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FOCUS ON: NEURO-ENDOCRINE TUMOURS

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CT/MRI of neuroendocrine tumours

Rodney H Reznek

St Bartholomew's Hospital, London, UK

Corresponding address: Rodney H Reznek, FRCP, FRCR, Professor of Diagnostic Imaging, Cancer Imaging, St Bartholomew's Hospital, London, UK. E-mail: r.h.reznek@qmul.ac.uk

Abstract

Neuroendocrine tumours (NETs) are often thought to be rare and rather recherché cancers which are of little concern to the general physician, surgeon or radiologist because of their rarity and esoteric nature. In fact, while relatively uncommon, the total group of gastro-entero-pancreatic (GEP) tumours incorporates the spectrum of all types of carcinoids, incuding bronchial carcinoids, and the whole gamut of islet-cell tumours. Some of these may present as functioning tumours, with a plethora of hormonal secretions and concomitant clinical syndromes, and GEPs in general have an incidence around 30 per million population per year. This means that in the whole European Union, for example, there will be in the region of 12 000 new patients every year presenting with one or another manifestation of these tumours. Furthermore, the comparatively long survival of many of these patients, compared to more common adenocarcinomas or epithelial tumours, implies that the point prevalence is also not inconsiderable. However, it is undoubtedly true that these tumours can be difficult to identify, especially in their early stages, and it is then that radiological investigation becomes of paramount importance. Having taken into account all these considerations, most investigators would initiate investigation of a suspected or biochemically proven islet-cell tumour with cross-sectional imaging—either CT or MRI. This will clearly identify the larger lesions, allow assessment of the entire abdomen, and provide valuable information on the presence of hepatic metastates.

Keywords: *Neuroendocrine tumours; CT; MRI.*

Introduction

Neuroendocrine tumours including pancreatic endocrine tumours (also known as pancreatic neuroendocrine tumours or PETs) and carcinoid tumours (also known as neuroendocrine tumours or NETs) are rare tumours arising from a putative common precursor, the APUD cell (amine precursor uptake and decarboxylation), although this term has fallen into disuse. These cells, which have been presumed to be of common embryological origin from the ectodermal ridge, spread throughout the body to form a network with common structural and functional features. Cells of this system also include chromaffin cells, which develop from neural crest cells. These neuroendocrine tumours are histologically closely related to melanoma, pheochromocytoma and medullary carcinoma of the thyroid, which are described elsewhere. All neuroendocrine tumours have the potential to synthesize and secrete hormones. Functioning tumours are those in which hormone secretion by the tumour results in a clinical syndrome. Non-functioning tumours are those in which either there is no hormone secretion or hormone secretion results in no recognizable clinical syndrome. Functioning tumours usually present relatively early, due to the clinical syndrome, and may be a challenge for the radiologist to localise as they are often small. Non-functioning tumours generally go unrecognised and present much later with mass effects. The malignant potential of neuroendocrine tumours varies. Malignancy is more common in some types, such as gastrinoma, whereas in others, such as insulinoma, malignancy is rare, but clinical behaviour is often difficult to predict. In some cases, the tumours are associated with genetic disorders such as the multiple endocrine neoplasia type 1 (MEN 1) syndrome.

Imaging of functioning tumours, in particular, is primarily directed at localisation and staging of the tumour. Preoperative localisation reduces the potential

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surgical complications and increases the chances of surgical resection, the only form of curative treatment for these tumours. However, imaging is also valuable in the follow-up of recurrent or metastatic disease, and nuclear imaging techniques may be used to direct treatment with radiopharmaceuticals.

In this paper, the clinical and imaging features of pancreatic neuroendocrine tumours and carcinoid neuroendocrine tumours are described. The roles of the different imaging and radionuclide techniques used are discussed.

Pancreatic endocrine tumours (PETs)

Pancreatic endocrine tumours arise from the islet cells of Langerhans and include:

- insulinoma
- gastrinoma
- VIPoma
- glucagonoma
- somatostatinoma
- pancreatic polypeptidoma (PPoma).

Epidemiology

Pancreatic endocrine tumours are rare, with a reported prevalence of 10 per million of population[1]. The incidence of clinically significant pancreatic endocrine tumours is 4 per million population per year. The majority of pancreatic endocrine tumours are functioning, with only 15%–30% being non-functioning pancreatic endocrine tumours[2,3]. Pancreatic endocrine tumours predominantly occur in patients in their third to sixth decades. Insulinomas, which are usually benign, are by far the most common pancreatic endocrine tumour, accounting for up to 50% of all cases[4]. There is a slight predominance of women in benign insulinomas (F6:M4) with an equal sex incidence in the rare malignant insulinomas. The remainder of pancreatic endocrine tumours are more likely to be malignant, with gastrinoma the next most common, accounting for 20% of cases,[2] seen in 0.5–3 patients per million population per year. There is a slight male predominance in gastrinomas. In 20% of patients with a gastrinoma there is a family history of disease and findings consistent with MEN 1[5]. There is an equal sex incidence in the remainder of pancreatic endocrine tumours, PPomas being the next most common. The other pancreatic endocrine tumours are even more rare, and are often found in the context of MEN 1. Patients with MEN 1 generally present younger, usually have multiple tumours, and may have prolonged survival compared with sporadic cases.

Aetiology

The aetiology of pancreatic endocrine tumours remains obscure. Abnormalities on chromosome 11q13 have been found in patients with MEN 1 and in patients with a sporadic gastrinoma[6,7]. MEN 1 is inherited as an autosomal dominant trait: the syndrome comprises hyperplasia and/or tumours of several endocrine organs, the parathyroid gland being most commonly involved, followed by the pancreas, in which islet cell tumours are seen in over 80% of patients with MEN 1. Pituitary tumours, particularly prolactinomas, are the third major arm of the syndrome, but a variety of other tumours such as lipomas and adrenocortical tumours are also seen. One-third of sporadic cases of gastrinoma have been shown to have similar chromosomal mutations to patients with MEN 1.

Histology

The histological appearance of pancreatic endocrine tumours is similar to that of carcinoid neuroendocrine tumours, characterised by uniform sheets of small round cells. Several different patterns of growth have been described, a glandular pattern, solid pattern, gyriform pattern and an unclassified pattern. However, the pattern of growth does not correlate with hormone production or malignant potential[5].

Classification and clinical presentation (Table 1)

It is now recognized that most pancreatic endocrine tumours secrete a variety of hormonally active peptides. However, the classification of pancreatic endocrine tumours is based on the presenting clinical syndrome, which is caused by the predominant hormone secreted by the tumour (Table 1). If no clinical syndrome is evident, the tumour is either classified by the hormone secreted (usually PPoma) or, if no hormone is secreted, then it is called a non-functioning pancreatic endocrine tumour.

Insulinoma

Insulinomas are solitary and intrapancreatic in over 90% of cases, with an equal distribution in the head, body and tail of the gland[4,8]. Ninety percent of the tumours are less than 2 cm and 40% less than 1 cm in diameter[3,9,10]. Insulinomas almost invariably present with the clinical syndrome caused by hypoglycaemia. The symptoms are variable and may be intermittent. There may be changes in personality or work performance and, in the elderly, there may be confusion or dementia. The association of symptoms with fasting may not be evident to the patient.

Table 1 Classification of pancreatic neuroendocrine tumours [2–5,16]

Tumour name	Frequency (%)	Syndrome	Pancreatic islet cell	Hormone produced	Malignant (%)	Anatomical location	Typical size
Insulinoma	50	Insulinoma	B cell	Insulin	10–15	Pancreas >90% (head = body = tail)	<2 cm 90%, <1 cm 40%
Gastrinoma	20–30	Zollinger–Ellison syndrome	G cell	Gastrin	60–75	Pancreas 30%–60%[a], duodenum 30%–40%[a], lymph nodes 10%–15%[a], other <5	0.3–3.0 cm
Non-functioning and PPoma	15–30	No syndrome	D1 cell	None or pancreatic polypeptide	60–90	Pancreas (most frequently in the head)	Large
VIPoma	3	Verner–Morrison syndrome; WDHA	D2 cell	Vasoactive intestinal peptide	50–80	Pancreas 90% (usually tail), adrenal 10%	Large
Glucagonoma	Rare	Glucagonoma	A cell	Glucagon	60	Pancreas	2–10 cm
Somatostatinoma	Rare	Somatostatinoma[b]	D cell	Somatostatin	50–70	Pancreas 56%, jejunum 44%	Large

[a] 90% are within the gastrinoma triangle.
[b] Somatostatinoma may be associated with NF 1.

The diagnosis is established clinically and biochemically prior to localisation, on the basis of Whipple's triad, i.e. hypoglycaemic attacks in the fasting state, blood glucose levels less than 2 mmol/l during an attack, with relief of symptoms following glucose administration. Other characteristic features include unusual levels of insulin and C-peptide and a negative screen for sulphonylureas [11,12].

Gastrinomas

Gastrinomas are the second most common pancreatic endocrine tumour, comprising about 20%–30% of the total; about 60% of gastrinomas are malignant with hepatic metastases at presentation, although there is a higher incidence of malignancy in those associated with MEN 1 [2,4]. Metastases are usually to peripancreatic lymph nodes and liver, but bone metastases have been reported in approximately 30% of cases [13]. About 90% of gastrinomas are located in the 'gastrinoma triangle' formed by the junction between the neck and body of the pancreas medially, the 2nd and 3rd parts of the duodenum inferiorly and the junction of the cystic and common ducts superiorly [5]. These tumours are more often extrapancreatic than insulinomas and tend to be even smaller, ranging in size from 0.3 to 3 cm. They also tend to be less vascular than insulinomas [14]. Patients generally present with recurrent, multiple or 'ectopic' peptic ulceration, the Zollinger–Ellison syndrome (ZES), although in some cases ulceration may be mild. Diarrhoea and malabsorption due to acid inactivation of pancreatic enzymes may be predominant. The finding of an elevated gastrin level together with a high basal acid output is diagnostic of a gastrinoma [15]. Investigation should be undertaken in the absence of histamine antagonists (>48 h) or proton pump inhibitors (>2 weeks), if possible. Once the diagnosis of gastrinoma has been confirmed, localisation with imaging should be undertaken to identify the primary site and to stage the disease.

Other functioning pancreatic endocrine tumours

The other functioning pancreatic endocrine tumours are very rare, frequently associated with MEN 1 and frequently malignant: 60%–70% of glucagonomas, 50%–80% of VIPomas and 50%–70% of somatostatinomas are malignant (see Table 1).

VIPomas, which comprise 3% of the total number of pancreatic endocrine tumours, are usually located within the pancreas (over 80%, usually in the pancreatic tail) but may also arise in the extrapancreatic tissue particularly the retroperitoneal sympathetic chain and the adrenal medulla [4,5]. The VIPoma syndrome, also known as watery diarrhoea, hypokalaemia and achlorhydria (WDHA), or Verner–Morrison syndrome, is caused by the secretion of vasoactive intestinal peptide. The symptoms are of marked watery diarrhoea, which causes hypokalaemia (the life-threatening aspect of the disease). Death may occur due to cardiac arrest. The diagnosis is made on clinical and biochemical features, with the demonstration of an elevated plasma VIP. Other peptides such as neurotensin and PHM may also be elevated.

Glucagonomas often arise within the body or tail of the pancreas and, in contrast with the other rare

tumours, they are usually large (2–10 cm) at the time of diagnosis[4,5,16]. The glucagonoma syndrome presents with a characteristic necrolytic migratory erythematous rash, seen typically in the groin region in 75% of patients. This may be associated with glossitis and angular stomatitis. The diagnosis is confirmed by demonstrating elevated plasma glucagon levels. Glucagonomas tend to present late, usually with metastases, which are most frequently hepatic but may also be within lymph nodes or the mesentery. The prognosis is usually poor.

Somatostatinomas are found in the pancreas in 56%–75% of cases (most often in the pancreatic head) but up to 50% are located in the duodenum, where they may be associated with neurofibromatosis[5,17]. Somatostatinomas are very slow growing tumours with relatively mild non-specific symptoms including diabetes mellitus, diarrhoea, steatorrhoea and weight loss, and the tumours thus tend to be very large at presentation. Metastases are present in up to 90% of cases, most commonly to liver, and also to lymph nodes and bone[18].

Non-functioning PETS

PPomas and pancreatic endocrine tumours that do not secrete any hormones do not result in a clinical syndrome and therefore present late as tumours causing mass effects[3]. They are slow-growing and tend to be large at diagnosis; approximately 60%–90% are malignant[4,16]. They usually lie in the pancreatic head and thus presentation may be similar to that of pancreatic adenocarcinoma, with biliary obstruction.

'Carcinoids' (gastrointestinal and bronchial neuroendocrine tumours)

The term carcinoid was first used in 1907 to describe a tumour of the gastrointestinal tract that was slow-growing and not as aggressive as an adenocarcinoma. In the 1950s the tumours were found to contain serotonin, and the carcinoid syndrome was described, where patients with a small intestinal carcinoid tumour and liver metastases presented with the characteristic symptoms of diarrhoea, flushing, asthma and right heart failure. However, only some 10% of such tumours are associated with the syndrome. The cells arise from the diffuse neuroendocrine system and have the potential to secrete a wide variety of amines and peptides, and therefore are now often referred to as neuroendocrine tumours (NETs) to reflect the wide range of clinical presentations[19,20].

Epidemiology (Table 2)

Carcinoid neuroendocrine tumours occur much more frequently than pancreatic endocrine tumours and account for 2% of malignant tumours of the GI tract. The reported incidence of carcinoids is 7.1 per million of population for men and 8.7 per million for women[21]. However, the annual incidence is higher in autopsy studies, at 21 per million population[22]. Carcinoids present between the second and ninth decades, with certain sites being more typical in certain age groups: cervical carcinoids present in the fourth decade, small intestine and respiratory tract in the early seventh, and rectal carcinoids in the late seventh decade[19,22,23].

Aetiology

The aetiology of carcinoids is not well understood. Certain disease states that result in hypergastrinaemia, such as pernicious anaemia and atrophic gastritis, appear to predispose to gastric carcinoids (see below). In Zollinger–Ellison syndrome, the development of a gastric carcinoid occurs most frequently in those with MEN 1. Various tumour growth factors may influence the development of carcinoids and, as in patients with MEN 1, changes in chromosome 11q13 have been reported in patients with sporadic carcinoid neuroendocrine tumours, particularly foregut neuroendocrine tumours, which are most commonly associated with MEN 1[20].

Histology

Histologically, the tumour comprises sheets of uniform round cells arising from the enterochromaffin cells, which are APUD cells of the diffuse endocrine system. It is not possible to differentiate benign from malignant carcinoids based on histological features alone, with the presence of local invasion or metastases indicating malignancy. In addition, carcinoids cannot be differentiated histologically from pancreatic endocrine tumours. Silver staining was used in the past to classify carcinoids into those that are argentaffin reaction positive (taking up and reducing silver) or those which are argyrophilic (taking up silver but not reducing it). The tumours may be characterised by the histological staining patterns, which reflect the type of neurosecretory granules and cytoplasmic proteins. The tumour cells contain neurosecretory granules which contain a wide variety of peptides and amines, such as 5-hydroxytryptamine (5-HT), neuron-specific enolase, hydroxytryptophan, synaptophysin, chromogranin A and C and several peptides such as insulin, growth hormone, adrenocorticotrophic hormone (ACTH) and gastrin as well as many others. More recently, certain immunohistochemical markers have been used to categorize the tumours, including serotonin, chromogranin A and B, and neuron-specific enolase (NSE)[20,24,25].

Table 2 Distribution of carcinoids by site at presentation from the National Cancer Institute Database[34,36]

	Location (% of total)			Incidence of metastases (%)		
	1950–1971 ($n = 4349$)	1973–1991 ($n = 5468$)	1992–1999 ($n = 4989$)	1950–1971	1973–1991	1992–1999
Foregut						
Stomach	2	3.8	5.9	22	31	10-33
Duodenum	2.6	2.1	3.8	20	—	—
Bronchus, lung	11.5	32.5	25.3	20	27	27–35
Midgut						
Jejunum	1.3	2.3	1.5	35	70	58–64
Ileum	23	17.6	13.4	35		
Appendix	38	7.6	2.4	2	35	39–45
Colon	4.3	6.3	9.5	60	71	51–61
Hindgut						
Rectum	13	10	9.4	3	14	4–18

Table 3 Classification of carcinoid neuroendocrine tumours[19,20]

Origin	Carcinoid syndrome	Metastases to bone	Organ	Clinical symptoms	Hormone production[a]
Foregut	May occur; usually in cases with liver metastases	Common	Thymus	Cushing's syndrome, acromegaly	CRH, ACTH, GHRH (low 5-HT)
			Lung	Cushing's syndrome, acromegaly	CRH, ACTH, GHRH, PP, hCG-alpha, neurotensin, 5-HTP, (low 5-HT), histamine
			Stomach	Cushing's syndrome, pernicious anaemia acromegaly, ZES	CRH, ACTH, GHRH, gastrin
			Duodenum	Somatostatinoma syndrome, ZES	Gastrin, somatostatin, neurotensin, tachykinins, (low 5-HT)
Midgut 'classical carcinoid'	Occurs frequently, in cases with metastases	Rare	Ileum	Carcinoid syndrome	Tachykinins, bradykinins, CGRP, high 5-HT
			Jejunum Proximal colon		
			Appendix	Not hormone related	(Tachykinins, 5-HT)
Hindgut	Rare	Common	Distal colon	Not hormone related	PP, HCG-alpha, PYY, somatostatin (rarely 5-HT)
			Rectum		

[a] CRH, corticotrophin-releasing hormone; ACTH, adrenocorticotrophic hormone; GHRH, growth hormone-releasing hormone; PP, pancreatic polypeptide; hCG, human chorionic gonadotrophin; CGRP, calcitonin gene-related peptide; PYY, peptide YY; 5-HTP, 5-hydroxytryptophan; 5-HT, 5-hydroxytryptamine (serotonin).

Classification and clinical presentation (Table 3)

Neuroendocrine carcinoid tumours can be classified according to their site of origin: the secretory products and hence the clinical manifestations and immunohistochemical staining patterns are similar for tumours arising from particular anatomical sites (Table 3). Foregut carcinoids include neuroendocrine tumours arising from the thymus, bronchus, gastric or duodenal mucosa, and pancreas; midgut carcinoids arise in the jejunum, ileum and proximal colon; while hindgut tumours arise in the distal colon and rectum. A more recent classification has been proposed, replacing the term *carcinoid* with *neuroendocrine tumour* (NETs)[24,26]. This reflects the diversity of carcinoids arising from different sites of origin; the classification is based upon the site of origin and the tumour behaviour. Pancreatic endocrine tumours (PETs) are usually classified separately from neuroendocrine tumours.

Carcinoids can arise in a very wide variety of sites, but are most commonly reported at four sites (Table 2):

bronchus (32.5%), jejuno-ileum (20%), appendix (8%) and rectum (10%), although in autopsy studies 76% are jejuno-ileal.

Foregut carcinoids

Bronchial carcinoids

Bronchial carcinoids are neuroendocrine tumours of the bronchial epithelium, arising from Kulchitsky cells, neuroepithelial bodies or pluripotential bronchial epithelial stem cells[27,28]. They have been classified into three groups, according to their malignant potential:

- benign or low-grade malignant (classical bronchial carcinoid)
- low grade malignant (atypical carcinoid)
- high-grade malignant (poorly differentiated carcinoma of the large cell or small cell type) neuroendocrine carcinoma.

The prognosis is excellent for classical bronchial carcinoids and poor for the small cell carcinomas. Bronchial carcinoids now account for 25% of all carcinoid tumours (up from 11.5%, Table 2). This may be due to changes in classification. There is no male or female predominance and the tumour may occur over a wide range of ages, with a mean patient age of 45 years; classical low-grade carcinoid tends to occur in younger patients, and atypical high-grade tumours in older patients. Classical bronchial carcinoids are not related to smoking and the mean age is younger than for bronchogenic carcinoma[29]. Although 25% of patients are asymptomatic, clinical presentation is usually related to bronchial obstruction, with cough and wheeze, and haemoptysis occurs in 50% of patients, due to the highly vascular nature of the lesion[29]. Cushing's syndrome (due to ACTH secretion) and carcinoid syndrome (in patients with liver metastases) occur in approximately 2% of cases[30]. Metastases may be seen in the liver, bones, adrenal glands and brain.

Thymic carcinoids

Neuroendocrine tumours of the thymus are rare and may be part of MEN 1. The tumour is usually non-functioning and presents with an anterior mediastinal mass. If functioning, then the tumour usually secretes ACTH, causing ectopic ACTH-dependent Cushing's syndrome, which occurs in a third of patients with a thymic NET[30]. In these cases, bilateral adrenal hyperplasia may be seen[31]. Other hormones may also be produced, including corticotrophin releasing hormone, growth hormone releasing hormone and 5-HT[32]. Carcinoid syndrome has never been described in association with a thymic neuroendocrine tumour. The prognosis is generally poor[30].

Gastric carcinoids

Neuroendocrine tumours arising in the stomach are rare, accounting for 0.3% of gastric neoplasms but 11%–41% of gastrointestinal neuroendocrine tumours[33]. They have been divided into three subtypes based on predisposing factors, endoscopic appearance and clinical course:

- Type I gastric carcinoid is the most common subtype and is associated with hypergastrinaemia and chronic atrophic gastritis, with or without pernicious anaemia. Hypergastrinaemia results in hyperplasia of enterochromaffin-like cells, which may lead to the development of the carcinoid tumour. Tumours are multicentric, <1 cm lesions, predominantly in the fundus and body of the stomach, and are surrounded by enterochromaffin-cell hyperplasia. The diagnosis is often made incidentally at endoscopy for dyspepsia. The disease is almost always benign, with metastases present in only 2% of cases.

- Type II gastric carcinoids are rare (5%–10% of cases). They are associated with the ZES and MEN 1: 30% of patients with MEN 1 have a gastric carcinoid. Tumours arise from the enterochromaffin-like cells, are multicentric, but have an increased tendency to metastasise to regional lymph nodes, although the prognosis is generally good.

- Type III gastric carcinoids are sporadic, are not associated with hypergastrinaemia and account for 13% of cases of gastric carcinoid. There is a strong male predominance (80%). The tumour is usually solitary, large and may ulcerate. Local invasion and metastases are common and there is only a 20% 5-year survival rate[33].

Midgut carcinoids

Midgut carcinoids are defined as neuroendocrine tumours arising beyond the ligament of Treitz to the level of the mid-transverse colon and are the commonest primary malignant tumour of the small intestine. They tend to have high a serotonin content, with relatively high urinary 5-HIAA levels. Forty-two percent of all gastrointestinal carcinoids arise in the small bowel[34]. Over the last 50 years, small bowel carcinoids account for approximately 30% of all carcinoid tumours and are the commonest cause of metastatic carcinoid (Table 2)[35,36]. However, the percentage of all carcinoids that arise in the small bowel has decreased gradually during this period. This may be due to changes in classification.

Abdominal pain is a relatively common presenting feature of carcinoid tumours of the GI tract and 40% present with symptoms of obstruction. Patients may have

colicky abdominal pain and diarrhoea due to increased intestinal motility. Obstruction may be due to the primary tumour, either with or without intussusception, although often the tumour is very small. Tumour-associated desmoplastic fibrosis, which causes tethering and kinking of the small bowel mesentry, may also cause obstruction. Metastases occur to liver, bone and lung [20]. The incidence of metastases from midgut carcinoids is dependent on tumour size [20,35]. In tumours <1 cm, 15%–25% have metastases; in tumours between 1 and 2 cm, metastases are present in 58%–80%; while in tumours >2 cm over 70% have metastases.

Hindgut carcinoids

Hindgut carcinoids include those arising in the colon (distal to the mid-transverse colon) and rectum. Rectal carcinoids are the most common hindgut carcinoid and in a large series between 1992 and 1999, these accounted for 27% of all gastrointestinal carcinoid tumours [34]. The proportion of GI carcinoids which are rectal has increased, as they represented 17% of all GI carcinoids in the period between 1950 and 1969 [34]. Rectal carcinoids account for 1% of all anorectal neoplasms [37]. The tumours are usually slow growing. However, in one large series, 30% of patients had metastatic disease at presentation [38]. Metastases, which occur to the liver, lungs and bones, are more common in patients with atypical histology and the incidence increases with the size of the tumour [38,39].

Imaging the primary tumour: pancreatic neuroendocrine tumours

Localization

A wide variety of imaging methods are advocated in the literature for the localisation of the primary disease and detection of metastases. This reflects the difficulties encountered in satisfactorily demonstrating these tumours. The use of different modalities in the literature also reflects differences in local expertise and experience. In addition, the diagnostic performances that are quoted in the literature reflect techniques at different stages of development, making comparison of techniques challenging. The various techniques and imaging features of pancreatic endocrine tumours are described below, together with a discussion concerning the advantages and disadvantages of each technique.

Ultrasound

Transabdominal ultrasound

Transabdominal ultrasound is non-invasive and widely available and does not use radiation, but has a relatively low sensitivity for localising small primary tumours, being in the range of 20%–86% [8,12,40]. However, it has been shown to have a high specificity and continues to be advocated as a first-line investigation. The scanning technique should be tailored to optimise pancreatic visualisation. The patient should drink water prior to scanning to allow the stomach to be used as an acoustic window; positioning the patient in both the standing position and lying in the left posterior oblique position may allow a more complete assessment. As with most of the imaging techniques available, sensitivity increases with the size of the lesion [40,41].

The tumour appearance is of a well-defined round mass, which is homogeneously hypoechoic in relation to the pancreas, and vascular on Doppler imaging. There may be a hyperechoic halo or distortion of the gland, an appearance that may help in detecting the lesion, particularly in younger patients where the tumours tend to be less conspicuous due to the generally lower echogenicity of the pancreas. Tumours that lie along the surface of the pancreas or in the duodenum are less conspicuous. Ultrasound contrast agents are currently under investigation for the localisation of pancreatic endocrine tumours, which enhance following contrast administration [42].

Endoscopic ultrasound (EUS)

Endoscopic ultrasound enables close proximity of the transducer to the pancreas allowing a high frequency US probe to be used (7.5–10 mHz), resulting in greatly improved image resolution. The pancreatic head and duodenum are scanned with the probe positioned in the duodenum, and the body and tail are scanned through the stomach. Although EUS is invasive and operator-dependent, it greatly improves the sensitivity for the detection of small tumours [43,44]. The advantages of the technique are:

- localisation of small tumours
- localisation of multiple tumours, particularly in MEN 1
- detection of small tumours in the pancreatic head, which may be difficult to palpate at surgery
- detection of tumours arising in the duodenal wall
- detection of lymph node enlargement to improve staging accuracy
- accurate depiction of the relations between vascular and biliary structures and the tumour.

The disadvantages of the technique are:

- technically challenging, requiring specialist training, and therefore not widely available; may not be suitable for all patients, e.g. where there is duodenal scarring in ZES

- reduced sensitivity in extra-pancreatic gastrinomas (e.g. stomach or duodenum) or in the tail of pancreas
- the liver cannot be fully assessed.

Although the diagnostic performance of EUS is difficult to evaluate, reports indicate that overall the technique is highly sensitive with sensitivities as high as 79%–100% being reported [44,45].

Intraoperative ultrasound (IOUS)

This technique has similar advantages to EUS (see list above) and may improve the intra-operative sensitivity for identifying small lesions in the head and multiple lesions to up to 97% [12]. It has been shown to change operative management in 10% of ZES cases, by identifying multiple gastrinomas or by demonstrating the malignant nature of a lesion [46]. IOUS has the advantage, over EUS, of being able to assess the liver. However, it is not as sensitive as surgical palpation in detecting extra-pancreatic lesions. The disadvantages of the technique are:

- increased time and complexity of operation, with complete mobilization of the pancreas required
- specialist experience is required for performing and interpreting the scan
- preoperative tumour localisation is still needed
- poor sensitivity in extrapancreatic/duodenal lesions
- overall, the technique is a useful addition to surgical palpation, particularly in small tumours such as insulinomas.

CT

CT is the most widespread diagnostic tool for the localisation and staging of pancreatic endocrine tumours. It has the advantage of being widely available and is not subject to some of the difficulties encountered with US, such as potentially poor visibility and operator-dependence. It is important that the technique should be optimised. The patient should be fasted to ensure that the stomach and duodenum are emptied of its contents. The stomach is distended with water and intravenous hyoscine butylbromide or another anti-peristaltic agent. An initial precontrast scan is performed to identify the level of the pancreas. Following intravenous administration of 150 ml of contrast medium at a rate of 3–5 ml/s with a monophasic rate of injection, biphasic scanning is recommended. Arterial phase scanning is started after a delay of 25 s and portal venous scanning after a delay of 60–70 s. The section thickness should not exceed 5 mm and the entire liver should be included in all phases.

Functioning tumours are usually small, reflecting their pathology (see above and Table 1) and subtle, with low inherent contrast between the tumour and surrounding pancreas. They are usually isodense with the pancreas on pre-contrast images. As in the angiography literature, the majority of islet cell tumours are hypervascular and will be best seen after intravenous injection of contrast medium. However, the best phase for the demonstration of those hyperattenuating small lesions is unclear. Our own experience concurs with others who report that tumour-to-pancreas contrast was greatest on arterial phase (AP) images compared to portal venous phase (PVP) imaging [47–49]. However, others have found the PVP significantly more helpful in identifying islet cell tumours [50]. At present, therefore, we recommend biphasic imaging following intravenous injection of contrast medium to optimise the sensitivity of the technique. Narrow window settings may help to improve detection. Rarely, insulinomas may be hypovascular or cystic and appear hypodense to the surrounding pancreas. Cystic pancreatic endocrine tumours represented 4 of 38 pancreatic islet cell tumours in one series, and these represented 14% of all pancreatic cystic lesions identified over a 10 year period [51]. Cystic pancreatic endocrine tumours are usually benign and non-functioning and cannot be reliably differentiated from other cystic pancreatic lesions neoplasms on imaging alone [51]. In patients with a suspected gastrinoma, particular attention should be given to the ‘gastrinoma triangle’ (see above).

Large tumours are more likely to be non-functioning and necrotic centrally, and are more likely to be malignant. The features which are associated with malignancy include large size, necrosis, overt infiltration of the surrounding retroperitoneal structures such as vessels, and calcification [3,52].

Early studies using non-spiral CT techniques reported a relatively high sensitivity of 78% for the detection of lesions [3]. Detection of the primary tumour is directly related to tumour size, with no tumours identified under 1 cm, 30% of tumours between 1 and 3 cm being detected, and 95% of tumours >3 cm in diameter demonstrated [3,5,53]. The location of the tumour also influences the ability of CT to detect the lesion. One prospective study detected 68% of primary tumours and 86% of hepatic metastases (confirmed at surgery, autopsy or percutaneous biopsy); 90% of pancreatic head tumours, 80% of pancreatic body tumours, and 45% of pancreatic tail tumours [53,54]. Small tumours of <1 cm in the duodenum are often missed on CT, and CT sensitivity for the detection of extra-hepatic and extra-pancreatic gastrinomas, which are often small at presentation, is only 30%–50% [14,53]. With the development of spiral and multi-detector technology, detection may improve.

MRI

Early studies with MR imaging reported a lower sensitivity than CT for the detection of both the primary

tumour and metastatic disease. However, with the marked improvements in MR technology that have occurred in the past decade, the diagnostic performance of MR has improved and in several studies has been shown to exceed or equal that of CT[50,55,56]. MR imaging has a higher sensitivity than angiography or CT for metastatic disease[57]. However, angiography remains more sensitive than MR for identifying the primary tumour. A sensitivity of 94% for pancreatic lesions, but less for extra-pancreatic lesions, has been reported[55,58]. As with the other cross-sectional modalities, tumour detection increases with tumour size. Multiple tumours, as in patients with MEN 1, are particularly difficult to detect.

The sensitivity of MR does depend on good quality images. Where there is image degradation due to movement artefact and a poor signal-to-noise ratio, for example in obese patients, sensitivity may be reduced. Optimal technique requires a quadrature phased-array coil. The imaging sequences should include:

- axial fat-suppressed T1-weighted spin echo and gradient echo
- axial fast spin echo T2-weighted
- axial dynamic contrast-enhanced gradient echo sequence.

The tumours usually appear of low signal intensity on T1-weighted sequences and high on T2-weighted sequences in relation to the pancreas. The tumours are most conspicuous on the fat suppressed T1-weighted image whether spin echo or gradient recalled[55,58]. Tumours which contain a high collagen or fibrous tissue content may return a low signal on T2-weighted images, but this is rare[50]. Following intravenous gadolinium, there is characteristic marked homogeneous enhancement, reflecting the highly vascular nature of these tumours. In cystic lesions, rim enhancement may be seen[55]. Liver specific contrast agents, such as mangofadopir DPDP, may have a role in improved lesion detection, but this is currently under investigation[59].

Angiographic techniques

Angiography

Angiography is rarely used nowadays in most centres, and when used, is usually combined with venous sampling. Detailed assessment of the vasculature is required in order not to miss a lesion, with selective catheterisation of all the branches of the celiac and superior mesenteric arteries. Sensitivities are fairly high. Both the primary tumour and liver metastases are seen as a well-defined blush in the capillary phase—early venous phase. Difficulties in diagnosis arise: when a tumour lies adjacent to a loop of bowel or spleen and the blush is not separately visible; if the tumour is very small; when there are multiple lesions; and when the tumour is hypovascular. All these problems may lead to false negative results. False positives arise from the blush of a splenunculus or normal pancreas or bowel.

Transhepatic portal venous sampling (THPVS)

Venous sampling is usually performed in conjunction with angiography. This technique may involve, in order to obtain 'downstream' venous samples, localising the tumour by identifying a high level of hormone at a particular site, rather than relying on visualising the tumour using imaging. Thus a tumour may be broadly localised to the tail, body or head of the pancreas/duodenum (these cannot be distinguished using this technique). This method is only useful for tumours that secrete a hormone and false negative results may occur if hormone secretion is intermittent. It has a limited role in patients with multiple tumours.

Arterial stimulation and venous sampling (ASVS)

Arterial stimulation venous sampling combines simultaneous hepatic venous sampling with selective arterial injection of a pancreatic secretagogue, a technique that is less invasive than THPVS. Many different specific secretagogues have been used in the past, but generally now calcium gluconate is used regardless of the specific secretory product. Following injection of the secretagogue, hepatic venous sampling is performed every 30 s for 2 min. A three-fold increase in the level of hormone indicates the presence of tumour, allowing the depiction of the tumour region, as with THPVS. This technique is most useful in cases where the tumour remains occult on other imaging modalities, predominantly with very small functional tumours. It can be performed as part of pancreatic angiography and is liable to some of the risks associated with THPVS such as hepatic arterio-venous fistulae, haematoma and superior mesenteric arterial occlusion. Reported sensitivities are high, up to 93%, and the stimulation technique improves the sensitivity of angiography alone[5].

Imaging the primary tumour: carcinoid neuroendocrine tumours

Localization

In some cases, the diagnosis of a carcinoid is made at endoscopy, particularly gastric, duodenal, rectal or colonic lesions. Endobronchial carcinoids may be diagnosed bronchoscopically. However, imaging is used extensively for the localisation of primary neuroendocrine tumours, as well as in staging the tumour. Many carcinoids do not present with a specific clinical syndrome, such as the carcinoid syndrome, and imaging may be performed to investigate non-specific symptoms of abdominal discomfort or diarrhoea. Image-guided

biopsy of a mass, liver lesions or lymph nodes may help to establish the diagnosis. CT is the main cross-sectional imaging modality for localising and staging carcinoid tumours. Ultrasound is used predominantly in the detection of liver metastases and for guiding biopsy. It is not a primary diagnostic tool in localising the tumour. Imaging is also useful in the investigation of second primary tumours, such as gastrointestinal and genitourinary tract adenocarcinoma, which are frequently described in association with carcinoid neuroendocrine tumours [34,60].

Appearance of primary carcinoids

Foregut carcinoids

Bronchial carcinoid

Imaging features of primary bronchial carcinoid are similar regardless of the grade of the tumour and the features depend on whether the tumour is located in the airways of the central/middle third of the lung (80% of cases) or the peripheral airways [29]. The tumour may be detected with plain radiology with the appearance of a well-demarcated round or ovoid mass, often notched [61]. Centrally located tumours may result in airway obstruction, with recurrent infection, lobar collapse, and a central mediastinal or hilar mass, which is usually smooth and lobulated, 2–5 cm in diameter [61]. However, they are usually small and thus CT scanning is the most sensitive cross-sectional technique available. On CT, the mass may be visible within the bronchial lumen, usually with both an intra- and extraluminal component. A peripheral bronchial neuroendocrine lesion is seen in 20% of cases, with the appearance of a solitary pulmonary nodule. The mass is typically round or ovoid with a smooth or lobulated border. Calcification is fairly common, either punctate or diffuse. Cavitation and hilar adenopathy are rare [61]. Rarely, there may be two lesions, in which case it may be impossible to separate the appearance from pulmonary metastases [61]. Aggressive lesions may demonstrate direct mediastinal invasion. Collapse or air-trapping beyond the central lesion can be seen if there is a ball-valve obstruction of the bronchial lumen. Following intravenous contrast medium, there is usually intense homogeneous enhancement, although this is not seen in all cases. Marked enhancement can create diagnostic difficulty, as the appearance may mimic a pulmonary varix or pulmonary artery aneurysm and a small vascular lesion may be overlooked, or interpreted as a normal vessel [29]. In patients with occult ectopic ACTH secretion, bronchial carcinoids are the most common source but can be elusive and difficult to identify. When a pulmonary lesion is suspected but cannot be seen on CT, MRI may play a role in localisation. Bronchial carcinoids have high signal on T2-weighted and STIR images, allowing distinction between a small mass and the pulmonary vasculature of the central and middle third of the lung [62]. In some cases, imaging with somatostatin receptor scintigraphy may help in the localisation and characterisation of a small peripheral lesion (see below). Marked nodular adrenal hyperplasia may be incidentally noted, if the lesion secretes ACTH, causing Cushing's syndrome.

Thymic carcinoids

These tumours usually present as an anterior mediastinal mass. The mass may be partly calcified and may cause SVC obstruction [31,63]. There is usually evidence of invasive disease, with seven of eight patients in one series having extension into the pleura, pericardium, great vessels or regional lymph nodes [64]. If the tumour is functioning and producing ACTH, then bilateral adrenal hyperplasia may also be seen [31]. Bone metastases, which may be sclerotic, lung and liver metastases may be present at the time of diagnosis [63–66].

Gastric carcinoids

Type I gastric carcinoids are small multicentric, <1 cm lesions, predominantly in the fundus and body of the stomach. The diagnosis is usually made endoscopically, not on imaging. The disease is almost always benign, with metastases present in only 2% of cases.

Type II gastric carcinoids, which are associated with the ZES and MEN 1, are multicentric. On CT, multiple masses are present within the gastric wall, which is diffusely thickened secondary to ZES. There is an increased tendency to metastasise to regional lymph nodes, although the prognosis is good [67].

Type III, sporadic gastric carcinoids are usually solitary, large and may ulcerate. Local invasion and metastases are common.

Midgut carcinoids

The primary tumour may not be seen in midgut carcinoids as it is usually a small tumour, which is not conspicuous against the small bowel or the ascending/transverse colon from which it arises. There may be multiple primary sites. The most frequent imaging findings are secondary features, which are described in below, under the section on metastatic disease in neuroendocrine tumours. Liver metastases are the most frequent finding, followed by tumour-associated desmoplastic fibrosis, which causes tethering and kinking of the small bowel mesentry may also cause obstruction. Bone and lung metastases also occur. The incidence of metastases from midgut carcinoids is dependent on tumour size [20]. In tumours <1 cm, 15%–25% have metastases; in tumours between 1 and 2 cm, metastases are present in 58%–80%; while in tumours >2 cm over 70% have metastases.

CT

The primary bowel wall tumour is rarely demonstrated on CT, and in one large series, was only seen in one of 52 cases, where an ileal tumour was causing an intussuception into the caecum[68]. Detecting small primary tumours in the small bowel remains one of the most difficult challenges yet to be overcome on imaging[68,69].

MRI

MRI was shown to demonstrate the primary tumour in 8 of 12 patients with a gastrointestinal carcinoid[70]. The best sequence for demonstrating the primary tumour was the post-gadolinium T1-weighted fat suppressed image. In four cases, the tumour was a nodular mass arising from the bowel wall; in four cases there was regional uniform bowel wall thickening. The primary tumour enhanced moderately/intensely following gadolinium[70].

Other imaging techniques

Angiography of the superior and inferior mesenteric artery has a reasonable sensitivity for the localisation of the primary tumour, lymph node and liver metastases. Rarely, transhepatic portal venous sampling may be helpful in localisation of tumours in the upper abdomen, but this is no longer in common use. Barium follow-through may be abnormal if there is a fibrotic or desmoplastic reaction within the mesentery, resulting in distortion of the small bowel loops. However, the technique is not sensitive in demonstrating the primary lesion. Echocardiography should be performed in all patients with the carcinoid syndrome to identify signs of carcinoid heart disease. There is recent evidence that the presence of structural heart disease secondary to carcinoid syndrome is an independent poor prognostic factor[71].

Hindgut carcinoids

These lesions are usually diagnosed at endoscopy, although barium studies may demonstrate an extrinsic filling defect. At endoscopy, they appear as solitary yellowish submucosal lesions and are typically between 1 and 2 cm in diameter[37,72]. As these lesions are small and disease is often confined to the rectum, minimally invasive techniques to allow local resection is the treatment of choice[72,73]. However, these techniques are only suitable in stage T1 (tumour confined to mucosa and submucosa) and T2 (invasion of muscularis propria) disease, with no evidence of extension to the serosa. Imaging may be used to identify cases suitable for local resection. Endoscopic ultrasound demonstrates the lesion as a homogeneously hypoechoic submucosal mass[74]. Endoscopic US may demonstrate invasion of the full rectal wall (stage T3) and invasion into adjacent structures (T4)[73]. In these cases, extended resection is required. MRI may have a role in local staging of the primary mass but this technique is under development. Both CT and MRI can be used to stage lymph node disease and distant metastatic disease as part of the preoperative planning. In one large series, 30% of patients had metastatic disease at presentation[38,39].

Metastases from pancreatic and carcinoid neuroendocrine tumours

Metastases are a common finding in neuroendocrine tumours. In a large autopsy series, 29% of patients with a carcinoid neuroendocrine tumour were found to have metastatic disease, the majority (61%) arising from small bowel carcinoids[22]. In this series, 90% of metastases were in lymph nodes, 44% in the liver, 14% in the lungs, 14% in the peritoneum and 7% in the pancreas. The imaging appearances of metastatic disease in both pancreatic and carcinoid neuroendocrine tumours are similar and are considered together.

Liver metastases

Liver metastases are seen in 40%–80% of patients with a midgut carcinoid at presentation, depending on the site of the primary tumour. Forty percent of ileal lesions and up to 80% of caecal lesions have liver metastases at the time of initial diagnosis[34]. Liver metastases are the most common imaging finding[68]. The extent of liver metastases is an important prognostic factor in pancreatic endocrine tumours[13]. In patients with a malignant gastrinoma, the presence of liver metastases alone moderately decreases survival. However, the development of Cushing's syndrome or bone metastases in combination with liver metastases results in a markedly decreased survival rate[13]. In patients with metastatic carcinoid, the 5-year survival rate of patients with no liver metastases is not significantly different to patients with a few liver metastases (fewer than 5) (73% vs. 79%). However, there is a significant decrease in 5 year survival rate in patients with extensive liver metastases (more than 5) (47%)[75].

Ultrasound

On transabdominal ultrasound, liver metastases tend to be hyperechoic, particularly in cases of metastatic gastrinoma, and are detected with a sensitivity of approximately 60%, although lesion conspicuity is reduced in patients with a fatty, hyperechoic liver[16,41]. EUS is not reliable in detecting liver metastases, due to its limited depth of penetration. IOUS can be helpful is the assessment of liver metastases, allowing accurate

depiction of relationships between a lesion and hepatic vessels, which may help in determining resectability[76].

CT

Neuroendocrine hepatic metastases may be difficult to identify and delineate on CT as they may be isointense to the liver on portal venous phase (PVP) imaging. A combination of pre-contrast, hepatic arterial-dominant phase (HAP) and PVP imaging will improve the sensitivity of detection, as in some cases a lesion may only be seen on one of the three phases[77]. Evidence points to the HAP being particularly helpful in the detection of liver metastases.

Liver metastases are most frequently of low attenuation in relation to the surrounding parenchyma on pre-contrast images and enhance strongly post-contrast, mimicking a haemangioma. Like the primary tumour, large lesions may become necrotic and may calcify. If the peak enhancement is missed due to the timing of the scan, the lesion may become isodense to the liver and thus lesion detection may be challenging.

In one study, CT was compared with selective angiography, the latter technique detecting 20% more liver metastases than CT, with a very high rate of detection[54].

MRI

On MRI, 75% of neuroendocrine liver metastases appear as low signal intensity on T1 and high signal intensity on T2 weighted images, with 94% of metastases being hypervascular on HAP post-gadolinium images: 15% of hepatic metastases were only seen on the immediate post-gadolinium images[70].

Mesenteric masses and peritoneal disease

Secondary mesenteric masses greater than 1.5 cm are seen in approximately 50%–75% of cases of midgut carcinoid, with a median size of 3 cm[68,70]. Masses are of soft-tissue density, and commonly have a ‘spoke-wheel’ appearance, with radiating strands of soft tissue (64%–100%). The degree of radiating strands increases as the degree of fibrosis increases, as seen on histology and caused by hormonally active substances, particularly serotonin. Calcification is commonly seen within mesenteric masses (40%–70%), and may be small stippled calcifications or bulky and conglomerate[25,68]. On histology, calcification is localised within areas of mature fibrous scarring within the mass[25]. Masses usually arise within the fat or nodal tissue of the small bowel mesentery, although the exact nidus of metastatic tumour growth in the mesentery is not certain[25].

Diffuse mesenteric/peritoneal disease, with peritoneal studding or ascites, is seen in 20%–30% of patients with a GI carcinoid and may be associated with obstruction[68,78]. Peritoneal disease is less common in pancreatic endocrine tumours; it was seen in 11% of non-gastrinoma pancreatic endocrine tumours but did not occur in association with a gastrinoma in one series[78].

Lymph node metastases

Regional lymph node metastases are the most frequent metastatic site at autopsy[22]. Retroperitoneal or mesenteric lymph node enlargement is seen in approximately 20%–30% of patients with a midgut carcinoid[68]. Retroperitoneal fibrosis may be seen in cases with retroperitoneal lymph node metastases and may cause ureteric obstruction. In thymic neuroendocrine tumours, mediastinal lymph node metastases are present in 60% at the time of resection[79].

Lung metastases

Lung metastases, which arise from a variety of neuroendocrine tumours, may be hormone secreting, although in most patients they are asymptomatic. Diagnosis is accurately made on CT. Local metastasectomy, where clinically appropriate, has been shown to improve outcomes when compared with medical management[80].

Bone metastases

Bone metastases are more commonly associated with foregut and hindgut carcinoids than midgut carcinoid tumours. The metastases are frequently sclerotic and may have the appearance of multiple small punctate sclerotic deposits[31]. Bone metastases have been reported in up to 30% of patients with malignant gastrinoma and are indicative of a poor prognosis, particularly when associated with liver metastases[13].

Follow-up

Surgical resection is the only curative technique in pancreatic and carcinoid neuroendocrine tumours. However, in non-resectable tumours imaging may play a role in treatment planning. Palliation of symptoms may be achieved by embolisation or chemo-embolisation of hepatic metastases, if the portal vein is patent[81]. CT (or MRI) is used to assess the response to therapy both in primary and metastatic disease. MR is the preferred modality for follow-up in patients with disorders such as MEN 1 where repeated imaging may be required for prolonged surveillance due to the frequent indolent nature of the disease.

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