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SURGICAL SYMPOSIUM CONTRIBUTION

Management of Locally Advanced and Unresectable Small Bowel Neuroendocrine Tumours

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Abstract Three subtypes of small bowel neuroendocrine tumours (SBNETs) have been described: Type A: SBNET with resectable mesenteric disease that does not involve the mesenteric root; Type B: "Borderline resectable" SBNET presenting with mesenteric nodal metastases and fibrosis adjacent but not encasing the main trunk of the superior mesenteric artery (SMA) and superior mesenteric vein (SMV); and Type C: "Locally advanced or irresectable" SBNET where tumour deposits and fibrosis encase the SMA and SMV. Type C SBNETs are rare and constitute around 5% of patients in reported series, although this may underestimate the prevalence. In these patients, almost all will present with symptoms of intestinal ischemia or obstruction and symptom management should be a primary main focus of treatment. All patients should be carefully staged with cross-sectional imaging and 68 Ga-dotate positron emission tomography, and discussed at a dedicated neuroendocrine tumour multidisciplinary meeting. Expert surgical review should always be sought as experienced centers have a high rate of successful resection of primary tumours and mesenteric disease. If resection is not feasible, surgical bypass should be considered in patients with a discrete and symptomatic point of obstruction. Non-operative management should emphasize symptomatic treatment with somatostatin analogs, nutritional advice and support and palliative care. Successful neoadjuvant approaches utilizing peptide radionucleide receptor therapy and systemic chemotherapy with everolimus or temazolamide/capecitabine have not been reported.

Introduction

Small intestinal neuroendocrine tumours (SBNETS) represent one third to one half of all small bowel tumours and have an annual incidence of 1.05/100,000 population [1]. Early SBNETS develop in a submucosal location and rarely cause symptoms [2]. However, the majority of SBNET patients present with metastatic disease (50–70% have lymph node metastases and 25–50% have liver, lung or bone metastases at presentation) [3] although these patients have a relatively favourable 60–70% 5-year survival [4]. A number of contemporary treatment options are now also available to enhance quality of life and extend survival in patients with metastatic SBNET [5]. Localized primary SBNETS are usually treated with small bowel resection and regional lymphadenectomy. However, in patients with advanced locoregional disease, resectability is usually determined by the presence of bulky lymph node metastases and their extent proximally along the superior mesenteric artery and vein, as well as the extent of mesenteric desmoplasia [6]. Consequently, some patients with locoregionally advanced SBNETs may be treatable with radical, oncological resection while others may

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be unresectable, but suitable for non-curative surgery to treat symptoms. Further potential modifiers of resectability for surgeons include the presence of distant metastatic disease and the presence of carcinoid heart disease. Additionally, there is evidence that subtotal or debulking surgery for primary SBNETS may improve survival and quality of life in carefully selected patient cohorts [2]. In patients with advanced primary SBNETS, regardless of metastatic status, careful surgical assessment must be made of the potential resectability of the primary and regional disease and, ideally, this should be performed within a specialized multidisciplinary team setting. In those patients that meet objective criteria for unresectability, every effort should be made actively treat and palliate tumour related symptoms.

This narrative review was undertaken to answer the following questions:

1. How common are unresectable SBNETs
2. What are the primary reasons for unresectability
3. What is the pathogenesis of mesenteric fibrosis in SBNETs
4. What are the management options currently available for patients with unresectable SBNET

How common are unresectable SBNETs?

In experienced centres, complete resection of the primary tumour and regional nodal metastases can be achieved in up to 80% of patients [7–9]. In most of the remaining patients significant cytoreductive surgery can be undertaken [7] and, if up to 90% of tumour can be removed [10], between 70–100% of these patients will report symptomatic relief [2]. In a large series of 559 patients from a specialist neuroendocrine (NET) centre in the Netherlands, Blazevic et al. [11] reported that 6% of patients were unable to undergo any form of resectional surgery and were managed with symptomatic control only. Although, in patients who underwent resectional surgery, resection was undertaken with curative intent in only 16% and palliative intent in 70% [11]. In addition, up to 5% of patients may be unresectable due to the presence of significant peritoneal metastatic disease resulting in a frozen abdomen and preventing surgical access [12].

What are the primary reasons for unresectability

Unlike other primary gastrointestinal tumours, irresectability in SBNETS is not due to locally advanced primary tumours (T_4 lesions). Primary SBNETS are usually small with Manguso et al. [13] reporting a median primary tumour size of 1.7 cm (range 0.4–5 cm), and presentation with fistulation or invasion into adjacent organs is rare [2, 11, 13]. Instead, resectability is determined by the extent of regional lymph node metastases and associated mesenteric fibrosis and desmoplasia. Regional lymphatic drainage from SBNETS extends proximally along mesenteric branches of the superior mesenteric artery (SMA) to nodes that lie adjacent to the main trunk of the SMA and thence to para-aortic lymphatics [14]. Mesenteric fibrosis occurs in association with mesenteric nodal disease and is usually centred around involved lymph nodes or mesenteric metastases [11, 15]. Blazevic et al. [11] have reported that 65% of patients with SBNETS present with a mesenteric mass and, in their series, that this was between 2.2 and 3.8 cm in diameter, with a further 17% of patients showing signs of diffuse mesenteric infiltration. Partelli et al. [14] have classified tumour resectability based on the extent of the mesenteric mass (Fig. 1a–c):

Type A: SBNET with resectable mesenteric disease (including both lymph node metastases and associated fibrosis) that does not involve the mesenteric root including the origin of the SMA.

Type B: "Borderline resectable" SBNET presenting with mesenteric nodal metastases and fibrosis adjacent to the main trunk of the SMA and superior mesenteric vein (SMV) but not encasing the vessels.

Type C: "Locally advanced or irresectable" SBNET where tumour deposits and fibrosis encase the SMA and SMV.

Pantongrag-Brown et al. [15] have described a computed tomography (CT) scan-based staging system for mesenteric fibrosis based on the degree of radiating strands within the mesentery and graded as mild (<10 thin strands), moderate >10 thin strands or <10 thick strands), and marked (>than 10 thick strands). This radiological grading system correlated with the histological degree of fibrosis and patients with a moderate or marked degree of fibrosis were more likely to have either focal or diffuse involvement of major mesenteric vasculature. However, the presence of mesenteric fibrosis alone has not been found to be a significant adverse prognostic factor for survival [6, 11]. although this is disputed [16], and the presence of desmoplasia has been found to be a negative prognostic factor in cancers other than SBNET [17].

Consequently, SBNET resectability is determined by the surgical potential to clear all, or at least 90% [2], of mesenteric nodal and fibrotic disease while maintaining arterial supply and venous drainage to remaining small bowel. In addition, determining the length residual small bowel following resection is also important. Since progressive branching of the SMA within the mesentery occurs, resections that must remove proximal mesenteric tissue will devascularise significant lengths of small bowel

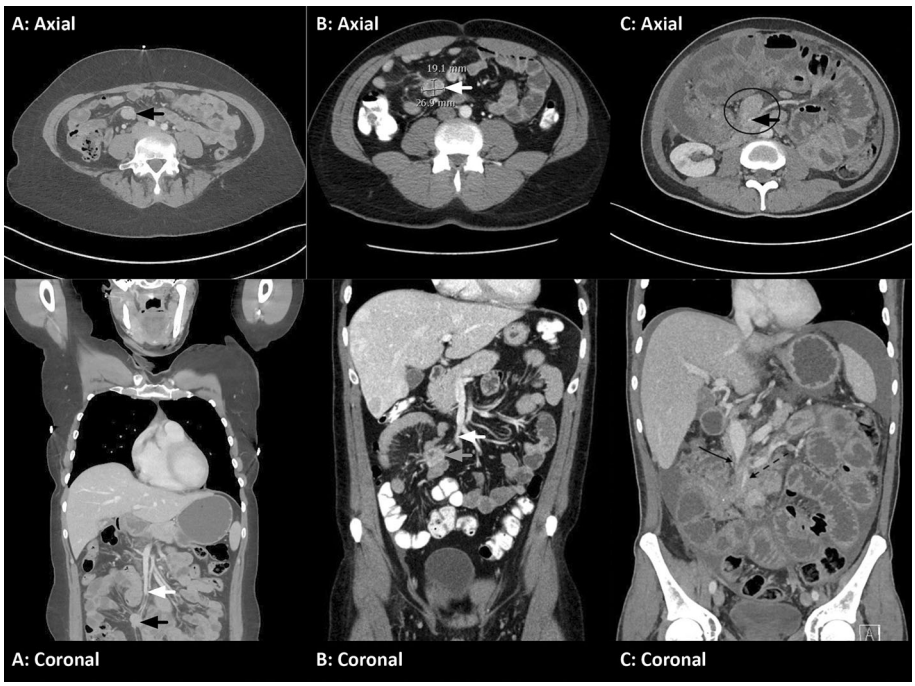

Fig. 1 Classification of mesenteric disease as proposed by Partelli et al. [14]. **a** Type A: Axial image. "Resectable" mesenteric disease (black arrow) that does not involve the mesenteric root including the origin of the superior mesenteric artery (SMA). Coronal image: Mass (black arrow) contained within the small bowel mesentery and well clear of the superior mesenteric artery (white arrow). **b** Type B: Axial image."Borderline resectable" SBNET presenting with mesenteric nodal mass (26.9 mm by 19.1 mm; white arrow) adjacent to the main trunk of the SMA and superior mesenteric vein (SMV) but not encasing the vessels. Coronal image: mesenteric mass (single gray arrow) abutting the SMA (white arrow). Courtesy of Dr J.L Pasieka. **c** Type C: Axial image."Locally advanced or irresectable" SBNET where tumour (black circle) encases the SMA (black arrow). Coronal image: Tumour narrowing and encasing the SMV (solid arrow) and the SMA (dashed arrow). Courtesy of Dr J.L Pasieka

("pizza pie resections") [14] and risk short gut syndrome. In general, an absolute minimum of 1 m of small bowel must be preserved for absorptive capacity with preservation of the terminal ileum and ileocecal valve prioritized, if possible [2, 5]. Partelli et al. [14] have also suggested "reverse" resections where the mesenteric lymph nodes are resected first and then the small bowel as a mechanism of reducing the magnitude of small bowel resection.

What is the pathogenesis of mesenteric fibrosis in SBNET

The pathophysiology and pathogenesis of mesenteric fibrosis remains unclear [6]. Multivariate analysis demonstrates that independent predictors of fibrosis are a urinary 5-hydroxy indole acetic acid (5-HIAA) $\geq$ 62 µmol/24 h, the presence of a mesenteric mass and a mass $\geq$ 27.5 mm in diameter [11], while patient age, disease stage, presence of liver metastases, serum chromogranin A level, and gender were not predictive [11]. However in spite of this finding, Laskaratos et al. [6] have shown no correlation between the severity of fibrosis and increasing levels of urinary 5-HIAA. Addition of a 5-hyroxytryptamine (HT) 2B receptor antagonist to an SBNET cell line reduces 5-HT release as well as the synthesis of profibrotic factors transforming growth factor (TGF)-β_1, connective tissue growth factor (CTGF) and fibroblast growth factor 2. This suggests that local synthesized 5-HT acting in a paracrine manner may be more important in the development of fibrosis than the endocrine effects of circulating 5-HT [16]. 5-HT has mitogenic effects in fibroblasts [18], and neuroendocrine tumour cells [19]. In addition, elevated platelet concentrations of 5-HT correlate with the presence of mesenteric fibrosis in patients with midgut NETS [20]. Similarly TGF-β is expressed in gastroenteropancreatic NETS and is known to stimulate collagen synthesis in fibroblasts [21], while CTGF is more commonly expressed in SBNETS than in bronchial, pancreatic, or rectal NETS and immunoreactive cells usually lie adjacent to areas of increased fibrovascular stroma [22]. Finally there is a direct correlation between the tissue concentrations of fibroblast growth factor and the amount of fibrous stroma present in SBNETS [23]. Collectively these observations indicate that the presence of mesenteric fibrosis is directly related to the presence of tumour and probably assists tumour growth and

development. However, while the desmoplastic stroma does not always contain malignant cells, its presence and extent, to a large degree is the rate limiting step in facilitating surgical resection of SBNETS [16].

What are the management options currently available for patients with unresectable SBNET

All SBNETS should be reviewed in a dedicated NET multidisciplinary meeting as there is evidence that experienced centres can successfully resect up to 90% of referred tumours [8, 9]. Radical resection should be considered in all patients with resectable disease; however, the finding of type C disease as described by Partelli et al. [14] with encasement of the main trunks of the SMA and/or SMV at the base of the small bowel mesentery confirms irresectability. For these patients, there are limited treatment options available and many are symptomatic from the SMV obstruction [13], mesenteric ischemia [13], or incipient small bowel obstruction [11]. Management of these patients is complex and may require input a number of services including nutrition support, gastroenterology, endocrinology, cardiology, surgery and palliative care. Consequently, management decisions are best made within the context of a multidisciplinary NET focused team with relief of symptoms and maintenance of nutritional status the primary aims of any treatment.

Somatostatin analogs

Somatostatin analogs reduced symptoms related to hormone hypersecretion and also exert an anti-proliferative effect on NET cells and their use is recommended in both functioning and non-functioning SBNETs [5]. Within the context of advanced SBNET somatostatin analogs may also reduce small bowel secretions and motility and provide some relief from obstructive symptoms.

Interferon

Interferon-α has a similar effect on symptom control to somatostatin but is less rapid in onset. Partial reductions in tumour size have been observed in 10–15% of treated patients. However, because of its side effect profile, it is recommended for consideration only in patients who have failed other lines of medical therapy [5].

Peptide receptor radionucleide therapy

Peptide receptor radionucleide therapy (PRRT) is effective at treating both local and metastatic SBNETs; however, its use in patients with severely symptomatic disease and borderline intestinal perfusion has not been recommended. PRRT is indicated after the failure of medical therapy in patients with strong expression of the somatostatin type 2 receptor [24], and may have a potential role as a neoadjuvant therapy in patients with locally advanced disease.

Systemic chemotherapy

Although not available in all jurisdictions, everolimus has shown significant activity against SBNETS with up to 30% of patients demonstrating a partial response [25]. Everolimus is recommended therapy in patients with bulky extrahepatic disease who have week or absent somatostatin receptor expression and who are therefore unsuitable for PRRT [25]. Similarly, doublet-based chemotherapy with capecitabine and temazolamide has been utilized in the treatment of metastatic SBNET with partial response rates of 15–20% [26]. However the successful use of any systemic therapy as a neoadjuvant to downstage local tumour resectability as a prelude to surgical resection has not been documented.

Cytoreductive surgery

Historically surgical resection has been considered if over 70% of visible tumour can be resected although much of the data underpinning this approach relates to hepatic metastatic disease and dates from an era prior to the widespread use of gatate PET for accurate staging [10]. For locally advanced SBNET, significant disease lies high in the mesentery around the SMV and SMA. Because of the location of tumour at the origin of the blood supply to most of the small bowel, symptoms related to ischemia, intussusception, kinking and luminal obstruction are common [11, 13, 14]. Further, because of the location of tumour any attempt to partial resect mesenteric tumour while leaving significant disease more proximally may result in loss of a significant amount of small bowel with persisting vascular compromise to the remaining small bowel and any anastomosis. Most importantly there is a high likelihood that these patients would continue to have significant symptoms. Any attempt to partially resect mesenteric disease should be carefully reviewed within a multidisciplinary context and consideration given to actively treating non-resected disease to control symptoms—e.g. with PRRT. In this context the use of phased or sequences of different treatment modalities for advanced SBNET is poorly understood. The use of aggressive vascular resection and surgical reconstruction of mesenteric vessels has also not been reported [6], although venous stenting of the SMV has been shown to relieve the symptoms of obstruction in selected patients [27].

Bypass surgery

Intestinal bypass (usually ileal or jejunocolic) has been used to treat patients presenting with obstruction and irresectable disease. Laskaratos et al. [6] utilized bypass in 5% of patients. Overall, there was no survival benefit compared to non-surgical management alone and, while the effects of bypass on symptomatology are not directed reported the authors suggested that bypass was only considered in patients with bowel obstruction secondary to unresectable disease [5].

Palliative care

For patients with advanced, symptomatic SBNETs a high standard of palliative care is the most important facet of their management regardless of whether other more active treatments are being undertaken. Good symptomatic control of pain and nausea with carefully titrated noses of analgesia and antiemetics administered orally or sub-dermally will significantly improve patient quality of life [5]. Similarly nutritional support with supplements and advice around frequency of eating and meal composition are also important.

Summary

Unresectable SBNETs are rare and constitute around 5% of patients in reported series, although this may underestimate the prevalence of this condition. Most commonly irresectability is due to tumour encasement of the main trunks of the SMV and SMA at the base of the small bowel mesentery in association with tumour associated fibrosis. Symptoms of intestinal ischemia and obstruction are common and must be a focus of treatment. All patients should be carefully staged with CT scan and dotatate PET and discussed at a dedicated NET MDM. Expert surgical review should be sought as experienced centres have a high rate of successful resection and symptom control. If resection is not feasible, surgical bypass should be considered in patients with a discrete and symptomatic point of obstruction. Non-operative management should emphasize symptomatic treatment with somatostatin analogs, nutritional advice and support and palliative care. Anti-proliferative therapy with everolimus, temazolamide/capcitabine or PRRT can also be considered in suitable patients.

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