**Name of Journal:** *World Journal of Gastrointestinal Surgery*

**Manuscript NO:** 82209

**Manuscript Type:** MINIREVIEWS

**Surgical aspects of small intestinal neuroendocrine tumors**

Kupietzky A *et al*. Surgical aspects of small intestinal NETs

Amram Kupietzky, Roi Dover, Haggi Mazeh

**Amram Kupietzky, Roi Dover, Haggi Mazeh,** Department of Surgery, Hadassah Medical Organization and Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem 91240, Israel

**Author contributions:** Kupietzky A, Dover R, and Mazeh H had substantial contributions to conception, writing and critically reviewing the research and manuscript; all authors have read and approve the final manuscript.

**Corresponding author: Haggi Mazeh, FACS, MD, Associate Professor,** Department of Surgery, Hadassah Medical Organization and Faculty of Medicine, Hebrew University of Jerusalem, 24035 POD, Jerusalem 91240, Israel. hmazeh@hadassah.org.il

**Received:** December 9, 2022

**Revised:** February 25, 2023

**Accepted:** March 27, 2023

**Published online:**

**Abstract**

Small intestinal neuroendocrine tumors (NETs) are a heterogeneous group of epithelial tumors with a predominant neuroendocrine differentiation. Although NETs are usually considered rare neoplasms, small intestinal NETs are the most common primary malignancy of the small bowel, with an increasing prevalence worldwide during the course of the past few decades. The indolent nature of these tumors often leads to a delayed diagnosis, resulting in over one-third of patients presenting with synchronous metastasis. Primary tumor resection remains the only curative option for this type of tumor. In this review article, the various surgical aspects for the excision of small intestinal NETs are discussed.

**Key Words:** Small bowel; Small intestine; Neuroendocrine tumors; Surgery; Metastases

Kupietzky A, Dover R, Mazeh H. Surgical aspects of small intestinal neuroendocrine tumors. *World J Gastrointest Surg* 2023; In press

**Core Tip:** Small intestinal neuroendocrine tumors (SINETs) are the most common primary malignancy of the small bowel. While many patients present with mesenteric and liver metastases the primary tumor resection poses a surgical challenge. In this review article, the various surgical aspects for the excision of small intestinal NETs are discussed.

**INTRODUCTION**

Small intestinal neuroendocrine tumors (SINETs) are neoplasms that arise from enterochromaffin cells, the endocrine cells of the small bowel[1]. These cells can be found from the ligament of Treitz to the ileocecal valve, though most are present in the distal 60 cm of the terminal ilium[2]. These tumors account for over 37% of small intestinal tumors, making them the most common small intestinal cancer[3]. SINETs are associated with an annual incidence of 0.67-1.20 per 100000 population in the United States, and their diagnosis has increased worldwide over the past half-century, most likely due to increased health care utilization and advances in imaging and diagnostic methods[4-7]. SINETs can manifest at any age, however, the incidence increases with age, with a mean age at diagnosis of between 60-65 years[3,8,9]. Although NETs are more prevalent in females than in males, in most SINETs series no gender predilection is demonstrated, with some series demonstrating a slight male preponderance[3,8-11]. SINETs have a variable malignant potential and were traditionally subdivided into three grades based on histopathological differentiation, Ki-67 proliferative index, mitotic rate, and invasiveness behavior[12]. Recently, the World Health Organization (WHO), in its 5th edition of classification of tumors of the digestive system, published a renewed system, divided to two new categories: NETs that are well‑differentiated and a second category for neuroendocrine carcinomas that are poorly differentiated, this differentiation is based on molecular differences (Table 1)[13,14]. SINETs are staged according to the American Joint Committee on Cancer staging system (Table 2).

As with other neuroendocrine tumors, SINETs can potentially produce and secrete several hormones, the most prominent of which are serotonin, bradykinin, histamine, and tachykinin peptide[15-17]. These hormonal agents are responsible to the paraneoplastic syndrome associated with SINETs: The carcinoid syndrome[18]. This syndrome typically consists of episodic attacks of facial and torso flushing, diarrhea, breathlessness, and wheezing and is usually present in patients with liver metastases[19,20]. Advanced manifestation of carcinoid syndrome is typically associated with fibrosis, which may eventually lead to carcinoid heart disease[21,22]. The common manifestation of this desmoplastic reaction is mesenteric fibrosis, which in turn can cause bowel obstruction and bowel ischemia[23]. Though historically referred to as “carcinoid”, most SINETs are nonfunctioning tumors, and patients may present with nonspecific symptoms such as abdominal pain, weight loss, partial bowel obstruction, and gastrointestinal (GI) bleeding[24,25].

SINETs are thought to have greater malignant potential than other NETs, irrespective of primary tumor size[26,27]. At the time of diagnosis, patients usually present with tumors larger than 2 cm with muscularis propria invasion[28]. The majority of patients (80%) will present with a metastatic disease to regional lymph nodes, and over 30% of patients will have hepatic metastases[7,27,29,30]. Despite the advanced stage at diagnosis, the prognosis is exceptional, with a median overall survival of 14 years in local disease, and median overall survival of over 5 years when metastatic disease is diagnosed[7].

Surgery remains the only curative modality for SINETs. Resection of the primary tumor, nodal metastases, and mesenteric masses remain the most important initial treatment, advocated even in the presence of a locally advanced or metastatic disease[31]. The objective of this article is to review the available literature on the surgical management of SINETs.

**Preoperative workup**

SINETs secrete several biochemical tumor markers, that can be elevated in body fluids. Laboratory testing of these markers may help in establishing the diagnosis of SINETs and enable an accurate biochemical surveillance. These markers include Chromogranin A and urine levels of 5-hydroxyindole acetic acid, among other secreted amines[32,33]. Chromogranin A levels may have a prognostic value, as higher levels in the serum have been linked to an increased tumor cell mass[34]. It is therefore recommended that these two biomarkers should be obtained as part of patients preoperative workup, and for follow-up after surgery[35].

Cross sectional abdominal imaging plays a pivotal role in preoperative diagnosis and the initial staging of SINETs, as imaging studies provide information regarding the location of the primary tumor, the extent of local invasion, and the presence of metastatic lesions[36]. Cross sectional imaging can also help plan the surgical resection, as it aids to identify the relation of the mesenteric tumor to the main mesenteric vessels, particularly the superior mesenteric artery (SMA) and superior mesenteric vein (SMV).

The imaging modalities used in the preoperative evaluation include anatomical imaging modalities, such as computed tomography (CT) and magnetic resonance imaging (MRI), and functional imaging modalities, such as positron emission tomography (PET) and single-PECT (SPECT) including octreotide scintigraphy and MIBG scintigraphy[36].

The optimal CT scan protocol should include 3-phases, an arterial phase, a venous phase, and a delayed phase. The primary tumor and metastases typically appear hyperdense on the arterial phase with a washout during the delay portal venous phase[37]. Although the reported sensitivity of this modality varies greatly between studies, it is generally accepted that the sensitivity in the detection of primary SINETs is lower than 50%[38]. CT enteroclysis has a higher detection rate, with sensitivity of up to 85%[39]. The detection rate can be further improved when considering mesenteric lymphadenopathy as an indicator of a SINET, even when a primary mass or bowel wall thickening are not observed[40]. MRI has the advantage of decreased radiation when compared with CT and is recommended in patients with renal failure or patients with an allergy to iodine contrast material. It has been argued that the MRI may be superior in detecting small liver metastasis when compared to CT, and that the CT may be more sensitive at detecting mesenteric disease. To date there is a consensus that either one can be used in the preoperative evaluation[35,41,42].

The functional study traditionally utilized was the somatostatin receptor scintigraphy (SRS). In SRS a radiolabeled octreotide, a somatostatin analog (SSA), is administered to patients and allows detection of local and distant disease. Recently, this functional study has been replaced with a superior functional test, the PET-CT with 68 Ga-labeled DOTA-conjugated peptides. This test has higher detection rates of small primary tumors and their metastases, with a sensitivity of up to 95% compared with conventional techniques, such as CT, MRI, and SRS[43,44].

Due to the multifocal nature of SINETs, found in 20%-44% of patients, the gold standard localization remains intraoperative palpation of the small intestine[45-47].

***Surgery in asymptomatic patients with a metastatic disease***

Due to their indolent nature, metastatic SINETs are often discovered incidentally upon abdominal imaging. Symptomatic patients suffering from abdominal pain, GI bleeding, obstruction, or carcinoid syndrome have an indication for surgery. However, in metastatic asymptomatic patients, surgical resection of the primary tumor is up to debate. In general, patients with metastatic disease in whom surgical resection with curative intent can be achieved, surgery should be performed. The benefits of surgical resection of liver metastases and the primary tumor have been demonstrated in terms of overall survival, with survival rates of 60%-80% at 5 years and with low mortality (0%-6%)[48]. When compared to patients who do not undergo surgery, the survival rate with liver metastases at 5 years is as low as 30%[49]. If a curative surgical resection approach seems no longer achievable, the benefit of resecting the primary tumor is not as clear. Regarding overall survival, two large metanalyses demonstrated that primary tumor resection in the presence of unresectable liver metastasis improved overall survival, with a pooled 5-year overall survival of roughly 73.1% *vs* 36.6% when the primary tumor is not resected[50,51]. Both studies warrant that the results should be interpreted with caution due to a potential selection and publication bias. The selection bias stems from the assumptions that patients that had better prognosis or fewer comorbidities were offered surgery while those with comorbidities or advanced disease were not. In 2018, a retrospective single center study with a cohort of 363 asymptomatic patients with stage IV SINETs found no difference in overall survival in patients who underwent upfront local resection within 6 mo of diagnosis *vs* those who did not[52].

The benefit of upfront surgical resection on patient-oriented outcomes, was recently evaluated in a retrospective propensity-matched comparative cohort study of 522 patients. Bennet *et al*[53] identified that early resection of the primary tumor in metastatic SINETs, was associated with a reduction in unplanned acute care admissions and subsequent small bowel-related surgery, compared to non-operative management. The authors conclude that upfront small bowel resection should be routinely discussed with patients diagnosed with metastatic SINETs. Regardless to whether the overall survival is affected by upfront resection, due to the natural history of this disease and the relatively long survival, patients will eventually become symptomatic and resecting the primary tumor at diagnosis can avoid future symptoms.

An additional benefit of surgery may be in slowing the progression of hepatic metastases in patients with unresectable disease. In a retrospective study by Givi *et al*[54] focusing on the progression of liver disease, 60 patients who underwent primary tumor resection were compared with 24 patients who did not. The authors identified a significant difference in time to progression of liver disease between patients who had their primary tumor resected compared to those who did not (56 mo *vs* 25 mo, *P* < 0.005), and conclude that the primary neoplasm resection could delay progression of liver metastases.

Surgical mortality following SINET resection must be discussed with asymptomatic patients, with a reported range from 0% to 9%, and no data comparing outcomes in patients operated on electively and those undergoing emergency surgery[50].

The current North American Neuroendocrine Tumor Society (NANETS) guidelines recommend upfront resection of primary SINETs in asymptomatic patients with metastatic disease, in selected patients, after factoring in patient specific issues such as performance status and degree of liver replacement[55]. The European Neuroendocrine Tumor Society (ENETS) 2016 guidelines stress that a direct causal relationship between primary tumor resection in asymptomatic patients and an improved overall outcome has not been proven to date, and therefore they recommend a case-to-case interdisciplinary discussion[35].

**Synchronous small bowel tumors**

On attentive palpation of the small intestine during surgery, 13%-45% of patients are found to have multifocal primary tumors[46,56-58]. These tumors can arise synchronously and independently or as a single clone with subsequent local and discontinuous metastasis *via* submucosal lymphatic dissemination[59,60]. A recent retrospective study by Choi *et al*[46] of 179 patients with surgically managed SINETs, demonstrated multifocal small bowel tumors in 81 patients (45.3%). When comparing clinicopathologic factors between patients with multifocal small bowel tumors and those without, no difference in tumor characteristics or in their clinical course was identified. However, they did demonstrate that synchronous tumors tend to be small and often submucosal, and easily missed when the bowel is palpated using graspers laparoscopically. They conclude that an open exploration of the small bowel with a direct bimanual palpation should be performed in all SINET surgeries.

Several techniques have been described to enable carful bowel palpation during laparoscopic surgery, including the use of the soft-tissue wound retractor and the hand-assisted laparoscopic device. Wang *et al*[61] described a successful laparoscopic SINET resection using these methods in 6 patients with unknown primary. Figueiredo *et al*[62] compared laparoscopic resection and open resection in a cohort of 73 patients. Laparoscopic technique was performed in 12 patients. They identified similar rates of multiple tumors when comparing both groups. To date, the trials comparing laparoscopic resection and open surgery are small and retrospective, and sufficient evidence is missing. However, the ENETS 2016 consensus states that the potential benefits of minimally invasive surgery should be weighed against the risk of missing multiple synchronous small SINETs, and that a minimally invasive approach can be considered[35].

**Surgical approach to the mesenteric root**

Recent studies have shown that the majority of patients with SINETs have lymph node metastases at presentation, and that a proper lymphadenectomy can increase the overall survival significantly[63,64]. Watzka *et al*[64] defined a proper lymphadenectomy as one that includes more than 6 lymph nodes that are resected with the primary tumor. They advocate that by doing so, there was an associated improved 5-year survival rate of 82.2% compared to 40.0% in patients with a less radical lymph node dissection. Landry *et al*[29] demonstrated in a retrospective analysis of 1364 patients with SINETs, that the excision of more than 7 nodes is associated with a better cancer-specific survival even after adjusting for age and tumor size. Zaidi *et al*[65] used a cohort of 199 patients and identified that a minimum of 8 lymph nodes were required for an accurate lymph node staging and that 4 or more positive lymph nodes were associated with earlier disease recurrence[65].

Current guidelines urge for a segmental resection with a wide lymphadenectomy. This includes a regional lymph node dissection along the segmental vessels of the small bowel up to their junction with the main trunk of the SMV[55,66]. This practice may be challenging technically. As SINETs invade the serosa they cause an intense desmoplastic reaction that produces mesenteric fibrosis. This fibrosis can lead to vascular encasement, making it extremely difficult to preserve the vascular supply to the rest of the bowel.

It has been proposed, that as with breast cancer and melanoma surgeries, SINET patients can benefit from intraoperative lymphatic mapping using blue dye[60]. It has been hypothesized that due to the extensive mesenteric fibrosis, the lymphatic drainage of the small bowel can be obstructed and SINETs may develop alternative lymphatic drainage paths. Wang *et al*[63] preformed lymphatic mapping procedures in 112 SINET surgeries and found that this practice changed the traditional resection margins in 92% of these cases. They concluded that lymphatic mapping could help preserve intestinal length without hampering the surgical outcomes and may even improve long-term survival. To date, this practice is not standardized and further research is needed to prove its necessity[35].

Ohrvall *et al*[66] described a staging classification used to determine whether the mesenteric involvement is operable. Stage 1 consisted of involved nodes located close to the SINET. Stage 2 of nodes along the distal arterial branches of the mesenteric artery. Stage 3 included nodes extending along the SMA trunk without encasing it. Stage 4 included nodal involvement encasing the SMA or the retroperitoneum. While stages 1 to 3 are considered operable, with a carful dissection around the vessels and over the nodes up to the root of the mesentery, stage 4 are considered inoperable. Partelli *et al*[47] proposed a similar classification scheme consisting of three types, with type A including a resectable mesenteric disease, type B a borderline resectable disease, and type C consisting of a locally advanced or irresectable disease causing encasement of the SMA and SMV[47]. Due to the complex nature of these surgeries, it is recommended that the pre-operative evaluation and the surgical procedures should be performed in specialized NET centers[55].

Patients with vascular encasement can suffer from severe symptoms due to the impeded arterial supply to the small intestine or from inadequate venous drainage of the small bowel. Hellman *et al*[67] described a non-surgical treatment technique by an insertion of a self-expandable stent through the stenotic SMV, in a small cohort of seven patients. They demonstrated that by doing so, an 80% resolution of symptoms in four patients was achieved. Other palliative techniques described include surgical intestinal bypass in patients with bowel obstruction secondary to unresectable disease[35]. Non-operative management in these patients include symptomatic treatment with somatostatin analogues, nutritional support, and palliative care, although a detailed discussion of these treatments is beyond the scope of this review[68].

**Surgical therapy of liver metastases**

Liver metastases are relatively common among SINET patients, with an incidence of 30%-50% at initial presentation[26,69]. These metastases can cause an excessive hypersecretion of hormones resulting in a carcinoid syndrome and can lead to liver failure due to hepatic replacement by tumor. Therefore, the goals of treatment of hepatic disease include biochemical and tumor control[42]. Surgery is generally proposed when curative intent is possible, though debulking with a threshold of 90% of hepatic metastatic disease has been shown to improve quality of life and overall survival[70]. Several studies have found that an R2 resection, is comparable to an R0 resection in terms of overall survival and disease specific survival[71-73]. Thus, surgical cytoreduction should be attempted in patients with an adequate performance status and a sufficient postoperative future liver remnant. Although a detailed discussion of these treatments is beyond the scope of this review, this generally includes major hepatic resections along with parenchymal-sparing procedures such as nonanatomic parenchymal resections, enucleations, and intraoperative ablation. In selected patients, with diffuse unresectable liver metastatic disease liver transplantation may be possible therapy option[48].

**Prophylactic Cholecystectomy in SINET Patients**

Somatostatin analogue treatment is the mainstay antisecretory therapy in functioning SINET and has become the first line therapy for the control of carcinoid symptoms[74,75]. Recent research demonstrates that beyond the symptomatic control, SSAs have an antiproliferative effect and inhibit tumor growth[76,77]. These have established SSA as the first-line treatment of functional and nonfunctional metastatic SINETs[78].

Long-term therapy with SSAs has its toll. The most serious adverse complication described with long-term SSA is biliary stone formation[79]. Previous small retrospective studies found that the prevalence of gallstones in patients on SSAs is as high as 52%[80,81]. A recent retrospective study by Brighi *et al*[82] demonstrated, in a cohort of 164 patients with a diagnosis of neuroendocrine neoplasms without a history of biliary stone, that 60 (36.6%) developed gallbladder stones after a mean of 36.7 mo from when SSA therapy was started, yet only 17 patients suffered from a symptomatic biliary disease. In a multicenter retrospective from 7 Italian centers, including a cohort of 478 patients started on SSA with a diagnosis of NET, 129 (27%) developed biliary stone disease, and 36 patients (7.5% of the cohort) developed biliary complications[83]. In this cohort the use of prophylactic ursodeoxycholic acid did not have a protective effect, however previous surgery for primary SINET was a significant risk factor for developing gallstones. Based on these data, the authors recommend a prophylactic cholecystectomy in all patients undergoing surgery for primary GI-NETs.

Regarding the surgical risk, preforming a concurrent prophylactic cholecystectomy at time of surgery for SINETs, did not increase postoperative morbidity in cholecystectomy *vs* no cholecystectomy groups (11.8% *vs* 11.1%, respectively; *P* = 0.79) or mortality (1.4% *vs* 0.6%, respectively; *P* = 0.29), in a large cohort of 1300 patients[84].

In the 2016 ENET guidelines for NET of the of the jejunum and ileum, the authors conclude that a cholecystectomy may be performed as a prophylactic measure against the development of gallstones in patients that will require SSA therapy, however, they stress that the benefit of this has never been prospectively proven[35]. In the ENET latest (2022) guidelines for carcinoid syndrome, this practice is further questioned, as the authors warn that a prophylactic cholecystectomy may worsen diarrhea in patients with previous small bowel resection[85].

The NANETS Consensus Guidelines for the surgical management of SINETs, recommend preforming a prophylactic cholecystectomy only in patients who are likely to receive SSA therapy, and only at the time of the initial small bowel operation[55]. Patients who aren’t planned for an abdominal operation and are receiving SSA should only undergo a cholecystectomy if biliary symptoms develop.

We believe that as long as prospective, multi-center, and randomized trials are lacking, patients should be informed about the option of preforming a simultaneous cholecystectomy, including the risks and benefits of this practice, and a joint consent should be reached.

**Perioperative Octreotide treatment**

Manipulation of SINETs during surgery, or even the administration of anesthetic agents, can lead to a sudden spike of circulating levels of serotonin and other vasoactive substances. This can cause sudden hemodynamic instability, known as a carcinoid crisis, a potentially life-threatening event[86]. Early reports have suggested that the administration of octreotide, an SSA, can rapidly reverse the symptoms and potentially resolve this crisis[87,88]. Furthermore, it has been generally accepted that the prophylactic administration of octreotide perioperatively can prevent a carcinoid crisis. In 2011, Kinney *et al*[89] described a cohort of 119 patients with metastatic NET undergoing abdominal surgery, of those patients, 45 received intraoperative octreotide and not one of them experienced intraoperative complications while of the 73 patients who did not receive octreotide eight (11.0%) suffered from intraoperative complications. They concluded that the use of octreotide intraoperatively was associated with a decreased frequency of intraoperative complications, however, due to the retrospective nature of this study, they cannot infer any causal relationship.

Based on the report by Kinney *et al*[89] a retrospective study was conducted by Massimino *et al*[90] that analyzed 97 patients with GI NETS who have undergone intraabdominal operations performed by a single surgeon, 90% were treated with prophylactic octreotide, and 56% received at least one additional intraoperative dose. Intraoperative complication occurred in 24% of the patients, without correlation to octreotide administration. The authors conclude that preoperative and intraoperative boluses of octreotide are insufficient for preventing intraoperative complications in patients with carcinoid yet suggest that a continuous infusion of octreotide may be more effective. A follow-up prospective study was published by Condron *et al*[91] in 2016. They enrolled 127 patients with carcinoid tumor, who have undergone 150 surgeries under a continuous octreotide infusion of 500 μg/h. They found that 30% experienced intraoperative complications associated with a carcinoid crisis, and concluded that octreotide infusions do not prevent intraoperative crises.

Woltering *et al*[92] published a retrospective study in 2016 on 150 consecutive patients with stage IV SINETs who underwent a total of 179 cytoreductive surgeries, and received a continuous 500 μg/h infusion of octreotide preoperatively, intraoperatively, and postoperatively. They considered episodes of hypotension lasting longer than 10 min as carcinoid crisis. The incidence of intraoperative carcinoid crisis was significantly lower than that of previous studies, 3.4% (6/179).

Finally, Kwon *et al*[93] published a retrospective study in 2019 on 75 patients with metastatic NETs who underwent liver resection, ablation, or embolotherapy. Twenty-nine patients received preoperative octreotide and 48 patients received an intraoperative infusion. As many as 32% of the patients experienced a carcinoid crisis or hemodynamic instability throughout the procedures. None of the prophylactic octreotide regimens were associated with a lower incidence of carcinoid crisis or hemodynamic instability. Despite their results, the authors suggest continuing the use of perioperative octreotide, given its overall safety profile, until larger prospective studies convincingly demonstrate a lack of efficacy.

Despite the lack of sufficient supporting evidence, most guidelines recommend perioperative prophylactic octreotide treatment with a continuous intravenous infusion starting from 12 h before surgery and continuing for at least 48 h postoperatively[94].

**CONCLUSION**

SINETs are unusual neoplasms, with an increasing incidence worldwide. As surgery remains the only curative treatment modality, surgeons will be facing increasing numbers of these patients, yet there are still several unanswered questions regarding their optimal surgical management. A significant part of the surgical common practice discussed in this review is based on expert opinions and small retrospective trials, and further prospective, multi-center, and randomized trials are required to shed lighter on important aspects of the surgical management of SINET patients. Nevertheless, it can be concluded, that patients with SINETs should be treated at high-volume experienced endocrine surgery centers where a multidisciplinary team is a routine part of patients’ evaluation and participates in decision making.

**REFERENCES**

1 **Anlauf M**, Sipos B, Boeck I, Baldus SE, Heikaus S, Krausch M, Knoefel WT, Begum N, Goretzki P, Schott M, Auernhammer CJ, Cremer B, Rinke A, Ezziddin S, Fottner C, Pöpperl G, Lahner H, Hörsch D, Gabbert HE, Komminoth P, Perren A, Klöppel G, Wiedenmann B, Pavel M, Pape U. [Neuroendocrine neoplasms of the distal jejunum and ileum]. *Pathologe* 2014; **35**: 283-93; quiz 294 [PMID: 24671468 DOI: 10.1007/s00292-013-1888-5]

2 **Keck KJ**, Maxwell JE, Utria AF, Bellizzi AM, Dillon JS, O'Dorisio TM, Howe JR. The Distal Predilection of Small Bowel Neuroendocrine Tumors. *Ann Surg Oncol* 2018; **25**: 3207-3213 [PMID: 30054825 DOI: 10.1245/s10434-018-6676-2]

3 **Bilimoria KY**, Bentrem DJ, Wayne JD, Ko CY, Bennett CL, Talamonti MS. Small bowel cancer in the United States: changes in epidemiology, treatment, and survival over the last 20 years. *Ann Surg* 2009; **249**: 63-71 [PMID: 19106677 DOI: 10.1097/SLA.0b013e31818e4641]

4 **Das S**, Dasari A. Epidemiology, Incidence, and Prevalence of Neuroendocrine Neoplasms: Are There Global Differences? *Curr Oncol Rep* 2021; **23**: 43 [PMID: 33719003 DOI: 10.1007/s11912-021-01029-7]

5 **Lee MR**, Harris C, Baeg KJ, Aronson A, Wisnivesky JP, Kim MK. Incidence Trends of Gastroenteropancreatic Neuroendocrine Tumors in the United States. *Clin Gastroenterol Hepatol* 2019; **17**: 2212-2217.e1 [PMID: 30580091 DOI: 10.1016/j.cgh.2018.12.017]

6 **Fraenkel M**, Kim M, Faggiano A, de Herder WW, Valk GD; Knowledge NETwork. Incidence of gastroenteropancreatic neuroendocrine tumours: a systematic review of the literature. *Endocr Relat Cancer* 2014; **21**: R153-R163 [PMID: 24322304 DOI: 10.1530/ERC-13-0125]

7 **Dasari A**, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, Shih T, Yao JC. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. *JAMA Oncol* 2017; **3**: 1335-1342 [PMID: 28448665 DOI: 10.1001/jamaoncol.2017.0589]

8 **Ellis L**, Shale MJ, Coleman MP. Carcinoid tumors of the gastrointestinal tract: trends in incidence in England since 1971. *Am J Gastroenterol* 2010; **105**: 2563-2569 [PMID: 20823835 DOI: 10.1038/ajg.2010.341]

9 **Lawrence B**, Gustafsson BI, Chan A, Svejda B, Kidd M, Modlin IM. The epidemiology of gastroenteropancreatic neuroendocrine tumors. *Endocrinol Metab Clin North Am* 2011; **40**: 1-18, vii [PMID: 21349409 DOI: 10.1016/j.ecl.2010.12.005]

10 **Garcia-Carbonero R**, Capdevila J, Crespo-Herrero G, Díaz-Pérez JA, Martínez Del Prado MP, Alonso Orduña V, Sevilla-García I, Villabona-Artero C, Beguiristain-Gómez A, Llanos-Muñoz M, Marazuela M, Alvarez-Escola C, Castellano D, Vilar E, Jiménez-Fonseca P, Teulé A, Sastre-Valera J, Benavent-Viñuelas M, Monleon A, Salazar R. Incidence, patterns of care and prognostic factors for outcome of gastroenteropancreatic neuroendocrine tumors (GEP-NETs): results from the National Cancer Registry of Spain (RGETNE). *Ann Oncol* 2010; **21**: 1794-1803 [PMID: 20139156 DOI: 10.1093/annonc/mdq022]

11 **Lepage C**, Bouvier AM, Manfredi S, Dancourt V, Faivre J. Incidence and management of primary malignant small bowel cancers: a well-defined French population study. *Am J Gastroenterol* 2006; **101**: 2826-2832 [PMID: 17026561 DOI: 10.1111/j.1572-0241.2006.00854.x]

12 **Klimstra DS**, Modlin IR, Coppola D, Lloyd RV, Suster S. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. *Pancreas* 2010; **39**: 707-712 [PMID: 20664470 DOI: 10.1097/MPA.0b013e3181ec124e]

13 **Nagtegaal ID**, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, Washington KM, Carneiro F, Cree IA; WHO Classification of Tumours Editorial Board. The 2019 WHO classification of tumours of the digestive system. *Histopathology* 2020; **76**: 182-188 [PMID: 31433515 DOI: 10.1111/his.13975]

14 **Popa O**, Taban SM, Pantea S, Plopeanu AD, Barna RA, Cornianu M, Pascu AA, Dema ALC. The new WHO classification of gastrointestinal neuroendocrine tumors and immunohistochemical expression of somatostatin receptor 2 and 5. *Exp Ther Med* 2021; **22**: 1179 [PMID: 34475969 DOI: 10.3892/etm.2021.10613]

15 **Modlin IM**, Oberg K, Chung DC, Jensen RT, de Herder WW, Thakker RV, Caplin M, Delle Fave G, Kaltsas GA, Krenning EP, Moss SF, Nilsson O, Rindi G, Salazar R, Ruszniewski P, Sundin A. Gastroenteropancreatic neuroendocrine tumours. *Lancet Oncol* 2008; **9**: 61-72 [PMID: 18177818 DOI: 10.1016/S1470-2045(07)70410-2]

16 **Mancuso K**, Kaye AD, Boudreaux JP, Fox CJ, Lang P, Kalarickal PL, Gomez S, Primeaux PJ. Carcinoid syndrome and perioperative anesthetic considerations. *J Clin Anesth* 2011; **23**: 329-341 [PMID: 21663822 DOI: 10.1016/j.jclinane.2010.12.009]

17 **Condron ME**, Jameson NE, Limbach KE, Bingham AE, Sera VA, Anderson RB, Schenning KJ, Yockelson S, Harukuni I, Kahl EA, Dewey E, Pommier SJ, Pommier RF. A prospective study of the pathophysiology of carcinoid crisis. *Surgery* 2019; **165**: 158-165 [PMID: 30415870 DOI: 10.1016/j.surg.2018.04.093]

18 **Kulke MH**, Mayer RJ. Carcinoid tumors. *N Engl J Med* 1999; **340**: 858-868 [PMID: 10080850 DOI: 10.1056/NEJM199903183401107]

19 **Bendelow J**, Apps E, Jones LE, Poston GJ. Carcinoid syndrome. *Eur J Surg Oncol* 2008; **34**: 289-296 [PMID: 18068329 DOI: 10.1016/j.ejso.2007.07.202]

20 **Eriksson B**, Klöppel G, Krenning E, Ahlman H, Plöckinger U, Wiedenmann B, Arnold R, Auernhammer C, Körner M, Rindi G, Wildi S; Frascati Consensus Conference participants. Consensus guidelines for the management of patients with digestive neuroendocrine tumors--well-differentiated jejunal-ileal tumor/carcinoma. *Neuroendocrinology* 2008; **87**: 8-19 [PMID: 18097129 DOI: 10.1159/000111034]

21 **Modlin IM**, Shapiro MD, Kidd M. Carcinoid tumors and fibrosis: an association with no explanation. *Am J Gastroenterol* 2004; **99**: 2466-2478 [PMID: 15571597 DOI: 10.1111/j.1572-0241.2004.40507.x]

22 **Bernheim AM**, Connolly HM, Hobday TJ, Abel MD, Pellikka PA. Carcinoid heart disease. *Prog Cardiovasc Dis* 2007; **49**: 439-451 [PMID: 17498524 DOI: 10.1016/j.pcad.2006.12.002]

23 **Daskalakis K**, Karakatsanis A, Stålberg P, Norlén O, Hellman P. Clinical signs of fibrosis in small intestinal neuroendocrine tumours. *Br J Surg* 2017; **104**: 69-75 [PMID: 27861745 DOI: 10.1002/bjs.10333]

24 **Vinik AI**, Chaya C. Clinical Presentation and Diagnosis of Neuroendocrine Tumors. *Hematol Oncol Clin North Am* 2016; **30**: 21-48 [PMID: 26614367 DOI: 10.1016/j.hoc.2015.08.006]

25 **Hellman P**, Lundström T, Ohrvall U, Eriksson B, Skogseid B, Oberg K, Tiensuu Janson E, Akerström G. Effect of surgery on the outcome of midgut carcinoid disease with lymph node and liver metastases. *World J Surg* 2002; **26**: 991-997 [PMID: 12016480 DOI: 10.1007/s00268-002-6630-z]

26 **Yao JC**, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, Abdalla EK, Fleming JB, Vauthey JN, Rashid A, Evans DB. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol* 2008; **26**: 3063-3072 [PMID: 18565894 DOI: 10.1200/JCO.2007.15.4377]

27 **Norlén O**, Stålberg P, Öberg K, Eriksson J, Hedberg J, Hessman O, Janson ET, Hellman P, Åkerström G. Long-term results of surgery for small intestinal neuroendocrine tumors at a tertiary referral center. *World J Surg* 2012; **36**: 1419-1431 [PMID: 21984144 DOI: 10.1007/s00268-011-1296-z]

28 **Klöppel G**, Perren A, Heitz PU. The gastroenteropancreatic neuroendocrine cell system and its tumors: the WHO classification. *Ann N Y Acad Sci* 2004; **1014**: 13-27 [PMID: 15153416 DOI: 10.1196/annals.1294.002]

29 **Landry CS**, Lin HY, Phan A, Charnsangavej C, Abdalla EK, Aloia T, Nicolas Vauthey J, Katz MH, Yao JC, Fleming JB. Resection of at-risk mesenteric lymph nodes is associated with improved survival in patients with small bowel neuroendocrine tumors. *World J Surg* 2013; **37**: 1695-1700 [PMID: 23657749 DOI: 10.1007/s00268-013-1918-8]

30 **Hallet J**, Law CH, Cukier M, Saskin R, Liu N, Singh S. Exploring the rising incidence of neuroendocrine tumors: a population-based analysis of epidemiology, metastatic presentation, and outcomes. *Cancer* 2015; **121**: 589-597 [PMID: 25312765 DOI: 10.1002/cncr.29099]

31 **Tran CG**, Sherman SK, Howe JR. The Landmark Series: Management of Small Bowel Neuroendocrine Tumors. *Ann Surg Oncol* 2021; **28**: 2741-2751 [PMID: 33452604 DOI: 10.1245/s10434-020-09566-4]

32 **Stridsberg M**, Eriksson B, Oberg K, Janson ET. A comparison between three commercial kits for chromogranin A measurements. *J Endocrinol* 2003; **177**: 337-341 [PMID: 12740022 DOI: 10.1677/joe.0.1770337]

33 **Vinik AI**, Silva MP, Woltering EA, Go VL, Warner R, Caplin M. Biochemical testing for neuroendocrine tumors. *Pancreas* 2009; **38**: 876-889 [PMID: 19855234 DOI: 10.1097/MPA.0b013e3181bc0e77]

34 **Arnold R**, Wilke A, Rinke A, Mayer C, Kann PH, Klose KJ, Scherag A, Hahmann M, Müller HH, Barth P. Plasma chromogranin A as marker for survival in patients with metastatic endocrine gastroenteropancreatic tumors. *Clin Gastroenterol Hepatol* 2008; **6**: 820-827 [PMID: 18547872 DOI: 10.1016/j.cgh.2008.02.052]

35 **Niederle B**, Pape UF, Costa F, Gross D, Kelestimur F, Knigge U, Öberg K, Pavel M, Perren A, Toumpanakis C, O'Connor J, O'Toole D, Krenning E, Reed N, Kianmanesh R; Vienna Consensus Conference participants. ENETS Consensus Guidelines Update for Neuroendocrine Neoplasms of the Jejunum and Ileum. *Neuroendocrinology* 2016; **103**: 125-138 [PMID: 26758972 DOI: 10.1159/000443170]

36 **Kaltsas G**, Rockall A, Papadogias D, Reznek R, Grossman AB. Recent advances in radiological and radionuclide imaging and therapy of neuroendocrine tumours. *Eur J Endocrinol* 2004; **151**: 15-27 [PMID: 15248818 DOI: 10.1530/eje.0.1510015]

37 **Dromain C**, de Baere T, Lumbroso J, Caillet H, Laplanche A, Boige V, Ducreux M, Duvillard P, Elias D, Schlumberger M, Sigal R, Baudin E. Detection of liver metastases from endocrine tumors: a prospective comparison of somatostatin receptor scintigraphy, computed tomography, and magnetic resonance imaging. *J Clin Oncol* 2005; **23**: 70-78 [PMID: 15625361 DOI: 10.1200/JCO.2005.01.013]

38 **Hofland J**, Kaltsas G, de Herder WW. Advances in the Diagnosis and Management of Well-Differentiated Neuroendocrine Neoplasms. *Endocr Rev* 2020; **41**: 371-403 [PMID: 31555796 DOI: 10.1210/endrev/bnz004]

39 **Pilleul F**, Penigaud M, Milot L, Saurin JC, Chayvialle JA, Valette PJ. Possible small-bowel neoplasms: contrast-enhanced and water-enhanced multidetector CT enteroclysis. *Radiology* 2006; **241**: 796-801 [PMID: 17053201 DOI: 10.1148/radiol.2413051429]

40 **Keck KJ**, Maxwell JE, Menda Y, Bellizzi A, Dillon J, O'Dorisio TM, Howe JR. Identification of primary tumors in patients presenting with metastatic gastroenteropancreatic neuroendocrine tumors. *Surgery* 2017; **161**: 272-279 [PMID: 27863780 DOI: 10.1016/j.surg.2016.05.055]

41 **Dromain C**, de Baere T, Baudin E, Galline J, Ducreux M, Boige V, Duvillard P, Laplanche A, Caillet H, Lasser P, Schlumberger M, Sigal R. MR imaging of hepatic metastases caused by neuroendocrine tumors: comparing four techniques. *AJR Am J Roentgenol* 2003; **180**: 121-128 [PMID: 12490490 DOI: 10.2214/ajr.180.1.1800121]

42 **Boudreaux JP**, Klimstra DS, Hassan MM, Woltering EA, Jensen RT, Goldsmith SJ, Nutting C, Bushnell DL, Caplin ME, Yao JC; North American Neuroendocrine Tumor Society (NANETS). The NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: well-differentiated neuroendocrine tumors of the Jejunum, Ileum, Appendix, and Cecum. *Pancreas* 2010; **39**: 753-766 [PMID: 20664473 DOI: 10.1097/MPA.0b013e3181ebb2a5]

43 **Koopmans KP**, de Vries EG, Kema IP, Elsinga PH, Neels OC, Sluiter WJ, van der Horst-Schrivers AN, Jager PL. Staging of carcinoid tumours with 18F-DOPA PET: a prospective, diagnostic accuracy study. *Lancet Oncol* 2006; **7**: 728-734 [PMID: 16945767 DOI: 10.1016/S1470-2045(06)70801-4]

44 **Sadowski SM**, Neychev V, Millo C, Shih J, Nilubol N, Herscovitch P, Pacak K, Marx SJ, Kebebew E. Prospective Study of 68Ga-DOTATATE Positron Emission Tomography/Computed Tomography for Detecting Gastro-Entero-Pancreatic Neuroendocrine Tumors and Unknown Primary Sites. *J Clin Oncol* 2016; **34**: 588-596 [PMID: 26712231 DOI: 10.1200/JCO.2015.64.0987]

45 **Dahdaleh FS**, Lorenzen A, Rajput M, Carr JC, Liao J, Menda Y, O'Dorisio TM, Howe JR. The value of preoperative imaging in small bowel neuroendocrine tumors. *Ann Surg Oncol* 2013; **20**: 1912-1917 [PMID: 23283442 DOI: 10.1245/s10434-012-2836-y]

46 **Choi AB**, Maxwell JE, Keck KJ, Bellizzi AJ, Dillon JS, OʼDorisio TM, Howe JR. Is Multifocality an Indicator of Aggressive Behavior in Small Bowel Neuroendocrine Tumors? *Pancreas* 2017; **46**: 1115-1120 [PMID: 28902780 DOI: 10.1097/MPA.0000000000000911]

47 **Partelli S**, Bartsch DK, Capdevila J, Chen J, Knigge U, Niederle B, Nieveen van Dijkum EJM, Pape UF, Pascher A, Ramage J, Reed N, Ruszniewski P, Scoazec JY, Toumpanakis C, Kianmanesh R, Falconi M; Antibes Consensus Conference participants. ENETS Consensus Guidelines for Standard of Care in Neuroendocrine Tumours: Surgery for Small Intestinal and Pancreatic Neuroendocrine Tumours. *Neuroendocrinology* 2017; **105**: 255-265 [PMID: 28237989 DOI: 10.1159/000464292]

48 **Pavel M**, Baudin E, Couvelard A, Krenning E, Öberg K, Steinmüller T, Anlauf M, Wiedenmann B, Salazar R; Barcelona Consensus Conference participants. ENETS Consensus Guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hindgut, and unknown primary. *Neuroendocrinology* 2012; **95**: 157-176 [PMID: 22262022 DOI: 10.1159/000335597]

49 **Kianmanesh R**, O'Toole D, Sauvanet A, Ruszniewski P, Belghiti J. [Surgical treatment of gastric, enteric pancreatic endocrine tumors. Part 2. treatment of hepatic metastases]. *J Chir (Paris)* 2005; **142**: 208-219 [PMID: 16335893 DOI: 10.1016/s0021-7697(05)80906-8]

50 **Almond LM**, Hodson J, Ford SJ, Gourevitch D, Roberts KJ, Shah T, Isaac J, Desai A. Role of palliative resection of the primary tumour in advanced pancreatic and small intestinal neuroendocrine tumours: A systematic review and meta-analysis. *Eur J Surg Oncol* 2017; **43**: 1808-1815 [PMID: 28583792 DOI: 10.1016/j.ejso.2017.05.016]

51 **Tsilimigras DI**, Ntanasis-Stathopoulos I, Kostakis ID, Moris D, Schizas D, Cloyd JM, Pawlik TM. Is Resection of Primary Midgut Neuroendocrine Tumors in Patients with Unresectable Metastatic Liver Disease Justified? A Systematic Review and Meta-Analysis. *J Gastrointest Surg* 2019; **23**: 1044-1054 [PMID: 30671800 DOI: 10.1007/s11605-018-04094-9]

52 **Daskalakis K**, Karakatsanis A, Hessman O, Stuart HC, Welin S, Tiensuu Janson E, Öberg K, Hellman P, Norlén O, Stålberg P. Association of a Prophylactic Surgical Approach to Stage IV Small Intestinal Neuroendocrine Tumors With Survival. *JAMA Oncol* 2018; **4**: 183-189 [PMID: 29049611 DOI: 10.1001/jamaoncol.2017.3326]

53 **Bennett S**, Coburn N, Law C, Mahar A, Zhao H, Singh S, Zuk V, Myrehaug S, Gupta V, Levy J, Hallet J. Upfront Small Bowel Resection for Small Bowel Neuroendocrine Tumors With Synchronous Metastases: A Propensity-score Matched Comparative Population-based Analysis. *Ann Surg* 2022; **276**: e450-e458 [PMID: 33214481 DOI: 10.1097/SLA.0000000000004647]

54 **Givi B**, Pommier SJ, Thompson AK, Diggs BS, Pommier RF. Operative resection of primary carcinoid neoplasms in patients with liver metastases yields significantly better survival. *Surgery* 2006; **140**: 891-7; discussion 897-8 [PMID: 17188135 DOI: 10.1016/j.surg.2006.07.033]

55 **Howe JR**, Cardona K, Fraker DL, Kebebew E, Untch BR, Wang YZ, Law CH, Liu EH, Kim MK, Menda Y, Morse BG, Bergsland EK, Strosberg JR, Nakakura EK, Pommier RF. The Surgical Management of Small Bowel Neuroendocrine Tumors: Consensus Guidelines of the North American Neuroendocrine Tumor Society. *Pancreas* 2017; **46**: 715-731 [PMID: 28609357 DOI: 10.1097/MPA.0000000000000846]

56 **Watson RG**, Johnston CF, O'Hare MM, Anderson JR, Wilson BG, Collins JS, Sloan JM, Buchanan KD. The frequency of gastrointestinal endocrine tumours in a well-defined population--Northern Ireland 1970-1985. *Q J Med* 1989; **72**: 647-657 [PMID: 2575263]

57 **Yantiss RK**, Odze RD, Farraye FA, Rosenberg AE. Solitary versus multiple carcinoid tumors of the ileum: a clinical and pathologic review of 68 cases. *Am J Surg Pathol* 2003; **27**: 811-817 [PMID: 12766586 DOI: 10.1097/00000478-200306000-00013]

58 **Burke AP**, Thomas RM, Elsayed AM, Sobin LH. Carcinoids of the jejunum and ileum: an immunohistochemical and clinicopathologic study of 167 cases. *Cancer* 1997; **79**: 1086-1093 [PMID: 9070484]

59 **Katona TM**, Jones TD, Wang M, Abdul-Karim FW, Cummings OW, Cheng L. Molecular evidence for independent origin of multifocal neuroendocrine tumors of the enteropancreatic axis. *Cancer Res* 2006; **66**: 4936-4942 [PMID: 16651451 DOI: 10.1158/0008-5472.CAN-05-4184]

60 **Wang YZ**, Joseph S, Lindholm E, Lyons J, Boudreaux JP, Woltering EA. Lymphatic mapping helps to define resection margins for midgut carcinoids. *Surgery* 2009; **146**: 993-997 [PMID: 19958925 DOI: 10.1016/j.surg.2009.09.005]

61 **Wang SC**, Parekh JR, Zuraek MB, Venook AP, Bergsland EK, Warren RS, Nakakura EK. Identification of unknown primary tumors in patients with neuroendocrine liver metastases. *Arch Surg* 2010; **145**: 276-280 [PMID: 20231629 DOI: 10.1001/archsurg.2010.10]

62 **Figueiredo MN**, Maggiori L, Gaujoux S, Couvelard A, Guedj N, Ruszniewski P, Panis Y. Surgery for small-bowel neuroendocrine tumors: is there any benefit of the laparoscopic approach? *Surg Endosc* 2014; **28**: 1720-1726 [PMID: 24380996 DOI: 10.1007/s00464-013-3381-x]

63 **Wang YZ**, Carrasquillo JP, McCord E, Vidrine R, Lobo ML, Zamin SA, Boudreaux P, Woltering E. Reappraisal of lymphatic mapping for midgut neuroendocrine patients undergoing cytoreductive surgery. *Surgery* 2014; **156**: 1498-502; discussion 1502-3 [PMID: 25456941 DOI: 10.1016/j.surg.2014.05.028]

64 **Watzka FM**, Fottner C, Miederer M, Weber MM, Schad A, Lang H, Musholt TJ. Surgical Treatment of NEN of Small Bowel: A Retrospective Analysis. *World J Surg* 2016; **40**: 749-758 [PMID: 26822157 DOI: 10.1007/s00268-016-3432-2]

65 **Zaidi MY**, Lopez-Aguiar AG, Dillhoff M, Beal E, Poultsides G, Makris E, Rocha F, Crown A, Idrees K, Marincola Smith P, Nathan H, Beems M, Abbott D, Barrett JR, Fields RC, Davidson J, Cardona K, Maithel SK. Prognostic Role of Lymph Node Positivity and Number of Lymph Nodes Needed for Accurately Staging Small-Bowel Neuroendocrine Tumors. *JAMA Surg* 2019; **154**: 134-140 [PMID: 30383112 DOI: 10.1001/jamasurg.2018.3865]

66 **Ohrvall U**, Eriksson B, Juhlin C, Karacagil S, Rastad J, Hellman P, Akerström G. Method for dissection of mesenteric metastases in mid-gut carcinoid tumors. *World J Surg* 2000; **24**: 1402-1408 [PMID: 11038214 DOI: 10.1007/s002680010232]

67 **Hellman P**, Hessman O, Akerström G, Stålberg P, Hennings J, Björck M, Eriksson LG. Stenting of the superior mesenteric vein in midgut carcinoid disease with large mesenteric masses. *World J Surg* 2010; **34**: 1373-1379 [PMID: 20066417 DOI: 10.1007/s00268-009-0361-3]

68 **Koea J**; Commonwealth Neuroendocrine Tumour Research Collaborative (CommNETs) Surgical Section. Management of Locally Advanced and Unresectable Small Bowel Neuroendocrine Tumours. *World J Surg* 2021; **45**: 219-224 [PMID: 32860138 DOI: 10.1007/s00268-020-05740-7]

69 **Pasieka JL**. Carcinoid tumors. *Surg Clin North Am* 2009; **89**: 1123-1137 [PMID: 19836488 DOI: 10.1016/j.suc.2009.06.008]

70 **Sarmiento JM**, Heywood G, Rubin J, Ilstrup DM, Nagorney DM, Que FG. Surgical treatment of neuroendocrine metastases to the liver: a plea for resection to increase survival. *J Am Coll Surg* 2003; **197**: 29-37 [PMID: 12831921 DOI: 10.1016/s1072-7515(03)00230-8]

71 **Mayo SC**, de Jong MC, Pulitano C, Clary BM, Reddy SK, Gamblin TC, Celinksi SA, Kooby DA, Staley CA, Stokes JB, Chu CK, Ferrero A, Schulick RD, Choti MA, Mentha G, Strub J, Bauer TW, Adams RB, Aldrighetti L, Capussotti L, Pawlik TM. Surgical management of hepatic neuroendocrine tumor metastasis: results from an international multi-institutional analysis. *Ann Surg Oncol* 2010; **17**: 3129-3136 [PMID: 20585879 DOI: 10.1245/s10434-010-1154-5]

72 **Graff-Baker AN**, Sauer DA, Pommier SJ, Pommier RF. Expanded criteria for carcinoid liver debulking: Maintaining survival and increasing the number of eligible patients. *Surgery* 2014; **156**: 1369-76; discussion 1376-7 [PMID: 25456912 DOI: 10.1016/j.surg.2014.08.009]

73 **Glazer ES**, Tseng JF, Al-Refaie W, Solorzano CC, Liu P, Willborn KA, Abdalla EK, Vauthey JN, Curley SA. Long-term survival after surgical management of neuroendocrine hepatic metastases. *HPB (Oxford)* 2010; **12**: 427-433 [PMID: 20662794 DOI: 10.1111/j.1477-2574.2010.00198.x]

74 **Stueven AK**, Kayser A, Wetz C, Amthauer H, Wree A, Tacke F, Wiedenmann B, Roderburg C, Jann H. Somatostatin Analogues in the Treatment of Neuroendocrine Tumors: Past, Present and Future. *Int J Mol Sci* 2019; **20** [PMID: 31234481 DOI: 10.3390/ijms20123049]

75 **Singh S**, Asa SL, Dey C, Kennecke H, Laidley D, Law C, Asmis T, Chan D, Ezzat S, Goodwin R, Mete O, Pasieka J, Rivera J, Wong R, Segelov E, Rayson D. Diagnosis and management of gastrointestinal neuroendocrine tumors: An evidence-based Canadian consensus. *Cancer Treat Rev* 2016; **47**: 32-45 [PMID: 27236421 DOI: 10.1016/j.ctrv.2016.05.003]

76 **Rinke A**, Müller HH, Schade-Brittinger C, Klose KJ, Barth P, Wied M, Mayer C, Aminossadati B, Pape UF, Bläker M, Harder J, Arnold C, Gress T, Arnold R; PROMID Study Group. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *J Clin Oncol* 2009; **27**: 4656-4663 [PMID: 19704057 DOI: 10.1200/JCO.2009.22.8510]

77 **Caplin ME**, Pavel M, Ćwikła JB, Phan AT, Raderer M, Sedláčková E, Cadiot G, Wolin EM, Capdevila J, Wall L, Rindi G, Langley A, Martinez S, Blumberg J, Ruszniewski P; CLARINET Investigators. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med* 2014; **371**: 224-233 [PMID: 25014687 DOI: 10.1056/NEJMoa1316158]

78 **Scott AT**, Howe JR. Management of Small Bowel Neuroendocrine Tumors. *J Oncol Pract* 2018; **14**: 471-482 [PMID: 30096273 DOI: 10.1200/JOP.18.00135]

79 **Grasso LF**, Auriemma RS, Pivonello R, Colao A. Adverse events associated with somatostatin analogs in acromegaly. *Expert Opin Drug Saf* 2015; **14**: 1213-1226 [PMID: 26184380 DOI: 10.1517/14740338.2015.1059817]

80 **Trendle MC**, Moertel CG, Kvols LK. Incidence and morbidity of cholelithiasis in patients receiving chronic octreotide for metastatic carcinoid and malignant islet cell tumors. *Cancer* 1997; **79**: 830-834 [PMID: 9024721 DOI: 10.1002/(sici)1097-0142(19970215)79:4<830::aid-cncr20>3.0.co;2-#]

81 **Norlén O**, Hessman O, Stålberg P, Akerström G, Hellman P. Prophylactic cholecystectomy in midgut carcinoid patients. *World J Surg* 2010; **34**: 1361-1367 [PMID: 20130865 DOI: 10.1007/s00268-010-0428-1]

82 **Brighi N**, Lamberti G, Maggio I, Manuzzi L, Ricci C, Casadei R, Santini D, Mosconi C, Lisotti A, Ambrosini V, Pantaleo MA, Campana D. Biliary stone disease in patients receiving somatostatin analogs for neuroendocrine neoplasms. A retrospective observational study. *Dig Liver Dis* 2019; **51**: 689-694 [PMID: 30314949 DOI: 10.1016/j.dld.2018.09.013]

83 **Brighi N**, Panzuto F, Modica R, Gelsomino F, Albertelli M, Pusceddu S, Massironi S, Lamberti G, Rinzivillo M, Faggiano A, Spallanzani A, Ferone D, Prinzi N, Rossi RE, Annibale B, Colao AM, Campana D. Biliary Stone Disease in Patients with Neuroendocrine Tumors Treated with Somatostatin Analogs: A Multicenter Study. *Oncologist* 2020; **25**: 259-265 [PMID: 32162819 DOI: 10.1634/theoncologist.2019-0403]

84 **Sinnamon AJ**, Neuwirth MG, Vining CC, Sharoky CE, Yang YX, Kelz RR, Fraker DL, Roses RE, Karakousis GC. Prophylactic Cholecystectomy at Time of Surgery for Small Bowel Neuroendocrine Tumor Does Not Increase Postoperative Morbidity. *Ann Surg Oncol* 2018; **25**: 239-245 [PMID: 29067602 DOI: 10.1245/s10434-017-6093-y]

85 **Grozinsky-Glasberg S**, Davar J, Hofland J, Dobson R, Prasad V, Pascher A, Denecke T, Tesselaar MET, Panzuto F, Albåge A, Connolly HM, Obadia JF, Riechelmann R, Toumpanakis C. European Neuroendocrine Tumor Society (ENETS) 2022 Guidance Paper for Carcinoid Syndrome and Carcinoid Heart Disease. *J Neuroendocrinol* 2022; **34**: e13146 [PMID: 35613326 DOI: 10.1111/jne.13146]

86 **Gade AK**, Olariu E, Douthit NT. Carcinoid Syndrome: A Review. *Cureus* 2020; **12**: e7186 [PMID: 32257725 DOI: 10.7759/cureus.7186]

87 **Kvols LK**, Martin JK, Marsh HM, Moertel CG. Rapid reversal of carcinoid crisis with a somatostatin analogue. *N Engl J Med* 1985; **313**: 1229-1230 [PMID: 2865675 DOI: 10.1056/NEJM198511073131915]

88 **Kvols LK**, Moertel CG, O'Connell MJ, Schutt AJ, Rubin J, Hahn RG. Treatment of the malignant carcinoid syndrome. Evaluation of a long-acting somatostatin analogue. *N Engl J Med* 1986; **315**: 663-666 [PMID: 2427948 DOI: 10.1056/nejm198609113151102]

89 **Kinney MA**, Warner ME, Nagorney DM, Rubin J, Schroeder DR, Maxson PM, Warner MA. Perianaesthetic risks and outcomes of abdominal surgery for metastatic carcinoid tumours. *Br J Anaesth* 2001; **87**: 447-452 [PMID: 11517130 DOI: 10.1093/bja/87.3.447]

90 **Massimino K**, Harrskog O, Pommier S, Pommier R. Octreotide LAR and bolus octreotide are insufficient for preventing intraoperative complications in carcinoid patients. *J Surg Oncol* 2013; **107**: 842-846 [PMID: 23592524 DOI: 10.1002/jso.23323]

91 **Condron ME**, Pommier SJ, Pommier RF. Continuous infusion of octreotide combined with perioperative octreotide bolus does not prevent intraoperative carcinoid crisis. *Surgery* 2016; **159**: 358-365 [PMID: 26603846 DOI: 10.1016/j.surg.2015.05.036]

92 **Woltering EA**, Wright AE, Stevens MA, Wang YZ, Boudreaux JP, Mamikunian G, Riopelle JM, Kaye AD. Development of effective prophylaxis against intraoperative carcinoid crisis. *J Clin Anesth* 2016; **32**: 189-193 [PMID: 27290972 DOI: 10.1016/j.jclinane.2016.03.008]

93 **Kwon DH**, Paciorek A, Mulvey CK, Chan H, Fidelman N, Meng L, Nakakura EK, Zhang L, Bergsland EK, Van Loon K. Periprocedural Management of Patients Undergoing Liver Resection or Embolotherapy for Neuroendocrine Tumor Metastases. *Pancreas* 2019; **48**: 496-503 [PMID: 30946246 DOI: 10.1097/MPA.0000000000001271]

94 **Bardasi C**, Benatti S, Luppi G, Garajovà I, Piacentini F, Dominici M, Gelsomino F. Carcinoid Crisis: A Misunderstood and Unrecognized Oncological Emergency. *Cancers (Basel)* 2022; **14** [PMID: 35158931 DOI: 10.3390/cancers14030662]

**Footnotes**

**Conflict-of-interest statement:** The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. There was no external funding for this manuscript.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** December 9, 2022

**First decision:** February 8, 2023

**Article in press:**

**Specialty type:** Surgery

**Country/Territory of origin:** Israel

**Peer-review report’s scientific quality classification**

Grade A (Excellent): A

Grade B (Very good): B, B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Chisthi MM, India; Losurdo G, Italy **S-Editor:** Chen YL **L-Editor:** A **P-Editor:**

**Table 1 World Health Organization classification 2019 and grading criteria for neuroendocrine neoplasms of the gastrointestinal tract**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Terminology** | **Differentiation** | **Grade** | **Ki-67 proliferative index (%)** | **Mitotic index (per 10 high-power fields)** |
| NET, G1 | Well-differentiated | Low | < 3 | < 2 |
| NET, G2 | Well-differentiated | Intermediate | 3-20 | 2-20 |
| NET, G3 | Well-differentiated | High | > 20 | > 20 |
| NEC, SCNEC | Poorly differentiated | High | > 20 | > 20 |
| NEC, LCNEC | Poorly differentiated | High | > 20 | > 20 |
| Mixed neuroendocrine-non-neuroendocrine neoplasm | Well or poorly differentiated | Variable | Variable | Variable |

NEC: Neuroendocrine carcinoma; SCNEC: Small cell type neuroendocrine carcinoma; LCNEC: Large cell type neuroendocrine carcinoma.

**Table 2 The American Joint Committee on Cancer 8th edition staging of small intestinal neuroendocrine tumors**

|  |  |
| --- | --- |
| **Tumor** | **Description** |
| TX | The primary tumor cannot be evaluated |
| T0 | No evidence of primary tumor |
| T1 | Tumor ≤ 1 cm and only involves the lamina propria or submucosa |
| T2 | Tumor > 1 cm or invades muscularis propria |
| T3 | Tumor invades through muscularis propria intoSub-serosal tissues without serosal invasion |
| T4 | Tumor invades serosa or other organs |
| Lymph nodes |  |
| NX | Lymph nodes cannot be assessed |
| N0 | No regional lymph node metastasis |
| N1 | Lymph node metastasis < 12 nodes |
| N2 | Lymph node metastasis ≥ 12 nodes or mesenteric masses > 2 cm |
| Metastases |  |
| M0 | No distant metastasis |
| M1 | Distant metastasis |
| M1a | Metastasis limited to the liver |
| M1b | Metastases in at least one extrahepatic site |
| M1c | Both hepatic and extrahepatic metastases |
| Stage |  |
| Stage I | T1, N0, M0 |
| Stage II | T2 or T3, N0, M0 |
| Stage III | T4, N0, M0; any T, N1 or N2, M0 |
| Stage IV | Any T, any N, M1 |