Islet cell tumours: surgical treatment

MC Aldridge

The majority of neuroendocrine tumours of the pancreas are malignant and surgical resection is the mainstay of treatment. The tumours are often small and intraoperative tumour localization is an important part of the operation. The type of tumour will dictate specific treatment.

Mr MC Aldridge is Consultant in General and Gastrointestinal Surgery, Queen Elizabeth II Hospital, East and North Hertfordshire NHS Trust, Welwyn Garden City, Hertfordshire AL7 4HQ

Neuroendocrine tumours of the pancreas are rare, occurring at a rate of approximately 0.4 per 100 000 population (Eriksson and Oberg, 2000). They are derived from the diffuse neuroendocrine system of the pancreas and may produce and secrete a variety of polypeptide hormones including insulin, gastrin, glucagon, vasoactive intestinal polypeptide (VIP) or pancreatic polypeptide (PP). Many of these tumours are malignant, the exception being insulinomas where the majority are benign.

The most practical classification is based on function (*Table 1*). The functional classification is based on the main clinical symptoms and the hormone produced. Not all tumours produce hormones and if serum levels are within the normal range, the tumour is labelled as 'non-functioning'. Such non-functioning tumours account for between 30 and 40% of neuroendocrine tumours of the pancreas.

TABLE 1.
Functional classification of pancreatic neuroendocrine tumours

Tumour type	Frequency (%)	Malignancy (%)	Hormone	Cell of origin
Insulinoma	70–75	<10	Insulin	B cell
Gastrinoma	20–25	>50	Gastrin	G cell
VIPoma	3–5	>50	VIP	D1 cell
Glucagonoma	1–2	>70	Glucagon	A cell
PPoma	<1	?	Pancreatic polypeptide	PP cell
Somatostatinoma	<1	>50	Somatostatin	D cell
Corticotrophinoma	<1	>99	Corticotrophin	?
PTHrPoma	<1	>99	PTHrP	?
Neurotensinoma	?	?	Neurotensin	?
Calcitoninoma	?	?	Calcitonin	?

PTHrP = Parathormone releasing peptide; VIP = vasoactive intestinal polypeptide

Surgical resection for cure is the mainstay of treatment for both functioning and non-functioning tumours. Careful localization of the primary tumour and any metastases, however, is essential. Preoperative tumour localization depends upon a variety of techniques including selective arteriography, ultrasonography, computed tomography (CT), magnetic resonance imaging and percutaneous transhepatic portal venous sampling. Pancreatic neuroendocrine tumours are often small and many will not be accurately localized before surgical exploration. In such circumstances, peroperative localization techniques are required. The cornerstone of these techniques is intraoperative ultrasound (IOUS) and proficiency in this diagnostic modality is essential for surgeons undertaking resection of these difficult tumours.

The results of surgical treatment will depend upon the completeness of removal of the primary tumour and the extent of nodal and liver metastases. These tumours are often slow growing, however, and if complete resection is not possible, a debulking procedure is still worthwhile.

Chemotherapy (streptozotocin and 5-fluorouracil) or alpha-interferon may be directed at the tumour itself and somatostatin analogues (octreotide and lanreotide) are used to reduce hormone levels. While surgery is a major component in the treatment of pancreatic neuroendocrine tumours, a multimodality and multidisciplinary approach is required if survival and quality of life are to be improved.

INSULINOMA

Indication for surgery

In patients with hypoglycaemia and elevated blood insulin levels resulting from insulinoma, surgery forms the only prospect for cure and

should be performed as soon as the tumour is located. Even if liver metastases are present, resection of the primary tumour is indicated to reduce hypoglycaemic symptoms and may be combined with hepatic embolization and/or chemotherapy.

Surgical strategy

The objectives at operation are first to identify the tumour by careful exploration of the pancreas both manually and by IOUS and second to remove all tumour tissue by enucleation or resection.

Exploration of the pancreas

A bilateral sub-costal or 'high gable' incision is used and a full laparotomy carried out. The head of the pancreas is exposed posteriorly by the Kocher manoeuvre and anteriorly by division of the covering peritoneum and areolar tissue. The body and tail are exposed from within the lesser sac. The adhesions between the stomach and pancreas are divided to expose the whole of the anterior surface of the gland. The pancreas is carefully inspected and then palpated between finger and thumb. An insulinoma may be seen as it is slightly darker than the surrounding parenchyma. The tumour can be palpated in approximately 10% of patients.

IOUS using a 7 MHz transducer should form a routine part of insulinoma surgery as it is of help in locating the few tumours which are impalpable. Its main benefit, however, is in determining the relationship between the tumour, the pancreatic duct and the vessels. If the tumour cannot be identified, the abdomen should be closed and the patient re-investigated. There is no place for 'blind' distal pancreatectomy.

Insulinoma resection

The surgical procedure of choice for a solitary insulinoma is enucleation, the aim being to conserve as much pancreatic parenchyma as possible. The tumour is carefully dissected from the surrounding parenchyma after division of the pancreatic capsule. IOUS is useful for identification of the pancreatic duct, thus helping the surgeon avoid damage to this structure. The cavity is inspected and if a ductal leak is detected, a Roux-en-Y loop should be brought up and anastomosed to the cavity (*Figure 1*).

A spleen-preserving distal pancreatectomy (Aldridge and Williamson, 1991) is an acceptable alternative for tumours located in the distal body or tail of the gland (*Figure 2*). Insulinomas in the head of pancreas pose a difficult problem and enucleation is the best option if the tumour can be accurately located. There is little justification for more extensive surgery (i.e. Whipple resection) for a benign insulinoma.

Peroperative monitoring of peripheral blood glucose levels is used routinely after tumour excision. Rebound hyperglycaemia probably indicates successful excision of a single insulinoma, while low blood sugar values should lead to re-examination to detect multiple lesions.

Surgical results and complications

The most common postoperative complication is pancreatic fistula which in a large multicentre review was found to occur in 10.7% of cases (Rothmund et al, 1990). Other complications such as pseudocyst formation and pancreatitis are rare (*Table 2*). In this review, the 30-day hospital mortality was 2% and the success of the first operation was 95% (Rothmund et al, 1990).

GASTRINOMA

Indications for surgery

Patients with sporadic gastrinoma without evidence of hepatic metastases are suitable for surgical exploration, the aim being excision of the tumour for cure. Surgical cure can be defined as resection of all gastrinoma tumour such that the patient becomes eugastrinaemic,

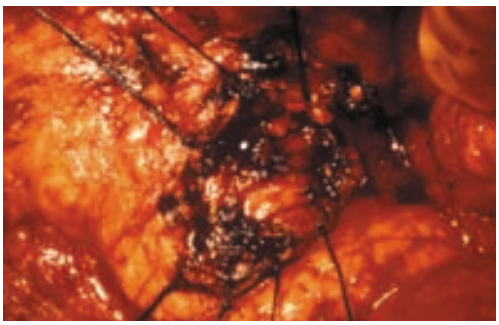

Figure 1. Enucleation of an insulinoma resulted in this cavity which required covering by a Roux-en-Y loop of jejunum.

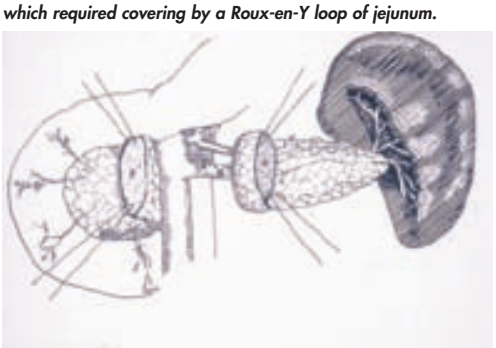

Figure 2. Spleen-preserving distal pancreatectomy: the technique.

TABLE 2.
Postoperative complications after 419 operations for benign insulinoma

Complication	*n*	Percentage
Pancreatic fistula	45	10.7
Acute pancreatitis	24	5.7
Intra-abdominal abscess	13	3.1
Wound infection	12	2.9
Peritonitis	8	2.0
Haemorrhage	7	1.7
Pseudocyst	4	1.0
Other complications	19	4.5

After Rothmund et al (1990)

requires no anti-ulcer medication and has no evidence of recurrence on long-term follow-up. The two categories of patients unlikely to be cured by surgery are those with hepatic metastases and those with multiple endocrine neoplasia type 1 (MEN-1) syndrome without identifiable tumour.

Surgical exploration for gastrinoma

The abdomen is opened and the pancreas explored as for insulinoma (see above). A detailed search is undertaken for both primary gastrinoma and regional nodal metastases. At least 88% of gastrinomas will be found within the boundaries of the 'gastrinoma triangle' (Stabile et al, 1984) (*Figure 3*). This is bounded by the junction of the cystic duct and common bile duct superiorly, the junction of the second and third parts of the duodenum inferiorly, and the junction of the neck and body of the pancreas medially.

The pancreas is fully exposed to allow careful manual examination and the use of IOUS. The duodenum is mobilized using the Kocher manoeuvre to allow examination of its posterior surface which is a frequent location for involved nodes (*Figure 4*). Any suspicious node is sent for frozen section examination. The duodenum is carefully palpated between finger and thumb

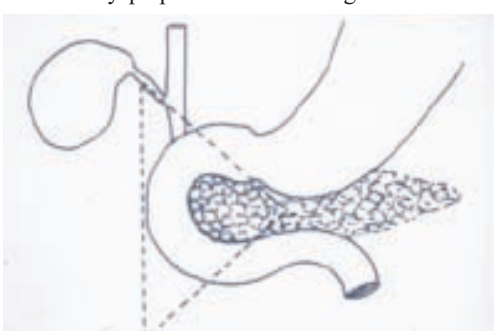

Figure 3. The gastrinoma triangle.

to identify microadenomas which can be felt as 'millet seeds' in the duodenal wall. If no tumour is discovered, a longitudinal duodenotomy is made and the duodenal mucosa carefully examined (eversion of the mucosa is vital here). Small gastrinomas located in this way may be removed by enucleation. Gastrinomas in the pancreas may be enucleated or excised. Rarely, pancreatoduodenectomy may be necessary for a deeply placed malignant gastrinoma in the head of pancreas.

In patients in whom a tumour cannot be identified, there are two options: either to perform a total gastrectomy (removing the 'target' organ) or to close the abdomen and treat the patient with either a histamine H_2-receptor antagonist (such as omeprazole) or a proton pump inhibitor (such as lansoprazole). Currently, total gastrectomy is only used in patients who do not respond to maximal drug therapy or who fail to comply.

Surgical results

Using the definition of 'cure' outlined above, cure rates of 82% have been reported (Howard et al, 1990). These workers explored 11 patients with sporadic gastrinoma with the intention of performing a curative resection. Tumour was found in 10, in all cases within the gastrinoma triangle. In 40% the tumours were multiple and lymph node metastases were identified in 64%. Nine of the 11 patients (82%) were 'cured' after a median follow-up of 15 months. Surgery does therefore seem to have a worthwhile place in the treatment of gastrinoma and may even alter the natural history of the disease as shown by a non-randomized trial from the National Institutes of Health in the USA (Fraker et al, 1994).

VIPOMA

Surgical treatment

All patients with the clinical VIPoma syndrome and elevated fasting concentrations of

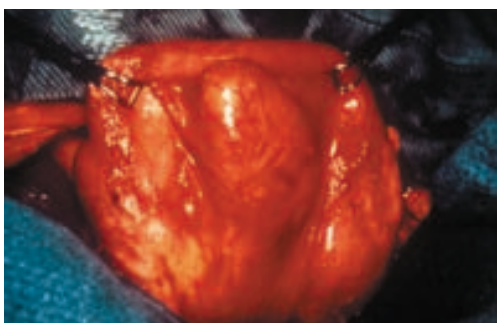

Figure 4. A solitary retroduodenal lymph node metastasis in a patient with a primary malignant gastrinoma in the uncinate process of the pancreas.

plasma VIP should undergo surgical exploration aimed at resection of the pancreatic tumour. In the presence of hepatic metastases, a debulking procedure is still indicated to reduce symptoms and allow more effective medical treatment.

Patients with benign VIPomas can be cured by surgery. The average survival for patients with malignant tumours is approximately 12 months (Smale and Reber, 1987).

GLUCAGONOMA

Surgical treatment

Glucagonomas are usually found in the body or tail of the pancreas and are malignant in a large proportion of patients. Distal pancreatectomy is required for complete removal. If hepatic or lymph node metastases are present, a debulking procedure may result in useful palliation by giving relief from symptoms (*Figure 5*).

NON-FUNCTIONING TUMOURS

Between 30 and 40% of pancreatic neuroendocrine tumours do not secrete a known peptide product and have no associated clinical syndrome. These tumours are slow growing and occur most commonly in the head of pancreas. They present in a similar fashion to pancreatic adenocarcinoma and symptoms may include obstructive jaundice, abdominal pain or an abdominal mass. Diagnosis may be made using a combination of ultrasound, CT and arteriography. A pancreatic neuroendocrine tumour should be suspected if the mass appears highly vascular on arteriography.

Treatment for these non-functioning pancreatic tumours is by surgical resection if feasible as the majority are malignant. They have a more favourable natural history than other varieties of pancreatic cancer and long-term survival is a possibility in some cases.

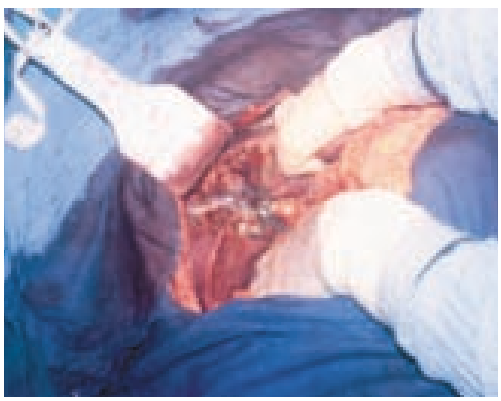

Figure 5. Segmental hepatic resection for metastatic glucagonoma in segment V of the liver.

CONCLUSIONS

Despite advances in the medical management of gastrointestinal hormonal syndromes, surgery still has a large part to play in the treatment of pancreatic neuroendocrine tumours. This is particularly the case for insulinoma which is usually small, benign and located in the body or tail of the gland, and gastrinoma which is usually malignant.

The challenge for the surgeon is to localize and then completely remove the tumour. Tumour localization can be difficult preoperatively and thus peroperative techniques have come to the fore. There is little doubt that IOUS has increased the chances of finding these small tumours and all surgeons who operate on such patients need to be familiar with the technique.

While surgery is a major component in the treatment of both benign and malignant pancreatic neuroendocrine tumours, the modern approach must be multimodal and multidisciplinary if survival and quality of life are to be improved. HM

Figures 3–5 *are reproduced from* Surgical Endocrinology *by Lynn & Bloom. Reprinted by kind permission of Butterworth Heinemann.*
Conflict of interest: none.

Aldridge MC, Williamson RCN (1991) Distal pancreatectomy with and without splenectomy. *Br J Surg* **78:** 976–9
Eriksson B, Oberg K (2000) Neuroendocrine tumours of the pancreas. *Br J Surg* **87:** 129–31
Fraker DL, Norton JA, Alexander HR, Venzon DJ, Jensen RT (1994) Surgery in Zollinger-Ellison syndrome alters the natural history of gastrinoma. *Ann Surg* **220:** 320–30
Howard TJ, Zinner MJ, Stabile BE, Passaro E Jr (1990) Gastrinoma excision for cure: a prospective analysis. *Ann Surg* **211:** 9–14
Rothmund M, Angelini L, Brunt M et al (1990) Surgery for benign insulinoma: an international review. *World J Surg* **14:** 393–9
Smale BF, Reber HA (1987) Vasoactive intestinal polypeptide (VIP) producing tumours. In: Howard JM, Jordan GL, Reber HA, eds. *Surgical Diseases of the Pancreas.* Lea and Febiger, Philadelphia: 860–4
Stabile BE, Morrow DJ, Passaro E Jr (1984) The gastrinoma triangle: operative implications. *Am J Surg* **147**: 25–31

KEY POINTS

- Insulinoma is the most frequently encountered functioning pancreatic neuroendocrine tumour and most are benign.
- Up to 40% of tumours are 'non-functioning' and these may present in a similar fashion to adenocarcinoma of the pancreas.
- Surgical resection is the mainstay of treatment for pancreatic neuroendocrine tumours.
- Preoperative tumour localization is important and techniques include selective arteriography, ultrasound, computed tomography, magnetic resonance imaging and percutaneous transhepatic venous sampling.
- Intraoperative ultrasound is the cornerstone of peroperative tumour localisation and proficiency in this technique is desirable for surgeons undertaking resection of these tumours.
- A multimodality and multidisciplinary approach to treatment is required if survival and quality of life are to be improved.