

## REVIEW

# Considerations concerning a tailored, individualized therapeutic management of patients with (neuro)endocrine tumours of the gastrointestinal tract and pancreas

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## Abstract

Endocrine tumours of the gastrointestinal tract and pancreas may present at different disease stages with either hormonal or hormone-related symptoms/syndromes, or without hormonal symptoms. They may occur either sporadically or as part of hereditary syndromes. In the therapeutic approach to a patient with these tumours, excessive hormonal secretion and/or its effects should always be controlled first. Tumour-related deficiencies or disorders should also be corrected. Subsequently, control should be aimed at the tumour growth. Surgery is generally considered as first-line therapy for patients with localized disease, as it can be curative. However, in patients with metastatic disease the role of first-line surgery is not clearly established and other therapies should be considered, such as non-surgical cytoreductive therapies, biotherapy (with somatostatin analogues or interferon- $\alpha$ ), embolization and chemoembolization of liver metastases, chemotherapy (with single or multiple dose regimens) and peptide receptor-targeted radiotherapy. The delicate balance of the use of the different therapeutical options in patients with endocrine tumours of the gastrointestinal tract and pancreas emphasizes the importance of team approach and team expertise.

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## Introduction

Endocrine tumours of the gastrointestinal tract and pancreas (Solcia *et al.* 2000), carcinoids of the digestive tract and bronchi, and islet cell tumours of the pancreas belong to a rare and heterogeneous group of tumours with great variability in clinical behaviour.

According to their different presentations and/or clinical manifestations, different diagnostic and therapeutic approaches can be followed; these have to be individualized between patients. In some areas there seems to be a consensus on the choice of the diagnostic and therapeutic approach, in other areas an individualized approach seems best at present. We have tried to design general as well as differential therapeutic recommenda-

tions for these tumours.

Knowledge about the natural history of endocrine tumours of the gastrointestinal tract and pancreas is essential in order to allow identification of prognostic factors and subgroups of patients with different prognoses. These tumours may present at different disease stages and accurate localization and staging can be difficult. In the near future, it should be more possible to make a more individual therapeutic approach on the basis of predicted tumour behaviour and identify when less or more aggressive therapy is warranted. In this respect, studies are now looking into reliable prognostic clinical, radiological, serum or histological markers (Stabile 1997).

## The role of the presentation and estimates of the degree of malignant behaviour

### Functioning vs non-functioning tumours

Endocrine tumours of the gastrointestinal tract and pancreas can be subdivided into those presenting with hormonal or hormone-related symptoms/syndromes and those without hormonal symptoms, the so-called 'non-functioning tumours'. In patients with these non-functioning tumours, morbidity and mortality mainly result from tumour expansion and spread, although these tumours may later in their disease course start producing biologically active hormones.

### Hereditary vs non-hereditary tumours

Pancreatic islet cell tumours may occur sporadically, or as part of the multiple endocrine neoplasia type I (MEN-I) syndrome (Medelian Inheritance in Man (MIM) 193300), von Hippel–Lindau syndrome (MIM 193300), neurofibromatosis type 1 (von Recklinghausen disease) (MIM 162200) and tuberous sclerosis (MIM 191100) (Griffiths *et al.* 1987, Swinburn *et al.* 1988, Brandi *et al.* 2001). As an example, it has been shown that (metastatic) gastrinomas, either sporadic or MEN-I associated, may follow highly variable patterns. Generally, 40–90% of MEN-I gene carriers develop pancreatic endocrine tumours (Calender 2000). Apart from the complications caused by the excessive hormone secretion by these tumours, MEN-I patients may also suffer from complications of the hormone excess caused by hypersecretion or tumours of other endocrine glands such as pituitary tumours and hyperparathyroidism. Nowadays, many of these complications can be radically treated surgically or medically. Improved genetic, hormonal, nuclear and radiological imaging screening programs and successive follow-up of carriers of MEN-I gene defects allows earlier diagnosis and treatment of *de novo* tumours in these gene carriers (Brandi *et al.* 2001). As a result, patients with gastrinomas and the MEN-I syndrome tend to live longer than some years ago. The National Institute of Health group of Jensen and co-workers (Gibril *et al.* 2001) was the first to prospectively follow a relatively large group of MEN-I-associated gastrinomas. At a mean follow-up of 8 years, these authors have shown that 14% of patients had aggressive growing gastrinomas, which were associated with decreased survival. In this study, factors predictive of aggressive growth of gastrinoma in MEN-I patients were: age at diagnosis of both gastrinoma and of MEN-I, age at diagnosis of Zollinger–Ellison syndrome, duration of Zollinger–Ellison syndrome before diagnosis, fasting gastrin levels, tumour size, presence of liver

metastases, presence of bone metastases and presence of gastric carcinoids (Gibril *et al.* 2001).

In neurofibromatosis type 1, duodenal somatostatinomas may occur. The vast majority of these tumours occur near the ampulla of Vater, where they tend to cause obstructive jaundice at an early stage (Griffiths *et al.* 1987). Because of their size these tumours are generally amenable to surgery. In contrast, even more rare sporadic gastrinomas usually occur in the pancreas and are diagnosed at a much later stage when features of hyperglycaemia, steatorrhoea, cholelithiasis and diarrhoea or abdominal pain have occurred (Ganda *et al.* 1977, Krejs *et al.* 1979).

### Parameters of malignant behaviour

Immunohistochemical markers for neuroendocrine tumours are: chromogranin A (CgA), synaptophysin, neurone specific enolase and protein gene product 9.5 (Oberge *et al.* 1999). Poorly differentiated and anaplastic endocrine tumours of the gastrointestinal tract and pancreas generally show no staining for CgA. In retrospective series, the presence of synchronous or development of metachronous distant metastases (and rapid progression of these metastases), loss of functionality of the tumour, tumour size larger than 4 cm, the presence of or development of ectopic hormone syndromes and synchronous/metachronous OctreoScan (Tyco Healthcare/Mallinckrodt, St Louis, MO, USA) negativity have been considered poor prognostic factors in patients with endocrine tumours of the gastrointestinal tract and pancreas (Kvols *et al.* 1992, Metz *et al.* 1993, Krenning *et al.* 1994, Weber *et al.* 1995, Sutliff *et al.* 1997, Yu *et al.* 1999). In these tumours, important histological markers of poor prognosis are: more than 2% Ki 67-positive cells, angioinvasion/perineural invasion, more than two mitoses/10 high power field (2mm<sup>2</sup>) and p53 overexpression (Chaudhry *et al.* 1992, La Rosa *et al.* 1996, Rindi *et al.* 1999, 2000, Rigaud *et al.* 2001). Loss of heterozygosity (LOH) analysis has also demonstrated high frequency of 6q and 11q LOH, but the clinical significance of these findings is not yet clear (Rigaud *et al.* 2001). Apart from the already mentioned prognostic parameters for endocrine tumours of the gastrointestinal tract and pancreas, studies in patients with carcinoid tumour have identified that sex, primary tumour site, tumour size, tumour invasiveness, presence of the carcinoid syndrome, elevated serum CgA levels and elevated urinary excretion of 5-hydroxy indole acetic acid (5-HIAA), as well as aneuploidy, are additional markers of poor prognosis in these patients (Greenberg *et al.* 1987, McDermott *et al.* 1994, Stridsberg *et al.* 1995, Tiensuu Janson & Oberge 1996,

Modlin & Sandor 1997, Nobels *et al.* 1997, Soga 1998, Jensen 2000).

## Peptide receptors

Endocrine tumours of the gastrointestinal tract and pancreas may produce one or several peptide hormones. It is possible to measure the levels of most peptides in the blood, providing suitable markers for disease stage and endocrinological activity. In addition, the high expression of receptors for some peptides by these tumours provides other valuable tumour markers and allows for therapy with receptor agonists or antagonists, diagnostic scintigraphy with radiolabelled analogues and therapy with radiolabelled or cytotoxic analogues (see later) (de Herder *et al.* 1996a, 2003, Hofland & Lamberts 2003, Reubi & Waser 2003).

Somatostatin receptor-binding studies, somatostatin mRNA determination and/or somatostatin receptor immunohistochemistry have identified abundant expression of somatostatin receptors in endocrine tumours of the gastrointestinal tract and pancreas (Reubi *et al.* 1987, 1990). In general, somatostatin receptor expression varies between patients and between tumours. Although most endocrine tumours of the gastrointestinal tract and pancreas have a rather homogeneous somatostatin receptor distribution some may show a more heterogeneous somatostatin receptor distribution. Complex patterns of somatostatin receptor subtype mRNA expression have been observed (Jais *et al.* 1997, Schaer *et al.* 1997, Wulbrand *et al.* 1998).

Non-endocrine gastrointestinal tumours can express the vasoactive intestinal polypeptide (VIP) receptor subtype VPAC1 (Reubi *et al.* 2000). The cholecystokinin (CCK) and gastrin receptor subtype CCK2 (CCK-B) are expressed in some of the endocrine tumours of the gastrointestinal tract and pancreas (in particular in insulinomas) and the subtype CCK1 (CCK-A) receptors can also be expressed (Reubi *et al.* 1997, Reubi & Waser 2003). The expression of bombesin and gastrin-releasing peptide (GRP) receptor subtypes (neuromedin B receptor subtype (BB1), GRP receptor subtype (BB2), BB3 and BB4) has been studied in both endocrine and non-endocrine tumours of the gastrointestinal tract and pancreas. Gastrinomas preferentially express GRP receptors and ileal carcinoids often express neuromedin B receptors (Reubi *et al.* 2002, Reubi & Waser 2003). Ongoing studies are examining the expression of neurotensin receptors (such as the receptor subtype NRT1), substance P (such as the receptor subtype NK1), neuropeptide Y and other peptides in endocrine tumours of the gastrointestinal tract and pancreas (Reubi & Waser 2003).

## Treatment objectives

### Hormonal control

In the stepwise therapeutic approach to a patient with an endocrine tumour of the gastrointestinal tract and pancreas, excessive hormonal secretion and/or its effects should always be controlled first. This includes the following.

#### *Islet cell tumours of the pancreas*

- Control of gastric acid hypersecretion and its effects in patients with the Zollinger–Ellison syndrome using high doses of proton pump inhibitors, frequent administration of high doses of histamine H<sub>2</sub>-receptor antagonists and/or somatostatin analogues. Nowadays, total gastrectomy and parietal cell vagotomy are almost obsolete (Jensen 1996).
- Control of hypoglycaemia in patients with insulinomas by administering frequent meals, and/or continuous or overnight glucose infusions and/or diazoxide therapy (Service 1993).
- Control of hyperglycaemia in patients with glucagonomas and somatostatinomas using insulin or oral blood glucose-lowering drugs, or somatostatin analogues (Krejs *et al.* 1979, Bloom & Polak 1987, Lamberts *et al.* 1996).

#### *Islet cell tumours of the pancreas and carcinoids*

- Control of diarrhoea and/or flushing in patients with the carcinoid syndrome or VIPoma by somatostatin analogues and loperamide or ondansetron (Stabile 1997, Caplin *et al.* 1998, Wymenga *et al.* 1998, Kulke & Mayer 1999).
- Control of Cushing's syndrome in patients with ectopic adrenocorticotrophin production by (combinations of) somatostatin analogues, ketoconazole, metyrapone, etomidate, or by laparoscopic biadrenalectomy (Lamberts *et al.* 1994, Wajchenberg *et al.* 1994, de Herder & Lamberts 1996, 1999).
- Control of acromegaly in patients with ectopic growth hormone-releasing hormone production by somatostatin analogues (Von Werder *et al.* 1984, Lefebvre *et al.* 1995, Drange & Melmed 1998, Doga *et al.* 2001).
- Control of humoral hypercalcaemia of malignancy in patients with paraneoplastic parathyroid hormone-related peptide production by somatostatin analogues (Wynick *et al.* 1990, Mantzoros *et al.* 1997, Barhoum *et al.* 1999).

#### *Carcinoids*

Carcinoids of the small intestine (previously designated as midgut carcinoids) are the most common carcinoids.

After metastasizing to the liver, bioactive amines may reach the systemic circulation and the carcinoid syndrome ensues. These small intestinal carcinoids account for 75–90% of all cases of the carcinoid syndrome (Oberg 1997, Jensen 1999). In the case of the carcinoid syndrome, somatostatin analogue therapy (using s.c. octreotide (Sandostatin; Novartis Pharma, Basle, Switzerland), i.m. Sandostatin LAR (Novartis Pharma), s.c. lanreotide (Somatuline; Beaufour Ipsen, Paris, France), i.m. lanreotide-PR (Somatuline-PR; Beaufour Ipsen) or s.c. Lanreotide Autogel (Beaufour Ipsen)) results in complete disappearance of flushing episodes in approximately 60% of patients, while in more than 85% the frequency and/or severity of the flushing periods can be reduced to less than 50%. Disappearance of diarrhoea is observed in more than 30%, and there is a more than 50% improvement in more than 75% of patients with this therapy. Biochemically, a significant reduction of the increased urinary excretion of 5-HIAA in more than 50% of patients has been found (Kvols *et al.* 1986, Kvols 1989, Oberg 1997, Caplin *et al.* 1998, Kulke & Mayer 1999). Also, objective transient anti-neoplastic effects have been reported with this therapy (see later). However, insensitivity (tachyphylaxis) to somatostatin analogues may develop in time (de Herder *et al.* 1996a).

### Correction of tumour-related deficiencies or disorders

Apart from therapies directly targeted at the tumour/tumour syndromes, tumour-related deficiencies and disorders should also be taken care of. This involves the following.

- Supplementation of nicotinic acid in patients with carcinoid syndrome and nicotinic acid deficiency (Swain *et al.* 1976).
- Topical or oral zinc therapy to ameliorate the necrolytic migratory erythema in patients with glucagonoma (Burton 1993, Chastain 2001).
- Aspirin therapy for the prevention of thrombo-embolic disease in patients with glucagonoma (Chastain 2001).
- Resection of mesenteric fibrosis and heart valve replacement in patients with carcinoid syndrome and carcinoid heart disease (Ahlman 1996, Westberg *et al.* 2001, Quaedvlieg *et al.* 2002, Moller *et al.* 2003).

Carcinoid heart disease, eventually leading to right-sided heart failure, is an important cause of death in patients with the carcinoid syndrome. In this disorder, plaques are deposited on the endocardium, leading to tricuspid valve insufficiency and pulmonary valve stenosis. In close collaboration with cardiologists and thoracic surgeons, protocols have been developed that include extensive cardiologic monitoring of patients with the carcinoid

syndrome, in whom surgical and/or medical therapy has reduced the effects of hormonal hypersecretion. This will eventually lead to a careful selection of patients and correct timing of valve replacement before end-stage heart failure develops (Connolly *et al.* 1995, Westberg *et al.* 2001, Quaedvlieg *et al.* 2002, Moller *et al.* 2003).

### Control of tumour growth

The second stage of the therapeutical work-up of a patient with an endocrine tumour of the gastrointestinal tract and pancreas is control of tumour growth. The sensitivity and specificity of the different imaging modalities for diagnosing and localizing primary endocrine tumours of the gastrointestinal tract and pancreas and their possible metastatic spread will not be extensively discussed in this paper (see Ricke *et al.* 2001). It is, however, obvious that meticulous localization is mandatory for the patient's work-up for therapy. Are we dealing with a patient with localized disease or metastatic disease? Again, knowledge of the natural history of the tumour is very essential. Less than 10% of insulinomas show malignant behaviour, whereas 60–90% of gastrinomas and 40–70% of VIPomas are malignant (Stabile 1997, Jensen 1999). Somatostatin receptor imaging (using OctreoScan) is currently considered to be the first-line imaging modality for the staging of patients with the Zollinger–Ellison syndrome (Gibril *et al.* 1996, Termanini *et al.* 1997, Alexander *et al.* 1998). Five-year survival for gastrinoma patients with liver metastases is low and varies between 40 and 75%, whereas it is almost 100% when no liver metastases are present (Weber *et al.* 1995, Sutliff *et al.* 1997, Madeira *et al.* 1998, Wiedenmann *et al.* 1998, Yu *et al.* 1999).

### Surgery

Surgery is generally considered as first-line therapy for patients with localized disease, as it can be curative (Doherty *et al.* 1991, Norton 1994, Wiedenmann *et al.* 1998, Norton *et al.* 1999). However, in patients with metastatic disease the role of first-line surgery is not clearly established. In patients with metastatic carcinoids with liver and mesenteric metastases, conservative resections of the intestine, mesenteric tumours and fibrotic areas may considerably improve symptoms and quality of life (Makridis *et al.* 1990, 1996, 1997, Sarmiento *et al.* 2003). Whether the reduction of tumour mass by surgical intervention enhances a favourable outcome for future medical treatment has not, however, been established (Gulec *et al.* 2002). The extent of a surgical resection should be well-balanced against morbidity and the role of medical and other therapies to control symptoms (Wiedenmann *et al.* 1998). Indeed, patients with liver metastases from endocrine tumours of the gastrointestinal tract and pancreas have a significant



decrease in survival as compared with patients with localized tumours with or without lymph node metastases (Modlin & Sandor 1997). Studies have also demonstrated that in the case of a gastrinoma, surgical removal of the primary tumour decreases the probability that liver metastases will develop. In the case of a limited number and extent of liver metastases, metastatectomy should, therefore, be considered (Ahlman *et al.* 1996, Jaeck *et al.* 2001, Goering *et al.* 2002, Sarmiento *et al.* 2003). However, liver metastases are often multiple and diffuse throughout the liver parenchyma, thus precluding resection in more than 90% of patients (McEntee *et al.* 1990).

The different clinical behaviour and prognosis of pancreatic islet cell tumours in the presence or absence of the MEN-I syndrome have been elegantly demonstrated for gastrinomas. Approximately 20–25% of gastrinoma patients have the MEN-I syndrome. MEN-I-associated gastrinomas usually present at an earlier age. Most MEN-I patients have coexisting hyperparathyroidism or pituitary disease at the time of presentation of the gastrinoma. Also, (generally multifocal) gastric carcinoid tumours from the enterochromaffin-like cells (so-called ‘ECLomas’) are more frequently found in patients with MEN-I-associated gastrinoma (15–30% of cases) than in sporadic gastrinomas (<5%). This implies that the therapeutic approach to endocrine tumours of the gastrointestinal tract and pancreas may differ between patients with and without the MEN-I syndrome (Jensen 1996, 1998, Norton *et al.* 1999).

### Liver transplantation

A limited number of liver transplantations have been performed in patients with either absent or resectable extrahepatic spread of endocrine tumours of the gastrointestinal tract and pancreas, which could then be completely resected with curative intent. The exact role and especially the exact timing of this procedure needs to be further defined. Early experiences have been obtained in patients who were generally younger than 55 years with a hepatic tumour mass involving less than 50% of total liver volume. These patients had either previously undergone curative metastatectomies or liver resections with curative intent, or had demonstrated progression of liver metastases after hepatic artery embolization. In a few patients, the indication for liver transplantation was uncontrollable life-threatening hormone production by non-anaplastic endocrine tumours of the gastrointestinal tract and pancreas (as in the case of metastatic VIPoma and metastatic insulinoma) (Doussset *et al.* 1996, Lehnert 1998, Ahlman *et al.* 2000, Olausson *et al.* 2002, Cahlin *et al.* 2003).

### Non-surgical cytoreductive therapies

#### Biotherapy

On the basis of *in vitro* studies demonstrating anti-proliferative and apoptotic effects of somatostatin analogues, uncontrolled prospective studies using standard doses of s.c. octreotide (Sandostatin), i.m. Sandostatin LAR, s.c. lanreotide (Somatuline), i.m. lanreotide-PR (Somatuline-PR) or s.c. lanreotide autogel have been designed in patients with progressive endocrine tumours of the gastrointestinal tract and pancreas (Imam *et al.* 1997). However, only limited numbers of patients have been studied. Anaplastic tumours were excluded from most studies. Stable disease lasting for a minimum of 3 months and a maximum of 5 years was attained in 20–70% of patients and a partial response only in less than 6% of patients (Saltz *et al.* 1993, Arnold *et al.* 1996, Di Bartolomeo *et al.* 1996, Ruzniewski *et al.* 1996, Wymenga *et al.* 1999, Ducreux *et al.* 2000, Aparicio *et al.* 2001, Shojamanesh *et al.* 2002, de Herder *et al.* 2003). Preliminary studies have shown that ultra-high doses of the currently available somatostatin analogues may cause tumour shrinkage in selected patients (Faiss *et al.* 1996, Eriksson *et al.* 1997). Therapy with interferon- $\alpha$  (either 2a or 2b) also causes a biochemical response in 44% (25–71%) of patients and a tumour response in 11% (0–27%) of patients with tumours with a low proliferative index (i.e. less than 2% Ki 67-positive cells) (Obergh *et al.* 1997, 2000, Faiss *et al.* 2003). Synergistic effects with combination therapy of somatostatin analogues with interferon- $\alpha$  have been reported and prospective trials have been designed to confirm these results (Joensuu *et al.* 1992, Janson & Obergh 1993, de Herder *et al.* 1996b, Lamberts *et al.* 1996, Frank *et al.* 1999, Obergh 2001, Fjallskog *et al.* 2002, Faiss *et al.* 2003).

#### Chemotherapy

To date, no single-agent or combination chemotherapy trial has demonstrated a significant beneficial effect in patients with well-differentiated endocrine tumours of the gastrointestinal tract (such as carcinoids) and pancreas. In contrast, chemotherapy may have important beneficial effects in selected patients with aggressive poorly differentiated tumours (grade 3 according to World Health Organization criteria (Solcia *et al.* 2000)). These tumours display an aggressive behaviour that is similar to small cell lung cancer. With combinations of streptozotocin and either 5-fluorouracil or doxorubicin, objective response rates up to 67% have been achieved in undifferentiated islet cell tumours (Chernicoff *et al.* 1979, Moertel *et al.* 1980, 1992, Bukowski *et al.* 1987, Eriksson *et al.* 1990, Rougier *et al.* 1991, Rivera & Ajani 1998, Rougier & Mitry 2000). Combination chemotherapy of fast-growing anaplastic neuroendocrine carcinomas with etoposide and

cisplatin resulted in objective responses in up to 41% of patients (Mitry *et al.* 1999). These chemotherapy schedules all had considerable side-effects and, despite the chemosensitivity of these tumours, their prognosis remains very poor with a short duration of response (up to a maximum median survival of 2 years) (Moertel 1987, Moertel *et al.* 1991, Rougier & Mitry 2000).

### Embolization and chemoembolization

In patients with significant (generally more than 50%) liver involvement by diffuse metastases of carcinoids, sequential selective hepatic artery embolization can result in objective tumour responses and a transient but significant reduction of hormone secretion. Higher response rates might be obtained by combining hepatic artery embolization with systemic chemotherapy or by chemoembolization. The latter procedure has the advantage of achieving higher intrahepatic intratumoural concentrations of the cytotoxic drugs in combination with decreased hepatic clearance and local ischaemia. These procedures can generally be repeated every 4–6 weeks to a maximum of three procedures, as the effect then decreases because of the development of collateral blood supply to the liver. In patients eligible for these therapies, extrahepatic spread should be less extensive than the hepatic spread. Complete portal vein thrombosis, hepatic failure (i.e. proaccelerin level <50%) and previous Whipple's procedure (which increases the risk of biliary ischaemia with biliary sepsis) are contra-indications. Generally, the procedures are carried out under general anaesthesia and under the cover of somatostatin analogues. The effects of (chemo-) embolization on symptomatic control of the carcinoid syndrome are encouraging: more than 50% decrease of urinary 5-HIAA excretion was achieved in 50–100% of patients and tumour progression was inhibited for a period of 0.5–3.5 years in 30–80% (Ruszniewski & Malka 2000). Another clinical indication for this type of therapy is uncontrollable hypoglycaemia caused by diffuse liver metastases of malignant insulinoma (Ruszniewski *et al.* 1993, Perry *et al.* 1994, Wangberg *et al.* 1996). Other therapies directed to reduce the number and size of liver metastases are: (percutaneous) ethanol injection, cryoablation and radiofrequency (Chung *et al.* 2001a, Jaeck *et al.* 2001, Siperstein & Berber 2001, Berber *et al.* 2002, Choy *et al.* 2002, Goering *et al.* 2002, Sheen *et al.* 2002). However, good prospective trials on these therapies are presently lacking.

### Peptide receptor-targeted radiotherapy

<sup>123</sup>I- and <sup>131</sup>I-meta-iodobenzylguanidine (MIBG) may accumulate in digestive endocrine tumour cells. Scintigraphy with this radiopharmakon demonstrates metabolic active tumours and metastases in more than 60% of

patients with endocrine tumours of the gastrointestinal tract and pancreas. This technique can also be used for the selection of patients for therapy with non-radioactive MIBG or <sup>131</sup>I-MIBG (Taal *et al.* 1996).

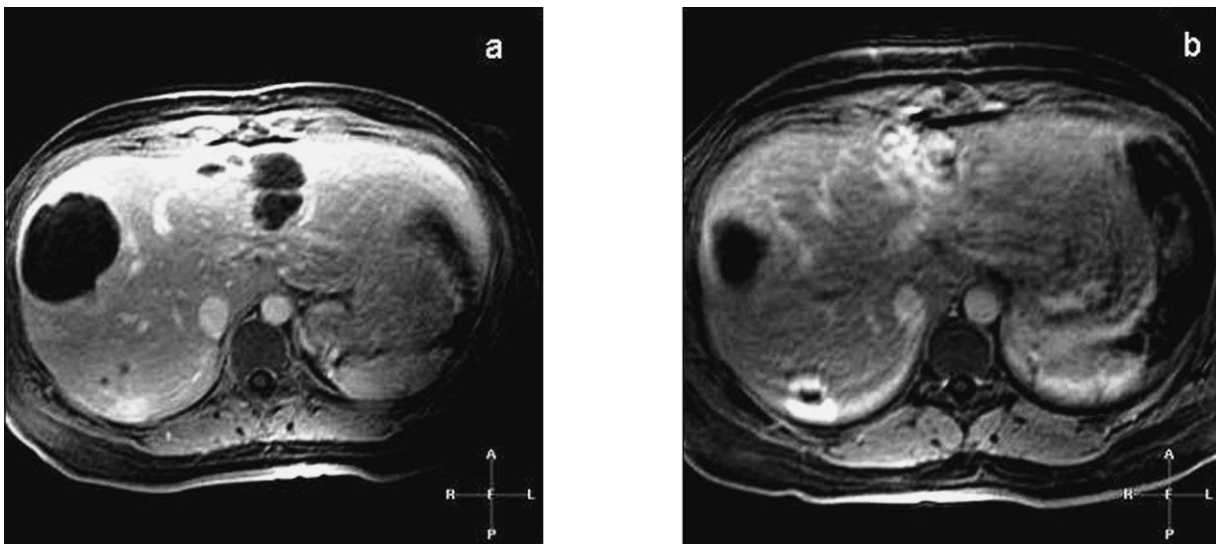
Somatostatin receptor-mediated endocytosis is of particular importance when radiotherapy or chemotherapy of somatostatin receptor subtype (sst)<sub>2</sub>- and sst<sub>5</sub>-positive metastatic carcinoids and pancreatic neuroendocrine tumours with  $\alpha$ - or  $\beta$ -emitting radionuclides or chemotherapeutics coupled to somatostatin analogues are considered (Hofland *et al.* 1999). The process of internalization might bring the radioligand or cytotoxic somatostatin analogue closer to the nucleus and its DNA (Janson *et al.* 2000). A high, selective uptake of radioactivity or the chemotherapeutic is necessary, as non-neoplastic tissues expressing somatostatin receptors should not be exposed to the toxic effects of the radioligand or cytotoxic analogue. [<sup>111</sup>In-DTPA<sup>0</sup>, D-Phe<sup>1</sup>]octreotide (<sup>111</sup>In-pentetreotide) emits both Auger electrons (which have a tissue penetration of only 0.02–10  $\mu$ m) as well as conversion electrons, with a tissue penetration of 200–500  $\mu$ m. High doses of <sup>111</sup>In-pentetreotide inhibited growth of sst<sub>2</sub>-positive tumour cells *in vitro* (Slooter *et al.* 1999). It has also been shown that <sup>111</sup>In-pentetreotide can inhibit the growth of liver metastases after injection of sst<sub>2</sub>-positive tumour cells into the portal vein of rats (Slooter *et al.* 1999). In patients with progressive metastatic neuroendocrine tumours, therapy with <sup>111</sup>In-pentetreotide (performed in three centres, *n* = 81 patients) resulted in a partial response in 7% of patients, a minor response in 7%, 57% of patients had stable disease and progressive disease was observed in 28% (McCarthy *et al.* 1998, 2000, de Jong *et al.* 1999, Krenning *et al.* 1999, Tiensuu *et al.* 1999, Caplin *et al.* 2000, Anthony *et al.* 2002, Valkema *et al.* 2002). Therapy with somatostatin analogues coupled to  $\beta$ -emitting radionuclides, such as <sup>90</sup>Y and <sup>177</sup>Lu, is potentially more effective, as higher tumour radiation doses can be achieved and the longer range of the  $\beta$ -particles (1–10 mm) may also lead to radiation of neighbouring receptor-negative tumour cells (so-called 'cross-fire'). Therapy of patients with endocrine tumours of the digestive tract and pancreas with [<sup>90</sup>Y-DOTA<sup>0</sup>, Tyr<sup>3</sup>]octreotide (<sup>90</sup>Y-DOTATOC or <sup>90</sup>Y-SMT487/OctreoTher; Novartis Pharma) has resulted in partial responses (including a few complete responses) in 18%, minor responses in 11%, 53% of patients had stable disease and progressive disease was observed in 17% (based on phase I/II data obtained in more than 100 patients) (Otte *et al.* 1998, 1999, Paganelli *et al.* 1999, 2001, Smith *et al.* 2000, Waldherr *et al.* 2001). Therapy with [<sup>177</sup>Lu-DOTA<sup>0</sup>, Tyr<sup>3</sup>]octreotate in 34 patients with endocrine tumours of the gastrointestinal tract and pancreas have shown partial

remission in 38% of patients (including one case with complete remission), 41% of patients had stable disease and 21% of patients had progressive disease (Kwekkeboom *et al.* 2001, 2003) (Fig. 1). Furthermore, [ $^{111}\text{In}$ -DOTA $^0$ ]lanreotide and [ $^{90}\text{Y}$ -DOTA $^0$ ]lanreotide can also be used for radiotherapy of *sst* $_2$ - and *sst* $_5$ -positive advanced, or metastatic endocrine tumours (Virgolini *et al.* 2002).

Several mechanisms may determine the amount of uptake of radiolabelled somatostatin analogues. These include: (1) the stability of the radioligand, (2) the density of *sst* expression on the tumour, (3) the type of *ssts* expressed by the tumour, (4) affinity of the radioligand for the *sst*, (5) the efficiency of *sst*-mediated internalization and recycling, (6) the final trapping of the radioisotopes within the tumour cells, as well as (7) the mass of the injected peptide (Nouel *et al.* 1997, Hukovic *et al.* 1999, Hofland & Lamberts 2003). The longer particle range of  $\beta$ -emitting radionuclides is an advantage for median to larger tumour lesions. In micrometastases, however, the absorbed fraction of the radiation energy in the tumour cells will be very low. In these small lesions, therapy with Auger electron and  $\alpha$ -particles emitting radiopharmaceuticals may be a better choice. These observations open the perspective of treating future patients with cocktails of radionuclides, irradiating larger lesions with  $\beta$ -emitting radiolabelled peptides and microscopic lesions with Auger or  $\alpha$ -particle-emitting peptides. It is also conceivable to use  $^{111}\text{In}$ -pentetreotide as neo-adjuvant therapy in patients with *sst* $_2$ -positive tumours operated with curative

intent to treat occult (micro)metastases. Major toxicities observed in trials with peptide receptor-targeted radiotherapy were the development of myelodysplastic syndrome and/or acute myeloid leukaemia in four patients, three in a phase I study with  $^{111}\text{In}$ -pentetreotide and one in a phase I study with [ $^{90}\text{Y}$ -DOTA $^0$ ,Tyr $^3$ ]octreotide and delayed renal insufficiency in a phase I study with [ $^{90}\text{Y}$ -DOTA $^0$ ,Tyr $^3$ ]octreotide without kidney protection with amino acids (Cybulla *et al.* 2001, Valkema *et al.* 2002). Furthermore, decline in platelets was generally mild and transient, leucocytopenia was without clinical implications, but there is evidence for impaired spermatogenesis with  $^{111}\text{In}$ -,  $^{90}\text{Y}$ - and  $^{177}\text{Lu}$ -labelled octreotide treatment based on a decline in serum inhibin B and an increase in serum follicle-stimulating hormone levels (Valkema *et al.* 2002). It is evident that with increasing tumour uptake, as for instance shown by  $^{111}\text{In}$ -pentetreotide scintigraphy (OctreoScan), the results of these therapies are more impressive and patients with OctreoScan-negative tumour deposits will not benefit.

Chelated and non-chelated octapeptide somatostatin analogues have also been attached to various cytotoxic compounds (Plonowski *et al.* 1999, 2000, 2001, 2002, Benali *et al.* 2000, Kiaris *et al.* 2001, Szepeshazi *et al.* 2001, 2002). Using the currently available analogues, somatostatin receptor-targeted chemotherapy may also prove to be only effective in *sst* $_2$ - and *sst* $_5$ -positive tumours (Kwekkeboom *et al.* 1999, Smith *et al.* 2001). Therapy studies with radiolabelled and non-radiolabelled somatostatin analogues linked with cytotoxic compounds



**Figure 1** A 31-year old woman with metastatic gastrinoma treated with four courses of [ $^{177}\text{Lu}$ -DOTA $^0$ ,Tyr $^3$ ]octreotate, cumulative dose 29.8 GBq. T1-weighted images with fat suppression after the administration of Gd-DTPA, arterial phase. a, baseline studies; b, studies performed after 7 months. Studies show a significant reduction of both the cystic and solid part of the liver metastases, classified as a partial response.

have so far been carried out in experimental tumour models only and are very promising. External beam radiation may be of benefit in patients with progressing bone metastases close to the central nervous system.

## Towards individualized therapeutic advice

### Disease-independent variables

It is important to realize that patient-dependent and disease-independent variables may also have an effect on the choice of treatment of endocrine tumours of the gastrointestinal tract and pancreas, variables such as the local availability of drugs or techniques, local expertise, the patient's preference and costs of health care systems/insurance companies. Also, accompanying medical conditions that can significantly shorten the patient's life expectancy should be taken into account.

### Multidisciplinary team advice

The delicate balance of the use of the different therapeutic options in patients with endocrine tumours of the gastrointestinal tract and pancreas emphasizes the importance of team approach and team expertise (Fig. 2). The experts participating in such a team could be endocrinologists, gastroenterologists, surgeons, pathologists, radiotherapist experienced in neuroendocrine problems, oncologists and physicians with knowledge of nuclear medicine.

### Future developments and questions

It seems evident that therapeutic strategies for the various subgroups of endocrine tumours of the gastrointestinal tract and pancreas may dramatically change in the near future with the introduction of new therapies. Somatostatin binds with high affinity to all ssts ( $ss_{1-5}$ ), whereas the octapeptide analogues octreotide and lanreotide only bind with a high affinity to  $ss_2$  and  $ss_5$  (Patel 1999). New classes of sst-selective analogues are being developed and tested. As every somatostatin receptor has distinct biological functions, these new analogues may prove valuable for the treatment of tumours that are already sensitive to the currently available octapeptide analogues, but also for tumours that express other ssts than  $ss_2$  and  $ss_5$ . A new so-called 'universal' somatostatin analogue, named SOM230, with high affinity for  $ss_1$ ,  $ss_2$ ,  $ss_3$  and  $ss_5$  is currently under evaluation in phase I–III trials (Lamberts *et al.* 2002, Bruns *et al.* 2002, Weckbecker *et al.* 2002). New drugs interacting with multi-receptor

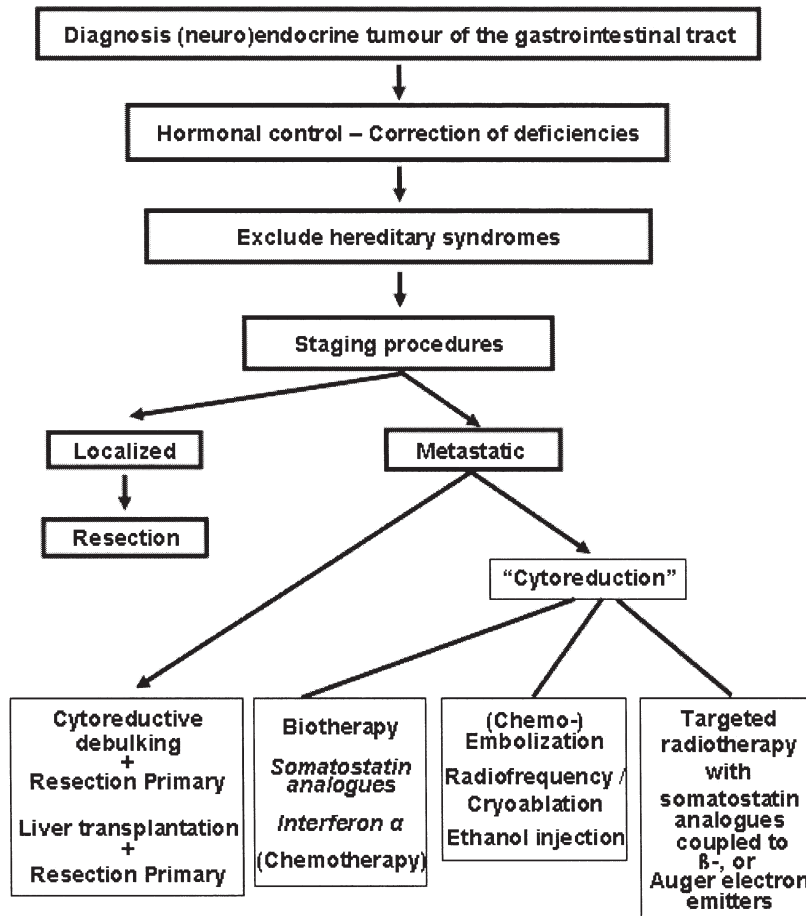
family cross-talk are being developed. These sst subtype homo- or heterodimers may have properties which are distinct from the individual receptors in terms of internalization, agonist-induced desensitization and functional activity (Rocheville *et al.* 2000a,b, Pfeiffer *et al.* 2001, 2002).

Powerful  $\beta$ -emitting radionuclides coupled to these somatostatin analogues will potentially increase the therapeutic potential of peptide receptor-targeted radiotherapy for metastatic somatostatin receptor-positive tumours. Also, as already eluded to, the concept of radiolabelled and non-radiolabelled somatostatin analogues coupled to cytotoxic drugs is interesting and challenging. Transfer of genes that encode for the expression of  $ss_2$  and  $ss_5$  to receptor-negative cancers may render these tumours responsive to these radiolabelled or cytotoxic somatostatin analogues (Smith *et al.* 2000, Benali *et al.* 2000, Jenkins *et al.* 2001). Somatostatin immunotherapy is another future treatment option for somatostatin receptor-positive tumours. As neuroendocrine tumours are generally highly vascularized, anti-angiogenesis agents may prove to be of value in future treatment regimens as well (Dreves *et al.* 2002).

Many questions still have to be solved in the near future. The most pressing ones should be studied in clinical trials aiming to answer the following.

- How do we identify patients with endocrine tumours of the digestive tract and pancreas who, after diagnosis, follow a very aggressive and malignant course and how do we address these tumours in these patients?
- What is or will still be the place for debulking surgery and what is the likelihood of cure after repeat surgery, especially when newer therapies (newer somatostatin analogues and/or peptide receptor-targeted radiotherapy) become widely available? Do both procedures prolong survival and improve quality of life?
- Does liver transplantation in a selected group of patients prolong survival and improve quality of life? What patient selection and work-up is then needed? Does neo-adjuvant peptide receptor-targeted radiotherapy prevent or delay regrowth of metastases in the transplanted liver?
- Is there still a place for new chemotherapeutics and anti-angiogenesis agents, or new trials with presently available chemotherapeutics?
- How can we prevent or suspend tachyphylaxis for the currently available somatostatin analogues and how do we handle this problem, once it has occurred? Do newer somatostatin analogues overcome this problem and is there a need for new and more receptor-specific somatostatin analogues?





**Figure 2** Subsequent steps in the diagnosis and management of patients with endocrine tumours of the pancreas and gastrointestinal tract.

- How can we prolong survival and improve quality of life of patients with anaplastic or dedifferentiated endocrine tumours of the digestive tract and pancreas.
- How can we improve the clinical work-up and care for MEN-I patients with endocrine tumours of the gastrointestinal tract and pancreas?
- What is the role of the currently available or the newer somatostatin analogues in clinically non-functioning neuroendocrine tumours?

## References

Ahlman H 1996 The role of surgery in patients with advanced midgut carcinoid tumours. *Digestion* **57** (Suppl 1) 86–87.  
 Ahlman H, Westberg G, Wangberg B, Nilsson O, Tylan U, Schersten T & Tisell LE 1996 Treatment of liver metastases of carcinoid tumors. *World Journal of Surgery* **20** 196–202.  
 Ahlman H, Wangberg B, Jansson S, Friman S, Olausson M, Tylan U & Nilsson O 2000 Interventional treatment of

gastrointestinal neuroendocrine tumours. *Digestion* **62** S59–S68.

Alexander HR, Fraker DL, Norton JA, Bartlett DL, Tio L, Benjamin SB, Doppman JL, Goebel SU, Serrano J, Gibril F & Jensen RT 1998 Prospective study of somatostatin receptor scintigraphy and its effect on operative outcome in patients with Zollinger–Ellison syndrome. *Annals of Surgery* **228** 228–238.  
 Anthony LB, Woltering EA, Espenan GD, Cronin MD, Maloney TJ & McCarthy KE 2002 Indium-111–pentetreotide prolongs survival in gastroenteropancreatic malignancies. *Seminars in Nuclear Medicine* **32** 123–132.  
 Aparicio T, Ducreux M, Baudin E, Sabourin JC, de Baere T, Mitry E, Schlumberger M & Rougier P 2001 Antitumour activity of somatostatin analogues in progressive metastatic neuroendocrine tumours. *European Journal of Cancer* **37** 1014–1019.  
 Arnold R, Trautmann ME, Creutzfeldt W, Benning R, Benning M, Neuhaus C, Jurgensen R, Stein K, Schafer H, Bruns C & Dennler HJ 1996 Somatostatin analogue octreotide and

- inhibition of tumour growth in metastatic endocrine gastroenteropancreatic tumours. *Gut* **38** 430–438.
- Barhoum M, Hutchins L & Fonseca VA 1999 Intractable hypercalcemia due to a metastatic carcinoid secreting parathyroid hormone-related peptide and interleukin-6: response to octreotide. *American Journal of the Medical Sciences* **318** 203–205.
- Benali N, Cordelier P, Calise D, Pages P, Rochemaix P, Nagy A, Esteve JP, Pour PM, Schally AV, Vaysse N, Susini C & Buscail L 2000 Inhibition of growth and metastatic progression of pancreatic carcinoma in hamster after somatostatin receptor subtype 2 (sst<sub>2</sub>) gene expression and administration of cytotoxic somatostatin analog AN-238. *PNAS* **97** 9180–9185.
- Berber E, Flesher N & Siperstein AE 2002 Laparoscopic radiofrequency ablation of neuroendocrine liver metastases. *World Journal of Surgery* **26** 985–990.
- Bloom SR & Polak JM 1987 Glucagonoma syndrome. *American Journal of Medicine* **82** 25–36.
- Brandi ML, Gagel RF, Angeli A, Bilezikian JP, Beck-Peccoz P, Bordi C, Conte-Devolx B, Falchetti A, Gheri RG, Libroia A, Lips CJ, Lombardi G, Mannelli M, Pacini F, Ponder BA, Raue F, Skogseid B, Tamburrano G, Thakker RV, Thompson NW, Tomassetti P, Tonelli F, Wells SA Jr & Marx SJ 2001 CONSENSUS: Guidelines for Diagnosis and Therapy of MEN Type 1 and Type 2. *Journal of Clinical Endocrinology and Metabolism* **86** 5658–5671.
- Bruns C, Lewis I, Briner U, Meno-Tetang G & Weckbecker G 2002 SOM230: a novel somatostatin peptidomimetic with broad somatotropin release inhibiting factor (SRIF) receptor binding and a unique antisecretory profile. *European Journal of Endocrinology* **146** 707–716.
- Bukowski RM, Johnson KG, Peterson RF, Stephens RL, Rivkin SE, Neilan B & Costanzi JH 1987 A phase II trial of combination chemotherapy in patients with metastatic carcinoid tumors. A Southwest Oncology Group Study. *Cancer* **60** 2891–2895.
- Burton JL 1993 Zinc and essential fatty acid therapy for necrolytic migratory erythema. *Archives of Dermatology* **129** 246.
- Cahlén C, Friman S, Ahlman H, Backman L, Mjornstedt L, Lindner P, Herlenius G & Olausson M 2003 Liver transplantation for metastatic neuroendocrine tumor disease. *Transplantation Proceedings* **35** 809–810.
- Calender A 2000 Molecular genetics of neuroendocrine tumors. *Digestion* **62** (Suppl) 3–18.
- Caplin ME, Buscombe JR, Hilson AJ, Jones AL, Watkinson AF & Burroughs AK 1998 Carcinoid tumour. *Lancet* **352** 799–805.
- Caplin ME, Mielcarek W, Buscombe JR, Jones AL, Croasdale L, Cooper MS, Burroughs AK & Hilson AW 2000 Toxicity of high-activity <sup>111</sup>In-Octreotide therapy in patients with disseminated neuroendocrine tumours. *Nuclear Medicine Communications* **21** 97–102.
- Chastain MA 2001 The glucagonoma syndrome: a review of its features and discussion of new perspectives. *American Journal of the Medical Sciences* **321** 306–320.
- Chaudhry A, Oberg K & Wilander E 1992 A study of biological behavior based on the expression of a proliferating antigen in neuroendocrine tumors of the digestive system. *Tumour Biology* **13** 27–35.
- Chernicoff D, Bukowski RM, Groppe CW Jr & Hewlett JS 1979 Combination chemotherapy for islet cell carcinoma and metastatic carcinoid tumors with 5-fluorouracil and streptozotocin. *Cancer Treatment Reports* **63** 795–796.
- Choy PY, Koea J, McCall J, Holden A & Osbourne M 2002 The role of radiofrequency ablation in the treatment of primary and metastatic tumours of the liver: initial lessons learned. *New Zealand Medical Journal* **115** U128.
- Chung MH, Pisegna J, Spirt M, Giuliano AE, Ye W, Ramming KP & Bilchik AJ 2001 Hepatic cytoreduction followed by a novel long-acting somatostatin analog: a paradigm for intractable neuroendocrine tumors metastatic to the liver. *Surgery* **130** 954–962.
- Connolly HM, Nishimura RA, Smith C, Pellikka PA, Mullany CJ & Kvols LK 1995 Outcome of cardiac surgery for carcinoid heart disease. *Journal of the American College of Cardiology* **25** 410–416.
- Cybulla M, Weiner SM & Otte A 2001 End-stage renal disease after treatment with 90Y-DOTATOC. *European Journal of Nuclear Medicine* **28** 1552–1554.
- Di Bartolomeo M, Bajetta E, Buzzoni R, Mariani L, Carnaghi C, Somma L, Zilembo N & di Leo A 1996 Clinical efficacy of octreotide in the treatment of metastatic neuroendocrine tumors. A study by the Italian Trials in Medical Oncology Group. *Cancer* **77** 402–408.
- Doga M, Bonadonna S, Burattin A & Giustina A 2001 Ectopic secretion of growth hormone-releasing hormone (GHRH) in neuroendocrine tumors: relevant clinical aspects. *Annals of Oncology* **12** S89–S94.
- Doherty GM, Doppman JL, Shawker TH, Miller L, Eastman RC, Gorden P & Norton JA 1991 Results of a prospective strategy to diagnose, localize, and resect insulinomas. *Surgery* **110** 989–996.
- Doussot B, Saint-Marc O, Pitre J, Soubrane O, Houssin D & Chapuis Y 1996 Metastatic endocrine tumors: medical treatment, surgical resection, or liver transplantation. *World Journal of Surgery* **20** 908–914.
- Drange MR & Melmed S 1998 Long-acting lanreotide induces clinical and biochemical remission of acromegaly caused by disseminated growth hormone-releasing hormone-secreting carcinoid. *Journal of Clinical Endocrinology and Metabolism* **83** 3104–3109.
- Dreys J, Laus C, Mendinger M, Schmidt-Gersbach C & Unger C 2002 Antiangiogenesis: current clinical data and future perspectives. *Onkologie* **25** 520–527.
- Ducreux M, Ruzsniwski P, Chayvialle JA, Blumberg J, Cloarec D, Michel H, Raymond JM, Dupas JL, Gouerou H, Jian R, Genestin E, Hammel P & Rougier P 2000 The antitumoral effect of the long-acting somatostatin analog lanreotide in neuroendocrine tumors. *American Journal of Gastroenterology* **95** 3276–3281.
- Eriksson B, Arnberg H, Lindgren PG, Lorelius LE, Magnusson A, Lundqvist G, Skogseid B, Wide L, Wilander E & Oberg K 1990 Neuroendocrine pancreatic tumours: clinical presentation, biochemical and histopathological findings in 84 patients. *Journal of Internal Medicine* **228** 103–113.

- Eriksson B, Renstrup J, Imam H & Oberg K 1997 High-dose treatment with lanreotide of patients with advanced neuroendocrine gastrointestinal tumors: clinical and biological effects. *Annals of Oncology* **8** 1041–1044.
- Faiss S, Scherubl H, Riecken EO & Wiedenmann B 1996 Drug therapy in metastatic neuroendocrine tumors of the gastroenteropancreatic system. *Recent Results in Cancer Research* **142** 193–207.
- Faiss S, Pape UF, Bohmig M, Dorffel Y, Mansmann U, Golder W, Riecken EO & Wiedenmann B 2003 Prospective, randomized, multicenter trial on the antiproliferative effect of lanreotide, interferon alfa, and their combination for therapy of metastatic neuroendocrine gastroenteropancreatic tumors—the International Lanreotide and Interferon Alfa Study Group. *Journal of Clinical Oncology* **21** 2689–2696.
- Fjallskog ML, Sundin A, Westlin JE, Oberg K, Janson ET & Eriksson B 2002 Treatment of malignant endocrine pancreatic tumors with a combination of alpha-interferon and somatostatin analogs. *Medical Oncology* **19** 35–42.
- Frank M, Klose KJ, Wied M, Ishaque N, Schade-Brittinger C & Arnold R 1999 Combination therapy with octreotide and alpha-interferon: effect on tumor growth in metastatic endocrine gastroenteropancreatic tumors. *American Journal of Gastroenterology* **94** 1381–1387.
- Ganda OP, Weir GC, Soeldner JS, Legg MA, Chick WL, Patel YC, Ebeid AM, Gabbay KH & Reichlin S 1977 ‘Somatostatinoma’: a somatostatin-containing tumor of the endocrine pancreas. *New England Journal of Medicine* **296** 963–967.
- Gibril F, Reynolds JC, Doppman JL, Chen CC, Venzon DJ, Termanini B, Weber HC, Stewart CA & Jensen RT 1996 Somatostatin receptor scintigraphy: its sensitivity compared with that of other imaging methods in detecting primary and metastatic gastrinomas. A prospective study. *Annals of Internal Medicine* **125** 26–34.
- Gibril F, Venzon DJ, Ojeaburu JV, Bashir S & Jensen RT 2001 Prospective study of the natural history of gastrinoma in patients with MEN1: definition of an aggressive and a nonaggressive form. *Journal of Clinical Endocrinology and Metabolism* **86** 5282–5293.
- Goering JD, Mahvi DM, Niederhuber JE, Chicks D & Rikkers LF 2002 Cryoablation and liver resection for noncolorectal liver metastases. *American Journal of Surgery* **183** 384–389.
- Greenberg RS, Baumgarten DA, Clark WS, Isacson P & McKeen K 1987 Prognostic factors for gastrointestinal and bronchopulmonary carcinoid tumors. *Cancer* **60** 2476–2483.
- Griffiths DF, Williams GT & Williams ED 1987 Duodenal carcinoid tumours, phaeochromocytoma and neurofibromatosis: islet cell tumour, phaeochromocytoma and the von Hippel–Lindau complex: two distinctive neuroendocrine syndromes. *Quarterly Journal of Medicine* **64** 769–782.
- Gulec SA, Mountcastle TS, Frey D, Cundiff JD, Mathews E, Anthony L, O’Leary JP & Boudreaux JP 2002 Cytoreductive surgery in patients with advanced-stage carcinoid tumors. *The American Surgeon* **68** 667–671.
- de Herder WW & Lamberts SW 1996 Is there a role for somatostatin and its analogs in Cushing’s syndrome? *Metabolism* **45** 83–85.
- de Herder WW & Lamberts SW 1999 Octapeptide somatostatin analogue therapy of Cushing’s syndrome. *Postgraduate Medical Journal* **75** 65–66.
- de Herder WW, Hofland LJ, van der Lely AJ & Lamberts SW 1996a Peptide receptors in gut endocrine tumours. *Baillière’s Clinical Gastroenterology* **10** 571–587.
- de Herder WW, van der Lely AJ & Lamberts SW 1996b Somatostatin analogue treatment of neuroendocrine tumours. *Postgraduate Medical Journal* **72** 403–408.
- de Herder WW, Hofland LJ, van der Lely AJ & Lamberts SW 2003 Somatostatin receptors in gastroenteropancreatic neuroendocrine tumours. *Endocrine-Related Cancer* **10** 451–458.
- Hofland LJ & Lamberts SW 2003 The pathophysiological consequences of somatostatin receptor internalization and resistance. *Endocrine Reviews* **24** 28–47.
- Hofland LJ, Breeman WA, Krenning EP, de Jong M, Waaijers M, van Koetsveld PM, Macke HR & Lamberts SW 1999 Internalization of [DOTA<sup>0</sup>,<sup>125</sup>I-Tyr<sup>3</sup>]Octreotide by somatostatin receptor-positive cells *in vitro* and *in vivo*: implications for somatostatin receptor-targeted radio-guided surgery. *Proceedings of the Association of American Physicians* **111** 63–69.
- Hukovic N, Rocheville M, Kumar U, Sasi R, Khare S & Patel YC 1999 Agonist-dependent up-regulation of human somatostatin receptor type 1 requires molecular signals in the cytoplasmic C-tail. *Journal of Biological Chemistry* **274** 24550–24558.
- Imam H, Eriksson B, Lukinius A, Janson ET, Lindgren PG, Wilander E & Oberg K 1997 Induction of apoptosis in neuroendocrine tumors of the digestive system during treatment with somatostatin analogs. *Acta Oncologica* **36** 607–614.
- Jaeck D, Oussoultzoglou E, Bachellier P, Lemarque P, Weber JC, Nakano H & Wolf P 2001 Hepatic metastases of gastroenteropancreatic neuroendocrine tumors: safe hepatic surgery. *World Journal of Surgery* **25** 689–692.
- Jais P, Terris B, Ruzsniwski P, LeRomancer M, Reyl-Desmars F, Vissuzaine C, Cadiot G, Mignon M & Lewin MJ 1997 Somatostatin receptor subtype gene expression in human endocrine gastroentero-pancreatic tumours. *European Journal of Clinical Investigation* **27** 639–644.
- Janson ET & Oberg K 1993 Long-term management of the carcinoid syndrome. Treatment with octreotide alone and in combination with alpha-interferon. *Acta Oncologica* **32** 225–229.
- Janson ET, Westlin JE, Ohrvall U, Oberg K & Lukinius A 2000 Nuclear localization of <sup>111</sup>In after intravenous injection of [<sup>111</sup>In-DTPA-D-Phe<sup>1</sup>]-octreotide in patients with neuroendocrine tumors. *Journal of Nuclear Medicine* **41** 1514–1518.
- Jenkins SA, Kynaston HG, Davies ND, Baxter JN & Nott DM 2001 Somatostatin analogs in oncology: a look to the future. *Chemotherapy* **47** (Suppl 2) S162–S196.
- Jensen RT 1996 Gastrointestinal endocrine tumours. Gastrinoma. *Baillière’s Clinical Gastroenterology* **10** 603–643.
- Jensen RT 1998 Management of the Zollinger–Ellison syndrome in patients with multiple endocrine neoplasia type 1. *Journal of Internal Medicine* **243** 477–488.

- Jensen RT 1999 Natural history of digestive endocrine tumors. In *Recent Advances in the Pathophysiology and Management of Inflammatory Bowel Diseases and Digestive Endocrine Tumors*, pp 192–219. Eds M Mignon & JF Colombel. Montrouge: John Libbey Eurotext.
- Jensen RT 2000 Carcinoid and pancreatic endocrine tumors: recent advances in molecular pathogenesis, localization, and treatment. *Current Opinion in Oncology* **12** 368–377.
- Joensuu H, Katka K & Kujari H 1992 Dramatic response of a metastatic carcinoid tumour to a combination of interferon and octreotide. *Acta Endocrinologica* **126** 184–185.
- de Jong M, Breeman WA, Bernard HF, Kooij PP, Slooter GD, van Eijck CH, Kwekkeboom DJ, Valkema R, Macke HR & Krenning EP 1999 Therapy of neuroendocrine tumors with radiolabeled somatostatin-analogues. *Quarterly Journal of Nuclear Medicine* **43** 356–366.
- Kiaris H, Schally AV, Nagy A, Szepeshazi K, Hebert F & Halmos G 2001 A targeted cytotoxic somatostatin (SST) analogue, AN-238, inhibits the growth of H-69 small-cell lung carcinoma (SCLC) and H-157 non-SCLC in nude mice. *European Journal of Cancer* **37** 620–628.
- Krejs GJ, Orci L, Conlon JM, Ravazzola M, Davis GR, Raskin P, Collins SM, McCarthy DM, Baetens D, Rubenstein A, Aldor TA & Unger RH 1979 Somatostatinoma syndrome. Biochemical, morphologic and clinical features. *New England Journal of Medicine* **301** 285–292.
- Krenning EP, Kwekkeboom DJ, Oei HY, de Jong RJ, Dop FJ, de Herder WW, Reubi JC & Lamberts SW 1994 Somatostatin receptor scintigraphy in carcinoids, gastrinomas and Cushing's syndrome. *Digestion* **55** (Suppl 3) S54–S59.
- Krenning EP, Valkema R, Kooij PP, Breeman WA, Bakker WH, de Herder WW, van Eijck CH, Kwekkeboom DJ, de Jong M & Pauwels S 1999 Scintigraphy and radionuclide therapy with [indium-111-labelled-diethyl triamine penta-acetic acid-D-Phe<sup>1</sup>]-octreotide. *Italian Journal of Gastroenterology and Hepatology* **31** (Suppl 2) S219–S223.
- Kulke MH & Mayer RJ 1999 Carcinoid tumors. *New England Journal of Medicine* **340** 858–868.
- Kvols LK 1989 Therapy of the malignant carcinoid syndrome. *Endocrinology and Metabolism Clinics of North America* **18** 557–568.
- Kvols LK, Moertel CG, O'Connell MJ, Schutt AJ, Rubin J & Hahn RG 1986 Treatment of the malignant carcinoid syndrome. Evaluation of a long-acting somatostatin analogue. *New England Journal of Medicine* **315** 663–666.
- Kvols LK, Reubi JC, Horisberger U, Moertel CG, Rubin J & Charboneau JW 1992 The presence of somatostatin receptors in malignant neuroendocrine tumor tissue predicts responsiveness to octreotide. *Yale Journal of Biology and Medicine* **65** 505–518.
- Kwekkeboom DJ, de Herder WW & Krenning EP 1999 Receptor imaging in the diagnosis and treatment of pituitary tumors. *Journal of Endocrinological Investigation* **22** 80–88.
- Kwekkeboom DJ, Bakker WH, Kooij PP, Konijnenberg MW, Srinivasan A, Erion JL, Schmidt MA, Bugaj JL, de Jong M & Krenning EP 2001 [<sup>177</sup>Lu-DOTA<sup>0</sup>Tyr<sup>3</sup>]octreotate: comparison with [<sup>111</sup>In-DTPA<sup>0</sup>]octreotide in patients. *European Journal of Nuclear Medicine* **28** 1319–1325.
- Kwekkeboom DJ, Bakker WH, Kam BL, Teunissen JJ, Kooij PP, de Herder WW, Feelders RA, van Eijck CH, de Jong M, Srinivasan A, Erion JL & Krenning EP 2003 Treatment of patients with gastro-entero-pancreatic (GEP) tumours with the novel radiolabelled somatostatin analogue [(177)Lu-DOTA(0),Tyr(3)]octreotate. *European Journal of Nuclear Medicine and Molecular Imaging* **30** 417–422.
- Lamberts SW, de Herder WW, Krenning EP & Reubi JC 1994 A role of (labeled) somatostatin analogs in the differential diagnosis and treatment of Cushing's syndrome. *Journal of Clinical Endocrinology and Metabolism* **78** 17–19.
- Lamberts SW, van der Lely AJ, de Herder WW & Hofland LJ 1996 Octreotide. *New England Journal of Medicine* **334** 246–254.
- Lamberts SW, van der Lely AJ & Hofland LJ 2002 New somatostatin analogs: will they fulfil old promises? *European Journal of Endocrinology* **146** 701–705.
- La Rosa S, Sessa F, Capella C, Riva C, Leone BE, Klersy C, Rindi G & Solcia E 1996 Prognostic criteria in nonfunctioning pancreatic endocrine tumours. *Virchows Archives* **429** 323–333.
- Lefebvre S, De Paepe L, Abs R, Rahier J, Selvais P & Maiter D 1995 Subcutaneous octreotide treatment of a growth hormone-releasing hormone-secreting bronchial carcinoid: superiority of continuous versus intermittent administration to control hormonal secretion. *European Journal of Endocrinology* **133** 320–324.
- Lehnert T 1998 Liver transplantation for metastatic neuroendocrine carcinoma: an analysis of 103 patients. *Transplantation* **66** 1307–1312.
- McCarthy KE, Woltering EA, Espenan GD, Cronin M, Maloney TJ & Anthony LB 1998 *In situ* radiotherapy with <sup>111</sup>In-pentetreotide: initial observations and future directions. *Cancer Journal from Scientific American* **4** 94–102.
- McCarthy KE, Woltering EA & Anthony LB 2000 *In situ* radiotherapy with <sup>111</sup>In-pentetreotide. State of the art and perspectives. *Quarterly Journal of Nuclear Medicine* **44** 88–95.
- McDermott EW, Guduric B & Brennan MF 1994 Prognostic variables in patients with gastrointestinal carcinoid tumours. *British Journal of Surgery* **81** 1007–1009.
- McEntee GP, Nagorney DM, Kvols LK, Moertel CG & Grant CS 1990 Cytoreductive hepatic surgery for neuroendocrine tumors. *Surgery* **108** 1091–1096.
- Madeira I, Terris B, Voss M, Denys A, Sauvanet A, Flejou JF, Vilgrain V, Belghiti J, Bernades P & Ruszniewski P 1998 Prognostic factors in patients with endocrine tumours of the duodenopancreatic area. *Gut* **43** 422–427.
- Makridis C, Oberg K, Juhlin C, Rastad J, Johansson H, Lorelius LE & Akerstrom G 1990 Surgical treatment of mid-gut carcinoid tumors. *World Journal of Surgery* **14** 377–383.
- Makridis C, Rastad J, Oberg K & Akerstrom G 1996 Progression of metastases and symptom improvement from laparotomy in midgut carcinoid tumors. *World Journal of Surgery* **20** 900–906.
- Makridis C, Ekblom A, Bring J, Rastad J, Juhlin C, Oberg K & Akerstrom G 1997 Survival and daily physical activity in



- patients treated for advanced midgut carcinoid tumors. *Surgery* **122** 1075–1082.
- Mantzoros CS, Suva LJ, Moses AC & Spark R 1997 Intractable hypercalcaemia due to parathyroid hormone-related peptide secretion by a carcinoid tumour. *Clinical Endocrinology* **46** 373–375.
- Metz DC, Kuchnio M, Fraker DL, Venzon DJ, Jaffe G, Jensen RT & Stetler-Stevenson M 1993 Flow cytometry and Zollinger–Ellison syndrome: relationship to clinical course. *Gastroenterology* **105** 799–813.
- Mitry E, Baudin E, Ducreux M, Sabourin JC, Rufie P, Aparicio T, Lasser P, Elias D, Duvillard P, Schlumberger M & Rougier P 1999 Treatment of poorly differentiated neuroendocrine tumours with etoposide and cisplatin. *British Journal of Cancer* **81** 1351–1355.
- Modlin IM & Sandor A 1997 An analysis of 8305 cases of carcinoid tumors. *Cancer* **79** 813–829.
- Moertel CG 1987 Karnofsky memorial lecture. An odyssey in the land of small tumors. *Journal of Clinical Oncology* **5** 1502–1522.
- Moertel CG, Hanley JA & Johnson LA 1980 Streptozocin alone compared with streptozocin plus fluorouracil in the treatment of advanced islet-cell carcinoma. *New England Journal of Medicine* **303** 1189–1194.
- Moertel CG, Kvols LK, O'Connell MJ & Rubin J 1991 Treatment of neuroendocrine carcinomas with combined etoposide and cisplatin. Evidence of major therapeutic activity in the anaplastic variants of these neoplasms. *Cancer* **68** 227–232.
- Moertel CG, Lefkopoulo M, Lipsitz S Hahn RG & Klaassen D 1992 Streptozocin-doxorubicin, streptozocin-fluorouracil or chlorozotocin in the treatment of advanced islet-cell carcinoma. *New England Journal of Medicine* **326** 519–523.
- Moller JE, Connolly HM, Rubin J, Seward JB, Modesto K & Pellikka PA 2003 Factors associated with progression of carcinoid heart disease. *New England Journal of Medicine* **348** 1005–1015.
- Nobels FR, Kwekkeboom DJ, Coopmans W, Schoenmakers CH, Lindemans J, de Herder WW, Krenning EP, Bouillon R & Lamberts SW 1997 Chromogranin A as serum marker for neuroendocrine neoplasia: comparison with neuron-specific enolase and the alpha-subunit of glycoprotein hormones. *Journal of Clinical Endocrinology and Metabolism* **82** 2622–2628.
- Norton JA 1994 Surgical management of carcinoid tumors: role of debulking and surgery for patients with advanced disease. *Digestion* **55** (Suppl 3) 98–103.
- Norton JA, Fraker DL, Alexander HR, Venzon DJ, Doppman JL, Serrano J, Goebel SU, Peghini PL, Roy PK, Gibril F & Jensen RT 1999 Surgery to cure the Zollinger–Ellison syndrome. *New England Journal of Medicine* **341** 635–644.
- Nouel D, Gaudriault G, Houle M, Reisine T, Vincent JP, Mazella J & Beaudet A 1997 Differential internalization of somatostatin in COS-7 cells transfected with SST1 and SST2 receptor subtypes: a confocal microscopic study using novel fluorescent somatostatin derivatives. *Endocrinology* **138** 296–306.
- Oberg K 1997 Carcinoid syndrome. In *Clinical Endocrine Oncology*, pp 411–421. Eds R Sheaves, PJ Jenkins & JA Wass. Oxford: Blackwell Science Ltd.
- Oberg K 2000 Interferon in the management of neuroendocrine GEP-tumors: a review. *Digestion* **62** (Suppl 1) 92–97.
- Oberg K 2001 Established clinical use of octreotide and lanreotide in oncology. *Chemotherapy* **47** (Suppl 2) 40–53.
- Oberg K, Janson ET & Eriksson B 1999 Tumour markers in neuroendocrine tumours. *Italian Journal of Gastroenterology and Hepatology* **31** (Suppl 2) S160–S162.
- Olausson M, Friman S, Cahlin C, Nilsson O, Jansson S, Wangberg B & Ahlman H 2002 Indications and results of liver transplantation in patients with neuroendocrine tumors. *World Journal of Surgery* **26** 998–1004.
- Otte A, Mueller-Brand J, Dellas S, Nitzsche EU, Herrmann R & Maecke HR 1998 Yttrium-90-labelled somatostatin-analogue for cancer treatment. *Lancet* **351** 417–418.
- Otte A, Herrmann R, Heppeler A, Behe M, Jermann E, Powell P, Maecke HR & Muller J 1999 Yttrium-90 DOTATOC: first clinical results. *European Journal of Nuclear Medicine* **26** 1439–1447.
- Paganelli G, Zoboli S, Cremonesi M, Macke HR & Chinol M 1999 Receptor-mediated radionuclide therapy with <sup>90</sup>Y-DOTA-D-Phe<sup>1</sup>-Tyr<sup>3</sup>-Octreotide: preliminary report in cancer patients. *Cancer Biotherapy and Radiopharmaceuticals* **14** 477–483.
- Paganelli G, Zoboli S, Cremonesi M, Bodei L, Ferrari M, Grana C, Bartolomei M, Orsi F, De Cicco C, Macke HR, Chinol M & de Braud F 2001 Receptor-mediated radiotherapy with <sup>90</sup>Y-DOTA-D-Phe<sup>1</sup>-Tyr<sup>3</sup>-octreotide. *European Journal of Nuclear Medicine* **28** 426–434.
- Patel YC 1999 Somatostatin and its receptor family. *Frontiers of Neuroendocrinology* **20** 157–198.
- Perry LJ, Stuart K, Stokes KR & Clouse ME 1994 Hepatic arterial chemoembolization for metastatic neuroendocrine tumors. *Surgery* **116** 1111–1116.
- Pfeiffer M, Koch T, Schroder H, Klutzny M, Kirscht S, Kreienkamp HJ, Holt V & Schulz S 2001 Homo- and heterodimerization of somatostatin receptor subtypes. Inactivation of sst(3) receptor function by heterodimerization with sst(2A). *Journal of Biological Chemistry* **276** 14027–14036.
- Pfeiffer M, Koch T, Schroder H, Lausch M, Holt V & Schulz S 2002 Heterodimerization of somatostatin and opioid receptors cross-modulates phosphorylation, internalization, and desensitization. *Journal of Biological Chemistry* **277** 19762–19772.
- Plonowski A, Schally AV, Nagy A, Sun B & Szepeshazi K 1999 Inhibition of PC-3 human androgen-independent prostate cancer and its metastases by cytotoxic somatostatin analogue AN-238. *Cancer Research* **59** 1947–1953.
- Plonowski A, Schally AV, Nagy A, Kiaris H, Hebert F & Halmos G 2000 Inhibition of metastatic renal cell carcinomas expressing somatostatin receptors by a targeted cytotoxic analogue of somatostatin AN-238. *Cancer Research* **60** 2996–3001.
- Plonowski A, Schally AV, Koppan M, Nagy A, Arencibia JM, Csernus B & Halmos G 2001 Inhibition of the UCI-107

- human ovarian carcinoma cell line by a targeted cytotoxic analog of somatostatin, AN-238. *Cancer* **92** 1168–1176.
- Plonowski A, Schally AV, Nagy A, Sun B & Halmos G 2002 Effective treatment of experimental DU-145 prostate cancers with targeted cytotoxic somatostatin analog AN-238. *International Journal of Oncology* **20** 397–402.
- Quaedvlieg PF, Lamers CB & Taal BG 2002 Carcinoid heart disease: an update. *Scandinavian Journal of Gastroenterology* **236** (Suppl) 66–71.
- Reubi JC & Waser B 2003 Concomitant expression of several peptide receptors in neuroendocrine tumours: molecular basis for *in vivo* multireceptor tumour targeting. *European Journal of Nuclear Medicine and Molecular Imaging* **30** 781–793.
- Reubi JC, Hacki WH & Lamberts SW 1987 Hormone-producing gastrointestinal tumors contain a high density of somatostatin receptors. *Journal of Clinical Endocrinology and Metabolism* **65** 1127–1134.
- Reubi JC, Kvols LK, Waser B, Nagorney DM, Heitz PU, Charboneau JW, Reading CC & Moertel C 1990 Detection of somatostatin receptors in surgical and percutaneous needle biopsy samples of carcinoids and islet cell carcinomas. *Cancer Research* **50** 5969–5977.
- Reubi JC, Schaer JC & Waser B 1997 Cholecystokinin(CCK)-A and CCK-B/gastrin receptors in human tumors. *Cancer Research* **57** 1377–1386.
- Reubi JC, Laderach U, Waser B, Gebbers JO, Robberecht P & Laissue JA 2000 Vasoactive intestinal peptide/pituitary adenylate cyclase-activating peptide receptor subtypes in human tumors and their tissues of origin. *Cancer Research* **60** 3105–3112.
- Reubi JC, Wenger S, Schmuckli-Maurer J, Schaer JC & Gugger M 2002 Bombesin receptor subtypes in human cancers: detection with the universal radioligand (125)I-[D-TYR(6), beta-ALA(11), PHE(13), NLE(14)] bombesin(6–14). *Clinical Cancer Research* **8** 1139–1146.
- Ricke J, Klose KJ, Mignon M, Oberg K & Wiedenmann B 2001 Standardisation of imaging in neuroendocrine tumours: results of a European delphi process. *European Journal of Radiology* **37** 8–17.
- Rigaud G, Missiaglia E, Moore PS, Zamboni G, Falconi M, Talamini G, Pesci A, Baron A, Lissandrini D, Rindi G, Grigolato P, Pederzoli P & Scarpa A 2001 High resolution allelotype of nonfunctional pancreatic endocrine tumors: identification of two molecular subgroups with clinical implications. *Cancer Research* **61** 285–292.
- Rindi G, Azzoni C, La Rosa S, Klersy C, Paolotti D, Rappel S, Stolte M, Capella C, Bordi C & Solcia E 1999 ECL cell tumor and poorly differentiated endocrine carcinoma of the stomach: prognostic evaluation by pathological analysis. *Gastroenterology* **116** 532–542.
- Rindi G, Villanacci V & Ubiali A 2000 Biological and molecular aspects of gastroenteropancreatic neuroendocrine tumors. *Digestion* **62** S19–S26.
- Rivera E & Ajani JA 1998 Doxorubicin, streptozocin, and 5-fluorouracil chemotherapy for patients with metastatic islet-cell carcinoma. *American Journal of Clinical Oncology* **21** 36–38.
- Rocheville M, Lange DC, Kumar U, Patel SC, Patel RC & Patel YC 2000a Receptors for dopamine and somatostatin: formation of hetero-oligomers with enhanced functional activity. *Science* **288** 154–157.
- Rocheville M, Lange DC, Kumar U, Sasi R, Patel RC & Patel YC 2000b Subtypes of the somatostatin receptor assemble as functional homo- and heterodimers. *Journal of Biological Chemistry* **275** 7862–7869.
- Rougier P & Mitry E 2000 Chemotherapy in the treatment of neuroendocrine malignant tumors. *Digestion* **62** (Suppl 1) 73–78.
- Rougier P, Oliveira J, Ducreux M, Theodore C, Kac J & Droz JP 1991 Metastatic carcinoid and islet cell tumours of the pancreas: a phase II trial of the efficacy of combination chemotherapy with 5-fluorouracil, doxorubicin and cisplatin. *European Journal of Cancer* **27** 1380–1382.
- Ruszniewski P & Malka D 2000 Hepatic arterial chemoembolization in the management of advanced digestive endocrine tumors. *Digestion* **62** (Suppl 1) 79–83.
- Ruszniewski P, Rougier P, Roche A, Legmann P, Sibert A, Hochlaf S, Ychou M & Mignon M 1993 Hepatic arterial chemoembolization in patients with liver metastases of endocrine tumors. A prospective phase II study in 24 patients. *Cancer* **71** 2624–2630.
- Ruszniewski P, Ducreux M, Chayvialle JA, Blumberg J, Cloarec D, Michel H, Raymond JM, Dupas JL, Gouerou H, Jian R, Genestin E, Bernades P & Rougier P 1996 Treatment of the carcinoid syndrome with the longacting somatostatin analogue lanreotide: a prospective study in 39 patients. *Gut* **39** 279–283.
- Saltz L, Trochanowski B, Buckley M, Heffernan B, Niedzwiecki D, Tao Y & Kelsen D 1993 Octreotide as an antineoplastic agent in the treatment of functional and nonfunctional neuroendocrine tumors. *Cancer* **72** 244–248.
- Sarmiento JM, Heywood G, Rubin J, Ilstrup DM, Nagorney DM & Que FG 2003 Surgical treatment of neuroendocrine metastases to the liver: a plea for resection to increase survival. *Journal of the American College of Surgeons* **197** 29–37.
- Schaer JC, Waser B, Mengod G & Reubi JC 1997 Somatostatin receptor subtypes sst1, sst2, sst3 and sst5 expression in human pituitary, gastroentero-pancreatic and mammary tumors: comparison of mRNA analysis with receptor autoradiography. *International Journal of Cancer* **70** 530–537.
- Service FJ 1993 Clinical review 42: Hypoglycemias. *Journal of Clinical Endocrinology and Metabolism* **76** 269–272.
- Sheen AJ, Poston GJ & Sherlock DJ 2002 Cryotherapeutic ablation of liver tumours. *British Journal of Surgery* **89** 1396–1401.
- Shojamanesh H, Gibril F, Louie A, Ojeaburu JV, Bashir S, Abou-Saif A & Jensen RT 2002 Prospective study of the antitumor efficacy of long-term octreotide treatment in patients with progressive metastatic gastrinoma. *Cancer* **94** 331–343.
- Siperstein AE & Berber E 2001 Cryoablation, percutaneous alcohol injection, and radiofrequency ablation for treatment of neuroendocrine liver metastases. *World Journal of Surgery* **25** 693–696.
- Slooter GD, Breeman WA, Marquet RL, Krenning EP & van Eijck CH 1999 Anti-proliferative effect of radiolabelled

- octreotide in a metastases model in rat liver. *International Journal of Cancer* **81** 767–771.
- Smith MC, Liu J, Chen T, Schran H, Yeh CM, Jamar F, Valkema R, Bakker W, Kvols L, Krenning E & Pauwels S 2000 OctreoTher: ongoing early clinical development of a somatostatin-receptor-targeted radionuclide antineoplastic therapy. *Digestion* **62** (Suppl 1) 69–72.
- Soga J 1998 Statistical evaluation of 2001 carcinoid cases with metastases, collected from literature: a comparative study between ordinary carcinoids and atypical varieties. *Journal of Experimental and Clinical Cancer Research* **17** 3–12.
- Solcia E, Kloppel G & Sobin LH 2000 *Histological Typing of Endocrine Tumours*. Berlin, Heidelberg, New York: Springer Verlag.
- Stabile BE 1997 Islet cell tumors. *Gastroenterologist* **5** 213–232.
- Stridsberg M, Oberg K, Li Q, Engstrom U & Lundqvist G 1995 Measurements of chromogranin A, chromogranin B (secretogranin I), chromogranin C (secretogranin II) and pancreastatin in plasma and urine from patients with carcinoid tumours and endocrine pancreatic tumours. *Journal of Endocrinology* **144** 49–59.
- Sutliff VE, Doppman JL, Gibril F, Venzon DJ, Yu F, Serrano J & Jensen RT 1997 Growth of newly diagnosed, untreated metastatic gastrinomas and predictors of growth patterns. *Journal of Clinical Oncology* **15** 2420–2431.
- Swain CP, Tavill AS & Neale G 1976 Studies of tryptophan and albumin metabolism in a patient with carcinoid syndrome, pellagra, and hypoproteinemia. *Gastroenterology* **71** 484–489.
- Swinburn BA, Yeong ML, Lane MR, Nicholson GI & Holdaway IM 1988 Neurofibromatosis associated with somatostatinoma: a report of two patients. *Clinical Endocrinology* **28** 353–359.
- Szepeshazi K, Schally AV, Halmos G, Sun B, Hebert F, Csernus B & Nagy A 2001 Targeting of cytotoxic somatostatin analog AN-238 to somatostatin receptor subtypes 5 and/or 3 in experimental pancreatic cancers. *Clinical Cancer Research* **7** 2854–2861.
- Szepeshazi K, Schally AV, Halmos G, Armatos P, Hebert F, Sun B, Feil A, Kiaris H & Nagy A 2002 Targeted cytotoxic somatostatin analogue AN-238 inhibits somatostatin receptor-positive experimental colon cancers independently of their p53 status. *Cancer Research* **62** 781–788.
- Taal BG, Hoefnagel CA, Valdes Olmos RA, Boot H & Beijnen JH 1996 Palliative effect of metaiodobenzylguanidine in metastatic carcinoid tumors. *Journal of Clinical Oncology* **14** 1829–1838.
- Termanini B, Gibril F, Reynolds JC, Doppman JL, Chen CC, Stewart CA, Sutliff VE & Jensen RT 1997 Value of somatostatin receptor scintigraphy: a prospective study in gastrinoma of its effect on clinical management. *Gastroenterology* **112** 335–347.
- Tiensuu Janson EM & Oberg KE 1996 Carcinoid tumours. *Baillière's Clinical Gastroenterology* **10** 589–601.
- Tiensuu JE, Eriksson B, Oberg K, Skogseid B, Ohrvall U, Nilsson S & Westlin JE 1999 Treatment with high dose [ $^{111}\text{In}$ -DTPA-D-PHE $^1$ ]-octreotide in patients with neuroendocrine tumors — evaluation of therapeutic and toxic effects. *Acta Oncologica* **38** 373–377.
- Valkema R, de Jong M, Bakker WH, Breeman WA, Kooij PP, Lugtenburg PJ, de Jong FH, Christiansen A, Kam BL, de Herder WW, Stridsberg M, Lindemans J, Ensing G & Krenning EP 2002 Phase I study of peptide receptor radionuclide therapy with [ $^{111}\text{In}$ -DTPA]octreotide: the Rotterdam experience. *Seminars in Nuclear Medicine* **32** 110–122.
- Virgolini I, Britton K, Buscombe J, Moncayo R, Paganelli G & Riva P 2002 In- and Y-DOTA-lanreotide: results and implications of the MAURITIUS trial. *Seminars in Nuclear Medicine* **32** 148–155.
- Von Werder K, Losa M, Muller OA, Schweiberer L, Fahlbusch R & del Pozo E 1984 Treatment of metastasising GRF-producing tumour with a long-acting somatostatin analogue. *Lancet* **ii** 282–283.
- Wajchenberg BL, Mendonca BB, Liberman B, Pereira MA, Carneiro PC, Wakamatsu A & Kirschner MA 1994 Ectopic adrenocorticotrophic hormone syndrome. *Endocrine Reviews* **15** 752–787.
- Waldherr C, Pless M, Maecke HR, Haldemann A & Mueller-Brand J 2001 The clinical value of [ $^{90}\text{Y}$ -DOTA]-D-Phe $^1$ -Tyr $^3$ -octreotide (90Y-DOTATOC) in the treatment of neuroendocrine tumours: a clinical phase II study. *Annals of Oncology* **12** 941–945.
- Wangberg B, Westberg G, Tylan U, Tisell L, Jansson S, Nilsson O, Johansson V, Schersten T & Ahlman H 1996 Survival of patients with disseminated midgut carcinoid tumors after aggressive tumor reduction. *World Journal of Surgery* **20** 892–899.
- Weber HC, Venzon DJ, Lin JT, Fishbein VA, Orbuch M, Strader DB, Gibril F, Metz DC, Fraker DL & Norton JA 1995 Determinants of metastatic rate and survival in patients with Zollinger–Ellison syndrome: a prospective long-term study. *Gastroenterology* **108** 1637–1649.
- Weckbecker G, Briner U, Lewis I & Bruns C 2002 SOM230: a new somatostatin peptidomimetic with potent inhibitory effects on the growth hormone/insulin-like growth factor-I axis in rats, primates, and dogs. *Endocrinology* **143** 4123–4130.
- Westberg G, Wangberg B, Ahlman H, Bergh CH, Beckman-Suurkula M & Caidahl K 2001 Prediction of prognosis by echocardiography in patients with midgut carcinoid syndrome. *British Journal of Surgery* **88** 865–872.
- Wiedenmann B, Jensen RT, Mignon M, Modlin CI, Skogseid B, Doherty G & Oberg K 1998 Preoperative diagnosis and surgical management of neuroendocrine gastroenteropancreatic tumors: general recommendations by a consensus workshop. *World Journal of Surgery* **22** 309–318.
- Wulbrand U, Wied M, Zofel P, Goke B, Arnold R & Fehmann H 1998 Growth factor receptor expression in human gastroenteropancreatic neuroendocrine tumours. *European Journal of Clinical Investigation* **28** 1038–1049.
- Wymenga AN, de Vries EG, Leijnsma MK, Kema IP & Kleibeuker JH 1998 Effects of ondansetron on gastrointestinal symptoms in carcinoid syndrome. *European Journal of Cancer* **34** 1293–1294.
- Wymenga AN, Eriksson B, Salmela PI, Jacobsen MB, Van Cutsem EJ, Fiasse RH, Valimaki MJ, Renstrup J,

- de Vries EG & Oberg KE 1999 Efficacy and safety of prolonged-release lanreotide in patients with gastrointestinal neuroendocrine tumors and hormone-related symptoms. *Journal of Clinical Oncology* **17** 1111–1117.
- Wynick D, Ratcliffe WA, Heath DA, Ball S, Barnard M & Bloom SR 1990 Treatment of a malignant pancreatic endocrine tumour secreting parathyroid hormone related protein. *British Medical Journal* **300** 1314–1315.
- Yu F, Venzon DJ, Serrano J, Goebel SU, Doppman JL, Gibril F & Jensen RT 1999 Prospective study of the clinical course, prognostic factors, causes of death, and survival in patients with long-standing Zollinger–Ellison syndrome. *Journal of Clinical Oncology* **17** 615–630.