

Case Study

## Advances in the diagnosis and management of small bowel neuroendocrine tumours

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### Key Learning Points

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Small bowel neuroendocrine tumours (SBNETs) are the most prevalent neoplasms of the small bowel. Their often unspecific symptoms mean that many patients present late with metastatic disease, most commonly to local lymph nodes in the small bowel mesentery, and metastases to the liver.

Chromogranin A is a biomarker used to monitor progression of SBNETs, but has an insufficient specificity or sensitivity to be utilised as a diagnostic test. A combination of novel tumour-specific micro RNA biomarkers may soon be used to diagnose patients with SBNETs, alleviating the need for invasive tumour biopsy. <sup>68</sup>Ga-DOTATATE PET is the current gold-standard imaging technique for staging SBNETs. It should be noted, however, that <sup>18</sup>F-DOPA PET/CT may have superior diagnostic efficacy. Finally, although medical management with Somatostatin Analogues (SSAs) has been shown to relieve symptoms and slow disease progression, surgical resection remains the only curative option.

In this case report, a patient undergoes surgical resection of her primary SBNET and several liver metastases. During the operation it becomes apparent that much of the metastatic liver spread is unresectable, and the aim of the surgery becomes tumour de-bulking. This report reveals the limitations of current SBNET imaging, biomarkers and surgical techniques, and explores recent advances.

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### Introduction

Neuroendocrine tumours (NETs) are a group of neoplasms arising from neural crest cells. Of these, small bowel NETs (SBNETs) are the most common<sup>1</sup>. NETs were first recorded in 1867 by Theodor Langhans, who described a poorly-differentiated but non-invasive “mushroom-shaped” intestinal polyp, during an autopsy of a 50 year-old woman<sup>2</sup>. In 1907 Siegfried Oberndorfer coined the term “karzinoide”, meaning “carcinoma-like” to describe the paradoxically slow spread and benign behaviour exhibited by the neoplasm, despite its histological resemblance to a carcinoma<sup>3</sup>. The term “carcinoid” is now discouraged in favour of neuroendocrine tumour, though intestinal NETs are still commonly referred to as “carcinoid” tumours due to their association with carcinoid syndrome and the production of 5HT.

SBNETs commonly present with non-specific abdominal pain, symptoms of intestinal obstruction, or “carcinoid syndrome” – a combination of symptoms such as diarrhoea and flushing, caused by hormone hypersecretion<sup>4</sup>. The incidence of SBNETs has been increasing since 1973, likely due to improved diagnostic techniques<sup>5</sup>. The current

incidence is 1.05 per 100,000, making SBNETs the most common tumour of the small bowel<sup>6</sup>.

This case report describes a patient, who underwent surgical resection of a SBNET and liver metastases, revealing the limitations of current diagnostic and treatment strategies for SBNETs, and discussing recent advances.

### Case History

KM is a 64-year-old female who first presented to her GP in December 2020 with a mild, burning epigastric pain, nausea, and vomiting, which she thought to be caused by a peptic ulcer. Her GP prescribed omeprazole, and her symptoms initially settled. However, she began to experience lower abdominal discomfort, and the epigastric pain later returned.

KM’s past medical history includes hypertension, a hysterectomy for menorrhagia and a parathyroidectomy in 2018 for hypercalcaemia. Two of her siblings also subsequently underwent parathyroidectomies for the same reason, but genetic screening for familial causes

of hyperparathyroidism did not reveal any pathogenic variants. Her only medications are Vitamin D, amlodipine and statins, and she has no known drug allergies. KM is a never smoker, has no history of alcohol excess and was fully active, with an ECOG performance status score of 0.

An abdominal ultrasound revealed a slightly expanded common bile duct and two liver lesions, leading to KM being referred for further investigations on the Two-Week Wait. A CT abdomen and pelvis confirmed the existence of an exophytic mass lesion in liver segment IVb, but it was unclear whether this was a metastasis or a primary malignancy. Unfortunately, an MRI liver could not be performed to characterise this lesion, due to KM's claustrophobia. An ultrasound liver with contrast was performed instead, but did not provide further information. An ultrasound liver biopsy in March 2021 finally revealed that the liver lesion was a well-differentiated (G1) NET, and review of her previous CT showed enlarged lymph nodes in her distal ileal mesentery, indicating a possible primary source in the small bowel. KM's NET biomarkers were largely normal, with a slightly elevated urinary 5-HIAA and normal gut hormone profile and serum Chromogranin A.

A DOTATATE PET scan in April 2021 revealed a primary lesion in the distal small bowel, with adjacent enlarged mesenteric lymph nodes, and 2 liver metastases. KM's case was discussed at the NET MDT, where it was advised that the primary and metastatic disease be surgically resected, and that she begins Somatostatin Analogue (SSA) therapy.

In May 2021, 5 months after KM's symptoms first began, she underwent a laparotomy to resect the primary tumour and metastases. Further metastatic lesions were discovered using intraoperative ultrasound. A cholecystectomy was carried out and is usually recommended as patients who are on long-term somatostatin analogues are at increased risk of gallstones and related complications. Multiple liver metastasectomies were performed in an effort to de-bulk the tumour. A total of 6 tumours were excised from 5 liver segments, and 3 more small tumours were ablated with diathermy. Intra-operative ultrasound further identified several small metastases that were too deep and close to vascular structures to be resected. 130 cm of small bowel was resected with accompanying mesenteric dissection and lymphadenectomy, ensuring vascular preservation of the remaining small bowel. There were no intraoperative complications.

KM recovered rapidly on the ward. During this time, her blood pressure was consistently at the lower end of the normal range, leading to her amlodipine being stopped. She was advised to monitor her blood pressure and organise a review with her GP if she becomes persistently hypertensive. She was discharged 5 days later with 28 days of dalteparin, oral opioid analgesia, and laxatives to prevent opioid-caused constipation.

### **<sup>68</sup>Ga-DOTATATE PET scanning is a sensitive and specific tool for detecting SBNETs**

<sup>68</sup>Ga-DOTATATE PET scanning is the gold standard imaging technique for the staging of NETs. This method exploits the fact that NETs express high levels of somatostatin receptor (SSR): DOTATATE is a somatostatin analogue which is transported into SSR-expressing cells by endocytosis, trapping the radioisotope <sup>68</sup>Ga inside NET cells. <sup>68</sup>Ga-DOTATATE PET has a sensitivity of 97.0% and a specificity of 95.1% for the detection of NETs, making it superior to CT, MRI, MIBG, Octreoscan and 18F-FDG PET/CT<sup>6,7</sup>.

Although there is strong data supporting the diagnostic efficacy of <sup>68</sup>Ga-DOTATATE PET for NETs, few investigations have compared imaging modalities specifically for SBNETs. Most recently, a meta-analysis by Piccardo et al., found that <sup>68</sup>Ga-DOTATATE PET had a sensitivity of only 82% for detection of SBNETs, while 18F-DOPA PET/CT had a 95% sensitivity<sup>8</sup>. Although this analysis included only 6 studies with a total of only 112 patients, the data showed a clear trend towards significance, indicating that 18F-DOPA PET/CT may be superior to <sup>68</sup>Ga-DOTATATE PET for staging SBNETs.

In KM's case, a <sup>68</sup>Ga-DOTATATE PET scan successfully identified the primary tumour, and staged the disease. However, this scan did not reveal the extent of metastatic spread in the liver. An MRI liver could have revealed some of this spread, helping to better plan the operation, but this additional scan would not have altered KM's management.

Chromogranin A is limited as a SBNET biomarker. Measuring biomarkers can predict a patient's prognosis, assess their response to treatment, and check for disease recurrence. Chromogranin A (CgA) is a protein secreted from neuroendocrine tissues, which is used widely as a marker of NET progression<sup>9</sup>.

However, CgA has a sensitivity and specificity of only 71% and 50%, respectively, when detecting imaging-confirmed NETs, making it a poor screening test for SBNETs<sup>11</sup>. This is because CgA is secreted by non-pathological neuroendocrine tissue, and is raised by proton-pump inhibitors, renal failure, congestive heart failure and inflammatory disease<sup>10</sup>. CgA levels also rise with increasing tumour tissue, so small SBNETs may not cause a raised CgA level. Furthermore, a recent evaluation of 5 biomarkers found that pancreastatin, a post-translational proteolytic peptide of CgA, better predicted survival and more sensitively and specifically detected progression of SBNETs<sup>11</sup>. This indicates that pancreastatin is superior to CgA for SBNET surveillance.

Urinary 5-HIAA is a 5-HT metabolite, and is also used in patients with SBNETs. It is specific, but has a sensitivity of only 35-73%, depending on the cut-off used<sup>12</sup>. Levels are usually normal in the absence of distant metastases, due to the first-pass metabolism of 5HT in the liver. It is usually elevated once patients have liver metastases. Despite her widespread disease, KM's biochemical tests showed only a slight elevation in urinary 5-HIAA and a normal serum CgA, indicating the limitation of these biomarkers for accurate diagnosis of SBNETs.

Tumour-specific microRNAs are exciting novel SBNET biomarkers. Malczewska et al. found a combination of 4 serum microRNAs which could distinguish patients with SBNETs from healthy controls, and identified 2 microRNAs which could detect residual disease after surgical resection<sup>15</sup>. However, a small sample size limited the power of this study, so large multicentre studies will be necessary to validate these findings and compare the accuracy of serum microRNAs to that of conventional biomarkers.

### **Classification**

A standardised tumour classification system is vital to ensure a common language for clinical decision-making. However, due to the multiple organ systems from which NETs may originate and their atypical "carcinoid" behaviour, the classification of NETs has been the subject of considerable debate. In 2017, the WHO updated the NET classification system, distinguishing NETs from poorly-

		<b>Grading</b>	
<b>Grade</b>	<b>Differentiation</b>	<b>Mitotic count (/10 high-power fields)</b>	<b>Ki67 proliferation index (%)</b>
G1	Well-differentiated: NET	<2	≤2
G2	Well-differentiated: NET	2-20	3-20
G3	Poorly-differentiated: NEC	>20	>20
		<b>Staging</b>	
<b>Primary tumour</b>			
T0	No evidence of primary tumour		
T1	The tumour is <1 cm, and has not grown into the muscularis propria		
T2	The tumour is >1 cm or has grown into the muscularis propria		
T3	The tumour has grown through the muscularis propria, but not outside the intestine		
T4	The tumour perforates the visceral peritoneum or directly invades other organs or structures		
<b>Nodes</b>			
N0	No spread to lymph nodes		
N1	1-12 regional lymph node metastasis		
N2	>12 lymph node metastasis, and/or the masses are >2 cm		
<b>Metastasis</b>			
M0	No distant spread		
M1	Distant metastasis: 1a = liver only, 1b = at least 1 area beyond the liver, 1c = metastasis to local and distant sites		

**Table 1:** The grading and staging of Small Bowel Neuroendocrine Tumours (SBNETs). Adapted from references (14, 15).

differentiated neuroendocrine carcinomas (NECs)<sup>14</sup>. The grading of SBNETs is based on the number of dividing cells seen on histology, measured as either the mitotic cell count in 10 high-powered fields, or as the percentage of cells expressing the proliferation marker Ki67 (Table 1). The highest-grade NETs are now classified as NECs. Upon liver lesion biopsy, KM's tumour was graded as G1, as the lesion's Ki67 proliferation index was <2%.

SBNETs are staged like other small-bowel cancers, with the Tumour-Node-Metastasis (TNM) classification (Table 1). T describes the size and local invasion of the primary tumour, N describes the tumour's invasion of lymph nodes, and M describes the extent of metastatic spread. Upon DOTATATE PET scanning, KM's tumour was classified as T2N1aM1a, as the tumour was >1 cm, had spread to <12 regional lymph nodes, and had metastasised to the liver only.

### The resection of both the primary tumour and liver metastases is justified

SBNETs present with unspecific symptoms, meaning that metastatic spread has already occurred in 30-60% of patients at diagnosis<sup>5</sup>. SBNETs most commonly metastasise to local lymph nodes, mesentery and the liver, as was unfortunately the case with KM. Liver failure is the most common cause of death patients with metastatic liver disease<sup>16</sup>. However, patients with metastatic SBNETs have a relatively long median survival time of 5.83 years, compared to other small bowel malignancies<sup>6</sup>. This raises the question: is resection of both the primary tumour site and liver metastases justified in these patients? A systematic review by Tsilimigras et al. found that in patients with SBNETs and unresectable liver metastases, resection of the primary tumour was associated with a decreased risk of death at 5 years (Hazard Ratio = 0.36)<sup>17</sup>. Even though primary site resection isn't curative, it slows disease spread and prevents complications such as small bowel obstruction. Furthermore, liver de-bulking surgery in these patients increased pooled 5-year overall survival from 36.6% to 73.1%, compared to resection of the primary

tumour alone<sup>17</sup>. Techniques such as thermal ablation can treat metastatic sites while sparing liver parenchyma, preventing post-operative liver failure caused by excessive resection. Therefore, both primary tumour resection and de-bulking of liver metastases can slow disease progression. In the case of KM, it became evident intraoperatively that without resection of the primary tumour, her small bowel would be in imminent danger of obstruction.

Patients are often contraindicated for liver debulking if they have high-grade disease, liver dysfunction, a poor performance status, or >50% liver replacement<sup>18</sup>. However, the percentage of tumour that the surgeons should be able to resect to make the operation worthwhile is the subject of considerable debate. Historic guidelines suggested that debulking should only be attempted if >90% of the metastatic load is resectable. However, more recent studies suggest that decreasing this threshold to >70% still results in improved pathology-free and overall survival<sup>19,20</sup>. Although operating on patients with larger unresectable tumour burdens will lead to smaller additional benefits, this alternative 70% threshold is still an arbitrary cut-off. Future studies are necessary to investigate the survival outcomes of patients with lower resection thresholds, to determine whether a lower cut-off is justified. Furthermore, the true extent of liver metastatic spread only becomes apparent with the use of intra-operative ultrasound, so improved pre-operative imaging techniques are necessary to better estimate the percentage of tumour which is resectable.

Liver transplantation may be a curative option for patients with unresectable metastases limited to the liver. Mazzaferro et al. published the Milan criteria for the selection of patients with NET liver metastasis for liver transplant (Table 2), and demonstrated that patients receiving a liver transplant based on these criteria had a superior overall survival at 10 years compared to a non-transplant group (88.8% vs 22.4%)<sup>21</sup>. Significantly, the authors stressed the importance of excluding metastatic spread outside the liver through careful staging using preoperative imaging, removal of local lymph nodes alongside the primary tumour, and careful intraoperative



### ***Inclusion criteria***

1	<i>Low grade (G1 or G2) NET confirmed on histology</i>
2	<i>Primary tumour, drained by the portal venous system, removed with a curative resection separate to the transplantation</i>
3	<i>Metastatic diffusion to the liver parenchyma <math>\leq 50\%</math></i>
4	<i>Good response or stable disease for <math>\geq 6</math> months pre-transplant</i>
5	<i>Age <math>\leq 55</math> years</i>

### ***Exclusion criteria***

1	<i>Small-cell carcinoma and high-grade neuroendocrine carcinomas</i>
2	<i>Non-gastrointestinal NETs, or tumours not drained by the portal venous system</i>
3	<i>Other medical/ surgical contraindications for liver transplant e.g. previous tumours</i>

**Table 2:** Milan criteria for the selection of patients with NET liver metastasis for liver transplant.

exploration of the abdominal cavity to exclude peritoneal deposits. However, the utility of this treatment is limited by the scarcity of transplantable livers, the risk of organ rejection, and the significant impact of lifelong post-transplant immunosuppression. Liver transplantation was not an option in the case of KM, as liver transplantation is not regularly carried out for this indication in the UK. Furthermore, KM's age would have excluded her based on the Milan criteria (Table 2).

### **Non-surgical treatment**

The Somatostatin Analogues (SSAs) octreotide and lanreotide make up the mainstay of medical treatment for SBNETs. They are used alongside surgical resection or for patients unfit for surgery. SBNET cells express high levels of SSRs, allowing SSAs to bind and inhibit hypersecretion of neuropeptides. This provides symptomatic relief in 65-72% of patients<sup>22</sup>. Furthermore, two landmark studies have demonstrated that SSAs can control NET growth through anti-proliferative effects: the PROMID and CLARINET trials demonstrated that octreotide and lanreotide, respectively, extend progression-free survival in gastrointestinal NET patients<sup>23,24</sup>. However, the overall survival outcomes of the PROMID trial showed that octreotide doesn't actually extend overall survival, although this data may have been confounded by the majority of patients in the placebo group receiving octreotide as their disease progressed<sup>25</sup>. Trials with larger patient samples and longer trial periods are necessary to definitively determine whether octreotide and lanreotide extend overall patient survival. KM was given 4-weekly injections of lanreotide, which have continued to date.

Peptide Receptor Radionuclide Therapy (PRRT) is used as a second-line treatment if patients show significant disease progression with SSAs. PRRT uses an SSA radiolabelled with 177-Lutetium (<sup>177</sup>Lu) to target radiotherapy directly to tumour cells. Recent completion of the landmark NETTER-1 trial demonstrated that <sup>177</sup>Lu-Dotatate combined with octreotide therapy had a longer overall survival of 48 months, compared to 36.3 months on high-dose octreotide alone<sup>26</sup>. However, this difference was not statistically significant, likely due to 36% of patients in the octreotide-only arm crossing over to the <sup>177</sup>Lu-Dotatate arm of the trial after disease progression. A future trial comparing PRRT alone to SSA therapy may be useful to tease apart the effect of PRRT on disease progression

A further second-line treatment option is everolimus. Everolimus is a potent inhibitor of mammalian Target Of Rapamycin (mTOR), a pathway which regulates cellular proliferation, apoptosis and autophagy. Subgroup-analysis of the RADIANT-4 trial found that patients in the everolimus arm had a median progression-free survival

time of 13.1 months, compared to 5.4 months in the placebo group, with benefits irrespective of whether the patients had previously received SSAs. However, it is important to note that the RADIANT-4 trial was funded by Novartis, the pharmaceutical responsible for marketing everolimus<sup>27</sup>. Limited evidence also exists for the use of sunitinib, a kinase inhibitor with activity against Vascular Endothelial Growth Factor Receptors (VEGFRs) expressed on NET cells. The SU-1111 trial demonstrated that compared to placebo, sunitinib significantly increased progression-free survival in patients with pancreatic NETs<sup>28</sup>. Results of the SUNLAND trial will reveal whether sunitinib is superior to placebo for the treatment of SBNETs when used in combination with the SSA lanreotide (ClinicalTrials.gov NCT01731925). PPRT, everolimus and sunitinib are all recommended by NICE as alternatives to SSAs for the treatment of unresectable or metastatic well-differentiated SBNETs.

### **Concluding Remarks**

The unspecific symptoms of SBNETs makes rapid recognition unlikely, meaning that many patients have metastatic disease at diagnosis. Currently used biomarkers such as CgA and urinary 5-HIAA are insensitive to be used widely for early diagnosis. Further research is necessary to identify specific and sensitive diagnostic biomarkers for earlier identification of SBNETs. It is possible that a combination of tumour-specific microRNAs may be used for diagnosis in the future. Imaging modalities such as <sup>68</sup>Ga-DOTATATE PET are too expensive to be used widely for diagnosis, but are excellent for staging disease progression.

In contrast to other metastatic neoplasms, surgical resection of SBNETs and their liver metastases is known to extend patient survival. This is true even if only 70% of the tumour load is resectable. Further studies are required to determine whether patients with <70% resectable tumour loads can still benefit from surgical de-bulking. Furthermore, liver transplantation could be an option for the subset of patients who meet the Milan Criteria. However, this is limited by organ availability and the risks of organ rejection and immunosuppression. Unfortunately, medical intervention is not curative. SSAs are used in combination with or instead of surgical resection, to relieve SBNET symptoms and to slow disease progression.

The case of KM is one that is typical of SBNET patients – a long prodrome with metastatic spread at diagnosis, followed by SSA therapy and tumour de-bulking to slow disease progression. KM's case demonstrates the need for better diagnostic biomarkers and medical treatment strategies. The rarity of SBNETs means that large multicentre and international efforts are necessary to design studies which are powerful enough to evaluate

potential diagnostic and treatment strategies.

### Conflicts of interest

None.

### Funding

None.

### Consent

The patient has consented to the publication of this case study.

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