REVIEW

Recent advances in the diagnosis and management of pancreatic neuroendocrine tumours

Andrew D Hopper,¹ Mustafa Jalal,¹ Alia Munir,² on behalf of Sheffield Teaching Hospitals European Neuroendocrine Tumour Centre

¹Department of Gastroenterology, Royal Hallamshire Hospital, Sheffield, UK

²Department of Endocrinology, Royal Hallamshire Hospital, Sheffield, UK

Correspondence to

Dr Andrew D Hopper, Department of Gastroenterology, Royal Hallamshire Hospital, Sheffield S10 2JF, UK; andydhopper@aol.com

Received 11 April 2018

Revised 12 September 2018

Accepted 14 September 2018

Published Online First

9 October 2018

ABSTRACT

The incidence of pancreatic neuroendocrine tumours (PNET) is rising mainly due to the increased use of cross-sectional imaging. Although many PNETs are asymptomatic and non-functioning, the overall 5-year survival is still less than 50%. In this article, we review the advances in diagnosis, classification and staging of PNET that have evolved with the development of new cross-sectional imaging methods and biopsy techniques. With accurate classification, evidence-based, individualised prognostic outcomes and treatments are able to be given which are also discussed.

INTRODUCTION

Pancreatic neuroendocrine tumours (PNET) account for only about 1%–2% of all pancreatic tumours with an annual incidence of 1/100 000 per year. Although much rarer than adenocarcinoma, the 5-year survival for PNET is much higher at 42% (compared with adenocarcinoma of <5%).^{1–3} PNETs are found in 1% of autopsies which is much higher than their clinical prevalence, this is thought to reflect the asymptomatic nature of smaller non-functioning PNETs (NF-PNET) which are now being detected with the increase use of contrast-enhanced cross-sectional imaging. Subsequently, the incidence of PNET is now increasing with the proportion of NF-PNET rising from 40% to over 90% in the last 30 years.^{3–5}

PRESENTATION

The majority of PNETs present in the sixth to eighth decades and are non-functioning, therefore the presentation is likely to be an incidental finding on ultrasound or cross-sectional imaging for a different indication. An NF-PNET will produce symptoms once it reaches a significant

size either locally with obstructive jaundice from bile duct compression or pain and weight loss from local invasion or metastatic spread, most commonly found in the liver.

Functioning PNETs (F-PNET) secrete active hormones; these most commonly are insulin or gastrin leading to symptoms even when the tumour is small (table 1). F-PNETs are rare; the small size, rarity and sometimes vague symptoms of these functioning tumours can make diagnosis and identification of the primary tumour challenging but given the usual early presentation and lower malignant potential, the survival outcome tends to be better. It is important to consider PNET when a patient is thought to have organic pathology, but investigations have been non-diagnostic so a fasting gut hormone screen may be helpful. F-PNET is associated with the multiple endocrine neoplasia type 1 (MEN-1) in 5% of insulinomas and up to 20% of gastrinomas, therefore further testing for associated tumours (pituitary, parathyroid, gastrinoma, family history) should be considered before treatment is started. There are other inherited disorders that have an increased incidence of PNET but are rare. Ten to seventeen per cent of patients with the autosomal dominant von Hippel-Lindau disease develop PNETs which are difficult to identify until they reach a significant size due to the multiple pancreatic cysts that are also present. PNETs are also seen in patients with neurofibromatosis type 1 (0%–10%) and tuberous sclerosis (<1%).⁶ Chromogranin-A is considered as inactive hormone secretion and can occur in both F-PNET and NF-PNET although it does not cause symptoms but and can be used as a diagnostic marker.

► <http://dx.doi.org/10.1136/flgastro-2019-101192>

Check for updates

© Author(s) (or their employer(s)) 2019. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Hopper AD, Jalal M, Munir A, et al. *Frontline Gastroenterology* 2019;**10**:269–274.

Table 1 Characteristics of functional pancreatic neuroendocrine tumours (F-PNET). VIP, vasoactive intestinal peptide³

F-PNET	Hormone	Signs or symptoms	Incidence per million	Primary location	Malignant (%)
Insulinoma	Insulin	Hypoglycaemia	1–4	Pancreas: 100%	5–15
Gastrinoma (Zollinger-Ellison syndrome)	Gastrin	Abdominal pain Diarrhoea reflux	0.5–4	Pancreas: 60% Duodenum: 30% Other: 10%	60–90
Glucagonoma	Glucagon	Rash anaemia Diabetes/ glucose intolerance Weight loss	0.04–0.12	Pancreas: 99%–100%	60
VIPoma	VIP	Severe watery diarrhoea Hypokalaemia	0.12–0.64	Pancreas: 90% Other: 10%	80
Somatostatinoma	Somatostatin	Diabetes mellitus Cholelithiasis diarrhoea		Pancreas: 56% Duodenum or jejunum: 44%	60

VIP, vasoactive intestinal peptide.

DIAGNOSIS

Pancreatic lesions can be detected on transabdominal ultrasound; however, contrast-enhanced CT is the most helpful study in the evaluation or detection of PNET. Contrast-enhanced CT is used as the initial diagnostic and staging investigation. PNETs are characterised with contrast uptake during an early arterial phase with ‘washout’ during the portal venous phase, a similar appearance is seen in liver metastases if present. PNETs usually appear as a well-circumscribed, solid and hypervascular mass, with 10% comprising a cystic component.⁷ Contrast-enhanced CT has a sensitivity of 63%–82% and a specificity of 83%–100% for detecting PNET.⁸ The lower sensitivity of CT tends to be with tumours smaller than 2 cm when alternative imaging with MRI can be helpful as it reports a higher sensitivity of 85%–100% and a specificity of 75%–100%.^{9–10} MRI of the liver is also superior to CT in detecting liver metastases and should be considered if there is any concern regarding metastatic spread.¹¹ Small PNETs are also able to be detected by endoscopic ultrasound which has a similar sensitivity to MRI of 95%–97% but additionally has the advantage of being able to obtain tissue by fine needle aspiration or biopsy for prognosis and staging.^{10–12}

Somatostatin receptor scintigraphy with a radiolabelled somatostatin analogue ‘octreotide’ can induce uptake in PNET. The sensitivity of octreotide scintigraphy for the detection of F-PNET and NF-PNET is 75%–100%.¹³ However, octreotide scintigraphy is unhelpful to detect insulinomas as they express low levels of somatostatin receptors.

Positron emission tomography (PET) with 18F-fluorodeoxyglucose (FDG) is generally unhelpful to detect a primary or metastases for PNET as although poorly differentiated tumours will display FDG uptake, most have low metabolic activity. The development of PET with 68-Ga DOTATATE, which currently is not widely available, has been shown to be more sensitive for detecting small lung lesions than octreotide scintigraphy.¹⁴ When compared, additional information is found with PET using 68-Ga DOTATATE (83%) compared with octreotide scintigraphy (68%) with a significant management impact in 47%.¹⁵

Chromogranin-A is detected in 60% of all PNETs which is inactive and produces no symptoms, however given this poor sensitivity, like all tumour markers it should be used with caution as a diagnostic test as it can also be raised in proton pump inhibitor use and renal and liver impairment and better serves as a response to treatment or recurrence detection.¹⁶

CLASSIFICATION

Recently, two classifications of PNET have been developed by European Neuroendocrine Tumour Society (ENETS) and the WHO. The WHO classified PNET based on mitotic count, Ki-67 index and differentiation stage. Well-differentiated tumours are divided into low (G1) and intermediate grade (G2) tumours. Poorly differentiated high-grade tumours are labelled neuroendocrine carcinomas (G3) (table 2).¹⁷ The ENETS staging system is based on the classic tumour, node and metastasis system (table 3).¹⁸ Both systems

Table 2 WHO classification of PNET^{17–20}

Differentiation	Grade	Proliferative rate Mitoses/10 HPF and Ki-67	Median survival (months)
Well differentiated	G1 (low)	<2; <3%	111 regional 33 metastatic
	G2 (intermediate)	2–20; 3%–20%	
Poorly differentiated	G3 (high)	>20; >20%	14 regional 5 metastatic

PNET, pancreatic neuroendocrine tumour.

Table 3 European Neuroendocrine Tumour Society staging system. TNM, tumour, node, metastases¹⁸ with 5-year survival¹⁹

Stage	TNM	5-year survival ¹⁹ (%)
I	T1 (<2 cm)	100
II	T2 (2–4 cm) T3 (>4 cm) Duodenum/bile duct	85
III	T4 Organ artery vessel invasion	85
IIIb	T×N1	
IV	T×N×M1	57

TNM, tumour, node, metastases with 5-year survival.

have been validated and can be used together as the WHO 2010 classification system has best reliability for predicting the 5-year survival of patients with PNET and the ENETS system can be used as a guideline for the treatment planning.^{19 20}

Despite the availability of a significant number of imaging modalities, there can be difficulty in differentiating a PNET from an adenocarcinoma or other pancreatic mass and given the variation in outcome for different grades and mitotic index of PNET a biopsy is usually required if any treatment is going to be considered. A reliable mitotic index from PNET can be obtained with endoscopic ultrasound with fine needle aspiration even in small lesions <2 cm²¹ (figure 1) although a biopsy from an alternative site can be obtained if metastases are present.

TREATMENT

Surgery

Given the poor outcome of PNET curative treatment with surgery is recommended where possible. Localised small PNETs less than 2 cm have an excellent prognosis of 100% 5-year survival when resected

and unlikely to ever die of the disease.²² This would suggest smaller PNETs might have the option of observation, confirmed by an observational study of very small (median size 1 cm) showing no progression after 45 months of follow-up.²³ ENETS guidelines suggest intensive observation is an option in NF-PNET less than 2 cm but risks and benefits must be considered carefully with detailed workup,²⁴ as although pancreatic surgery is a significant undertaking and smaller lesions are shown to be more benign, studies have shown that in lesions less than 2 cm 6%–29% still have malignant potential or lymph node metastases.^{22 25}

Patients with an insulinoma can be successfully cured with minimally invasive surgery in over 90%–100%^{26 27} with tumour localisation prior to resection possible with imaging and/or tattoo ink injected with endoscopic ultrasound.²⁸ Success of cure is lower in gastrinoma treatment with a 60% 5-year recurrence but has been shown to increase survival. Surgery is to be avoided if possible in patients with MEN-1 due to the multiple small NF-PNETs and gastrinomas which would require significant pancreatic resections to remove all the lesions, and unless they are greater than 2 cm seem to not alter a patent prognosis.^{29 30}

Enucleation or minimal invasive robotic surgical options are available. Enucleation for well-differentiated low-risk tumours (such as insulinomas) that are less than 3 cm has been shown to have a reduced morbidity, this includes reduced length of stay following pancreaticoduodenectomy for head lesions and the advantage of preserving splenic function for tail lesions.³¹

Primary PNET surgical excision with more advanced disease is also beneficial if possible with surgery having a significant effect on survival of 114 months vs 35 months without surgery in a large study including 728 local, regional and metastatic PNETs.³² A further study

Figure 1 Radiological assessment of pancreatic neuroendocrine tumours. (A) Incidental finding of well-circumscribed lesion on ultrasound. Lesion seen on CT arterial phase (B, C1) with demonstration of vascular washout on portal venous phase (C2). Subsequent endoscopic ultrasound with lesion highlighted dark blue (indicating a hard lesion) on elastography (D) and also allowing fine needle aspiration demonstrating a low mitotic index of <1% (the three black stained cells) with Ki-67 staining (E). Radiolabelled isotope scanning is effective as a diagnostic (octreotide) and treatment (gadolinium) modality (F).

of 63 patients with PNET, primary tumour resection from the body and tail of patients with liver metastases improved overall survival from 52 to 111 months but had little effect in patients with a high Ki-67 index or very high liver tumour burden.³³ Localised liver metastases can be resected especially to aid symptom control with progression-free survival. A study of gastropancreatic neuroendocrine tumours, including PNET, found symptomatic relief following surgery in 95% of patients following hepatic metastasis resection, with subsequent 3, 5 and 10-year overall survival rates of 83%, 71% and 42%, respectively. Poor outcomes for liver metastasis resection were due to poorly differentiated tumour, incomplete resection and extrahepatic disease.^{34 35} Ablation techniques for liver metastases are also available and discussed below if surgery not felt appropriate.

Specific functional PNET treatments

Tumour localisation and removal in gastrinoma can be difficult or present with advanced disease, therefore acid hypersecretion needs to be controlled long term. Proton pump inhibitors (all types) are effective at a dose of equivalent to omeprazole 40–60 mg once to twice a day.³⁶

Insulinomas should be treated with surgery but prior to this or if the surgery is not possible frequent small feeding helps with diazoxide inhibiting insulin release by direct action on the beta cells,³⁷ however oedema, weight gain and hirsutism are reported with use.³⁶

Somatostatin analogues can suppress vasoactive intestinal peptide (VIP)omas, glucagonoma and somatostatinoma, however should generally be avoided in insulinomas as can worsen hypoglycaemia.³⁸

Chemotherapy

Chemotherapy for PNET is non-curative; however it can have significant effect on tumour progression or symptoms. Chemotherapy can be given for recurrence after curative or palliative surgery and other interventions discussed below, but adjuvant use before or after curative surgery has not been shown to be helpful.

Although somatostatin analogues have been used to treat symptoms from hormone secretion in neuroendocrine tumours they also have an antitumour effect in low and moderate-grade (Ki-67 <10%) NF-PNETs that are somatostatin receptor positive. Somatostatin analogues are well tolerated with minor side effects (up to 26% with diarrhoea) enabling them to be used as a first-line treatment. The 'CLARINET' study used lanreotide 120 mg every 4 weeks and included 91 patients with NF-PNET. When lanreotide was compared with placebo there was a significantly prolonged progression-free survival with the median not reached in the lanreotide group versus a median of 18.0 months in the placebo group ($p < 0.001$), an HR of 0.58 (95% CI 0.32 to 1.04) for disease progression was specifically identified for PNET.³⁹ For PNET progressing on

somatostatin analogues molecular targeting therapies have been shown to slow progression. Both everolimus and sunitinib have shown to increase progression-free survival in large, placebo-controlled, randomised trials from 4.6–5.5 to 11–11.4 months, HR: 0.35–0.42 (95% CI 0.26 to 66).^{40 41} This has resulted in support in the UK from the National Institute for Health and Care Excellence recommending it for treating non-resectable or metastatic PNET.⁴²

In patients with poorly differentiated PNET, more familiar gastrointestinal-type chemotherapy is possible with the combination of cisplatin and etoposide, which have been shown to have a 70% response rate with an 8-month response duration.⁴³

Peptide receptor radionuclide therapy

Peptide receptor radionuclide therapy (PRRT) is possible by using the octreotide receptor seen in PNET. Radionuclides (¹⁷⁷Lutetium) attached to somatostatin analogues are able to deliver ¹⁷⁷LU-DOTATATE. Initial studies have shown a 22%–28% clinical response rate in progressive metastatic NF-PNET^{44 45} and a further randomised trial in non-PNETs showed a progression-free survival increase from 8 to 40 months. Significant side effects of renal toxicity (0%–10%) and bone marrow toxicity (1%–2%) are reported.^{45 46} Recent withdrawal of cancer drug funding has made access to PRRT available in only in a few centres in the UK.

Tumour ablation

There are a number of methods available to ablate liver metastases when tumour burden is less than 75%, metastases are less than 5 cm and there are no extrahepatic metastases.²⁴ Radiofrequency ablation (RFA) via percutaneous or laparoscopic approach provides local control with over 90% symptomatic relief in patients initially, follow-up has shown local recurrence is up to 22% with disease-free survival 1.3 years after treatment.⁴⁷ PNET liver metastases mainly receive blood supply from the hepatic artery, whereas the rest of the liver is supplied by the portal vein, therefore transarterial embolisation (TAE) or with the coadministration of chemotherapeutic agents (transarterial chemoembolisation, TACE) affects the tumour much more than normal liver tissue. Both TAE and TACE have shown 25%–85% of patients to have a tumour mass reduction with a mean response of 6–45 months.⁴⁸ Also available is selective internal radiation therapy, which acts by delivering microspheres of glass or resin, labelled with ⁹⁰Yttrium to deliver radiation directly into the hepatic artery. A radiological response of up to 63.2% of patients with stable disease in 22.7% has been reported.⁴⁹

Successful primary PNET ablation has been reported by using endoscopic ultrasound-guided ethanol injection or RFA. This has mainly been in case reports and series for insulinoma-type F-PNET where significant

symptoms are present but risks of surgery and comorbidity have been an issue.^{50 51}

CONCLUSION

With the increasing incidence of PNET and their apparent heterogeneity from benign incidental lesions to malignant carcinoma the management of patients with a PNET is complex. This heterogeneity and the multiple effective treatment options discussed in this review has led to the development of a patient-centred, personalised approach to treatment. Along with the important acknowledgement of the role of cancer nurse specialists and multidisciplinary team input, recent developments to form specialist ENETS centres of excellence across Europe have been started to ensure regional centres are equipped and supported to deal with these challenges. In the meantime with the incidence increasing of asymptomatic lesions more evidence is required to better define the best timing and sequence of the increasing list of effective therapies for patients with PNET.

FURTHER READING

Cancer research UK. Pancreatic Cancer Survival. <http://www.cancerresearchuk.org/about-cancer/pancreatic-cancer/survival>. Last accessed 8 January 2018.

European Neuroendocrine Tumour Society. https://www.enets.org/enets_home.html. Last accessed 3 January 2018.

Falconi M *et al.*²⁴ ENETS consensus guidelines for the management of patients with digestive neuroendocrine neoplasms of the digestive system: well-differentiated pancreatic non-functioning tumours. *Neuroendocrinology* 2012;95:120-34.

Contributors ADH designed and drafted the original manuscript. MJ and AM reviewed and updated subsequent and final drafts for important intellectual content of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- Ries LAG, Young JL, Keel GE, *et al.* SEER survival monograph: cancer survival among adults: U.S. SEER Program, 1988-2001, patient and tumor characteristics. national cancer institute, SEER Program, NIH Pub. No. 07-6215, Bethesda, MD, 2007. https://seer.cancer.gov/archive/publications/survival/seer_survival_mono_lowres.pdf (accessed 8 Jan 2018).
- Cancer research UK. Pancreatic cancer survival. <http://www.cancerresearchuk.org/about-cancer/pancreatic-cancer/survival> (accessed 8 Jan 2018).
- Halfdanarson TR, Rubin J, Farnell MB, *et al.* Pancreatic endocrine neoplasms: epidemiology and prognosis of pancreatic endocrine tumors. *Endocr Relat Cancer* 2008;15:409-27.
- Vagefi PA, Razo O, Deshpande V, *et al.* Evolving patterns in the detection and outcomes of pancreatic neuroendocrine neoplasms: the Massachusetts General Hospital experience from 1977 to 2005. *Arch Surg* 2007;142:347-54.
- McKenna LR, Edil BH. Update on pancreatic neuroendocrine tumors. *Gland Surg* 2014;3:258-75.
- Alexakis N, Connor S, Ghaneh P, *et al.* Hereditary pancreatic endocrine tumours. *Pancreatol* 2004;4:417-33. discussion 34-5.
- Singhi AD, Chu LC, Tatsas AD, *et al.* Cystic pancreatic neuroendocrine tumors: a clinicopathologic study. *Am J Surg Pathol* 2012;36:1666-73.
- Sundin A. Radiological and nuclear medicine imaging of gastroenteropancreatic neuroendocrine tumours. *Best Pract Res Clin Gastroenterol* 2012;26:803-18.
- Sundin A, Vullierme MP, Kaltsas G, *et al.* ENETS consensus guidelines for the standards of care in neuroendocrine tumors: radiological examinations. *Neuroendocrinology* 2009;90:167-83.
- Caramella C, Dromain C, De Baere T, *et al.* Endocrine pancreatic tumours: which are the most useful MRI sequences? *Eur Radiol* 2010;20:2618-27.
- Dromain C, de Baere T, Lumbroso J, *et al.* Detection of liver metastases from endocrine tumors: a prospective comparison of somatostatin receptor scintigraphy, computed tomography, and magnetic resonance imaging. *J Clin Oncol* 2005;23:70-8.
- James PD, Tsolakis AV, Zhang M, *et al.* Incremental benefit of preoperative EUS for the detection of pancreatic neuroendocrine tumors: a meta-analysis. *Gastrointest Endosc* 2015;81:848-56.
- de Herder WW, Kwekkeboom DJ, Valkema R, *et al.* Neuroendocrine tumors and somatostatin: imaging techniques. *J Endocrinol Invest* 2005;28:132-6.
- Buchmann I, Henze M, Engelbrecht S, *et al.* Comparison of 68Ga-DOTATOC PET and 111In-DTPAOC (Octreoscan) SPECT in patients with neuroendocrine tumours. *Eur J Nucl Med Mol Imaging* 2007;34:1617-26.
- Hofman MS, Kong G, Neels OC, *et al.* High management impact of Ga-68 DOTATATE (GaTate) PET/CT for imaging neuroendocrine and other somatostatin expressing tumours. *J Med Imaging Radiat Oncol* 2012;56:40-7.
- Campana D, Nori F, Piscitelli L, *et al.* Chromogranin A: is it a useful marker of neuroendocrine tumors? *J Clin Oncol* 2007;25:1967-73.
- Rindi G, Petrone G, Inzani F. The 2010 WHO classification of digestive neuroendocrine neoplasms: a critical appraisal four years after its introduction. *Endocr Pathol* 2014;25:186-92.
- Rindi G, Klöppel G, Alhman H, *et al.* TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. *Virchows Arch* 2006;449:395-401.
- Rindi G, Falconi M, Klersy C, *et al.* TNM staging of neoplasms of the endocrine pancreas: results from a large international cohort study. *J Natl Cancer Inst* 2012;104:764-77.
- Ellison TA, Wolfgang CL, Shi C, *et al.* A single institution's 26-year experience with nonfunctional pancreatic neuroendocrine tumors: a validation of current staging systems and a new prognostic nomogram. *Ann Surg* 2014;259:204-12.
- Unno J, Kanno A, Masamune A, *et al.* The usefulness of endoscopic ultrasound-guided fine-needle aspiration for the diagnosis of pancreatic neuroendocrine tumors based on the World Health Organization classification. *Scand J Gastroenterol* 2014;49:1367-74.
- Bettini R, Partelli S, Boninsegna L, *et al.* Tumor size correlates with malignancy in nonfunctioning pancreatic endocrine tumor. *Surgery* 2011;150:75-82.
- Lee LC, Grant CS, Salomao DR, *et al.* Small, nonfunctioning, asymptomatic pancreatic neuroendocrine tumors (PNETs): role for nonoperative management. *Surgery* 2012;152:965-74.

- 24 Falconi M, Bartsch DK, Eriksson B, *et al.* ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms of the digestive system: well-differentiated pancreatic non-functioning tumors. *Neuroendocrinology* 2012;95:120–34.
- 25 Regenet N, Carrere N, Boulanger G, *et al.* Is the 2-cm size cutoff relevant for small nonfunctioning pancreatic neuroendocrine tumors: A French multicenter study. *Surgery* 2016;159:901–7.
- 26 Ayav A, Bresler L, Brunaud L, *et al.* Laparoscopic approach for solitary insulinoma: a multicentre study. *Langenbecks Arch Surg* 2005;390:134–40.
- 27 Isla A, Arbuckle JD, Kekis PB, *et al.* Laparoscopic management of insulinomas. *Br J Surg* 2009;96:185–90.
- 28 Leelasinjaroen P, Manatsathit W, Berri R, *et al.* Role of preoperative endoscopic ultrasound-guided fine-needle tattooing of a pancreatic head insulinoma. *World J Gastrointest Endosc* 2014;6:506–9.
- 29 Triponez F, Goudet P, Dosseh D, *et al.* Is surgery beneficial for MEN1 patients with small (< or = 2 cm), nonfunctioning pancreaticoduodenal endocrine tumor? An analysis of 65 patients from the GTE. *World J Surg* 2006;30:654–62. discussion 63–4.
- 30 Norton JA, Alexander HR, Fraker DL, *et al.* Comparison of surgical results in patients with advanced and limited disease with multiple endocrine neoplasia type 1 and Zollinger-Ellison syndrome. *Ann Surg* 2001;234:495–505. discussion 6..
- 31 Pitt SC, Pitt HA, Baker MS, *et al.* Small pancreatic and periampullary neuroendocrine tumors: resect or enucleate? *J Gastrointest Surg* 2009;13:1692–8.
- 32 Hill JS, McPhee JT, McDade TP, *et al.* Pancreatic neuroendocrine tumors: the impact of surgical resection on survival. *Cancer* 2009;115:741–51.
- 33 Bertani E, Fazio N, Radice D, *et al.* Assessing the role of primary tumour resection in patients with synchronous unresectable liver metastases from pancreatic neuroendocrine tumour of the body and tail. A propensity score survival evaluation. *Eur J Surg Oncol* 2017;43:372–9.
- 34 Saxena A, Chua TC, Perera M, *et al.* Surgical resection of hepatic metastases from neuroendocrine neoplasms: a systematic review. *Surg Oncol* 2012;21:e131–41.
- 35 Birnbaum DJ, Turrini O, Vigano L, *et al.* Surgical management of advanced pancreatic neuroendocrine tumors: short-term and long-term results from an international multi-institutional study. *Ann Surg Oncol* 2015;22:1000–7.
- 36 Jensen RT, Cadiot G, Brandi ML, *et al.* ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms: functional pancreatic endocrine tumor syndromes. *Neuroendocrinology* 2012;95:98–119.
- 37 Guettier JM, Gorden P. Insulin secretion and insulin-producing tumors. *Expert Rev Endocrinol Metab* 2010;5:217–27.
- 38 Kulke MH, Anthony LB, Bushnell DL, *et al.* NANETS treatment guidelines: well-differentiated neuroendocrine tumors of the stomach and pancreas. *Pancreas* 2010;39:735–52.
- 39 Caplin ME, Pavel M, Ćwikła JB, *et al.* Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med* 2014;371:224–33.
- 40 Raymond E, Dahan L, Raoul JL, *et al.* Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med* 2011;364:501–13.
- 41 Yao JC, Shah MH, Ito T, *et al.* Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med* 2011;364:514–23.
- 42 National Institute for Health and Care Excellence (NICE) Technology appraisal guidance [TA449], 2017. Everolimus and sunitinib for treating unresectable or metastatic neuroendocrine tumours in people with progressive disease. <https://www.nice.org.uk/guidance/ta449> (accessed 1 Jan 2018).
- 43 Moertel CG, Kvols LK, O'Connell MJ, *et al.* Treatment of neuroendocrine carcinomas with combined etoposide and cisplatin. Evidence of major therapeutic activity in the anaplastic variants of these neoplasms. *Cancer* 1991;68:227–32.
- 44 Kwekkeboom DJ, de Herder WW, Kam BL, *et al.* Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0,Tyr3]octreotate: toxicity, efficacy, and survival. *J Clin Oncol* 2008;26:2124–30.
- 45 Delpassand ES, Samarghandi A, Zamanian S, *et al.* Peptide receptor radionuclide therapy with 177Lu-DOTATATE for patients with somatostatin receptor-expressing neuroendocrine tumors: the first US phase 2 experience. *Pancreas* 2014;43:518–25.
- 46 Strosberg J, El-Haddad G, Wolin E, *et al.* Phase 3 Trial of (177) Lu-Dotatate for midgut neuroendocrine tumors. *N Engl J Med* 2017;376:125–35.
- 47 Harring TR, Nguyen NT, Goss JA, *et al.* Treatment of liver metastases in patients with neuroendocrine tumors: a comprehensive review. *Int J Hepatol* 2011;2011:154541.
- 48 Ito T, Lee L, Jensen RT. Treatment of symptomatic neuroendocrine tumor syndromes: recent advances and controversies. *Expert Opin Pharmacother* 2016;17:2191–205.
- 49 Kennedy AS, Dezarn WA, McNeillie P, *et al.* Radioembolization for unresectable neuroendocrine hepatic metastases using resin 90Y-microspheres: early results in 148 patients. *Am J Clin Oncol* 2008;31:271–9.
- 50 Armellini E, Crinò SF, Ballarè M, *et al.* Endoscopic ultrasound-guided ethanol ablation of pancreatic neuroendocrine tumours: a case study and literature review. *World J Gastrointest Endosc* 2016;8:192–7.
- 51 Lakhtakia S, Ramchandani M, Galasso D, *et al.* EUS-guided radiofrequency ablation for management of pancreatic insulinoma by using a novel needle electrode (with videos). *Gastrointest Endosc* 2016;83:234–9.