ISSN 1948-9366 (online)

World Journal of

Gastrointestinal Surgery

World J Gastrointest Surg 2023 April 27; 15(4): 495-744

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Surgery

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The *WJGS* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 Edition of Journal Citation Reports® cites the 2021 impact factor (IF) for *WJGS* as 2.505; IF without journal self cites: 2.473; 5-year IF: 3.099; Journal Citation Indicator: 0.49; Ranking: 104 among 211 journals in surgery; Quartile category: Q2; Ranking: 81 among 93 journals in gastroenterology and hepatology; and Quartile category: Q4.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Gastrointestinal Surgery

ISSN
ISSN 1948-9366 (online)

LAUNCH DATE
November 30, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Peter Schemmer

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1948-9366/editorialboard.htm

PUBLICATION DATE
April 27, 2023

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https://www.wjgnet.com/bpg/gerinfo/204

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https://www.wjgnet.com/bpg/GerInfo/287

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World J Gastrointest Surg 2023 April 27; 15(4): 566-577

DOI: 10.4240/wjgs.v15.i4.566

ISSN 1948-9366 (online)

MINIREVIEWS

Surgical aspects of small intestinal neuroendocrine tumors

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Specialty type: Surgery

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

Peer-review model: Single blind

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

Received: December 9, 2022
Peer-review started: December 9, 2022
First decision: February 8, 2023
Revised: February 25, 2023
Accepted: March 27, 2023
Article in press: March 27, 2023
Published online: April 27, 2023

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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 metastases. 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

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.

Citation: Kupietzky A, Dover R, Mazeh H. Surgical aspects of small intestinal neuroendocrine tumors. *World J Gastrointest Surg* 2023; 15(4): 566-577
URL: https://www.wjgnet.com/1948-9366/full/v15/i4/566.htm
DOI: https://dx.doi.org/10.4240/wjgs.v15.i4.566

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 welldifferentiated 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 of 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

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

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 prospective 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 complic-

ations 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 uncommon 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.

FOOTNOTES

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.

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.

Country/Territory of origin: Israel

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S-Editor: Chen YL
L-Editor: A
P-Editor: Zhao S

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