Somatostatinoma

16

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16.1 Introduction

Somatostatinomas are rare neuroendocrine tumours (NETs) that arise in the pancreas or duodenum. They are the fifth most common pancreatoduodenal NET (after insulinomas, non-functioning tumours, gastrinomas and VIPomas), with an incidence of 1 in 40 million [1–3]. They tend to be non-functioning, although they are rarely active and can produce a spectrum of symptoms called 'somatostatinoma syndrome' [4–6]. A degree of discord exists regarding the functional component of a somatostatinoma; some clinicians argue that a 'syndrome' of clinical symptoms must be present for the diagnosis of somatostatinoma and others that the diagnosis is purely immunohistochemical [7]. As most of these tumours are biochemically inert, they are either detected incidentally or by causing mass-effect pressure symptoms, and most will have metastasised by the time of diagnosis [6, 8, 9].

There is little to distinguish somatostatinomas from other pancreatoduodenal NETs on radiological imaging or preoperative histology, but the presence of strong and diffuse positive somatostatin staining on immunohistochemistry is diagnostic [4]. Thus, many somatostatinomas are only diagnosed postoperatively when the histopathologist has had access to the resected specimen [6]. Like most NETs, operative resection even in the presence of metastases is recommended, with somatostatin analogues and chemotherapy reserved for patients not amenable to operation [10]. A variety of techniques exist for the management of metastases, with operative resection being advocated when suitable [7, 10–12]. Outcomes tend to much be more favourable than for an associated adenocarcinoma of the pancreas or duodenum, largely due to the indolent nature of these tumours.

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16.2 Incidence

Somatostatinoma was first described in 1977 [1], and since then, approximately eight cases per year have been reported [2]. The suggested incidence of 1 in 40 million may increase with improved understanding and diagnosis of the tumour [1, 2]. They are the fifth most common NET in the pancreas [4], while in the duodenum, they account for 15 % of all NETs [13]. Patients typically present between the ages of 40–60 years of age, and there is a possible slight female predominance [6, 14, 15]. There are no known environmental risk factors [3]. Somatostatinomas can either be functioning or non-functioning: cases in the literature have not been associated with somatostatinoma syndrome.

Somatostatinomas tend to be solitary and almost exclusively confined to the pancreas or duodenum, presumably reflecting the high concentration of delta cells in these organs [3, 6, 14]. Between 50 and 60 % of somatostatinomas originate in the pancreas, where there is a preference for the head of the gland (50 %), followed by the tail (25 %), and then diffuse infiltration of the gland (25 %) [6, 10, 13]. Of the remaining extrapancreatic lesions, approximately 50 % originate in the duodenum and 50 % precisely at the ampulla; less than 1 % arise from the jejunum, and isolated cases in the colon and rectum have been reported [6, 16, 17].

Somatostatinomas are associated with malignancy rates of up to 78 %, while 70–92 % have metastatic disease at presentation [6, 8, 9]. Rates of malignancy and metastasis are highest for pancreatic tumours [18, 19]. The liver is most commonly involved, followed by regional lymph nodes and then bony deposits [6]. The presence of metastatic disease is thought to be as a consequence of late diagnosis and does not appear to be dependent upon the tissue of origin [6].

16.3 Associations

Most somatostatinomas are sporadic, but there are well-known associations with MEN (multiple endocrine neoplasia) type 1 and neurofibromatosis type 1 (NF1), also known as von Recklinghausen disease. Less than 1 % of somatostatinomas are associated with MEN, however, this percentage being lower than for other pancreatoduodenal NETs [20]. Duodenal somatostatinomas are associated with NF1 in up to 50 % of patients, but there is less of a clear-cut association for pancreatic tumours [9, 14]. NF1 patients have an inherited mutation of the NF1 gene on chromosome 17q11, which codes for the protein neurofibromin. Somatostatinomas diagnosed in the presence of NF1 are thought to have a lower risk of metastases at presentation. There is a well-recognised association between NF1, duodenal somatostatinomas and pheochromocytomas, so that the presence of an adrenal lesion should be sought in this group of patients [3, 15, 21].

There have been occasional case reports of somatostatinomas in combination with conditions including von Hippel-Lindau disease [22, 23], tuberous sclerosis [24] and gastrointestinal stromal tumours [25, 26].

16.4 Biochemistry

16.4.1 Somatostatin

Somatostatin is also known as growth hormone-inhibiting hormone (GHIH), somatotropin release-inhibiting factor (SRIF) or somatotropin release-inhibiting hormone. It is a small cyclic peptide derived from proteolytic processing of two larger molecules (prepro-somatostatin and pro-somatostatin) [14]. Somatostatin is secreted from exocrine cells in the gastrointestinal (GI) tract and from delta cells of the pancreas under physiological conditions. It has two active forms, somatostatinoma-14 and somatostatin-28 (consisting of 14 and 28 amino acids, respectively) [27].

Somatostatin has a general inhibitory effect up on the gastrointestinal tract. It affects gastrointestinal motility, gastric acid production, pancreatic enzyme secretion, bile secretion and colonic fluid secretion [27]. It also inhibits the secretion of pancreatic and intestinal hormones such as insulin, glucagon, secretin and vasoactive intestinal polypeptide. Some of these actions are thought to occur via paracrine modulation and a reduction in splanchnic perfusion [3]. Somatostatin may also control cell proliferation both in normal tissues and NETs [27].

Since these effects have therapeutic benefits, somatostatin analogues, such as octreotide, octreotate, edotreotide and lanreotide, can be used in a variety of clinical contexts, including the palliation of vomiting, symptomatic control in neuroendocrine and thyroid tumours and prevention of complications following pancreatic surgery.

16.4.2 Somatostatin Receptors

The physiological effects of somatostatin are mediated by a family of seven G-protein-coupled transmembrane receptors; five subtypes exist ($SST_{1–5}$), each being coded by its relevant gene (SSTR1–5) [27, 28]. Most cells within the body express somatostatin receptors in various concentrations [29]. Of note, SSTR1 is expressed in its highest concentrations in the jejunum (and stomach), and SSTR3 is expressed in its highest concentrations in pancreatic islet cells [28]. The expression of somatostatin receptors by a tumour does not necessarily indicate that it is functional, but it can influence patient management [8, 9]. Approximately 80 % of all NETs express somatostatin receptors [10].

Tumours that express SST2 and SSTR5 are associated with a better outcome than those that do not [30]. In addition, tumour expression of receptors can be useful for both diagnostic and treatment purposes (see below): somatostatin receptor scintigraphy (SRS) relies on this expression for the accurate location of both primary tumours and metastatic foci [6, 29, 31]. Somatostatin analogues (e.g. octreotide, octreotate, edotreotide and lanreotide) can be used to control symptoms and inhibit cell growth [5, 7, 10, 32], while radionuclide therapy (via radiolabelled somatostatin analogues) can be used to deliver targeted radiotherapy to the tumour [4, 31, 33].

16.5 Pathology

Immunohistochemistry is the diagnostic investigation of choice for somatostatinomas as it reveals characteristic immunoreactivity for somatostatin [3, 13]. Management and survival of somatostatinomas is based on pathological findings, the Ki-67 index and the TNM (tumour, node, metastases) staging. All pathology reports from NETs should include a minimum data set of tumour site, immunohistochemical staining, grade (mitotic rate and Ki-67 index), presence of non-ischaemic tumour necrosis and presence of other pathological components (e.g. non-neuroendocrine components) [34].

16.5.1 Macroscopic

Macroscopic examination of a somatostatinoma reveals a round lesion which is well demarcated [13]. Lesions are typically solitary and measure 1–5 cm in diameter [3]. There is nothing to distinguish these tumours from other pancreatoduodenal NETs on macroscopic appearance.

16.5.2 Microscopic

Most somatostatinomas show typical features of a NET on histological examination: they tend to be well differentiated and show a glandular pattern (Fig. 16.1)

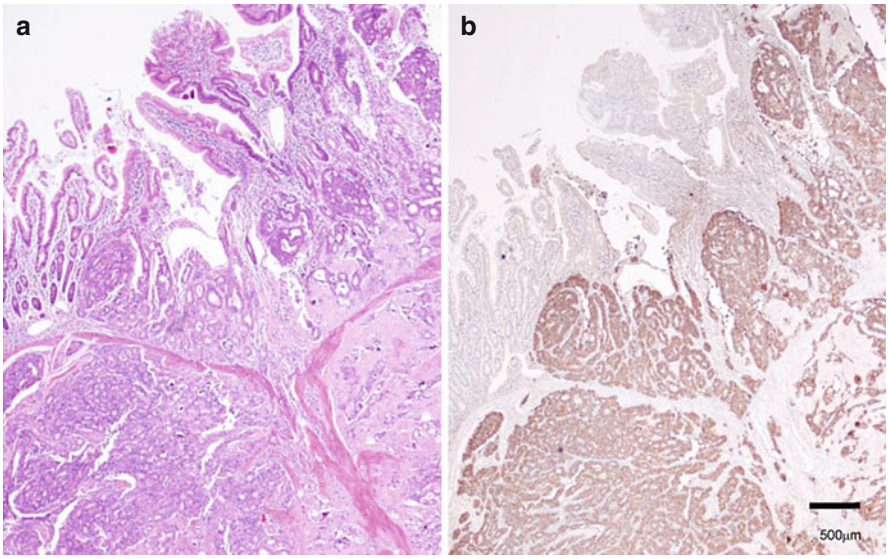

Fig. 16.1 (**a**, **b**) Microscopic appearances of ampullary somatostatinoma. Haematoxylin and eosin staining (*left*) and strongly positive immunostaining with somatostatin (*right*) (ANNALS IMAGE)

[3, 6, 13]. Some somatostatinomas show a mixed picture, with separate zones of well-differentiated and anaplastic cells. The differentiated areas have cells arranged in lobular or acinar patterns, which are separated by fibrovascular stroma. The less well-differentiated areas have cells interrupted by fibrous septa [6].

Psammoma bodies (round collections of calcium that arise after infarction and calcification) may be present in somatostatinomas. They are circular in appearance and are laminar, acellular and basophilic on histological examination. Psammomas are more commonly found in duodenal lesions and may be associated with neurofibromatosis [13].

16.5.3 Differentiation

Tumour differentiation – the extent of resemblance to normal cellular architecture – plays a role in assessing how aggressive a NET is [35]. Most somatostatinomas are well differentiated and have a uniform cellular pattern consistent with the organ of origin. Cells produce abundant neurosecretory granules and may also be arranged in nesting, trabecular or gyriform patterns [13, 35]. Poorly differentiated somatostatinomas less closely resemble non-neoplastic cells and have a more sheet-like or diffuse structural arrangement, with irregular nuclei and less cytoplasmic granularity.

16.5.4 Immunohistochemistry

Most NETs reveal some positivity for somatostatin immunohistochemistry due to the presence of somatostatin receptors. Somatostatinomas show diffuse positive immunoreactivity for somatostatin, and this expression is characteristic (Fig. 16.1) [3, 6, 13]. The immunoexpression is related to the differentiation of the tumour, with well-differentiated somatostatinomas revealing strong immunoreactivity for somatostatin staining and poorly differentiated tumours showing less immunoreactivity [35]. The absence of staining for other NET hormones (vasoactive intestinal polypeptide (VIP), gastrin, insulin and glucagon) also confirms the diagnosis. In addition, there may be immunoexpression of general neuroendocrine markers such as chromogranin A and synaptophysin [35].

16.5.5 Grading

Although no grading system can fully predict the behaviour of somatostatinoma, an estimate of the biological aggressiveness of NET can provide significant information on prognosis [35]. Biological activity can be assessed by cellular mitotic activity and the Ki-67 index (to estimate the growth fraction of a cellular population). Both of these measures assess tumour proliferative rate; mitotic activity requires counting the number of mitoses seen over a microscopic field,

Table 16.1 Grading system for foregut neuroendocrine tumours [35, 36]

Grade	Mitotic count (10 HPF)	Ki-67 index (%)
Low grade G1	<2	≤2
Intermediate grade G2	2–20	3–20
High grade G3	>30	>20

10 HPF high-power field = 2 mm^2, at least 40 fields (at 40× magnification) evaluated in areas of highest mitotic density, *Ki-67 index* labelling with MIB1 antibody; % of 2,000 tumour cells in areas of highest nuclear labelling

whereas the Ki-67 index provides a percentage of cells reacting to labelling with MIB1 antibody [35, 36]. These measures are broadly equivalent in assessing grading but can sometimes give conflicting information (in which case the more aggressive score is adopted) [35]. If limited amounts of tissue are available (e.g. following biopsy), a mitotic index may not be possible to perform as it requires counting 40–50 high-power microscopic fields (more than most biopsy samples contain). In these cases, Ki67 staining provides a more accurate assessment of proliferative rate [35].

Histological grading for pancreatoduodenal NETs is either low (G1), intermediate (G2) or high (G3) (Table 16.1). Low-grade NETs are relatively indolent, while intermediate grade tumours have a less predictable, moderately aggressive course [35]. Somatostatinomas that are either G1 or G2 tend to be well-differentiated NETs, while G3 tumours are poorly differentiated neuroendocrine tumours [35, 36].

16.6 Staging

A number of different staging systems exist to classify the extent of tumour spread for NETs, and while the criteria for assessment vary between each method, the underlying basic data are similar [35]. The TNM staging system is becoming the most widespread method for assessment; it reveals the extent of invasion into the organ of origin and regional or distant spread (Table 16.2) [35, 36].

16.7 Presentation

The functionality of the somatostatinoma greatly influences presentation. Non-functional tumours, which are not associated with somatostatinoma syndrome, tend to present with local mass effects, though many are detected incidentally. Symptoms are non-specific but include upper abdominal pain, abdominal swelling and mass, jaundice, weight loss, nausea and vomiting [3]. Some patients will present with tumour burden from metastatic disease. Often non-functioning tumours are detected incidentally during investigation of non-specific gastrointestinal symptoms in the same manner as other gastroduodenal NETs.

Table 16.2 TNM classification for pancreatoduodenal neuroendocrine tumours

TNM grade	Duodenum/ampulla/proximal jejunum	Pancreas
Tx	Primary tumour cannot be assessed	Primary tumour cannot be assessed
T0	No evidence of primary tumour	In situ tumour/dysplasia
T1	Tumour invades lamina propria or submucosa and size ≤1 cm	Tumour invades lamina propria or submucosa for ≤1 cm
T2	Tumour invades muscularis propria or size ≥1 cm	Tumour invades muscularis propria or subserosa for ≥1 cm
T3	Tumour invades the pancreas of the retroperitoneum	Tumour penetrates serosa
T4	Tumour invades peritoneum or other organs	Tumour invades adjacent structures
Nx	Regional lymph nodes cannot be assessed	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis	No regional lymph node metastasis
N1	Regional lymph node metastasis	Regional lymph node metastasis present
Mx	Distant metastases cannot be assessed	Distant metastases cannot be assessed
M0	No distant metastases	No distant metastases
M1	Distant metastases	Distant metastases

Adapted from Rindi et al. [36]
T primary tumour (add (m) for multiple tumours), *N* regional lymph nodes, *M* distant metastases
M1 specific sites as defined according to Sorbin and Wittekind [37]

16.7.1 Somatostatinoma Syndrome

Functioning tumours are rare and cause somatostatinoma syndrome as a result of overexpression of somatostatin. This syndrome comprises diarrhoea (secondary to decreased pancreatic enzyme and bicarbonate secretion), steatorrhoea and diabetes (resulting from insulin inhibition), gallstones (from cholecystokinin inhibition) and hypochlorhydria [4–6]. Some authors argue that this syndrome must be present for a secure diagnosis of somatostatinoma [7]. Functioning tumours are likely to present earlier than non-functioning tumours, given their symptomatology and consequent investigation.

16.8 Investigation

Although radiology provides the mainstay of investigation, it will only reveal the presence of a pancreatoduodenal NET rather than a definitive diagnosis of a somatostatinoma [3]. Nuclear medicine and endoscopic assessment play an increasingly important role in the management of this group of tumours. Biochemical assessment may also reveal the presence of a NET, and it can be diagnostic for somatostatinoma. Definitive diagnosis tends to come from tissue diagnosis and immunohistochemistry (either biopsy or pathological specimen).

16.8.1 Biochemical and Haematological Assessment

Patients with pancreatoduodenal NETs should be investigated with both standard and specific blood tests. Routine full blood count, liver function tests, urea and electrolytes and clotting screen should be performed to check for any derangement in organ function: significant hepatic metastases may result in derangement in liver function. Blood glucose should also be measured for signs of diabetes, either due to somatostatin syndrome or to pancreatic dysfunction secondary to tumour invasion. These tests should also be used as a workup for further management, both in terms of radiological investigation and suitability for operative intervention.

Chromogranin A and pancreatic polypeptide are non-specific markers for pancreatoduodenal NETs; elevated levels are found in 50–80 % of tumours, including somatostatinomas [20]. Although elevated plasma somatostatin levels (SLI) are strongly indicative of somatostatinoma, they are rarely found [5, 7]. Pancreatic somatostatinomas tend to have higher SLI concentrations (up to 50 times normal) compared to intestinal somatostatinomas in which the concentration is often normal [6]. Patients with high plasma levels of somatostatin are thought to present earlier than those with normal levels [4].

16.8.2 Radiological Imaging

Accurate imaging of the primary tumour and the extent of disease is vital in all stages of management of somatostatinomas. Imaging should provide the location and extent of the primary tumour and assist in determining whether operative intervention should be performed, either curative resection or debulking. In addition, local invasion and the presence of metastases should be sought on investigation. Functional somatostatinomas may be harder to identify than tumours without somatostatinoma syndrome, as they are likely to be smaller at initial presentation.

Conventional imaging provides the mainstay of initial investigation. Computed tomography (CT), ultrasound scanning and magnetic resonance imaging (MRI) can all be employed to assist diagnosis, with selective use of small bowel series (barium or Gastrografin) (Fig. 16.2) and angiography (Fig. 16.3) [3]. Dual-phase, thin-slice CT (Fig. 16.4) is the usual first-line investigation; detection rates are proportional to the size of the lesion. Somatostatinomas are isodense (and thus not visible on unenhanced CT), but intravenous contrast will reveal a characteristic hypervascular lesion [38]. Typically lesions are 5 cm in diameter at presentation [34]. More than 70 % of lesions greater than 3 cm in size can be identified, but only 50 % of lesions measuring less than 1 cm are detected [10, 39]. Thus, small somatostatinomas and hepatic metastases may be missed. Dual-phase CT and MRI have equivalent sensitivities for the detection of NETs; CT is thought to be better for detection of peritoneal and mesenteric disease than MRI, which is more sensitive for detecting liver and bony metastases [6, 40].

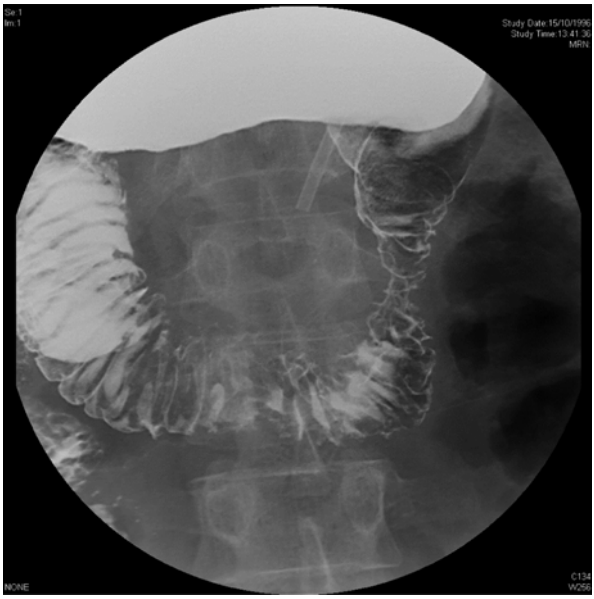

Fig. 16.2 Small bowel Gastrografin study showing constricting lesion in the second part of the duodenum (patient in prone position). Lesion subsequently confirmed as somatostatinoma on postoperative immunohistochemistry

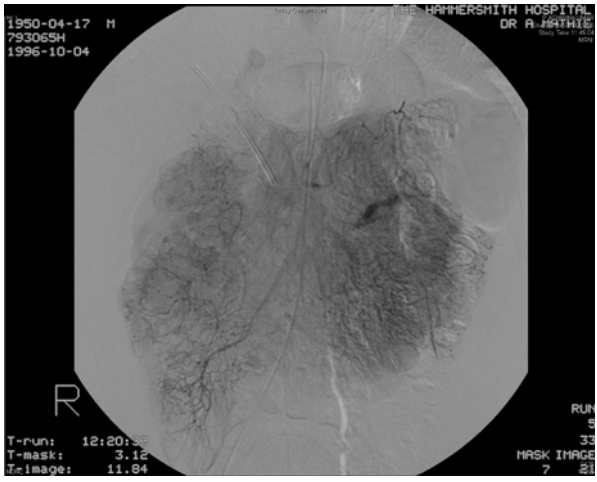

Fig. 16.3 Visceral angiography of patient with duodenal somatostatinoma. Increased tumour 'blush' noted at the right-hand side of the image, but no gross vascular invasion present (patient subsequently underwent successful pylorus-preserving proximal pancreatoduodenectomy)

Transabdominal ultrasound is not used routinely because it has a low sensitivity (9–64 %) for pancreatic lesions [10, 39]. Angiography may reveal a characteristic tumour blush and can be combined with selective visceral cannulation and assessment of hormonal gradients. These techniques have now been largely superseded by other imaging modalities, notably CT.

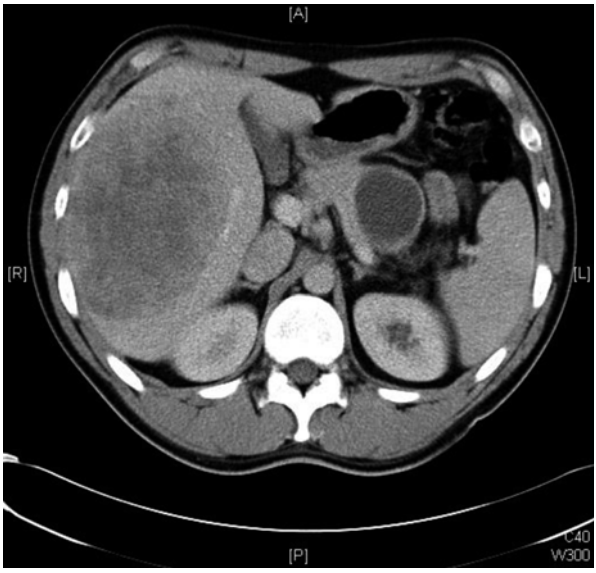

Fig. 16.4 Computed tomography showing the presence of a large pancreatic primary somatostatin and hepatic metastases

16.8.3 Nuclear Medicine Imaging

16.8.3.1 Somatostatin Receptor Scintigraphy

The overexpression of somatostatin receptors (particularly subtypes SSTR2 and SSTR5) by more than 80 % of pancreatoduodenal NETs has allowed the development of somatostatin receptor scintigraphy (SRS) [31, 41, 42]. A number of different radiolabelled somatostatin analogues will bind to the receptors with high affinity. One of the agents most widely used worldwide for SRS is ^{111}IN-DTPA-octreotide (Octreoscan), which has an overall sensitivity of 80–90 % [6, 10, 20, 31, 43]. SRS allows whole body scanning, which is invaluable in detecting metastases (especially at unexpected locations), but it does not provide information on tumour size or resectability [4, 6]. After the radiolabelled agent is injected into the patient, scans are generally performed at either 4–6 h or at 24 h. With earlier scans, lesions may be obscured by a relatively high background activity. Delayed scans provide better contrast (due to lower background activity) but can result in false-positive results secondary to physiological bowel activity [6].

16.8.3.2 SPECT (Somatostatin Receptor Scintigraphy Combined with Computed Tomography)

SPECT is more sensitive than conventional imaging for detection of both the primary somatostatinoma and its metastases [31, 44]. Seventy per cent of primary lesions and more than 90 % of distant disease can be detected with SPECT [31, 44]. It has the additional advantage over conventional imaging that it can provide whole body scanning at one time, and it alters patient management in up to 47 % of patients

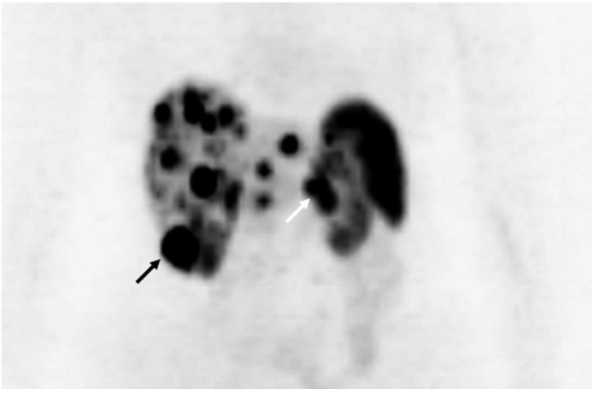

Fig. 16.5 PET scan showing extensive hepatic metastases as well as uptake in the inferior pole of the right kidney (*black arrow*) and the pancreatic primary tumour (*white arrow*)

[7, 31]. False-positive localisations can occur in up to 12 % of patients, but this figure can be reduced to 3 % when findings are corroborated with clinical assessment [7, 10, 31].

16.8.3.3 Positron Emission Tomography

Positron emission tomography scanning (Fig. 16.5) has greater sensitivity than either SRS or conventional cross-sectional imaging [10]. As a result, this new technique is becoming increasingly employed for the detection of all pancreatoduodenal NETs, including somatostatinomas [3]. Two main agents are used: ^{11}C-5-HTP and 68gallium-labelled somatostatin analogues.

16.8.4 Endoscopic Examination

Endoscopy allows direct visualisation of the upper gastrointestinal tract and can help diagnose gastroduodenal lesions. It should be combined with concurrent endoscopic ultrasound, which can detect lesions as small as 0.5 cm [45]. Endoscopic ultrasound is more effective at localising tumours in the pancreas than the duodenum, although the tail of the gland can be inaccessible [7, 46]. Fine needle aspirates can be taken, which can be useful in providing cytological assessment of suspect lesions.

16.8.5 Intraoperative Techniques

Both intraoperative ultrasonography and endoscopic transillumination are recommended to assist in detection of small lesions not appreciated on conventional imaging [7, 10]. In addition they can be used to help plan the route of resection and enucleation of lesions [4]. However, these techniques may fall out of routine use with the increasing availability and sensitivity of nuclear imaging.

16.9 Management

The overall 5-year survival rate in pancreatic and periampullary somatostatinoma is 60–100 % with localised disease or 15–60 % in metastatic disease [15, 47]. Large size (>3 cm), poor differentiation and lymph node involvement are poor prognostic markers. Tumours that are hormonally inactive (non-functioning), which predominate, have a worse prognosis than functioning somatostatinomas.

Operative resection, when feasible, is recommended for all pancreatoduodenal NETs, including somatostatinomas. Curative resection is the aim of intervention, but in the presence of liver metastases, either complete resection or debulking of primary tumour is recommended. Medical management, in the form of chemotherapy, somatostatinoma analogues or radionucleotide therapy, plays an important role in controlling both symptoms and tumour growth, but it is not considered a first-line intervention.

16.9.1 Medical

16.9.1.1 Somatostatin Analogues

Somatostatin analogues, such as octreotide, octreotate, edotreotide and lanreotide, help control the symptoms of pancreatoduodenal NETs [5, 7]. These analogues act on somatostatin receptors and stimulate the inhibitory effects of somatostatin. Long-acting depot forms of these analogues allow monthly injection therapy, which increases patient convenience and therefore compliance [10]. Long-term treatment may be associated with symptomatic breakthrough, in which case a stronger or more frequent doses may be required; in some cases a treatment 'holiday' is required before recommencing the analogue [10]. These analogues have mild side effects in up to half of all patients, including flatulence, diarrhoea/steatorrhoea, nausea, gallstones and glucose intolerance [5, 7]. The addition of α-interferon therapy may help control symptoms if first-line intervention is inadequate [20].

In addition to symptomatic relief, somatostatin analogues are thought to have tumourostatic effect in 40–80 % of patients, but have not been shown to cause tumour regression [7, 10, 31]. This stabilisation of disease has increased progression-free survival for midgut neuroendocrine tumours [4, 48].

16.9.2 Chemotherapy and Radiotherapy

Generally pancreatoduodenal NETs do not respond well to oncological agents because they are slow growing and thus have an inherent resistance to therapies targeted at rapidly dividing cells. Nevertheless, chemotherapy and radiotherapy are frequently employed for disease that is not amenable to operative resection. A number of different chemotherapeutic regimes have been employed, with an overall objective response rate of 10–45 % [4]. Chemotherapeutic agents include streptozotocin, doxorubicin, 5-FU, temozolomide, dacarbazine and chlorozotocin;

streptozotocin is thought to be the best therapy with response rates as high as 70 % [3, 4]. However, these regimes result in appreciable toxicity. Complete tumour response to any therapy is rare, and all drugs are associated with side effects that may make the regime intolerable. Trans-arterial chemoembolisation (TACE) can also be successfully employed for the treatment of hepatic metastases (see below).

Systemic radiotherapy is not usually suitable for patients with somatostatinomas (or any pancreatoduodenal NETs) due to the location of the primary tumour and associated lymphatic spread. Its use is not supported in the literature except for providing symptom relief for bony metastases [4].

16.9.3 Peptide Receptor Radionuclide Therapy [PRRT]

Radionuclide therapy is a novel technique which is being increasingly utilised for the treatment of inoperable or metastatic pancreatoduodenal NETs [33, 49]. This therapy delivers targeted local radionucleotides that release γ-radiation or β-radiation to the tissues, thus decreasing overall radiation exposure to the patient [31, 33]. The exact dosage of radiation needs to be calculated to ensure that sensitive organs, for example, the kidneys and bone marrow, do not suffer irreversible damage [33].

The overexpression of somatostatin receptors by most NETs, particularly somatostatinomas, makes targeted peptide receptor radionuclide therapy (PRRT) particularly appealing. Radiolabelled somatostatin analogues with attached radionuclides of ^{177}lutrium, ^{90}yttrium or ^{111}indium can be used to target pancreatoduodenal NETS. No randomised controlled studies exist, but several studies have reported favourable response rates [4, 31, 49]. Of all the agents commercially available, [^{177}Lu-DOTA^{0},Tyr3]octreotate (DOTATATE) has showed a complete response rate in 2 % of patients, a partial response in 32 % and stabilisation of disease in 34 % [49]. Overall, median survival rates with DOTATATE of more than 40 months have been reported.

16.9.4 Surgery

Operative resection of the primary tumour, even in the presence of metastases, is recommended for all pancreatoduodenal NETs unless the patient has [10]:

1. Another medical condition limiting life expectancy or increasing surgical risk
2. Diffuse metastatic liver disease
3. One of the inherited PNET syndromes

This strategy is governed, in part, by better outcomes of operative resection and the traditionally poor outcomes associated with nonoperative interventions. When curative resection cannot be performed, surgical debulking of the primary tumour is advocated; hepatic resection of metastatic disease is also advocated when possible, although there are a number of alternatives to hepatectomy (see below). Any

resection should be combined with cholecystectomy, because of the likelihood of gallstone formation with increasing somatostatin levels (with associated cholecystokinin inhibition) postoperatively [4].

16.9.4.1 Curative Resection

Any patient without metastatic disease should be considered for curative resection of the tumour. Unfortunately with up to 90 % of patients presenting with metastatic disease, curative resections are not that common particularly when sensitive whole body scanning, in the form of SRS or PET, is now commonplace [6, 8, 9]. When possible, somatostatinomas should be locally excised or enucleated, with major resections reserved for more extensive disease in patients who are fit enough to tolerate the operation [7, 10, 20]. As somatostatinomas are located in the periampullary duodenum or pancreatic head, a pylorus-preserving pancreatoduodenectomy or Whipple's procedure is the most common resection, although total pancreatoduodenectomy may occasionally be required for multiple tumours or bulky tumours in the pancreatic neck [3].

Well-defined and localised intrapancreatic lesions can be resected laparoscopically, but most somatostatinomas are approached by laparotomy. An extensive abdominal exploration has traditionally been recommended to search for lymph node metastases, although this may not be required given the sensitivity of SRS and PET [7, 10, 20].

16.9.4.2 Palliative Resection

By definition, tumours that have metastasised cannot undergo curative resection, but resection of the primary tumour even in the presence of hepatic metastases is advocated [3, 10]. There are many options for the management of hepatic metastases (see below) that can improve patient survival and alter the natural history of the disease process [50]. A recent systematic review has shown a trend towards improved survival post resection of primary lesion in the presence of metastases, although it is unknown whether this is a true reflection or simply that patients in the operative group are healthier than those not deemed for surgery, i.e. a positive selection bias for treatment in patients with better overall performance status [12]. Regardless of the underlying mechanism, a 30 % improvement in 5-year survival in patients undergoing resection has been reported [12].

Thus all patients should be considered for operative intervention if complete (or near-complete) resection of hepatic metastases can be achieved [50]. Resection of the primary tumour should be undertaken in the same manner as outlined above, and it can be combined with concurrent resection of metastatic disease.

16.9.4.3 Debulking of Primary Tumour

Operative tumour debulking, to remove at least 90 % of primary tumour volume, is only possible in 5–15 % of patients [7, 10, 51, 52]. Although there is little evidence to suggest that cytoreductive surgery improves symptoms and survival, it is generally advocated especially since other interventions have low efficacy [4, 7, 51–53].

Some studies have shown that debulking can improve symptoms associated with 'tumour mass', i.e. pain and vomiting, with up to half of patients reporting benefit for a mean duration of 39 months, compared to best combination chemotherapy offering a median survival of 26 months [53, 54].

16.9.5 Management of Liver Metastases

Given that most non-functioning somatostatinomas are indolent and present with metastatic deposits, aggressive management of these liver lesions is advocated; hepatectomy should be considered in all cases and can be performed in isolation or in combination with other hepatic interventions (see below). Patients who are deemed unresectable, either due to co-morbidities or diffuse hepatic involvement, may be managed with targeted tissue destruction.

16.9.5.1 Resection of Liver Metastases

Aggressive resection of liver metastases is associated with better long-term outcomes compared with nonoperative intervention, such as hepatic artery embolisation (HAE), radio-frequency ablation or radioactive octreotide [3]. Five-year survival rates of 76 % have been reported following hepatectomy, compared with 50 % for HAE and 26 % for medical therapy [53]. Complete resection of hepatic metastases improves survival threefold compared with incomplete resection [55]. For young, otherwise healthy patients, liver transplantation for widespread hepatic metastatic infiltration should be considered, especially if the patient's symptoms cannot be managed by other therapies [10].

16.9.5.2 Nonoperative Management of Liver Metastases

Several hepatic interventions exist for the management of metastatic disease, but no randomised studies exist comparing the efficacy of any procedure either against each other or against resection [4, 11]. Nonoperative intervention is recommended for palliation in patients who are unsuitable for surgical resection provided they have an otherwise preserved performance status, with disease confined to the liver and a patent portal vein [10, 11]. These techniques are considered particularly relevant for patients with hormone excess who cannot be controlled by any other means [11]. Nonoperative strategies include gel foam embolisation, transhepatic arterial chemoembolisation (TACE), hepatic artery embolisation (HAE) with radioactive microspheres, percutaneous alcohol ablation, radio-frequency ablation and cryoablation.

Clinical response rates following TACE are generally greater than 50 % and are measured by radiographic regression and/or a decrease in serum hormones [11]. No data exist showing superiority of any one of the TACE techniques (bland embolisation, chemoembolisation, embolisation with chemotherapy beads and embolisation using radioisotopes) compared with each other. RFA, Microwave Ablation (MWA) and cryoablation are recommended only in selected patients who have low-volume

disease [10, 11]. All these techniques can be performed either intraoperatively (either combined with resection of primary metastatic disease or during separate laparoscopy) or via a percutaneous approach [10].

16.10 Surveillance

Like most pancreatoduodenal NETs, somatostatinoma has an indolent course compared with pancreatic adenocarcinoma. These tumours therefore generally have a longer overall survival even if untreated [4]. The natural history of the disease is not fully understood, and as such, there are no guidelines for prognosis or surveillance of disease. Generally patient surveillance is advocated, especially when operative resection has occurred. Patients should have their chromogranin A, pancreatic polypeptide and plasma somatostatin levels monitored in addition to periodic cross-sectional imaging of the abdomen [10]. Some clinicians advocate yearly postoperative SRS studies to detect signs of disease recurrence [10].

16.10.1 Tumour Recurrence or Progression

No established guidelines exist for the management of patients with progressive or recurrent disease. Options include reoperation (including debulking for symptom relief from space-occupying lesions or hormonal effects) and systemic chemotherapy. Therapy should be based on the individual's characteristics, site of recurrence and prior therapy [4].

Conclusion

Somatostatinomas are rare neuroendocrine tumours that arise in the pancreas or peripancreatic duodenum. They are a fascinating group of tumours that are poorly understood and relatively unpredictable. These tumours are relatively indolent and present late, often with metastatic disease. Although there is some dispute as to whether functional activity (somatostatinoma syndrome) is required for diagnosis, most tumours are diagnosed histologically on diffuse positive immunoreactivity to somatostatin. An increased awareness of this group of tumours and improved imaging (particularly in the form of SRS and PET scanning) is thought to be related to an increasing incidence of disease.

Operative resection provides the mainstay of treatment for both primary lesions and metastatic disease, with somatostatin analogues, chemotherapy and radionucleotide therapy considered second-line intervention. No randomised control trials for the management of somatostatinomas exist to guide treatment, owing to their rarity and the difficulty with correct preoperative diagnosis. Survival is generally good and certainly much better than for an equivalent pancreatoduodenal adenocarcinoma.

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