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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

ASO Practice Guidelines Series: Surgical Management of Gastrointestinal (Midgut) Neuroendocrine Neoplasms

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ABSTRACT Gastrointestinal midgut neuroendocrine neoplasms (NENs) are a heterogeneous group of uncommon malignancies. For well-differentiated NENs, known as neuroendocrine tumors (NETs), surgery is a cornerstone of management in localized and metastatic disease. Because of heterogeneous tumor behaviour, association with endocrine syndrome, and prognosis, the management of NETs must be individualized to all these factors in addition to the primary site. With the fast pace of advancement in the field, both for therapies and understanding of tumoral etiology and behaviour, it is important for surgical oncologists to remain updated on guidelines recommendations and suggested treatment pathways. Those guidelines provide important guidance for management of NETs but are largely based on expert opinions and interpretation of retrospective evidence. This article reviews highlights of most recent practice guidelines for midgut (gastric, duodenal, small intestinal, and appendiceal) NETs.

While once considered a rare malignancy, neuroendocrine neoplasms (NENs) have risen in incidence over the past decades to reach 5.86–6.98 per 100,000 in North America; such an increase has not been observed in other malignancies.[1,2] NENs can occur in any organ (including lungs, thyroid, adrenals, ovaries, prostate) but are most commonly found in the gastrointestinal tract.[1–3] Most NENs have an indolent progression, such that patients with NENs can survive for many years even with active advanced or metastatic disease, with overall survival at 10 years reaching more than 50%.[1,2] The combination of prolonged survival with active disease and rising incidence explains why the prevalence of NENs has now surpassed the combined prevalence of pancreas, gastric, and esophageal cancer.[2,4] Therefore, most surgical oncologists will eventually encounter patients with NENs and awareness about guidelines for their management is crucial to improve outcomes and ensure quality care for patients.

NENs are a heterogeneous group of malignancies that differs in behaviour and prognosis from better known malignancies. Those differences are paramount to understand how to devise care plans that are tailored to the specificities of patients with NENs. First, cancer-specific survival shows that for some non-metastatic NENs, such as gastric and intestinal primaries, noncancer deaths exceed cancer deaths shortly after diagnosis.[5] Therefore, the risk presented by the NENs has to be carefully weighed against to potential toxicities of therapy. Second, NENs can lead to long-lasting debilitating symptoms with significant impact on quality of life via endocrine repercussions systematically as well as local tumor impacts. For instance, endocrine syndromes, most commonly carcinoid syndrome related to excess of serotonin production by the tumor, can produce systemic symptoms including diarrhea, flushing, wheezing, and heart failure. Locally, the release of serotonin and tumor factors in the tumor microenvironment leads to a desmoplastic reaction around gastrointestinal NENs primaries and lymph nodes tumors which if left untreated can result in severe repercussions of mesenteric angina, venous ischemia, intestinal obstruction, and ureteric fibrosis.[6–8] These symptoms do not necessarily reduce survival and can impact patients for years.[8] As such, care plans for gastrointestinal NENs

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involves prevention and treatment of those long-lasting systemic and local repercussions.

Finally, not all NENs are the same. There is a lot of heterogeneity in tumoral and endocrine behaviour. The 2022 World Health Organization (WHO) classification divides NENs in neuroendocrine tumors (NETs) and neuroendocrine carcinomas (NECs) (Table 1).[9] NETs are diagnosed on immunohistochemistry as being well-differentiated and are characterized by slower growth patterns. They are subdivided based on their proliferation index assessed by the Ki67: Ki67 < 3% for grade 1, Ki67 3–20% for grade 2, and Ki67 > 20% for grade 3. NECs are characterized as being poorly differentiated on immunohistochemistry and are aggressive malignancies. Survival often falls below 12 months even with surgery for NECs, such that there is no routine role for surgical management of NECs. Moreover, tumor behaviour and prognosis differs based on the primary tumor site; gastrointestinal NENs harbour better prognosis than NENs, for example.[1,2,5] Therefore, care plans must be tailored to the site of primary NENs as well as their prognosis defined by the WHO classification.

In this ASO practice guidelines review, we will focus on the surgical management of gastrointestinal midgut NETs. This review is based on published guidelines by the North American Neuroendocrine Tumors Society (NANETS), the European Neuroendocrine Tumors Society (ENETS), the National Comprehensive Cancer Network (NCCN), the European Society of Medical Oncology (ESMO), and the Commwealth Neuroendocrine Tumors Society (CommNETS).[10–17]

GASTRIC NEUROENDOCRINE TUMORS

Four types of gastric NENs are described. Types 1, 2, and 3 are considered NETs. Type 1 gastric NETs are sporadic, small (<2 cm), multifocal, well-differentiated, low-grade NETs that are associated atrophic gastritis, which leads to hypergastrinemia and overstimulates gastric enterochromaffin cells, resulting in endocrine hyperplasia and eventually small gastric NETs. They are indolent, rarely spread (<1%), and have an excellent prognosis with close to 100% overall survival at 5 years.[18] Type 2 gastric NETs are small (<2 cm), multifocal, well-differentiated, low-grade NETs, resulting in associated with Zollinger-Ellison syndrome and are a manifestation of hypergastrinemia due to the presence of a separate gastrinoma. Their treatment and prognosis are tied to that of the gastrinoma. Type 3 gastric NETs are sporadic, large (≥2 cm), isolated, well-differentiated tumors of any grade that are not associated with atrophic gastritis and arise with noromogastrinemia. They often have nodal and hematogenous spread, and their prognosis is akin to that of gastric adenocarcinoma. Finally, type 4 gastric NENs are poorly differentiated high-grade, small- or large-cell tumors and therefore considered NECs. Their prognosis is limited, they can respond well to cytotoxic chemotherapy, and there is no role for surgical management.

TABLE 1 Summary of 2022 World Health Organization classification for gastrointestinal neuroendocrine neoplasms

Grade	Differentiation	Ki67 index
Neuroendocrine tumors		
Grade 1	Well differentiated	0–2%
Grade 2		3–20%
Grade 3		> 20%
Neuroendocrine carcinoma		
Any	Poorly differentiated	Any

Diagnosis and Workup

Endoscopy is the cornerstone of diagnosis and recommended by both ENETS and NCCN. In addition to biopsies of the index tumor, biopsies of the antrum and fundus are needed to assess the type of gastric NETs by identifying atrophic gastritis. Endoscopic ultrasound is indicated for tumors >1 cm, mostly for assessment of the depth of invasion and planning for endoscopic resection if appropriate. Serum gastrin levels are helpful to confirm the type of gastric NETs (elevated in types 1 and 2, and normal in type 3). However, gastrin levels are not reliable in patients on proton pump inhibitors therapy due to false positives; proton pump inhibitors should be stopped 7 days before drawing serum gastrin if patient symptoms allow. Chromogranin A measurement is not recommended due to limited sensitivity and specificity.[16,19–21] In patients with atrophic gastritis, ENETs further recommends measuring hemoglobin and vitamin B12 for assessment of associated macrocytic anemia. While NCCN does not distinguish imaging based on type of gastric NETs, ENETS provides more specific guidance.[14,16] Cross-sectional imaging, including arterial phases and somatostatin receptors (SSTR)-PET scan (such as Ga^{68}), are recommended for staging and identification of the primary gastrinoma for type 2 gastric NETs and for staging in type 3 gastric NETs. Imaging is not recommended for type 1 gastric NETs, except in the presence of high-risk features (grade 2 or T2 invasion on EUS).

Surgical Management

Type 1 gastric NETs have benign behaviour and can be managed with endoscopic surveillance and resection of prominent tumors, as outlined by the ENETS and NCCN guidelines (Fig. 1).[14] ENETS provides further details on this approach.[14,16] Only tumors >1 cm should be resected endoscopically via endoscopic mucosal, submucosal, or

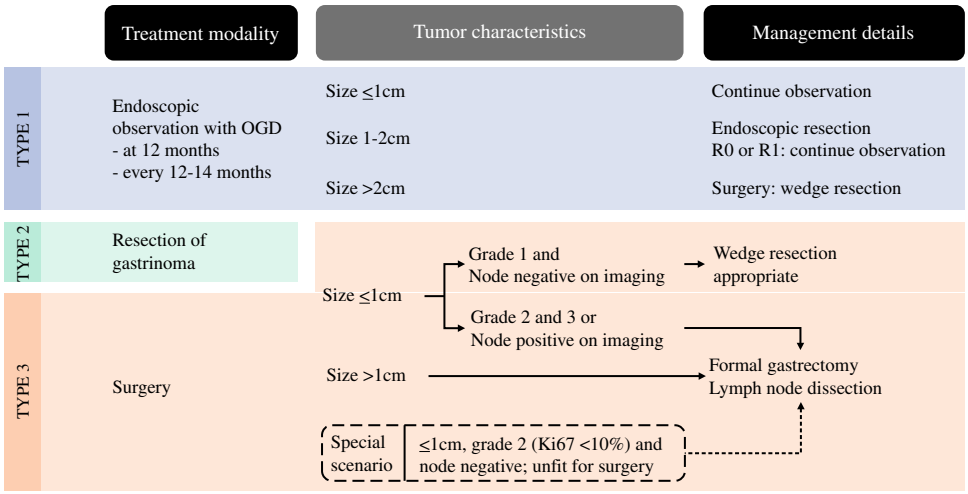

FIG. 1 Summary of guidelines recommendations for the surgical management of gastric NETs

full-thickness resection as per the endoscopist preference (no data show evidence of superiority of one technique); smaller lesions can be observed without resection or repeat biopsies. In case of R1 after endoscopic resection, a repeat attempt at endoscopic resection can be done; however, evidence of recurrence after R1 resection in extremely rare and endoscopic observation also is considered appropriately.[22] Surgical resection is not recommended to management of R1 after endoscopic resection for type 1 gastric NETs. Surgical resection is recommended for larger type 1 gastric NETs >2 cm if endoscopic resection is not technically feasible and to be considered for tumors between 1 and 2 cm with high-risk features (grade 2 and invasion of muscle layers). When surgery is needed, a wedge resection aiming for R0 margins is sufficient, and formal gastrectomy is not recommended. Surveillance of type 1 gastric NETs involves a first endoscopic follow-up with oesophago-gastro-duodenoscopy within 12 months of initial identification or of endoscopic resection and every 12 to 24 months subsequently according to ENETS or every 24 to 36 months according to NCCN.[14,16] In addition to monitoring of the type 1 gastric NETS, ENETS outlines the additional role of endoscopic surveillance related to the risk of gastric adenocarcinoma with atrophic gastritis.[14,21]

For type 2 gastric NETs, the treatment is that of the gastrinoma, and the stomach is not the focus of therapy. Workup and management should follow recommendations for functional duodenal and pancreatic NENs.

For type 3 gastric NETs, surgical resection is typically recommended. ENETS guidelines indicates that endoscopic resection is appropriate for grade 1 tumors <1 cm and can be considered for grade 2 tumors (maximum Ki67 of 10%) <1 cm if patients would be high-risk for surgery. Above 1 cm, the risk of nodal metastases increases, such that a more formal resection is recommended. ENETS guidelines suggest surgery with localized or wedge resection for grade 1 or 2 tumors < 2 cm with no evidence of positive lymph nodes on preoperative assessment. The typical standard of care for type 3 gastric NETs is anatomical resection (subtotal or total gastrectomy) with corresponding lymphadenectomy (D1 in the absence of data in gastric NETs).[14,22] In case of R1 after endoscopic resection, completion (salvage) gastrectomy should be considered.

DUODENAL NEUROENDOCRINE TUMORS

Most duodenal NETs are sporadic and nonfunctional. Approximately 25% are related to genetic syndromes, such as Multiple Endocrine Neoplasia type 1 and Neurofibromatosis type 1.[14,23] Functional duodenal NETs most often secrete excess gastrin or somatostatin. The workup and management of those functional duodenal NETs are covered by guidelines on functional pancreatic NETs. Herein, we will review guidance for the care of nonfunctioning duodenal NETs.

Workup and Diagnosis

The recommended workup of duodenal NETs relies on endoscopic assessment with biopsies to establish histology diagnosis and grading (Ki67) for classification, localization in relationship with the ampulla, and endoscopic ultrasound to assess the depth of invasion in tumors >1 cm.[16] In addition to confirming the diagnosis, endoscopic examination is crucial for treatment planning. The ENETS guidelines mention important tumor characteristics linked to worse prognosis: periampullary localization, functional status, grades 2 and 3, and invasion beyond the submucosa.[11,14] CT or MRI enterogram imaging focused on the duodenum are encouraged for optimal localization of the tumor and planning of resection. Imaging for staging should include cross-sectional imaging including arterial phases and SSTR-PET. Finally,

endocrine syndromes should be assessed clinically and biochemical testing performed accordingly.[14]

Surgical Management

Overall, existing guidelines highlight the scarcity of evidence regarding the management of duodenal NETS (Fig. 2).[14,16] Endoscopic resection is favoured for small duodenal NETs up to 1 cm, with endoscopic mucosal or submucosal resection techniques. The ENETS guidelines outline a high 15–25% risk of perforation with such resections to be taken into consideration, especially in the second duodenum.[16,17] For patients with small duodenal NETs <5 mm, who are not fit for surgery or endoscopic resection, endoscopic monitoring is considered reasonable by the ENETS guidelines, albeit with limited evidence.[23,24]

Surgical resection is favoured for tumors >1 cm, those invading beyond the submucosa, and grades 2 and 3 tumors.[12,22] The ENETS guidelines provide details regarding the surgical approach.[12,23] For periampullary tumors or tumors with positive nodes on imaging, this requires a formal pancreatoduodenectomy. When possible (tumor away from ampulla and no clinically positive nodes), less extensive resections are encouraged, such as partial segmental or wedge duodenectomy or duodenotomy with tumor resection. Local resections are recommended considering the lack of evidence regarding therapeutic benefits of lymph node dissection for occult nodal disease.

ILEO-JEJUNAL NEUROENDOCRINE TUMORS

Ileo-jejunal, or small intestine, NETs are one of the most common sites for NENs. They present with synchronous metastases in 20% of cases and another 40% will develop metachronous metastases[12,24] Key considerations for workup and management include the presence of carcinoid syndrome and need for hormonal control, multifocality of primary intestinal tumors, risk and repercussions of locoregional desmoplastic reaction, as highlighted in both the ENETS and NANETS guidelines.[12,25] The management of carcinoid syndrome focuses on controlling the level of endocrine hypersecretion to reduce the repercussions of excess serotonin. In addition, the risk of carcinoid-related diarrhea during follow-up means that preservation of intestinal length and ileo-cecal valve is important for future management. More than 50% of patients will have multifocal small intestine primaries, most often located in the distal 100 cm of the ileum.[26] This means that exploration for and identification of multiple primaries is important for tumor control. Desmosplatic reaction, which manifests as mesenteric or retroperitoneal fibrosis, happens in 50% of patients with small intestine NETs and is associated with mesenteric angina, venous ischemia, intestinal obstruction, and ureteric obstruction, all leading to chronic abdominal pain and inability to eat. This points towards the need to consider treatment of desmoplastic reaction and prevention of its repercussions as part of management.

Workup and Diagnosis

The diagnosis of small intestine NETs relies on the identification of a small intestine tumor and histology confirmation of NET along with grading (Ki67) for classification. In instances when tissue diagnosis is not feasible, typical imaging features along with SSTR avidity on SSTR-PET scan also can be diagnostic and confirm the tumor is well-differentiated. The recommended initial workup for small intestine NETs includes cross-sectional imaging including arterial phases for distant staging, enterogram protocol CT or MRI to identify primary and multifocal tumors, MRI with liver-specific contrast in case of liver lesions, and SSTR-PET scan.[12,16,27] This should be supplemented by endocrine workup with 24-hr urinary 5HIAA, and echocardiogram in case of elevated 5HIAA to screen for carcinoid heart disease.[12,16,27] Chromogranin A is not recommended as a tumor marker due to low specificity and sensitivity.[12,27]

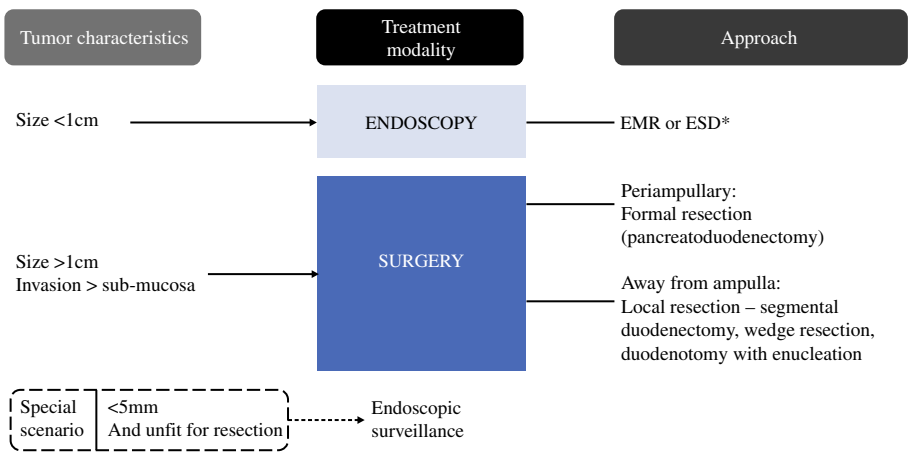

FIG. 2 Summary of guidelines recommendations for the surgical management of nonfunctional duodenum NETs. *Reported risk of perforation 15–25%

Surgical Management

For locoregional disease with no evidence of positive nodes on imaging (enlarged nodes), resection of the primary tumor with lymphadenectomy. The extent of lymphadenectomy in the absence of visible or palpable nodal masses should aim for ≥8 nodes.[12,27] Both guidelines acknowledge that the target for nodal harvest is based on retrospective cohort studies, indicating more accurate staging but that it is not therapeutic.

For locoregional disease with positive nodes on imaging, often identified as a mesenteric mass, resection of the primary tumor with the nodal mass using intestinal sparing approach is favoured. Nodal masses are described at 4 levels in the mesentery (Fig. 3): level 1 nodes sit near the intestinal border, level 2 nodes are located along branches from the main superior mesenteric vessels, level 3 nodes are found along the border of the main superior mesenteric vessels, and level 4 nodes are at the root of the superior mesenteric vessels and often extend behind the pancreatic neck into the retroperitoneum.[28] The NANETS guidelines highlight the importance of sparing intestinal length while resecting mesenteric nodal masses, even when proximal on the axis of the superior mesenteric artery. R1 for the purpose of resecting nodal masses while sparing major mesenteric vessels is accepted. The technique utilized by high-volume NETs surgeons and described by the NANETS expert consensus involves peeling the nodal mass off mesenteric vessels.[12,29,30] As such, they also outline the need for (un)resectability to be determined by high-volume surgeons with NETs expertise before determining a tumor unresectable. Similarly, the ENETS guideline determine that only mesenteric masses involving the root of the mesenteric vessels (extending retroperitoneally) are considered unresectable and that other large masses without involvement of the vessels' root are deemed borderline resectable.[12,27] Both guidelines mention the importance of pursuing aggressive resection of mesenteric masses to prevent devastating repercussions of mesenteric fibrosis. Finally, all guidelines recommend exploration of the entire small intestine from the angle Treitz to the ileocecal valve with bi-digital palpation to look for multifocal tumors.[12,16,26]

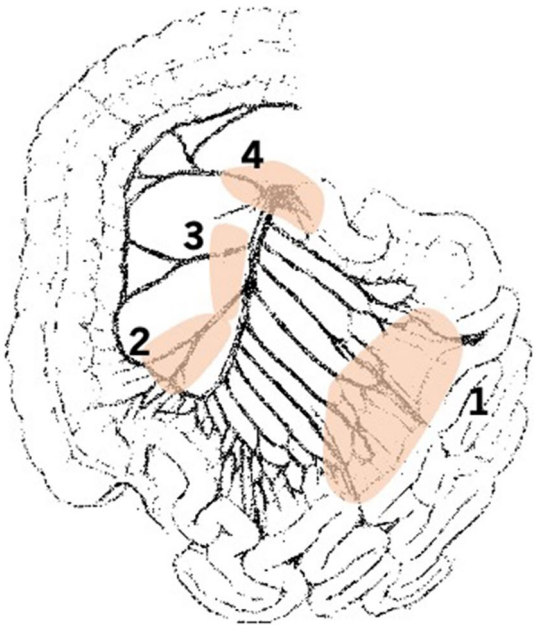

FIG. 3 Level of mesenteric nodes for small-intestine NETs. Level 1 nodes are near the intestinal border, level 2 nodes are along named branches from the superior mesenteric vessels, level 3 nodes are on the border of the superior mesenteric vessels, and level 4 nodes are at the root of the superior mesenteric vessels. [27] Adapted from Öhrvall U et al. *World J Surg*. 2014;24(11):1402-8.

Finally, the NANETS guidelines provide guidance regarding the surgical approach for resection of small intestine NETs, whether open or laparoscopic. Achieving all goals of the operating is the most important consideration: resection of the primary tumor and mesenteric masses, thorough abdominal staging, and ensuring safety. Laparoscopic techniques allow for palpation of the entire small intestine for assessment of multifocal disease if this is through an extraction site or via hand-port. Resection of complex mesenteric masses with techniques specific to NETs may not be accomplished with laparoscopy. Therefore, these guidelines recommend that open surgery remains the accepted surgical approach and that purely laparoscopic approach are not adequate. Laparoscopic approaches that include a small incision (such as extraction site) for intestinal examination can be an acceptable alternative.[12,16,27]

Resection of the Primary Tumor with Metastatic Disease

Patients with metastatic small intestine NETs have prolonged survival, with up to 13 years median overall survival even when metastases are present.[31] This implies a long time to experience complications from unresected primary tumors, as previously described as it relates to desmoplastic reaction. In symptomatic patients, ENETS, NANETS, and NCCN guidelines all recommend resection of the primary small intestine tumor in the setting of unresectable metastases.[28,29] In patients deemed symptomatic, recommendations involve a more nuanced thought process and interpretation of retrospective evidence coupled with clinical experience of NETs experts. NANETS outlines that few patients are truly asymptomatic as most of them tend to cope with symptoms for years prior to clinical assessment and the fact that they had investigations leading to diagnosis of metastatic NETs suggests some level of symptoms.[28,31] Studies reporting up to 80% symptom relief reported after surgery by patients initially considered asymptomatic.[28,32] ENETS guidelines

state that palliative primary tumor resection with lymphadenectomy should be considered to prevent and/or relieve symptoms related to fibrosis.[10,16] NCCN outlines the need for primary tumor resection to prevent future obstruction, mesenteric ischemia, bleeding, or perforation.[10] Ultimately, all guidelines suggest consideration of primary tumor resection in the setting of unresectable liver metastases in asymptomatic patients. ENETS recommends multidisciplinary discussion for decision-making, NCCN recommends consideration of resection to prevent the repercussions of mesenteric fibrosis, and NANETS recommends consideration of resection to avoid future symptoms while carefully weighing in the patient's performance status and degreed of liver tumoral replacement (with shorter survival if >50–70% replacement).

APPENDICEAL NEUROENDOCRINE TUMORS

Appendiceal NETs are most often diagnosed incidentally following appendectomy of other reasons.[33–35] Workup is then performed and decisions must be made regarding the need for additional surgery and for surveillance. Decision-making is based on the size of the tumor, the presence of high-risk features. The vast majority of appendiceal NETs are grade 1 (80–95%) and they are seldomly association with functional endocrine syndromes.[33–35] Contemporary guidelines specific to the management of appendiceal NETs come from ENETS and NCCN, with guidelines from NANETS dating back to 2010.[10,16,36]

Workup and Diagnosis

Because risk assessment and decision-making rely heavily on tumor characteristics, a complete and detailed histopathologic assessment is key. The use of synoptic report is suggested by ENETS (templates are available through the Society), with reports including at a minimum: tumor size, tumor localization (tip, body, or base), staining for neuroendocrine markers (synaptophysin and chromogranin), grading, local extension (mesoappendix), and lymphovascular invasion.[12,16,30] They further specify the importance of distinguishing true tumor perforation from appendicitis-related tip perforation, which is very common.

Imaging staging is only recommended for tumors with high-risk features and is based on cross-sectional imaging including arterial phases, with SSTR-PET scan reserved in cases of positive findings on cross-sectional imaging. Tumor markers are not routinely recommended, especially Chromogranin A, which is of limited value as in other primary sites. Twenty-four–hour urinary 5HIAA is recommended only if carcinoid syndrome symptoms or metastases are identified and only after a concomitant small intestine NET is ruled out.

Surgical Management

Management was traditionally determined by tumor size and high-risk features, which were the presence of mesoappendix invasion >3 mm, grade 2 or 3 tumors, and lymphovascular invasion (Fig. 4). However, the most recent evidence from retrospective cohort studies shows that the most important criteria associated with risk of nodal metastases and survival is tumor size >2 cm, with a lesser role for other traditional high-risk features.[10,37–39] Both ENETS and NCCN guidelines outline tumor size as the most important risk factor.[12,16,33] With regards to grade, high grade 2 tumors are reported to have higher risk for nodal metastases; although there is overall agreement that a continuum of risk exist across Ki67 levels in grade 2 tumors, no definite Ki67 cut-off is recommended to dichotomize risk.[12,16,36] On the topic of risk stratification, the ENETS guidelines point out that positive lymph nodes are overall rare in appendiceal

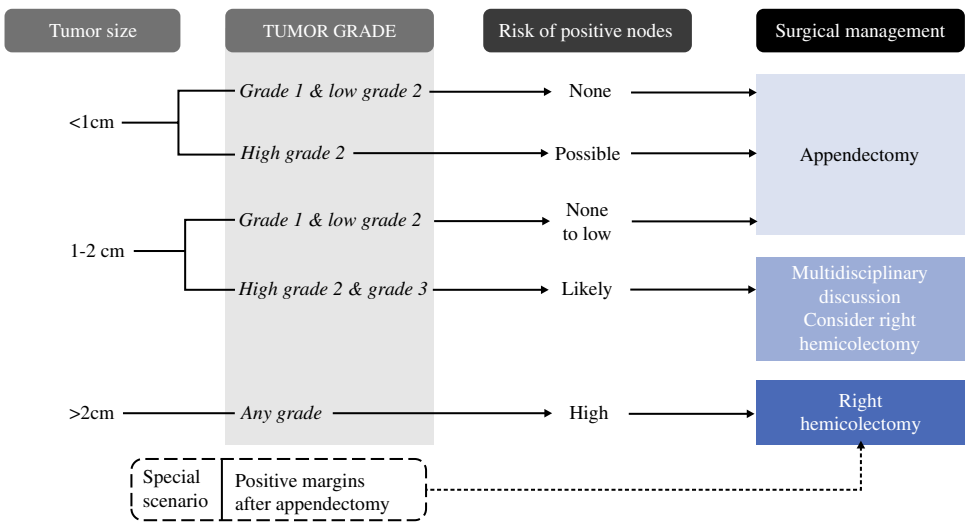

FIG. 4 Summary of guidelines recommendations for the surgical management of appendiceal NETs. [10] Adapted from ENETS guidance document, Kaltsas G et al. *J Neuroendocrinology*. 2023;EPublication.

NETS even in tumors with the highest traditional risk features, with only one of four of those found to have nodal disease. Furthermore, recent observational studies have shown that micrometastatic nodal disease is not associated with overall survival, risk of recurrence, or risk of metastases. This all puts into question the role of high-risk features in defining the need for nodal harvest (and completion right hemicolectomy) for appendiceal NETs <2 cm. Indeed, the ENETS guidelines outline an important retrospective cohort study examining the outcomes of patients undergoing right hemicolectomy compared with those who did not for high-risk features in <2 cm appendiceal NETS. In that study, positive nodal disease was found to be clinically relevant and there was no metastatic recurrence of tumour-related death in patients who did not have a right hemicolectomy during 10 years of follow-up. The morbidity and functional repercussions of right hemicolectomy, especially in young patients, also are brought up. Overall, those important data are reflected in the recommendations for surgical management from both ENETS and NCCN.[12,16,25,36]

Current guideline recommendations include a completion right hemicolectomy for appendiceal NETS >2 cm and in case of positive margins. Right hemicolectomy is not recommended for appendiceal NETs ≤2 cm where a simple appendectomy with negative margins is considered appropriate. For appendiceal NETS between 1–2 cm with higher grade (defined as "high grade 2" with no specific Ki67 cutoff and grade 3), completion right hemicolectomy could be performed with considerations for multidisciplinary discussion and patients' expectations. Finally, right hemicolectomy is not recommended for management of appendiceal NETs with serosal perforation because of to lack evidence and the rarity of true tumor perforation (vs. appendicitis-related perforation).[12,16,37]

METASTATIC DISEASE

For metastatic NETs to the liver, surgical cytoreduction is the cornerstone of therapy, although the indications differ depending on the type of primary NETs. For gastric and duodenal NETs, resection of metastatic disease is performed for functional tumors, with the intent to control the burden of endocrine secretion and associated symptoms. For type 3 gastric NETs, appendiceal NETs, and rectal NETs, resection of liver metastases is not routinely recommended in any guidelines, because there is no demonstrated evidence of oncologic benefit and no endocrine symptom benefits for nonfunctional tumors. Liver cytoreduction is mostly recommended for small-intestine NETs.[12,16,40]

The goals of liver resection for metastatic small-intestine NETs are tumor and endocrine control. All guidelines mention numerous retrospective cohort studies reporting on improved survival for patients undergoing liver resection compared with those who do not, which are all fraught by selection bias.[12,16,25,40] It also is reported that whether R0, R1, or R2 resection is achieved does not significantly alter survival and that almost all patients with liver metastases have micrometastases beyond the ones that can be identified with preoperative and intraoperative imaging.[12,41,42] As such, R0 resection and curative-intent hepatectomy for NETs cannot truly be achieved and the goal is for cytoreduction. The most contemporary recommendations come from NANETS (2017) and NCCN (2023).[40] They recommend that surgical cytoreduction of NETs liver metastases be attempted if the patient is an operative candidate. The threshold for cytoreduction is suggested at 70% by NANETS guidelines based on the most recent evidence regarding progression-free survival.[43] Further guidance is provided about the technique for liver resection of NETs metastases. Formal anatomical hepatectomy are discouraged. Parenchymal-sparing procedures are recommended whereby metastases are enucleated and/or ablated one by one for maximal cytoreduction.[44] Finally, NANETS guidelines provide a discussion of scenarios when liver cytoreduction should not be performed; those include patients with poor performance status, evidence of hepatic dysfunction or cirrhosis, and high liver tumor replacement (>70%). The summary approach to resection for NETs liver metastases is depicted in Fig. 5.

Resection of extrahepatic NETs metastases, most commonly peritoneal, also is suggested in selected cases, albeit based on very limited retrospective evidence. This applies mostly to the 20% of patients with small intestinal NETs who have peritoneal carcinomatosis.[45] The NANETS guidelines recommend considering resecting as much peritoneal disease as possible as part of overall cytoreduction if it can be done with minimal morbidity. Hyperthermic intraperitoneal chemotherapy (HIPEC) is not recommended.[16,37]

When surgery for liver metastases is not feasible, other liver-directed therapies should be considered if the pattern of metastases is liver-dominant, especially for patients with functional symptoms.[16,40] These include hepatic artery bland embolization, chemoembolization, and radioembolization. There is no evidence of the superiority of one of those modalities over the others, such that there is no specific recommendation for this, and the choice of embolization therapy should be based on the different long and short-term toxicity profiles.

SURVEILLANCE AFTER RESECTION

Recommendations for monitoring of NETs managed non-operatively are detailed in the site-specific section (type 1 gastric and nonfunctioning small duodenal NETs) (Table 2). Comprehensive recommendations regarding surveillance after surgical managements of NETs come from expert consensus of the Commonwealth Neuroendocrine Tumors

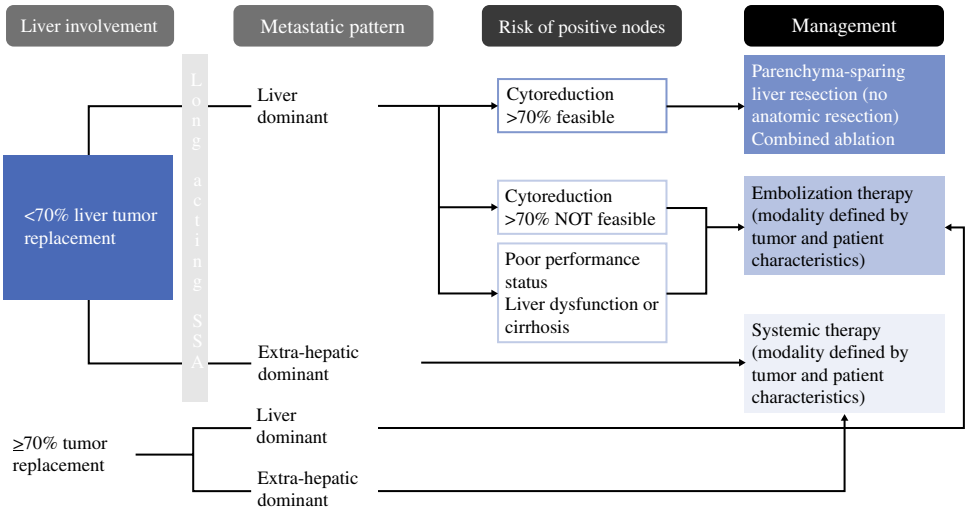

FIG. 5 Summary of guidelines recommendations for the surgical management of NETs liver metastases. [12] Adapted from NANETS expert consensus guideline, Howe JR et al. Pancreas 2017;46(6):715–31.

TABLE 2 Summary of CommNETS expert consensus recommendations for surveillance after complete resection of midgut NETs

	Expert consensus
Interval	Every 1 year for 3 years
	Every 1–2 years thereafter
Imaging	Multiphasic CT scan of abdomen and pelvis
	MRI or US if needed to avoid CT scan
	(chest imaging not recommended)
Laboratory tests	Not recommended
SSTR-PET scan	Investigational
Duration	10 years minimum
	Discussion with patient after
Special considerations	
Can reduce frequency	Grade 1
	T1 or T2
	Negative nodes
Can increase frequency	Ki67 >10%
	Higher lymph node ratio
Appendiceal	<1c m, grade 1, and R0 margins: no surveillance
	>2 cm or grade 2 or 3: can increase frequency

From Singh et al. *JAMA Oncol*. 2018;4(11):1597–604.[45]

SSTR-PET somatostatin receptor PET

Society (CommNETS).[43] These recommendations are based on knowledge of recurrence rates after complete resection and of the availability of effective therapies for long-term control of NETs upon recurrence.[46] The patter of recurrence after resection is driven by the slow-growing pace of NETs; the initial risk of recurrence increases steadily but slowly over the first 10 years after resection and subsequently slows down but never completely plateaus.[46] Recommendations for resected gastrointestinal NETs are for cross-sectional abdomen and pelvis imaging (CT or MRI) every 12 to 24 months for 10 years, with hormonal measures (such as urinary 5HIAA) only if initially elevated at diagnosis. Of note, chromogranin A is not recommended for surveillance due to concerns regarding specificity and sensitivity, and SSTR-PET scan is not recommended for follow-up due to lack of data in that aspect of care. The frequency of surveillance can be adjusted to more frequent assessments with higher-risk features, such as node-positive disease and grade 2 or 3 tumors. After 10 years, a discussion with patients regarding discontinuation of surveillance is suggested.[39] The NCCN endorses similar guidance for surveillance, with the addition of an initial assessment with imaging within 12 weeks of surgery.[16]

It is important to note that these recommendations apply to completely resected NETs and not to cytoreduction procedures. There is no established consensus regarding the optimal monitoring strategy for patients with residual disease after surgery.

CONCLUSIONS

Gastrointestinal NETs are associated with prolonged survival and unique endocrine manifestations. They also are heterogeneous tumors in their behaviour and repercussions on patients' lives. Optimal management differs significantly depending on the primary tumor site, extent of disease, tumor grade, and associated endocrine syndromes. Therefore, careful assessment is paramount to determine the specific characteristics of each NETs and tailor care accordingly. Although existing guidelines recommendations provide important guidance for management, they are largely based on expert opinions and interpretation of retrospective evidence. The background information and qualifying statements accompanying the guidelines are key in understanding the recommendations and how to apply them in clinical

practice. Finally, consultation with a multidisciplinary team as well as with surgeons and oncologists experienced in the care of NETs is crucial to devise treatment plans.

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