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## INVITED REVIEW

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# Imaging Islet Cell Tumours

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### ABSTRACT

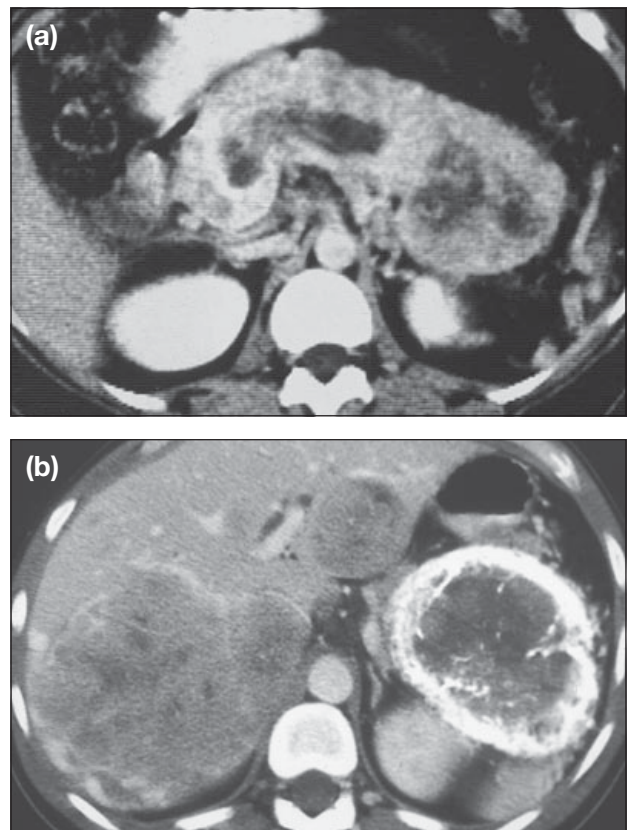
*Islet cell tumours are rare lesions. The majority (85%) are functioning hormone-producing tumours, insulinomas and gastrinomas being the most common. Approximately 15% of islet cell tumours are non-functioning. These are usually larger lesions, often presenting at an advanced stage as a pancreatic mass or with metastatic disease. This review will focus on the role of endoscopic ultrasound in the detection of pancreatic islet cell tumours and its complementary role to computed tomography and other imaging techniques. The potential for endoscopic ultrasound-guided biopsy will also be discussed.*

*Key Words: Endoscopic ultrasound, Islet cell tumours*

Islet cell tumours are rare lesions. The majority (85%) are functioning hormone-producing tumours and are named after the main hormone secreted, insulinomas and gastrinomas being the most common tumours. Approximately 15% of islet cell tumours are non-functioning. These are usually larger lesions, often presenting at an advanced stage as a pancreatic mass or with metastatic disease. The malignant potential of all islet cell tumours varies between 10% and 90% according to the cell type. They may be associated with other syndromes such as multiple endocrine neoplasia (MEN) type 1 (4%) and von Hippel Lindau syndrome (17%).<sup>1</sup>

Large islet cell tumours are usually relatively easily detected. There may be characteristic features that suggest the diagnosis such as calcification or cystic degeneration (Figure 1). Diagnosis is dependent on the visualisation of a mass on imaging, occasionally as an incidental finding in non-functioning tumours. Functioning tumours are frequently extremely small and present a diagnostic challenge. Identification of the presence of such tumours is based on specific clinical and biochemical abnormalities, and typical syndromes are described reflecting the biochemical effects of the hormones produced. The role of imaging is not in detection but in

localisation. There is increasing surgical reliance on the preoperative localisation of tumours as this enables appropriate surgical planning. Small tumours may be



**Figure 1.** Computed tomography scan demonstrating (a) large necrotic non-functioning islet cell tumour infiltrating the pancreas; and (b) densely calcified non-functioning islet cell tumour of the pancreatic tail. There are 2 large metastatic deposits in the liver.

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suitable for enucleation and the relationship of the tumour to the main pancreatic duct is important. The presence of multiple tumours or of islet cell hyperplasia (nesidioblastosis) may require more extensive surgical resection. Features suggesting malignancy are important and the identification of metastatic disease will clearly influence the therapeutic approach.

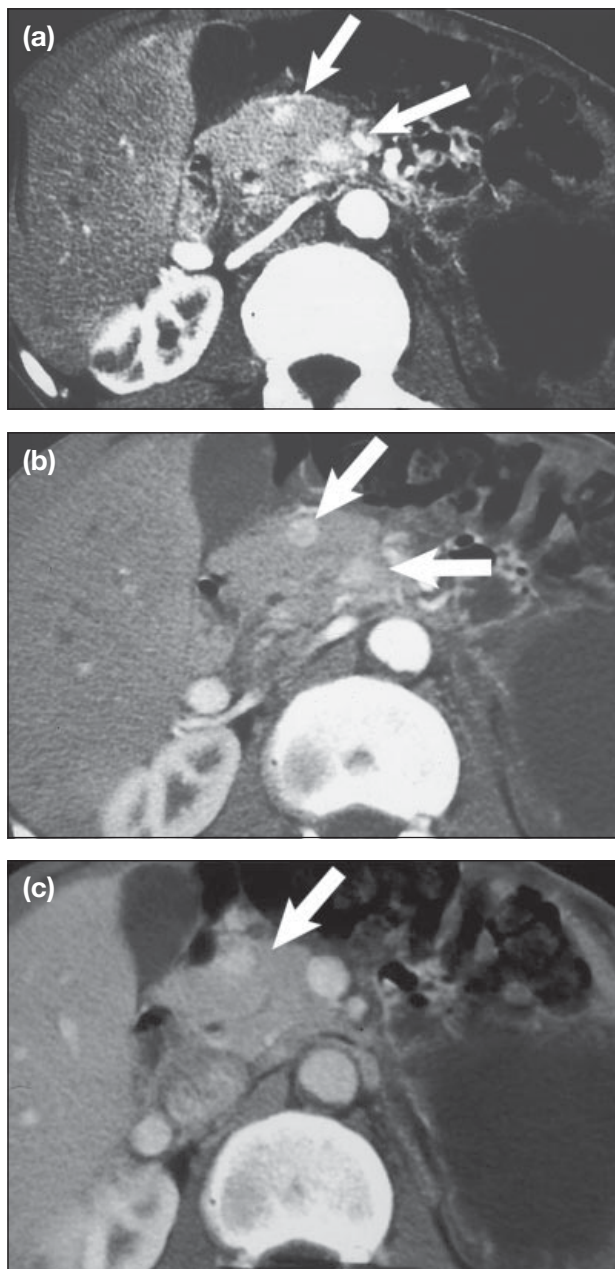
Many different imaging techniques have been directed to the detection of these typically small and frequently occult lesions. Ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), radionuclide scanning, and more invasive tests such as angiography and intraoperative ultrasound have all been utilised with varying reported sensitivities. The selection of the best diagnostic test is challenging as the sensitivities of the various available tests changes rapidly with technological improvements. For example, although detection with conventional CT scanning is relatively poor,<sup>2</sup> excellent rates of detection with new multiphase multi-slice scanners are beginning to emerge.<sup>3-5</sup> Similarly, the use of new sequence design and faster imaging techniques with MRI<sup>6-8</sup> has influenced detection rates with this technique. Although conventional ultrasound has a relatively limited sensitivity, intraoperative ultrasound and endoscopic ultrasound (EUS) are reported to have high sensitivities in the detection of small tumours.<sup>9-11</sup>

This review will focus on the role of EUS in the detection of pancreatic islet cell tumours and its complementary role to CT and other imaging techniques. The potential for EUS-guided biopsy will also be discussed.

At the Department of Diagnostic Imaging at St Bartholomew's Hospital, London, we have had approximately 10 years' experience of using EUS. Scans are performed with a radial endoscope (GF-UM20 Olympus, Tokyo, Japan) which, in general, provides excellent imaging of the pancreas from a transgastric and transduodenal approach.

### Insulinomas

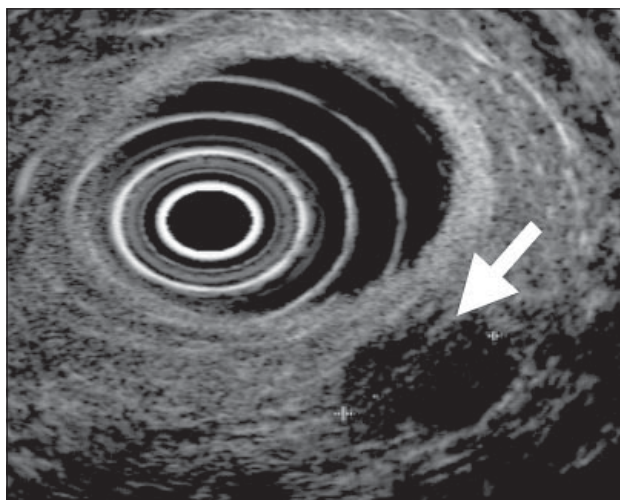
More than 90% of insulinomas are benign. They are typically solitary and the majority measure less than 1.5 cm with some tumours as small as 2 to 3 mm. They are evenly distributed between the head, body, and tail of the gland and the overwhelming majority are intrapancreatic with only up to 5% lying outside the pancreas. In 5% to 10% of patients with a clinical diagnosis of insulinoma, the hormone hypersecretion will



**Figure 2.** Triple-phase contrast-enhanced computed tomography demonstrates 2 small brightly enhancing insulinomas (a) on the arterial phase at 25 seconds and (b) on the pancreatic phase at 40 seconds; and (c) 1 lesion at 65 seconds on the portal venous phase.

be due to islet cell hyperplasia rather than a localised tumour. Less than 10% of insulinomas are malignant. Typical features of insulinomas on CT are of a hypervascular lesion. The detection of these lesions is dependent on the phase of contrast enhancement, with tumours typically being best seen in arterial or pancreatic phases of imaging (Figures 2a, 2b, and 2c). At EUS, insulinomas are typically seen as small well-defined hypoechoic lesions within the glandular tissues (Figure 3). Lesions as small as 2 mm can be identified



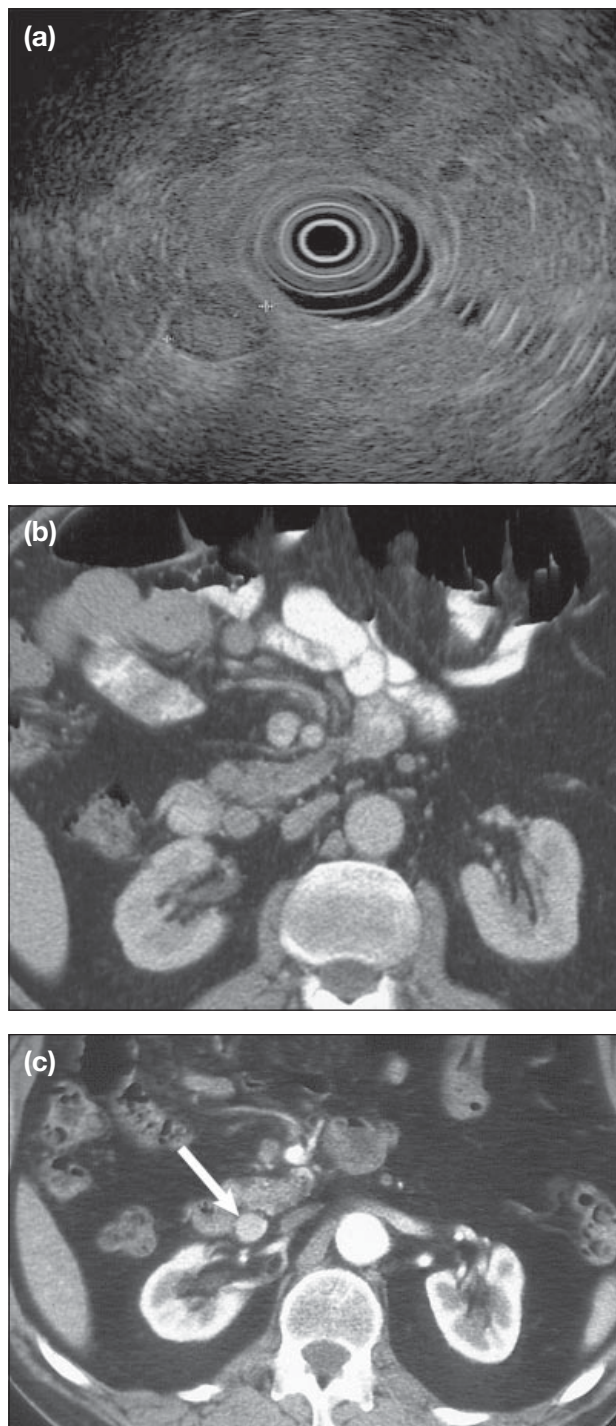


**Figure 3.** Well-defined hypoechoic insulinoma in the mid-body of the pancreas.

relatively easily. Tumours that are pedunculated or isoechoic within the glandular tissue may be more difficult to identify, and there is reduced sensitivity for tumours located in the pancreatic tail as this region can be more difficult to visualise. The hypervascular nature of these tumours on CT can create pitfalls in imaging where partial volume imaging of a tortuous splenic artery can be misinterpreted as a tumour. Small splenunculi may also mimic pedunculated tumours. EUS may be valuable for problem-solving in these cases.

### Gastrinomas

Gastrinomas are the second most common functional tumour and are classically associated with the Zollinger-Ellison syndrome of recurrent peptic ulceration and diarrhoea. Typically, these tumours are small, with 40% measuring less than 1 cm. Ninety percent of tumours occur in what is known as the 'gastrinoma triangle', which is the region bounded by the first, second, and third parts of the duodenum including the pancreatic head. Detection of these tumours may be difficult as up to 50% are extrapancreatic in position (Figures 4a, 4b, and 4c). Of these tumours, 50% to 60% are malignant with spread to peripancreatic nodes and the liver. Thirty percent of tumours are associated with MEN type 1 syndrome in which pancreatic islet cell tumour (insulinomas/gastrinomas) are associated with parathyroid adenomas or hyperplasia, pituitary adenomas, and adenomas of the adrenal and thyroid glands. These patients often present a challenge for imaging as the tumours are frequently small, measuring less than 2 mm, often multiple, and diffusely distributed.<sup>12</sup> EUS may demonstrate submucosal tumours in the stomach and duodenum that may be associated gastric carcinoids.<sup>11,13</sup>



**Figure 4.** (a) Mid-level echogenic infrapancreatic mass seen on endoscopic ultrasound. (b and c) Computed tomography scans from 2001 and 2002 — the mass 'gastrinoma' was overlooked on the initial scan but was clearly evident on the arterial phase-enhanced scan (arrowed).

### Imaging features

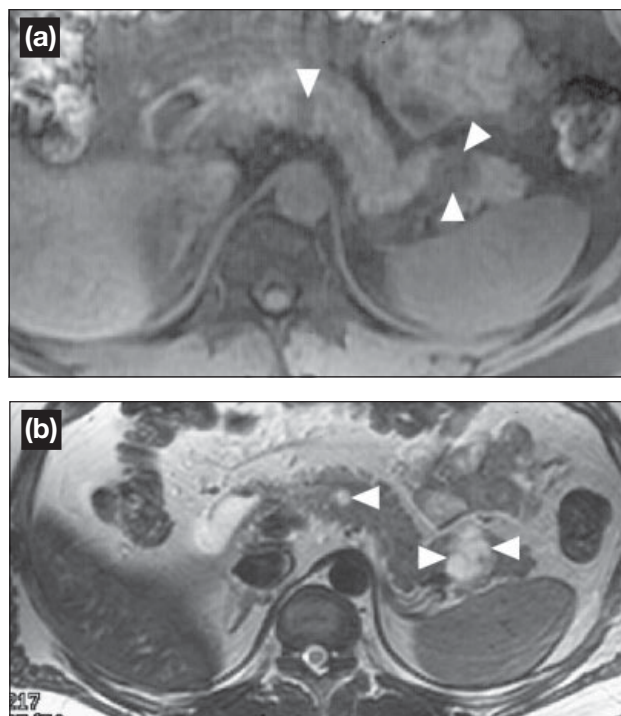
There are some features on EUS that help to differentiate benign from malignant tumours. In general, malignant tumours are larger than 3 cm and may have a heterogeneous echotexture with an irregular margin and

**Table 1.** Accuracy of endoscopic ultrasound in the detection of pancreatic islet cell tumours.<sup>13</sup>

	Preoperative endoscopic ultrasound versus final diagnosis		
	All tumours (n = 75)	Suspected gastrinoma (n = 36)	Suspected insulinoma (n = 36)
Sensitivity	93%	100%	88%
Specificity	95%	94%	100%
Positive predictive value	98%	95%	100%
Negative predictive value	83%	100%	43%
Accuracy	93%	97%	89%

occasionally irregular echogenicity.<sup>14</sup> The sensitivity of EUS in the detection of pancreatic islet cell tumours is reported to be 93% (Table 1).

There have been several reports of the sensitivity of MRI in the detection of islet cell tumours with continuing refinement of the sequences employed. Several authors have reported high sensitivities using T1-weighted fat-saturated sequences, and the typical MRI appearance of these tumours is of low signal on T1-weighted and high signal on T2-weighted sequences (Figures 5a and 5b).<sup>7,8</sup> Lesions demonstrate variable enhancement with gadolinium, but one group of authors has recently reported delayed enhancement of tumours at 5 to 10 minutes post-gadolinium with a reported sensitivity of approximately 75%.<sup>6</sup> Octreotide — a synthetic analogue of somatostatin — may be linked with a radioisotope for scintigraphic somatostatin receptor scanning



**Figure 5.** Magnetic resonance imaging of multifocal insulinomas. (a) Low signal on fat-saturated T1-weighted image (arrowheads); and (b) high signal on T2-weighted image (arrowheads).

**Table 2.** Relative accuracy of different imaging modalities in the detection of pancreatic islet cell tumours.<sup>6,7,11</sup>

	Sensitivity (%)
Computed tomography	65-75
Magnetic resonance imaging	70-85
Endoscopic ultrasound	75-85
Scintigraphy	61/80*
Selective angiography/venous sampling	80-90

\* Insulinomas/gastrinomas.

(SSRS). The sensitivity of this investigation is higher for gastrinomas and other tumours (80% to 90%), whereas the sensitivity for insulinomas is only approximately 50%. However, the technique is valuable in the detection of metastatic disease and may identify very small lesions.<sup>15,16</sup> Overall, the sensitivity of CT and MRI is similar and both will detect between 65% and 85% of tumours (Table 2). A recent study has suggested that a combination of multislice thin section CT with EUS can detect 100% of insulinomas prior to surgery.<sup>17</sup>

**Biopsy**

EUS has additional benefits in that it may provide a mechanism for biopsy. The surgical strategy for large or malignant pancreatic endocrine tumours tends to be more aggressive with a reported overall 5-year survival rate of more than 75%. It may therefore be important to establish the histological nature of a possible islet cell tumour prior to surgery as a more aggressive approach may be utilised. Although the diagnostic accuracy of EUS fine-needle aspiration biopsy for pancreatic adenocarcinoma is high, at approximately 81%, it is lower for neuroendocrine tumours, at 46%.<sup>18</sup> This may relate to difficulties in positioning for the biopsy and the presence of stromal fibrosis in some tumours, which makes them difficult to penetrate. Some neuroendocrine tumours, because of their vascular nature, may result in a haemorrhagic specimen that results in a false-negative diagnosis.

**CONCLUSION**

CT and MRI have similar sensitivities in the detection of islet cell tumours. Multiphase CT imaging with

arterial, pancreatic, and portal phase imaging post-contrast offers the best potential for diagnosis. On MRI, T1-weighted fat-saturated and T2-weighted images may suffice, but delayed post-contrast imaging may also detect additional lesions.

EUS is highly sensitive in the detection of insulinoma and can be used as a primary investigation. Detection of gastrinoma is less sensitive and EUS should be used in conjunction with other cross-sectional techniques. In large tumours, EUS may provide information in relation to resectability and has the potential for providing cytology or histology.

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