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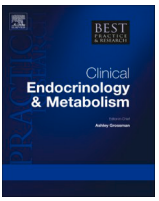

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Optimal surgical approach for digestive neuroendocrine neoplasia primaries: Oncological benefits versus short and long-term complications

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The rising incidence and the accumulating prevalence of neuroendocrine neoplasia (NEN) in the population makes this a common, prevalent and a clinically relevant disease group. Surgical resection represents the only potentially curative treatment for digestive NENs. Thus, resection should in principle be considered for all patients with NEN, although taking the patients age, relevant comorbidity, and performance status into account for operability. Patients with insulinomas, NEN of the appendix and rectal NENs are usually cured by surgery alone. However, less than a third of patients are amendable to curative surgery alone at time of diagnosis. Furthermore, recurrence is common and may occur years after primary surgery, hence the long follow-up time recommended in most NENs (> 10 years). As many patients with NENs present with locoregional or metastatic disease, there is considerable debate regarding the role of debulking surgery in these settings. However, good long-term survival can be achieved in a considerable proportion of patients, with 50–70% alive up to 10 years after surgery. Location and grade are the main determinants of long-term survival. Here we present considerations to surgery for primary neuroendocrine tumors in the digestive tract.

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Introduction

The incidence of neuroendocrine neoplasia (NEN) is increasing, as documented across several population-based investigations [1–5]. The crude incidence is reported to be 6–7 per 100.000 per year [1,3,4], which is a doubling compared to incidence rates only two decades ago and a 6-fold increase since the early 1970s [4]. The increase is likely due to better detection by widespread use of cross-sectional imaging in the population, increased knowledge about this disease among clinicians and pathologists, and better classifications of the disease. However, an actual increase in the disease may not be excluded, although no well-known risk factors of exposure have been identified. Some NEN develop on a background of genetic syndromes, most notably multiple endocrine neoplasia (MEN1) and von-Hippel-Lindau disease (VHL) and occasionally tuberous sclerosis complex (TSC) [6]. Due to an overall good prognosis and improvements in disease control, the prevalence has been estimated to be around 35 per 100,000 population, with the real prevalence possibly much higher due to change in actual disease recognition.

For each separate organ location, NENs are relatively rare tumors with a wide spectrum of presentation and outcomes. However, collectively, the rising incidence and the accumulating prevalence of NEN in the population makes this a common, prevalent and a clinically relevant disease group. Indeed, GEP-NENs are proposed to be collectively the second commonest of digestive cancers in terms of prevalence [7]. NENs may develop in the lung and thymus, but location in the luminal gastrointestinal (GI) tract or pancreas makes up the majority, reported from 55% to 70% (Fig. 1) and collectively known as gastroenteropancreatic NENs (GEP-NENs) [8,9]. GEP-NENs constitute a heterogeneous group of tumors and may present in many different ways, although an increasing number of patients are presenting as "incidentalomas" (small, indolent lesions detected during work-up for different indications). However, a considerable delay from onset of symptoms to eventual diagnosis is characteristic for several of these tumors. This review will focus on the role of surgical resection in primary GEP-NENs and considering the complications, and short and long-term outcomes to this disease group. A brief overview of diagnosis, role of resection and the potential complications from surgical treatment will be discussed. Specific points for each anatomical location will be discussed from GEP-NENs covering the upper to the lower gastrointestinal tract.

Diagnostic work-up

In primary NEN, cross-sectional imaging may suffice to pursue surgical resection for some patients, e.g. patients presenting urgently with small bowel obstruction or with symptomatic/emergency presentation. In most other situations, decision-making is based on a proper diagnosis based on proper cross-sectional imaging by means of a multi-phase, contrast-enhanced computed tomography (CT) with

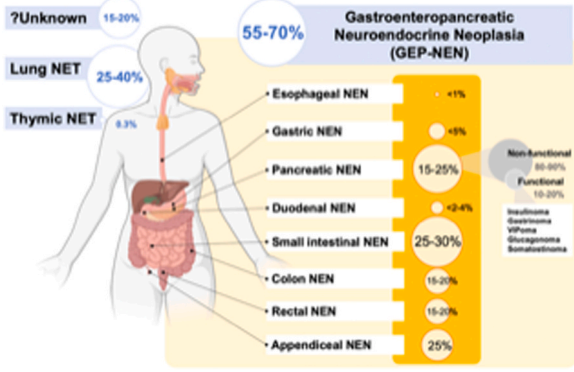

Fig. 1. Distribution of neuroendocrine neoplasia by anatomical location. Legend: Distribution according to best estimates accumulated from several epidemiological studies.

or without magnetic resonance imaging (MRI) scanning for evaluation of diffusion-weight imaging [10] or presence of metastasis to the liver. However, specific functional imaging has an increasing role in diagnosis and staging. Functional imaging involves nuclear imaging techniques that help in predicting biological behavior in vivo, staging, and diagnosing certain NENs, which are otherwise occult on conventional imaging by CT/MRI. Hence, functional imaging may include somatostatin receptor scintigraphy, 18-FDG PET, and 68-Galium DOTA-PET [10–12].

While liquid biopsy-based diagnostic tests such as the NETest has been proposed this is not in widespread use [13]. Diagnosis should be made by biopsy or surgical resection for histological evaluation as fine needle aspiration or cytology is insufficient for a specific diagnosis and evaluation of proliferation. Tissue-based markers such as the insulinoma-associated protein 1(INSM1) has robust diagnostic properties but has yet to replace other conventional markers [14]. The updated World Health Organization (WHO 2019) classification separates NENs into 4 grades (Table 1). The G3 NENs and NECs are overlapping (Fig. 2), and shown to be a quite heterogeneous patient group concerning prognosis and treatment benefit, depending on factors such as the primary tumor site, differentiation, proliferation rate, and molecular alterations [15–17].

Surgery for primary NENs according to location

National and international guidelines recommend surgery for most primary NENs[9,18–29]. Surgical resection represents the only potentially curative treatment for GEP-NENs. Thus, resection should in principle be considered for all patients with NEN, although taking the patients age, relevant comorbidity and performance status into account for operability[30]. In particular, some elderly patients with incidental or law grade NENs may be at higher risk from surgical morbidity and mortality than their overall life-time risk of cancer-related deaths. Hence, the all-cause risk of death needs to be weighed against the intentional benefit of the specific location and cancer-surgery needed to remove any NEN lesion (Table 2). Also, less invasive strategies (e.g. endoscopic removal in the stomach) are available in some locations, with higher risk of recurrence (that can often be treated with re-resection endoscopically) but similar overall survival reported[31].

Surgery is the main treatment for most NENs and is provided to 71% of patients, followed by use of (alone or in addition) somatostatin analogues (32%), chemotherapy (20%), peptide receptor radionuclide therapy (PRRT) (9%) and targeted therapies (8%) [32]. Patients with insulinomas, NEN of the appendix and rectal NENs are usually cured by surgery alone. In general, due to the biology and nature of presentation, less than a third of patients are amendable to curative surgery alone at time of diagnosis. Furthermore, recurrence is common and may occur years after primary surgery, hence the long follow-up time recommended in most NENs (> 10 years). As many patients with NENs present with locoregional or metastatic disease, there is considerable debate regarding the role of debulking surgery in these settings. This will be discussed for the specific locations, in the specific paragraphs below.

Complications after surgery for GEP-NENs

The rate of complications after surgery is largely described in retrospective, single-center cohort studies. However, a large registry-based cohort study from the EUROCRINE database explored the

Table 1
WHO 2019 classification for NENs of the digestive system.

Grade	Mitotic count (2 mm^2)[a]	Ki-67 Index (%)[b]	Morphology
G1	< 2	< 3	Well differentiated NETs
G2	2–20	3–20	Well differentiated NETs
G3	> 20	> 20	Well differentiated NETs
NEC	> 20	> 20	Poorly differentiated NECs

NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumour; WHO, World Health Organization, HPF, high power fields

[a] 10 HPF = 2 mm^2, at least 40 fields (at ×40 magnification) evaluated in areas of highest mitotic density.

[b] MIB1 antibody; percentage of 500–2000 tumour cells in areas of highest nuclear labelling.

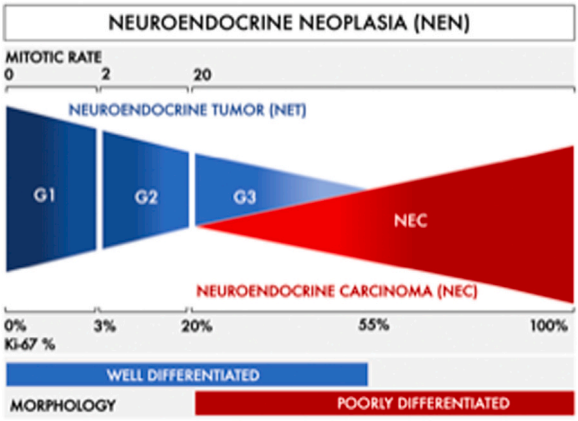

Fig. 2. Grading criteria for NENs into NETs and NEC. Legend: Separation of NEC into Ki-67 ≥ 55% defines a further particular subgroup of tumors with prognostic, therapeutic and clinical relevance.

Table 2
Short-term and long-term complications.

Organ location	Resection*	Short-term risk**	Long-term risk
Esophagus	Local excision	Leakage	Recurrence risk
	Esophagectomy	Anastomotic leak Periop complications	Local symptoms; nutritial/ stenosis
Stomach	Local excision	Recurrence Perforation	Recurrence
	Gastric resection	Anastomotic leak Delayed gastric emptying	Local symptoms; nutritial issues; anastomotic stenosis
Duodenum	Pancreatoduodenectomy	Pancreatic fistula risk (15–30%) Post-op complications/ morbidity in up to 50%	Exocrine and endocrine insufficiency
	Local excision	Leakage	Stricture (rare)
Small Bowel	Small bowel resection	Loss of small bowel Remaining length Anastomotic leak	Adhesions Short-bowel syndrome Fibrosis/desmoplasia
Pancreas	Pancreatoduodenectomy	Pancreatic fistula rate 15–25% Post-op complications/ morbidity in up to 50%	Exocrine and endocrine insufficiency
	Distal resection	Pancreatic fistula 20–30% Post-op morbidity less compared to pancretoduodenectomy	Exocrine and endocrine insufficiency
	Local resection (enucleation)	Pancreatic fistula 13–27%	Recurrence
Colon	Segmental resection	Anastomotic leak < 3–5%	Recurrence
Rectum	Local excision Total mesorectal excision Rectal amputation Pelvic exenteration	Recurrence Anastomotic leak	Recurrence Function, LARS

* Procedure complications in short term are related to the magnitude of the intervention, e.g. for endoscopic procedures typically perforation or bleeding. For organ resections, it follows the typical pattern of the type of surgery involved.

** most risk profiles follow that for conventional organ surgery, however a recognized higher risk for post-operative pancreatic fistulae is noted for pancreatic resections due to a typically soft gland and a small duct (both pancreatic and biliary duct), compared to surgery for other cancers. Distal pancreatic resections may have higher risk of post-operative fistulae, but usually of lesser severity.

complication rate in 376 patients with GEP-NEN having undergone resection [33]. In the EUROCRINE cohort study, severe complications (Dindo-Clavien ≥ 3) occurred in 56 (14.9%) patients, with 1.1% perioperative mortality. Severe complications occurred significantly more frequent in surgery for pancreatic or duodenal NENs (n = 31; 22.0%) compared with small intestinal NENs (11.4%), in patients with lymph node metastases operated with curative aim of surgery (n = 24; 21.4%) versus non-metastasized tumors or palliative surgery (n = 32; 12.1%) (p = 0.020), and in functioning tumors (n = 20; 23.0%) versus non-functioning tumors (n = 30; 13.5%) (p = 0.042). Complication rates were not significantly associated with tumor stage or grade.

While this study gives an overview of the collective complication rate, the specific risk for any individual is based on the location of the tumor and the tumor burden and the comorbidity and performance score of the patient. Hence, a limited small bowel resection for a small intestinal NET may have a considerable different risk-profile compared to a large Pancreatic NET requiring a pancreatoduodenectomy with concomitant portal vein resection and reconstruction (Table 2). Thus, the specific complications and considerations are best discussed for each location and for the individual patient.

Esophageal NET

Esophageal NENs are very rare and make up < 1% of all GEP-NENs (Fig. 1). Most cases are incidental findings found on endoscopy [34,35]. In Japan, esophageal location contributes to 5.8% of all NECs [36]. Based on data obtained from the Surveillance, Epidemiology, and End Results (SEER) database, more than 50% of esophageal NECs present with metastasis at time of diagnosis [37]. In a study from the National Cancer database (NCDB) in the Unites States, esophageal NETs made up < 0.01% of all esophageal cancers treated between 2004 and 2017 [38]. Median age at presentation was 65 years and two-thirds were male. In this study [38], over 43% had metastasis at presentation, and were more likely to present with advanced stage (T4 tumors) compared to other cancers in the esophagus. Esophageal NETs were also less likely to undergo surgical resection (done in only 28%), and < 19% had a local resection [38]. Surgery was associated with favorable survival, also when compared to propensity-score matched patients with regular adenocarcinoma of the esophagus. Patients who received systemic (neoadjuvant) chemotherapy had better outcomes [38]. The data compares to a similar study from the US [39], but both are hampered by the administrative registry nature of data, with no regular NEN classification to guide the prognosis.

No standard treatment is established for esophageal NECs, but observations suggest that surgery with chemotherapy is associated with improved outcomes.

Gastric NETs

Gastric neuroendocrine tumors (NETs) make up < 7% of all neoplastic lesions in the stomach [40]. Type I and II gastric NETs are usually incidental findings during upper gastrointestinal endoscopy, with type I caused by chronic atrophic gastritis and type II developing in patients with gastrin-producing NETs [41,42]. Gastric NETS are usually multiple, small (< 2 cm) and have a low Ki-67% index (≤5%). Evaluation by endoscopic ultrasound and surveillance is recommended. Local excision by endoscopic techniques may be performed in most, while surgery is reserved for those with multiple, or large lesions or lesions invading into the muscularis propria. Lymphovascular invasion (LVI) may also prompt a different treatment than endoscopic resection, usually by gastrectomy according to location.

Type III gastric NETs make up < 20% of all gastric locations. These lesions are sporadic, and not associated with hypergastrinemia, and may present with dyspepsia, bleeding, or obstruction. More than half of patients have metastasis at time of diagnosis, and for those systemic therapy is indicated. Surgical resection should be performed in patients who are operative candidates and have localized disease, in a similar manner as for gastric adenocarcinoma employing a partial or subtotal gastrectomy with lymphadenectomy [18]. However, some emerging data suggest that surveillance or endoscopic resection may be a feasible option to some of the type III gastric NENs [43], particular those of grade 1 or 2 and of smaller size (< 10 mm).

Duodenal NETs

Duodenal NETs are usually detected as an incidental finding during endoscopy [18] but considerable heterogeneity in presentation, treatment and outcome exist for duodenal NETs [44]. More than 50% may have metastatic disease at time of presentation [44,45].

If located away from the ampulla and staged as a small (≤10 mm), localized, grade 1, non-functioning, NET this lesion can be locally resected by endoscopy or surgery, or considered for surveillance [46–48] with 5-year recurrence free survival reported at 90% [49]. Such small duodenal NENs behave indolently with very low risks of progression and no tumor-related deaths [50]. "Watch and wait" appears to be a safe alternative management strategy for selected duodenal NETs, although some investigators question the safety of this approach [45].

Duodenal NETs located at or near the ampulla of Vateri should be resected. A NEN location at or near the Ampulla that is not amenable to endoscopic removal would necessitate a pancreatoduodenectomy in operable patients for radical resection as this allows for appropriate lymph node harvest and staging [45,51]. A transduodenal ampullectomy can be considered in select patients.

Functional NETs in the duodenum are rare but require resection. A systematic review of 43 patients of ampullary somatostatinoma reported good outcomes and survival up to 13 years after resection[52]. The most common functional NET in this area is however found as part of the gastrinoma complex (Zollinger-Ellison syndrome) for which most are sporadic[53], but a hereditary background as for MEN-1 should be considered in these lesions.

Pancreas NETs

Pancreatic neuroendocrine tumors (PanNET) have an increasing incidence and a reported unfavorable prognosis compared to other NEN primaries. The majority of pNET are non-functional without hormonal activity (80%). Besides functional syndromes, size is a key determinant for treatment decision-making (2 cm cut off). Histologic or cytologic diagnosis should be performed, mostly via endosonographic route, with demonstration of endocrine markers and proliferation index (Ki-67) to grade the lesion accordingly. Analysis of DAXX/ATRX loss and expression of Somatostatin Receptor (SSTR) is recommended to stratify for biological behavior and indication for surgery [54,55]. To date, no clear recommendation for biomarkers can be made, but chromogranin A (CgA) might be useful to monitor the disease [56]. More recently the NETest, a multigene liquid biopsy blood biomarker panel has shown potential in the initial diagnoses and prediction of recurrence of disease in multiple neuroendocrine tumors, including pNETs [13].

After complete staging, including CT with arterial-phase contrast and preferably PET (SSTR) imaging, the local extent of the tumor and its resectability must be elucidated. Pancreatic surgery has a reported morbidity of up to 50% and mortality of less than 3% in experienced high-volume centers [57–59]. Therefore, a careful risk– benefit ratio has to be assessed, especially in small lesions with indolent biological behavior and slow tumor growth. Additionally, the pancreatic tissue around pNET is usually soft with non-dilated ducts, having an impact on the risk of postoperative pancreatic fistula (POPF) and its associated morbidity [60,61]. Resectability of pNET is not consensually defined, for locally advanced tumors (stage T3 and T4 according to ENETS and AJCC staging systems) the same criteria apply as for pancreatic adenocarcinoma in which the National Comprehensive Cancer Network (NCCN) rules are most widely applied [62].

In general, resection of non-functioning (NF) panNET achieves 5-year survival rates up to 80% [63]. These oncologic results need to be compared with the potential harms of surgery and potential long term endocrine and exocrine complications. Therefore, parenchymal sparing strategies (enucleation) can be considered for small lesions, clear of the main pancreatic duct [64]. However, meta-analysis of this strategy demonstrates association with an increased rate of POPF [64]. Recently, several studies have elucidated the optimal management of small PanNET lesions < 2 cm. Two ongoing prospective trials – PANDORA [65] and ASPEN [66] have shown stable disease in 80% of patients during careful surveillance at interim analyses.

In patients with panNET and non-resectable metastasis, the role of primary tumor resection is controversial. In some register-based series that may be prone to selection bias, there is a reported overall survival benefit with resection of the primary tumor [67]. The re is very little data to support

resection and none of the existing guidelines provide any vetted information on this controversial topic [68]. Comparison of historic data may also be difficult, as treatments options have changed and institutional variation in aggressiveness hampers comparison across series. However, reasonable long-term survival can be expected in selected patients when multimodal therapies can be applied [69,70].

Small intestinal NETs

Though small bowel neuroendocrine tumors (SB-NETs) are characterized by slow growth, non-specific symptoms and delays in diagnosis often results in advanced stage presentation (Fig. 3), with up to 30% of patients having metastases at diagnosis [1,4]. Both loco-regional and metastatic SB-NETs can severely impair quality of life. For metastatic disease, the manifestations of carcinoid syndrome are well-described, including flushing, diarrhea, wheezing, and eventually carcinoid heart disease. For loco-regional tumors, 50% of patients will develop mesenteric and retroperitoneal fibrosis due to the fibroblastic reaction surrounding the primary tumor and nodal metastases [71,72]. Such fibrosis can lead to mesenteric angina and ischemia, venous congestion, partial or complete bowel obstruction, and ultimately

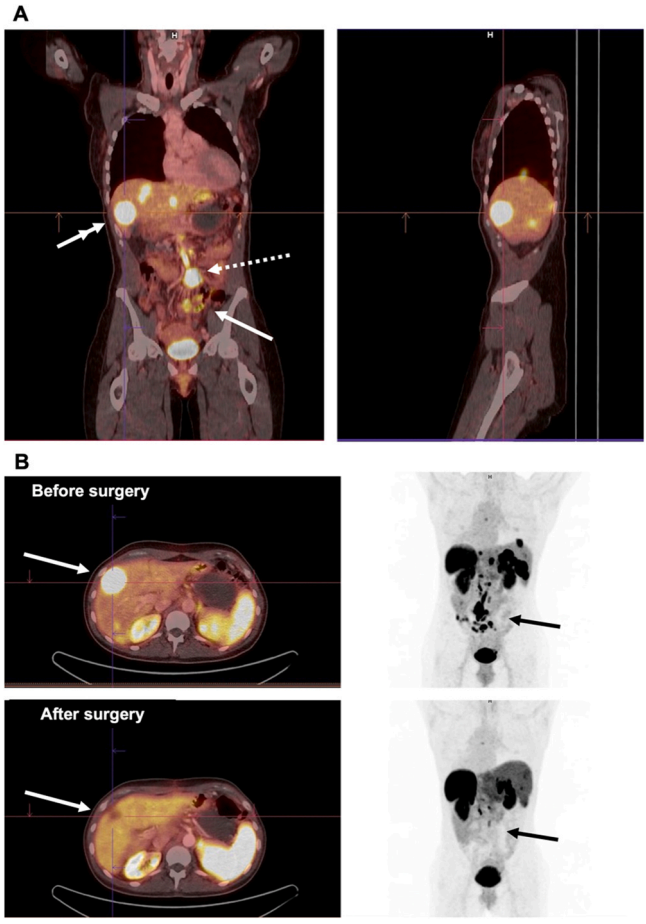

Fig. 3. Patient with small bowel NET and liver metastasis. Legend: A. Gallium-DOTATOC PET-CT showing small bowel tumor (arrow) with mesenteric metastasis (pointed line arrow) and liver metastasis (double arrow). B. Patient underwent debulking surgery of the small bowel with lymphadenectomy, mesenteric tumor debulking and liver resection. Images are before (top) and after (bottom) surgery.

chronic abdominal pain, malabsorption, malnutrition, and cachexia [73]. Loco-regional SB-NETs can be treated with curative intent, with high risk of recurrence, while metastatic SB-NETs can rarely be cured but can be treated with prolonged survival with persistent disease [74–77]. Goals of care for SB-NETs and management of the primary SB tumor depend on the extent of disease. In general, focus is on control of tumor burden, control of endocrine secretion, and prevention of complications that could impair quality of life, such as obstruction, mesenteric angina, and gastrointestinal bleeding [77–79]. Small bowel resection for SB-NETs can be performed with low morbidity and mortality, with 30-day mortality and morbidity reported below 2% and 20%, respectively [80–82].

Loco-regional SB-NETs with clinically negative nodal disease

For localized SB-NETs with negative clinically positive nodes (no enlarged mesenteric nodes on imaging), resection of the primary tumor along with regional lymph node to target resection of 8 or more lymph nodes for staging is the standard of care for curative-intent. The extent of resection depends on the number and location of potentially multifocal SB-NETs. With clinically negative nodal disease, lymph node dissection (LND) aims for the identification of microscopic nodal metastases for staging and prevention of growth and subsequent fibrosis symptoms [83]. A minimum of 8 lymph nodes is suggested for LND [84,85]. In case of multifocal tumors, if resection with complete LND would lead to loss of extensive intestinal length, more limited mesenteric resection should be undertaken to ensure nodal harvest while preserving intestinal function. In addition, efforts should be made to preserve the ileo-cecal artery. Both those considerations are crucial in case of carcinoid syndrome or subsequent need for re-resection in case of recurrence (up to 60% at 15 years) [83].

Loco-regional SB-NETs with clinically positive nodal disease

Overall, about half of all patients will present with nodal mesenteric masses at diagnosis [84,86]. For loco-regional clinically node positive SB-NETs, every attempt should be made at resection of the primary tumor and the nodal mesenteric mass for curative-intent management and to prevent debilitating complications from mesenteric fibrosis. Approximately one in two patients with mesenteric nodal masses present with abdominal pain or intestinal obstruction, and resection of the mesenteric mass can provide relief of symptoms and prolonged survival [74,75,87]. SB-NETs mesenteric masses are categorized in 4 levels: level 1 is near the intestinal border, level 2 is sitting on arterial branches from the SMA, level 3 is located along the border of the SMA, and level 4 extends in the retroperitoneum to root of the SMA. For levels 1 and 2, traditional small bowel resection and LND can be undertaken. For levels 3 and 4, a mesenteric-sparing approach is favored to allow for resection for complex proximal nodal masses while preserving intestinal length and function. Mesenteric-sparing small bowel resection allow for resection of proximal nodal masses to prevent complications related to the desmoplastic reaction while avoiding short bowel syndrome [76,88]. As such, all patients with SB-NETs with nodal mesenteric mass should be assessed by experienced NETs surgeons to confirm that proximal mesenteric-sparing resection is not feasible. Key steps for mesenteric-sparing resection include [76]: 1) elevation of the mesenteric root including mobilization of the cecum, ascending colon and hepatic flexure; 2) continue dissection of the mesenteric root by following the axis of the SMA and SMV to the level of the third duodenum and pancreatic; 3) incision of the peritoneum overlying edge of the nodal mass; 4) dissection of the nodal mass by “peeling it off” arterial and venous branches (alternating dissection anteriorly and posteriorly on the mass can help); 5) proximal and distal transection of the intestine as determined by devascularization after maximal nodal dissection, and; 6) creation of a wide side-to-side anastomosis to prevent temporary partial obstruction related to anastomotic oedema after extensive mesenteric dissection [76].

Resection of primary SB-NETs with unresectable metastases

In patients with unresectable metastases, consideration should be given to resection of the primary tumor since primary tumors and nodal masses left in situ may lead to mesenteric fibrosis with a myriad of repercussions to surrounding structures. Upfront resection of the primary SB-NETs despite metastatic disease has been suggested to prevent loco-regional complication related mostly to mesenteric fibrosis

as well as potentially improve oncologic outcomes. Favorable long-term survival and prevention of complications (and their repercussions in terms of symptoms and need for intervention) have been reported in retrospective cohort studies [81,89,90]. For instance, in a meta-analysis of 6 studies, Almond et al. [90] reported a pooled hazard ratio of 0.47 (95% confidence interval 0.35–0.55) for upfront primary tumor resection compared to no resection for stage IV SB-NETs. In a population-based analysis, Bennett et al. reported that upfront small bowel resection was associated with a reduction in unplanned acute care admissions and receipt of subsequent small bowel-related surgeries, compared to initial non-operative management [89]. This supports the hypothesized benefits of primary tumor resection in SB-NETs with unresectable metastases in order to avoid loco-regional complications for a cancer with a chronic course of disease. Indeed, the 2017 ENETS and NANETS consensus statements both recommend resection of the primary tumor and regional disease in this setting[29,91].

Appendiceal NENs

Most NENs diagnosed in the appendix present on a clinical background of "appendicitis" with the NEN identified incidentally on final histopathology, usually at a rate of 1–2% [92]. Appendiceal NETs make up about a quarter of all GEP-NENs in some series [3]. Appendiceal NETs have been considered a problematic and controversial area of decision making for years, in particular regarding the role of additional hemicolectomy for appendiceal lesions between 1 and 2 cm in size [93–95]. Where consensus suggest those with NETs < 1 cm are cured by appendectomy alone, and those with larger NETs(> 2 cm) are generally considered as candidates for a completing right hemicolectomy, the tumors between (1–2 cm) has been considered controversial regarding its management. One needs to keep in mind that most of the incidental findings may occur in the relatively young age population on a background of clinical appendicitis, for which a further resection by right hemicolectomy may be a considerable undertaking.

A large study from France included 403 patients with appendiceal NETs [96], of which 100 (25%) underwent additional right hemicolectomy with lymphadenectomy. Of these, 25 had positive lymph nodes on histopathology of the specimen. Even though patients were upstaged by the additional surgery, no results regarding recurrence or survival were provided in the study. Hence, no conclusions may be drawn on the clinical impact of the additional surgery from the study.

In a recent retrospective cohort study (inclusion between 2000 and 2010), pooled data from 40 hospitals in 15 European countries for patients (any age and performance status) with a histopathology-confirmed appendiceal NET of 1–2 cm in size who had a complete resection of the primary tumor. Patients (n = 278) either had an appendectomy only (n = 163, 59%) or an appendectomy with oncological right-sided hemicolectomy or ileocecal resection. Median follow up was 13 years. Two patients had peritoneal metastasis (1%) and 2 had liver metastasis (1%), all metastases were diagnosed synchronously with no tumor-related deaths during follow-up [97].

Based on the results, the investigators concluded that right-sided hemicolectomy is not indicated after complete resection of an appendiceal NET of 1–2 cm in size by appendectomy, that regional lymph node metastases of appendiceal NETs are clinically irrelevant, and that an additional postoperative exclusion of metastases and histopathological evaluation of risk factors is not supported [97]. Hence, the most recent data suggest that right hemicolectomy can be omitted in appendix NETS of 1–2 cm in size found on appendectomy.

Colorectal NETs

Incidentally detected lesion in both the colon and the rectum has increased and hence colorectal NETs are making up a larger share of recent series of GEP-NENs than in the past. More widespread use of endoscopy and introduction of screening programs for colorectal cancer likely has a direct influence on the detection of such early, sporadic lesions for which a majority have a favorable prognosis [98]. Metastasis are rare in smaller tumors < 2 cm, but risk of metastasis increase with size > 2 cm [22]. Colonic NETs are rare (< 1% of all) and G1-G2 tumors are treated by conventional resection for most cases, using formal surgical oncological principles with adequate lymph node dissection.

Rectal NETs are often diagnosed incidentally; the smallest (< 1–2 cm) can be resected endoscopically and makes up about half of all rectal NETs [99]. A randomized, non-inferiority trial found no difference between type of endoscopic resection in the rectum for small (< 10 mm) rectal NETs [100]. For tumors < 2 cm it is recommended to perform transanal ultrasound/endoscopic ultrasound to assess depth of invasion. For tumors invading the muscular propria, an endoscopic removal is contraindicated, and treatment should follow regular principles for oncological rectal surgery, depending on location in rectum and involvement of tumor. More aggressive (G3) or large lesions (> 2 cm) need an oncological resection [101]. However, for high-grade NETS or NEC, the prognosis is overall poor [102].

Advanced grade NENs (G3 and NECs) – any role for surgery?

The vast majority of GEP-NENs are NET Grade 1 and 2, but 10–20% are classified as NET G3 or NEC (Fig. 2). In the NORDIC study [17] of 196 patients with metastatic disease, NET G3 was found in 12.3%, NEC with a Ki-67 < 55% (NEC < 55) in 29.6%, and NEC with a Ki-67 ≥ 55% (NEC≥ 55) in 56.6%. Further classification into morphological and molecular distinct features seem to justify this clinical distinction [15,103–107]. GEP-NETs G3 and GEP-NECs present significant differences in driver genes (TP53, Rb1) and disease origin [17,103,106]. With a considerable variation in prognosis, an aggressive tumor biology and often reported poor outcome, there has been a question regarding the role of surgery in high-grade G3 and NEC patients [104,108–111]. In a meta-analysis, comprising 1810 surgical and 910 non-surgical patients, there was a survival benefit in selected patients with G3 GEP-NENs compared to those not undergoing surgery [108]. Surgery of the primary tumour in patients with loco-regional high-grade GEP-NEN or MiNEN led to good long-term results and should be considered if an R0 resection is considered achievable[102]. Highly selected patients with limited stage IV disease may also benefit from surgery. Furthermore, liver directed surgery of PanNET metastatic disease, can provide good outcomes, particularly when excision of > 70% is possible to achieve [112]. Biological imaging assessment according to increasing FDG-PET uptake discordant with Ga68 DOTATATE imaging (NETPET score) may reflect disease that will not respond to SSTR therapy and therefore may influence management decisions [113]. Surgery with radical intent might represent a valid option for GEP-NEN G3 patients with locoregional disease, especially with Ki67 value ≤ 55% [110].

Long-term survival after resection of digestive NENs

Survival after resection is good and 50–70% of patients are reported to be alive 5–10 years after surgery in non-selected cohort series [75,114,115]. In the first analysis of the European Neuroendocrine Tumour Society registry [32], comprising 10,102 patients with NEN from 7 European countries, the 5-years overall survival was 74%, influenced by grade, stage and tissue of origin in multivariate analysis. A Ki67 cut-off value set at 55% (Fig. 1) within the G3 group allowed to separate 2 groups with a meaningful different overall survival [32], corroborating data from the Nordic study [17].

Summary

Surgery should be considered for all patients with NEN, if the patient is considered operable. Short term complications from surgery usually follow the same pattern as seen for organ resection for other indications. For some locations in the gastrointestinal tract with small tumors a strategy of surveillance or endoscopic management may be a viable alternative to surgery, given a proper biopsy for assessing diagnosis and grading. This pertains in particular to lesions of the esophagus, stomach, colon and rectum. However, surgery is indicated in large tumors or tumors showing invasive growth. Small bowel NETs should be considered for resection, even in the presence of metastasis, as this may have a survival benefit and avoid symptoms. In pancreatic NETs < 2 cm, surveillance is emerging as a preferred strategy, but long-term data is awaited from ongoing trials. Surgery is otherwise the preferred management, with controversy concerning G3 tumors as data are equivocal in terms of benefit. However, a high level of evidence is lacking for firm decision-making in terms of choice between surgery and alternative strategies for several NETs.

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Practice points

- Surgery is the treatment of choice for local or locoregional disease in low grade neuroendocrine tumors (NET, G1 or G2) in all operable, fit patients.
- Some NETs located in anatomical parts accessible for endoscopy (esophagus, stomach, colon, rectum) may benefit from a conservative or surveillance strategy over surgery, or treatment by endoscopic techniques
- Surgery is indicated in most small bowel NENs by performing macroscopic radical resection with systematic lymphadenectomy
- Surgery is indicated in pancreatic NETs over > 2 cm but comes with higher risk of complications compared to non-NEN lesions in the pancreas
- Hemicolectomy in addition to appendectomy is not indicated in appendiceal NETs of 1–2 cm as prognosis is excellent and recurrence risk very low.

Research agenda

- Few trials are available that compares surgery to an alternative treatment strategy
- Implementation of molecular profiling characterization is necessary in future trials to guide treatment and better inform risk of surgery versus observation.
- Testing and validation of promising liquid biopsy multi-gene panels for detection, risk assessment and surveillance are warranted before clinical implementation

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