

Surgical management of small intestinal neuroendocrine tumours

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Introduction

Gastroenteropancreatic neuroendocrine neoplasms (NENs) originate from neuroendocrine cells across the body; they are increasing in incidence and prevalence, as documented across several regions^{1–3}. The most frequent sites of NENs include the small intestine and the pancreas. The prevalence of small intestinal NENs was most recently estimated at 45 per 100 000

people and that of pancreas NENs at 35 per 100 000 people compared with 10 per 100 000 people for pancreatic adenocarcinoma for example^{3,4}. As a result, most surgeons will encounter gastroenteropancreatic NENs in their practice. The management of gastroenteropancreatic NENs, including work-up, diagnosis, staging, and treatment, varies based on the specific site of the primary tumour. NENs include neuroendocrine tumours (NETs) and neuroendocrine carcinomas (NECs); NETs are

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well-differentiated malignancies while NECs are poorly differentiated and present with more aggressive behaviour⁵. This article will focus on NETs.

Small intestinal neuroendocrine tumours (SI-NETs) have different biology compared with other epithelial cancers and, hence, have different considerations for management than most other gastrointestinal cancers. Three features of SI-NETs drive these considerations: prolonged survival, endocrine hypersecretion, and fibrosis within the tumour environment. Prolonged survival is often observed, even in patients with locally advanced or widely metastatic disease^{2,3}. Both endocrine hypersecretion and fibrosis (desmoplastic reaction) can contribute to deteriorating quality of life over the course of disease via systemic endocrine syndrome and locoregional complications^{6–8}. As such, oncological control must be pursued along with preservation of intestinal function and quality of life. To do so, multidisciplinary care involving several disciplines is critical to devise tailored management plans.

Despite the prevalence of SI-NETs in surgical practice, the operative management of SI-NETs lacks standardization. Decision-making and recommendations are informed largely by retrospective, single-centre (often single-surgeon) series. Compared with systemic therapy for NETs, surgical evidence is sparse and heterogeneous. Indeed, the field overall has advanced rapidly, particularly in biomarker discovery, imaging, and systemic therapy, but surgical strategies have remained largely unchanged. This contrast underscores the opportunity for better evidence and innovation in the operative care of patients with SI-NETs.

This article aims to provide insights into existing clinical dilemmas in the surgical care of patients with SI-NETs as well as current and future directions. Rather than attempt to provide an exhaustive review of SI-NETs, it focuses on key clinical challenges that commonly arise in practice and areas where evidence is evolving and likely to influence surgical management.

BJS Commission development process

To undertake this overview, experts within the different domains of management of SI-NETs were selected by two BJS Editors. All those selected had a significant record of high-quality publications within the fields of interest. Once a list of expert authors was compiled, it was then approved by the BJS Editorial Team and, of those invited, all agreed to take part in this BJS Commission. The authors were also asked to include 'future experts' at a senior trainee or early consultant level, to compliment the authorship group. Authors were then split into seven groups, each tasked with providing a detailed contemporary review of certain key aspects of the management of SI-NETs. By selecting an international group of experts, the aim was to formulate a balanced and collaborative analysis that represents SI-NET practice, globally.

Preoperative considerations—selection for surgery

Should the primary SI-NET be resected with unresectable stage IV disease?

Primary tumour resection of an asymptomatic SI-NET with unresectable stage IV disease remains controversial. While retrospective studies have suggested potential benefits in overall survival (OS) and prevention of future complications, these must be weighed against the risks of surgical morbidity, even if

those risks are generally considered acceptably low^{9,10}. The lack of definitive prospective data continues to fuel uncertainty.

Any potential oncological or symptom-related benefits must be balanced against the risk of perioperative complications, as a surgical intervention may expose otherwise asymptomatic patients with a long life expectancy (despite malignancy) to unnecessary morbidity. Primary tumour resection may benefit the patient in two ways: help them live longer and/or better. Multiple retrospective studies have demonstrated an association between primary tumour resection and improved survival of unresectable stage IV patients. These mainly include population-based studies using the National Cancer Database, the Surveillance, Epidemiology and End Results (SEER) Registry, and the California Cancer Registry^{11–16}. Appropriate statistical techniques were performed to attempt to control for confounding, but the nature of these databases plus the inherent selection bias in surgical decision-making make it hard to confidently attribute the improved survival to primary tumour resection. Other population-based studies have demonstrated no association between primary tumour resection and survival^{17,18}.

One of the more novel studies took advantage of a natural experiment whereby one centre (Netherlands Cancer Institute (NKI), Amsterdam, The Netherlands) adopted a policy of primary tumour resection for all patients while another (Aintree University Hospital (AUH), Liverpool, UK) only performed primary tumour resection for symptoms¹⁹. While this study was not a randomized trial, the retrospective analysis of patients treated from 2000 to 2018 relied on thoughtful statistical analysis and provided important insight. Overall, 93 patients with asymptomatic stage IV SI-NETs were treated at NKI (78% upfront primary tumour resection) and 52 patients at AUH (8% upfront primary tumour resection). In the AUH cohort, 19% required surgery for complications during a median follow-up of 4.9 years. Median disease-specific survival (DSS) was 16.5 years at NKI versus 8.9 years at AUH ($P < 0.001$). A statistically significant improvement in DSS was also seen when comparing primary tumour resection with non-primary tumour resection, regardless of institution. Proving that primary tumour resection leads to improved survival would require a randomized trial similar to the JCOG1007 trial for colorectal cancer (which showed no survival benefit)²⁰. This trial was completed for a much more common cancer after a median follow-up of only 22 months. Given the lower incidence of SI-NETs and the prolonged survival of patients with SI-NETs, such a trial is unlikely to be feasible.

Even if the possibility of improved survival remains controversial or difficult to prove, primary tumour resection may lead to better locoregional disease control, thereby decreasing the risk of obstruction, bleeding, perforation, peritoneal carcinomatosis, or emergency surgery. Given the prolonged life expectancy of patients with SI-NETs, even those with stage IV disease, there is a long window of time for the primary SI-NET to become symptomatic and compromise quality of life. A population-based study from Ontario, Canada, reported a median OS of 13.2 years for all patients with stage IV SI-NETs. It also observed that upfront primary tumour resection was associated with decreased unplanned hospital admissions and subsequent small intestine-related surgery²¹. Adding to the clinical dilemma of primary tumour resection in unresectable stage IV SI-NETs is the perception that some patients are asymptomatic. The prevalence of truly asymptomatic SI-NET primary tumours is actually low. Among stage IV SI-NET patients undergoing surgery in Iowa, only 10% had no

preoperative symptoms (diarrhoea, flushing, or pain)²². A large study of surgical patients in Sweden also identified that, in retrospect, they believed their symptoms began on average 1.25 years before diagnosis, which speaks to the insidious nature and normalization of the symptoms²³.

In addition, for patients being evaluated for liver transplantation in the setting of unresectable NET liver metastases, primary tumour resection and regional nodal disease clearance is generally required to minimize future complications and ensure eligibility for transplantation. This underscores the importance of early and comprehensive surgical assessment, even when metastatic disease appears to dominate the clinical picture.

The current recommended approach for all patients with stage IV SI-NETs is for assessment by a multidisciplinary team with NET expertise, including a surgeon, and that strong consideration should be given towards primary tumour resection, even in the absence of recognized symptoms and for patients with unresectable metastatic disease. This is supported by consensus opinion from international NET societies across the world^{24,25}. This approach is most likely to improve subtle gastrointestinal symptoms that patients may have coped with and normalized over time, prevent future locoregional complications, and potentially lead to improved survival. While a randomized trial would be challenging, collaborative networks such as the Collaborative of sUrgical Teams for NeuroEndocrine Tumors (CUTNETs) could facilitate the collection of high-quality, multicentre, prospective data on such patients, including symptoms, treatments, complications, quality of life, and survival²⁶.

Highlights

Most patients can benefit from primary tumour resection, even those with unresectable metastases, as it likely prevents future obstruction, bleeding, and mesenteric complications, and may improve survival. Decisions should be made in multidisciplinary NET centres, with surgery strongly considered, even when patients appear 'asymptomatic' as this cannot be reliably assessed for NETs.

When should peritoneal carcinomatosis from SI-NETs be resected?

NET peritoneal metastases are relatively uncommon but are increasingly recognized due to advances in imaging and prolonged patient survival. Peritoneal metastases present unique diagnostic and therapeutic challenges distinct from hepatic or nodal metastases. Approximately 20% of patients with SI-NETs have peritoneal involvement, often alongside liver or nodal disease^{5,27–29}. The biological behaviour of NET peritoneal metastases is heterogeneous and influenced by tumour grade, primary site, and overall disease burden. While many cases follow an indolent course, a subset progresses to symptomatic peritoneal carcinomatosis, leading to complications such as ascites, bowel obstruction, and malnutrition²⁸. Selected patients may achieve meaningful long-term survival with aggressive local management, highlighting the need for clear guidance on diagnosis, patient selection, and appropriate integration of surgical and systemic therapy²⁹.

Accurate diagnosis and staging for risk stratification

Early and accurate diagnosis is essential yet challenging, given the subtle presentation and limitations of conventional imaging. Small-volume peritoneal implants in NETs may be underappreciated. Additionally, precise grading is critical for distinguishing between NETs (G1–G3) and poorly differentiated

NECs. The Ki-67 index and mitotic count should be interpreted cautiously in metastases due to potential heterogeneity. Pathology review by an experienced NET pathologist is highly recommended⁵. Of note, NEC of the small intestine is exceedingly rare.

Assessment of tumour burden helps anticipate resectability. Common scoring systems include the Lyon Staging System and the Peritoneal Cancer Index (PCI) (Fig. 1)^{30–32}. Both systems are validated for prognostication and patient selection in peritoneal surface malignancy, but the PCI is preferred for its reproducibility and detailed mapping of disease extent, especially in the context of cytoreductive surgery (CRS).

Imaging and biomarkers are increasingly used for further assessment and risk stratification. Somatostatin receptor (SSTR) PET-CT provides greater sensitivity than conventional CT or fluorodeoxyglucose (FDG) PET for detecting NETs but may underestimate peritoneal spread if implants are small, exhibit low SSTR uptake, or are located adjacent to the small intestine with background SSTR uptake³³. Traditional markers such as serum chromogranin A (s-CgA) and pancreastatin may aid prognostication but lack specificity and are rarely used. Circulating tumour DNA (ctDNA) is an emerging tool under investigation for minimal residual disease monitoring²⁷.

Challenges with systemic therapy

Systemic therapy for peritoneal NETs depends heavily on tumour grade and biology. Currently, no high-level evidence specifically addresses systemic therapy efficacy for peritoneal-dominant disease⁸. Therefore, decisions are guided by typical pathways for systemic therapy for advanced NETs: first-line treatment typically includes long-acting somatostatin analogues (SSAs), while radioligand therapy and targeted agents may be considered for progression, and cytotoxic chemotherapy is rarely used due to limited activity against slow-growing NETs. Overall, the limited and somewhat unknown efficacy of systemic therapies in significantly reducing peritoneal tumour burden often shifts the treatment approach towards surgical intervention.

Safety of radioligand therapy for NET peritoneal metastases

In patients with peritoneal involvement, the use of radioligand therapy presents a unique clinical dilemma. While it is an effective systemic option for many patients with advanced NETs, its safety in the setting of extensive peritoneal disease remains uncertain. Patients with peritoneal involvement face a clinically meaningful risk of bowel obstruction or worsening abdominal symptoms when treated with radioligand therapy. In one retrospective cohort, approximately 6% of patients with pre-existing peritoneal or mesenteric involvement developed bowel obstruction within 3 months of receiving radioligand therapy, with some requiring surgical intervention. Another real-world series similarly reported that patients with mesenteric or peritoneal metastases can experience bowel-related toxicities, including severe (grade 5) events^{34,35}. Patients with extensive peritoneal carcinomatosis appear particularly vulnerable, with bowel obstruction or ascites reported in up to 28% of such cases after radioligand therapy³. The American Society of Clinical Oncology advises that individuals with a high burden of peritoneal or mesenteric disease be considered at elevated risk of bowel obstruction with radioligand therapy and should be approached with caution³⁴. Radiation-induced inflammation is believed to contribute to these risks.

Patients at high risk of radioligand therapy-related obstruction episodes have been described as those with extensive peritoneal

	Lyon staging system	Peritoneal cancer index (PCI)
 Purpose	Stages peritoneal carcinomatosis by extent	Quantifies tumour burden by lesion size and distribution
 Structure	4 stages (I–IV)	13 abdominopelvic regions, each scored 0–3
 Scoring	Based on number, size, and distribution of nodules	Sum of lesion size scores across 13 regions (0–39 total)
 Lesion size	Cut-offs for nodule size per stage	LS-0: none, LS-1: ≤0.5 cm, LS-2: 0.5–5 cm, LS-3: >5 cm
 Anatomy	Low details (generalized regions)	Detailed regions: 9 abdominopelvic, 4 small bowel
 Prognostic	Correlates with survival	Strong linear correlation with survival and resectability
 Use	Less commonly used; historical	Widely used; standard for CRS/HIPEC selection
 Ease of use	Simple, rapid	Requires systematic intraoperative survey
 Cut-offs	Stage I/II: limited Stage III/IV: extensive	PCI <12: favourable PCI >20: poor prognosis
 Limitations	Less precise localization	More time-consuming; interobserver variability

Fig. 1 Scoring of peritoneal cancer disease burden

LS, lesion size; CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy.

implants (>10) or a mesenteric mass with mesenteric fibrosis tethering small bowel loops. The management of small bowel obstruction in the context of radioligand therapy and NET peritoneal carcinomatosis is complex. Corticosteroids may help manage symptoms in the acute setting by mitigating the tumour-flare reactions (such as pain or obstruction), but surgical options ought to be considered³⁴. Some clinical guidance recommends a short (1–2 week) course of a steroid, though optimal use and dosing remain unclear^{36,37}. In instances when urgent surgery is needed early after radioligand therapy, the risk of exposure for the surgical team should be considered. While formal guidelines addressing perioperative precautions in this setting are lacking, some guidance has been issued for management of decedents with ¹⁷⁷Lu³⁸. During surgery, the risks of radiation to staff would be two-fold: external radiation hazards and internal radiation hazards; those risks vary depending on the type of isotope, the dose used, and the time since therapy. General principles of radiation safety would apply. The way to shield against those hazards relies on time,

distance, and shielding, including minimizing the time spent in the operating room, ample personal protective equipment (masks, double gloving, face shields), and lead shielding for all staff who may come into contact with any body fluids.

Why peritoneal cytoreduction?

Retrospective series suggest that CRS may prolong survival and palliate symptoms in carefully selected patients with NETs and limited peritoneal metastases^{28,29}. However, prospective data remain scarce. A major challenge in managing peritoneal carcinomatosis from NETs is the absence of standardized criteria to assess the extent of cytoreduction and define optimal debulking thresholds. Current estimates of tumour debulking are often subjective, imprecise, and highly variable, influenced by the surgeon's experience and the methods used for intraoperative assessment. The lack of robust evidence to guide target thresholds further complicates decision-making and limits reproducibility across centres. Given the limited prospective data for CRS for NETs with peritoneal involvement,

collaborative registries and trials are needed to define optimal management strategies. Incorporating molecular profiling, advanced SSTR imaging, and eventually ctDNA tests for NETs may refine risk stratification and surveillance.

Favourable outcomes are seen in patients with low PCI scores, absence of unresectable extra-abdominal metastases, and good functional status. The goals of cytoreduction are also debated. The commonly cited tumour debulking threshold of ≥ 70 –90% is extrapolated from large series on hepatic NET metastases and may not directly apply to peritoneal disease, which has a worse prognosis and a higher risk of progression after surgery than liver metastases^{39,40}. The goal of CRS should be maximal debulking (ideally $>90\%$), symptom control, and preservation of quality of life. In asymptomatic patients, the benefit of CRS is not clear. For those with symptomatic disease—such as pain, obstruction, or malnutrition—surgery can provide meaningful palliation. Furthermore, some favour a general debulking goal, whereas others argue that it makes more sense to tailor targets based on the metastasis locations and their clinical impact on the patients. The distinction is especially important in patients with both liver and peritoneal metastases. In these patients, the potential higher risk of morbidity from synchronous resections needs to be carefully weighed against the possible benefits, particularly in patients with indolent tumours and limited symptoms. Additionally, consideration for cytoreduction can be given to patients who may otherwise be ineligible for systemic therapy such as radioligand therapy to diminish the burden of disease, but this should be done in a multidisciplinary fashion with thorough considerations of risk and benefit to the patient.

The addition of hyperthermic intraperitoneal chemotherapy (HIPEC) has not shown a clear survival advantage in NET peritoneal metastases and carries significant morbidity. Current North American Neuroendocrine Tumor Society (NANETS) and European Neuroendocrine Tumor Society (ENETS) guidelines do not recommend routine HIPEC for gastroenteropancreatic NET peritoneal metastases due to insufficient evidence and higher complication rates²⁹.

Overall, aggressive surgical management of NETs with peritoneal metastases, particularly CRS, can extend survival when complete (or near-complete) resection is achievable, but careful patient selection is crucial to balance benefit and morbidity. Of note, CRS for NECs is rarely appropriate except for palliation of complications such as obstruction or bleeding, given their aggressive biology and high recurrence rates⁴¹.

Highlights

CRS can help carefully selected patients with limited peritoneal burden, but decisions must account for grade, PCI, symptoms, and the limited evidence regarding efficacy. CRS should aim for maximal safe debulking ($>90\%$), with HIPEC not recommended.

When should liver metastases from SI-NETs be debulked?

Why pursue liver debulking?

Liver debulking for SI-NETs can prolong life and alleviate tumour-related symptoms in selected patients. Because CRS risks significant morbidity and is not curative, careful patient selection is critical. Unlike other secondary liver malignancies, metastases from SI-NETs are usually more indolent and patients with metastatic SI-NETs tend to experience prolonged survival^{2,42}. While retrospective studies from single institutions and large databases have reported associations between

debulking and improved OS, these findings are subject to inherent selection bias^{9,10,43–46}. By reducing tumour volume, debulking surgery can provide tumoral and endocrine control, alleviate symptoms, and preserve quality of life, and potentially extend progression-free survival. Importantly, progression is expected and reaches 95% at 5 years and close to 100% at 10 years after liver debulking for NET metastases^{45–50}. With expanding systemic therapy options that are well tolerated and prolong time to progression^{47–52}, the decision to operate must weigh surgical risks and benefits carefully. Proponents of aggressive surgical management are quick to assert that adverse effects of systemic therapies have their own long-term consequences of varying severity. In selected patients, early surgical approaches can allow patients a prolonged treatment-free interval, effectively turning back the clock before use of systemic treatments. Taken together, benefits regarding quality of life and long-term disease control must be balanced against patient values and co-morbidities.

Role of liver debulking among other therapeutic options

Liver debulking can improve quality-of-life scores and improve symptoms⁵³. One single-centre retrospective cohort found a direct correlation between the extent of debulking and the duration of the symptom-free interval, with up to 96% of patients experiencing symptom relief⁵⁴. Debulking is also the most effective method for achieving endocrine control (approximately 95%), which current systemic therapies cannot match^{9,10,43,46,55–57}. While endocrine symptom control is not a consideration for non-functional tumours, there may be a benefit to both quality and quantity of life by preventing or delaying hypersecretion and the attendant repercussions of carcinoid syndrome.

Reducing the liver tumour burden has non-endocrine benefits that apply to both functional and non-functional tumours. Debulking can prolong the effectiveness of first-line systemic therapies such as long-acting SSAs. Subgroup analyses from the PROMID and CLARINET trials for octreotide long-acting repeatable (octreotide LAR) and lanreotide outlined better time to progression results for patients with a lower liver tumour burden ($<10\%$ for PROMID and $<25\%$ for CLARINET). This points towards the importance of liver debulking as a ‘therapy-sparing’ strategy for patients who will require multiple lines of therapy over the years, for both functional and non-functional tumours.

The sequencing and combination of debulking with systemic and other liver-directed therapies is not yet established. Preoperative systemic therapy may offer an opportunity to trigger a tumour response to convert unresectable liver metastases into resectable (debulkable) disease or to assess tumour biology before committing to surgery. In both scenarios, therapies other than long-acting SSAs would need to be examined; indeed, SSAs have low response rates making them low yield for conversion and the time to progression was long in the SSA trials indicating that very prolonged tests of time would be needed to assess the biology of this therapy, which is not practical⁵⁵. Combining surgical debulking with other liver-directed therapies, such as embolization or ablation, may further enhance overall tumour control. In this approach, lower levels of debulking achieved through surgery may be acceptable if followed by liver embolization to target smaller residual disease, resulting in a higher overall debulking. Large, dominant tumour conglomerates that are less responsive to embolization may be prioritized for enucleation, even if the surgical debulking is $<70\%$, with embolization planned shortly after to address

remaining disease. This may make complex liver metastases amenable to surgery for debulking⁵⁸. Liver embolization is not favoured before debulking: first, because downstaging is not truly needed when aiming for debulking (not complete resection) and when using parenchymal-sparing techniques (not anatomical resection); and, second, because the tumour changes resulting from embolization hamper the ability to proceed with parenchymal-sparing enucleations. Finally, targeted debulking of liver oligo-progression sites is an emerging strategy, particularly relevant as the pathophysiology of oligo-progression is better understood and this scenario becomes more common with patients increasingly receiving multiple lines of systemic therapy over time.

Debulking goals

As surgery is considered, surgeons must account for realistic expectations for tumour burden reduction. By definition, liver debulking surgery aims for R2 resection for NET liver metastasis. Historically, the liver debulking target was set at 90%^{43,57,59}. More recently the aim for debulking changed to 70% removal of tumour burden, after analyses showed superior results compared with <70% debulking; after debulking of 70% of liver metastases, a median progression-free survival of >21 months and a median OS of >134 months can be achieved^{9,10,46,55}.

How to define and measure the level of debulking remains a matter of debate. The percentage of debulking has been used traditionally but is measured subjectively and varies depending on the surgeon and the imaging modalities and protocols used. The importance of the residual tumour volume has been brought up recently^{60,61}. This recognizes that the percentage of debulking is a relative measure and may yield different end results depending on the baseline liver tumour burden. More work is needed to define objective measurements of debulking to aid in selecting patients most likely to benefit from surgery and in standardizing care. As more tools are developed in NET care, such measurements may go beyond structural imaging and integrate biomarkers, such as circulating tumour cells before and after debulking for example, or radiographic quantification of visible disease volume relative to 'normal' liver. The role of extrahepatic disease in defining debulking levels will also need to be studied to define whether measurement of tumour burden should focus solely on the liver tumour burden or also account for other disease (that may be resected or not).

Debulking technique in liver surgery

How to perform the liver resection also influences the assessment of the level of debulking that can be achieved. With detailed pathology studies showing frequent microscopic disease in resected lobes and even in macroscopically normal liver after resection for NET liver metastases, R0 resection is not achievable^{60,61}. Thus, large anatomical resections are often unjustified in this setting. Instead, parenchyma-sparing techniques like enucleation are strongly recommended (Fig. 2)^{62,63}. This approach exploits the expansile and non-invasive growth pattern of NETs by following the tumour capsule to enucleate tumours one by one from the liver parenchyma and can be used to take large tumours off major intrahepatic structures such as hepatic veins and portal pedicles (Fig. 3)⁶⁴. Intraoperative ablation can be added to treat smaller lesions deeper within the liver parenchyma and reach higher debulking levels. These approaches preserve liver function, avoid compromising future liver-directed therapy such as embolization, are aligned with the unique biology

of SI-NETs, and expand the ability to perform meaningful liver debulking.

Other considerations

There are of course many other important considerations to be undertaken before debulking for SI-NET liver metastases. These include if or when to proceed with major liver surgery in the presence of extrahepatic disease and whether liver transplantation could be an alternative in selected patients. It is also important to note that if operating on liver metastases, the primary small intestinal tumour should also be controlled surgically, whether as an earlier resection or as a resection that is synchronous with the liver debulking. Perioperative work-up and optimization of patients with metastatic SI-NETs for liver resection also include work-up and management of carcinoid syndrome and the risk of carcinoid heart disease⁶⁵⁻⁶⁹.

Highlights

Liver debulking may prolong survival and improve endocrine and mass-effect symptoms in selected patients, but demands thoughtful patient selection and realistic goals, as recurrence is expected. Parenchyma-sparing enucleation and multimodal combinations (for example ablation) are preferred to maintain future treatment options.

When to consider liver transplantation for SI-NET liver metastases?

Why liver transplantation for SI-NET liver metastases?

In patients with SI-NETs, liver involvement represents a pivotal turning point in the disease course, often determining long-term prognosis and quality of life. While locoregional and systemic treatments may provide durable symptom control and disease stabilization in selected cases, a subset of patients develops diffuse, unresectable liver-only NET metastases for whom curative-intent options remain limited^{65,70-72}.

Within this specific clinical scenario, liver transplantation has been proposed as an extreme but potentially curative strategy, based on the complete replacement of the hepatic parenchyma. Early experiences and selected series have reported favourable long-term survival of carefully selected patients with liver metastases from SI-NETs, with 5- and 10-year OS exceeding those observed with non-transplant strategies in retrospective series. These results have positioned liver transplantation as a unique therapeutic option, particularly for patients with otherwise controlled extrahepatic disease⁷³. The original Milan criteria for liver transplantation for NETs include low-grade NETs with Ki67 <10%, primary tumour drained by the portal system and resected, metastatic diffusion to liver parenchyma ≤50%, good response or stable disease for ≥6 months during the pre-transplantation interval, and age ≤55 years⁷⁴.

What is the contemporary role of liver transplantation?

Enthusiasm for liver transplantation for SI-NETs must be tempered by persistent uncertainties. Much of the available evidence derives from retrospective cohorts and historical series, often predating the systematic use of modern imaging modalities (such as SSTR PET) and biomarkers for assessment and selection and contemporary surgical debulking techniques allowing safe resection of more extensive liver metastases. As a result, the true oncological benefit of liver transplantation in the contemporary era remains difficult to quantify.

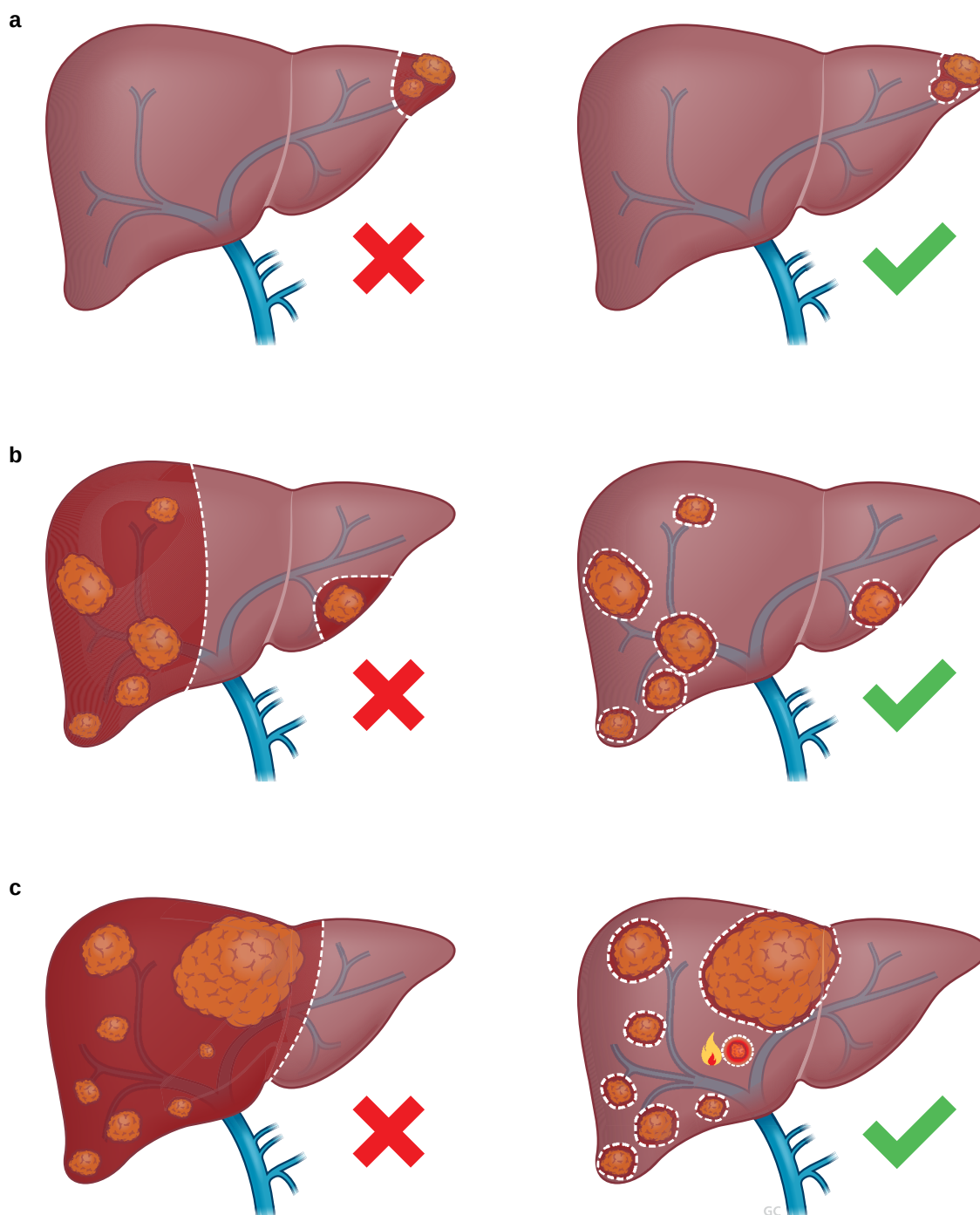


Fig. 2 Parenchyma-sparing strategies for liver debulking for SI-NET liver metastases using enucleation to avoid anatomical resection

Shaded brown areas indicate areas of resection. Shaded area with flame indicates use of ablation. Ticks indicate recommended parenchymal-sparing approach and crosses indicate anatomical resection to be avoided. SI-NET, small intestinal neuroendocrine tumour.

Despite excellent reported OS, long-term disease control after liver transplantation remains suboptimal. Recurrence rates are high, with disease-free survival substantially lower than OS and late recurrences frequently documented⁷⁵. While those patients undergoing liver transplantation who meet the original Milan criteria have favourable OS, those undergoing liver transplantation who do not meet the original Milan criteria have less favourable OS, often below that achieved using other established liver-directed strategies^{74,75}. With contemporary disease assessment and surgical indications, most patients

meeting the Milan criteria (including replacement of liver parenchyma <50%) would be eligible for surgical cytoreduction with parenchymal-sparing techniques. The majority of those patients considered unresectable nowadays would not meet the Milan criteria. Thus, the role of liver transplantation in the management of unresectable liver metastases from SI-NETs is not clearly defined. Critical questions exist regarding patient selection, timing of transplantation, and the biological behaviour of SI-NETs in the post-transplant setting. As a result, current international guidelines restrict liver transplantation for

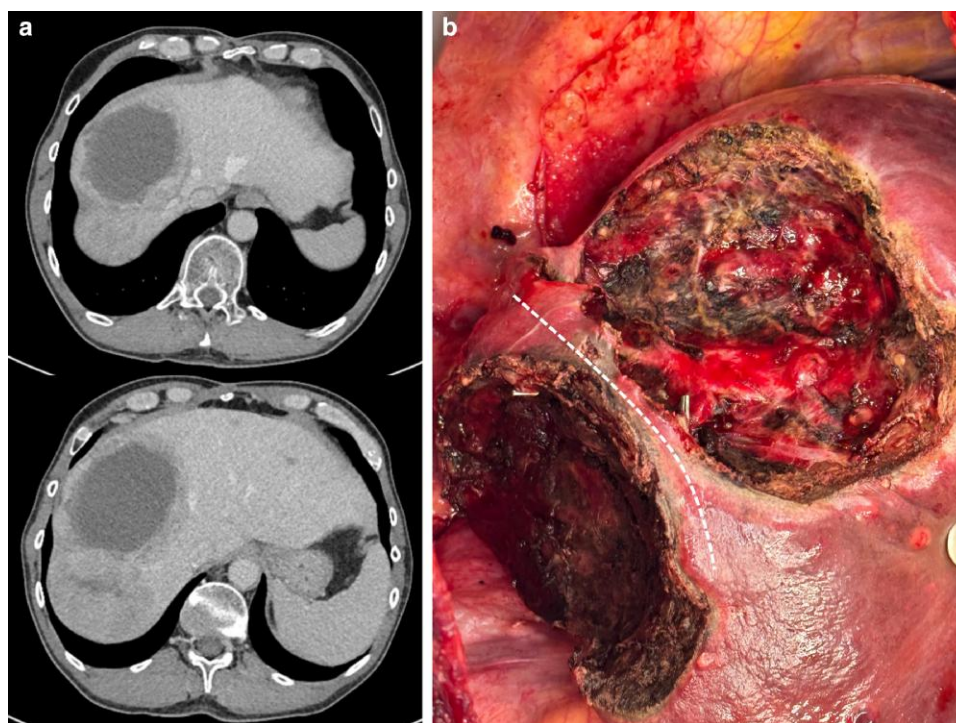


Fig. 3 Enucleation of large SI-NET liver metastases sparing the right hepatic vein (broken line showing its trajectory) liver parenchyma
a Preoperative CT. **b** Surgical bed after enucleation. SI-NET, small intestinal neuroendocrine tumour.

SI-NET liver metastases to highly selected patients, typically those with unresectable liver disease and favourable tumour biology, often in the setting of functioning tumours refractory to systemic therapy^{71,72,76}. Defining which patients truly benefit from liver transplantation, and how to balance OS gains against recurrence risk and organ allocation constraints, remains one of the most debated and unresolved issues in the management of metastatic SI-NETs.

What is the future role of liver transplantation?

In the evolving landscape of SI-NET management, the optimal role of liver transplantation remains highly debated. In the absence of definitive evidence demonstrating a clear survival advantage of liver transplantation over contemporary systemic and liver-directed therapies, and given the practical and ethical challenges of conducting RCTs in this rare disease setting, a shift towards structured, large-scale collaborative research is imperative. International registries are essential to enable longitudinal data collection at scale and to support the development of robust prognostic models integrating clinical, pathological, and molecular variables. Future research must incorporate refined biological risk stratification, including molecular profiling and advanced functional imaging such as SSTR-based PET-CT. Comprehensive molecular characterization of explanted livers and paired primary tumours, encompassing genomic, transcriptomic, and epigenomic analyses, will be critical to identify biological signatures associated with durable disease control *versus* post-transplant recurrence. Specific markers, including *DAXX/ATRX* mutations, an alternative lengthening of telomeres (ALT) phenotype, and differential expression of SSTR subtypes (SSTR2 and SSTR5), warrant systematic investigation in this context.

The expanding concept of 'transplant oncology' further supports evaluation of downstaging strategies. With such

approaches, patients initially exceeding conventional selection criteria for transplantation may be considered after demonstrating exceptional responses to systemic therapies (such as peptide receptor radionuclide therapy (PRRT)) or liver-directed therapies (such as transarterial embolization). The optimal perioperative and post-transplant role of systemic therapies also ought to be assessed, especially for mammalian target of rapamycin (mTOR) inhibitors. Given their demonstrated benefit with regard to improving disease-free survival for patients with metastatic NETs, their integration into immunosuppressive regimens may represent a promising strategy to enhance post-transplant tumour control^{77–79}.

In summary, defining the optimal use of liver transplantation for patients with NET liver metastases requires a coordinated international research effort combining prospective studies and high-quality registry data. Such an approach is essential to integrate modern diagnostic tools, advanced predictive modelling, standardized selection and treatment pathways, optimized immunosuppressive strategies, and dynamic adaptation of organ allocation systems, while preserving the principles of equity and utility in an evolving landscape of liver transplantation indications. At this time, one prospective study of liver transplantation for NET liver metastases is ongoing, through the UK and Ireland Liver Transplantation Pilot Programme^{77,80}; this prospective registry-based cohort study is examining outcomes after liver transplantation across two planned phases. In phase 1, restricted criteria for liver transplantation will be applied, including G1/G2 histology, gastroenteropancreatic primary tumours completely resected, <50% liver metastatic burden, stable disease or response to therapy for ≥6 months before transplant consideration, and age <60 years. In phase 2, the criteria will be expanded to other primary tumours, small-volume residual extrahepatic disease, and metastatic burden >50%.

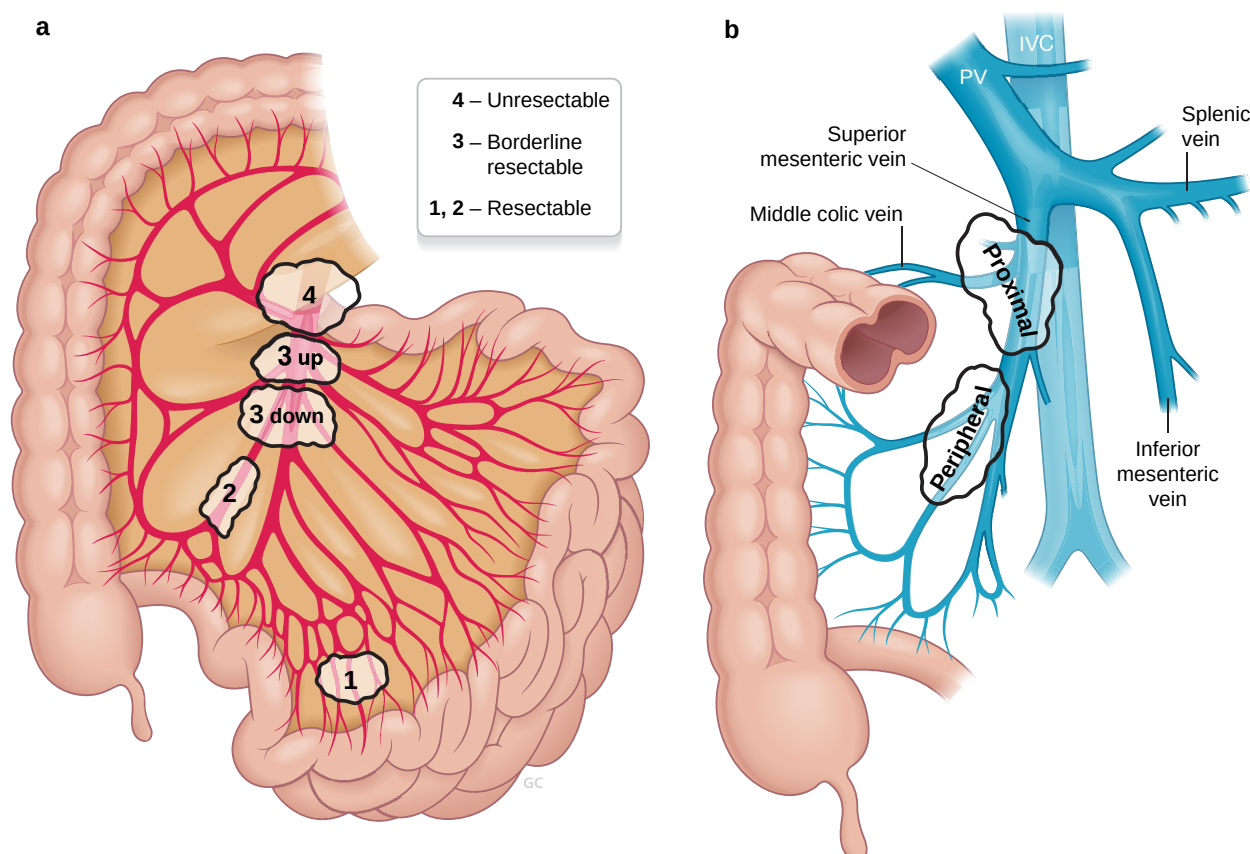


Fig. 4 Classification of SI-NET mesenteric nodal masses

a Based on relationships with the SMA and its tributaries. **b** Based on relationships with the superior mesenteric vein and its tributaries. SI-NET, small intestinal neuroendocrine tumour; SMA, superior mesenteric artery.

Highlights

Liver transplantation for SI-NET liver metastases remains a highly selective and controversial option, with favourable OS reported for carefully chosen patients but high recurrence rates and uncertain benefit in the contemporary era. Advances in imaging, surgical cytoreduction, and systemic therapies have narrowed the population for whom transplantation may add value if applying traditional selection criteria. This underscores the need for refined and somewhat redefined selection.

Intraoperative considerations—surgical techniques

How to perform resection for SI-NETs?

The surgical management of SI-NETs is highly complex, particularly when dealing with advanced mesenteric masses. It benefits from centres and surgeons experienced in NET care. Decisions must always balance maximal oncological resection with the preservation of small bowel function, including conserving enough intestinal length and the ileocaecal valve whenever possible.

Preoperative assessment and planning

‘Accurate preoperative assessment’ is crucial to avoid unnecessary laparotomies or R2 resection. A standardized work-up (combining triphasic CT, diffusion-weighted MRI, and SSTR PET imaging) along with ‘detailed vascular mapping’ and

multidisciplinary team review is required to evaluate lesion multifocality and to assess resectability criteria, such as the extent of nodal and vascular involvement, mesenteric fibrosis, and signs of peritoneal carcinomatosis^{78,79,81}. However, in emergency presentations (such as intestinal obstruction or bleeding), the ability to complete such staging is limited; it tends to increase the risk of non-radical surgery in non-expert centres, which can lead to the need for reoperation⁸².

Almost 50% of patients will have a mesenteric nodal mass at the time of diagnosis⁸³. Vascular mapping with assessment of the relationship between mesenteric masses and arterial and venous branches within the mesentery is essential. Mesenteric nodal masses are classified based on their anatomical relationship with the superior mesenteric artery (SMA) axis (Fig. 4a). Stage 0 indicates no macroscopic mesenteric nodes, while stage I involves nodal disease along the mesenteric border of the intestine, stage II describes nodal masses affecting distal SMA branches up to their origin, stage III is encasement of the SMA trunk, further stratified into stage III-down (with ≥ 3 –4 free jejunal branches) and stage III-up (with < 3 –4 free jejunal branches), and stage IV represents encasement of the SMA up to its root and retroperitoneal extension behind the pancreatic neck⁸⁴. Stage I to stage III-down disease is generally considered resectable and stage III-up disease is generally considered borderline resectable and requires intraoperative perfusion assessment (for example use of vascular clamping tests). Stage IV disease is typically deemed unresectable. In addition to arterial encasement, venous involvement is also key when

assessing resectability and planning surgery. The superior mesenteric vein axis should be evaluated for proximal involvement, defined as encasement at the origin of the middle colic vein, or peripheral involvement, which occurs distal to this point (Fig. 4b)⁸⁵. In a retrospective analysis including detailed imaging review, stage III-up and stage IV disease as well as proximal superior mesenteric vein involvement were the main drivers of failure to resect SI-NET mesenteric masses⁸⁵. Assessment, classification, and documentation of both arterial and venous involvement of SI-NET mesenteric nodal masses are essential and often best achieved through triphasic CT imaging with both arterial and venous phases. This vascular roadmap guides operative planning, particularly when considering techniques to preserve small bowel length while achieving oncological clearance and preventing future complications from mesenteric fibrosis related to the nodal mass^{85–87}.

Multifocality is a key feature of SI-NETs that must be carefully assessed during preoperative work-up. Synchronous multifocal primary tumours are observed in up to 56% of patients, with the majority (77%) located within the distal 100 cm of the ileum⁸⁸. These lesions are often sub-centimetre and easily missed on routine imaging. While SSSTR PET-CT has revolutionized systemic staging for NETs, its sensitivity for detecting multifocality is limited, with a reported negative predictive value of only 62%⁸⁹. Dedicated CT or magnetic resonance enterography remains the most reliable modality for identifying multifocal disease before surgery. Accurate identification of all primary sites is essential for surgical planning to ensure complete resection.

Future directions to improve patient selection and optimize preoperative work-up include examining how to perform reproducible and standardized vascular mapping and exploring functional lymphatic or radio-guided mapping for nodal assessment.

Extent of resection

Extent of resection and lymphadenectomy remain critical, especially for tumours involving the root of the mesentery (that is superior mesenteric vein and/or artery) as described above⁸⁵. Key surgical questions in assessing resectability of the primary tumour include what constitutes an adequate lymph node dissection, how many jejunal arteries or veins must be preserved to maintain intestinal viability, whether and how all multifocal tumours should be resected, and whether to resect residual or recurrent mesenteric nodal masses⁸⁴.

In the absence of a macroscopic mesenteric nodal mass, lymph node dissection with retrieval of 8–12 lymph nodes improves staging accuracy and may be associated with better survival⁹⁰. However, the therapeutic benefit of lymphadenectomy has not been clearly established and a larger lymph node harvest may sometimes come at the price of resecting a larger section of the small intestine. Whether a right hemicolectomy is needed for lymph node clearance or if resection of the small intestine with preservation of the ileocaecal valve is sufficient is another challenge. That decision requires standardized assessment and careful preoperative planning balancing functional and oncological outcomes⁹¹.

Achieving an appropriate balance between radical oncological clearance and intestinal preservation is particularly challenging in central mesenteric disease with fibrosis or vascular encasement⁹². Previous series have shown that effective lymph node dissection and resection of proximal mesenteric nodal masses can be accomplished without extensive small bowel resection. Up to 20 lymph nodes can be harvested with only

100 cm of small intestine resected and no association has been found between the length of the bowel resected and the lymph node yield⁸⁴.

For nodal disease extending up to stage III-up, mesenteric-sparing techniques (described below) enable resection high on the SMA axis while preserving intestinal length (Fig. 5)^{24,84,86,87}. Aggressive resection of proximal mesenteric nodal masses is warranted not only for disease control but also to prevent debilitating fibrosis-related complications. A desmoplastic reaction can lead to mesenteric ischaemia, venous congestion, bowel obstruction, and progressive symptoms such as chronic pain, malabsorption, and cachexia^{6,7,93,94}. With mesentery-sparing techniques, lesions that were previously considered unresectable may become operable, with the goal to relieve or prevent symptoms while preserving intestinal function. For unresectable nodal masses (stage IV mostly), some have suggested and reported good outcomes for debulking with regard to improving quality of life⁹². Some have also reported small intestine transplantation for such patients, although this remains investigational and is rarely performed⁹⁵. The exceptional role of small intestine transplantation could be explored in highly selected cases moving forward.

The role of reoperation after initial resection of SI-NETs must be carefully considered, particularly in the context of incomplete staging or residual macroscopic nodal disease. Repeat operations may be needed after either elective or emergency small bowel resections, with recent data showing that fewer than half of reoperations are performed after prior emergency procedures⁸². The most common indication is residual mesenteric nodal disease, which—if left untreated—can lead to progressive fibrosis, ischaemia, and symptom burden, in addition to further cancer spread, as previously described. In appropriately selected patients, reoperation can provide meaningful benefits in terms of both oncological control and symptom relief. Reoperative strategies follow the same guiding principles of maximal preservation of intestinal length and mesenteric-sparing dissection when needed. When undertaken at experienced centres, these procedures can be performed safely and with durable benefit with >80% of patients reported to remain disease-free at long-term follow-up⁸². These outcomes highlight the importance of thorough restaging after initial surgery. In cases of suspected or known residual disease, referral to a specialized NET centre would be considered to evaluate candidacy for repeat intervention and to ensure optimal multidisciplinary management.

While many questions exist, general principles for the resection of locoregional SI-NETs include: preservation of intestinal length with sparing of the ileocaecal valve when possible and of as many mesenteric vessels (arteries and veins) as possible; complete or near-complete resection of at-risk mesenteric nodal masses; and identifying and addressing multifocal and sometimes small primary tumours. Future validation of predictive criteria for safe intestinal preservation would support standardization of decision-making and surgical techniques to avoid unnecessary intestinal loss and provide better outcomes for a greater number of patients.

Surgical approach and new technology

The choice between open, laparoscopic, or robotic surgery remains debated. Minimally invasive surgery may limit lymph node retrieval and miss synchronous submucosal tumours, which are identified intraoperatively in up to 40% of patients only through systematic small intestine palpation^{85,96}. Minimally invasive

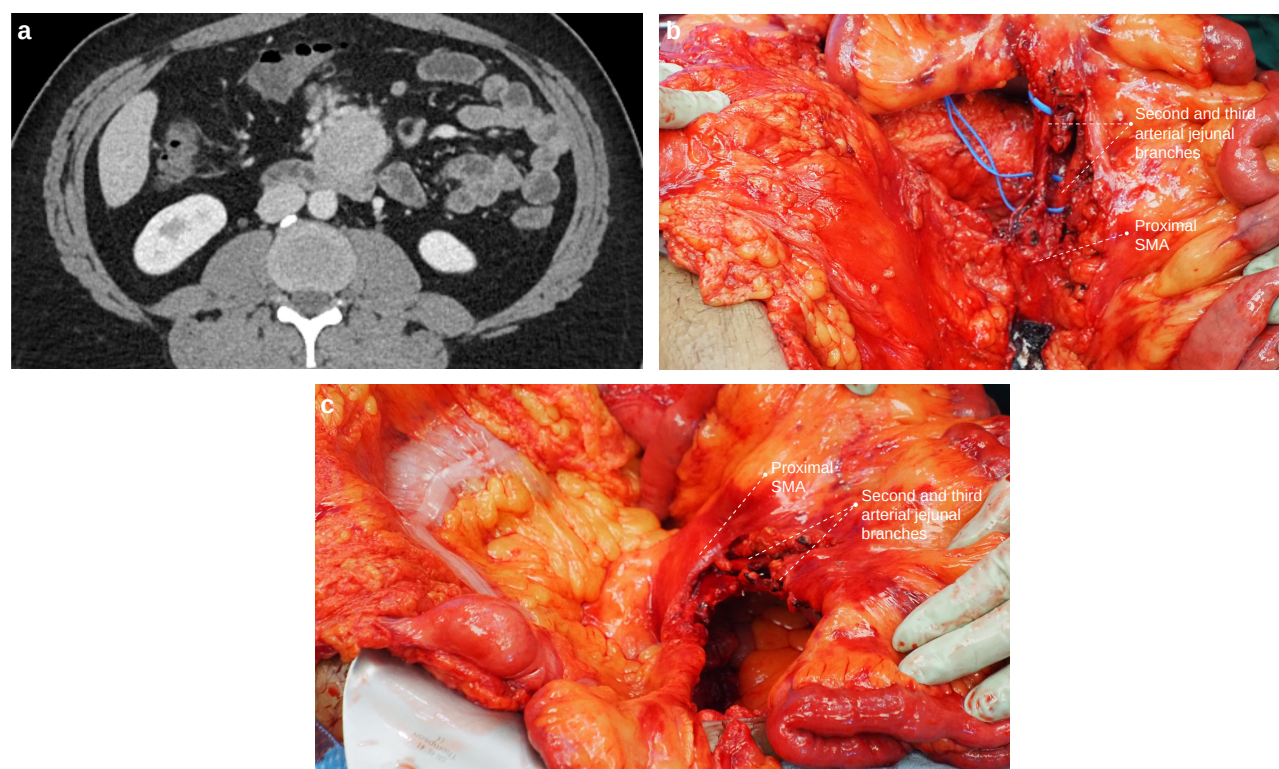


Fig. 5 Resection of level III-up mesenteric nodal mass with mesentery-sparing resection

a Preoperative CT. **b** Posterior mesenteric view. **c** Anterior mesenteric view. SMA, superior mesenteric artery.

surgery can be considered in selected patients with monofocal disease or distal mesenteric masses, provided that key oncological principles are strictly respected. Those include visualization if not palpation of the entire small intestine for synchronous tumours, high ligation of ileocolic vessels, clearance of all macroscopic nodal disease or sufficient LND, sparing of mesentery, and preservation of intestinal length.

For resection of mesenteric nodal masses, mesentery- or intestinal-sparing techniques are favoured over formal anatomical resections to avoid short bowel syndrome while maintaining disease control. Anatomical studies showed that the first and second jejunal arteries can supply up to 195 cm of small bowel, allowing for proximal vascular dissection while maintaining perfusion⁹⁷. Preserving the right colon and ileocaecal valve when feasible further supports postoperative bowel function, which is particularly important for patients at risk of carcinoid syndrome-related diarrhoea. In this context, an R1 margin is often considered acceptable due to the indolent growth of NETs and the low risk of recurrence at the margin, particularly when weighed against the morbidity of an extensive resection. Mesentery-sparing resections involve meticulous intramesenteric dissection to identify and preserve critical arterial and venous branches. Tumours abutting but not invading vascular structures may be peeled away from the underlying vessel; those can often be identified on preoperative imaging with 'smooth' vessel contour, in contrast with a 'scalloped' appearance that suggests adventitial invasion. Before dividing proximal jejunal branches, intraoperative test clamping (such as with bulldog clamps) can aid in determining intestinal viability and planning transection sites. Initiating the surgery with complete mobilization of the right colon and the small intestine mesentery up to the level of the third duodenum is key

to get access to the mesenteric mass (Fig. 6). It also often frees the mass to reveal it is sitting less proximal than anticipated.

Innovations in surgical technology offer new opportunities to enhance the safety and completeness of resection of SI-NETs, though their true benefit remains to be defined. The integration of tools such as indocyanine green fluorescence for bowel perfusion assessment and lymph node mapping is already established in colorectal surgery but is not utilized commonly in SI-NET surgery and its true benefit must be evaluated⁹⁸. When combined with clamping tests, it could provide intraoperative assessment of bowel perfusion, assist with nodal mapping, and support more confident mesenteric and intestinal preservation. Another emerging innovation is radio-guided surgery using β probes. These handheld detectors identify β radiation emitted by radiotracers such as ^{68}Ga -DOTATOC or ^{177}Lu -DOTATATE, which bind to SSTRs expressed on NETs. By converting β emissions into audible or visual signals, these probes help localize subtle or occult disease, including small nodal metastases and peritoneal deposits, that may be missed by conventional inspection or palpation. Early studies suggest this approach can improve the completeness of resection⁹⁹. As with any novel tool, however, these technologies require critical evaluation to ensure that oncological safety is not compromised.

Standardization of care and NET expertise gap

The next step in advancing SI-NET surgery is to transition from expert-dependent variability to standardized, evidence-based pathways. In parallel with technical innovations, the field must move beyond individual expertise to more structured evidence-based care. Future frameworks should classify mesenteric masses as resectable, borderline, or unresectable,

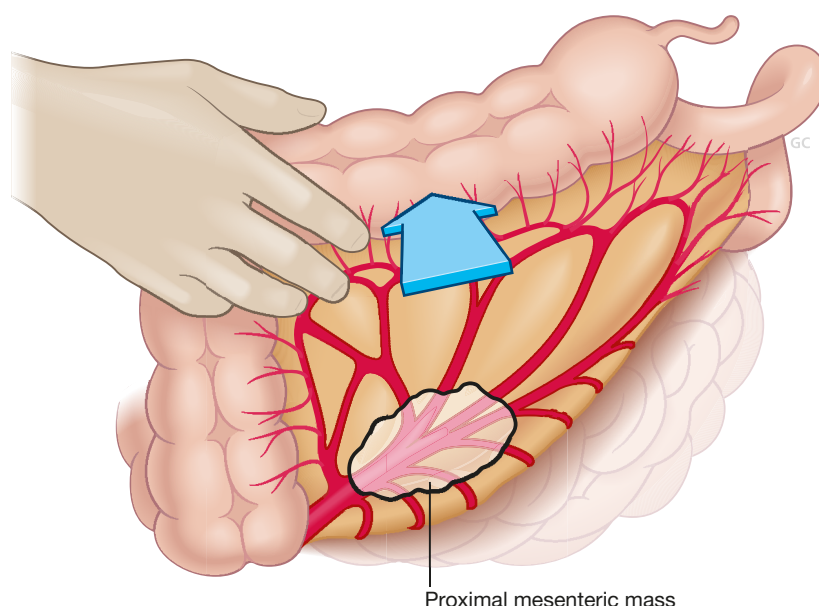


Fig. 6 Mobilization of the right colon and small bowel mesentery to root of the mesentery at the level of the third to expose proximal mesenteric mass

and define which bowel- and/or valve-preserving techniques should be preferred.

Patients treated at centres with NET expertise are more likely to undergo adequate staging, undergo complete resection, and receive appropriate multimodal care¹⁰⁰. Yet, access to such expertise remains inconsistent and a lack of standardized referral or shared-care models can contribute to variation in care received by patients with NETs. National or regional networked referral systems could help ensure that patients with complex presentations, such as extensive mesenteric fibrosis or multifocal tumours, receive optimal multidisciplinary input, including from both NET and colorectal surgical teams.

Similarly, optimal surgical timing and perioperative strategies remain poorly defined. In cases with initially unresectable central mesenteric disease, induction therapy may offer downstaging to resectability, or even symptom control and disease stabilization when that is not possible. Perioperative therapy for NETs has been mostly examined for pancreatic NETs, with few if any studies addressing its role for SI-NETs. As more therapies are developed, this ought to change. Radioligand therapy offers an opportunity in this space, though may be limited by potential side effects in the mesentery (as discussed in the section on peritoneal disease). In a multicentre cohort study, radioligand therapy led to significant symptomatic improvement in patients with inoperable mesenteric disease, including reductions in pain and bowel obstruction symptoms, even though radiological downstaging sufficient to enable resection occurred in only a minority of patients^{101–103}. These findings suggest that the primary benefit of radioligand therapy in this setting may lie in optimizing timing, improving patient condition, and reducing surgical risk, rather than achieving resectability per se. Ultimately, more robust evidence and trials are needed to guide surgical decisions in advanced disease and to balance oncological radicality with intestinal and functional preservation, while ongoing research focuses on biomarkers and systemic therapies^{35,52,99,101,104}.

Highlights

SI-NET surgery must balance oncological clearance with preservation of intestinal length, relying on meticulous vascular

mapping and mesenteric-sparing techniques to avoid short bowel syndrome and make more mesenteric masses amenable to resection. Complete or near-complete resection of mesenteric nodal masses, identification of multifocal primaries, and tailored lymphadenectomy remain central principles.

How should intraoperative carcinoid crisis be managed?

Intraoperative carcinoid crisis is the sudden onset of haemodynamic instability, typically profound hypotension, that can occur during operations on patients with NETs. It occurs in approximately 25% of operations. Risk factors for crisis include liver metastases, carcinoid syndrome, and longer operating time^{102,103,105}. If not promptly treated, it can progress to total circulatory collapse and death. Patients who experience crises have an increased incidence of postoperative complications^{102,103,105}. Historically, this event has been called intraoperative carcinoid crisis.

Pathophysiology of intraoperative carcinoid crisis

NETs are known to secrete a variety of vasoactive amines and peptides, including serotonin, histamine, bradykinin, and kallikrein, which are implicated in the clinical manifestation of carcinoid syndrome. Historically, intraoperative carcinoid crisis has been attributed to a sudden massive release of hormones from a tumour. While this theory was never clearly proven, octreotide, an SSA that inhibits the synthesis and release of hormones from NETs and has been used as a treatment for carcinoid syndrome, has traditionally been recommended as both treatment for and prophylaxis against intraoperative carcinoid crisis.

Recent data have challenged the traditional understanding of intraoperative carcinoid crisis. A prospective study on the pathophysiology of intraoperative carcinoid crisis showed that patients who had crises had higher serum serotonin levels at the beginning of the operation with a mean of 1055 ng/ml compared with 436 ng/ml in patients who did not have crises. There were no significant differences in mean levels of histamine, bradykinin, or kallikrein between patients who did

and did not have crises. However, no increased release of hormones during crises was detected. Rather, the levels of all measured hormones, including serotonin, during crises were actually lower than at the beginning of the operation. Crisis was found to be a form of distributive shock, with a reduction in systemic vascular resistance. The higher a patient's serum serotonin level was, the lower their systemic vascular resistance was during crisis. The correct treatment for distributive shock being intravenous fluids and vasopressors, not octreotide, this study questioned the role of octreotide for prevention or treatment of carcinoid crisis.

Prevention and treatment of perioperative carcinoid crisis—historical approach

The traditional recommendation of octreotide as prophylaxis against and therapy for carcinoid crisis stems from a case report from the Mayo Clinic of a patient having a carcinoid crisis with profound hypotension after induction of anaesthesia for an abdominal operation¹⁰⁶. The hypotension seemingly did not respond to standard resuscitative measures. As systolic blood pressure approached zero, the patient was administered two boluses of 50 µg intravenous octreotide and the patient immediately responded with a rise in systolic blood pressure that quickly returned to normal. Marsh et al.¹⁰⁶ then recommended having doses of short-acting octreotide available to treat crises during operations. A subsequent series from the Mayo Clinic reported comparison of outcomes of abdominal operations before and after the advent of octreotide¹⁰⁷. Intraoperative events occurred in 7% of patients before octreotide, but there were no events among 45 patients administered intraoperative boluses of octreotide, either with or without a preoperative dose. Kinney et al.¹⁰⁷ also commented that hypotensive events that did occur were generally less severe and responded rapidly to additional boluses of intravenous octreotide.

Subsequent guidelines for treatment of patients with NETs recommended perioperative octreotide for both prevention and treatment of intraoperative carcinoid crisis^{108–110}. However, these guidelines varied widely with respect to timing, dose, and route of administration. They also lacked supporting data other than the above reports and single case reports.

Prevention and treatment of perioperative carcinoid crisis—updated evidence

Since the initial reports of using octreotide for intraoperative carcinoid crisis, several series have failed to show that octreotide significantly reduces the incidence of intraoperative carcinoid crisis. This is regardless of whether the octreotide was administered as long-acting repeatable (LAR), a preoperative bolus, an intraoperative bolus, or a continuous intravenous infusion^{102,103,111}. A meta-analysis also failed to show a protective effect¹¹².

In a subsequent series of 195 consecutive operations on patients at risk of intraoperative crisis, for whom no prophylactic or therapeutic octreotide was administered, intravenous fluids and vasopressors were used to treat crises¹⁰⁵. The series showed no increase in the rate of crisis, no increase in the duration of crisis, and no increase in the rate of postoperative complications compared with previous series that used perioperative octreotide. The study showed that perioperative octreotide may be safely omitted¹⁰⁵.

The effectiveness of octreotide to treat intraoperative crisis in 150 consecutive operations was subsequently compared with vasopressors in 195 consecutive operations. Treatment with vasopressors resulted in significantly shorter crisis duration

(with no crises lasting >10 min compared with 27% of crises treated with octreotide), no aborted operations compared with 2% with octreotide, shorter operating times, and shorter length of hospital stay¹¹³. Guidelines have also traditionally stated that administration of β -adrenergic agonists should be avoided in patients with NETs because they could trigger release of hormones and trigger a crisis or, if used to treat a crisis, trigger a secondary crisis. Contemporary data indicate that α -adrenergics or vasopressin should be used instead. A comparison of the effects of β -adrenergics and α -adrenergics to treat intraoperative crises showed that patients responded equally well to β -adrenergics and no secondary crises were ever observed¹¹⁴. This indicated that β -adrenergic agonists may be safely administered if α -adrenergic agonists do not produce sufficient responses.

Updated clinical guidance and ongoing studies

An international consensus process using modified Delphi methodology has recently produced the first dedicated expert recommendations on the perioperative management of carcinoid crisis. Developed by a multidisciplinary panel of NET specialists, the consensus outlines 41 statements addressing risk stratification, preoperative optimization, intraoperative monitoring and crisis management, and postoperative care.

A key contribution is the adoption of a standardized definition of intraoperative carcinoid crisis: abrupt, significant haemodynamic instability not attributable to other factors, with significant haemodynamic instability defined as systolic blood pressure <80 mmHg or >180 mmHg, heart rate >120 beats per minute, or physiology that would result in end organ dysfunction if not corrected. This definition enables more consistent identification and reporting of carcinoid crisis during operations. This consensus also marks a paradigm shift in management: routine prophylactic use of octreotide before or at the beginning of surgery is not recommended, as current evidence does not support its efficacy in preventing crisis. For treatment, vasopressors are endorsed as first-line treatment when crisis occurs, with short-acting SSAs reserved as adjuncts if other treatments fail to resolve the crisis. This expert consensus endorsed by NANETS marks a critical step towards standardizing care, reducing practice variability, and improving outcomes for patients with NETs undergoing surgery.

To further refine the management of carcinoid crisis and develop new therapeutic plans, ongoing studies are attempting to determine if there are significant cut-off values for preoperative serotonin levels and 24-h urinary 5-hydroxyindolacetic acid levels that better predict which patients are at highest risk of intraoperative carcinoid crisis. If such levels can be defined, then a study of a course of preoperative telotristat ethyl (an inhibitor of an enzyme involved in serotonin biosynthesis), which can lower levels of serotonin, could be undertaken to see if it significantly reduces the incidence of crisis.

Nomenclature of intraoperative carcinoid crisis

Until now, the term carcinoid crisis has been used to describe two different clinical situations that have different clinical presentations and may have different aetiologies. First, classical carcinoid crisis is seen in patients with metastatic SI-NETs with extensive hormone production and is considered to be an aggravation of carcinoid syndrome with sudden secretion of large amounts of hormones. This condition is characterized by severe flushing, some degree of bronchial obstruction, and hypotension or hypertension. Before the introduction of SSAs for the treatment of carcinoid syndrome, carcinoid crises were seen

in the clinical setting as well as during procedures when the tumour was manipulated. Today, with SSAs being part of the basic therapy, clinical carcinoid crisis is a rare event. Second, intraoperative carcinoid crisis refers to the clinical event described during surgery and addressed above. The use of the same term for both events may be confusing, especially as new evidence indicates that their pathophysiology and management differ. With likely different aetiology, the treatment needed for those events differs. Therefore, a new term to refer to the intraoperative event may be needed, which would clearly distinguish both processes. The intraoperative event that occurs during surgery for NETs may be referred to as neuroendocrine intraoperative haemodynamic instability (NIHI), while the clinical aggravation of carcinoid syndrome (outside of surgery) would continue to be termed clinical carcinoid crisis.

Highlights

The understanding of crisis has shifted: prophylactic octreotide does not prevent events and vasopressors—not octreotide—are the recommended first-line treatment for intraoperative events. A standardized definition and updated algorithm now guide prevention, monitoring, and management, marking a major evolution from historical practice.

Postoperative considerations

When to give adjuvant therapy for completely resected SI-NETs?

Why adjuvant therapy after resection of SI-NETs?

Surgery with an aim to eliminate locoregional disease and distant metastases is the only potentially curative treatment option for patients with SI-NETs^{24,115,116}. Despite surgery, recurrence occurs frequently. Recurrence rates after surgery for SI-NETs range from <20% to 30–43% in published series with a median follow-up of 49–81 months^{117–121}. As an example, in a series of 129 patients with stage I–III midgut NETs who underwent R0/R1 resection, the recurrence rate was 31% after a median follow-up of 81 months¹¹⁷. Median disease-free survival was 138 months. The most frequent sites of recurrence were liver, mesentery, and pelvic lymph nodes. Patients at highest risk of recurrence are those with resected synchronous or metachronous liver metastases. While 5-year and 10-year OS are favourable, recurrence rates after resection of neuroendocrine liver metastases are 70% at 3 years and up to 94% at 5 years^{54,122}.

Because of high recurrence rates after curative-intent surgery, the role of adjuvant therapy has been a topic of debate for some time. Published data on adjuvant therapy for SI-NETs are scarce. Fisher *et al.*¹²³ concluded that adjuvant SSA therapy contributed to favourable long-term recurrence-free survival and OS of patients with R0 resected ileal NETs with metastases to the lymph nodes and liver. In contrast, Barrett *et al.*¹²⁴ reported that adjuvant therapy after resection of gastroenteropancreatic NETs provided no recurrence or survival benefit; however, the study included a very heterogeneous group of NENs registered by the US Neuroendocrine Tumor Study Group, with no stratification according to primary tumour site and lack of discriminators such as morphological grade, differentiation, and resection status (R0 versus R1).

Existing guidance

Several expert groups have issued guidance regarding adjuvant therapy for resected SI-NETs. According to an ENETS 2024

Table 1 Factors associated with high risk of recurrence in resected SI-NETs

High-risk feature	Clinical implication
Nodal involvement (≥N1) ^{79,127}	Strongly associated with higher recurrence rates, especially if four or more nodes involved
High tumour burden, for example T3–T4 tumours or bulky mesenteric disease ¹²⁵	Deeper invasion or perforation → higher metastatic risk
Lymphovascular invasion (LVI) ¹²⁸	Marker of microscopic spread → risk of distant recurrence (raises concern for occult spread)
Perineural invasion (PNI) ¹²⁹	May indicate more aggressive behaviour
Positive margins (R1) ⁷⁹ Higher Ki-67 (≥grade 2) ¹³⁰	Increased risk of local recurrence Higher Ki-67 correlates with higher recurrence and progression

SI-NETs, small intestinal neuroendocrine tumours.

guidance paper for the management of SI-NETs, adjuvant treatment is not recommended and should only be considered in the setting of clinical trials, as its role has not yet been established⁷⁹. European Society of Medical Oncology (ESMO) guidelines from 2020 do not recommend adjuvant treatment for G1 and G2 NETs, but adjuvant platinum-based chemotherapy can be considered for G3 NECs (distinct entities with more aggressive biology than NETs)¹²⁵. Guidelines from the National Comprehensive Cancer Network (NCCN) in the USA note that there is no known role for systemic treatment in the adjuvant setting for NETs and guidance regarding adjuvant treatment for SI-NETs is not included in the 2017 NANETS guidelines^{24,125}. In a Delphi-like Belgian multidisciplinary expert discussion on the management of gastroenteropancreatic NETs, unanimous consensus was reached that postoperative SSAs should not be administered if no residual disease is visible¹²⁶.

Despite a current lack of evidence to support adjuvant treatment, this remains an important research topic. Because tumour recurrence is of paramount clinical relevance, it is time to establish adjuvant treatment concepts that incorporate tumour-specific risk profiles.

Risk stratification for adjuvant therapy

Parameters identified as predictors of prognosis for SI-NETs could be used to identify patients at high risk of recurrence after surgery to inform indications for adjuvant therapy.

Pathological risk factors that have been associated with recurrence after primary tumour surgery include nodal involvement, higher T staging, lymphovascular and perineural invasion, mesenteric disease, grade, and resection status (Table 1). The prognostic significance of lymph node metastases, which are present in 46–98% of patients, has been a controversial issue^{86,131,132}. More precise information, such as lymph node ratio (number of positive lymph nodes among the total number of total lymph nodes resected), might be of higher prognostic relevance^{117,133}. Additionally, the number of resected lymph nodes may be an important consideration. In a case series from the US Neuroendocrine Tumor Study Group, the number of lymph node metastases was not of relevance if fewer than eight lymph nodes were resected¹²¹; in contrast, if eight or more lymph nodes were resected, the 3-year recurrence-free survival was worse in those with four or more positive lymph nodes compared with those with fewer than four positive lymph nodes. High toll-like receptor 7 expression in lymph node

metastases from SI-NETs has been shown to be associated with dismal prognosis¹³⁴. Extramural venous invasion (EMVI), which is associated with colorectal cancer recurrence, also appears to be of prognostic relevance in SI-NETs. In an analysis by Liu and Polydorides¹³⁵, 53.3% of patients with SI-NETs with EMVI developed metachronous liver metastases compared with 0 of 42 patients without EMVI. The presence of mesenteric tumour deposits in mesenteric perivisceral adipose tissue was recently shown to correlate with peritoneal carcinomatosis and an increased risk of death¹³².

Various nomograms incorporating clinicopathological factors such as age, WHO performance status, Ki-67 index ($\geq 10\%$), chromogranin A level, elevated liver function tests, distant metastases, and depth of invasion ($\geq T3$) have been developed to predict the survival of patients with SI-NETs^{131,136,137}. Although burdened with limitations, these tools may be able to provide additional information when selecting patients for adjuvant therapy.

Molecular profiling of SI-NETs has revealed distinct subgroups of primary tumours with significant differences in progression-free survival after resection. Karpathakis et al.¹³⁸ identified 21 epigenetically dysregulated genes including *CDX1*, *CELSR3*, *FBPI*, and *GIPR* that were associated with a recurrence rate of up to 85%. In the study reported by Andersson et al.¹³⁹, gene expression profiling defined three clusters of SI-NETs correlating with patient survival. For example, *FOXM1* was identified as the most powerful upstream regulator activated in tumours with gain of chromosome 14 and was associated with shorter patient survival.

Liquid biopsy is another novel tool that could help to identify patients at high risk of recurrence who might benefit from adjuvant treatment. Profiling of serum microRNAs showed that circulating miR-125b-5p and miR-362-5p have the potential to detect residual disease in R0/R1 resected SI-NETs¹⁴⁰. A multigenomic mRNA signature (NETest) can also identify residual disease in patients after surgery and predict NET recurrence¹⁴¹.

Potential regimens for adjuvant therapy

Systemic agents that are utilized in the management of patients with metastatic SI-NETs may be beneficial as adjuvant therapy in the postoperative setting. These therapies vary in their mechanism of action with some agents including SSAs, everolimus, and tyrosine kinase inhibitors having primarily cytostatic effects with low objective response rates compared with other treatments such as radioligand therapy with ¹⁷⁷Lu-DOTATATE that are associated with higher objective response rates^{47–49,52,69,142}. Because the goals of adjuvant therapy are primarily to prevent disease recurrence, the mechanism of action may influence the efficacy and the necessary duration of therapy in the adjuvant setting. If SSAs are utilized in the adjuvant setting, a more prolonged duration of therapy may be required. Although an optimal duration of adjuvant treatment has not been established, SSAs are typically continued for 6–12 months after surgery in high-risk cases (for example R1 resection, high-risk nodal metastases), followed by re-evaluation, and consideration of treatment for up to 5 years depending on individual patient considerations including treatment tolerance, preferences, and imaging results.

Prospective clinical trials are critical to understanding the impact of adjuvant therapy for SI-NETs. The APSIN trial is a multicentre randomized phase III trial in the set-up phase, evaluating relapse-free survival after treatment with two cycles of adjuvant ¹⁷⁷Lu-DOTATATE versus no radioligand therapy after curative surgery for locoregional SI-NETs. Adjuvant radioligand therapy is also being investigated in patients with resected

metastatic disease in the NELMAS trial (NCT05987176), a multicentre randomized trial investigating adjuvant ¹⁷⁷Lu-DOTATATE versus standard of care in patients with G1/G2 gastroenteropancreatic NETs who have undergone R0/R1 resection of liver metastases. Both trials will provide evidence, which is currently lacking, regarding the benefits of adjuvant therapy for patients with SI-NETs.

Currently, adjuvant therapy is not routinely recommended for R0/R1 resected SI-NETs. Prospective data demonstrating clear improvement in disease-free survival with adjuvant therapy do not exist. Current international guidelines generally recommend observation with close surveillance but acknowledge the need for individualized decisions for high-risk cases. If pursued, adjuvant therapy should ideally be given in the context of a clinical trial. Results of ongoing randomized trials and future studies incorporating tools to identify high-risk patients will better inform the role of adjuvant therapy for patients with resected SI-NETs.

Highlights

Adjuvant therapy is not routinely recommended after R0/R1 resection, as no evidence supports a survival benefit. Surveillance remains standard. High-risk patients may be candidates for clinical trials, as ongoing studies (for example APSIN, NELMAS) will clarify the role of adjuvant radioligand therapy and other systemic options.

Conclusions

Surgery for SI-NETs demands a fundamentally different mindset that balances oncological management with preservation of function, symptom control, and decades-long survivorship with active disease. This BJS Commission brought together international expertise to distil best current practice across the perioperative continuum, from meticulous preoperative work-up and mesentery-sparing techniques to evidence-based crisis management and the role of perioperative systemic therapy.

While much of current practice has been guided by tradition and single-centre experience, a shift is being witnessed. Advances in biomarkers, imaging, and systemic therapy provide a strong foundation on which to refine and expand surgical strategies. Key questions, such as those involving the optimal timing and extent of resection, selection for cytoreduction, the role of transplantation, and perioperative management, remain. Answering them will require sustained international collaboration, prospective multi-institutional data, and working hand in hand with other oncology specialists involved in the care of patients with NETs. There are unique opportunities for coordinated efforts to close the evidence gaps outlined herein, reduce variation in surgical care, and deliver the best possible outcomes for every patient with SI-NETs.

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Data availability

Not applicable.

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