BJS, 2024, znae082
https://doi.org/10.1093/bjs/znae082
Review Article

Surgery for advanced neuroendocrine tumours of the small bowel: recommendations based on a consensus meeting of the European Society of Endocrine Surgeons (ESES)

Klaas Van Den Heede[1,*], Dirk-Jan van Beek[2], Sam Van Slycke[1,3,4], Inne Borel Rinkes[2], Olov Norlén[5], Peter Stålberg[5] and Erik Nordenström[6,7]

[1]Department of General and Endocrine Surgery, Onze-Lieve-Vrouw (OLV) Hospital Aalst-Asse-Ninove, Aalst, Belgium
[2]Department of Endocrine Surgical Oncology, University Medical Center Utrecht, Utrecht, The Netherlands
[3]Department of General Surgery, AZ Damiaan, Ostend, Belgium
[4]Department of Head and Skin, University Hospital Ghent, Ghent, Belgium
[5]Department of Surgical Sciences, Uppsala University Hospital, Uppsala, Sweden
[6]Department of Surgery, Skåne University Hospital, Lund, Sweden
[7]Department of Clinical Sciences, Lund University, Lund, Sweden

*Correspondence to: Klaas Van Den Heede, Department of General and Endocrine Surgery, Onze-Lieve-Vrouw (OLV) Hospital Aalst-Asse-Ninove, Moorselbaan 164, 9300 Aalst, Belgium (e-mail: klaas.van.den.heede@olvz-aalst.be)

Abstract

Background: Small bowel neuroendocrine tumours often present with locally advanced or metastatic disease. The aim of this paper is to provide evidence-based recommendations regarding (controversial) topics in the surgical management of advanced small bowel neuroendocrine tumours.

Methods: A working group of experts was formed by the European Society of Endocrine Surgeons. The group addressed 11 clinically relevant questions regarding surgery for advanced disease, including the benefit of primary tumour resection, the role of cytoreduction, the extent of lymph node clearance, and the management of an unknown primary tumour. A systematic literature search was performed in MEDLINE to identify papers addressing the research questions. Final recommendations were presented and voted upon by European Society of Endocrine Surgeons members at the European Society of Endocrine Surgeons Conference in Mainz in 2023.

Results: The literature review yielded 1223 papers, of which 84 were included. There were no randomized controlled trials to address any of the research questions and therefore conclusions were based on the available case series, cohort studies, and systematic reviews/meta-analyses of the available non-randomized studies. The proposed recommendations were scored by 38–51 members and rated 'strongly agree' or 'agree' by 64–96% of participants.

Conclusion: This paper provides recommendations based on the best available evidence and expert opinion on the surgical management of locally advanced and metastatic small bowel neuroendocrine tumours.

Introduction

The incidence of small bowel neuroendocrine tumours (SBNETs) has risen[1–3]. This rise is partially attributable to an increased awareness of SBNETs and improved diagnosis and detection of localized disease. Whereas rates of regional disease have remained stable, rates of metastatic disease have decreased over 15 years[2].

SBNETs are derived from the serotonin-producing enterochromaffin cells, but their behaviour is different from other neuroendocrine tumours of the digestive tract, as they are usually characterized by a low proliferation rate (Ki-67 less than 20%) and indolent growth, but are usually discovered at an advanced stage[4].

Patients with SBNETs often present with non-specific symptoms and 30–40% are diagnosed with distant metastases, limiting curative treatment options[5]. Metastases are predominantly found in the lymph nodes (LNs) and the liver[1,6]. Mesenteric LN metastases are present in more than 80% of patients at diagnosis, regardless of the size of the primary tumour[7].

Radical surgical resection represents the only possible cure for these tumours. However, the slow progression and indolent nature of SBNETs and the improved treatment options result in favourable overall survival, even in the presence of metastatic disease at initial diagnosis[2,8,9].

Due to the rarity of the disease, prospective randomized trials are limited or non-existent, and most recommendations are based on retrospective studies, case series, or expert opinions. This is especially true for surgical treatment options[4].

Existing guidelines date back several years, did not focus on advanced, metastatic disease, or have not specifically addressed surgery[10]. Current controversies in the surgical management of

Received: November 10, 2023. Revised: February 19, 2024. Accepted: March 04, 2024

advanced, metastatic SBNETs include: the role of surgery in high-grade (grade 3 (G3)) SBNETs and small bowel neuroendocrine carcinomas (SBNECs; the surgical management of extrahepatic, hepatic, and LN disease; and the role of primary tumour resection in otherwise inoperable metastatic disease.

This guidance document with recommendations on surgical treatment of patients with advanced, metastatic SBNETs is based on a literature review and represents a consensus of the 2023 working group of the European Society of Endocrine Surgeons (ESES), subsequently voted upon at the ESES Conference in Mainz in 2023.

Methods

Working group

This consensus statement was developed by the ESES. The society composed a working group on advanced SBNETs consisting of general, hepatopancreatobiliary, and endocrine surgeons with a special interest in neuroendocrine tumours. The ESES had no influence on the context of the consensus statement and no financial support from the medical industry was received.

Methods and literature search

Current controversies in the surgical treatment of advanced, metastatic SBNETs were summarized into 11 clinically relevant research questions by the working group. These questions were discussed among members of the group until consensus was reached. This review did not aim to provide evidence-based recommendations regarding the workup for advanced SBNETs, which is covered in the North American Neuroendocrine Tumour Society (NANETS)[11,12], the European Neuroendocrine Tumour Society (ENETS)[13], and the National Comprehensive Cancer Network (NCCN)[14] guidelines.

A systematic literature search was performed in MEDLINE by the first author and last updated in October 2022. The full search string is documented in the *Supplementary Methods*. Different spellings were accounted for and medical subject headings were incorporated in the search. All included articles were manually cross-referenced for additional relevant articles. The results of the literature search was uploaded to the Rayyan® platform[15], allowing removal of duplicate cases. Titles and abstracts were screened for relevance by one group member with extensive experience in conducting high-quality systematic reviews. In case of doubt, a second group member was asked to referee. Thereafter, the full texts of those articles deemed potentially relevant were assessed. Reasons for exclusion during the full-text screening were recorded. Regardless of the quality of the studies, all studies matching the inclusion criteria were included.

Both prospective and retrospective studies were eligible from 1995 until the date of the final search. Existing reviews and guidelines were reviewed for possible additional studies. Neuroendocrine tumours of the appendix were excluded from this review, as were animal studies, case reports, case series with fewer than five cases, conference abstracts, and editorials. Languages were restricted to Danish, Dutch, English, French, German, Norwegian, and Swedish. If more than one paper on the same study population was found, that with the largest cohort and most comprehensive statistical analysis was included.

Whenever possible, study and patient characteristics, and outcomes were extracted. Outcome data (such as survival percentages or HRs) were also obtained. Survival data were not pooled. Because of the differentiation between G3 and neuroendocrine carcinoma in clinical practice since 2017, only papers after this date were included when discussing G3 SBNETs or SBNECs.

To score the quality of the evidence and the strength of the recommendations, the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system was used[16,17]. For the final recommendations (in favor or against surgical treatment), the following criteria were considered: the quality of the available evidence; the balance of desirable and undesirable outcomes; preferences and values; and use of resources. The recommendations were stated as 'recommended' (strong recommendation) and 'suggest' (weak recommendation)[18].

The results and recommendations were presented and discussed in a plenary session with input from the ESES delegates at the 10th ESES Conference in Mainz, Germany, on 20 May 2023. At this conference, the recommendations from the working group were voted upon using a five-point Likert scale including 'strongly agree', 'agree', 'neutral', 'disagree', and 'strongly disagree'. This paper was adjusted based on the input received during the meeting. The final paper was critically reviewed by all members of the working group.

Results

Literature search

The literature search yielded a total of 1223 articles (*Supplementary Methods*). After title and abstract review, 104 full texts were assessed for eligibility (*Fig. 1*).

Voting results

A summary of the voting results is available in *Tables S1–S11*.

High-grade small bowel neuroendocrine tumours/small ball neuroendocrine carcinomas

Question 1: Should surgical exploration be considered in patients with metastatic high-grade tumours?

Very few studies have reported on the role of local therapy (such as surgery) in high-grade SBNETs (well differentiated) and SBNECs (poorly differentiated), especially in the metastatic setting[19]. High-grade SBNETs (Ki-67 greater than 20%) carry a less favourable prognosis, with a more aggressive disease course. The optimal first-line management of high-grade SBNETs and SBNECs, and sequencing of subsequent therapies, remain a challenge. Moreover, it has increasingly become clear that the outcomes of high-grade lesions vary greatly and that tumour grading based on the Ki-67 index alone is insufficient[20]. In the context of metastatic disease, cytoreductive surgery is not recommended in high-grade SBNECs[19]. In general, most current guidelines recommend excluding high-grade SBNETs from upfront surgery, as the risk of recurrence after radical surgery is significantly higher compared with low- and medium-grade SBNETs[19,21,22].

However, a recent retrospective analysis of 32 patients with high-grade gastroenteropancreatic neuroendocrine neoplasms (in the absence of primary small bowel tumours) suggested a survival benefit in neuroendocrine carcinomas after intended curative resection and/or ablation, in particular where Ki-67 was greater than 55%[23]. Some additional, small, retrospective studies have also indicated a potential survival benefit in high-grade neuroendocrine tumour/neuroendocrine carcinoma patients after aggressive locoregional therapy (with only limited or no small bowel primary tumours)[24,25]. Moreover, a recent

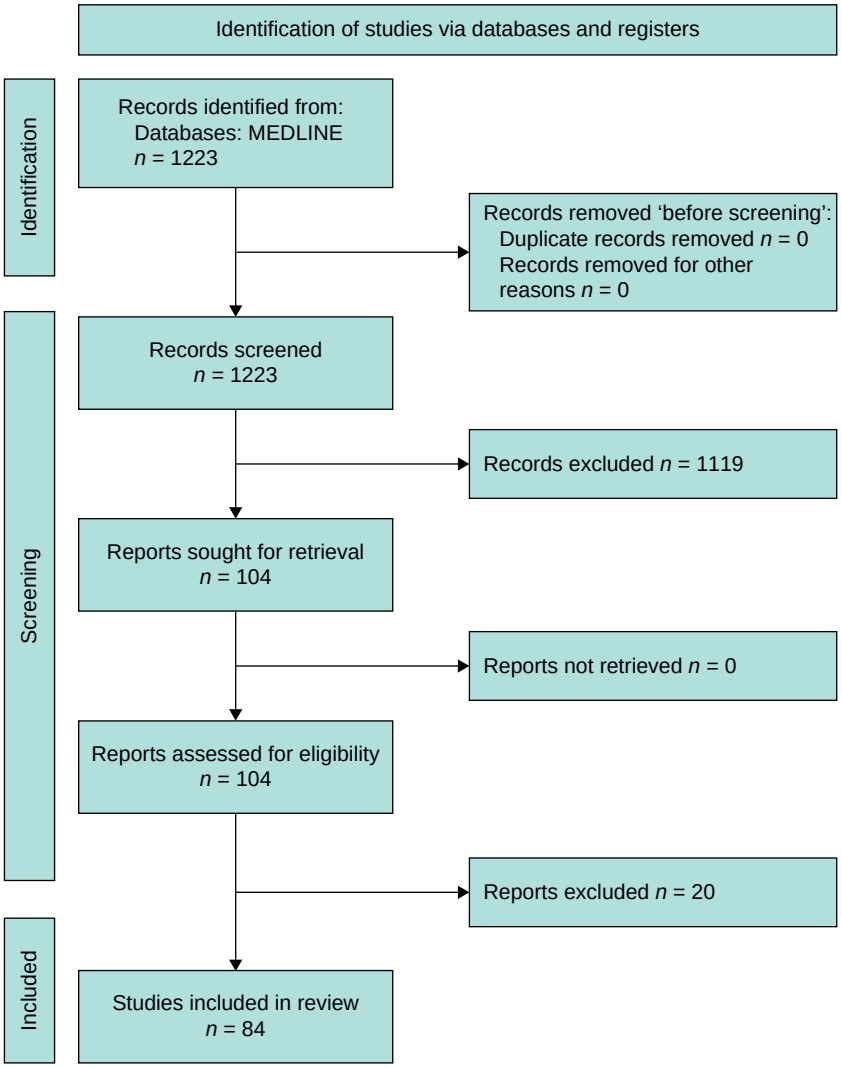

Fig. 1 PRISMA flow diagram of included studies

state-of-the-art systematic review on the treatment of liver metastases (LMs) from SBNETs included a subgroup analysis on high-grade SBNETs, showing improved 5-year overall survival after resection of LMs[26]. Finally, Borbon *et al.*[27] recently reviewed a single-institution prospective neuroendocrine neoplasm database, including 39 high-grade neuroendocrine tumours and 5 high-grade neuroendocrine carcinomas, half of them of midgut origin, and over 90% with distant metastases at the time of diagnosis. The median overall survival was 50 months for high-grade neuroendocrine tumours and 28 months for high-grade neuroendocrine carcinomas. The median overall survival significantly exceeded that of a comparative, non-surgically treated cohort (median overall survival of 19 months for high-grade neuroendocrine tumours and 12 months for high-grade neuroendocrine carcinomas) and that of an historical non-surgical high-grade neuroendocrine neoplasm series (median overall survival of 11–19 months), suggesting surgery should be considered in carefully selected patients, especially those with well-differentiated tumours[27].

These very limited data support the ENETS 2012 consensus guidelines that the presence of LMs and extrahepatic disease are not contraindications for surgical intervention, but resection should be considered on an individual patient basis[4]. Indeed, in clearly resectable G3 SBNETs with metastases, a thorough multidisciplinary evaluation is recommended to consider surgical resection. The possible benefits of (incomplete) debulking remain unknown. In the metastatic disease setting, surgery should always be compared with other non-surgical treatment modalities.

Recommendation: Patients with well-differentiated high-grade SBNETs with distant metastases can be considered to undergo surgical resection after thorough multidisciplinary evaluation.

Strength of recommendation: Moderate

Quality of the evidence: Low

Extrahepatic disease

Question 2: What is the optimal approach for peritoneal and diaphragmatic metastases found at exploration?

Peritoneal metastases (PMs) are present in approximately 5–20% of patients with SBNETs[28,29] and are independently associated with a poor prognosis[30,31]. When feasible, complete surgical resection is the only potentially curative treatment. Cytoreductive surgery may improve a patient's prognosis and avoids local complications (such as chronic occlusion or pain)[10,21,29,32,33]. The ENETS proposes the Gravity Peritoneal

Carcinomatosis Score (GPS), which considers not only whether PMs can be resected but also the locations of the disease. This score has not been validated prospectively[32]; however, several retrospective studies have evaluated the impact of cytoreduction. Wonn *et al.*[34] analysed 98 patients with SBNETs and PMs, of which 80% had concomitant LMs, demonstrating that, the greater the degree of cytoreduction, the better the overall survival. Benhaim *et al.*[35] analysed 5-year overall survival in 88 patients (of which 62% had SBNETs) who underwent complete cytoreduction of LMs and/or PMs. Overall survival in patients with PMs, LMs, and PMs with LMs was 81%, 78%, and 72% respectively. The median survival of 219 patients (of which 33% did not have metastases, 37% had LMs, 6% had PMs, and 24% had LMs and PMs) was 156, 133, and 82 months in case of liver, peritoneal, and both metastases respectively[36].

In cases of complete cytoreduction, the added value of hyperthermic intraperitoneal chemotherapy (HIPEC) remains unclear. Two small retrospective studies (including 28 and 36 patients respectively) could not show any additional benefits in terms of postoperative evolution and survival in patients with advanced SBNETs. Moreover, it seems to be associated with higher morbidity[33,37]. The possible benefits of cytoreduction should always be balanced against the potential morbidity of such aggressive surgery.

Recommendation: Where complete cytoreduction is not expected and/or GPS is greater than A, debulking surgery is not recommended; however, complete resection of PMs from SBNETs is recommended in patients with limited disease. There is no evidence supporting the use of HIPEC.

Strength of recommendation: Moderate

Quality of the evidence: Low

Lymph node involvement and locally advanced disease

Question 3: What is the optimal regional lymphadenectomy during segmental bowel resection?

Lymphadenectomy is always required in SBNET surgery, even in cases of small primary tumours (less tham 1 cm), as mesenteric LN metastases are almost always present (80–93%)[30,38–40]. Moreover, lymphadenectomy improves survival and may avert acute, local morbidity[30,38,40–43]. The optimal cut-off for the number of LNs to be resected remains controversial. No studies report the influence of LN ratios, as most report the overall number of resected LNs and survival in light of the number that are positive. A retrospective registry analysis suggested that at least 8 (or possibly 12) LNs need to be removed to improve overall survival[38–40]. A multicentre analysis of 154 patients with SBNETs could not identify a statistically significant difference in 3-year recurrence-free survival between patients with LN-positive and LN-negative disease. Patients with four positive LNs had worse 3-year recurrence-free survival compared with those with one to three or no positive LNs (82% *versus* 91% *versus* 92% respectively; $P = 0.01$). Retrieval of eight or more LNs, however, accurately discriminated between patients with four or more, one to three, or no positive LNs (3-year recurrence-free survival of 79.9% *versus* 89.6% *versus* 92.9% respectively; $P = 0.05$)[44]. A single retrospective study reported the presence of LN skip metastases (14 of 21, mainly metastatic patients), supporting a systematic dissection up to the retropancreatic area; however, the benefits of such an extended lymphadenectomy need to be demonstrated given the potential morbidity[45].

Recommendation: Patients with SBNETs should have systematic lymphadenectomy. The risks and benefits of an extended lymphadenectomy should be carefully considered given the potential morbidity of the intervention and conflicting data on clinical outcomes.

Strength of recommendation: Moderate

Quality of the evidence: Low

Question 4: What is the optimal management of lymph nodes that are encasing the superior mesenteric vein and/or the superior mesenteric artery?

For mesenteric LN metastases, the main challenge is not the identification but the assessment of resectability[7]. A classification based on the relationship between mesenteric LN metastases and the superior mesenteric vessels, with a view to predicting the difficulties with resection, has been proposed[46]. Moreover, lymphadenectomy may be especially challenging in the presence of extensive mesenteric fibrosis or large mesenteric LN metastases surrounding the superior mesenteric vasculature[7]. Mesenteric LN metastases with fibrosis are considered locally advanced or irresectable when surrounding the origin of the mesenteric vessels[21]. Symptoms may vary from no symptoms to chronic mesenteric ischaemia or small bowel obstruction; however, no data exist on what proportion of patients suffer from these severe complications. In symptomatic patients, aggressive surgery including radical or partial debulking preserving the first jejunal arteries and therefore small bowel vascular supply could relieve symptoms[10,21,47–50]. The radicality and aggressiveness of the resection should be balanced against the length of bowel resected and functional outcomes[51]. Chambers *et al.*[49] evaluated the aggressive surgical clearance of both mesenteric and hepatic disease in 66 patients with advanced neuroendocrine tumours (including 59 SBNETs) and found improved symptom relief and 5-year overall survival of 74%. However, Blazevic *et al.*[52] found that the presence of mesenteric fibrosis had no effect on survival in a multivariable analysis. Additionally, no benefit of resecting a mesenteric mass or prophylactic surgery on overall survival was demonstrated in a retrospective analysis of 559 patients with advanced SBNETs. The median survival of 82 (95% c.i. 43 to 120) months in patients undergoing resection of mesenteric fibrosis was not significantly different to 100 (95% c.i. 90 to 111) months ($P = 0.485$) in patients not undergoing resection[52]. For asymptomatic patients, no data are available on medical *versus* surgical treatment to avoid mesenteric ischaemia.

When debulking cannot be performed or when symptoms are not relieved, self-expandable stents in the superior mesenteric vein at the level of the mass have been inserted via the portal vein, with conflicting results[48,53].

Recommendation: The risks and benefits of an extended lymphadenectomy of LNs encasing the superior mesenteric vein and/or the superior mesenteric artery should be carefully considered given the potential morbidity of the intervention and the conflicting data on clinical outcomes. Stenting of the superior mesenteric vein may be performed for unresectable disease in the presence of severe symptoms.

Strength of recommendation: Low

Quality of the evidence: Low

Question 5: What is the optimal management of nodes beyond the root of the mesentery?

In the absence of a retropancreatic target on preoperative imaging, lymphadenectomy is usually conducted along the

trunk of the superior mesenteric vessels below the pancreas[7]. A single retrospective study reported the presence of LN skip metastases (14 of 21, mainly metastatic patients), supporting a systematic dissection up to the retropancreatic area; however, the risks and benefits of such an extended lymphadenectomy need to be considered given the potential morbidity[45]. In such cases, surgery should always be considered alongside other non-surgical treatment modalities.

Recommendation: There is currently no evidence supporting extended lymphadenectomy beyond the root of the mesentery.

Strength of recommendation: Low

Quality of the evidence: Low

Liver disease

Question 6: What is the role for surgical exploration in patients with a cancer of unknown primary neuroendocrine tumor and metastatic liver disease (CUP-NET)?

According to the Surveillance, Epidemiology, and End Results (SEER) programme data, the primary tumour location of a neuroendocrine lesion could not be identified in 4752 (13%) cases among the 35 618 registered neuroendocrine tumours over 31 years[8]. Patients with occult primary lesions are significantly more likely to have a delay in referral for surgery from the time of onset of symptoms compared with those with identified lesions[54].

However, due to advancements in medical imaging, it is unusual to have a completely occult lesion that has not been found on upper endoscopy, multiphase contrast-enhanced chest and abdominal CT, MRI, endoscopic ultrasonography, and/or colonoscopy[55,56].

Early surgical evaluation of patients with metastatic neuroendocrine tumours is appropriate and should not be predicated on successful identification of the primary tumour. Most tumours can be identified during surgery and even patients without an identifiable primary lesion may benefit from cytoreduction[54]. Few studies have commented on the localization of an unknown primary tumour during surgery, with reports of 60–100% of unknown primaries found at surgery (*Table 1*)[54–59]. Most unknown primary lesion are SBNETs, often identified by palpation. These lesions are often multifocal (25–54%)[30,60,61] and significantly smaller (1.4 *versus* 1.9 cm; $P = 0.03$)[55]. The role of ^{68}Ga-DOTATOC and ^{18}F-DOPA PET/CT in this setting is currently being investigated, but falls outside the scope of this question[62,63].

Recommendation: The inability to identify the primary lesions should not inhibit or delay treatment of advanced disease, as most occult lesions will be found in the small bowel at the time of surgery.

Strength of recommendation: Moderate

Quality of the evidence: Low

Question 7: Should primary small bowel neuroendocrine tumours be removed in asymptomatic patients with irresectable metastatic liver disease?

Palliative surgical strategies aim to relieve symptoms and delay a fatal outcome. Resection of asymptomatic local disease is still a matter of debate in the context of irresectable distant metastases, as only retrospective data are available. Arguments in favour of primary tumour resection in this clinical scenario are preventing local complications (such as intestinal obstruction, bowel ischaemia, or desmoplastic reactions), controlling disease to allow a focus on liver treatment, and improving overall survival. Results from a recent meta-analysis showed that primary tumour resection was associated with improved survival compared with no resection in patients with irresectable metastatic disease (HR 0.55, 95% c.i. 0.47 to 0.66). The survival benefit remained in favour of primary tumour resection after including studies only reporting patients with SBNETs (HR 0.57, 95% c.i. 0.45 to 0.74) and studies reporting patients undergoing primary tumour resection without concomitant liver surgery (HR 0.60, 95% c.i. 0.48 to 0.75)[64]. Unfortunately, the included studies were often biased toward an aggressive surgical approach in patients with a better baseline health status, so the answer remains unclear in asymptomatic patients. After this meta-analysis, a recent propensity score-matched study reported results from the SEER database and did not show a benefit of primary tumour resection with respect to 5-year overall and cancer-specific survival (56% *versus* 51% ($P = 0.402$) and 63% *versus* 52% ($P = 0.166$) respectively)[65]. A randomized trial is currently open to address this question (NCT03442959)[26].

The results of the meta-analyses supporting palliative surgery must be weighed against available high-level evidence from randomized trials (PROMID, CLARINET, RADIANT-4, and NETTER-1), showing improved long-term survival in metastatic patients receiving systemic therapies[9,10,66–68]. Apart from the NCCN guidelines, most current academic recommendations (those of the ENETS, the UKINETS [UK and Ireland Neuroendocrine Tumour Society], the NANETS, and the TNCD [Thésaurus National de Cancérologie Digestive]) promote local disease resection in cases of asymptomatic localized tumours and irresectable LMs[4,11,42,69]. Both resection and non-resection of the primary tumour in the context of irresectable LMs are acceptable; however, each case should be thoroughly discussed in a multidisciplinary team meeting.

Recommendation: Primary tumour resection in asymptomatic patients with SBNETs and irresectable metastatic liver disease may be considered to avoid future complications; however, a delayed surgical strategy with initial medical management and surgery as needed is also feasible.

Strength of recommendation: Moderate

Quality of the evidence: Low

Question 8: Should patients in whom less than 90% of metastases can be debulked undergo hepatic cytoreduction?

No clear data are available to answer this question. To decrease local or hormonal symptoms, or even to improve progression-free and overall survival, major hepatic resections have been supported if 90%, or more recently even greater than 70%, of the metastatic liver burden can be excised[11,49,50,59,70–77]. By recently lowering the threshold from 90% to 70%, 76% of patients with SBNETs and LMs may be candidates for cytoreduction, as progression-free survival is prolonged after this intervention[72]. A recent cohort of 188 hepatic cytoreductive procedures including 128 SBNETs confirmed a significantly better overall survival when greater than 70% cytoreduction was obtained compared with less than 70% (134 *versus* 38 months respectively)[77]. It remains difficult to state if the relationship between the intervention and the outcome is causal or whether confounding factors or selection bias may have influenced the results. There are no adequate data to support a benefit in OS given the heavily biased retrospective cohort studies and absence of RCTs (*Table 2*). The ENETS guidelines recommend considering radical surgery if it can be achieved with acceptable predicted morbidity (less than 30%) and mortality (less than5%) rates[79]. The additional value of other parenchymal-sparing procedures is covered in research question 9. In cases of advanced

Table 1 Studies reporting on the identification of primary tumours in cancers of unknown primary as neuroendocrine tumours (CUP-NET)

Reference	Country	Cohort	Study inclusion interval	Study size, *n*	Number of unknown primaries (%)	Number of primary tumours localized during surgery (%)	Age (years), mean	Male, %	Outcome
Wang *et al.*[55]	USA	Single RCS	1993–2008	123	15 (12)	13 (87)	57	54	Identification of UP is accomplished most of the time
Massimino *et al.*[57]	USA	Single RCS	2006–2010	63	52 (82)	39 (75)	NA	NA	SBNETs 70%, appendix 3%, pancreas 3%, colon 2%, and ovarian 2%
Bartlett *et al.*[54]	USA	Single RCS	1998–2012	61	28 (46)	25 (89)	58	48	Five-year OS 73% *versus* 60% ($P = 0.57$)
Wang *et al.*[58]	USA	Single RCS	2009–2012	342	22 (6)	22 (100)	56	54	All alive after short FU (1–3 years)
Keck *et al.*[56]	USA	Single RCS	1999–2016	134	10 (7)	6 (60)	63	58	Primaries identified before surgery in 84%
Woltering *et al.*[59]	USA	Single RCS	2003–2016	800	138 (17)	124 (90)	55	46	Descriptive analysis

RCS, Retrospective Cohort Study; UP, Unknown Primary; NA, Not Announced; SBNETs, Small Bowel Neuroendocrine Tumour; OS, Overall Survival; FU, Follow Up.

metastatic disease, surgery should always be compared with other non-surgical treatment modalities.

Recommendation: Thorough discussion at a multidisciplinary team meeting is required to consider and support the potential value of an incomplete cytoreduction for symptom relief or control of disease progression.

Strength of recommendation: Moderate

Quality of the evidence: Low

Question 9: Are major hepatic resections necessary or are parenchymal-sparing procedures reasonable?

No clear data are available to answer this question. Patients fit for cytoreductive surgery with major liver involvement should be considered for parenchymal-sparing procedures, as they preserve more functional hepatic parenchyma.

Radical treatment of LMs is sometimes more palliative than curative. Even if radical liver resection is achieved, recurrence is often seen after long-term follow-up (67–78% after 5 years and 89–94% after 10 years)[7]. As disease recurrence is common, surgical strategies have evolved to allow for surgical resection/debulking as much disease as possible, while preserving adequate functional liver parenchyma. Parenchymal-sparing procedures (such as enucleation, non-anatomic (wedge) resection, or intraoperative ablation) have all been successfully used. Several retrospective studies have combined cytoreduction with these parenchymal-sparing procedures to achieve improved 5-year survival rates from 60% to 75%, comparable to reported outcomes of studies using mainly major hepatic resections[70,72,80].

A recent state-of-the-art meta-analysis has addressed the topic of which treatment modality confers the greatest overall survival in patients with LMs from SBNETs. A statistically significant benefit in 5-year overall survival was found in favour of resection compared with no resection (OR 0.15, 95% c.i. 0.05 to 0.42; $P < 0.001$), in favour of any surgery compared with chemotherapy (OR 0.05, 95% c.i. 0.01 to 0.21; $P < 0.001$), and in favour of any surgery compared with embolization (OR 0.18, 95% c.i. 0.05 to 0.61; $P = 0.006$). There are no data comparing parenchymal-sparing procedures against each other. The meta-analysis is limited by the rarity of the disease, the low number of interventional studies, and the lack of randomized controlled trials. A total of 11 retrospective cohort studies are included, representing 1108 patients, of which only 164 had SBNETs[26]. A combination of surgical resection with parenchymal-sparing procedures appears to achieve equivalent survival outcomes with reduced morbidity.

Recommendation: Thorough discussion at a multidisciplinary team meeting is required to evaluate those patients fit for cytoreductive surgery with major liver involvement for parenchymal-sparing procedures in combination with surgical resection.

Strength of recommendation: Moderate

Quality of the evidence: Low

Question 10: What are the survival advantages and other benefits (for example symptom control) of R0, R1, and R2 resections for metastatic (hepatic and extrahepatic) small bowel neuroendocrine tumours?

Long-term survival and prognostic factors in patients with advanced SBNETs were recently analysed in a meta-analysis, with weighted 5- and 10-year overall survival of 67% and 37% respectively. Meta-regression identified younger age and primary tumour resection to be associated with a better prognosis[81]. Another recent meta-analysis evaluated the impact of the extent of resection of LMs on survival. No prospective studies have compared differences in survival advantages or other benefits (for example symptom control) of R0 (macroscopic and microscopic resection of all disease), R1 (microscopic disease remnant), and R2 (macroscopic disease remnant) resections. However, several retrospective single-centre and multicentre studies have shown that (hepatic) cytoreduction is associated with improved survival and improved control of hormonal symptoms. The 5-year overall survival ranged from 70% to 100% after R0 and R1 resections and from 26% to 89% after R2 resection[82]. Many of the included studies have shown little to no difference in overall survival whether an R0, R1, or R2 resection was achieved. The threshold for an 'optimal' R2 resection has not been set, but cytoreduction of advanced SBNET disease should be attempted when clinically and anatomically feasible, with the possible benefit of resection balanced against potential morbidity[83].

Recommendation: Patients with metastatic SBNETs appear to benefit from cytoreduction in terms of symptom control,

Table 2 Studies reporting on the degree of hepatic cytoreduction

Reference	Country	Cohort	Study inclusion interval	Study size, *n*	Number of patients with a small bowel NET (%)	Threshold of cytoreduction achieved in the liver, %	Age (years)	Male, %	Outcome
Sarmiento *et al.*[73]	USA	RCS	1977–1998	170	120 (71)	90	57	43	Operation controlled symptoms in 104 of 108 patients, but the recurrence rate at 5 years was 59%
Chambers *et al.*[49]	Canada	RCS	1995–2007	66	59 (89)	NA	60	62	Overall symptoms of CS improved (86% of patients who underwent hepatic cytoreduction and 64% of those receiving medical therapy alone ($P = 0.064$))
Landry *et al.*[75]	USA	RCS	1998–2006	54	29 (54)	NA	58	38	Hepatic resection had statistically significantly improved 5-year OS (75% *versus* 62% ($P < 0.05$))
Mayo *et al.*[70]	USA	RCS	1985–2009	339	83 (24)	NA	55	53	Synchronous disease (HR 1.9), non-functional NET hormonal status (HR 2.0), and extrahepatic disease (HR 3.0) predictive of worse survival (all $P < 0.05$)
Norlén *et al.*[87]	Sweden	PSM	1985–2012	376	376 (100)	NA	63	NA	No difference in 5-year OS or DSS (both 74% ($P = 0.87$) and 74% *versus* 78% ($P = 1.00$) respectively); proportion of PFS lower (2 of 18 *versus* 8 of 18 ($P < 0.01$))
Boudreaux *et al.*[71]	USA	RCS	2006–2012	189	189 (100)	NA	59	42	The 5-, 10-, and 20-year Kaplan– Meier survival rates from diagnosis were 87%, 77%, and 41% respectively
Graff-Baker *et al.*[74]	USA	RCS	2007–2011	52	24 (46)	70	58	33	Five-year DSS was 73% for patients <50 years old and 97% for older patients ($P = 0.03$); age was the only prognostic factor
Maxwell *et al.*[72]	USA	RCS	1999–2015	108	80 (74)	70	60	61	Patients who achieved 70% cytoreduction had improved PFS (median 3.2 years) and OS (median not reached)
Chan *et al.*[78]	Canada	RCS	2003–2014	55	44 (80)	NA	59	49	Five-year OS was 77% and 5-year PFS was 51% in setting of extrahepatic disease
Scott *et al.*[77]	USA	RCS	1999–2007	188	128 (68)	NA	58	55	Greater than 70% cytoreduction was associated with better OS than <70% cytoreduction (134 *versus* 38 months respectively)

NET, Neuroendocrine Tumour; RCS, Retrospective Cohort Study; NA, Not Announced; CS, Carcinoid Syndrome; OS, Overall Survival; PSM, Propensity Score Matching; DSS, Disease Specific Survival; PFS, Progression Free Survival.

regardless of margin status; therefore a surgical attempt can be made after thorough discussion at a multidisciplinary team meeting.

Strength of recommendation: Moderate

Quality of the evidence: Low

Question 11: When is liver cytoreduction indicated in metastatic small bowel neuroendocrine tumours?

Not all patients with SBNET LMs are eligible for cytoreduction. Patients with diffuse, bi-lobar metastases are the most challenging and might benefit from other liver-directed strategies. Moreover, palliative surgery remains a part of the multimodal strategy including thermal ablation, arterial embolization, chemoembolization, Peptide Receptor Radionuclide Therapy, and liver transplantation.

As most SBNETs have a relatively low aggressive behaviour, SBNET LMs are an accepted indication for liver transplantation[84,85]. Selection criteria include irresectable liver disease, absence of any other organ involvement, and pre-transplant excision of all extrahepatic lesions[86]. Moreover, the Milan and ENETS criteria have to be met. The Milan criteria and ENETS guidelines require that tumours be low grade (Ki-67

less than 10% per ENETS), the primary tumour has to be removed, there is no extrahepatic disease (by ^{68}Ga PET/CT), stable disease has been demonstrated in the prior 6 months, age must be less than 55 years, and there has to be less than 50% liver involvement (or less than 75% with refractory symptoms per ENETS)[86]. Recent studies report 5-year overall and disease-free survival after liver transplantation of 47–71% and 31–57% respectively[86]. This confirms previous findings of young patients (less than 65 years old) with SBNETs and LMs having a favourable survival with standardized multimodality treatment, as most survival figures reported after liver transplantation for neuroendocrine tumours do not surpass survival percentages observed with multimodality treatment[87]. No studies have directly compared liver transplantation with other multimodality treatment options.

Recommendation: Liver transplantation remains controversial, but may be a treatment option for highly selected patients if the ENETS and Milan criteria are met and after thorough discussion at a multidisciplinary team meeting.

Strength of recommendation: Low

Quality of the evidence: Low

Discussion

This consensus statement provides evidence-based recommendations on 11 clinically relevant surgical questions in patients with locally advanced or metastatic SBNETs. A systematic literature review was performed to identify relevant papers for the predefined research questions. Some 1223 abstracts were found, of which 104 studies or relevant papers were included. The stated recommendations, created by the ESES working group, were discussed during the ESES Conference in 2023. The proposed recommendations were rated as 'strongly agree' or 'agree', ranging from 64% to 96% for the individual statements, and, as such, provide evidence-based recommendations that are supported by members of the ESES community and specialist surgeons in the field.

This paper emphasizes and confirms the key role of the surgeon for locally advanced and metastatic SBNETs, especially in the setting of a multidisciplinary team. There is currently no evidence supporting extended lymphadenectomy, but standard lymphadenectomy should always be performed. Resection of the primary tumour in the presence of irresectable hepatic and extrahepatic metastatic disease remains controversial. Liver transplantation should be reserved for highly selected cases. Furthermore, cohort studies from expert or tertiary centres show that multivisceral resections and cytoreductive surgery are feasible and can result in favourable long-term outcomes, with acceptable short-term postoperative morbidity and mortality. These findings confirm the variety of surgical indications, even in the advanced and metastatic setting.

The major strengths of this paper include the extensive literature review (yielding a substantial number of studies or reviews), the evidence grading according to currently recommended methods, and the plenary discussion and consensus voting among the ESES members. Most recommendations, however, are based on low-quality evidence. In addition to the inherent selection bias within the included studies, some studies have analysed patients with a variety of gastroenteropancreatic neuroendocrine tumours, making it challenging to discern reliable results exclusive to those with SBNETs. Studies reporting on LMs or extrahepatic disease had a different radiological workup that often did not specify the extent of the metastases or whether liver surgery could be curative and some studies included high-grade tumours.

Given the rarity and heterogeneity of SBNETs it remains challenging to conduct prospective studies. Given the lack of clear evidence for most research questions, the low number of interventional studies, and the lack of randomized controlled trials, levels of evidence were generally low. In this respect it is difficult to develop standardized treatment strategies and run multicentre randomized trials. Nevertheless, to be able to answer these clinical questions, international multicentre collaborations with standardized data collection and predefined outcome measures could be an important step towards improving the quality of the available research.

This paper provides the ESES recommendations on the surgical management of advanced SBNETs; however, there are other well-respected societies (such as the ENETS and the American Association of Endocrine Surgeons (AAES)) that have not been involved in the process of developing these specific guidelines. Recommendations were reached by consensus among the working group members and the ESES members subsequently voted on these statements; however, no structured Delphi process was used to develop the recommendations.

Considering the rarity of SBNETs and the multimodal treatment options, the authors advocate that all patients with distant metastases from SBNETs should be discussed in high-volume referral centres with specialized multidisciplinary team meetings for neuroendocrine tumours, preferably in ENETS Centres of Excellence. In line with the advancements in treatment options for SBNETs, every surgical intervention should always be compared with less-invasive options and taken in context of future adjuvant treatment modalities.

In conclusion, this consensus statement provides evidence-based recommendations regarding the surgical management of different surgical scenarios in locally advanced and metastatic SBNETs. In patients with advanced disease, the surgeon continues to play a central role in the multidisciplinary team discussing and evaluating the multiple treatment modalities. Prospective international and multicentre studies or randomized controlled trials must be conducted to improve the quality of the existing evidence.

Funding

The authors have no funding to declare.

Author contributions

Klaas Van Den Heede (Conceptualization, Formal analysis, Methodology, Writing), Dirk-Jan van Beek (Conceptualization, Formal analysis, Methodology, Writing—review & editing), Sam Van Slycke (Conceptualization, Formal analysis, Supervision, Writing—review & editing), Inne Borel Rinkes (Conceptualization, Formal analysis, Supervision, Writing—review & editing), Olov Norlén (Conceptualization, Supervision, Writing—review & editing), Peter Stålberg (Conceptualization, Formal analysis, Supervision, Validation, Writing—review & editing), and Erik Nordenström (Conceptualization, Formal analysis, Methodology, Resources, Supervision, Validation, Writing—review & editing)

Disclosure

The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS* online.

Data availability

The (raw) data that support the findings of this paper are available on reasonable request from the senior author (E.N).).

References

1. Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y *et al.* Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. *JAMA Oncol* 2017;**3**:1335–1342
2. Wyld D, Moore J, Tran N, Youl P. Incidence, survival and stage at diagnosis of small intestinal neuroendocrine tumours in Queensland, Australia, 2001–2015. *Asia Pac J Clin Oncol* 2021;**17**: 350–358
3. Kaçmaz E, Sarasqueta AF, van Eeden S, Dreijerink KMA, Klumpen HJ, Tanis PJ *et al.* Update on incidence, prevalence, treatment and survival of patients with small bowel neuroendocrine neoplasms in the Netherlands. *World J Surg* 2021;**45**:2482–2491
4. Pavel M, O'Toole D, Costa F, Capdevila J, Gross D, Kianmanesh R *et al.* ENETS consensus guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms (NEN) and NEN of unknown primary site. *Neuroendocrinology* 2016;**103**:172–185
5. Riihimaki M, Hemminki A, Sundquist K, Sundquist J, Hemminki K. The epidemiology of metastases in neuroendocrine tumors. *Int J Cancer* 2016;**139**:2679–2686
6. Hallet J, Law CH, Cukier M, Saskin R, Liu N, Singh S. Exploring the rising incidence of neuroendocrine tumors: a population-based analysis of epidemiology, metastatic presentation, and outcomes. *Cancer* 2015;**121**:589–597
7. Deguelte S, Perrier M, Hammoutene C, Cadiot G, Kianmanesh R. Surgery and perioperative management in small intestinal neuroendocrine tumors. *J Clin Med* 2020;**9**:2319
8. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE *et al.* One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol* 2008;**26**:3063–3072
9. Rinke A, Muller HH, Schade-Brittinger C, Klose KJ, Barth P, Wied M *et al.* Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID study group. *J Clin Oncol* 2009;**27**:4656–4663
10. Howe JR, Cardona K, Fraker DL, Kebebew E, Untch BR, Wang YZ*et al.* The surgical management of small bowel neuroendocrine tumors: consensus guidelines of the North American Neuroendocrine Tumor Society. *Pancreas* 2017;**46**: 715–731
11. Boudreaux JP, Klimstra DS, Hassan MM, Woltering EA, Jensen RT, Goldsmith SJ *et al.* The NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: well-differentiated neuroendocrine tumors of the jejunum, ileum, appendix, and cecum. *Pancreas* 2010;**39**:753–766
12. Anthony LB, Strosberg JR, Klimstra DS, Maples WJ, O'Dorisio TM, Warner RR *et al.* The NANETS consensus guidelines for the diagnosis and management of gastrointestinal neuroendocrine tumors (NETs): well-differentiated NETs of the distal colon and rectum. *Pancreas* 2010;**39**:767–774
13. Niederle B, Pape UF, Costa F, Gross D, Kelestimur F, Knigge U *et al.* ENETS consensus guidelines update for neuroendocrine neoplasms of the jejunum and ileum. *Neuroendocrinology* 2016; **103**:125–138
14. Shah MH, Goldner WS, Benson AB, Bergsland E, Blaszkowsky LS, Brock P *et al.* Neuroendocrine and adrenal tumors, version 2.2021, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2021;**19**:839–868
15. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan —a web and mobile app for systematic reviews. *Syst Rev* 2016;**5**: 210
16. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S *et al.* Grading quality of evidence and strength of recommendations. *BMJ* 2004;**328**:1490
17. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P *et al.* GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;**336**:924–926
18. Andrews JC, Schunemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA *et al.* GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. *J Clin Epidemiol* 2013;**66**:726–735
19. Garcia-Carbonero R, Sorbye H, Baudin E, Raymond E, Wiedenmann B, Niederle B *et al.* ENETS consensus guidelines for high-grade gastroenteropancreatic neuroendocrine tumors and neuroendocrine carcinomas. *Neuroendocrinology* 2016;**103**: 186–194
20. Sonbol MB, Halfdanarson TR. Management of well-differentiated high-grade (G3) neuroendocrine tumors. *Curr Treat Options Oncol* 2019;**20**:74
21. Partelli S, Bartsch DK, Capdevila J, Chen J, Knigge U, Niederle B *et al.* ENETS consensus guidelines for standard of care in neuroendocrine tumours: surgery for small intestinal and pancreatic neuroendocrine tumours. *Neuroendocrinology* 2017; **105**:255–265
22. Strosberg JR, Coppola D, Klimstra DS, Phan AT, Kulke MH, Wiseman GA *et al.* The NANETS consensus guidelines for the diagnosis and management of poorly differentiated (high-grade) extrapulmonary neuroendocrine carcinomas. *Pancreas* 2010;**39**:799–800
23. Galleberg RB, Knigge U, Tiensuu Janson E, Vestermark LW, Haugvik SP, Ladekarl M *et al.* Results after surgical treatment of liver metastases in patients with high-grade gastroenteropancreatic neuroendocrine carcinomas. *Eur J Surg Oncol* 2017;**43**:1682–1689
24. Crippa S, Partelli S, Bassi C, Berardi R, Capelli P, Scarpa A *et al.* Long-term outcomes and prognostic factors in neuroendocrine carcinomas of the pancreas: morphology matters. *Surgery* 2016;**159**:862–871
25. Du S, Wang Z, Sang X, Lu X, Zheng Y, Xu H *et al.* Surgical resection improves the outcome of the patients with neuroendocrine tumor liver metastases: large data from Asia. *Medicine (Baltimore)* 2015;**94**:e388
26. Kacmaz E, Heidsma CM, Besselink MGH, Dreijerink KMA, Klumpen HJ, Nieveen van Dijkum EJM *et al.* Treatment of liver metastases from midgut neuroendocrine tumours: a systematic review and meta-analysis. *J Clin Med* 2019;**8**:403
27. Borbon LC, Tran CG, Sherman SK, Ear PH, Chandrasekharan C, Bellizzi AM *et al.* Is there a role for surgical resection of grade 3 neuroendocrine neoplasms? *Ann Surg Oncol* 2022;**29**:6936–6946

28. Norlen O, Edfeldt K, Akerstrom G, Westin G, Hellman P, Bjorklund P *et al.* Peritoneal carcinomatosis from small intestinal neuroendocrine tumors: clinical course and genetic profiling. *Surgery* 2014;**156**:1512–1521; discussion 1521–1522
29. de Mestier L, Lardiere-Deguelte S, Brixi H, O'Toole D, Ruszniewski P, Cadiot G *et al.* Updating the surgical management of peritoneal carcinomatosis in patients with neuroendocrine tumors. *Neuroendocrinology* 2015;**101**:105–111
30. Norlen O, Stalberg P, Oberg K, Eriksson J, Hedberg J, Hessman O *et al.* Long-term results of surgery for small intestinal neuroendocrine tumors at a tertiary referral center. *World J Surg* 2012;**36**:1419–1431
31. Merola E, Prasad V, Pascher A, Pape UF, Arsenic R, Denecke T *et al.* Peritoneal carcinomatosis in gastro-entero-pancreatic neuroendocrine neoplasms: clinical impact and effectiveness of the available therapeutic options. *Neuroendocrinology* 2020; **110**:517–524
32. Kianmanesh R, Ruszniewski P, Rindi G, Kwekkeboom D, PapeUF, Kulke M *et al.* ENETS consensus guidelines for the management of peritoneal carcinomatosis from neuroendocrine tumors. *Neuroendocrinology* 2010;**91**:333–340
33. Elias D, David A, Sourrouille I, Honore C, Goere D, Dumont F *et al.* Neuroendocrine carcinomas: optimal surgery of peritoneal metastases (and associated intra-abdominal metastases). *Surgery* 2014;**155**:5–12
34. Wonn SM, Limbach KE, Pommier SJ, Ratzlaff AN, Leon EJ, McCully BH *et al.* Outcomes of cytoreductive operations for peritoneal carcinomatosis with or without liver cytoreduction in patients with small bowel neuroendocrine tumors. *Surgery* 2021;**169**:168–174
35. Benhaim L, Faron M, Hadoux J, Gelli M, Sourrouille I, Burtin P *et al.* Long-term results after surgical resection of peritoneal metastasis from neuroendocrine tumors. *Neuroendocrinology* 2021;**111**:599–608
36. Wright MF, Cates J, Gonzalez RS, Das S, Berlin JD, Shi C. Impact of peritoneal metastasis on survival of patients with small intestinal neuroendocrine tumor. *Am J Surg Pathol* 2019;**43**:559–563
37. Hajjar R, Mercier F, Passot G, Pasquer A, Gelli M, Levine EA *et al.* Cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy for small bowel neuroendocrine tumors with peritoneal metastasis. *Eur J Surg Oncol* 2022;**48**: 1626–1630
38. Landry CS, Lin HY, Phan A, Charnsangavej C, Abdalla EK, AloiaT, *et al.* Resection of at-risk mesenteric lymph nodes is associated with improved survival in patients with small bowel neuroendocrine tumors. *World J Surg* 2013;**37**:1695–1700
39. Motz BM, Lorimer PD, Boselli D, Hill JS, Salo JC. Optimal lymphadenectomy in small bowel neuroendocrine tumors: analysis of the NCDB. *J Gastrointest Surg* 2018;**22**:117–123
40. Chen L, Song Y, Zhang Y, Chen M, Chen J. Exploration of the exact prognostic significance of lymphatic metastasis in jejunoileal neuroendocrine tumors. *Ann Surg Oncol* 2018;**25**: 2067–2074
41. Pasquer A, Walter T, Hervieu V, Forestier J, Scoazec JY, Lombard-Bohas C *et al.* Surgical management of small bowel neuroendocrine tumors: specific requirements and their impact on staging and prognosis. *Ann Surg Oncol* 2015;**22**:S742–S749
42. de Mestier L, Lepage C, Baudin E, Coriat R, Courbon F, Couvelard A *et al.* Digestive neuroendocrine neoplasms (NEN): French intergroup clinical practice guidelines for diagnosis, treatment and follow-up (SNFGE, GTE, RENATEN, TENPATH, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO, SFR). *Dig Liver Dis* 2020;**52**:473–492
43. Walsh JC, Schaeffer DF, Kirsch R, Pollett A, Manzoni M, Riddell RH *et al.* Ileal "carcinoid" tumors-small size belies deadly intent: high rate of nodal metastasis in tumors ≤1 cm in size. *Hum Pathol* 2016;**56**:123–127
44. Zaidi MY, Lopez-Aguiar AG, Dillhoff M, Beal E, Poultsides G, Makris E *et al.* Prognostic role of lymph node positivity and number of lymph nodes needed for accurately staging small-bowel neuroendocrine tumors. *JAMA Surg* 2019;**154**:134–140
45. Pasquer A, Walter T, Rousset P, Hervieu V, Forestier J, Lombard-Bohas C *et al.* Lymphadenectomy during small bowel neuroendocrine tumor surgery: the concept of skip metastases. *Ann Surg Oncol* 2016;**23**:804–808
46. Lardiere-Deguelte S, de Mestier L, Appere F, Vullierme MP, Zappa M, Hoeffel C *et al.* Toward a preoperative classification of lymph node metastases in patients with small intestinal neuroendocrine tumors in the era of intestinal-sparing surgery. *Neuroendocrinology* 2016;**103**:552–559
47. Hellman P, Lundstrom T, Ohrvall U, Eriksson B, Skogseid B, Oberg K *et al.* Effect of surgery on the outcome of midgut carcinoid disease with lymph node and liver metastases. *World J Surg* 2002;**26**:991–997
48. Daskalakis K, Karakatsanis A, Hessman O, Stuart HC, Welin S, Tiensuu Janson E *et al.* Association of a prophylactic surgical approach to stage IV small intestinal neuroendocrine tumors with survival. *JAMA Oncol* 2018;**4**:183–189
49. Chambers AJ, Pasieka JL, Dixon E, Rorstad O. The palliative benefit of aggressive surgical intervention for both hepatic and mesenteric metastases from neuroendocrine tumors. *Surgery* 2008;**144**:645–651; discussion 651–653
50. Boudreaux JP, Putty B, Frey DJ, Woltering E, Anthony L, Daly I *et al.* Surgical treatment of advanced-stage carcinoid tumors: lessons learned. *Ann Surg* 2005;**241**:839–845; discussion 845–846
51. Hallet J, Law C. Extent of lymph node dissection for small bowel neuroendocrine tumors. *World J Surg* 2021;**45**:197–202
52. Blazevic A, Zandee WT, Franssen GJH, Hofland J, van Velthuysen MF, Hofland LJ *et al.* Mesenteric fibrosis and palliative surgery in small intestinal neuroendocrine tumours. *Endocr Relat Cancer* 2018;**25**:245–254
53. Hellman P, Hessman O, Akerstrom G, Stalberg P, Hennings J, Bjorck M *et al.* Stenting of the superior mesenteric vein in midgut carcinoid disease with large mesenteric masses. *World J Surg* 2010;**34**:1373–1379
54. Bartlett EK, Roses RE, Gupta M, Shah PK, Shah KK, Zaheer S *et al.* Surgery for metastatic neuroendocrine tumors with occult primaries. *J Surg Res* 2013;**184**:221–227
55. Wang SC, Parekh JR, Zuraek MB, Venook AP, Bergsland EK, Warren RS *et al.* Identification of unknown primary tumors in patients with neuroendocrine liver metastases. *Arch Surg* 2010; **145**:276–280
56. Keck KJ, Maxwell JE, Menda Y, Bellizzi A, Dillon J, O'Dorisio TM *et al.* Identification of primary tumors in patients presenting with metastatic gastroenteropancreatic neuroendocrine tumors. *Surgery* 2017;**161**:272–279
57. Massimino KP, Han E, Pommier SJ, Pommier RF. Laparoscopic surgical exploration is an effective strategy for locating occult primary neuroendocrine tumors. *Am J Surg* 2012;**203**:628–631
58. Wang YZ, Chauhan A, Rau J, Diebold AE, Opoku-Boateng A, Ramcharan T *et al.* Neuroendocrine tumors (NETs) of unknown primary: is early surgical exploration and aggressive debulking justifiable? *Chin Clin Oncol* 2016;**5**:4
59. Woltering EA, Voros BA, Beyer DT, Wang YZ, Thiagarajan R, Ryan P *et al.* Aggressive surgical approach to the management of neuroendocrine tumors: a report of 1,000 surgical

cytoreductions by a single institution. *J Am Coll Surg* 2017;**224**:434–447
60. Choi AB, Maxwell JE, Keck KJ, Bellizzi AJ, Dillon JS, O'Dorisio TM *et al.* Is multifocality an indicator of aggressive behavior in small bowel neuroendocrine tumors? *Pancreas* 2017;**46**:1115–1120
61. Gangi A, Siegel E, Barmparas G, Lo S, Jamil LH, Hendifar A *et al.* Multifocality in small bowel neuroendocrine tumors. *J Gastrointest Surg* 2018;**22**:303–309
62. Sadowski SM, Neychev V, Millo C, Shih J, Nilubol N, Herscovitch P *et al.* Prospective study of ^{68}Ga-DOTATATE positron emission tomography/computed tomography for detecting gastro-entero-pancreatic neuroendocrine tumors and unknown primary sites. *J Clin Oncol* 2016;**34**:588–596
63. Ouvrard E, Mestier L, Boursier C, Lachachi B, Sahakian N, Chevalier E *et al.* ^{18}F-DOPA PET/CT at the forefront of initial or presurgical evaluation of small-intestine neuroendocrine tumors. *J Nucl Med* 2022;**63**:1865–1870
64. Van Den Heede K, Chidambaram S, Van Slycke S, Brusselaers N, Warfvinge CF, Ohlsson H *et al.* Effect of primary tumour resection without curative intent in patients with metastatic neuroendocrine tumours of the small intestine and right colon: meta-analysis. *Br J Surg* 2022;**109**:191–199
65. Yan H, Yin L, Han H, Jin Y, Liu Z. Relationship between primary tumor resection for metastatic small intestine neuroendocrine tumors and survival: a propensity score-matched analysis. *J Invest Surg* 2022;**35**:1239–1247
66. Pavel M, Cwikla JB, Lombard-Bohas C, Borbath I, Shah T, Pape UF *et al.* Efficacy and safety of high-dose lanreotide autogel in patients with progressive pancreatic or midgut neuroendocrine tumours: CLARINET FORTE phase 2 study results. *Eur J Cancer* 2021;**157**:403–414
67. Yao JC, Fazio N, Singh S, Buzzoni R, Carnaghi C, Wolin E *et al.* Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. *Lancet* 2016;**387**:968–977
68. Strosberg JR, Caplin ME, Kunz PL, Ruszniewski PB, Bodei L, Hendifar A *et al.* ^{177}Lu-Dotatate plus long-acting octreotide versus high–dose long-acting octreotide in patients with midgut neuroendocrine tumours (NETTER-1): final overall survival and long-term safety results from an open-label, randomised, controlled, phase 3 trial. *Lancet Oncol* 2021;**22**:1752–1763
69. Kulke MH, Shah MH, Benson AB III, Bergsland E, Berlin JD, Blaszkowsky LS *et al.* Neuroendocrine tumors, version 1.2015. *J Natl Compr Canc Netw* 2015;**13**:78–108
70. Mayo SC, de Jong MC, Pulitano C, Clary BM, Reddy SK, Gamblin TC *et al.* Surgical management of hepatic neuroendocrine tumor metastasis: results from an international multi-institutional analysis. *Ann Surg Oncol* 2010;**17**:3129–3136
71. Boudreaux JP, Wang YZ, Diebold AE, Frey DJ, Anthony L, Uhlhorn AP *et al.* A single institution's experience with surgical cytoreduction of stage IV, well-differentiated, small bowel neuroendocrine tumors. *J Am Coll Surg* 2014;**218**:837–844
72. Maxwell JE, Sherman SK, O'Dorisio TM, Bellizzi AM, Howe JR. Liver-directed surgery of neuroendocrine metastases: what is the optimal strategy? *Surgery* 2016;**159**:320–333
73. Sarmiento JM, Heywood G, Rubin J, Ilstrup DM, Nagorney DM, Que FG. Surgical treatment of neuroendocrine metastases to the liver: a plea for resection to increase survival. *J Am Coll Surg* 2003;**197**:29–37
74. Graff-Baker AN, Sauer DA, Pommier SJ, Pommier RF. Expanded criteria for carcinoid liver debulking: maintaining survival and increasing the number of eligible patients. *Surgery* 2014;**156**:1369–1376; discussion 1376–1377
75. Landry CS, Scoggins CR, McMasters KM, Martin RC II. Management of hepatic metastasis of gastrointestinal carcinoid tumors. *J Surg Oncol* 2008;**97**:253–258
76. Norlen O, Stalberg P, Zedenius J, Hellman P. Outcome after resection and radiofrequency ablation of liver metastases from small intestinal neuroendocrine tumours. *Br J Surg* 2013;**100**:1505–1514
77. Scott AT, Breheny PJ, Keck KJ, Bellizzi AM, Dillon JS, O'Dorisio TM *et al.* Effective cytoreduction can be achieved in patients with numerous neuroendocrine tumor liver metastases (NETLMs). *Surgery* 2019;**165**:166–175
78. Chan DL, Dixon M, Law Chl, Koujanian S, Beyfuss KA, Singh S *et al.* Outcomes of cytoreductive surgery for metastatic low-grade neuroendocrine tumors in the setting of extrahepatic metastases. *Ann Surg Oncol* 2018;**25**:1768–1774
79. Steinmuller T, Kianmanesh R, Falconi M, Scarpa A, Taal B, Kwekkeboom DJ *et al.* Consensus guidelines for the management of patients with liver metastases from digestive (neuro)endocrine tumors: foregut, midgut, hindgut, and unknown primary. *Neuroendocrinology* 2008;**87**:47–62
80. Saxena A, Chua TC, Perera M, Chu F, Morris DL. Surgical resection of hepatic metastases from neuroendocrine neoplasms: a systematic review. *Surg Oncol* 2012;**21**:e131–e141
81. Van Den Heede K, Chidambaram S, Van Slycke S, Brusselaers N, Warfvinge CF, Ohlsson H *et al.* Long-term survival of metastatic small intestine neuroendocrine tumors: a meta-analysis. *Endocr Relat Cancer* 2022;**29**:163–173
82. Kulkarni R, Kabir I, Hodson J, Raza S, Shah T, Pandanaboyana S *et al.* Impact of the extent of resection of neuroendocrine tumor liver metastases on survival: a systematic review and meta-analysis. *Ann Hepatobiliary Pancreat Surg* 2022;**26**:31–39
83. Albers MB, Almquist M, Bergenfelz A, Nordenstrom E. Complications of surgery for gastro-entero-pancreatic neuroendocrine neoplasias. *Langenbecks Arch Surg* 2020;**405**:137–143
84. Le Treut YP, Gregoire E, Klempnauer J, Belghiti J, Jouve E, Lerut J *et al.* Liver transplantation for neuroendocrine tumors in Europe-results and trends in patient selection: a 213-case European liver transplant registry study. *Ann Surg* 2013;**257**:807–815
85. Moris D, Tsilimigras DI, Ntanasis-Stathopoulos I, Beal EW, Felekouras E, Vernadakis S *et al.* Liver transplantation in patients with liver metastases from neuroendocrine tumors: a systematic review. *Surgery* 2017;**162**:525–536
86. Kim J, Zimmerman MA, Hong JC. Liver transplantation in the treatment of unresectable hepatic metastasis from neuroendocrine tumors. *J Gastrointest Oncol* 2020;**11**:601–608
87. Norlén O, Daskalakis K, Öberg K, Åkerström G, Stålberg P, Hellman P. Indication for liver transplantation in young patients with small intestinal NETs is rare? *World J Surg* 2014;**38**:742–747