Therapeutic management of patients with gastroenteropancreatic neuroendocrine tumours

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Abstract

Patients with neuroendocrine tumours (NETs) are best managed in a specialist centre as part of a multidisciplinary team comprising gastroenterologists, oncologists, endocrinologists, gastrointestinal and hepatopancreaticobiliary surgeons, pathologists, nuclear medicine physicians and technicians, radiologists, specialist nurses, pharmacists, biochemists and dieticians. This should ideally be led by a clinician with experience and interest in NETs. Although the number of medical treatments and clinical trials has increased in the decade, there is still a lack of prospective randomised trials; thus, management is mainly based on limited often single-centre studies, although there are now formal guidelines based on consensus expert opinion. We have outlined the current optimal management of patients with NETs. We have reviewed therapeutic options including surgery, somatostatin analogues and other biotherapies and peptide receptor-targeted therapy. We have discussed the challenge in managing hepatic metastases including hepatic artery embolisation, ablation and orthotopic liver transplant. In addition, we have briefly reviewed the emerging therapies such as the mammalian target of rapamycin and angiogenic inhibitors and the newer somatostatin analogues.

General objectives

In localised cases, cure may be achievable with surgical resection. In some cases with liver metastases, where the primary is resectable, resection of the liver metastases +/- ablation of non-resectable lesions may be considered as a curative approach.

Often neuroendocrine tumours (NETs) have metastases present at the time of diagnosis; therefore, curative resection is usually not possible, and when surgery is undertaken, it can be considered palliative in view of residual disease. Thus, the aim of treatment is to control tumour growth, prolong survival and improve symptoms and quality of life. Treatment choice depends on site of primary, grade of tumour, co-morbidities, patient tolerability and availability of options. Management should be guided by the Consensus Guidelines for Management of NETs, for example those produced by the European Neuroendocrine Tumour Society (ENETS).

In low- and intermediate-grade metastatic midgut NETs, somatostatin analogues are the mainstay of treatment. Until recently, these were only used in functioning midgut NETs with ‘carcinoid syndrome’. However, recent evidence suggests that their use might be extended to non-functioning midgut NETs to prolong progression-free survival (Rinke et al. 2009). If clinical or radiological progression occurs in metastatic midgut patients, options include radio-nuclide therapy (if functional imaging is positive), interferon (IFN), or if hepatic disease is predominant, liver ablative/embolisation/chemoembolisation or liver surgery. For well-differentiated pancreatic NETs, chemotherapy is often the first-line choice of therapy with good evidence of efficacy (Kouvaraki et al. 2004, Turner et al. 2010). Ongoing and recent studies
suggest that biotherapies may have a role for these patients. The algorithm below (Fig. 1) outlines the multitude of choices, which we will discuss in the chapter. Chemotherapy is the first-line treatment for poorly differentiated and high-grade NETs. All therapeutic options should be discussed within a multidisciplinary team.

**Surgery**

**General approach**

Surgical resection is the only curative treatment for NETs. However, few cases are detected early enough to avoid residual disease or liver metastases. Surgery may also be considered in a palliative setting by way of debulking for alleviation of pressure and hormonal or obstructive symptoms. It is also recommended that patients undergoing surgery who are on (or potentially may be prescribed) somatostatin analogues should undergo cholecystectomy due to the predisposition to gallstones with this class of drugs (Norlen et al. 2010).

**Emergency abdominal surgery**

Patients may often present in the emergency situation with intestinal obstruction. Peritumoural fibrosis with midgut NETs can lead to intestinal obstruction by adhesions of intestinal loops or luminal stricture, which may lead to ileus. After emergency laparotomy, the subsequent diagnosis of midgut NET is made on the surgical specimen. Following definitive histopathology, further resection may be required. In the case of midgut NETs, a limited small bowel resection for an obstructing tumour can be followed at a later date by elective surgery to remove further small bowel or nodal disease. However, at emergency laparotomy, the tumour may be deemed unresectable and an intestinal bypass procedure is performed.

Another common emergency situation may arise where patients presenting with appendicitis only have their NETs diagnosed on the surgical specimen after appendectomy is performed. Further management may be required as explained below. Rarely, a hindgut NET may present with large bowel obstruction with emergency resection and Hartmann’s procedure. Similarly, the diagnosis of NET is made on the surgical specimen.

**Stomach**

There are three types of gastric carcinoid that are often found incidentally as polyps during upper gastrointestinal endoscopy: type I associated with hypergastrinaemia, type II associated with Zollinger–Ellison syndrome, and type III. The diagnosis is made on the histology of the surgical specimen. Type I and II are usually cured by simple resection, whereas type III may require more extensive surgery. Type III can also present with symptoms related to the release of hormones such as vasoactive intestinal peptide (VIP) and serotonin (5-HT).

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**Figure 1** Algorithm for the management of patients with NETs (adapted from Ramage et al. (2005)). 5-HIAA, 5-hydroxyindole acetic acid; SSRS, somatostatin receptor scintigraphy; CgA, chromogranin A; STZ, streptozocin; MIBG, metaiodobenzylguanidine; chemoT, chemotherapy; \(^{68}\)Ga-oct PET, \(^{68}\)Ga-DOTA-octreotate positron emission topography.

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syndrome and MEN1 and type III that is sporadic. Management is dependent on the type of gastric NETs as suggested by the ENETS guidelines (Ruszniowski et al. 2006). Type I gastric NETs are associated with hypergastrinaemia and chronic atrophic gastritis. They frequently present incidentally at gastroscopy as multiple polyps resulting from the hypergastrinaemia causing hyperplasia and proliferation of enterochromaffin-like cells (ECL). Endoscopic observation is often all that is required in those with polyps <10 mm in size. The metastatic potential is very low, and in the majority of cases, only annual endoscopic surveillance is required with serial mucosal biopsies done due to the risk of gastric adenocarcinomas developing from intestinal metaplasia (Borch et al. 2005). In larger tumours of 10–20 mm in size, endoscopic ultrasound (EUS) is required to assess depth of invasion, and endoscopic resection is recommended for up to six polyps not involving the muscularis propria. For other patients with polyps over 20 mm, local surgical tumour resection should be considered with antral resection to avoid repeated and chronic gastrin stimulation of gastric ECL cells. This is effective in 80% of type I tumours (Ahlman 1999).

Type II gastric NETs are caused by hypergastrinaemia due to Zollinger–Ellison syndrome almost exclusively in MEN1 (Solcia et al. 1990). These can be more aggressive especially in those >20 mm. Endoscopic or local resection may be required as with type I gastric NETs. Consideration should be taken to search for and resect the gastrin-secreting primary tumour. No clinical study indicates how often annual endoscopic surveillance is recommended with endoscopic (mucosal) resection of polyps over 10 mm.

Type III gastric NETs are more aggressive. Local excision endoscopically or at surgery may be appropriate for lesions <2 cm; however, for larger lesions, the management should be similar to that for gastric adenocarcinomas – partial or total gastrectomy with lymph node dissection. EUS in addition to computed tomography/magnetic resonance imaging (CT/MRI) is important in staging the tumour.

**Midgut NETs**

Surgical resection of midgut NETs depends on how early diagnosis is made since at this time, tumours are usually over 2 cm, have invaded the muscularis propria and have also metastasised to regional lymph nodes. For those with NETs of the distal jejunum–ileum and localised disease, surgery should aim to be curative. Surgery of the primary should adhere to oncological principles and should involve clearance of lymph node metastases aiming to preserve vascular supply and limit intestinal resection (Ahlman et al. 2000, Goede & Winslet 2003). This may be done through an open or laparoscopic approach.

During laparotomy, careful exploration of the abdominal cavity including the entire small intestine should be undertaken in order not to miss a second location, which occurs in up to 30% of cases. There is a lack of positive phase III studies in an adjuvant situation.

In patients with limited liver metastases, curative resection involving removal of the primary, regional lymph nodes and resectable liver metastases is possible in up to 20% of patients (Lehnert & Knaebel 1997, Frilling et al. 1998, Ahlman et al. 2000). Further evidence of surgery for liver metastases is given below.

According to the ENETS Consensus Guidelines, in the presence of unresectable metastases or unresectable small intestinal NET, resection of jejunal–ileal NETs should be considered to prevent intestinal obstruction or ischaemic complications due to the desmoplastic reaction or compression of the mesenteric vein due to tumour mass (Erikkson et al. 2008). Symptoms correlate with tumour mass and a reduction of tumour mass provides symptomatic relief in 70–100% of cases. Surgery should be performed according to oncological criteria and may include resection of nodal metastases with associated desmoplasia. This has been reported to increase survival benefit from 69 to 130 months, but this data includes mostly patients with less extensive disease and various other therapies affecting survival (Soreide et al. 1992, Wangberg et al. 1996). Commonly, the associated desmoplasia may preclude tumour resection, and in these cases, bypass procedures should be undertaken to prevent obstructive symptoms. Palliative or cytoreductive surgery can be considered in patients in whom 90% of the tumour load can be removed safely. This may involve resection of the primary with locoregional metastases or intra-abdominal debulking or synchronous resection of primary and liver metastases (Sarmiento & Que 2003, Steinmuller et al. 2008).

**Colorectum**

Colonic NETs can be aggressive and management is based on surgery similar to colonic adenocarcinomas. Since most invade through the muscularis propria and are >2 cm in diameter, colectomy and oncological resection of lymph drainage is recommended (Ramage et al. 2008). Management differs from adenocarcinomas in invasive or advanced disease where the primary is resected due to obstruction with management of liver
metastases as described below. Removal of primary tumour according to oncological criteria may be indicated to prevent intestinal obstruction or ischaemic complications especially if there is desmoplastic reaction in proximal colonic lesions similar to that of classical midgut NETs.

Rectal NETs often present as polyps incidentally found at endoscopy with low risk of metastases (3%) in those with a diameter <10 mm. Muscularis propria invasion, size and high Ki-67 are indicators of aggressive behaviour. Small lesions <10 mm can be excised at endoscopy or by transanal surgery. Outcome of rectal NETs between 10 and 20 mm is unclear but management should be guided by histology including Ki-67 proliferation index and EUS to assess invasion. In general, those <20 mm with low Ki-67 can be removed by local resection at endoscopy or another transanal method. Larger lesions >20 mm commonly invade the muscularis propria and require total mesorectal excision due to higher metastatic potential (Ramage et al. 2005). Locoregional resection can be considered in metastatic disease to control local symptoms without any impact on survival. Although there is no evidence for adjuvant chemotherapy, this can be contemplated in poorly differentiated tumours with incomplete resection.

Appendix

Diagnosis of appendix NET is often made after histopathological assessment on an appendix resected after acute appendicitis. When the tumour is at the base of appendix, or ≥20 mm diameter, or shows >3 mm mesoappendiceal invasion, or histology suggests goblet cell (adenocarcinoid), a right hemicolectomy (open or laparoscopic) with locoregional lymphadenectomy is usually indicated (Bak & Jørgensen 1987, Moertel et al. 1987, Makridis et al. 1990). Such patients require long-term follow-up. However, prognosis is excellent.

A particular note should be made of mixed endocrine/exocrine tumours of the appendix, so-called goblet cell appendiceal NET, sharing histological properties of both adenocarcinoma and NET, comprising ~6% of appendiceal NETs. They also have a higher metastatic potential with 20% presenting with metastases compared with 2–5% of classical appendiceal NETs with high Ki-67 as a risk factor for metastases (Toumpanakis et al. 2007b). Thus, full staging with CT or MRI should be undertaken. Liver metastases are uncommon and most metastases occur in lymph nodes or through transcoelomic spread to ovaries conferring a poorer overall survival, median 12 months. Therefore, right hemicolectomy is recommended after an appendectomy demonstrating goblet cell appendiceal NET. Chemotherapy in metastatic cases is a moderately effective treatment option, but a clear regimen is yet to be defined (Toumpanakis et al. 2007b).

Pancreas

Historically, non-functioning pancreatic NETs were diagnosed post-operatively on the resection sample. However, typical radiological features of NETs together with EUS and fine needle aspiration now allow a pre-operative diagnosis, which facilitates planning of surgery. Whipple pancreaticoduodenectomy, distal or even total pancreatectomy, may be appropriate in functioning and non-functioning pancreatic NETs. Localised tumours >2 cm should have aggressive surgery and resection of nearby organs if required (Norton et al. 2003). With tumours <2 cm, surgical cure needs to be weighed with postoperative complications and morbidity due to lack of evidence. Small, easily accessible tumours can be treated with enucleation or middle pancreatectomy. The laparoscopic approach may be considered in expert hands for insulinomas and small non-functioning tumours in the body or tail near the surface not in contact with the main duct or vessels or in distal pancreatectomy. Resection of locally advanced non-functioning pancreatic NETs may prolong survival with a 5-year survival up to 80% (Solorzano et al. 2001).

With regard to metastatic non-functioning pancreatic NETs, resection of the primary fails to improve survival but may reduce symptoms in hormonally active primary tumours (Solorzano et al. 2001). Surgery for liver metastases is discussed below.

There is controversy – in patients with MEN1 as they often have multiple small NETs throughout the pancreas and in gastrinoma patients throughout the duodenum. However, fit patients with sporadic gastrinomas with resectable disease should be considered for surgical exploration for cure.

Liver metastases

Since the frequency of liver metastases at the time of diagnosis is high, management decisions have to take this factor into account prior to therapy. Liver surgery includes metastasis enucleation, segmental or wedge resection, hemihepatectomy, or extended hemihepatectomy. Intra-operative ultrasonography is essential in detecting all metastases. Surgery can be proposed in all patients with gastroenteropancreatic-NETs (GEP-NETs) regardless of the site of primary, although
resection with metastatic hindgut NETs is rare. The minimum criteria for liver surgery with ‘curative intent’ are as follows: i) resectable well-differentiated liver disease with acceptable morbidity and <5% mortality, ii) absence of right heart insufficiency, iii) absence of extra-abdominal metastases (previously assessed by CT scan and somatostatin receptor scintigraphy (SRS)) and iv) absence of diffuse peritoneal carcinomatosis (Steinmuller et al. 2008). The primary tumour is also usually deemed resectable (or has been resected previously). If cardiac surgery is required, it should be planned 3 months prior to liver surgery for anticoagulation purposes.

Surgery can be undertaken together with resection of the primary with a curative intent in 10% of cases if confined to one lobe. With bilobar metastases, it may also be undertaken as a cytoreductive procedure to alleviate symptoms of carcinoid syndrome particularly if there is resistance to medical therapy. Radiofrequency ablation (RFA) can be performed either before or during surgery (O’Toole et al. 2003).

With bilobar metastases, the difficulty is achieving adequate tumour resection whilst maintaining sufficient liver function. There are a few options including a two-stage procedure, the first step involving resection of the primary tumour and left liver metastases (+/− RFA) and ligature of the right branch of the portal vein (or embolisation of the right branch of the portal vein). The second step is a right hepatectomy (which can be extended to segments I and IV) 4–6 weeks later after left liver hypertrophy is obtained (Kianmanesh et al. 2008). Other approaches to bilobar liver metastases include repeated hepatectomies or a combination of surgical resection and local ablative methods (Jaeck et al. 2001). Perioperative mortality is <5% in most reports and postoperative 5-year survival rate is 61% or higher (Que et al. 1995, Chen et al. 1998, Pederzoli et al. 1999, Chamberlain et al. 2000, Nave et al. 2001, Sarmiento & Que 2003, Sarmiento et al. 2003) compared with 30–40% reported from non-controlled studies with patients not resected (Wangberg et al. 1996, Sarmiento & Que 2003, Steinmuller et al. 2008).

A small group of patients with bilobar liver metastases without extrahepatic disease can be considered for total tumour hepatectomy with liver transplantation in two situations: i) with the intent to cure or ii) to palliate from life-threatening hormonal disturbances (Blonski et al. 2005, Pfitzmann et al. 2007). In an analysis of all UK transplants for NETs, survival was 62% at 1 year and 23% at 5 years, similar to a study from France. However, these include cases from many years ago with inferior imaging technology to the present day and some cases were undoubtedly transplanted with extrahepatic disease. Various studies have shown good initial outcomes but poor long-term cure rates with very low 5-year disease-free survival (Table 1). Survival is better with metastatic small intestinal NETs compared with metastatic pancreatic NETs. Patients <50 years of age, with low expression of Ki-67 and E-cadherin, are most likely to be benefited (Rosenau et al. 2002, Ahlman et al. 2004). Currently, orthotopic transplant should only be considered in exceptional circumstances with a comprehensive assessment to exclude extrahepatic disease whilst the issues of perioperative morbidity and ethical distribution of donor organs are contemplated.

### Perioperative prophylaxis

When a functioning tumour is diagnosed before surgery, there is a risk of carcinoid crisis when the tumour is operated on. This should be prevented by the

**Table 1** Single-centre studies of patients with liver transplantation for metastatic neuroendocrine tumours (adapted from Steinmuller et al. (2008))

<table>
<thead>
<tr>
<th>Authors</th>
<th>n</th>
<th>Median follow-up (months)</th>
<th>1-year survival (%)</th>
<th>5-year survival (%)</th>
<th>Disease-free survival at 5 years</th>
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<tr>
<td>Dousset et al. (1996)</td>
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<td>29</td>
<td>33</td>
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<td>Anthuber et al. (1996)</td>
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<td>11</td>
<td>25</td>
<td>0</td>
<td>0</td>
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<td>Frilling et al. (1998)</td>
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<td>50</td>
<td>50</td>
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<td>Pascher et al. (2000)</td>
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<td>100</td>
<td>50</td>
<td>1</td>
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<td>Ringe et al. (2001)</td>
<td>5</td>
<td>22</td>
<td>80</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>Coppa et al. (2001)</td>
<td>9</td>
<td>39</td>
<td>100</td>
<td>70</td>
<td>–</td>
</tr>
<tr>
<td>Rosenau et al. (2002)</td>
<td>19</td>
<td>38</td>
<td>89</td>
<td>80</td>
<td>3</td>
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<tr>
<td>Florman et al. (2004)</td>
<td>11</td>
<td>30</td>
<td>36</td>
<td>36</td>
<td>1</td>
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<tr>
<td>Frilling et al. (2006)</td>
<td>15</td>
<td>61</td>
<td>78</td>
<td>67</td>
<td>0</td>
</tr>
<tr>
<td>van Vilsteren et al. (2006)</td>
<td>19</td>
<td>22</td>
<td>88</td>
<td>–</td>
<td>2</td>
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<tr>
<td>Olaussen et al. (2007)</td>
<td>10</td>
<td>67</td>
<td>95</td>
<td>90</td>
<td>2</td>
</tr>
<tr>
<td>Bonaccorsi-Riani et al. (2010)</td>
<td>9</td>
<td>68</td>
<td>88</td>
<td>33</td>
<td>1</td>
</tr>
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</table>
administration of continuous i.v. octreotide at a dose of 50 µg/h for 12 h prior to and at least 48 h after surgery (Roy et al. 1987). Boluses of 100–200 µg octreotide can be given as required. It is also important to avoid drugs that release histamine or activate the sympathetic nervous system (Dougherty & Cronau 1998). Similarly, prophylaxis with glucose infusion for insulinoma surgery, proton pump-inhibitor and octreotide for gastrinomas may be required.

**Biotherapy**

**Somatostatin analogues**

The foundation of current NET therapy, especially in functional midgut NETs, is based on the long-acting somatostatin analogues. They act to alleviate symptoms in carcinoid syndrome, stabilise tumour growth and improve quality of life.

There are at least five subtypes of the somatostatin receptor (sst1–5), a G-protein-coupled membrane receptor to which native somatostatin peptides bind with high affinity (Nilsson et al. 1998). SSTRs, predominantly sst5, are present in the majority of NETs (70–95%) but in only half of insulinomas and less in poorly differentiated NETs and somatostatinomas (Patel et al. 1995, Kulaksiz et al. 2002). As a result of ligand activation, there is inhibition of the release of many hormones and impairment of hormonally mediated exocrine function. By this mechanism, somatostatin analogues prevent spontaneous and provoked flushing and secretory diarrhoea in patients with carcinoid syndrome (Thulin et al. 1978, Kvols et al. 1986).

The elimination half-life of natural somatostatin peptides is only a few minutes, which necessitated the need for a synthetic agent, octreotide, with a half-life of several hours, and a high affinity for sst2 and sst5. It is administered by s.c. injection or i.v. infusion with s.c. dosing starting at 50–100 µg two to three times daily to a maximum daily dose of 3000 µg (Bax et al. 1996). Other short-acting somatostatin analogues include lanreotide (Taylor et al. 1988). In a prospective crossover study, no differences in symptom control or biochemical response were seen between octreotide and lanreotide (O’Toole et al. 2000). Short-acting somatostatin analogues are used in testing patient tolerability, immediate relief of carcinoid syndromic symptoms and stabilisation of symptoms for 10–14 days before converting to long-acting therapy (Oberg et al. 2009). It is also used in rescue therapy when carcinoid syndrome symptoms occur despite long-acting analogues and also perioperatively to prevent and treat carcinoid crises by either s.c. or i.v. routes (Kvols et al. 1985). However, the mainstay of NET therapy is in the form of long-acting somatostatin analogues, a summary of studies of which are shown in Table 2. The development of long-acting depot formulations, octreotide LAR and lanreotide Autogel, has allowed clinically practical administration of these drugs by i.m. and deep s.c. routes every 28 days. Biochemical response rates with an inhibition of hormone production are seen in 30–70% with symptom control in the majority of patients (Tomassetti et al. 1998, 2000, Ricci et al. 2000b, Garland et al. 2003, Ruszniewski et al. 2004, Bajetta et al. 2006, Toumpanakis et al. 2009). Escalation of dose is often required over time for symptom control due to poorly understood ‘tachyphylaxis’. Minor differences may exist between long-acting octreotide and long-acting lanreotide but it has been demonstrated that tumours refractory to one analogue may respond to the treatment of another (Raderer et al. 2001). When symptoms recur on somatostatin analogue therapy, options include dose escalation, a reduction in interval between administration, switching to an alternate somatostatin analogue or other therapy as stated below.

Recently, it has been confirmed that somatostatin analogues have a role in non-functioning small intestinal tumours. Data derived from the PROMID phase III study has shown that long-term administration of octreotide LAR inhibits tumour growth in midgut NETs with low-volume metastatic disease, with time to progression twice as long as the placebo arm (Rinke et al. 2009). Tumour growth inhibition is more likely in midgut compared with foregut tumours (Aparicio et al. 2001, Faiss et al. 2003), but the results of lanreotide autogel in non-functioning pancreatic NETs are awaited.

Other benefits of somatostatin analogues may include prevention of the advancement of carcinoid heart disease and intestinal fibrosis but studies are conflicting (Modlin et al. 2004).

Few side effects have been reported with somatostatin analogues and these include fat malabsorption, gallstones, gall bladder dysfunction, vitamins A and D malabsorption, headaches, diarrhoea, dizziness and hypo- and hyperglycaemia (Buchanan et al. 1990, Tomassetti et al. 1998, O’Toole et al. 2000, Toumpanakis et al. 2009).

**Interferon-α**

IFN-α was introduced as a treatment for GEP-NETs in the early 1980s and exerts an anti-proliferation and anti-secretory effect. As well as inhibition of tumour
cell cycle progression, it has anti-angiogenic properties (Detjen et al. 2000, 2002). The usual dose employed is 3–5 million units subcutaneously, three to five times a week. Symptomatic and biochemical responses have been noted in ~50% of patients with disease stabilisation in 60–80% at a follow-up of 4 years. However, significant tumour reduction only occurs in 10–15% (Oberg et al. 1986, Oberg 2000). Limitations in use of IFN include its side effects that include flu-like symptoms, bone marrow suppression, thyroid disorders, psychiatric phenomenon and chronic fatigue syndrome. Therefore, it may be considered as second-line therapy. It has been suggested that patients not responding to either somatostatin analogues or IFN-α alone may show an improved response with inhibition of tumour growth and prolonged survival with the combination treatment of those two agents. However, prospective, randomised trials have not demonstrated any benefit (Frank et al. 1999, Faiss et al. 2003, Arnold et al. 2005). More recently, the longer acting weekly pegylated IFNs have been used with anecdotally at least similar efficacy, and IFN-γ has been tested in phase II studies with similar effect (Stuart et al. 2004). Studies including IFN in NETs are shown in Table 3.

### Specific treatment of rare functioning tumours

VIPomas (Werner Morrison syndrome) are often treated with rehydration, which may improve the clinical condition considerably. Patients with this rare syndrome may respond dramatically with use of somatostatin analogues that alleviates diarrhoea in 80–90% of cases and reduction of VIP in 60–80% (Soga & Yakuwa 1998, Nikou et al. 2005). Some extreme cases may require long-term parenteral fluid and electrolyte replacement at home, with regular electrolyte monitoring, analogous to fluid replacement in short-bowel syndrome.

Patients with glucagonomas also respond to somatostatin analogues with good biochemical and symptomatic response including improvement of the characteristic rash of necrolytic migratory erythema (O’Toole et al. 2006a).

Acid hypersecretion with gastrinomas causing peptic ulceration and dyspepsia is usually well controlled with high-dose proton pump inhibitors or to a lesser extent high dose H2-blockers. Somatostatin analogues may be used if resistance to proton pump inhibitors (PPIs) develop (Saijo et al. 2003).

### Table 2 Clinical studies on the efficacy of different long-acting somatostatin analogues (adapted from Modlin et al. (2010))

<table>
<thead>
<tr>
<th>Authors</th>
<th>n</th>
<th>SSA</th>
<th>Dose</th>
<th>Symptomatic response (%)</th>
<th>Tumour response (%)</th>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CR</td>
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<tr>
<td>Scherubl et al. (1994)</td>
<td>12</td>
<td>LAN depot</td>
<td>30 mg q 7–14 days</td>
<td>85.7 (flush)</td>
<td>0</td>
</tr>
<tr>
<td>Ruszniewski et al. (1996)</td>
<td>39</td>
<td>LAN SR</td>
<td>30 mg q 14 days</td>
<td>41.7 (diarrhoea)</td>
<td>54 (flush)</td>
</tr>
<tr>
<td>Tomassetti et al. (1998)</td>
<td>18 (10 CT, 5 NF)</td>
<td>LAN SR</td>
<td>30 mg q 10 days</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Wymenga et al. (1999)</td>
<td>55 (48 CT)</td>
<td>LAN SR</td>
<td>30 mg q 14 days</td>
<td>53.8 (flush)</td>
<td>6</td>
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<tr>
<td>Rubin et al. (1999)</td>
<td>18</td>
<td>OCT LAR</td>
<td>10</td>
<td>42.1 (diarrhoea)</td>
<td>66.7</td>
</tr>
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<td>Ricci et al. (2000)a</td>
<td>15 (7 CT, 8 EPT)</td>
<td>OCT LAR</td>
<td>20 mg q 28 days</td>
<td>75</td>
<td>0</td>
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<tr>
<td>Tomassetti et al. (2000)</td>
<td>16 (10 CT)</td>
<td>OCT LAR</td>
<td>20 mg q 28 days</td>
<td>87.5 (flush)</td>
<td>0</td>
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<td>Garland et al. (2003)</td>
<td>27</td>
<td>OCT LAR</td>
<td>20–30 mg q 28 days</td>
<td>77 (prior s.c. OCT)</td>
<td>92.8 (OCT-naïve)</td>
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<td>Ruszniewski et al. (2004)</td>
<td>71</td>
<td>LAN PR</td>
<td>60–120 mg q 28 days</td>
<td>38: 65/81b (flush)</td>
<td>18/75b (diarrhoea)</td>
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<td>Bajetta et al. (2006)</td>
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<td>LAN MP</td>
<td>60 mg q 21 days</td>
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<tr>
<td>30</td>
<td>LAN AG</td>
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<td>67.9</td>
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<td>Toumpanakis et al. (2009)</td>
<td>108</td>
<td>OCT LAR</td>
<td>10–30 mg q 28 days</td>
<td>100 (24 sustained)</td>
<td>0</td>
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</tbody>
</table>

SSA, somatostatin analogue; CT, carcinoid tumour; EPT, endocrine pancreatic tumour; NF, non-functioning. Formulation: OCT, octreotide; LAN, lanreotide; SR, sustained release; PR, prolonged release; MP, microparticles; AG, autogel tumour response. Tumour response: CR, complete response; PR, partial response; SD, stable disease.

aAfter failure of lanreotide.
bAny improvement from baseline at the end of study.
cPrior treatment with octreotide in 15 patients.
In insulinoma patients, diazoxide is often used as a first-line drug and is effective in controlling hypoglycaemic symptoms by inhibiting the release of insulin from normal B cells, but with common side effects such as hirsutism and fluid retention, its use should only be considered short term or in patients that are unsuitable for surgery or not cured by surgery. Only half of the insulinomas express sst2 and thus not all benefit from somatostatin analogues. However, if somatostatin receptor scintigraphy (SSRS) is positive, then somatostatin analogues can be beneficial for symptom control.

Systemic chemotherapy (see below) may be used for progressive metastatic rare functioning tumours with combinations of streptozocin (STZ) and 5-fluorouracil (5-FU) (or capecitabine) and/or doxorubicin (DOX; Delaunoit et al. 2004, Kouvaraki et al. 2004). There is limited experience with peptide receptor radionuclide therapy (PRRT) in the treatment of rare functioning tumours. However, its efficacy in other advanced pancreatic NETs with positive SSRS has been demonstrated (Waldherr et al. 2002, Kwekkeboom et al. 2005).

### Chemotherapy

Systemic chemotherapy is widely used, but its precise role is not known due to studies including various grades, sites and inconsistent response criteria. Thus, there is no standard regimen. Systemic chemotherapy has been the standard treatment for pancreatic NETs based on the data from Moertel et al. (1992) with an objective response of 69%. This study used one of the first combinations with STZ and 5-FU. This group also demonstrated that the combination of STZ and DOX may be better than STZ/FU with a major response rate of 69 vs 45%, respectively, but this was not confirmed in later studies, which demonstrates problems with comparing studies. The main indication for STZ + 5-FU or DOX includes well-differentiated malignant pancreatic NETs. STZ-based combinations in pancreatic NETs may help control symptoms and achieve tumour response in ~40%. A recent study (n = 79) combined 5-FU, cisplatin and STZ (FCiSt) in chemo-naive patients with metastatic or locally advanced NETs (Turner et al. 2010). Response rates were 38% for pancreatic and 25% for non-pancreatic sites with median time to progression 9.1 months and median overall survival 31.5 months with an acceptable toxicity profile and an advantageous 1-day outpatient administration.

It is difficult to assess whether subgroups of pancreatic NETs respond differentially due to small numbers, inconsistent assessment criteria and variable regimens amongst studies. Response rates treating pancreatic islet cell tumours with 5-FU, STZ and adriamycin vary between 40 and 70% (Bajetta et al. 2002). However, in another study, none of the 11 patients with gastrinomas responded to STZ/FU/DOX whilst four of the nine (44%) patients with other functioning tumours responded according to RECIST criteria (Kouvaraki et al. 2004). Similarly, a failure of major objective response was reported retrospectively with STZ and DOX in islet cell carcinomas (Cheng & Saltz 1999).

The use of chemotherapy in midgut and hindgut NETs has a much lower response rate, with <20% of patients deriving benefit, which may only last 6–8 months with STZ/FU/DOX, cyclophosphamide

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### Table 3 Summary of interferon studies (adapted from Plockinger & Wiedenmann (2007))

<table>
<thead>
<tr>
<th>Authors</th>
<th>Interferon</th>
<th>n</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith et al. (1987)</td>
<td>rIFN-α 2b</td>
<td>14</td>
<td>–</td>
<td>–</td>
<td>10</td>
<td>NI</td>
</tr>
<tr>
<td>Moertel et al. (1989)</td>
<td>rIFN-α</td>
<td>20</td>
<td>–</td>
<td>4</td>
<td>NI</td>
<td>NI</td>
</tr>
<tr>
<td>Oberg et al. (1989)</td>
<td>rIFN-α 2b</td>
<td>17</td>
<td>–</td>
<td>–</td>
<td>16</td>
<td>NI</td>
</tr>
<tr>
<td>Doberauer et al. (1991)</td>
<td>IFN</td>
<td>14</td>
<td>–</td>
<td>–</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Oberg &amp; Eriksson (1991)</td>
<td>hIFN/rIFN-α</td>
<td>111</td>
<td>–</td>
<td>16</td>
<td>74</td>
<td>21</td>
</tr>
<tr>
<td>Tiensuu Janson et al. (1992)</td>
<td>IFN-α</td>
<td>20</td>
<td>–</td>
<td>–</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>Janson et al. (1992)</td>
<td>rIFN-α</td>
<td>12</td>
<td>–</td>
<td>2</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Schober et al. (1992)</td>
<td>rIFN-α 2b</td>
<td>26</td>
<td>–</td>
<td>4</td>
<td>17</td>
<td>NI</td>
</tr>
<tr>
<td>Jacobson et al. (1995)</td>
<td>rIFN-α 2b</td>
<td>25</td>
<td>–</td>
<td>–</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>Dirix et al. (1996)</td>
<td>IFN-α</td>
<td>15</td>
<td>–</td>
<td>3</td>
<td>NI</td>
<td>NI</td>
</tr>
<tr>
<td>Stuart et al. (2004)</td>
<td>IFN-γ</td>
<td>48</td>
<td>–</td>
<td>3</td>
<td>28</td>
<td>15</td>
</tr>
</tbody>
</table>

Total 274 29/274 166/239 41/182

IFN, interferon; rIFN, recombinant interferon; hIFN, human leucocyte interferon; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NI, interferon neutralising antibodies.
regimens (Engstrom et al. 1984, Bukowski et al. 1987a, O’Toole et al. 2004). The alkylating agent temozolomide, in combination with thalidomide in a phase II trial, induced a response rate of 25% with median duration of response 13.5 months (Kulke et al. 2008). A more recent retrospective analysis found that temozolomide monotherapy achieved radiological response in 14% and stable disease in 53% (Ekeblad et al. 2007). It is generally well tolerated with minimal side effects including leucopenia, nausea and abdominal pain. Its response rate and duration of effect are similar to those of other established regimens.

Tumours with a low expression of O-6-methylguanine DNA methyltransferase – a DNA repair enzyme thought to induce resistance to O-6-alkylating agents – have better response to temozolomide (Hegi et al. 2004). Poorly differentiated or anaplastic NETs are more aggressive, and etoposide and cisplatin combinations have been used to induce response rates of over 50% albeit with short median survival rates and significant toxicity (Moertel et al. 1992, Mitry et al. 1999). The efficacy of combination regimens in various NETs are summarised in Table 4.

### Peptide receptor radionuclide therapy

PRRT involves directing radioactivity internally to the tumour site delivered by a radionuclide coupled to a tumour-targeting molecule with or without a chelating agent for stability. This often involves substitution of the γ-emitting diagnostic imaging radionuclide by a therapeutic β (Auger)-emitting therapy radionuclide, e.g. 131I-MIBG instead of 123I-MIBG, 90Y or 177Lu instead of 111In-octreotide or 68Ga-octreotate. They are generally reserved for those tumours expressing the receptor of interest on nuclear medicine imaging with avid uptake of 123I-MIBG or 111In-octreotide scintigraphy (or, e.g. 68Ga-octreotate positron emission topography (PET)). The aim of radionuclide therapy is to induce DNA damage to target cells resulting in apoptosis together with damage of tumour cells by spread of radiation or toxic metabolites.

Current evidence for PRRT mainly comes from non-blinded, non-randomised trials with varying activities and protocols. Bone metastases may indicate bone marrow infiltration and if treated, there is a risk of bone marrow suppression. Practical constraints apply when

### Table 4 Response rate for combination of cytotoxic agents for metastatic neuroendocrine tumours (adapted from Toumpanakis et al. (2007a))

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of tumour</th>
<th>Regimen</th>
<th>n</th>
<th>Objective response (%)</th>
<th>Response duration (months)</th>
<th>Median survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moertel &amp; Hanley (1979)</td>
<td>Midgut</td>
<td>5FU + cyclophosphamide</td>
<td>47</td>
<td>26</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Moertel et al. (1980)</td>
<td>Pancreatic</td>
<td>STZ + 5FU</td>
<td>42</td>
<td>33</td>
<td>17</td>
<td>16.5</td>
</tr>
<tr>
<td>Engstrom et al. (1984)</td>
<td>Midgut</td>
<td>STZ</td>
<td>42</td>
<td>63</td>
<td>16</td>
<td>26</td>
</tr>
<tr>
<td>Bukowski et al. (1987a)</td>
<td>Pancreatic</td>
<td>CTZ + 5FU</td>
<td>44</td>
<td>36</td>
<td>11</td>
<td>-</td>
</tr>
<tr>
<td>Bukowski et al. (1987b)</td>
<td>Midgut</td>
<td>STZ + DOX + 5FU + cyclophosphamide</td>
<td>56</td>
<td>31</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Eriksson et al. (1990)</td>
<td>Pancreatic</td>
<td>STZ + 5FU or DOX</td>
<td>44</td>
<td>45</td>
<td>27.5</td>
<td>-</td>
</tr>
<tr>
<td>Moertel et al. (1991a)</td>
<td>Poorly differentiated</td>
<td>Cisplatin + etoposide</td>
<td>18</td>
<td>67</td>
<td>8</td>
<td>19</td>
</tr>
<tr>
<td>Moertel et al. (1992)</td>
<td>Pancreatic</td>
<td>STZ + DOX</td>
<td>36</td>
<td>69</td>
<td>18</td>
<td>26</td>
</tr>
<tr>
<td>Mitry et al. (1999)</td>
<td>Poorly differentiated</td>
<td>Cisplatin + etoposide</td>
<td>41</td>
<td>42</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>Cheng &amp; Saltz (1999)</td>
<td>Pancreatic</td>
<td>STZ + DOX</td>
<td>16</td>
<td>6</td>
<td>18</td>
<td>-</td>
</tr>
<tr>
<td>Hou et al. (2003)</td>
<td>Poorly differentiated</td>
<td>Irinotecan + etoposide</td>
<td>14</td>
<td>43</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>McCollum et al. (2004)</td>
<td>Pancreatic</td>
<td>STZ + DOX</td>
<td>16</td>
<td>6</td>
<td>3.9</td>
<td>20.2</td>
</tr>
<tr>
<td>Kouvaraki et al. (2004)</td>
<td>Pancreatic</td>
<td>STZ + DOX + 5FU</td>
<td>84</td>
<td>39</td>
<td>9.3</td>
<td>40</td>
</tr>
<tr>
<td>Sun et al. (2005)</td>
<td>Midgut</td>
<td>DOX + 5FU</td>
<td>25</td>
<td>15.9</td>
<td>4.5</td>
<td>15.7</td>
</tr>
<tr>
<td>Ekeblad et al. (2007)</td>
<td>Pancreatic</td>
<td>Temozolomide</td>
<td>12</td>
<td>8</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Turner et al. (2010)</td>
<td>Various</td>
<td>5FU + STZ + cisplatin</td>
<td>79</td>
<td>33</td>
<td>9.1</td>
<td>31.5</td>
</tr>
</tbody>
</table>

STZ, streptozocin; 5FU, 5-fluorouracil; DOX, doxorubicin.
considering patients for PRRT as they may require a period of admission in relative isolation. Therefore, treating patients who have a high dependency on nursing or daily care may not be appropriate. Proposed selection criteria are shown in Table 5. Long-acting somatostatin analogues should ideally be stopped 6 weeks prior to radiolabelled-somatostatin analogue therapy. A summary of 90Y and 177Lu studies is shown in Table 6.

### 131I-MIBG therapy

Phaeochromocytomas, paragangliomas together with some predominantly midgut gastroenteropancreatic NETs and medullary thyroid carcinomas selectively concentrate meta-iodobenzylguanidine (MIBG) via VMAT1 and VMAT2 (Ahlman 2006). If a tumour or metastasis is MIBG avid on 123I-MIBG imaging, patients may benefit from 131I-labelled MIBG therapy. In the UK, prescribed activities vary from 5.5 to 11.2 GBq administered at 3–6 monthly intervals with a wide range of cumulative activities. Potassium iodide/iodate thyroid blockade is given pre-treatment to prevent thyroidal uptake of free radioiodine. Although treatment is not curative, this study has shown ~80% symptomatic improvement with 5-year survival of ~50% (Bomanji et al. 1993, Mukherjee et al. 2001). However, most studies were retrospective and did not have a control group. Treatment is well tolerated with

### Table 5 Patient selection criteria for peptide receptor radionuclide therapy

<table>
<thead>
<tr>
<th>Indications and inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inoperable/metastatic NET with clinically or radiologically progressive disease</td>
</tr>
<tr>
<td>Good performance status: self-caring</td>
</tr>
<tr>
<td>Radiopharmaceutical uptake at all known tumour sites</td>
</tr>
<tr>
<td>Minimum haematological and biochemical criteria</td>
</tr>
<tr>
<td>Haemoglobin &gt; 10 g/L</td>
</tr>
<tr>
<td>White cell count 3 × 10⁹/L</td>
</tr>
<tr>
<td>Platelets &gt; 100 × 10⁹/L</td>
</tr>
<tr>
<td>Urea &lt; 10 mM/L</td>
</tr>
<tr>
<td>Creatinine &lt; 160 μM/L</td>
</tr>
<tr>
<td>GFR &gt; 40 mL/min</td>
</tr>
<tr>
<td>Absolute contraindications</td>
</tr>
<tr>
<td>Pregnancy/lactation</td>
</tr>
<tr>
<td>Inability to comply with radiation protection instructions</td>
</tr>
<tr>
<td>Unmanageable urinary incontinence</td>
</tr>
<tr>
<td>Precautions</td>
</tr>
<tr>
<td>Myelosuppression</td>
</tr>
<tr>
<td>Bone marrow metastases</td>
</tr>
<tr>
<td>Renal impairment</td>
</tr>
<tr>
<td>Extensive hepatic involvement</td>
</tr>
<tr>
<td>Chemotherapy in preceding 6 weeks</td>
</tr>
<tr>
<td>Poor performance status/not self-caring</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reference</th>
<th>90Y-DOTATOC</th>
<th>90Y-lanreotide</th>
<th>90Y-DOTATATE</th>
<th>177Lu-DOTATATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Otte et al. (1999)</td>
<td>29</td>
<td>0</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Waldherr et al. (2002)</td>
<td>39</td>
<td>5</td>
<td>18</td>
<td>–</td>
</tr>
<tr>
<td>Valkema et al. (2002)</td>
<td>52</td>
<td>0</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Virgolini et al. (2002)</td>
<td>39</td>
<td>0</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Baum et al. (2003)</td>
<td>75</td>
<td>0</td>
<td>37</td>
<td>–</td>
</tr>
<tr>
<td>Cwikla et al. (2010)</td>
<td>60</td>
<td>0</td>
<td>23</td>
<td>–</td>
</tr>
<tr>
<td>Toumpanakis et al. (2010)</td>
<td>82</td>
<td>0</td>
<td>10</td>
<td>–</td>
</tr>
<tr>
<td>Kwekkeboom et al. (2008)</td>
<td>310</td>
<td>2</td>
<td>28</td>
<td>16</td>
</tr>
</tbody>
</table>

CR, complete response; PR, partial response; MR, minor response; SD, stable disease; PD, progressive disease; DOTATOC, DOTA-D-Phe-Tyr³-octreotide; DOTATATE, DOTA-Ø-Tyr³-octreotate.
mild nausea and vomiting reported initially and temporary myelosuppression at 4–6 weeks after treatment (Pathirana et al. 2001). This warrants post-therapy blood testing weekly for 8 weeks and fortnightly thereafter.

**90Y-octreotide therapy**

There has been increasing use of DOTA-D-Phe-Tyr3-octreotide (DOTATOC) labelled with yttrium. Usual cumulative activities range from 9 to 18 GBq administered in 3–6 GBq fractions at 8–12 weekly intervals. Most patients have reported subjective improvement after two fractions. Non-blinded studies with either historical or no controls have found that the majority of patients achieve tumour stabilisation from progressive disease but only 10–24% achieving partial response (de Jong et al. 1999, Krenning et al. 2000, Waldherr et al. 2002). Toxicity includes myelosuppression, particularly lymphopenia, and nephrotoxicity (Cybulla et al. 2001, Schumacher et al. 2002). Pretreatment with amino acids, particularly L-lysine, reduces tubular octreotide binding and minimises renal damage (Schumacher et al. 2002).

**177Lu-DOTA-octreotide therapy**

[DOTA0, D-Phe1, Tyr3]-octreotate (DOTATATE) labelled with lutetium has higher affinity for sst2 receptors due to the binding affinity of octreotide. 177Lu has a lower tissue penetration than 90Y allowing higher absorbed doses to smaller tumours. In the largest study to date (n = 504), patients received cumulative activities of 27.8–29.6 GBq in 4.7–7.4 GBq fractions at intervals of 6–10 weeks. Partial response was seen in 28%, complete remission in 2%, with median time to progression 40 months, and a survival benefit of 40–72% for those with multiple non-resectable and small metastases, often present in NETs. Although numbers are small with limited follow up, two-thirds have achieved partial response (Seregni et al. 2010).

**90Y-lanreotide therapy**

Experience with DOTA-lanreotide (DOTALAN) labelled with yttrium is limited as 111In-lanreotide imaging is required to ensure radionuclide uptake. A European multicentre study found partial response of 14% and stable disease in 41% of 154 patients with progressive disease (Virgolini et al. 2002). Over 3 years of follow up, 20.5% had tumour regression and 43.6% had stable disease.

**Other symptomatic treatment**

Cyproheptadine is now considered a historic treatment for carcinoid syndrome but may be used occasionally with good effect (Moertel et al. 1991b). Ondansetron is useful for general symptom control in carcinoid syndrome. Pancreatic enzyme supplementation with meals and snacks is useful in for pancreatic insufficiency caused by somatostatin analogues or as a result of pancreatic resection may be beneficial (Gullo 1996). This may ease steatorrhoea and help weight gain. Similarly, cholestyramine for bile salt malabsorption after intestinal resection may control diarrhoea. Vitamin B supplementation is recommended to prevent pellagra from increased conversion of tryptophan to serotonin.

Zinc therapy can be used to prevent further skin lesions in glucagonoma, and prophylactic anticoagulation with low molecular weight heparin may be of some benefit in small vessel mesenteric ischaemia caused by desmoplasia.

**Emboliisation and ablative methods**

With many patients having multiple liver metastases at diagnosis, embolisation of a hepatic artery branch is performed for those with multiple non-resectable and hormone-secreting tumours. The intention is to reduce disease who failed other therapies, thus PRRT as second- or third-line agent, demonstrates 10% partial response, 68% achieving stable disease and 22% progressive disease (Toumpanakis et al. 2010). Alternating this radionuclide with the lutetium-based molecule has been used in treating 26 patients in a recent study. The rationale behind this is alternating the long-range β-emitting yttrium molecule with the shorter range β-emitting lutetium molecule may deliver killing radiation therapy to both large and small metastases, often present in NETs. Although numbers are small with limited follow up, two-thirds have achieved partial response (Seregni et al. 2010).
tumour bulk and thus hormone output, which may improve quality of life and survival. It can be effective in both symptom control and as an anti-proliferative treatment.

Symptomatic response is achieved in 40–80%, biochemical response in 50–60% with overall 5-year survival, and 50–60% post-embolisation (Eriksson et al. 1998, Brown et al. 1999, Dominguez et al. 1999, 2000, Kim et al. 1999, Yao et al. 2001, Roche et al. 2003, Marrache et al. 2007, Sward et al. 2009). The mechanism is to induce ischaemia in tumour cells, thus reducing their hormone output. There are two types: particle and chemoembolisation. Obliterating agents include polyvinyl chloride and gel-foam powder. It appears that ischaemia may increase the sensitivity to chemotherapeutic agents, hence the rationale behind transarterial chemoembolisation utilising concomitant DOX or cisplatin (Drougas et al. 1998). Contraindications to embolisation include complete portal vein obstruction, hepatic insufficiency, biliary reconstruction and severe carcinoid heart disease. Only one lobe should be embolised per session and portal vein patency should be confirmed prior to embolisation. Mortality has been quoted as 2–6% with adverse events in 8–17%, the most common being post-embolisation syndrome (nausea, fever and abdominal pain). Rates are improved in more recent studies.

Octreotide therapy should be used prophylactically as with perioperative prophylaxis in syndromic patients. Some units use prophylactic antibiotics and allopurinol pre-dosing to prevent tumour lysis syndrome. Adequate hydration and analgesics are recommended (Clouse et al. 1994).

Selective internal radiotherapy/microspheres

Selective internal radiotherapy (SIRT) using resin microspheres labelled with $^{90}$Y is mechanistically a combination of embolisation and radionuclide therapy targeting unresectable liver metastases and some recent studies have shown promising results (Kalinowski et al. 2009). These $^{90}$Y-labelled microspheres are infused into the hepatic artery, which results in high dose radiation being selectively delivered to metastases with sparing of neighbouring normal liver parenchyma. A prospective trial of SIRT with systemic 5-FU achieved symptomatic response in 55%, partial response in 32% and an overall survival of 30% (King et al. 2008). A large retrospective study achieved partial response in 61% and stable disease in 23%. It is possibly more tolerable than the above embolisation procedures.

Radiofrequency ablation

RFA has been used in reducing tumour size in liver metastases from colorectal cancers and in hepatocellular cancer. Randomised trials are lacking in NET metastases but studies indicate that patients with bilobar metastases less than five in number with diameter $<$ 5 cm may be benefitted in terms of relief from the symptoms of NET liver metastases and in achieving local control of the metastases. It may also be considered in combination with resection with a better survival rate than with RFA alone (Abdalla et al. 2004).

RFA is a low-risk procedure with a mortality rate of 0.5% in a study of 608 cases with liver metastases from multiple tumour types (Nave et al. 2001). Through the percutaneous or laparoscopic approach, RFA can reduce hormone secretion and reduce tumour burden. However NETs, in comparison to colorectal cancer metastases, often have multiple tiny metastases and destruction of the largest lesion may not reduce hormone secretion. It may thus be necessary to ablate at least 90% of visible tumour (Skogseid et al. 1998, Siperstein & Berber 2001).

In one large study, 34 patients with a total of 234 NET metastases were treated with RFA (Berber et al. 2002). Eighty per cent experienced complete or significant relief from symptoms lasting an average of 10 months and 41% showed no evidence of progression. Another study found similar results with 69% demonstrating relief from tumour-related symptoms (Gillams et al. 2005). One must bear in mind, however, that it becomes increasingly difficult to fully eradicate tumours $>$ 3 cm.

Bone metastases

Bone metastases may be treated with bisphosphonates and palliative radiotherapy for pain control. Radionuclide therapy may be considered for intractable pain due to bone metastases but caution should be taken in view of the increased risk of myelosuppression. When vertebral metastases result in spinal cord compression, radiotherapy and surgical therapy should be considered (Arnold et al. 2010).

Emerging therapies

Tyrosine kinase and angiogenesis inhibitors

The tyrosine kinase receptor family comprises $\sim$ 20 different classes including platelet-derived growth factor receptors (PDGFRs), c-kit and epidermal growth factor receptor (EGFR). Targeting PDGFR/c-kit, for example, using agents that are used in acute
myelogenous leukaemia such as imatinib mesylate, has been disappointing. Sunitinib, an oral tyrosine kinase inhibitor with action against all VEGFR, PDGFR, stem cell factor receptor and FMS-like tyrosine kinase-3, has shown some promise in phase II studies (Kulke et al. 2008). One hundred and seven patients received sunitinib with 16.7% of pancreatic NETs achieving objective response, 68% achieving stable disease; median time to progression 7.7 months in pancreatic NETs, 10.2 months in midgut NETs. The recent phase III study of sunitinib versus placebo in slowly progressing pancreatic NETs (n=171) was halted due to the interim analysis showing significant benefit with progression-free survival (PFS) of 11.4 months with Sunitinib versus 5.5 months with placebo (Raymond et al. 2011).

Sorafenib, a small molecule inhibitor of Raf kinase, VEGFR-2 and PDGFR tyrosine kinase domains, has been explored in metastatic NETs with 10% partial response and 29% minor response in 41 patients. However, 43% in this study developed grade 3–4 toxicity (Hobday et al. 2007).

NETs are highly vascular and express vascular endothelial growth factor (VEGF), a promoter of angiogenesis. A small phase II study looking at octreotide and bevacizumab versus octreotide and PEG-IFN found that 18% (n=4) in the bevacizumab arm had partial response and 95% PFS at 18 weeks compared with one partial response and 68% PFS at 18 weeks in the IFN arm (Yao et al. 2008). A phase II study looking bevacizumab and temozolomide has also shown promising results (Kulke et al. 2006).

Mammalian target of rapamycin inhibitors

Mammalian target of rapamycin (mTOR) is a threonine kinase and part of the phosphatidylinositol-3-kinase/AKT/mTOR pathway, which is crucial in regulation of cell survival and proliferation. It also mediates signalling downstream to growth factor receptors including IGF receptor and EGFR. It has been shown that mTOR has a role to play in islet cell tumours in patients with tuberous sclerosis as well as in sporadic NETs (Eledrisi et al. 2002). Rapamycin and RAD001, inhibitors of mTOR, lead to a decrease in IGF1 and NET cell growth in studies on pancreatic neuroendocrine cell lines (BON-1) (Von Wichert et al. 2000, Zitzmann et al. 2007). Thirty-seven patients with advanced NETs and evidence of progressive disease were treated with the mTOR inhibitor, temsirolimus, as a single agent in a phase II study. Disease stabilisation occurred in 58 cases and partial radiological response in two cases (6%) with median time to progression 6 months (Duran et al. 2006). This modest effect was balanced by adverse events such as fatigue, rash and hyperglycaemia experienced in a number of patients.

In a key paper, Yao et al. published the results of RAD001 In Advanced NETs-1 (RADIANT 1), a phase II study evaluating everolimus alone versus everolimus and depot octreotide in patients with advanced NET who had progressed on first-line chemotherapy. In the combined treatment arm (n=45), 80% achieved stable disease and 4.4% partial response with a median progression-free survival of 17 months (Yao et al. 2010). In the arm with everolimus alone (n=115), partial responses were seen in 10% and stable disease in 68%; median progression-free survival of 9.7 months. These promising results have led to two everolimus trials, RADIANT-2 and RADIANT-3. RADIANT-2 is a randomised, double-blind, placebo-controlled, multicentre, phase III study of octreotide combined with everolimus or placebo in patients with advanced NETs. RADIANT-3 is a randomised, double-blind, placebo-controlled, multicentre phase III study of everolimus plus best supportive care versus placebo and best supportive care in patients with progressive advanced pancreatic NETs. Results from the latter have recently been published (n=410) and demonstrate prolonged PFS with median PFS of 11.0 months with RAD001 (everolimus) compared with 4.6 months with placebo (Yao et al. 2011).

Newer somatostatin analogues

Pasireotide (SOM 230) is a newer multiligand SST analogue with high affinity to sst1, 2, 3 and 5 receptors (Kvols et al. 2007). Preclinical evidence and early phase II trial data have shown that it may have promised as a new treatment for patients with symptoms of metastatic carcinoid tumours refractory or resistant to somatostatin analogue (Schmid 2008). Co-expression of dopamine and SST receptors has been demonstrated in BON-1 (a pancreatic neuroendocrine cell line) as well as in patients with NET (Lemmer et al. 2002, O’Toole et al. 2006b). Dimerisation of these membrane receptors following response to external signal is a well-recognised phenomenon (Duran-Prado et al. 2008) and there is also evidence of hetero-oligomerisation of SST and dopamine receptor (Rochelleville et al. 2000, Duran-Prado et al. 2008). New SST-dopamine chimeric compounds such as BIM-23A387 have shown promising results in in vitro studies in pituitary adenomas and also NET cell lines (Kidd et al. 2008). Further clinical work is in process to evaluate their use in NET and pituitary tumours.

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Surveillance and observation protocol

Although there is no evidence to guide surveillance, when monitoring patients with stable NETs for progression, serial imaging at 6 month intervals using CT or MRI is appropriate and at 3–4 monthly intervals in more aggressive tumours. Three to six monthly imaging will be required to monitor response to therapy. Although there is a lack of prospectively validated biomarkers, chromogranin A is the global marker used for surveillance and monitoring often on a 3–6 monthly basis. In patients with other elevated markers, e.g. urinary 5-hydroxyindole acetic acid or relevant serum ‘gut peptide’, these should also be measured at the same time. The use of functional imaging with scintigraphy (or PET) in surveillance is unclear but annual or 2-yearly assessment as a determination of functional disease following therapy seems appropriate. Annual gastroscopy surveillance can be used for type I gastric NETs and flexible sigmoidoscopy for rectal NETs.

Conclusion

There is increasing understanding of the biology and heterogeneity of NETs. This is providing a more appropriate rationale towards therapy. Such therapies need to be assessed in multicentre, randomised phase III studies and management should be confined to multidisciplinary teams within specialist centres.

Declaration of interest

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