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HOT TOPIC (JOSE DIAZ, SECTION EDITOR)

Small Bowel Neuroendocrine Tumors: Focus on Pathologic Aspects and Controversial Surgical Issues

Antonella Pino[1] · Francesco Frattini[1] · Antonio Ieni[2] · Carla Colombo[3,4] · Simone De Leo[4] · Stefano Rausei[5] · Luigi Boni[6] · Georgios Lianos[7] · Guido Fadda[2] · Kim Hoon Yub[8] · Sergio Baldari[9] · Alfredo Campennì[9] · Gianlorenzo Dionigi[10]

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Abstract

Purpose of the Review The aim of the review is to present an updated overview on the pathologic aspects and the surgical approach to small bowel neuroendocrine tumors, focusing on the following debated issues: role of laparoscopic surgery, lymph node dissection, prophylactic cholecystectomy, mesenteric fibrosis, and surgery of distant metastases.

Recent Findings Neuroendocrine tumors of the small intestine, formerly known as midgut carcinoid tumors, are a rather rare disease with an incidence of less than 1 per 100,000 in the general population. However, the neuroendocrine tumors of the small intestine are among the most common malignancies, accounting for more than 20% of all neuroendocrine tumors in Europe and the USA. Preoperative diagnosis of neuroendocrine tumors of the small intestine is challenging. Diagnosis is often late due to the rather unspecific clinical complaints. At the time of the operation, a third of the patients already have hepatic metastasis. The biology of these tumors is different from other neuroendocrine neoplasms of the digestive tract. There is no correlation between tumor size and tumor stage. Also, small tumors < 10 mm can already have lymphatic or distant metastases, so that the radical nature of the operation is not determined by the size of the primary tumor. Colon-sparing resection with systematic lymphadenectomy along the superior mesenteric artery and removal of the retropancreatic lymph nodes is also recommended in the localized stage. Multiple primary tumor foci can be identified in around one third of patients. Thorough palpation of the entire small intestine is therefore mandatory. Pronounced mesenteric fibrosis can also occur in the small neuroendocrine tumors and limit the

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✉ Francesco Frattini
francescofrattini79@gmail.com

[1] Division of Surgery, Istituto Auxologico Italiano IRCCS Capitanio, Via Mercalli 28, 20122 Milan, Italy

[2] Section of Pathological Anatomy, Department of Human Pathology "Gaetano Barresi", A.O.U. Polyclinic G. Martino, Messina, Italy

[3] Department of Endocrine and Metabolic Diseases, IRCCS Istituto Auxologico Italiano, Milan, Italy

[4] Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy

[5] Department of Surgery, ASST Valle Olona, Viale Eusebio Pastori 4, 21013 Gallarate, Italy

[6] Department of Surgery, Fondazione IRCCS-Ca' Granda-Ospedale Maggiore Policlinico, University of Milan, Milan, Italy

[7] Department of Surgery, University of Ioannina, Ioannina, Greece

[8] Department of Surgery, Division of Breast and Endocrine Surgery, Minimally Invasive Surgery and Robotic Surgery Center, KUMC Thyroid Center Korea University, Anam Hospital, Seoul, Republic of Korea

[9] Nuclear Medicine Unit, Department of Biomedical and Dental Sciences and Morpho-Functional Imaging, University Hospital G. Martino, University of Messina, Messina, Italy

[10] Division of Surgery, Istituto Auxologico Italiano IRCCS Capitanio, University of Milan, Milan, Italy

possibilities of laparoscopic resection too. Short bowel syndrome must be avoided.

Summary Laparoscopic surgery presents some concerns and limits in small bowel net treatment as it could miss multifocal tumors. Laparoscopic visceral resection could be very challenging and not radical because of the extensive involvement of lymph nodes and mesentery. Prophylactic cholecystectomy can be indicated if postoperative therapy with somatostatin analogs is indicated. Lymph node resection is crucial in the surgical therapy of net both for staging purposes and for survival advantage. Limphadenectomy has to be extensive and complete but the number of lymph nodes resected is not necessarily related to the length of resected small bowel. Primary tumor resection regardless of metastatic disease seems to be associated to an improvement of survival.

Keywords Neuroendocrine tumors · Small bowel · Laparoscopic surgery · Lymph nodes

Introduction

Small bowel-neuroendocrine tumors (SB-NET) are a rather rare disease with an incidence of around 0.3–1.0 per 100,000 inhabitants [1]. On the basis of autopsy studies, the prevalence of SB-NET can be estimated at 1.22 per 100,000 inhabitants [2].

In recent decades, the incidence has increased [3]. SB-NET have overtaken adenocarcinoma as the most common type of small bowel tumors: SB-NET have significantly increased from 27.2% and 52.1% in 1973–1977 to 38.6% and 63.6% in 1998–2002, whereas over the same time period, small intestinal adenocarcinomas have decreased [1–4]. The increase in SB-NET incidence may in part be explained by increased clinical awareness of the disease along with more SB-NET incidentally discovered, novel epidemiological data and technology, improved pathology and biology investigations and imaging techniques (capsule endoscopy) [1–5].

The clinical course of SB-NET may vary from a slowly progressive to highly aggressive disease with heterogeneous patient outcomes [6, 7]. This variability poses significant challenges in treatment and medical decision-making [7, 8].

SB-NET are one of the most common locations along with the neuroendocrine tumors of the pancreas and duodenum [1–4, 9].

Within the small intestine, the tumors are mainly found in the distal jejunum and ileum and their incidence increases from proximal to distal [1–4, 10]. About 70% of the tumors are found in the terminal ileum [1–4, 11].

SB-NET of jejunum and ileum are usually diagnosed in the sixth/seventh decade but, in opposition to duodenal NETs, have no gender preference [12, 13].

Another special feature of the SB-NET is the multifocality [14, 15]. Multifocal manifestations can be identified in up to 30% of patients [1–4, 16].

Most of SB-NET are nonfunctioning tumors [17, 18]. Unlike the neuroendocrine tumors of the duodenum or pancreas, SB-NET produce serotonin almost exclusively [1–4]. Clinically, the patients are therefore initially characterized by rather unspecific gastrointestinal complaints, the cause of which is regularly not recognized even with the usual examination modalities [19, 20]. Later on, the patients are often noticed by ileus complaints or intestinal ischemia [21, 22].

Patients with small intestinal and ileal NETs had significant nonlocalized disease. It is not uncommon that liver metastasis and the associated symptoms of serotonin production ultimately lead to the diagnosis [23, 24]. Up to 20% of patients with liver metastases develop carcinoid syndrome caused by the hormone excess [25, 26]. Flush (90%) and diarrhea (80%), bronchoasthmatic symptoms, and the heart valve insufficiency (Hedinger's syndrome) are found [1–4]. These data emphasize the malignant potential of SB-NET [2–29].

In this narrative review, we highlight some controversial and debated surgical aspects in SB-NET treatment as the role of laparoscopic surgery, lymph node dissection, prophylactic cholecystectomy, and surgery of distant metastases. A thorough review of the current literature was assessed for each of these issues.

Materials and Methods

A review of the literature of the last twenty years was performed by two authors on Pubmed and Google Scholar. Searched terms included [small bowel] [neuroendocrine tumors] [laparoscopy].

[cholecystectomy] [lymph node dissection] [mesenteric fibrosis].

We included original research articles and current guidelines in SB-NET diagnosis and treatment. After first screening for duplicates and case reports, we excluded articles that did not focus on SB-NET. We included updated articles related to clinico-pathological aspects of SB-NET, use of laparoscopy in SB-NET surgical treatment, prophylactic cholecystectomy, lymph node dissection, mesenteric fibrosis, and treatment of distant metastases. Reference lists from studies selected by the electronic search were reviewed manually to identify further relevant articles.

After the first analysis, only papers with well-defined and complete surgical data and quality of the results were included in the review for each of the selected issues.

SB-NET Behavior

The impression gained with other endocrine neoplasms that small tumors (i.e., < 10–20 mm) are more likely to be associated with an indolent course cannot be confirmed for the SB-NET [30]. Among diagnosed SB-NET, non-metastatic disease is a rarity, since the majority of patients already present with metastasis at diagnosis (Table 1) and early lesion without symptoms are left undetected. Initial metastases are usually noted in regional lymph nodes, then in the liver, and finally in distant sites such as bone [31]. In small bowel NET, the liver is the most common site of metastasis [30, 31]. The majority of the alimentary tract is drained by the portal venous system, explaining the dominance of liver metastases [32]. Distant metastases were found in about one third of patients and over 80% of patients already had a lymphatic metastasis before [30]. Interestingly, the risk of lymphatic and / or distant metastasis is not influenced by the size of the tumor.

NET preference to metastasize to liver was studied by Edfeldt et al. but no specific gene expression profile could distinguish between liver metastases and lymph node metastases [33–35]. Nevertheless, a frequent chromosome 18 loss was associated with ileal NET, which rapidly metastasizes to the liver [33–35]. This and other results provide some evidence that chromosomal instability would increase the metastatic potential of NET [33–35].

For the above reasons, the radical nature of the operation must not be influenced by the size of the tumor.

Walsh et al., in a unicentric, retrospective analysis, revealed that in 70% of the patients with a primary tumor < 10 mm, a lymphatic metastasis was already present [31] (Table 1). Distant metastasis already existed in 33% and the tumor was multifocal in 28% [31]. In this study, only 17% of the patients with small bowel NET < 10 mm had stage pT1 [31]. Almost 60% of the patients already showed a tumor perforation of the tunica serosa (pT3) [31].

Thus, even small tumors already show a locally aggressive behavior. This is remarkable, since the proliferation of these tumors is generally very low. In the studies by Walsh et al., 90% of the tumors were classified as G1 [31]. The observations by Walsh et al. coincide with other larger studies (Table 1) [14, 31, 32, 36]. Predicting outcomes in patients is complex, and data always must be correlated to the cases diagnosed and treated, noting that these remain a small part since early lesions are missing. These tumors are biologically heterogeneous, and outcomes vary depending on whether the disease course is indolent or aggressive. While lymph node status is an important factor in the staging system, current classification does not factor in the extent of lymph node involvement. There was also no connection between the proliferation index (Ki67) and lymph node involvement [14, 31, 32, 36] (Figs. 1 and 2). Other working groups also found no connection between tumor size and prognosis. Still much work has to be done in order to fully understand this disease. Watzka et al. in a collective of 89 patients treated between 1990 and 2014 showed that there was no correlation between tumor size and overall survival [32]. It was also shown that a localized tumor stage (i.e., ENETS European Neuroendocrine Tumor Society stage I and II; pT1–3, pN0, pM0) does not correlate with survival [5, 32] (Table 2).

In contrast, the Surveillance, Epidemiology, and End Results (SEER) database analysis, which included 3548

Table 1 SB-NET behavior. The characteristically indolent growth of NETs has led to their description as cancers in slow motion; however, this slow growth should not be conflated with benign behavior

Author, [reference], year	Number of patients	pT1 N, (%)	Localized N, (%)	Regional Lymph nodes Metastasis N, (%)	Distant Metastasis N, (%)
Scherübl H et al. [36], 2010	21	9/151	8/167	56/168	104/172
		(6)	(5)	(33)	(60)
Walsh et al. [31], 2016	21	3/17	2/14	5/14	7/21
	(< 10 mm)	(17)	(14)	(35)	(33)
Watzka et al. [32], 2016	83	6/83	12/83	13/83	58/83
		(7)	(14)	(16)	(70)
Fata et al. [14], 2017	132	6/132	22/132	29/132	77/132
		(4)	(16)	(22)	(58)

Metastases at presentation are seen in approximately 30% of patients with SB-NETs in large, population-based database studies and in more than 60% of patients at large referral centers

patients with small bowel NET, identified the primary tumor size as a risk factor for overall survival [20].

For the above reasons, after the diagnosis of SB-NET, thorax X-ray, CT or MRI of the abdomen, and pelvis coupled with somatostatin receptor scintigraphy (SRS) should be done to assess disease extent and search for distant metastasis [37]. Liver MRI, which is more selective than a CT scan for the detection of liver metastases, is usually required to characterize their resectability [37]. Liver MRI should include T2-weighted sequences and diffusion-weighted sequences, which are more sensitive [37]. Liver metastases can be classified into three groups: one metastasis of any size (type I); one metastasis accompanied by smaller lesions in both lobes (type II); and disseminated metastatic spread with both liver lobes always involved (type III) [37].

For mesenteric lymph node metastases, the challenge is not the identification of the lesion but the assessment of its resectability [37]. For a precise assessment, attention must be focused on the first jejunal arteries located along the right side of the mesenteric artery on both axial and frontal slices, on an early arterial phase contrast-enhanced abdominal-pelvic CT and/or MRI [37]. At least three free jejunal arteries have been arbitrarily deemed necessary to preserve a sufficient length of vascularized residual small bowel [37–39].

In SB-NET, carcinomatosis and ovarian metastases are, respectively, found in 20% and 4% of patients [1–5]. As in other diseases, the sensitivity of CT, MRI, and metabolic imaging is poor for the detection of peritoneal carcinomatosis [37, 40].

The Limit of Laparoscopic Surgery

Any surgical procedure should follow the principles of oncological surgery [23, 40]. A carcinoma's multifocality

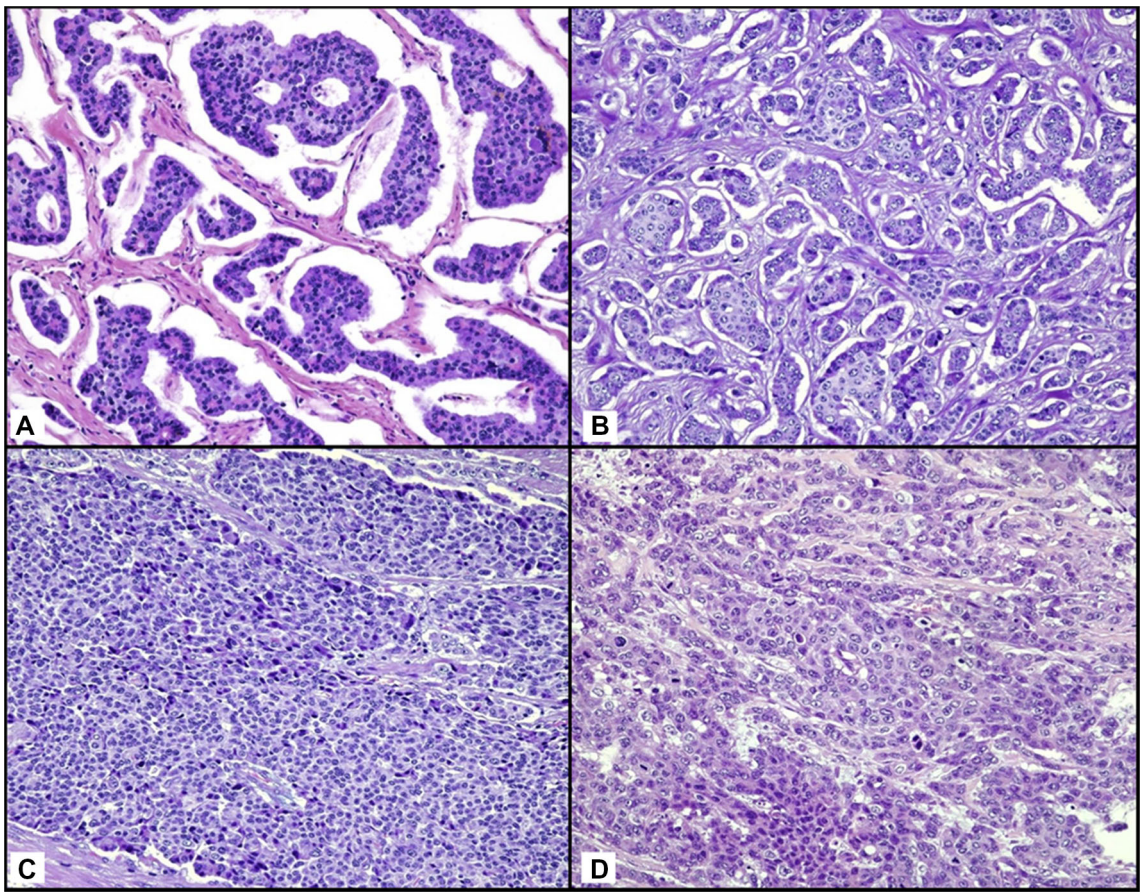

Fig. 1 Histologically well-differentiated NET G1 displays a trabecular-glandular architecture composed of uniform epithelial elements with abundant cytoplasm, bland nuclei with salt and pepper chromatin. Rare mitotic figures (**A** haematoxylin and eosin stain; original magnification, ×200). The typical trabecular pattern with mild atypia and coarser chromatin of neoplastic elements in well-differentiated NET G2 (**B** haematoxylin and eosin stain; original magnification, ×200). The morphology of well-differentiated NET G3 in solid nests arrangement showing cells with vesicular nuclei, rare slight nucleoli, and moderate amphophilic cytoplasm (**C** haematoxylin and eosin stain; original magnification, ×200). Poorly differentiated NEC characterized by large cell types with a high nucleus-to-cytoplasm ratio, hyperchromatic nuclei, vesicular chromatin, and prominent nucleoli. Note multiple mitotic figures. (**D** haematoxylin and eosin stain; original magnification, ×200)

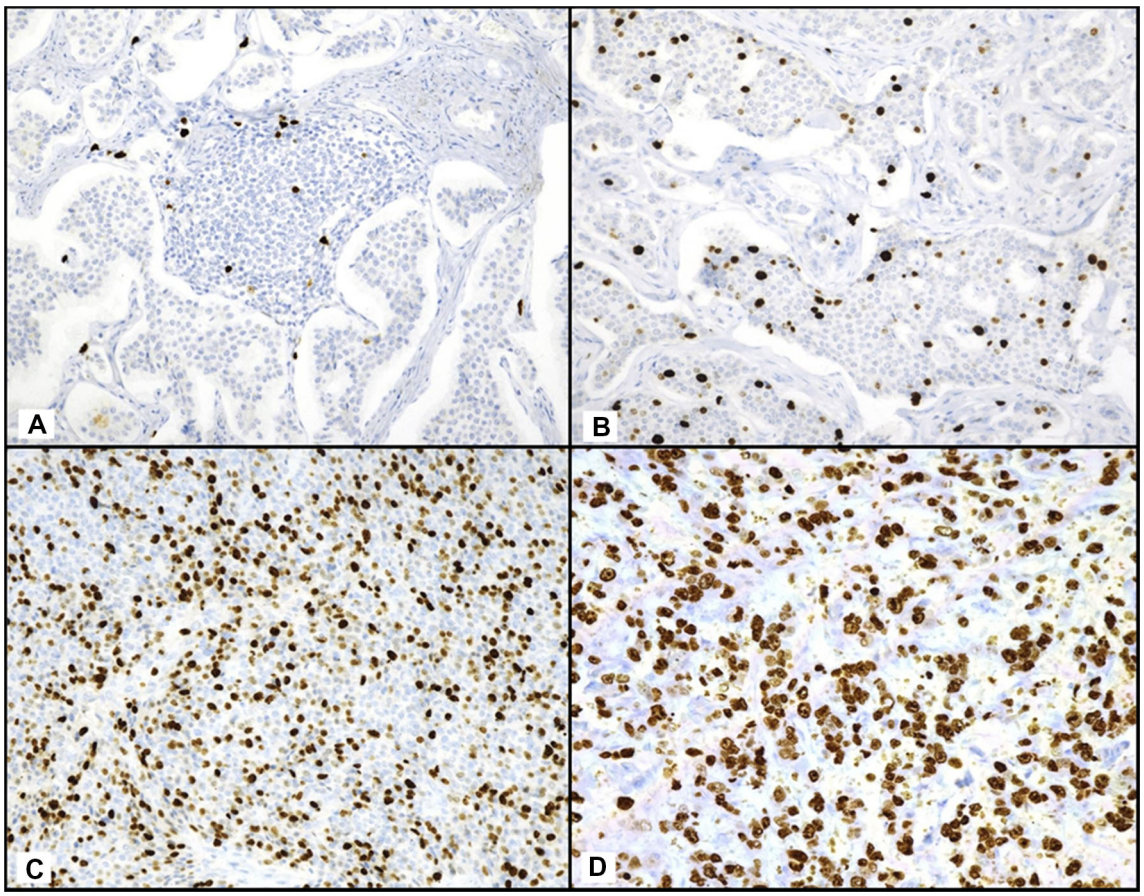

Fig. 2 Ki67 labeling index distribution in neuroendocrine tumors: < 3% in well-differentiated NET G1 (A, Mayer's haemalum counterstain. Original magnification ×200); 3–20% in well-differentiated NET G2 (B, Mayer's haemalum counterstain. Original magnification ×200); > 20% in well-differentiated NET G3 (C, Mayer's haemalum counterstain. Original magnification ×200); > 20% in poorly differentiated NEC (D, Mayer's haemalum counterstain. Original magnification ×400)

Table 2 UICC/ENETS stage grouping for SB-NET

Stage	Primary tumor *	Regional lymph node ^	Distant Metastasis §
Localized			
I	pT1	pN0	pM0
IIa	pT2	pN0	pM0
IIb	pT3	pN0	pM0
IIIa	pT4	pN0	pM0
Regional			
IIIb	Any T	pN1	pM0
Metastatic			
IV	Any T	Any N	pM1

Staging does not include if the tumor is functioning or not, single vs. multiple primary tumors, the miotic count, Ki-67 index, tumor size, the presence of carcinosis, surgery with macroscopic radical intent, resectable or unresectable distant metastases

ENETS European Neuroendocrine Tumor Society, *UICC* Union for International Cancer Control

[*] *T1* tumor invades lamina propria or submucosa, *T2* tumor invades muscularis propria, *T3* tumor invades through muscularis propria into the submucosa, *T4* tumor perforates the vascular peritoneum or directly invades other organs, including mesentery, abdominal wall, and pancreas

[^] *N0* no regional lymph node metastases, *N1* regional lymph node metastases

[§] *M0* no distant metastasis, *M1* distant metastasis

is defined by multiple separate tumors at the primary site, which may be due to cancer-priming local factors leading to polyclonal tumor growth, predisposing germline variants, or monoclonal local spread [41].

SB-NET often displays a curious synchronous multifocal phenotype with several intestinal tumors centered around a regional lymph node metastasis. Adjacent or distant, often smaller, difficult to localize preoperatively, multiple SB-NET may be revealed in one third of the patients (Table 3) [12, 21, 25, 31]. Often these multiple primary tumor foci can only be identified thorough palpation [23, 40]. At the beginning of the surgical procedure, the small bowel needs to be palpated in its full length to detect or exclude multifocal disease [23, 40].

The current ENETS guidelines rightly point out that the advantages of laparoscopic resection must be critically contrasted with the risk of incomplete and less radical surgery in systematic lymphadenectomy [23].

The study by Ethun et al. shows that a multifocal tumor was identified in only 21% of the patients during the laparoscopic operation. In contrast, a multifocal primary tumor was found in 50% of the patients in the context of open exploration and resection [12]. Laparoscopic approaches resected fewer tumors compared to open approaches (1.5 vs. 4; $P = 0.034$). The rate of identified primary tumor sites in the open operation was on average 4.9, more than twice as high as in the minimally invasive operation [12].

Another concerning argument against the minimally invasive approach is challenging vascular dissection due to large mesenteric masses and infiltration of mesenteric vessels.

Currently, there is still a lack of comparative studies between laparoscopic and laparotomic approach in SB-NET resection due to the low volume of cases.

A recent survey by Kaçmaz et al. [42] offers a realistic overview of the use of a laparoscopic approach in SB-NET surgery. For a total of 58 respondents, 42% preferred an open approach, 44% a laparoscopic approach, and 14% a robotic approach. More accurate lymphadenectomy and pathologic staging along with more complete resection are the most reported reasons to prefer an open approach.

With the reported statements, we do not want to exclude the importance of laparoscopy in intestinal staging and resections; rather, we want to remember that if the resection is laparoscopic, a careful extracorporeal evaluation of the intestine is important, as well as the experience of the surgeon.

The Question of Prophylactic Cholecystectomy

Somatostatin analogs (SSA) are the mainstay of NET treatment [23].

Biliary stone disease is reported as a common side effect of SSA, with a frequency ranging from 10 to 63% [23]. Studies on SSA-treated patients for acromegaly report an increased incidence of biliary stone disease compared with the general population, whereas there are limited data on patients with NET [43].

Cholecystolithiasis favored by SSA is usually asymptomatic [23, 40]. A prophylactic cholecystectomy as part of the resection of the SB-NET was therefore advocated.

However, the current ENETS guidelines indicate that the evidence for this recommendation is low [23]. It is based on a single retrospective study on 144 patients, 15% of whom developed gallbladder-associated complications during SSA therapy [24]. In most cases, again, this is asymptomatic [30].

A routine cholecystectomy must be indicated in individual cases [23, 40]. Especially in the localized stage, when postoperative SSA therapy is not indicated, the indication should always be critically examined [23, 40]. Prophylactic cholecystectomy must be critically examined in particular in the case of localized neuroendocrine tumors of the small intestine and the lack of an indication for SSA therapy [23, 40].

Table 3 Frequency of the multifocal SB-NET

Study, [reference], year	Number of patients N	Multifocal primitive tumor N, (%)
Ethun et al. [12], 2016	93	34 (36)
Lardiere-Deguelte et al. [21], 2016	72	37 (51)
Pasquer et al. [25], 2016	21	7 (33)
Walsh et al. [31], 2016	21 (< 10 mm)	6 (28)

Notably, adjacent lymph node metastases arose from a single, typically centrally located, SB-NET. Multifocal SB-NETs form may represent a primarily independent somatic evolution rather than local metastatic spread

The limitation of this statement is that sometimes the above SB-NET features (i.e., staging) are only known after surgery.

Clinical Significance of Lymph Node Metastasis

The neuroendocrine tumors of the small intestine are characterized by early lymph node metastasis (Table 1). It is not possible to safely rule out lymphatic spread on the basis of tumor size or other parameters, so that systematic lymphadenectomy is an important part of surgical therapy [40]. This is especially true under the aspect that the lymph node metastases are often larger than the primary.

Furthermore, the current staging guidelines for SB-NET differentiate between the presence (N1) and absence (N0) of lymph node metastases. De facto, in both the American Joint Committee on Cancer (AJCC) and ENETS staging classifications, SB-NET are classified as an N0 or N1 disease based on the absence or presence of lymph node metastases, respectively (Table 2). Thus, accurate N staging of SB-NET is critical for patient management and research [40].

Kim MG et al., used the Surveillance, Epidemiology and End Results (SEER) database to identify patients with histologically confirmed, surgically resected SB-NET diagnosed between 1988 and 2010 [44]. Patients were classified into three groups by the lymph node ratio (number of positive lymph nodes/number of total lymph nodes examined, LNR): ≤ 0.20, > 0.20–0.5, and > 0.5. The Author identified 2,984 surgically resected patients with stage IIIb (N1, M0) SB-NET with detailed LN data [44]. Higher LNR was significantly associated with worse SB-NET cancer-specific survival ($p < 0.0001$). Ten-year NET-specific survival was 85%, 77%, and 74% for patients in the ≤ 0.2, > 0.2–0.5, and > 0.5 LNR groups, respectively. In stratified analyses, higher LNR groups had worse survival only in early tumor (T1, T2) disease ($p < 0.0001$) [44]. The Authors concluded that the extent of LN involvement provides independent prognostic information in patients with LN positive SB-NETs [44]. This information may be used to identify patients at high risk of recurrence and inform decisions about use of adjuvant therapy.

Watzka et al. showed that systematic compared to selective lymphadenectomy offers a clear survival advantage (70% vs. 40%, 10-year survival rate; [32]). The working group regards more than 6 resected lymph nodes as the limit value for systematic lymphadenectomy. The extent to which the number of resected lymph nodes has a prognostic significance and potentially stands as a surrogate marker for the quality of the operation has not been conclusively clarified. The ENETS guidelines do not give any recommendations regarding the minimum number of resected lymph nodes [23].

In the study by Landry et al., the removal of 8 or more lymph nodes is identified as a positive prognostic parameter (hazard ratio [HR] 0.66, $p = 0.023$; [20]). However, other groups could not find any direct correlation between the number of removed lymph nodes and survival [25].

In addition to the absolute number of distant lymph nodes, the ratio of affected lymph nodes to the total number of lymph nodes also seems to play a role [40]. The data from Landry et al. show that a proportion of $> 29\%$ positive lymph nodes correlates significantly with survival (HR 1.5, $p = 0.03$) [20].

Lymph Node Dissection

In patients with SB-ET, surgical resection of the primary tumor and associated mesenteric LNs is recommended, but is not well standardized and can be risky in patients with superior mesenteric vessel involvement [40].

Between July 2013 and December 2015, all consecutive patients who underwent resection of at least one SB-NET in the European Neuroendocrine Tumor Society Center of Excellence were prospectively included [23]. The resection and pathological analysis of LNs were standardized using three groups: group 1, along the small intestine; group 2, along the mesenteric vessel; and group 3, retropancreatic and mesenteric vessel origin [23]. Twenty-eight patients with SB-NET resection were prospectively enrolled in the study, with seven patients being excluded from the analysis because it was impossible to divide the operative piece into nodal groups due to retractile mesenteritis. Among the remaining 21 patients, 95% had LNs involved; 8 (38%) in group 1, 13 (62%) in group 2, and 12 (57%) in group 3. Skip metastases were found in 67% of patients: 19% with an invasion pattern of group 3 + without group 2 + , and 57% with an invasion pattern of group 2 + or group 3 + without group 1 + . The authors nicely concluded that as a result of skip metastases, systematic, extensive LN resection in retropancreatic portion may be required to prevent unresectable locoregional recurrence [23].

Lardiere-Deguelte et al. evaluated the correlation between the length of resected small bowel and the number of removed LN, and proposed a preoperative morphological classification of SB-NET-associated LN [21]. The records of patients operated on for SB-NETs at two expert centers between August 2005 and November 2013 were analyzed [21]. Two specialist radiologists reviewed the preoperative imaging and classified mesenteric LNs into five stages according to their proximity to the trunk and/or branches of the superior mesenteric artery. 72 patients were included. The mean number of removed LNs was 12 ± 15, and the length of removed small intestine was 53 ± 43 cm.

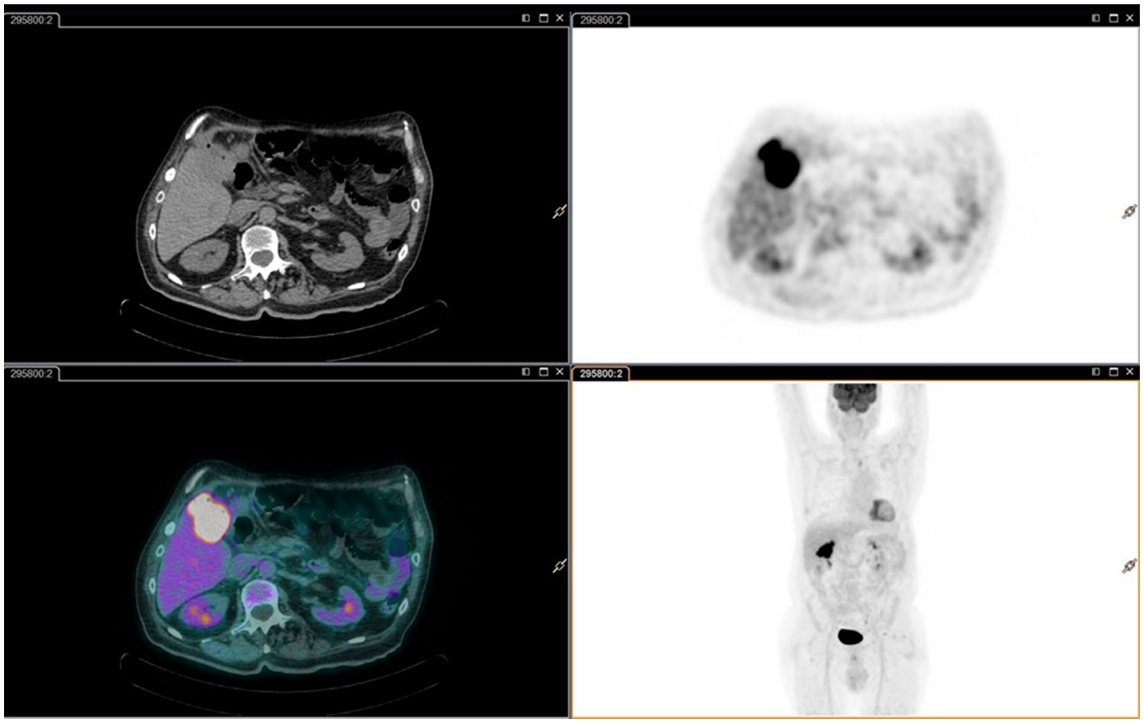

Fig. 3 SB-NET hepatic metastasis

No correlation existed between the length of small bowel resection and the number of removed LNs. Overall, 12%, 18%, 50%, 19%, and 0 patients were classified into LN stages 0, I, II, III, and IV. The correlation rate between the two observers was 0.98. Patients with LN stage III (hardly resectable) had more removed LNs than those with LN stages 0, I, or II (easily removable). The authors concluded that optimal lymphadenectomy is not always associated with extended small bowel resection [21]. In the era of small bowel-sparing surgery, the preoperative classification of mesenteric LNs could help to standardize the surgical management of patients with SB-NETs.

The Effect of Mesenteric Fibrosis

SB-NET is associated with the development of mesenteric fibrosis [44, 45]. This mesenteric involvement often leads to a desmoplastic reaction of the connective tissue with shortening of the mesentery [44, 45].

Even with small, localized SB-NET, mesenteric fibrosis occurs in around 10% of cases [7, 18]. In the study by Gonzales et al., the mean tumor size in the patients with mesenteric tumor mass was 1.8 cm, compared to a size of 1.5 cm in the patients who had no mesenteric tumor mass [18]. Mesenteric fibrosis without evidence of a mesenteric tumor mass is significantly less common (44% vs. 96%, $p < 0.01$) [7, 18, 44, 45]. Mesenteric fibrosis is present in approximately 50% of patients with mesenteric lymphadenopathy [7, 18, 43, 44].

Typically, the presence of mesenteric desmoplasia is determined radiologically or at surgery [44, 45].

Mesenteric fibrosis remains an under-researched area of neuroendocrine neoplasia and its pathophysiology is poorly understood [46, 47]. The importance of serotonin and other cytokines released from tumor cells may induce fibrosis, leading to carcinoid heart disease and abdominal fibrotic reactions, is still debated. However, no drug treatment options can currently be derived from this. Surgery is the only treatment option [46]. The mesenteric fibrosis and tumor mass have a decisive influence on surgical therapy and strategy. Mesenteric fibrosis is associated with significant morbidity (mechanical ileus, intestinal ischemia, and/or obstructive uropathy) and may also adversely affect patient prognosis (hepatic metastasis, stage IV) and overall survival [44–46]. The presence of fibrosis often leads to the conversion of the operation from laparoscopy to open surgery. The risk of mechanical ileus due to mesenteric fibrosis is high and is over 25% [46]. Especially when the fibrosis encloses the superior mesenteric artery or vein, the possibility of a curative resection is limited. Short bowel syndrome, malabsorption, and malnutrition are other postoperative morbidities (Fig. 4) [46].

Increased awareness and improved understanding of the molecular pathogenesis of mesenteric fibrosis in SB-NENs may provide better diagnostic and predictive tools for its

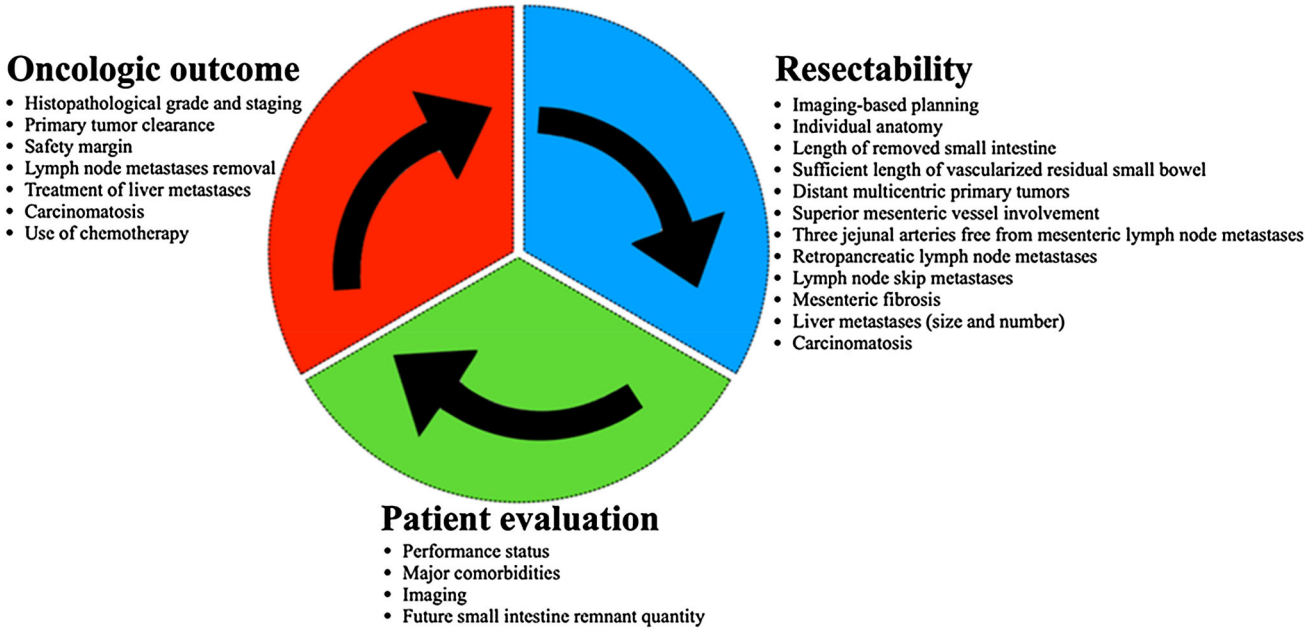

Fig. 4 Risk assessment, decision-making, and oncological outcomes in SB-NET resection

timely recognition and intervention and also facilitate the development of agents targeting mesenteric fibrosis [47].

Surgical Strategy for Distant Metastases

In SB-NETs, metastasis is often already present at the time of the first diagnosis [48, 49]. It is still questionable whether stage IV primary tumor resection (PTR) offers a survival advantage [48, 49]. Few studies have examined the effect of primary site and grade on resection and survival [48, 49].

In particular, the palliative, prophylactic intervention of SB-NET in the presence of synchronous hepatic metastatic disease is often questioned [48, 49] (Fig. 3). The aim of a recent study by Lewis A. et al. was to determine the results of primary tumor resection in metastatic neuroendocrine tumors at all primary tumor sites [48]. In detail, this is a retrospective study of patients with metastatic SB-NETs at presentation between 2005 and 2011 using data from the California Cancer Registry (CCR) combined with the longitudinal database of hospitalized patients of the California Office of Statewide Health Planning and Development (OSHPD). The primary outcome of the study was overall survival (OS). The study included a total of 854 patients with metastases at presentation who underwent 392 PTRs. Liver metastases occurred in 430 patients; 240 received one or more liver treatments. PTR improved OS in patients with untreated metastases (median survival 10 vs 38 months, $P < 0.001$). On multivariate analysis for demographics, tumor stage, histopathological grade, use of chemotherapy, Charlson comorbidity index, primary tumor location, or treatment of liver metastases, PTR with / without liver treatment improved OS compared with no treatment [hazard ratio (HR) 0.50, $P < 0.001$ and 0.39, $P < 0.001$, respectively]. Additionally, PTR offered a survival benefit at all grades (low grade, HR 0.38, $P = 0.002$, and high grade, HR 0.62, $P = 0.025$) [48].

The authors conclude that PTR of SB-NET is associated with improved survival, with or without treatment of liver metastasis, and regardless of tumor grade. This study supports primary tumor resection in patients with metastatic SB-NETs, regardless of liver treatment [48].

In addition, the median survival of a stage IV SB-NET was 17 months. When liver-directed metastasis therapy was performed at the same time, the survival advantage was even more pronounced (HR 0.39, $p < 0.001$) [48].

The results of this retrospective study, however validly documented on the basis of the large data set, justify the authors' recommendation to consider a PTR despite liver metastases in gut NET, at least on an individual basis [48, 49] (Fig. 4).

Conclusions

SB-NET are rare tumors. However, their incidence is increasingly reported in recent years.

Local extension, lymph node infiltration, distant metastases, mesenteric fibrosis, and mesenteric vessels involvement are controversial keypoints of this type of tumors.

Although advances in diagnosis and therapy have been made, there are still unsolved questions about their SB-NET management and surgical approach, owing to the rarity of these tumors and the difficulty to perform comparative studies.

Choice of the most appropriate surgical approach has to be tailored to the patient, as well as staging and pathologic features of the tumor. Surgical approaches for SB-NET are challenging and demand a high level of experience and skills, owing to the high risk of complications related to the extension of the tumor.

Accurate planning of the surgical approach in a multidisciplinary setting with pathologists, radiologists, and endocrinologists is crucial.

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Compliance with Ethical Guidelines

Conflict of interest No Authors of this study have financial relationships with the surgical industry or other personal, professional, or financial conflicts of interest in the publication of this study.

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