Chapter 5: Surgery for Neuroendocrine Neoplasms

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Practice Points

- Decisions regarding individualised treatment for neuroendocrine neoplasms (NENs) should routinely be made in a multidisciplinary setting.
- In metastatic disease, resection should be performed where complete resection of primary and metastatic lesions is feasible or if the tumour is likely to cause symptoms refractory to medical management.
- Indications for surgical debulking are uncommon and are limited to functional tumours, patients with favourable tumour biology (G1/2) or where there is likely to be symptomatic benefit.
- Surgical metastasectomy is not recommended for Grade 3 NET or neuroendocrine carcinoma.
- A full pre-operative anaesthetic and endocrine review is advised for patients at risk of carcinoid syndrome with functional NENs.

Introduction

The following are broad guidelines for the surgical management of neuroendocrine neoplasms. Sub-specialty considerations and nuances related to tumours in particular anatomic sites may not be covered and are within the discretion of specialised units experienced in their management.

There is currently a paucity of high level randomised evidence to guide decisions regarding the role of surgical resection in neuroendocrine neoplasms (NENs). Therefore, many of the following points are guidelines based on expert opinion. Decisions regarding surgery for NENs should routinely be discussed in a multidisciplinary meeting in units with high volume expertise.

Surgery for localised NEN

Neuroendocrine tumour	Treatment
Gastric	**Type 1 (hypergastrinaemia)** Metastatic risk has been shown to be associated with tumours ≥10mm in diameter.(1) Endoscopic resection (e.g. EMR/ESD) is an effective and safe treatment modality for tumours <10mm.(2) Partial gastric resection and lymphadenectomy should be advocated for tumours ≥10mm. **Type 2 (Zollinger-Ellison Syndrome)** See "gastrinoma" below **Type 3 (Sporadic)** Radical gastric resection and lymphadenectomy
Duodenal (excluding gastrinoma)	≤10mm – endoscopic resection is an effective treatment modality with low risk of recurrence(3) 1-2cm – The decision for endoscopic vs. surgical resection should be individualised based on patient fitness for surgery. EUS evaluation of the tumour is recommended to aid determination for endoscopic resection. >2cm – surgical resection is recommended. This may necessitate pancreaticoduodenectomy. Ampullary (any size) – pancreaticoduodenectomy is recommended. No correlation has been demonstrated between tumour size and tumour biology in this setting.(4, 5)
Pancreatic (non-functional)	<2cm –The decision to resect vs. surveillance should be made on an individualised basis, considering the institution's risk of surgery based on the location of the tumour, and also the wishes and comorbidities of the patient. Patients should be evaluated with Ga-DOTATATE scans. FDG-PET may be considered for tumours > grade 1. Resection should be considered in those with tumours <2cm if FDG positive, Ki-67 > 5% on biopsy, young patients, and where growth of the lesion is demonstrated on serial imaging. It is reasonable to have a lower threshold for resection in distal pancreatic lesions compared with lesions in the head of the pancreas, where surgery is associated with a higher risk of morbidity and mortality. ≥2cm – Resection should be offered in fit individuals without evidence of distant metastatic disease on DOTATATE PET/CT, given that a significant proportion of individuals with ≥2cm tumours have lymph node metastases, lymphadenectomy should be considered in these patients.

Neuroendocrine tumour	Treatment
Pancreatic (insulinoma)	All insulinomas should be considered for resection. Enucleation, where possible, remains the operation of choice.

Gastrinoma	**Sporadic**
	- Pancreas
	  o Head
	  ▪ Tumours close to the main pancreatic duct should be resected as part of a pancreaticoduodenectomy + periduodenal lymph node dissection.
	  ▪ Tumours separate from the main pancreatic duct may be suitable for enucleation + periduodenal lymph node dissection.
	  o Body/tail
	  ▪ Patients should be offered distal pancreatectomy + splenectomy + regional lymph node dissection.
	- Duodenum
	  o Exploration and excision via duodenotomy or pancreaticoduodenectomy. Lymphadenectomy should be performed.
	
	MEN1-related (syndrome almost always due to multiple duodenal tumours)
	≤2cm - endoscopic excision or resection
	>2cm – resection (usually pancreaticoduodenectomy [PD] with lymphadenectomy)

Small bowel	As these tumours are most often low grade, surgical resection most often results in cure.(6) A segmental resection of small bowel with associated lymphadenectomy(7) with the aim of R0 resection should be offered.
Appendiceal	**Simple appendicectomy** - ≤ 2cm **Right hemicolectomy** - > 2cm, positive margins, positive nodes or deep meso-appendiceal invasion >3mm, vascular or lymphatic invasion, ≥G2, goblet cell carcinoid or neuroendocrine carcinoma (NEC) (+ consider bilateral salpingo-oophorectomy for goblet cell carcinoid).
Colonic	**<2cm** – endoscopic resection **≥2cm, incomplete margins, or G3** – local resection using standard oncological approaches.
Rectal	<1cm – endoscopic resection 1-2cm – ESD or EMR may be considered in this group. Small retrospective series have not found an increased risk of recurrence in this group.(8) ≥2cm – anterior resection

Neuroendocrine tumour	Treatment
Lung	Peripheral tumours – lobectomy/segmentectomy + lymphadenectomy (at least six lymph nodes) Central airway tumours – parenchymal-sparing resection + lymphadenectomy Endoluminal bronchoscopic resection may be suitable for those at too high risk for major lung resection.

Prophylactic cholecystectomy

Prophylactic cholecystectomy should be considered at laparotomy to prevent complications from gallstone disease as a result of long-term somatostatin analogue use (occurring in 27% of patients on SSA)(9). Retrospective analysis of ACS-NSQIP dataset of small bowel NET resections has shown that added cholecystectomy is not associated with any increase in operative morbidity or mortality.(10) Furthermore it may prevent local complications from liver directed therapy.

Metastatic NEN

General Principles

- There are no randomised controlled data conclusively demonstrating the survival benefit of surgical resection in the setting of metastatic NEN. Recommendations are based on retrospective single and multi-centre series. Many early studies did not include molecular imaging and very few compare surgery to systemic or liver directed therapies. All patients should be discussed at a multidisciplinary meeting (tumour board) and surgery should be undertaken in experienced centres of excellence.
- Current data suggests that selected patients may derive survival benefit from NEN metastasectomy, but almost all will develop recurrence despite "curative intent" surgery.(11, 12)

Surgical management of the primary tumour in the setting of metastatic NEN

- Resection of the primary tumour should be performed where:
    - Complete resection of metastatic lesions for curative intent is also planned; and/or
    - there is multidisciplinary consensus that the primary will cause local complications in the patient's lifetime.
- Resection of primary disease leaving hepatic metastatic disease may be indicated if it can be safely performed with low morbidity. This allows therapy to be directed at the hepatic metastases alone using liver directed or targeted therapies.
- For patients with midgut NENs, surgery to prevent or treat intestinal obstruction or ischaemic complications secondary to desmoplastic mesenteric reaction is the optimal mode of symptom control and may be associated with increased survival.(13, 14)
- The decision to resect pancreatic NENs in the setting of metastatic disease should be individualised based on the risk of surgery and location of the primary tumour. There may be a palliative role for surgery if the primary tumour is causing local complications of obstruction or bleeding.

Surgical management of the metastatic site in the setting of metastatic NEN

- **General principles**

    1. In G1/2 NEN where complete resection of all disease can be performed, curative intent surgery may be considered. For poorly differentiated tumours (G3 NEN or NEC), the preference is for systemic and/or locoregional therapies.

    2. Where possible, the goal should be for complete resection of all tumour, as this is associated with more favourable survival outcomes compared with incomplete resection.(12)

    3. In low volume, asymptomatic and/or indolent disease, patients may be observed with/without octreotide/lanreotide therapy.

    4. Where complete resection of tumour is not possible, surgical resection should be reserved for cases where there is clear palliative intent.

- **Hepatic metastases**

1. G1/2 NEN

a. Complete resection (R0/R1) possible

- Patients should be offered resection of the primary tumour and metastatic lesions.

b. Complete resection not possible

- First line treatment in this instance is with systemic therapy, including peptide receptor radionuclide therapy (PRRT), which has randomised controlled trial evidence of increased progression free survival (and preliminary evidence for overall survival) in metastatic midgut NENs compared with high-dose long-acting octreotide.(15)
- Indications for surgical debulking are uncommon and are limited to:
  - Functional tumours – Cytoreductive surgery could be considered, particularly where endocrinopathies are refractory to medical management.
  - Non-functional-tumours – Systemic therapies should be considered as first line. In some instances, cytoreductive surgery may be offered to fit individuals with favourable tumour biology (G1/2). Available data is limited to retrospective cohort studies and their associated selection biases. Some retrospective series have shown both symptomatic and survival benefit for patients where ≥90% of tumour burden is resected.(12, 16)

c. Liver transplantation

- Liver transplantation is not routinely recommended in the setting of metastatic NEN. At most, it may be considered in highly selected cases.
- Five-year overall survival in liver transplantation for NEN is similar to orthotopic liver transplantation for HCC (36-89%) but less than that for non-malignant conditions. Studies evaluating registry data from larger cohorts of patients estimate five-year overall survival to be 50-60%. The use of liver transplantation for metastatic NEN is the subject of ongoing evaluation.(20-22)

2. G3 NEN or NEC

Surgical metastasectomy is not recommended for these patients. Systemic therapy should be offered if appropriate.

Perioperative management of patients with or at risk of carcinoid syndrome

A full pre-operative anaesthetic and endocrine review is advised for patients at risk of carcinoid syndrome or those with functional NENs.

Link to Chapter 7 Functional NEN/carcinoid syndrome section.

Carcinoid syndrome

- Most often affects patients with metastatic small bowel NENs.
- Characterised by diarrhoea, bronchospasm and cutaneous flushing.
- Perioperatively, the patients with carcinoid syndrome may experience (i) carcinoid heart failure and/or (ii) carcinoid crisis.

1. Carcinoid heart disease
    - A formal preoperative evaluation by a cardiologist and echocardiogram is advised for all patients with carcinoid syndrome.
    - Characterised by right-sided valvular (tricuspid and/or pulmonary) thickening, regurgitation and/or stenosis. This can lead to right-sided heart failure and low cardiac output.
    - Low central venous pressure (CVP) may be difficult to achieve for patients with right heart failure, which may increase bleeding during liver resection.
    - In cases of severe right-sided valvular heart disease, the patient may benefit from cardiothoracic intervention prior to surgical resection of the NEN(s).

2. Carcinoid crisis
    - May occur intraoperatively even during minor procedures such as radiofrequency ablation or endoscopy.
    - Characterised by sudden hypotension or hypertensive crisis, hyperthermia, flushing, and bronchospasm.
    - Risk factors include patients with liver metastases from small bowel NEN, carcinoid heart disease, high levels of urinary 5-HIAA and/or plasma chromogranin A. Such patients should be evaluated by an endocrinologist pre-operatively and may be commenced on long-acting somatostatin analogues to prevent carcinoid crisis.
    - Patients at risk of carcinoid crisis may also be commenced on a perioperative intravenous octreotide infusion (50-200µg/h) from 24 hours prior to surgery.

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