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CONTROVERSY

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Controversies in NEN: An ENETS position statement on the management of locally advanced neuroendocrine neoplasia of the small intestine and pancreas without distant metastases

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Abstract

Locally advanced neuroendocrine neoplasms (NENs) are defined by extensive local invasion in the absence of distant metastases, although specific definitions may vary among study groups. While most patients with NENs present with localized or metastatic disease, a smaller subset is diagnosed with locally advanced tumors. Management of this subgroup remains particularly challenging, owing to the limited evidence base and lack of consensus regarding optimal therapeutic strategies. This guidance document synthesizes the current evidence and expert knowledge on the management of locally advanced NENs of the small intestine and pancreas, addressing four clinically relevant key questions that aim to inform best practice in these patients.

KEYWORDS
locally advanced, neuroendocrine, NET, NEC, pancreas, small intestine, tumor

1 | INTRODUCTION AND GENERAL BACKGROUND

This European Neuroendocrine Tumor Society (ENETS) guidance paper aims to answer four major questions on the management of locally advanced non-metastatic neuroendocrine neoplasia of the small intestine and pancreas (Table 1). Neuroendocrine neoplasia (NEN) constitutes a heterogeneous group of neoplasms, most commonly affecting the gastrointestinal tract and pancreas. NENs are divided into more slow-growing, well-differentiated neuroendocrine tumours (NETs) grades 1, 2 or 3, and aggressive, poorly differentiated neuroendocrine carcinoma (NEC). Locally advanced NENs are characterised by extensive local invasion, mainly of vessels or involvement of adjacent structures, without evidence of distant metastases. In general, non-metastatic, locally advanced NENs are initially deemed unresectable due to vascular involvement or extensive local spread. The primary goal would be to achieve complete surgical resection by 'induction' treatment. This review focuses on the management of non-metastatic, locally advanced NENs (NETs or NECs) arising from the small intestine or pancreas, including discussion of pre-treatment strategies to achieve resectability and post-operative (adjuvant) options. Data were identified by MEDLINE database searches, and expert opinion/recommendations were given according to the best available evidence and authors' experience.

2 | Q1 WHAT IS THE DEFINITION OF LOCALLY ADVANCED SMALL INTESTINE NEN

In several solid cancers (e.g. pancreatic ductal adenocarcinoma), local resectability is well defined according to the 'ABC' concept (Anatomic resectability, Biological resectability, Constitutional resectability). Such an ABC classification has not yet been proposed for small intestine NEN (SI-NEN). Resectability is still defined by the anatomical situation and the health status of the patient.

2.1 | Q1.1 Anatomical locally advanced SI-NEN

According to the generally applied cancer definition, *locally advanced* means that a cancer has grown outside the organ in which it started, but has not yet spread to other parts of the body (*American Cancer Society*). In some tumours, locally advanced implies the tumour is not resectable because of significant invasion of life-essential vessels. For small intestine neuroendocrine carcinoma (SI-NEC), the generally applied cancer definition is therefore used. In small intestine NET (SI-NET), resectability is not determined by the primary tumour(s), but by the extent of the mesenteric disease, namely the regional lymph node metastases and the associated mesenteric desmoplasia along the branches of the superior mesenteric artery (SMA) to lymph nodes located adjacent to its root and thence to para-aortic lymph nodes. Several classifications have been proposed based on the relationship between mesenteric lymph node metastases and the superior mesenteric vessels, particularly with the goal of predicting complete radical resection.[1–3] Lymphadenomectomy becomes more challenging in the presence of extensive mesenteric desmoplasia and mesenteric lymph node metastases towards the root of the superior mesenteric vessels. Based on a previous ENETS proposal,[4] Bartsch et al.[5] recently classified SI-NET disease as locally advanced or unresectable when the mesenteric disease (nodal metastases and desmoplasia) encircles the mesenteric vessel root, including the first two jejunal arteries, above the level of the inferior wall of the horizontal part of the duodenum and/or extends to the retroperitoneum (Table 2 and Figure 1).

TABLE 1 Major questions on the management of locally advanced non-metastatic neuroendocrine neoplasia (NEN) of the small intestine and pancreas.

Q1 What is the definition of locally advanced small intestine NEN?
Q2 What is the definition of locally advanced pancreatic NEN?
Q3 Is there a role for induction therapy?
Q4 Is there a role for post-operative therapy after surgery?

2.2 | Q1.2 Biologically unresectable SI-NEN

No criteria have yet been established for biological unresectability in SI-NET. Tumour markers such as chromogranin A are of no practical value in this context. Whether SI-NET G3 or NEC, both of which are extremely rare, should be considered biologically unresectable cannot be reliably answered due to the rarity of this condition.

In the same way, no data exist to include functionality in the decision-making for resection of locally advanced SI-NET. As hormonal secretions from abdominal tumour masses drained by the portal vein are usually metabolised in the liver, the presence of carcinoid syndrome should not influence decision-making.

2.3 | Q1.3 Constitutional unresectable SI-NEN

Although not as yet defined for SI-NEN, patients with an ECOG score ≥3 might be considered unresectable based on their health status, if

TABLE 2 Classification of local resectability in small intestine neuroendocrine tumours (SI-NET).

Resectable	Mesenteric disease (nodal metastases and desmoplasia) up to the outlet of the ileocolic artery from the superior mesenteric artery.
Borderline resectable	Mesenteric disease up to the level of the inferior pancreatic body, without encircling the mesenteric vessel root, nor the first two jejunal arteries, and without extension to the retroperitoneum.
Locally advanced (unresectable)	Mesenteric disease that encircles the mesenteric vessel root, including the first two jejunal arteries, located above the level of the inferior wall of the horizontal part of the duodenum and/or extending to the retroperitoneum.

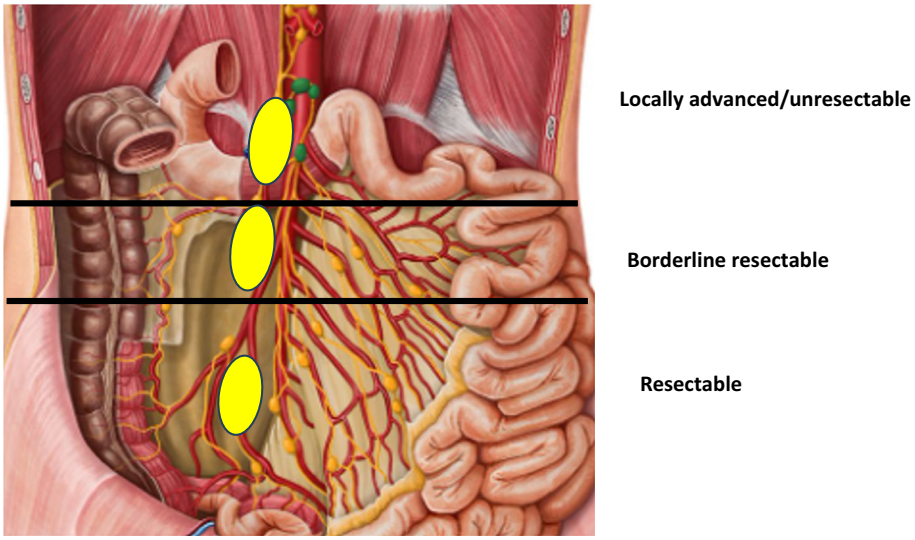

FIGURE 1 Graphic representation of the classification of lymph node involvement and local resectability in SI-NET.[5] Yellow circles indicate mesenteric disease. SI-NET, small intestine neuroendocrine tumours.

they have extended mesenteric disease that might require lymph node dissection around the first three jejunal arteries due to its associated potential morbidity.

2.4 | Q1.4 Is there a role for extended resection with vascular reconstruction to achieve an R0 resection?

There is at least one anecdotal report of a partial abdominal evisceration with intestinal autotransplantation to achieve complete resection of a locally advanced SI-NET with associated occlusion of the superior mesenteric vein in a 60-year-old male patient.[6] This patient was disease-free 28 months after surgery. This highly sophisticated procedure, prone to potential complications, must be considered experimental and may only be indicated in the very rare situation of a locally advanced SI-NEN without distant metastases. In such rare locally advanced cases, however, long-term survival of more than 10 years could also be achieved by local debulking surgery.[5,7]

2.5 | Q1.5 Is there a role for incomplete local resection in locally advanced SI-NET?

Treatment options in locally advanced SI-NET are limited. Management of these patients is complex and may require input from several disciplines, including gastroenterology, internal medicine, nuclear medicine, interventional radiology, surgery, allied health professionals and palliative care. In such cases, even the use of aggressive surgery with resection of mesenteric vessels and their reconstruction has been reported.[2,8–10] It is important to recognise, however, that the vast majority of patients have advanced, incurable Stage IV disease, with liver, peritoneal and bone metastases and carcinoid syndrome.[2,5,9,11,12] Therefore, the aggressiveness and extent of surgery must be carefully balanced against the potential benefit of symptom relief and the risk of spreading the tumour within the peritoneal cavity, if not already present. One major goal of palliative local debulking surgery must be to avoid a short bowel syndrome caused by resection of too much small intestine. A recent well-designed experimental human cadaver study demonstrated that the first two jejunal arteries originated from the left side of the SMA in two-thirds and from the posterior wall of the SMA in one-third of subjects, and the median small bowel length perfused by the first two jejunal arteries was 220 cm.[13] The mean distance of origin of the first two jejunal arteries was 4.6 and 6.0 cm, respectively. In a recent study, more than 200 cm of small bowel could be preserved in over 80% of patients by a ventral decompression approach.[5] In this approach, the SMA and SMV were exposed by incising desmoplastic tissue or metastatic lymph nodes, and then dissected free from tumour deposits ventrally—performing ventral decompression—between the inferior border of the pancreatic body and the level of the inferior border of the horizontal part of the duodenum. This decompression should usually preserve the first two jejunal arteries and mesenteric venous branches, which are located in this region (Figure 1). In a Dutch series,[11] 6% and in a French series,[14] 5% of patients were unable to undergo any form of debulking surgery due to the presence of advanced peritoneal metastases, resulting in a frozen abdomen that prevented surgical access.

Local debulking of mesenteric disease in locally advanced SI-NET seems to be quite effective for symptom control of intestinal ischaemia and obstruction, with acceptable morbidity when performed by experienced surgeons. Improvement of abdominal symptoms was reported in 80%–100% of patients from tertiary referral centres,[2,5,7,11,12] although symptoms were neither pre- nor postoperatively assessed by standardised questionnaires in these retrospective studies. The reported rate of relevant postoperative complications in this setting ranged between 14% and 22%, with mortality rates between 0% and 3.4%. Thus, although the level of evidence is low, adequate local debulking of a locally advanced SI-NET might be beneficial in selected patients.

3 | Q2 WHAT IS THE DEFINITION OF LOCALLY ADVANCED PANCREATIC NEUROENDOCRINE NEOPLASMS

3.1 | Q2.1 Anatomical resectability pancreatic NEN

The classification of resectability in pancreatic neuroendocrine neoplasms (PanNENs) follows the criteria established for the more common pancreatic ductal adenocarcinoma (PDAC). According to the *National Comprehensive Cancer Network* guidelines, PDAC is categorised into three groups: resectable, borderline resectable and locally advanced disease.[14] The resectable category includes tumours without vascular involvement. Borderline resectable disease is defined by limited venous or arterial involvement, which may still allow for margin-negative resection with appropriate surgical techniques. Locally advanced disease, on the other hand, is characterised by extensive vascular invasion, generally precluding a curative resection.

However, the application of this classification to PanNENs presents several limitations, especially for PanNET, as PanNEC behaves more similarly to PDAC. First, it was designed for PDAC, which may differ significantly from PanNETs in biological behaviour and tumour aggressiveness. Vascular invasion, both venous and arterial, is much less frequent in PanNETs than in PDAC or PanNEC. Although data on vascular invasion in PanNETs are scarce, some surgical series have reported rates between 8 and 11% of vein invasion requiring vascular resection.[15,16] A multicentre retrospective study comparing pancreatico-duodenectomy with and without portal vein resection for PanNETs found no significant difference in perioperative morbidity. Before matched comparison, the study also found that vascular invasion was associated with worse progression-free and overall survival. Similarly, a single-centre analysis reported a 5-year overall survival of 45% for PanNET patients undergoing portal vein resection, further suggesting that vascular involvement is a significant prognostic factor. Similarly, a single-centre analysis reported that portal vein resection in PanNETs had a 5-year overall survival of 45%, suggesting that vascular involvement is a relevant prognostic factor.

3.2 | Q2.2 Biologically unresectable PanNEN

Another limitation of the current classification of resectability is its predominant focus on technical rather than biological factors. For instance, superior mesenteric artery involvement is a defining feature of locally advanced disease, whereas splenic artery involvement does not constitute an unresectability criterion. However, both cases reflect an infiltrative tumour behaviour, potentially associated with a worse prognosis.

The concept of resectability is influenced by the expertise and technical skills of the operating surgeon. Complex vascular resections, including arterial reconstructions, may allow for an R0 resection, even in cases classified as locally advanced based on standard criteria. Thus, the introduction of a 'biological borderline resectability' concept is warranted, where the definition is not based solely on technical feasibility, but also on the risk of early recurrence after surgery. Several prognostic factors, mainly related to biological behaviour, have been identified in the literature as predictive of recurrence risk. These include adjacent organ or vascular invasion, tumour size, neoplastic venous thrombosis and tumour grading,[17] in particular, tumours with a Ki-67 index above 20% (especially PanNEC) should be considered at high risk for recurrence and categorised as biologically borderline resectable. The possibility of early recurrence after surgery suggests that certain preoperative characteristics may indicate residual systemic disease, ultimately undermining the effectiveness of radical surgical treatment.

A refined classification of locally advanced, borderline resectable and resectable PanNENs should therefore integrate both technical and biological aspects. From a technical perspective, beyond the above-mentioned criteria, the evaluation of resectability should be tailored to the individual surgeon's expertise, considering also potential downstaging after preoperative therapy. From a biological standpoint, patient-specific factors (age, comorbidities and symptoms) and tumour-related characteristics (size, grade, vascular invasion, neoplastic venous thrombosis, presence of lymph node metastases on preoperative imaging) should be incorporated into treatment decisions. This approach would allow a more personalised surgical strategy, balancing the risks and expected benefits of surgery in non-metastatic PanNENs. A new classification integrating both technical feasibility as well as biological risk factors is therefore needed to better define locally advanced cases and guide treatment decisions. In the meantime, the definition of locally advanced PanNENs should be determined on a case-by-case basis, considering multiple factors, including the surgeon's assessment of technical resectability and preoperatively retrievable parameters that may influence the risk of 'early recurrence,' defined as the risk of recurrence within 2 years from the resection.

4 | Q3 IS THERE A ROLE FOR INDUCTION THERAPY?

Concerning terminology, neoadjuvant treatment is given before surgery, as an alternative to or in combination with adjuvant treatment after surgery. A potential advantage of this approach is to test tumour biology ('test of time') before surgery for disease that may be more aggressive and to determine whether a high risk of early recurrence is likely, in which case achieving tumour stability becomes a priority. Neoadjuvant therapy can also be chosen in the hope of improving survival and maintaining quality of life, or to lessen the extent of resection for locally advanced or borderline resectable disease, in which cases therapy with a clinically relevant response rate is needed. Finally, downstaging tumours with tumour-reductive therapy may convert locally advanced, unresectable disease into resectable disease. Overall, a clear desire exists for guidance and feasibility data on neoadjuvant or preoperative treatment in patients with locally advanced small intestinal or PanNENs.

4.1 | Q3.1 Induction Therapy—tyrosine kinase inhibitors

The role of tyrosine kinase inhibitors (TKIs) in the treatment of advanced NETs is well established. Neuroendocrine tumour cells overexpress various types of proangiogenic molecules and receptors, and their dysregulation plays a role in the growth of the well-differentiated NET, which are generally hypervascular tumours.[18,19] Several growth factors, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor and their receptors, as well as tyrosine kinase pathways, are involved in angiogenesis, tumour growth and progression in NETs.[19] Inhibition of tyrosine kinase receptors by TKIs, particularly those with anti-angiogenic properties, results in anti-proliferative effects in NETs, in which high vascularisation is not synonymous with aggressiveness.[18]

More than a decade ago, sunitinib—an oral multi-targeted TKI with anti-angiogenic properties—was approved for the systemic treatment of advanced well-differentiated PanNETs.[20] Recently, cabozantinib, an oral multi-kinase inhibitor targeting VEGFR, c-MET, AXL and RET, demonstrated an improvement in progression-free survival (PFS) in previously treated patients with progressive advanced extra-pancreatic and PanNETs, irrespective of primary tumour, prior therapy, SSTR status or hormone secretion in the CABINET Phase III Trial[21] which has recently led to FDA approval.

Nevertheless, data on the role of TKIs as induction therapy for locally advanced disease are scarce. A literature research revealed only one Japanese retrospective study which assessed overall survival (OS) and disease-free survival in patients receiving surgery following induction therapy with sunitinib in 106 metastatic and/or locally advanced PanNETs, irrespective of WHO 2017 classification grade.[22] This study concluded that surgical resection following sunitinib administration improved OS in advanced PanNENs. However, only eight patients with locally advanced disease were included, and only three out of eight underwent subsequent surgery; this makes it very challenging to draw any conclusions.

4.2 | Q3.2 Induction Therapy—chemotherapy with or without radiotherapy

Very little data are available on induction chemoradiation (CRT) for patients with locally advanced PanNET, SI-NET or NECs. However, the relatively high rate of margin-positive resections (27%) observed in upfront resectable digestive NECs ($n = 519$), along with the generally favourable response of NECs to CRT, suggests that neoadjuvant therapy could potentially improve complete resection rates and reduce the risk of both local and systemic recurrence.[23] In the US National Cancer Database, of 127 patients with localised oesophageal NEC, the three-year survival was superior after chemoradiation compared to surgery and chemotherapy (50% vs. 24%).[24] Results were especially better after chemoradiation of locally advanced disease. Chemoradiation for patients with locally advanced oesophageal NECs resulted in a 77% clinical complete response rate. The benefit of chemoradiation for locally advanced PanNECs or SI-NECs is unknown, but it seems reasonable to pursue initial chemoradiation in patients with locally advanced (irresectable) NECs if all tumour sites fit within a radiation field with acceptable toxicity.

Induction chemotherapy can downsize the primary tumour in the case of a PanNET or SI/PanNEC, thus improving resectability and consequently R0 resection rates. Furthermore, it allows for better selection of patients who may benefit from delayed primary tumour surgery, thereby sparing those who develop metastatic disease during neoadjuvant chemotherapy from unnecessary surgery and its associated morbidity. These advantages are especially relevant for NECs, which have a high rate of distant recurrence following surgery. Neoadjuvant chemotherapy for locally advanced SI-NENs is not routinely employed. However, for patients with locally advanced, nonmetastatic NECs of the small intestine or pancreas, neoadjuvant chemotherapy is often recommended. Standard regimens include combinations such as etoposide with a platinum-based agent (cisplatin or carboplatin). This approach aligns with guidelines from organisations such as the *North American Neuroendocrine Tumor Society* (NANETS), which advocate systemic therapy in these cases, given the high risk of systemic recurrence, and the potential to avoid surgery in patients progressing on chemotherapy.[25]

A systematic review and meta-analysis in neoadjuvant treatments for patients with PanNETs, encompassing nine studies with 468 patients, revealed that neoadjuvant therapies—including chemotherapy, peptide receptor radionuclide therapy (PRRT), and targeted agents—led to partial responses in approximately 43.6% of patients and stable disease in 51.3%. The overall resection rate post-neoadjuvant therapy was 68.2%, with an R0 (complete) resection rate of 60.2%. All 9 studies were rather small, with a median sample size of only 29 (range: 5–112).[26] Five out of 9 studies used chemotherapy as the neoadjuvant regimen. One study did not mention the specific chemotherapy regimen used.[27] Of the four remaining studies using chemotherapy, two used the capecitabine and temozolomide (CAPTEM) regimen, and the other two used the 5-fluorouracil, doxorubicin and streptozocin (FAS) regimen. In the two studies using CAPTEM, the mean or median number of treatment cycles was 4–5.[28,29] In the two studies using FAS, the median number of treatment cycles was 4.[30,31] No significant differences were observed in resection rates between the two regimens. Of the 297 cases included, 264 cases documented whether the tumour was initially resectable: of these, 242 cases (91.67%) were borderline resectable or unresectable tumours, and in 167 cases (63.26%) there were hepatic metastases.

Chemotherapy is not routinely used for patients with metastatic SI-NETs due to generally low response rates.[32] In cases of locally advanced SI-NETs, where effective downstaging is essential, induction chemotherapy is not routinely recommended.

4.3 | Q3.3 Induction Therapy—PRRT

Preoperative therapy with PRRT, using any radioisotope labelled to a somatostatin analogue for patients with GEP-NETs, has only rarely

been investigated, and is currently not well defined. Although reported in multiple retrospective cohorts, with varying degrees of success, preoperative therapy with PRRT has not been investigated in a systematic way. To date, application of PRRT in the first-line setting is still limited, as reported in a recent real-world data analysis of 213 German patients (1995–2023).[33] In that analysis, first-line PRRT accounted for 13.3% of the total population, in which most patients were found to have stable disease at 6-month follow-up (7/12 patients or 58.3%). These data predated the completion of the NETTER-2 study, in which PRRT with [^{177}Lu]Lu-DOTATATE was recently demonstrated as safe and feasible first-line therapy for G2/G3 GEP-NET. As patients with unresectable G2/G3 GEP-NET are now eligible for first-line PRRT, we expect more real-world data to be generated in locally advanced disease, further clarifying the role and feasibility of PRRT as a neoadjuvant or induction therapy.

But, at this time, evidence on induction PRRT is largely confined to retrospective observational studies, all primarily focusing on PanNETs and cases of unresectable disease. Initial data on this concept originate from 2008 by Kwekkeboom et al., from 2011 by Sowa-Staszczak et al. and from 2012 by Barber et al.[34–36] Kwekkeboom et al.[34] described successful surgical resection following PRRT ([^{177}Lu]Lu-DOTATATE 7.4 GBq/cycle, interval 8–10 weeks, mean 4 cycles). Within their larger cohort series, three out of four patients with an unresectable PanNET prior to PRRT had a partial response on imaging and underwent successful surgical resection following PRRT. Sowa-Staszczak et al.[35] reported six cases of unresectable PanNETs treated with PRRT in the first line ([90Y]Y-DOTATATE 7.4GBq/m2; interval 6–9 weeks; 4–5 cycles). Following induction PRRT, 33% (2/6 patients) achieved a partial response and were subsequently resected. Barber et al. specifically described the results of induction PRRT with [^{177}Lu]Lu-DOTATATE (mean activity 8.6 GBq, variable number of cycles, variable intervals) with concomitant therapies (external beam radiotherapy and/or chemotherapy) in five patients with primary unresectable, pancreatic ($n = 4$) or duodenal ($n = 1$) NET.[36] At 3 months, all five patients achieved a radiological partial response, and subsequently one patient with a PanNET was eligible for surgical resection (R0 resection).

Following these initial reports and other case reports, the Rotterdam group reported their retrospective data on 29 patients with solitary unresectable PanNETs undergoing PRRT therapy in 2015.[37] Within this cohort, nine patients (31%) were successfully downstaged to resection, and the authors reported improved PFS (69 months resected cases vs. 49 months non-resected cases). More recently, in 2021, Opalinska et al.[38] reported the results in a retrospective cohort of 114 patients, with 32 patients receiving PRRT as first-line therapy, including 9 patients with unresectable primary tumours. The primary tumours comprised a variety of origins: six PanNETs, two lung NETs and one SI-NET. Following PRRT, only one partial response on imaging was reported, and 45% ($n = 4$) subsequently went for surgical resection. Only two patients achieved an R0 resection, both with a PanNET.

In the same year, Parghane et al. published an assessment of 57 patients with unresectable GEP-NET receiving induction PRRT, looking at resectability on imaging following PRRT.[39] The majority of patients had a PanNET (56%), followed by a SI-NET (23%) and duodenal NET (21%). The population was divided into two groups: presence ($n = 34$) or absence ($n = 23$) of (potentially) resectable liver metastases. Following PRRT (7.4GBq/cycle; 8–10 weeks interval; 4–5 cycles), 26% (15/57 patients) became resectable. Using additional interval imaging studies after 2 cycles, only 1 out of those 15 patients was considered resectable after 2 cycles, whilst the remaining 14 patients were considered resectable only after 4–5 cycles of PRRT. No data are provided on surgical outcomes.

Another approach to neoadjuvant PRRT is the utilisation of the 'test of time'. As surgical resection remains the primary modality with curative intent, evaluating biological tumour behaviour in patients with (suspected) more aggressive tumour biology prior to resection may prevent unnecessary invasive surgery as new metastases may develop. Partelli et al. described the outcome of patients with (potentially) resectable PanNET with 'high-risk factors' (>4 cm, organ or vascular involvement and/or potentially resectable liver metastases), clinically considered for induction PRRT.[40] In their subpopulation of 23 patients, following PRRT (1–6 cycles, either [^{177}Lu]Lu-DOTATATE or [^{90}Y]Y-DOTATOC, variable amounts of activity) all patients underwent surgical resection: 70% ($n = 16$) demonstrated a partial response on follow-up imaging preoperatively and following surgery, and 70% ($n = 16$) achieved an R0 resection. In their survival analysis, improved PFS is suggested in the induction PRRT group compared to an upfront surgery historical cohort, also in a sub-analysis in patients having R0 resections in both groups. The same group recently published the results of the NEOLUPANET study, which was a single arm, Phase II study utilising neoadjuvant PRRT and assessed safety and efficacy.[41] Thirty-one patients received neoadjuvant PRRT (7.4GBq/cycle, 6–8 weeks interval, four cycles) in sporadic (potentially) resectable, PanNETs. Twenty-nine patients subsequently underwent surgical exploration. Prior to surgery, 58% (18/31 patients) achieved radiological partial response, while following surgery 83% (24/29 patients) had an R0 resection. In both studies, no cases exhibiting progressive disease were reported.

Summarising the current literature, there are data that induction PRRT might induce sufficient tumour reduction (i.e. downstaging for surgical resection) in 20%–45% of initially considered unresectable primary tumours (either in the presence or absence of potentially resectable liver metastases). Furthermore, in patients with borderline resectable disease or in patients with potential aggressive tumour biology, neoadjuvant PRRT allows physicians to have a ''test-of-time'' to observe tumour biological behaviour prior to invasive surgical resection. As demonstrated by NETTER-2,[42] no additional adverse events or known side effects were reported in these studies. In the limited cohort of patients resected, complication rates do not appear to be increased, thereby supporting the safety of PRRT as neoadjuvant therapy.

The data on SI-NET are sparse, based on case reports and reported as part of mixed populations; by Parghane et al. and Opalinska et al. ($n = 13$ and $n = 1$, respectively).[38,39] As mentioned afore, in SI-NETs, the emphasis is on the resectability of a mesenteric lymph

node metastasis/mesenteric mass. In general, based on other retrospective cohorts, obtaining an objective response of SI-NET-related mesenteric masses after PRRT is unlikely. Al Mansour et al.[43] reported a partial response rate of only 4% according to RECIST 1.1, following PRRT ([^{177}Lu]Lu-DOTATATE; 7.4GBq/cycle; four cycles) and concluded that PRRT predominantly results in disease stability, but can alleviate related symptoms in 46% of patients with progressive SI-NET-related mesenteric masses. Mamulashvili Bessac et al.[44] reported organ-specific responses following PRRT ([^{177}Lu]Lu-DOTATATE; 7.4GBq/cycle; four cycles) based on standardised uptake value (SUV) metrics, reporting a significant decrease in SUV_{max} in mesenteric disease; however, no changes in tumour volume based on [^{68}Ga]Ga-DOTATOC PET/CT. Data particularly addressing different tumour grades and radiological responses of a mesenteric mass following PRRT are absent. Based on the limited evidence, the use of PRRT as a downstaging modality in SI-NET-related mesenteric masses is not currently recommended, due to limited tumour reductive potential.

To summarise, for all scenarios using PRRT as (neo)adjuvant treatment, data remain limited, predominantly retrospective and primarily in patients with a PanNET or duodenal NET. With NETTER-2 providing evidence on PRRT in the first-line advanced setting, new data will likely be generated in the coming years. But the need for prospective data will remain for a better understanding of influencing factors and accurate estimation of the success rate of induction PRRT in all patients with locally advanced GEP-NETs, not only PanNETs. At this time, eligibility for neoadjuvant PRRT should be discussed in multidisciplinary tumour boards for PanNETs. At this time, there is no clear rationale for PRRT as (neo) adjuvant therapy for SI-NET-related mesenteric masses. Multidisciplinary tumour board discussion is essential, as technical developments occur at a high pace (surgical equipment, e.g., robotics and imaging equipment, long-axial field of view PET/CT), directly influencing the management of the patient.

5 | Q 4 IS THERE A ROLE FOR POST-OPERATIVE THERAPY AFTER SURGERY?

There is no proven role for adjuvant therapy after curative surgery for SI or PanNETs.[45] There are minimal retrospective data.[46] Somatostatin analogues (SSA) are indicated as first-line treatment in patients with carcinoid syndrome and for their anti-proliferative effect, based on the results of two Phase III trials.[47,48] Following curative resection, current evidence for adjuvant SSA therapy is low as no prospective data are available, and there is no evidence supporting the use of adjuvant SSA.

According to the results of the NETTER-1 trial, PRRT improved progression-free survival in patients with SI-NETs who progressed on SSA therapy.[49] To date, PRRT is not recommended as an adjuvant therapy after curative surgery for SI-NET. A randomised phase III French study (TERAVECT) is underway to assess the efficacy of PRRT with ^{111}In-pentetreotide as a consolidation treatment following complete resection of liver metastases in patients with well-differentiated digestive neuroendocrine tumours (https://clinicaltrials.gov/study/NCT02465112). If this study shows OS benefit, the next step will be to evaluate this adjuvant treatment in patients with high-risk, locally advanced SI or PanNET, although preferably as a neoadjuvant option. The German prospective, randomised APSIN trial will soon begin to test adjuvant PRRT (two cycles of *Lutathera*) vs. surveillance in patients with completely resected Stage III SI-NETs.[50] The currently available evidence supporting the use of PRRT as adjuvant treatment in locally advanced SI or PanNET is sparse. In relation to resected neuroendocrine liver metastases, adjuvant PRRT will be investigated in the NELMAS trial (where the initial primary had already been removed) (NCT05987176).

The majority of patients with digestive NECs with Stage III disease undergoing resection will develop recurrence, mostly distant, suggesting that there is a place for adjuvant chemotherapy, especially for locally advanced, if not given pre-operatively. In a large cohort study with 1,861 patients with digestive NECs, 519 patients underwent curative resection, and postoperative chemotherapy ($n = 224$) was associated with improved survival (HR 0.58).[51]

Adjuvant chemotherapy may offer a survival benefit in certain high-risk patients with locally advanced small intestine or pancreatic NECs. However, the current evidence is not definitive due to the rarity of the disease and the lack of specific studies. The aggressive nature of high-grade small intestine or pancreatic NECs may warrant an approach similar to that for pancreatic ductal adenocarcinoma.

6 | CONCLUSIONS

Locally advanced, non-metastatic NETs of the small intestine or pancreas present a therapeutic challenge. Multimodal strategies, including PRRT or chemotherapy, may render previously unresectable tumours operable. Induction chemotherapy or PRRT shows promising results in managing locally advanced PanNETs by potentially downstaging tumours to allow surgical resection. While current evidence supports its use in selected cases, standardised treatment regimens and further research are needed to optimise outcomes. Surgery remains central to curative treatment, while the role of (neo)adjuvant systemic therapy is evolving. Personalised treatment planning within a multidisciplinary team is essential to optimise outcomes.

Locally advanced NECs of the small intestine or pancreas are so extremely rare that clinical decisions should be individualised, and there is a pressing need for prospective studies to better define the role of (neo)adjuvant systemic therapy in this patient population. The aggressive nature of high-grade small intestine or pancreatic NECs and their chemotherapy sensitivity indicate that chemotherapy, with or without radiotherapy, plays an important role in the treatment of these patients.

AUTHOR CONTRIBUTIONS

M. E. T. Tesselaar: Conceptualization; writing – original draft; investigation; methodology; writing – review and editing; data curation. **S. Partelli:** Writing – review and editing; writing – original draft. **A. J. A. T. Braat:** Writing – original draft; writing – review and editing;

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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