and progression while on octreotide. Tumors were SSTR-positive based on SSTR scintigraphy. The treatment arm consisted of 4 cycles of ^{177}Lu-Dotatate and 30 mg/28 days octreotide LAR ($n = 116$) versus 60 mg/28 days octreotide LAR ($n = 113$). At a median follow-up of 14 months, PFS was longer in the ^{177}Lu-Dotatate group compared with control (median PFS not reached vs. 8.4 months; HR 0.21, $P < 0.001$).[65] Interim analysis of OS found that the HR for death was 0.40 ($P = 0.004$) in the ^{177}Lu-Dotatate group, but data were not mature enough to determine median OS (Fig. 4).

Based in part on the findings of the NETTER-1 trial, the FDA approved ^{177}Lu-Dotatate for treatment of SSTR-positive GEP NETs.[66] Strengths of NETTER-1 include a trial design that incorporated SSA-treatment, the existing

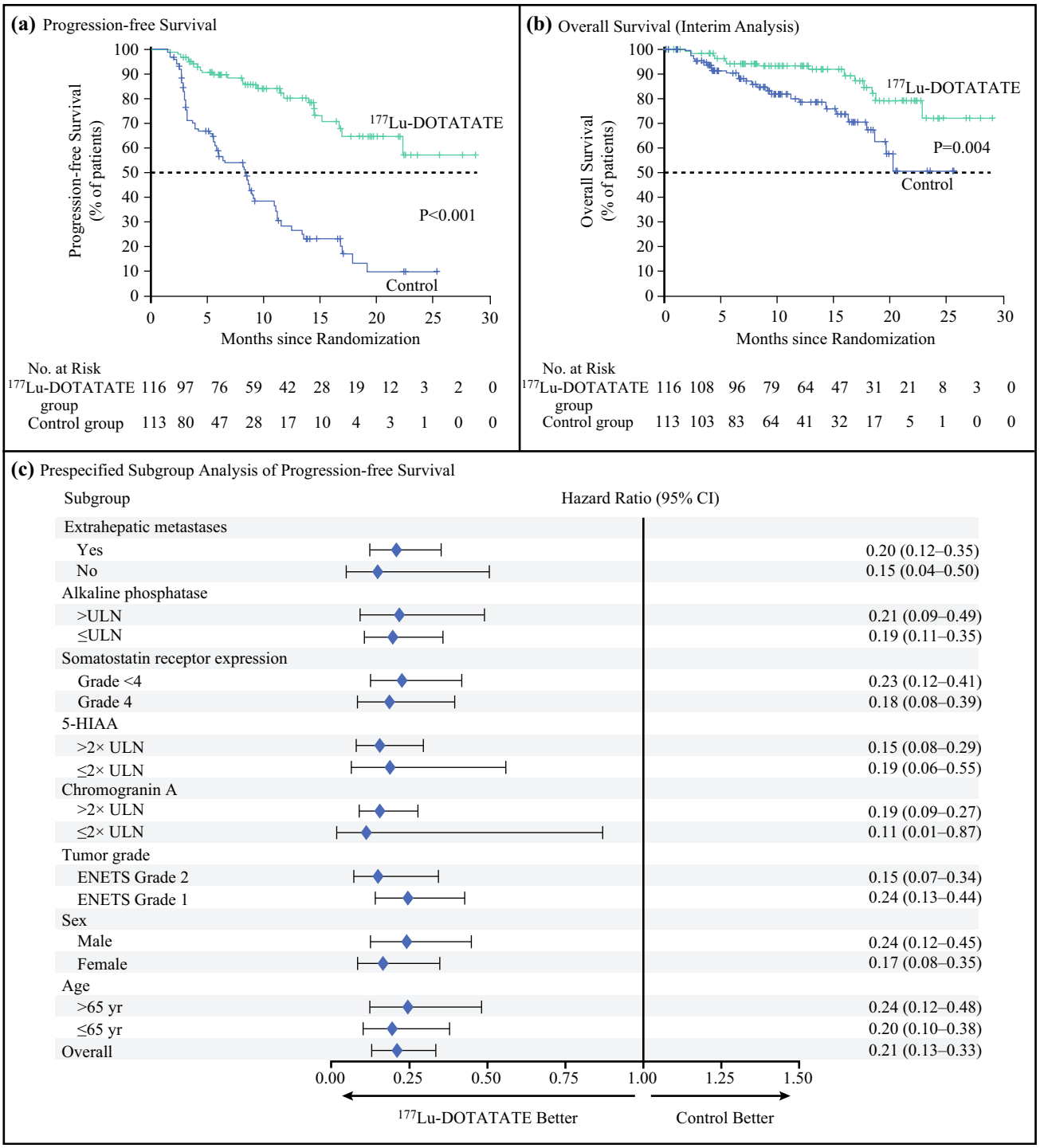

FIG. 4 Survival outcomes from the NETTER-1 trial.[65] Kaplan–Meier analyses of **a** PFS and **b** OS comparing patients with advanced midgut NETs who received ^{177}Lu-Dotatate PRRT and octreotide LAR (30 mg/28 days) or high-dose octreotide LAR (60 mg/28 days). The ^{177}Lu-Dotatate group had longer PFS (median not reached vs. 8.4 months; HR 0.21, $P < 0.001$). The hazard ratio for death was 0.4 ($P = 0.004$) in the ^{177}Lu-Dotatate group, but data were not mature enough to determine median OS. **c** Effect of ^{177}Lu-Dotatate treatment on PFS in prespecified subgroups. *HR* Hazard ratio, *LAR* Long-acting repeatable, *NET* Neuroendocrine tumor, *OS* Overall survival, *PFS* Progression-free survival, *ULN* Upper limit of normal range

standard of care, making it representative of real-world practice. Higher objective response rates (18%) than those seen with other treatments and a strong suggestion of an OS benefit have moved PRRT to a first line option for progressive, unresectable, SSTR-positive SBNETs. The NANETS and ENETS guidelines generally recommend

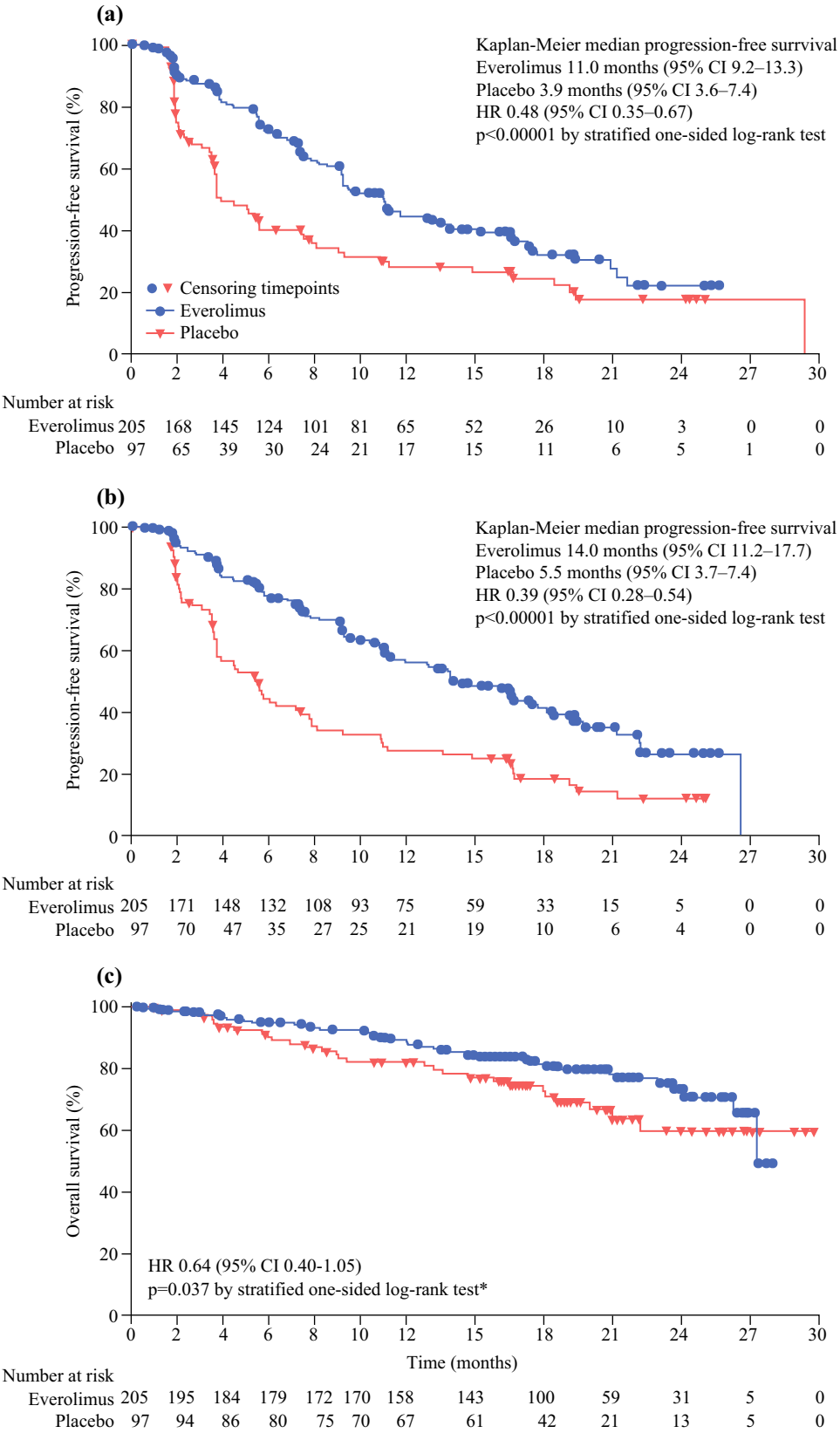

FIG. 5 Survival outcomes from the RADIANT-4 trial comparing patients with advanced lung or GEP NETs who received everolimus or placebo.[71] Kaplan–Meier curves of **a** PFS based on central radiology review, **b** PFS as determined by local investigators, and **c** OS. The everolimus group had improved PFS (median PFS 11.0 vs. 3.9 months; HR 0.48, $P < 0.001$). The difference in OS was not statistically significant based on the boundary for significance of 0.0002. *GEP NET* Gastroenteropancreatic neuroendocrine tumor, *OS* Overall survival, *PFS* Progression-free survival

PRRT for patients with SSTR-positive GEP NETs and adequate renal function, functional status, and hematopoietic reserves.[67], 68

RADIANT-4 TRIAL

The mTOR inhibitor everolimus demonstrated anti-tumor effects in advanced pancreatic NETs in the RADIANT-3 trial and a trend toward improved PFS in patients with advanced lung and GEP NETs in the RADIANT-2 trial.[69,70] The RADIANT-4 study was a phase III, randomized, double-blind, placebo-controlled study.[71] Patients with advanced, nonfunctional, well-differentiated lung or GEP NETs were randomized 2:1 to treatment with everolimus (n = 205) or placebo (n = 97). Crossover from placebo to everolimus group was not allowed during the study. Patients who received everolimus had improved PFS compared with placebo (median PFS 11.0 vs. 3.9 months; HR 0.48, $P < 0.001$; Fig. 5). There was a trend toward improved OS in the everolimus group (HR 0.64, P = 0.037, significance boundary 0.0002), but the data were not sufficiently mature to estimate median OS.

Building on the results of the RADIANT-2 trial, the RADIANT-4 trial provided evidence of the antitumor effect of everolimus in advanced lung and GEP NETs. However, subsequent analyses of the SBNET subgroup have returned mixed results.[72,73] While RADIANT-2 included 52% SBNET patients, RADIANT-4 only included 31%, and larger treatment effects were seen in patients with nonsmall bowel primaries.[70,72,73] Thus, while everolimus is an option for SBNET treatment in patients with progression on SSAs, SSAs remain preferred in the first-line setting, while PRRT shows greater tumor response and longer PFS.

CONCLUSIONS

Management of SBNETs has grown increasingly complex with development of several effective medical treatment options. Indolent tumor growth, long patient survival, and patients frequently crossing over to treatment arms have made it impossible to determine whether there are benefits in OS. Nevertheless, SSAs, PRRT, and everolimus delay time to progression in high-quality, randomized studies, and epidemiologic data show improved SBNET survival over the past decade,[8,74] suggesting their use could be playing a role in improving survival, although this also could be attributed to increased recognition and earlier diagnosis through widespread use of imaging. Surgical treatment remains first line for SBNET management, but there have been barriers to conducting randomized trials studying surgical outcomes in SBNETs. These include lack of clinical equipoise, difficulty accruing subjects with a rare disease, and the fact that patients may not agree to randomization. Observational studies suggest that resection of the primary tumor and cytoreduction can improve symptoms and survival, even in the setting of unresectable metastatic disease. In the absence of high-quality data, the role and timing of surgery is not standardized. Given the complexity of diagnosing and treating SBNETs, patients benefit from multidisciplinary treatment at centers with experience managing this disease.

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