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THE ROLE OF SOMATOSTATIN ANALOGUES IN THE TREATMENT OF NEUROENDOCRINE TUMOURS

Simona Grozinsky-Glasberg^{1,2}, Ashley B. Grossman¹ and Márta Korbonits¹

¹Department of Endocrinology, William Harvey Research Institute, Barts and the London, Queen Mary School of Medicine, University of London, EC1M 6BQ, UK, and

²Department of Endocrinology, Beilinson Hospital, Rabin Medical Center, and Sackler Faculty of Medicine, Tel Aviv, 49100, Israel.

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Address all correspondence to:
Márta Korbonits MD, PhD
Reader in Endocrine Research
Department of Endocrinology
William Harvey Research Institute
Barts and the London Medical School
Charterhouse Square
London EC1M 6BQ

Tel +44 20 7882 6238
Fax +44 20 7882 6197
email: m.korbonits@qmul.ac.uk

Abstract

Neuroendocrine tumours belong to a heterogeneous family of neoplasms, originating in endocrine glands (such as the pituitary, parathyroid or the neuroendocrine adrenal glands), in endocrine islets (within the thyroid or pancreas) as well as in endocrine cells dispersed between exocrine cells throughout the digestive or respiratory tracts. The clinical behaviour of neuroendocrine tumours is variable; they may be functioning or not functioning, ranging from well-differentiated slow growing neuroendocrine tumours to poorly-differentiated neuroendocrine tumours, which are highly aggressive malignant tumours. The development of somatostatin analogues as important diagnostic and treatment tools have revolutionised the clinical management of patients with neuroendocrine tumours. However, although symptomatic relief and stabilisation of tumour growth for various periods of time are observed in many patients treated with somatostatin analogues, tumour regression is rare. Development of new somatostatin analogues and new drug combination therapies should further improve the clinical management of these patients.

Introduction

Neuroendocrine tumours (NETs) comprise a family of neoplasms that present with a fascinating range of morphologic, functional and behavioural characteristics (Oberg, 2005).

The traditional classification of NETs include tumours originating in the adrenal medulla and sympathetic ganglia, C cells of the thyroid gland, islets of the pancreas as well as in the endocrine cells distributed throughout the digestive or the respiratory tracts (Rindi *et al.*, 2000; Solcia *et al.*, 1999). NETs were first described in 1888 by Otto Lubarsch who found multiple ileal tumours in two patients at autopsy. It was then 15 years later that Oberndorfer introduced the term carcinoid for ileal tumours that presented a more benign disease course than that of colon carcinomas (Modlin *et al.*, 2004). Subsequently, endocrine tumours of the gastrointestinal tract as well as lesions from other organs were called carcinoids, and were classified on the basis of the anatomic site of origin into *foregut carcinoids* (lung, thymus, stomach, pancreas, duodenum, upper jejunum), *midgut carcinoids* (lower jejunum, ileum, appendix, proximal colon) and *hindgut carcinoids* (transverse colon, sigmoid and rectum) (Caplin *et al.*, 1998; Ganim & Norton, 2000; Vinik *et al.*, 1989). NETs originating from the gastrointestinal tract and the pancreas are also called gastroenteropancreatic neuroendocrine tumours (GEP NETs). According to the latest World Health Organization (WHO) classification (Solcia *et al.*, 2000), which is based on tumour histology, tumour size and the presence or absence of local/distant metastases, NETs should be stratified into (a) well-differentiated neuroendocrine tumours, (b) well-differentiated endocrine carcinomas, (c) poorly differentiated neuroendocrine carcinomas and (d) mixed exocrine-endocrine carcinomas. The great majority of NETs are relatively slow growing (well-differentiated), while some of them may

present with more aggressive behaviour (poorly differentiated neuroendocrine carcinoma); these latter are fast growing tumours and, therefore, highly malignant. The well-differentiated NETs have the important ability to uptake neuroamines and to express specific receptors on their cells membranes, such as somatostatin receptors (SSTR), although not in all cases; this characteristic may be of great value for the localisation and the treatment of these tumours (Kaltsas *et al.*, 2001). While a relatively wide variety of therapeutic options are available for treating these patients (e.g., surgery, somatostatin analogue therapy, interferon- α , peptide receptor radiotherapy, chemotherapy, chemo-embolisation, etc.), few are curative and most treatments are palliative. It is unclear as to why certain of these tumours remain localised and respond well to therapy, while others present with inoperable metastatic disease and severe hormonal symptoms (Eriksson & Oberg, 1999). Therefore, successful treatment of these diseases necessitates a multidisciplinary approach in order to control symptoms, to stabilise or prevent further growth and, rarely, to achieve cure.

The response of the tumour to different therapeutic options may be defined, according to established WHO criteria, as: 1) complete response (complete regression of all clinical, radiological and hormonal evidence of tumour); 2) partial response (a 50% or greater reduction in all measurable tumour, clinical symptoms and hormonal levels, with no appearance of new lesions); 3) stable disease (less than 50% reduction or no greater than 25% increase in tumour size, clinical symptoms and hormonal measurements) and 4) progression (appearance of new lesions, or an increase of 25% or more in tumour size, and clinical/hormonal deterioration) (Arnold *et al.*, 2000).

In this review we will summarise the literature regarding the role of somatostatin analogues in the diagnosis and mostly in the treatment of gastroenteropancreatic (GEP) NETs and of other NETs, including NETs originating from parafollicular C cells of the thyroid, bronchial carcinoids, thymic carcinoids, ovarian carcinoid tumours and pheochromocytomas/paragangliomas.

I. The role of somatostatin in the diagnostic and the treatment of gastroenteropancreatic neuroendocrine tumours (GEP NETs)

Overall, GEP NETs constitute approximately 2% of all malignant tumours of the gastrointestinal system (Moertel, 1987). Midgut carcinoids, which originate from serotonin-producing enterochromaffin cells, constitute the largest group, while the second largest group includes endocrine pancreatic tumours. Pancreatic tumours may be subdivided depending on the predominant hormone production and the clinical picture. Patients may have symptoms for many years before the diagnosis is made and therefore, in order to diagnose these tumours, the index of suspicion must be high.

During the last decade, the diagnostic and therapeutic approach of endocrine GEP tumours has considerably improved, mainly due to better imaging techniques with CT, MRI, PET and somatostatin analogue-based imaging methods, as well as receptor subtype characterisation and the introduction of long-acting somatostatin analogues.

Somatostatin receptor imaging of GEP NET

Somatostatin (somatotropin release-inhibiting hormone (SRIF)) is a peptide hormone present in two natural forms (14 and 28 amino-acids) which bind with high affinity to

5 different subtypes of specific somatostatin receptors (Patel *et al.*, 1990). The very short half life of the natural compound (around 3 minutes) has resulted in the development of synthetic analogues: short-acting analogues (octreotide, lanreotide or vapreotide, which need to be administered subcutaneously several times per day), or long-acting analogues (octreotide long-acting release, LAR, and lanreotide autogel, both with monthly administration) (Heron *et al.*, 1993). Tumours and metastases that express the somatostatin receptor subtypes SSTR2, SSTR3 or SSTR5 can be visualised *in vivo* using injection of radiolabelled somatostatin analogues (e.g. ^{111}In -pentetreotide) (de Herder *et al.*, 2006a). SSTR2 and SSTR5 are expressed in about 70%-90% of GEP NET. Except for benign insulinomas in which, due to the lower expression of SSTR2, the sensitivity of the scintigraphy is only about 40-50%, the overall sensitivity of SSTR scintigraphy is high, from 86% to 95% for gut carcinoid tumours to 75%-100% for pancreatic endocrine tumours (Lamberts *et al.*, 2002a; van Eyck *et al.*, 1993).

SSTR scintigraphy has become a very important tool in the accurate staging and treatment of GEP NETs due to its ability to detect tumour sites which are not visualised by conventional imaging methods. It may also help to decide which patients are suitable for surgery, on suitability for treatment with somatostatin analogues (octreotide or lanreotide), or for tumour-targeted radioactive therapy using one of the radiolabelled somatostatin analogues (Janson *et al.*, 1999; Krenning *et al.*, 1999; Kwekkeboom *et al.*, 2005; Lamberts *et al.*, 1990; Lamberts *et al.*, 2002a; Oberg, 2004; van Eyck *et al.*, 1993). Several reviews are available discussing this topic in detail (de Herder & Lamberts, 2002; de Herder *et al.*, 2003; Kaltsas *et al.*, 2005).

The role of somatostatin analogues in the treatment of specific GEP NETs

The somatostatin analogue octreotide has been in clinical use for treatment of NETs since the early 1980s, having both cytotoxic and cytostatic actions; it was shown to influence cell growth and induce apoptosis, particularly at high doses (Garcia *et al.*, 2002).

[A] Somatostatin analogues for the treatment of the endocrine tumours of the gastric mucosa

The enterochromaffin like (ECL) cells originating in the gastric mucosa may develop into endocrine tumours (gastric carcinoids) and may be divided into four distinct categories: type A, associated with chronic atrophic gastritis, type B, associated with the Zollinger-Ellison syndrome, type C, which is sporadic (Gough *et al.*, 1994b; Kulke & Mayer, 1999; Soga, 1997), and type D, poorly differentiated endocrine carcinomas (Rindi *et al.*, 1999). A fifth group can be added to this, ghrelin-secreting gastric carcinoids (Tsolakis *et al.*, 2004). The majority of gastric carcinoids (~75%) are type A carcinoids; these patients have hypochlorhydria and hypergastrinaemia with ECL cell hyperplasia, and approximately 50% have associated pernicious anemia. Most of these tumours are small (less than 1 cm in diameter) and multifocal (Akerstrom, 1996); they are usually indolent, metastasising in 8%-23% (distant metastases in 3-5%) with a low overall mortality (Granberg *et al.*, 1998). Between 5% and 10% of gastric carcinoids are associated with the Zollinger-Ellison syndrome; they occur almost exclusively in the context of Multiple Endocrine Neoplasia type 1 (MEN1), are multiple and may metastasise (5-10% of the cases) (Granberg *et al.*, 1998). Type C gastric carcinoids (15-25%) are sporadic, usually solitary and greater

than 1 cm in diameter. These tumours are highly aggressive, the great majority being metastatic at diagnosis and associated with a high mortality rate (Akerstrom, 1996; Gough *et al.*, 1994a; Rindi *et al.*, 1996). One of the gastric endocrine hormones is ghrelin, synthesised in the ghrelin cells (previously known as X/A cells). Ghrelin is a 28 amino-acid hormone with growth hormone-releasing and appetite-inducing functions and it has been shown to be expressed in gastrointestinal stromal tumours (Ekeblad *et al.*, 2006). A case-report has described a patient with a metastasising gastric neuroendocrine tumour which presented intense immunoreactivity for ghrelin and extremely high circulating levels of ghrelin (Tsolakis *et al.*, 2004). Pancreatic tumours have also been described with excess ghrelin secretion (Corbetta *et al.*, 2003).

In the last few years, patients with type A or B gastric carcinoids have increasingly been treated with somatostatin analogues. While treatment with proton-pump inhibitors is very effective in reducing hypergastrinaemia-induced gastric acid hypersecretion (Tomassetti *et al.*, 2005), it does not improve the ECL cell hyperplasia. In a case-report of a patient with multiple type A gastric carcinoids, treatment with the long-acting somatostatin analogue octreotide-LAR for a period of 9 months induced normalisation of serum gastrin levels and permanent disappearance of the tumours (Prommegger *et al.*, 2003). In another study (Fykse *et al.*, 2004), five patients with hypergastrinaemia and gastric carcinoids were treated for a period of 1 year with monthly injections of octreotide-LAR; at the end of the study, although gastrin levels did not totally normalise, there was a significant reduction in tumour load, ECL cell density and normalisation of circulating chromogranin A levels, indicating a possible direct antiproliferative effect of the treatment. Furthermore, another study presented 3 patients suffering from Zollinger-Ellison syndrome who were treated with lanreotide

or octreotide for a period of 1 year, showing a significant reduction in the gastrin levels and no evidence of the tumours at the end of the study (Tomassetti *et al.*, 2000a). Although the number of patients included in these studies is small, these results suggest that the somatostatin analogues have an important antiproliferative effect under some circumstances. However, there is little known regarding the effect of somatostatin analogues on cell proliferation in patients with gastric carcinoids type C or poorly differentiated endocrine carcinomas: in these tumours, such treatment may be considered only as palliative, reducing symptoms related to carcinoid syndrome.

[B] The role of somatostatin in the treatment of the midgut and hindgut carcinoid tumours

Midgut carcinoids constitute approximately 50% of all carcinoid tumours, the most common of the GEP NETs, affecting about 5-7 new patients per million population per year. These tumours are usually slow-growing; the clinical presentation may be related to pain, due to the tumour mass effect or to fibrosis in the mesentery. Another group of patients (around 10%-15%) suffer from the typical signs of the 'carcinoid syndrome' (watery diarrhoea, flushing, right-sided heart failure and bronchial constriction), which is related to the tumour hypersecretion of a variety of endocrine substances, the most frequent of which are serotonin (5-hydroxytryptamine) and the tachykinins (Kulke & Mayer, 1999). Since the majority of these patients have metastatic disease at the time of diagnosis, surgery is rarely curative and therefore medical treatment has to be considered (Oberg, 2002). These tumours frequently express somatostatin receptors (80%-100% of cases); SSTR2 is the most frequently

expressed (Reubi, 2004), and therefore somatostatin analogues are an important palliative tools for these patients.

Somatostatin analogues as symptomatic treatment

Many studies show that somatostatin analogues, at variable dosages (from 100µg twice a day to 200µg three times a day for octreotide, 10-30mg octreotide-LAR every 4 weeks or 30mg lanreotide every 10-14 days), may significantly improve symptoms such as diarrhoea, flushing or other manifestations of the carcinoid syndrome (between 38-88% in different studies); they may also significantly lower the levels of urinary-5HIAA (hydroxyindoleacetic acid), the metabolite of serotonin (Kvols *et al.*, 1986; O'Toole *et al.*, 2000; Oberg *et al.*, 1991; Rubin *et al.*, 1999b; Vinik *et al.*, 1986; Wymenga *et al.*, 1999).

A multicentre study of 33 patients with the carcinoid syndrome compared treatment with lanreotide (30mg im every 10 days) versus octreotide (200µg sc twice or thrice daily) in terms of patient preference and efficacy in controlling symptoms (O'Toole *et al.*, 2000). No significant differences were found in terms of quality of life. Disappearance or improvement in flushes and diarrhoea occurred in 53.8% and 45.4% respectively, of the patients treated with lanreotide, while they were observed in 68% and 50% respectively, of those on octreotide. Both drugs were equally effective in reducing urinary 5HIAA levels and plasma serotonin levels. In a multicentre study on 71 patients with the carcinoid syndrome, 6 treatments of prolonged-release lanreotide Autogel were administered in various doses (60mg, 90mg or 120mg) depending on symptom response over a period of 6 months (Ruszniewski *et al.*, 2004); 65% of the patients with flushing and 18% of diarrhoea patients achieved more than 50%

reduction of symptoms from baseline, with important reductions in urinary 5-HIAA and chromogranin A levels (24 and 38% respectively).

Another randomised double-blind trial which compared octreotide-LAR at 10, 20, and 30mg every 4 weeks with open-label sc octreotide every 8 hours for the treatment of carcinoid syndrome has shown that the efficacy of short-acting octreotide and of the long-acting octreotide-LAR was the same once plasma octreotide steady-state concentrations were achieved (Rubin *et al.*, 1999a). Data from this study suggested that the starting dose for octreotide-LAR should be 20mg.

Somatostatin analogue effect on tumour growth

The antiproliferative effect of somatostatin analogues on the growth of the midgut carcinoids is largely unknown; overall, partial or complete responses were observed in fewer than 10% of the patients, while stabilisation of tumour growth was noticed in 24%-57% of the patients (Plockinger *et al.*, 2004).

The administration of somatostatin analogues in *regular doses* produced stabilisation of tumour growth in 40%-50% of the patients in various studies (Arnold *et al.*, 1996; Di Bartolomeo *et al.*, 1996; Saltz *et al.*, 1993), which persisted for varying periods of time (between 2 and 60 months). Tumour regression was partial in two out of 38 patients included in one of these studies (Di Bartolomeo *et al.*, 1996), while no tumour regression was reported in the other two studies.

There are studies that indicate that using a *higher than usual dose* of somatostatin analogues may have a more prominent effect on tumour size. High-dose treatment with lanreotide (up to 12mg/day) produced tumour size reduction in 5% and stabilisation in 70% of the 19 patients included in one study (Eriksson *et al.*, 1997). In another study in which 30 patients were treated with sc injections of 5mg lanreotide

three times a day for a period of one year, one complete and one partial remission were observed in patients with functional midgut NETs; in the same study, 11 patients had stable disease (36%) and 11 patients showed continuing tumour growth after 3-12 months of treatment (Faiss *et al.*, 1999). In a study where biopsy specimens were taken before and during somatostatin analogue treatment the treatment with high-dose somatostatin analogues induced apoptosis in neuroendocrine tumours, while this was not found during treatment with low-dose somatostatin (Imam *et al.*, 1997). According to these results, it is still hard to predict which patient will respond to the treatment in terms of tumour growth inhibition.

The effect of the combination of somatostatin analogues and interferon on tumour growth has been assessed in only a few studies, with variable results. One of these studies showed that this combination may be of benefit in patients where the usual octreotide treatment failed to achieve a biochemical and symptomatic control (Tiensuu Janson *et al.*, 1992); another study indicates that this combination seemed to reduce the tumour progression compared with octreotide treatment alone, but without a significant effect on 5-year survival (Kolby *et al.*, 2003). A third study suggested that the addition of alpha-interferon to octreotide showed antiproliferative efficacy in a subgroup of patients with advanced metastatic disease unresponsive to octreotide monotherapy, and prolonged survival was reported in the responder group (Frank *et al.*, 1999). However, most published data do not support a major effect of interferons over and above that of somatostatin analogues.

Hindgut carcinoid tumours are rarely associated with a clinical syndrome; in such patients treatment with somatostatin analogues may be used for symptomatic relief, but there are no studies regarding their effect on tumour growth in hindgut tumours.

[C] The role of somatostatin in the treatment of the pancreatic endocrine tumours

Endocrine pancreatic tumours are divided depending on their secretory ability into functioning or non-functioning tumours. The non-functioning tumours constitute the largest group, representing approximately 50% of the endocrine pancreatic tumours (Evans *et al.*, 1993); following in incidence are the insulinomas (25%) (de Herder *et al.*, 2006b) and gastrinomas (15%) (Roy *et al.*, 2000), while the remaining 15% include VIP-omas (Soga & Yakuwa, 1998), glucagonomas (Chastain, 2001) and somatostatinomas (Soga & Yakuwa, 1999). Most of these tumours are sporadic, while about 15–30% are hereditary and appear in the context of MEN1 or von Hippel-Lindau syndromes.

Somatostatin receptors have been extensively mapped in different pancreatic tumours by means of autoradiography, reverse-transcription polymerase chain reaction, in situ hybridization and immunohistochemistry. SSTR1, 2, 3 and 5 are usually expressed in the majority of pancreatic NETS, the exception being the benign insulinoma in which the SSTR2 is less expressed (Janson & Oberg, 2003). Another study examining 81 functioning and non-functioning GEP NETs showed that the vast majority expressed SSTR1, 2, 3 and 5, while SSTR4 was detected only in a small minority (Papotti *et al.*, 2002). Pancreatic insulinomas had heterogeneous SSTR expression, while 100% of somatostatinomas expressed SSTR5 and 100% gastrinomas and glucagonomas expressed SSTR2.

The role of somatostatin analogues in the treatment of insulinomas

Insulinoma is a rare but an important cause of endogenous hypoglycaemia, occurring with an incidence of about 1/million population per year (Service *et al.*, 1991).

Somatostatin analogue treatment can improve (inhibition of insulin release) or worsen (profound suppression of counter-regulatory hormones GH and glucagon) the symptoms associated with hypoglycaemia (Maton, 1993). Therefore, treatment has to be started in a hospital setting, using a gradually increasing dose escalation of the drug, and frequent monitoring of blood glucose levels. Recently, a study of 17 patients with insulinoma assessed the efficacy of octreotide on hypoglycaemia and its relation to a positive octreoscan and with immunostaining with anti-SSTR2 and anti-SSTR5 antibodies (Vezzosi *et al.*, 2005). Octreotide was effective in the control of hypoglycaemia in more than 50% of the patients, and a positive subcutaneous short octreotide test (100µg octreotide sc in fasting patients, with improvement in hypoglycaemia) was a better marker of responsive patients than positive scintigraphy. The treatment was effective in all SSTR2-positive patients and in a few SSTR2 negative ones, while no relation between treatment effectiveness and the expression of SSTR5 was observed. These results are in concordance with other case reports and smaller series of insulinoma patients reported in the literature (Hearn *et al.*, 1988a; Tanaka *et al.*, 2000; Verschoor *et al.*, 1986; von Eyben *et al.*, 1994). Given the fact that surgical excision is the definitive treatment of insulinoma, there are no clear data in the literature regarding the potential antiproliferative effect of the somatostatin analogues on these tumours.

We have conducted a study regarding the effects of somatostatin analogues on cell proliferation in the rat-derived insulinoma cell line (INS1). Our preliminary data show that octreotide has a significant inhibitory effect on cell proliferation, as assessed by cell counting and MTS assay, and on phosphorylation states of a number of proteins in the PI3K/Akt/mTOR pathway (Franchi *et al.*, 2007).

The role of somatostatin analogues in the treatment of gastrinomas

Gastrinomas are the second most frequent functional endocrine tumours of the pancreas, occurring either in a sporadic form or, in up to 25%, in the context of MEN1 syndrome (Jensen, 1996). The effects of gastric acid hypersecretion dominate the clinical picture of the gastrinomas; therefore, proton pump inhibitors are currently the therapy of choice for the control of gastric-acid associated symptoms (Metz *et al.*, 1993). Few data are available regarding the role of somatostatin analogues in the treatment of gastrinomas. In a study of 15 malignant gastrinoma patients (Shojamanesh *et al.*, 2002), treatment with octreotide-LAR was administered with a primary goal of assessing its effect on tumour size; in about 50% of these patients, octreotide had an antiproliferative effect, including 1 patient with tumour regression and another 7 patients with tumour stabilisation (for a mean period of 25 months). An important observation of this study was that patients with slow-growing tumours were more likely to respond to this treatment; therefore, the authors recommended that octreotide treatment should replace chemotherapy as the standard treatment for these patients. Recently, the high expression of somatostatin receptors on gastrinomas has been considered as an opportunity to administer radiolabeled somatostatin analogues, in order to achieve a cytotoxic effect (^{111}In -labelled analogues, $^{90}\text{yttrium}$ or $^{177}\text{lutetium}$) (Jensen, 2004).

The role of somatostatin analogues in the treatment of glucagonomas

Glucagonomas are rare slow-growing pancreatic tumours, originating in the α -cells of the pancreas; the majority are sporadic, and rarely they may be associated with

familial syndromes (MEN1 or familial adenomatous polyposis) (Chastain, 2001). Somatostatin analogue treatment may be indicated in glucagonoma patients for alleviating the symptoms related to the characteristic skin rash (necrolytic migratory erythema) or diarrhoea (Casadei *et al.*, 1999; Tomassetti *et al.*, 2000b; Wermers *et al.*, 1996). There are no data available on their SSTR expression patterns.

The role of somatostatin analogues in the treatment of somatostatinomas

Somatostatinomas are very rare tumours, originating either in pancreas or in the small intestine (Soga *et al.*, 1990; Soga & Yakuwa, 1999); the symptoms are usually related to somatostatin hypersecretion (hyperglycaemia, cholelithiasis, diarrhoea and steatorrhoea, hypochlorhydria) or to the mass effect (Soga & Yakuwa, 1999). It is an interesting concept to treat patients with elevated somatostatin levels and symptoms related to the high somatostatin levels with a somatostatin analogue. In a study of three patients with metastatic somatostatinomas, octreotide treatment was shown to be effective in reducing plasma levels of somatostatin and improving the related symptoms; an octreoscan detected somatostatinomas tumour lesions in all three patients studied (Angeletti *et al.*, 1998).

The role of somatostatin analogues in the treatment of VIP-omas

VIP-omas are rare pancreatic endocrine tumours which secrete vasoactive intestinal polypeptide (VIP). VIP is a potent stimulant of adenylate cyclase, which will cause hypersecretion of water and electrolytes by the intestinal mucosa, contributing to a typical clinical syndrome (Verner-Morrison syndrome) characterised by watery diarrhoea, hypokalaemia, achlorhydria and metabolic acidosis (Bloom *et al.*, 1973; Schwartz *et al.*, 1974). 50% of these tumours are malignant and the mortality rate may

be as high as 30% due to the serious metabolic consequences of the syndrome. Intravenous fluid and electrolyte replacement is essential, together with octreotide, which will control symptoms promptly in more than 90% of patients (O'Dorisio *et al.*, 1989). A recent retrospective review described four cases of VIP-oma in which octreotide was very successful as an adjuvant therapy for symptom control and for reducing the serum elevated VIP levels (Ghaferi *et al.*, 2007), improving the diarrhoea and the electrolyte imbalance. Corticosteroids may be used in patients not responding to somatostatin analogues.

Somatostatin analogues and non-functioning endocrine pancreatic tumours

The place of somatostatin analogues in the treatment of these tumours is unclear, as few studies have been published in these patients. A prospective multicentre trial investigated the octreotide effects on tumour growth after 1 year of treatment in 103 metastatic GEP NETs patients and included 15 patients with diagnosed non-functional pancreatic tumours (Arnold *et al.*, 1996); in this subgroup, tumour growth stabilised in only 3 patients, while in another 8 patients the tumour progressed (the outcome of the remaining 4 patients was not clear). Recently, a case report described that octreotide-LAR was useful in achieving tumour regression in one and in preventing tumour progression in another patient diagnosed with a metastatic non-functioning neuroendocrine pancreatic tumour (Koehler *et al.*, 2007).

II. The role of somatostatin analogues in the diagnosis and treatment of other neuroendocrine tumours

Medullary thyroid carcinoma (MTC)

MTC is a rare tumour of the thyroid (3%-10% of all thyroid carcinomas) originating in the parafollicular C cells. This tumour can be sporadic, while in about 25% it may be hereditary, as part of the multiple endocrine neoplasia syndrome 2 (MEN2) type A or type B, or as an isolated familial form (Familial MTC) (Marsh *et al.*, 1995). MTC may synthesise and secrete calcitonin in high amounts, as well as other peptides such as carcinoembryonic antigen (CEA), neuron specific enolase (NSE), chromogranin A or ACTH resulting in diarrhoea, facial flushing or Cushing's syndrome (Kebebew *et al.*, 2000; Raue, 1998). Total thyroidectomy with central lymph node dissection is the initial and the only potentially curative treatment of choice (Giuffrida & Gharib, 1998).

The distribution of somatostatin receptors (SSTR1-5) in MTC was analysed by immunohistochemistry in a large retrospective study including 51 MTC specimens; the results were correlated with expression of somatostatin peptide, tumour pathology and clinical outcome (Papotti *et al.*, 2001). 49% of the tumours were positive for SSTR1, 43% for SSTR2, 47% for SSTR3, 4% for SSTR4, and 57% for SSTR5, with 75% of the specimens expressing the octreotide-sensitive receptor subtypes (SSTR2 and SSTR5) and even higher percentage potentially expressing pasireotide (SOM230)-sensitive SSTRs. In this study, no correlation between SSTR1-5 expression and age, sex, tumour size or staging, histological type or clinical outcome was found.

Studies assessing the effect of somatostatin analogues in the treatment of symptomatic MTC are limited and controversial. In one study, this treatment produced a significant improvement in symptoms such as diarrhoea, weight loss or malaise in all of the three patients with metastatic MTC which were included, with a parallel decrease in the calcitonin and CEA levels (Mahler *et al.*, 1990). In another study, 14 post-

thyroidectomy metastatic MTC patients were treated with continuous subcutaneous infusion of 500µg/day of octreotide, for 90 days, in order to assess the effect of the treatment on tumour regression (Modigliani *et al.*, 1992). Continuous infusion of octreotide did not induce any morphological improvement or a significant decrease in calcitonin levels; in 4 patients calcitonin levels fell during treatment (between 15% and 50%), while in 9 patients calcitonin increased (from 22% to 130%) after cessation of therapy. In patients with advanced metastatic disease, the administration of octreotide combined with interferon was studied; in a study of 8 patients with advanced MTC, patients received octreotide (at a starting dose of 150µg/day sc for 6 months, followed by a dose of 300µg/day sc for another 6 months) combined with rIFN-alpha-2b (at a dose of 5 million IU/day im 3 times a week, for 12 months) (Lupoli *et al.*, 1996); while significant symptomatic improvement was observed in some of the treated patients (diarrhoea, in four patients, and flushing, in one), no significant changes in the size of metastases were observed. A maximum decrease of calcitonin was reached after 3 months in 4 patients, while in all patients the CEA levels decreased during treatment. In another study, disease stabilisation was achieved in three patients and minor tumour regression in two patients out of the 7 patients included (Vitale *et al.*, 2000).

Radionuclide therapy using somatostatin analogues has been used occasionally in these patients: a few patients with MTC have received ¹¹¹In-octreotide or ⁹⁰Y-lanreotide in the MAURITIUS trial (Virgolini *et al.*, 2002) and the initial results were encouraging, suggesting that more prospective studies are needed. To summarise, somatostatin analogues may produce symptomatic improvement in some patients with metastatic MTC, with a transient effect on the hormonal levels; however, their effect on tumour growth and proliferation is still unclear.

Bronchial carcinoid tumours

Bronchial carcinoid tumours belong to the foregut carcinoids, accounting for about 2.5% of all pulmonary neoplasms and for 12-15% of carcinoid tumours overall. They originate from the neuroendocrine cells of bronchial mucosa, presenting a wide range of clinical and biological behaviour; this includes their potential to synthesise and secrete peptide hormones, particularly ACTH, serotonin, somatostatin and bradykinin. Neuroendocrine lung tumors were previously subdivided into typical and atypical carcinoids (Arrigoni *et al.*, 1972), and small cell lung carcinomas, but several other classifications have later been proposed (Capella *et al.*, 1995; Travis *et al.*, 1998; Warren & Gould, 2002; Warren *et al.*, 2006), and a fourth category, termed large cell neuroendocrine carcinomas, was defined; the major WHO morphological categories of lung neuroendocrine tumours include low-grade typical carcinoid (TC), intermediate-grade atypical carcinoid (AC), the high grade small cell carcinoma (SCLC) and large cell neuroendocrine carcinoma (LCNEC) (Beasley *et al.*, 2005). Neuroendocrine lung tumours are characterised structurally by the presence of dense core granules, and immunohistochemically by the production of small polypeptides. Many of the patients with bronchial carcinoids (13%–51%) are asymptomatic, the tumour being detected on routine chest X-ray. Presenting symptoms may include cough, hemoptysis, dyspnoea, wheezing, chest pain and recurrent pulmonary infections; the carcinoid syndrome (with flushing, diarrhoea, wheezing and elevated urinary 5-HIAA) is infrequent, occurring in 2%–12% of the patients (Dusmet & McKneally, 1994; Soga *et al.*, 1999a). Liver metastases are detected in most patients displaying the carcinoid syndrome (Davila *et al.*, 1993; Dusmet & McKneally, 1994).

An atypical carcinoid syndrome (with severe generalised flushing, swelling, lacrimation, asthma and diarrhoea), due to histamine secretion, may be observed. Ectopic Cushing's syndrome, due to secretion of ACTH or CRH, is seen in 2%–6% of bronchial carcinoid patients (Soga *et al.*, 1999b).

Regarding the expression of SSTRs, a study that assessed the expression of SSTR2A immunoreactive cells in normal lung tissue using a highly specific SSTR2A antibody (R2-88) demonstrated only rare SSTR2A positive cells in bronchi and bronchioles, which could represent stem/progenitor cells (Gugger *et al.*, 2004). In another study in which several methods (e.g., receptor binding, in situ hybridisation, and immunohistochemistry) were combined and correlated SSTR2A in different human tumours, demonstrated the expression of these receptors in some of the bronchial carcinoids (Reubi *et al.*, 1998). The analysis of tumor tissue from 5 patients with bronchial carcinoid tumors using polyclonal antibodies directed against SSTR2 and consequently immunohistochemistry demonstrated that only one of these patients stained positive with the SSTR2 antibodies, whereas the other four were negative (Janson *et al.*, 1998). This result correlated well with the uptake of the tumour on octreoscan: the only patient with a positive stain at immunohistochemistry also showed uptake at scintigraphy. By contrast, it was showed that small cell lung carcinomas often possess somatostatin receptors (Reubi *et al.*, 1990; Reubi *et al.*, 1994).

In a study of 28 patients with histologically-confirmed bronchial carcinoids who underwent octreoscan examination, and had their results compared with CT, MRI and bone scan, 20 patients (71%) had octreoscan-positive tumours, including 2/5 patients with ectopic ACTH secretion and 8/9 patients with carcinoid syndrome. The primary tumour was octreoscan-positive in 13/16 patients and could be detected on CT in

15/16 patients. The authors concluded that in patients with bronchial carcinoids, octreoscan is less sensitive for detection of the primary tumour and liver metastases than CT, and the conventional bone scan is more effective than the octreoscan for identification of bone metastases (Granberg *et al.*, 2003). Nevertheless, the octreoscan may be useful in the follow-up of patients with somatostatin-receptor positive bronchial carcinoid tumours and should be performed in all these patients prior to attempts at curative surgery. There are several case reports in which the octreoscan identified the primary tumour in patients with occult ectopic Cushing's syndrome (Carretta *et al.*, 1997; Mansi *et al.*, 1997; Phlipponneau *et al.*, 1994).

Octreotide has mainly symptomatic effects in patients with bronchial carcinoids, while its effect on tumour growth is controversial. In a study of 31 patients with metastatic pulmonary carcinoids (Granberg *et al.*, 2001), somatostatin analogues given as single drug treatment were associated with progressive disease; the combination of α -interferon and octreotide produced efficient symptomatic relief, but stabilised the tumour growth in only 15% of the cases. However, in another study, the administration of octreotide at a daily dosage of 1500 μ g sc controlled the symptoms associated with carcinoid syndrome in all patients and induced reduction/complete resolution of the liver metastases in 3 out of the 7 patients included (Filosso *et al.*, 2002).

In patients with ectopic Cushing's syndrome due to ACTH secretion from lung carcinoids, administration of the somatostatin analogue octreotide was shown to be effective in reducing the circulating ACTH levels (Hearn *et al.*, 1988b).

Thymic carcinoid tumours

The thymus is one of the rarest sites for the development of neuroendocrine tumours and they usually carry a poor prognosis. Eight cases of thymic carcinoids were first described in 1972 as a different entity from thymic carcinomas (Rosai & Higa, 1972) and ~150 cases have been reported since. Rarely, these tumours may appear in association with multiple endocrine neoplasia type 1 (MEN1) (Rosai *et al.*, 1972). Thymic carcinoids are frequently metastatic, have a poor outcome and are commonly associated with ectopic ACTH production, but not with the carcinoid syndrome (Moran & Suster, 2000).

Regarding SSTR expression by these tumours, the literature is limited; in one study, none of the 12 thymic carcinoid specimens analysed stained positively for somatostatin receptors (Tiffet *et al.*, 2003), while expression of somatostatin receptors was demonstrated in another study of a thymic carcinoid tumour, which was subsequently visualised on somatostatin receptor scintigraphy (Nilsson *et al.*, 1998). The usefulness of octreoscanning as a diagnostic technique in these patients was confirmed in 4 of 7 patients with distant intra- and extrathoracic metastases involving lymph nodes, liver, bone, skin, and adrenal glands (Ferolla *et al.*, 2005). However, in another study, the octreoscan was unable to detect the development of bone metastases in two out of the 7 patients with metastatic thymic carcinoids included (Gibril *et al.*, 2003). There are a number of case reports in which somatostatin analogues were efficient in the detection and symptomatic relief in patients with thymic carcinoid tumours associated with ectopic growth hormone-releasing hormone (GHRH) (Boix *et al.*, 2002) or ectopic ACTH secretion (Matejka *et al.*, 1996). The efficacy of somatostatin receptor scintigraphy in the detection of small thymic lesions has not been completely established. There are no data in the literature regarding the effect of somatostatin analogues on the growth of thymic carcinoids.

Ovarian carcinoids

These are rare tumours (0.52%–1.7% of ovarian tumours in different series) which usually present with either pain in the pelvic area or pain with defaecation (Davis *et al.*, 1996). Some of these tumours are cystic teratomas with a more benign course, fewer incidences of regional and hepatic metastases and a 5-year survival of almost 100%, while others have a 5-year survival rate of about 84%. The carcinoid syndrome is present in approximately 30% of patients, while ectopic ACTH secretion inducing the clinical picture of Cushing's syndrome has also been reported (Schlaghecke *et al.*, 1989).

The expression of SSSTR specifically by ovarian carcinoids is unclear; however, in a study in which 47 different ovarian tumour specimens were analysed (Schulz *et al.*, 2002), 18 tumours (38%) revealed no somatostatin receptor immunoreactive staining, while 14 (30%) expressed more than one somatostatin receptor subtype; this was independent of patient age, diagnosis and histological grade.

The treatment of choice for these tumours is surgical excision; there are a limited number of published case reports in which octreotide was used as a symptomatic therapy, for alleviating symptoms associated with carcinoid syndrome, or intraoperatively in patients with carcinoid associated right heart failure (Vergani *et al.*, 1998; Watson *et al.*, 1990).

There are no data in the literature regarding the antiproliferative effect of somatostatin analogues in the treatment of these tumours.

Phaeochromocytomas and paragangliomas

Pheochromocytomas and paragangliomas are NETs arising from chromaffin cells and may occur in sporadic or familial forms (associated with MEN2A or 2B, von Hippel-Lindau syndrome, Neurofibromatosis 1, Carney's triad, or mutations of succinic dehydrogenase subunits C, D and particularly B) (Goldstein *et al.*, 1999; Astuti *et al.*, 2003; Astuti *et al.*, 2004; Mhatre *et al.*, 2004; Neumayer *et al.*, 2007). Pheochromocytomas are chromaffin cell tumours originating in the adrenal medulla (Shapiro & Fig, 1989), while paragangliomas derived from the paraganglia (sympathetic, localised mainly in the retroperitoneum and thorax, or parasympathetic, occurring in the area of the aortic arch, neck, and skull base). Very approximately, about 10% of chromaffin cell tumours are malignant, 10% are familial, 10% are not associated with hypertension, 10% are extra-adrenal, 10% are bilateral, and 10% occur in children (Schlumberger *et al.*, 1992) although recent data suggest that the proportion of apparently sporadic tumours associated with germline mutations may be as high as 30% (Cascon *et al.*, 2004; Castellano *et al.*, 2006). The catecholamines (epinephrine/adrenaline, norepinephrine/noradrenaline and dopamine) are the main secretory products of chromaffin cells. A number of hormones have been described in patients with functioning catecholamine secreting tumours: secretion of ACTH, inducing Cushing's syndrome; substance P, tachykinins and histamine inducing hypotension; VIP and calcitonin gene-related peptide (CGRP) which may produce flushing (Bravo & Tagle, 2003).

In a study which assessed the SSTR expression in 10 pheochromocytomas, no SSTR5 expression was found, while SSTR1 was present in nearly all of these tumours (Ueberberg *et al.*, 2005). SSTR protein expression, including staining pattern, distribution and subcellular localisation of receptor subtypes, was evaluated in another study including 52 pheochromocytomas (Mundschenk *et al.*, 2003).

Although the vast majority of tumours (90%) showed positive immunohistochemical staining for SSTR3, immunoreactive SSTR2A was seen only in 13 tumours (25%). All other somatostatin receptor subtypes were less frequently detected. Interestingly, a dissociation between the SSTR positive expression followed by a positive response to somatostatin analogues *in vitro*, and a negative octreoscan *in vivo*, was described (Zatelli *et al.*, 2003), indicating that somatostatin analogues may be helpful in the treatment of pheochromocytomas even when the octreoscan is negative.

Because chromaffin cell tumours often express SSTRs, the octreoscan may be used for the tumour localisation, particularly in cases of ^{123}I -MIBG-negative lesions (Kaltsas *et al.*, 2001).

Following the stabilisation of the clinical symptoms with specific antihypertensive treatment, surgical excision of the tumour should be performed in order to obtain disease-free, long-term survival (Bravo, 2002). Short-term or long-term administration of somatostatin analogues has not been shown to be of any benefit, although rarely biochemical responses have been observed (Kopf *et al.*, 1997), being capable of lowering the levels of norepinephrine, but with no consistent effect on blood pressure (Invitti *et al.*, 1993; Lamarre-Cliche *et al.*, 2002). However, another study demonstrated that sometimes octreotide may control the blood pressure before surgery in some patients with pheochromocytoma-induced uncontrolled hypertension (Koriyama *et al.*, 2000). Rarely, malignant pheochromocytomas may be octreotide - but not MIBG - avid; in such cases therapy with octreotide could be of value (van der Harst *et al.*, 2001); occasionally, disease stabilisation has been reported in a few patients with malignant chromaffin cell tumours treated with radionuclide somatostatin analogues, such as ^{111}In -octreotide and ^{90}Y -octreotide (DOTATOC) (Valkema *et al.*, 2002).

III. New therapies in NETs

Pasireotide (SOM230) and other somatostatin analogues

The natural compound somatostatin is capable to bind with a high affinity to all SSTR subtypes (SSTR1, 2, 3, 4, and 5), while its synthetic analogues have only limited affinity, binding mainly to SSTR2, with lesser affinity for SSTR3 and SSTR5 (Patel, 1999). Therefore, new somatostatin analogues are being studied: SOM230 (pasireotide), which is discussed in more detail elsewhere in this volume, is a new “universal” or “pan-receptor” somatostatin analogue, which possess a high affinity for SSTR1, 2, 3, and 5 subtypes, being under evaluation in phase I-III trials (Bruns *et al.*, 2002; Lamberts *et al.*, 2002b; Weckbecker *et al.*, 2002). Its receptor binding profile is 30- to 40-times higher for SSTR1 and SSTR5 than octreotide. In a phase II open-label, multicentre study including 21 patients with metastatic carcinoid tumours whose symptoms (diarrhoea and flushing) were refractory to octreotide-LAR, pasireotide at dosages between 450-1200µg twice a day effectively controlled symptoms in one-third of these patients and was generally well tolerated (Kvols *et al.*, 2005).

It has been shown that subtypes of somatostatin and dopamine receptors may form homo- and hetero-dimers at the membrane level, and that this receptor “association” may be induced by addition of either dopamine or somatostatin. The development of somatostatin receptor subtype-specific analogues or chimeric analogues binding to SSTR2, SSTR5 and dopamine 2 receptors has demonstrated some promising clinical results. Recently, a number of new interesting compounds (subtype selective analogues and antagonists, as well as bi-specific and hybrid somatostatin/dopamine compounds), have been developed (Ferone *et al.*, 2007). The effects of these chimeric

molecules have been studied in animal and human cell lines, and also in primary cultures from human tumours. Their activity is complex and heterogeneous, and further studies are needed to understand their biological effects.

Radiolabelled somatostatin analogues and the peptide receptor radionuclide therapy (PRRT)

Somatostatin receptor targeted radiotherapy represents a new advance in the treatment of NETs. It is based on the presence of SSTRs in a higher density in these tumours (compared with the normal surrounding parenchyma), and on their ability to form a receptor-ligand complex, permitting therefore the internalisation and the accumulation of the radiopharmaceutical inside the tumour.

PRRT was performed initially using indium-111, with only a few objective responses-rates (Fjalling *et al.*, 1996; Kwekkeboom *et al.*, 2005). The development of radio-metal labelling chelators, such as DOTA (1,4,7,10-tetrazacyclo-dodecane-*N,N',N'',N'''*-tetraacetic acid), which may be combined with metal ions (such as gallium, yttrium or lutetium), has allowed new therapeutic applications (Heppeler *et al.*, 2000). In a phase II study which evaluated the tumour response to targeted irradiation with the radiolabelled somatostatin analogue ^{90}Y -DOTATOC in 41 patients with GEP NET and bronchial tumours, the overall response rate was 24% (36% for endocrine pancreatic tumours) (Waldherr *et al.*, 2001). Complete remissions were observed in 2% (1 of 41), partial remissions (PR) in 22% (9 of 41), a minor response in 12% (5 of 41), stable disease in 49% (20 of 41) and progressive disease in 15% (6 of 41). The median duration of response had not been reached at 26 months, and the two-year survival time was $76 \pm 16\%$. There was a significant reduction of symptoms (83% from the patients suffering from the malignant carcinoid syndrome),

and the treatment was well tolerated. Promising results were obtained using ($[^{177}\text{Lu}]\text{octreotate}$) (Kwekkeboom *et al.*, 2005), in a study of 103 patients with NETs, mostly GEP tumours: complete remission in three patients (2%), partial remission in 32 patients (26%), a minor response (tumor diameter decrease of 25% to 50%) in 24 patients (19%), stable disease in 44 patients (35%), and progressive disease in 22 patients (18%). Higher remission rates were positively correlated with high uptake on pre-therapy somatostatin receptor imaging and a limited number of liver metastases, whereas progressive disease was significantly more frequent in patients with a low performance score and extensive disease. Median time to progression in 103 patients who either had stable disease or tumour regression was more than 36 months. In a preclinical study using the combination of ^{90}Y - and ^{177}Lu -labeled analogs (de Jong *et al.*, 2005), this combination had superior antitumor effects when compared with either ^{90}Y - or ^{177}Lu -analog alone in animals bearing tumours of various sizes. In the future, treatment with both ^{90}Y - and ^{177}Lu coupled to a somatostatin analogue might come into clinical trials, as ^{177}Lu may be more effective for smaller tumours whereas ^{90}Y may be more effective for larger tumours (Oberg & Eriksson, 2005; Chan & Kulke, 2007).

The use of PRRT appears to be an important progress in the treatment of these tumours; nevertheless, there are still unresolved questions, such as which is the best time for its administration, and what is the most appropriate radioligand/combination to be useful in a certain patient.

Conclusions

Although the somatostatin analogues have been shown to be very useful for the symptomatic and biochemical improvement in patients with NETs, specifically

functional GEP tumours, their antiproliferative effects are less impressive. A certain proportion of patients achieve tumour growth stabilisation, while reduction in the size of the tumour is rare. Therefore, prospective studies including large number of patients and using higher dose, more potent somatostatin analogues or analogues with wider SSSTR profile are needed for assessing the real antiproliferative ability of these drugs.

Reference List

- Akerstrom, G. 1996. Management of carcinoid tumors of the stomach, duodenum, and pancreas. *World J. Surg.* 20, 173-182.
- Angeletti, S., Corleto, V.D., Schillaci, O., Marignani, M., Annibale, B., Moretti, A., Silecchia, G., Scopinaro, F., Basso, N., Bordi, C. & Delle, F.G. 1998. Use of the somatostatin analogue octreotide to localise and manage somatostatin-producing tumours. *Gut* 42, 792-794.
- Arnold, R., Simon, B. & Wied, M. 2000. Treatment of neuroendocrine GEP tumours with somatostatin analogues: a review. *Digestion* 62 Suppl 1, 84-91.
- Arnold, R., Trautmann, M.E., Creutzfeldt, W., Benning, R., Benning, M., Neuhaus, C., Jurgensen, R., Stein, K., Schafer, H., Bruns, C. & Dennler, H.J. 1996. Somatostatin analogue octreotide and inhibition of tumour growth in metastatic endocrine gastroenteropancreatic tumours. *Gut* 38, 430-438.
- Arrigoni, M.G., Woolner, L.B. & Bernatz, P.E. 1972. Atypical carcinoid tumors of the lung. *J. Thorac. Cardiovasc. Surg.* 64, 413-421.
- Astuti, D., Hart-Holden, N., Latif, F., Laloo, F., Black, G.C., Lim, C., Moran, A., Grossman, A.B., Hodgson, S.V., Freemont, A., Ramsden, R., Eng, C., Evans, D.G. & Maher, E.R. 2003. Genetic analysis of mitochondrial complex II subunits SDHD, SDHB and SDHC in paraganglioma and pheochromocytoma susceptibility. *Clin. Endocrinol. (Oxf)* 59, 728-733.
- Astuti, D., Morris, M., Krona, C., Abel, F., Gentle, D., Martinsson, T., Kogner, P., Neumann, H.P., Voutilainen, R., Eng, C., Rustin, P., Latif, F. & Maher, E.R. 2004. Investigation of the role of SDHB inactivation in sporadic pheochromocytoma and neuroblastoma. *Br. J. Cancer* 91, 1835-1841.
- Beasley, M.B., Brambilla, E. & Travis, W.D. 2005. The 2004 World Health Organization classification of lung tumors. *Semin. Roentgenol.* 40, 90-97.
- Bloom, S.R., Polak, J.M. & Pearse, A.G. 1973. Vasoactive intestinal peptide and watery-diarrhoea syndrome. *Lancet* 2, 14-16.
- Boix, E., Pico, A., Pinedo, R., Aranda, I. & Kovacs, K. 2002. Ectopic growth hormone-releasing hormone secretion by thymic carcinoid tumour. *Clin. Endocrinol. (Oxf)* 57, 131-134.
- Bravo, E.L. 2002. Pheochromocytoma. *Cardiol. Rev.* 10, 44-50.
- Bravo, E.L. & Tagle, R. 2003. Pheochromocytoma: state-of-the-art and future prospects. *Endocr. Rev.* 24, 539-553.
- 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. *Eur. J. Endocrinol.* 146, 707-716.
- Capella, C., Heitz, P.U., Hofler, H., Solcia, E. & Kloppel, G. 1995. Revised classification of neuroendocrine tumours of the lung, pancreas and gut. *Virchows Arch.* 425, 547-560.

- Caplin,M.E., Buscombe,J.R., Hilson,A.J., Jones,A.L., Watkinson,A.F. & Burroughs,A.K. 1998. Carcinoid tumour. *Lancet* 352, 799-805.
- Carretta,A., Chiesa,G., Magnani,P., Songini,C., Melloni,G., Zannini,P. & Grossi,A. 1997. Imaging of bronchial carcinoid tumors associated to Cushing syndrome with ¹¹¹In-Octreoscan scintigraphy and immunoscintigraphy with anti-chromogranin monoclonal antibodies. Report of two cases. *J. Cardiovasc. Surg. (Torino)* 38, 191-194.
- Casadei,R., Tomassetti,P., Rossi,C., la Donna,M., Migliori,M. & Marrano,D. 1999. Treatment of metastatic glucagonoma to the liver: case report and literature review. *Ital. J. Gastroenterol. Hepatol.* 31, 308-312.
- Cascon,A., Ruiz-Llorrente,S., Fraga,M.F., Leton,R., Telleria,D., Sastre,J., Diez,J.J., Martinez Diaz-Guerra,G., Diaz Perez,J.A., Benitez,J., Esteller,M. & Robledo,M. 2004. Genetic and epigenetic profile of sporadic pheochromocytomas. *J. Med. Genet.* 41, e30
- Castellano,M., Mori,L., Giacche,M., Agliozzo,E., Tosini,R., Panarotto,A., Cappelli,C., Mulatero,P., Cumetti,D., Veglio,F. & Agabiti-Rosei,E. 2006. Genetic mutation screening in an italian cohort of nonsyndromic pheochromocytoma/paraganglioma patients. *Ann. N. Y. Acad. Sci.* 1073, 156-165.
- Chan,J.A. & Kulke,M.H. 2007. Emerging therapies for the treatment of patients with advanced neuroendocrine tumors. *Expert. Opin. Emerg. Drugs* 12, 253-270.
- Chastain,M.A. 2001. The glucagonoma syndrome: a review of its features and discussion of new perspectives. *Am. J. Med. Sci.* 321, 306-320.
- Corbetta,S., Peracchi,M., Cappiello,V., Lania,A., Lauri,E., Vago,L., Beck-Peccoz,P. & Spada,A. 2003. Circulating ghrelin levels in patients with pancreatic and gastrointestinal neuroendocrine tumors: identification of one pancreatic ghrelinoma. *J. Clin. Endocrinol. Metab.* 88, 3117-3120.
- Davila,D.G., Dunn,W.F., Tazelaar,H.D. & Pairolero,P.C. 1993. Bronchial carcinoid tumors. *Mayo Clin. Proc.* 68, 795-803.
- Davis,K.P., Hartmann,L.K., Keeney,G.L. & Shapiro,H. 1996. Primary ovarian carcinoid tumors. *Gynecol. Oncol.* 61, 259-265.
- de Herder,W.W., Hofland,L.J., van der Lely,A.J. & Lamberts,S.W. 2003. Somatostatin receptors in gastroentero-pancreatic neuroendocrine tumours. *Endocr. Relat Cancer* 10, 451-458.
- de Herder,W.W., Kwekkeboom,D.J., Feelders,R.A., van Aken,M.O., Lamberts,S.W., van der Lely,A.J. & Krenning,E.P. 2006a. Somatostatin receptor imaging for neuroendocrine tumors. *Pituitary.* 9, 243-248.
- de Herder,W.W. & Lamberts,S.W. 2002. Somatostatin and somatostatin analogues: diagnostic and therapeutic uses. *Curr. Opin. Oncol.* 14, 53-57.
- de Herder,W.W., Niederle,B., Scoazec,J.Y., Pauwels,S., Kloppel,G., Falconi,M., Kwekkeboom,D.J., Oberg,K., Eriksson,B., Wiedenmann,B., Rindi,G., O'Toole,D. & Ferone,D. 2006b. Well-differentiated pancreatic tumor/carcinoma: insulinoma. *Neuroendocrinology* 84, 183-188.

- de Jong,M., Breeman,W.A., Valkema,R., Bernard,B.F. & Krenning,E.P. 2005. Combination radionuclide therapy using ¹⁷⁷Lu- and ⁹⁰Y-labeled somatostatin analogs. *J. Nucl. Med.* 46 Suppl 1, 13S-17S.
- 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.
- Dusmet,M. & McKneally,M.F. 1994. Bronchial and thymic carcinoid tumors: a review. *Digestion* 55 Suppl 3, 70-76.
- Ekeblad,S., Nilsson,B., Lejonklou,M.H., Johansson,T., Stalberg,P., Nilsson,O., Ahlman,H. & Skogseid,B. 2006. Gastrointestinal stromal tumors express the orexigen ghrelin. *Endocr. Relat. Cancer* 13, 963-970.
- Eriksson,B. & Oberg,K. 1999. Summing up 15 years of somatostatin analog therapy in neuroendocrine tumors: future outlook. *Ann. Oncol.* 10 Suppl 2, S31-S38
- 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. *Ann. Oncol.* 8, 1041-1044.
- Evans,D.B., Skibber,J.M., Lee,J.E., Cleary,K.R., Ajani,J.A., Gagel,R.F., Sellin,R.V., Fenoglio,C.J., Merrell,R.C. & Hickey,R.C. 1993. Nonfunctioning islet cell carcinoma of the pancreas. *Surgery* 114, 1175-1181.
- Faiss,S., Rath,U., Mansmann,U., Caird,D., Clemens,N., Riecken,E.O. & Wiedenmann,B. 1999. Ultra-high-dose lanreotide treatment in patients with metastatic neuroendocrine gastroenteropancreatic tumors. *Digestion* 60, 469-476.
- Ferolla,P., Falchetti,A., Filosso,P., Tomassetti,P., Tamburrano,G., Avenia,N., Daddi,G., Puma,F., Ribacchi,R., Santeusano,F., Angeletti,G. & Brandi,M.L. 2005. Thymic neuroendocrine carcinoma (carcinoid) in multiple endocrine neoplasia type 1 syndrome: the Italian series. *J. Clin. Endocrinol. Metab.* 90, 2603-2609.
- Ferone,D., Saveanu,A., Culler,M.D., Arvigo,M., Rebora,A., Gatto,F., Minuto,F. & Jaquet,P. 2007. Novel chimeric somatostatin analogs: facts and perspectives. *Eur. J. Endocrinol.* 156, 23-28.
- Filosso,P.L., Ruffini,E., Oliaro,A., Papalia,E., Donati,G. & Rena,O. 2002. Long-term survival of atypical bronchial carcinoids with liver metastases, treated with octreotide. *Eur. J. Cardiothorac. Surg.* 21, 913-917.
- Fjalling,M., Andersson,P., Forssell-Aronsson,E., Gretarsdottir,J., Johansson,V., Tisell,L.E., Wangberg,B., Nilsson,O., Berg,G., Michanek,A., Lindstedt,G. & Ahlman,H. 1996. Systemic radionuclide therapy using indium-111-DTPA-D-Phe1-octreotide in midgut carcinoid syndrome. *J. Nucl. Med.* 37, 1519-1521.
- Franchi,G., Grozinsky-Glasberg,S., Ribeiro de Oliveira Jr,A., Salahuddin,N., Korbonits,M. & Grossman,A.B. 2007. Somatostatin analogues and the PI3K-AKT-MTOR-P70S6K pathway: how do they control the proliferation of neuroendocrine tumours? *Endocrine Abstracts* 14.

- Frank,M., Klose,K.J., 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. *Am. J. Gastroenterol.* 94, 1381-1387.
- Fykse,V., Sandvik,A.K., Qvigstad,G., Falkmer,S.E., Syversen,U. & Waldum,H.L. 2004.
Treatment of ECL cell carcinoids with octreotide LAR. *Scand. J. Gastroenterol.* 39, 621-628.
- Ganim,R.B. & Norton,J.A. 2000b. Recent advances in carcinoid pathogenesis, diagnosis and management. *Surg. Oncol.* 9, 173-179.
- Garcia,d.I.T., Wass,J.A. & Turner,H.E. 2002. Antiangiogenic effects of somatostatin analogues. *Clin. Endocrinol. (Oxf)* 57, 425-441.
- Ghaferi,A.A., Chojnacki,K.A., Long,W.D., Cameron,J.L. & Yeo,C.J. 2007. Pancreatic VIPomas: Subject Review and One Institutional Experience. *J. Gastrointest. Surg.*
- Gibril,F., Chen,Y.J., Schrump,D.S., Vortmeyer,A., Zhuang,Z., Lubensky,I.A., Reynolds,J.C., Louie,A., Entsuah,L.K., Huang,K., Asgharian,B. & Jensen,R.T. 2003. Prospective study of thymic carcinoids in patients with multiple endocrine neoplasia type 1. *J. Clin. Endocrinol. Metab.* 88, 1066-1081.
- Giuffrida,D. & Gharib,H. 1998. Current diagnosis and management of medullary thyroid carcinoma. *Ann. Oncol.* 9, 695-701.
- Goldstein,R.E., O'Neill,J.A., Jr., Holcomb,G.W., III, Morgan,W.M., III, Neblett,W.W., III, Oates,J.A., Brown,N., Nadeau,J., Smith,B., Page,D.L., Abumrad,N.N. & Scott,H.W., Jr. 1999. Clinical experience over 48 years with pheochromocytoma. *Ann. Surg.* 229, 755-764.
- Gough,D.B., Thompson,G.B., Crotty,T.B., Donohue,J.H., Kvols,L.K., Carney,J.A., Grant,C.S. & Nagorney,D.M. 1994a. Diverse clinical and pathologic features of gastric carcinoid and the relevance of hypergastrinemia. *World J. Surg.* 18, 473-479.
- Gough,D.B., Thompson,G.B., Crotty,T.B., Donohue,J.H., Kvols,L.K., Carney,J.A., Grant,C.S. & Nagorney,D.M. 1994b. Diverse clinical and pathologic features of gastric carcinoid and the relevance of hypergastrinemia. *World J. Surg.* 18, 473-479.
- Granberg,D., Eriksson,B., Wilander,E., Grimfjard,P., Fjallskog,M.L., Oberg,K. & Skogseid,B. 2001. Experience in treatment of metastatic pulmonary carcinoid tumors. *Ann. Oncol.* 12, 1383-1391.
- Granberg,D., Sundin,A., Janson,E.T., Oberg,K., Skogseid,B. & Westlin,J.E. 2003. Octreoscan in patients with bronchial carcinoid tumours. *Clin. Endocrinol. (Oxf)* 59, 793-799.
- Granberg,D., Wilander,E., Stridsberg,M., Granerus,G., Skogseid,B. & Oberg,K. 1998. Clinical symptoms, hormone profiles, treatment, and prognosis in patients with gastric carcinoids. *Gut* 43, 223-228.
- Gugger,M., Waser,B., Kappeler,A., Schonbrunn,A. & Reubi,J.C. 2004. Immunohistochemical localization of somatostatin receptor sst2A in human gut and lung tissue: possible implications for physiology and carcinogenesis. *Ann. N. Y. Acad. Sci.* 1014, 132-136.

- Hearn,P.R., Ahmed,M. & Woodhouse,N.J. 1988a. The use of SMS 201-995 (somatostatin analogue) in insulinomas. Additional case report and literature review. *Horm. Res.* 29, 211-213.
- Hearn,P.R., Reynolds,C.L., Johansen,K. & Woodhouse,N.J. 1988b. Lung carcinoid with Cushing's syndrome: control of serum ACTH and cortisol levels using SMS 201-995 (sandostatin). *Clin. Endocrinol. (Oxf)* 28, 181-185.
- Heppeler,A., Froidevaux,S., Eberle,A.N. & Maecke,H.R. 2000. Receptor targeting for tumor localisation and therapy with radiopeptides. *Curr. Med. Chem.* 7, 971-994.
- Heron,I., Thomas,F., Dero,M., Gancel,A., Ruiz,J.M., Schatz,B. & Kuhn,J.M. 1993. Pharmacokinetics and efficacy of a long-acting formulation of the new somatostatin analog BIM 23014 in patients with acromegaly. *J. Clin. Endocrinol. Metab* 76, 721-727.
- Imam,H., Eriksson,B., Lukinius,A., Janson,E.T., Lindgren,P.G., Wilander,E. & Oberg,K. 1997. Induction of apoptosis in neuroendocrine tumors of the digestive system during treatment with somatostatin analogs. *Acta Oncol.* 36, 607-614.
- Invitti,C., De,M., I, Bolla,G.B., Pecori,G.F., Maestri,E., Leonetti,G. & Cavagnini,F. 1993. Effect of octreotide on catecholamine plasma levels in patients with chromaffin cell tumors. *Horm. Res.* 40, 156-160.
- Janson,E.T., Kalkner,K.M., Eriksson,B., Westlin,J.E. & Oberg,K. 1999. Somatostatin receptor scintigraphy during treatment with lanreotide in patients with neuroendocrine tumors. *Nucl. Med. Biol.* 26, 877-882.
- Janson,E.T. & Oberg,K. 2003. Neuroendocrine tumors--somatostatin receptor expression and somatostatin analog treatment. *Cancer Chemother. Biol. Response Modif.* 21, 535-546.
- Janson,E.T., Stridsberg,M., Gobl,A., Westlin,J.E. & Oberg,K. 1998. Determination of somatostatin receptor subtype 2 in carcinoid tumors by immunohistochemical investigation with somatostatin receptor subtype 2 antibodies. *Cancer Res.* 58, 2375-2378.
- Jensen,R.T. 1996. Gastrointestinal endocrine tumours. Gastrinoma. *Baillieres Clin. Gastroenterol.* 10, 603-643.
- Jensen,R.T. 2004. Gastrinomas: advances in diagnosis and management. *Neuroendocrinology* 80 Suppl 1, 23-27.
- Kaltsas,G., Korbonits,M., Heintz,E., Mukherjee,J.J., Jenkins,P.J., Chew,S.L., Reznick,R., Monson,J.P., Besser,G.M., Foley,R., Britton,K.E. & Grossman,A.B. 2001. Comparison of somatostatin analog and meta-iodobenzylguanidine radionuclides in the diagnosis and localization of advanced neuroendocrine tumors. *J. Clin. Endocrinol. Metab.* 86, 895-902.
- Kaltsas,G.A., Papadogias,D., Makras,P. & Grossman,A.B. 2005. Treatment of advanced neuroendocrine tumours with radiolabelled somatostatin analogues. *Endocr. Relat Cancer* 12, 683-699.

- Kebebew,E., Ituarte,P.H., Siperstein,A.E., Duh,Q.Y. & Clark,O.H. 2000. Medullary thyroid carcinoma: clinical characteristics, treatment, prognostic factors, and a comparison of staging systems. *Cancer* 88, 1139-1148.
- Koehler,U., Meyer,S., Schaefer,S., Ivan,D. & Kann,P.H. 2007. Tumor regression in a nonfunctioning pancreatic neuroendocrine tumor during somatostatin analogue treatment. *Exp. Clin. Endocrinol. Diabetes* 115DOI:10,
- Kolby,L., Persson,G., Franzen,S. & Ahren,B. 2003. Randomized clinical trial of the effect of interferon alpha on survival in patients with disseminated midgut carcinoid tumours. *Br. J. Surg.* 90, 687-693.
- Kopf,D., Bockisch,A., Steinert,H., Hahn,K., Beyer,J., Neumann,H.P., Hensen,J. & Lehnert,H. 1997. Octreotide scintigraphy and catecholamine response to an octreotide challenge in malignant pheochromocytoma. *Clin. Endocrinol. (Oxf)* 46, 39-44.
- Koriyama,N., Kakei,M., Yaekura,K., Okui,H., Yamashita,T., Nishimura,H., Matsushita,S. & Tei,C. 2000. Control of catecholamine release and blood pressure with octreotide in a patient with pheochromocytoma: a case report with in vitro studies. *Horm. Res.* 53, 46-50.
- Krenning,E.P., de Jong,M., Kooij,P.P., Breeman,W.A., Bakker,W.H., de Herder,W.W., Van Eijck,C.H., Kwekkeboom,D.J., Jamar,F., Pauwels,S. & Valkema,R. 1999. Radiolabelled somatostatin analogue(s) for peptide receptor scintigraphy and radionuclide therapy. *Ann. Oncol.* 10 Suppl 2, S23-S29
- Kulke,M.H. & Mayer,R.J. 1999. Carcinoid tumors. *N. Engl. J. Med.* 340, 858-868.
- Kvols,L., Oberg,K., de Herder,W., Anthony,L., Glusman,J., Tran,L. & Wiedenmann,B. 2005. Early data on the efficacy and safety of the novel multi-ligand somatostatin analog, SOM230, in patients with metastatic carcinoid tumors refractory or resistant to octreotide LAR. *J. Clin. Oncol.* 23, 8024
- Kvols,L.K., Moertel,C.G., O'Connell,M.J., Schutt,A.J., Rubin,J. & Hahn,R.G. 1986. Treatment of the malignant carcinoid syndrome. Evaluation of a long-acting somatostatin analogue. *N. Engl. J. Med.* 315, 663-666.
- Kwekkeboom,D.J., Teunissen,J.J., Bakker,W.H., Kooij,P.P., de Herder,W.W., Feelders,R.A., Van Eijck,C.H., Esser,J.P., Kam,B.L. & Krenning,E.P. 2005. Radiolabeled somatostatin analog [¹⁷⁷Lu-DOTA0,Tyr3]octreotate in patients with endocrine gastroenteropancreatic tumors. *J. Clin. Oncol.* 23, 2754-2762.
- Lamarre-Cliche,M., Gimenez-Roqueplo,A.P., Billaud,E., Baudin,E., Luton,J.P. & Plouin,P.F. 2002. Effects of slow-release octreotide on urinary metanephrine excretion and plasma chromogranin A and catecholamine levels in patients with malignant or recurrent pheochromocytoma. *Clin. Endocrinol. (Oxf)* 57, 629-634.
- Lamberts,S.W., Bakker,W.H., Reubi,J.C. & Krenning,E.P. 1990. Treatment with Sandostatin and in vivo localization of tumors with radiolabeled somatostatin analogs. *Metabolism* 39, 152-155.
- Lamberts,S.W., de Herder,W.W. & Hofland,L.J. 2002a. Somatostatin analogs in the diagnosis and treatment of cancer. *Trends Endocrinol. Metab.* 13, 451-457.

- Lamberts, S.W., van der Lely, A.J. & Hofland, L.J. 2002b. New somatostatin analogs: will they fulfil old promises? *Eur. J. Endocrinol.* 146, 701-705.
- Lupoli, G., Cascone, E., Arlotta, F., Vitale, G., Celentano, L., Salvatore, M. & Lombardi, G. 1996. Treatment of advanced medullary thyroid carcinoma with a combination of recombinant interferon alpha-2b and octreotide. *Cancer* 78, 1114-1118.
- Mahler, C., Verhelst, J., de Longueville, M. & Harris, A. 1990. Long-term treatment of metastatic medullary thyroid carcinoma with the somatostatin analogue octreotide. *Clin. Endocrinol. (Oxf)* 33, 261-269.
- Mansi, L., Rambaldi, P.F., Panza, N., Esposito, D., Esposito, V. & Pastore, V. 1997. Diagnosis and radioguided surgery with ¹¹¹In-pentetreotide in a patient with paraneoplastic Cushing's syndrome due to a bronchial carcinoid. *Eur. J. Endocrinol.* 137, 688-690.
- Marsh, D.J., Learoyd, D.L. & Robinson, B.G. 1995. Medullary thyroid carcinoma: recent advances and management update. *Thyroid* 5, 407-424.
- Matejka, G., Toubeau, M., Bernard, A., Belleville, Y., Vaillant, G. & Brun, J.M. 1996. [Thymic carcinoid tumor causing paraneoplastic Cushing syndrome. Diagnostic value of double-labelled tomoscintigraphy]. *Presse Med.* 25, 1201-1202.
- Maton, P.N. 1993. Use of octreotide acetate for control of symptoms in patients with islet cell tumors. *World J. Surg.* 17, 504-510.
- Metz, D.C., Strader, D.B., Orbach, M., Koviack, P.D., Feigenbaum, K.M. & Jensen, R.T. 1993. Use of omeprazole in Zollinger-Ellison syndrome: a prospective nine-year study of efficacy and safety. *Aliment. Pharmacol. Ther.* 7, 597-610.
- Mhatre, A.N., Li, Y., Feng, L., Gasperin, A. & Lalwani, A.K. 2004. SDHB, SDHC, and SDHD mutation screen in sporadic and familial head and neck paragangliomas. *Clin. Genet.* 66, 461-466.
- Modigliani, E., Cohen, R., Joannidis, S., Siame-Mouro, C., Guliana, J.M., Charpentier, G., Cassuto, D., Bentata, P.M., Tabarin, A., Roger, P. & . 1992. Results of long-term continuous subcutaneous octreotide administration in 14 patients with medullary thyroid carcinoma. *Clin. Endocrinol. (Oxf)* 36, 183-186.
- Modlin, I.M., Shapiro, M.D. & Kidd, M. 2004. Siegfried Oberndorfer: origins and perspectives of carcinoid tumors. *Hum. Pathol.* 35, 1440-1451.
- Moertel, C.G. 1987. Karnofsky memorial lecture. An odyssey in the land of small tumors. *J. Clin. Oncol.* 5, 1502-1522.
- Moran, C.A. & Suster, S. 2000. Neuroendocrine carcinomas (carcinoid tumor) of the thymus. A clinicopathologic analysis of 80 cases. *Am. J. Clin. Pathol.* 114, 100-110.
- Mundschenk, J., Unger, N., Schulz, S., Holtt, V., Schulz, S., Steinke, R. & Lehnert, H. 2003. Somatostatin receptor subtypes in human pheochromocytoma: subcellular expression pattern and functional relevance for octreotide scintigraphy. *J. Clin. Endocrinol. Metab.* 88, 5150-5157.
- Neumayer, C., Moritz, A., Asari, R., Weinhausel, A., Holzenbein, T., Kretschmer, G., Niederle, B. & Haas, O.A. 2007. Novel SDHD germ-line mutations in pheochromocytoma patients. *Eur. J. Clin. Invest* 37, 544-551.

- Nilsson,O., Kolby,L., Wangberg,B., Wigander,A., Billig,H., William-Olsson,L., Fjalling,M., Forssell-Aronsson,E. & Ahlman,H. 1998. Comparative studies on the expression of somatostatin receptor subtypes, outcome of octreotide scintigraphy and response to octreotide treatment in patients with carcinoid tumours. *Br. J. Cancer* 77, 632-637.
- O'Dorisio,T.M., Mekhjian,H.S. & Gaginnella,T.S. 1989. Medical therapy of VIPomas. *!Lost Data* 18, 545-556.
- O'Toole,D., Ducreux,M., Bommelaer,G., Wemeau,J.L., Bouche,O., Catus,F., Blumberg,J. & Ruszniewski,P. 2000. Treatment of carcinoid syndrome: a prospective crossover evaluation of lanreotide versus octreotide in terms of efficacy, patient acceptability, and tolerance. *Cancer* 88, 770-776.
- Oberg,K. 2002. Carcinoid tumors: molecular genetics, tumor biology, and update of diagnosis and treatment. *Curr. Opin. Oncol.* 14, 38-45.
- Oberg,K. 2004. Future aspects of somatostatin-receptor-mediated therapy. *Neuroendocrinology* 80 Suppl 1, 57-61.
- Oberg,K. 2005. Neuroendocrine tumors of the gastrointestinal tract: recent advances in molecular genetics, diagnosis, and treatment. *Curr. Opin. Oncol.* 17, 386-391.
- Oberg,K. & Eriksson,B. 2005. Nuclear medicine in the detection, staging and treatment of gastrointestinal carcinoid tumours. *Best. Pract. Res. Clin. Endocrinol. Metab* 19, 265-276.
- Oberg,K., Norheim,I. & Theodorsson,E. 1991. Treatment of malignant midgut carcinoid tumours with a long-acting somatostatin analogue octreotide. *Acta Oncol.* 30, 503-507.
- Papotti,M., Bongiovanni,M., Volante,M., Allia,E., Landolfi,S., Helboe,L., Schindler,M., Cole,S.L. & Bussolati,G. 2002. Expression of somatostatin receptor types 1-5 in 81 cases of gastrointestinal and pancreatic endocrine tumors. A correlative immunohistochemical and reverse-transcriptase polymerase chain reaction analysis. *Virchows Arch.* 440, 461-475.
- Papotti,M., Kumar,U., Volante,M., Pecchioni,C. & Patel,Y.C. 2001. Immunohistochemical detection of somatostatin receptor types 1-5 in medullary carcinoma of the thyroid. *Clin. Endocrinol. (Oxf)* 54, 641-649.
- Patel,Y.C. 1999. Somatostatin and its receptor family. *Front. Neuroendocrinol.* 20, 157-198.
- Patel,Y.C., Murthy,K.K., Escher,E.E., Banville,D., Spiess,J. & Srikant,C.B. 1990. Mechanism of action of somatostatin: an overview of receptor function and studies of the molecular characterization and purification of somatostatin receptor proteins. *Metabolism* 39, 63-69.
- Phlipponneau,M., Nocaudie,M., Epelbaum,J., De Keyzer,Y., Lalau,J.D., Marchandise,X. & Bertagna,X. 1994. Somatostatin analogs for the localization and preoperative treatment of an adrenocorticotropin-secreting bronchial carcinoid tumor. *J. Clin. Endocrinol. Metab.* 78, 20-24.
- Plockinger,U., Rindi,G., Arnold,R., Eriksson,B., Krenning,E.P., de Herder,W.W., Goede,A., Oberg,K., Reubi,J.C., Nilsson,O., Delle,F.G., Ruszniewski,P., Ahlman,H. & Wiedenmann,B. 2004. Guidelines for the Diagnosis and Treatment of

- Neuroendocrine Gastrointestinal Tumours. A consensus statement on behalf of the European Neuroendocrine Tumour Society (ENETS). *Neuroendocrinol.* 80, 394-424.
- Prommegger,R., Bale,R., Ensinger,C., Sauper,T., Profanter,C., Knoflach,M. & Moncayo,R. 2003. Gastric carcinoid type I tumour: new diagnostic and therapeutic method. *Eur. J. Gastroenterol. Hepatol.* 15, 705-707.
- Raue,F. 1998. German medullary thyroid carcinoma/multiple endocrine neoplasia registry. German MTC/MEN Study Group. *Medullary Thyroid Carcinoma/Multiple Endocrine Neoplasia Type 2. Langenbecks Arch. Surg.* 383, 334-336.
- Reubi,J.C. 2004. Somatostatin and other Peptide receptors as tools for tumor diagnosis and treatment. *Neuroendocrinology* 80 Suppl 1, 51-56.
- Reubi,J.C., Kappeler,A., Waser,B., Laissue,J., Hipkin,R.W. & Schonbrunn,A. 1998. Immunohistochemical localization of somatostatin receptors sst2A in human tumors. *Am. J. Pathol.* 153, 233-245.
- Reubi,J.C., Kvolts,L., Krenning,E. & Lamberts,S.W. 1990. Distribution of somatostatin receptors in normal and tumor tissue. *Metabolism* 39, 78-81.
- Reubi,J.C., Schaer,J.C., Waser,B. & Mengod,G. 1994. Expression and localization of somatostatin receptor SSTR1, SSTR2, and SSTR3 messenger RNAs in primary human tumors using in situ hybridization. *Cancer Res.* 54, 3455-3459.
- 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., Bordi,C., Rappel,S., La Rosa,S., Stolte,M. & Solcia,E. 1996. Gastric carcinoids and neuroendocrine carcinomas: pathogenesis, pathology, and behavior. *World J. Surg.* 20, 168-172.
- Rindi,G., Villanacci,V. & Ubiali,A. 2000. Biological and molecular aspects of gastroenteropancreatic neuroendocrine tumors. *Digestion* 62 Suppl 1, 19-26.
- Rosai,J. & Higa,E. 1972. Mediastinal endocrine neoplasm, of probable thymic origin, related to carcinoid tumor. *Clinicopathologic study of 8 cases. Cancer* 29, 1061-1074.
- Rosai,J., Higa,E. & Davie,J. 1972. Mediastinal endocrine neoplasm in patients with multiple endocrine adenomatosis. A previously unrecognized association. *Cancer* 29, 1075-1083.
- Roy,P.K., Venzon,D.J., Shojamanesh,H., Abou-Saif,A., Peghini,P., Doppman,J.L., Gibril,F. & Jensen,R.T. 2000. Zollinger-Ellison syndrome. Clinical presentation in 261 patients. *Medicine (Baltimore)* 79, 379-411.
- Rubin,J., Ajani,J., Schirmer,W., Venook,A.P., Bukowski,R., Pommier,R., Saltz,L., Dandona,P. & Anthony,L. 1999. Octreotide acetate long-acting formulation versus open-label subcutaneous octreotide acetate in malignant carcinoid syndrome. *J. Clin. Oncol.* 17, 600-606.
- Ruszniewski,P., Ish-Shalom,S., Wymenga,M., O'Toole,D., Arnold,R., Tomassetti,P., Bax,N., Caplin,M., Eriksson,B., Glaser,B., Ducreux,M., Lombard-Bohas,C., de Herder,W.W.,

- Delle,F.G., Reed,N., Seitz,J.F., Van Cutsem,E., Grossman,A., Rougier,P., Schmidt,W. & Wiedenmann,B. 2004. Rapid and sustained relief from the symptoms of carcinoid syndrome: results from an open 6-month study of the 28-day prolonged-release formulation of lanreotide. *Neuroendocrinology* 80, 244-251.
- 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.
- Schlaghecke,R., Kreuzpaintner,G., Burrig,K.F., Juli,E. & Kley,H.K. 1989. Cushing's syndrome due to ACTH-production of an ovarian carcinoid. *Klin. Wochenschr.* 67, 640-644.
- Schlumberger,M., Gicquel,C., Lumbroso,J., Tenenbaum,F., Comoy,E., Bosq,J., Fonseca,E., Ghillani,P.P., Aubert,B. & Travagli,J.P. 1992. Malignant pheochromocytoma: clinical, biological, histologic and therapeutic data in a series of 20 patients with distant metastases. *J. Endocrinol. Invest.* 15, 631-642.
- Schulz,S., Schmitt,J., Quednow,C., Roessner,A. & Weise,W. 2002. Immunohistochemical detection of somatostatin receptors in human ovarian tumors. *Gynecol. Oncol.* 84, 235-240.
- Schwartz,C.J., Kimberg,D.V., Sheerin,H.E., Field,M. & Said,S.I. 1974. Vasoactive intestinal peptide stimulation of adenylate cyclase and active electrolyte secretion in intestinal mucosa. *J. Clin. Invest.* 54, 536-544.
- Service,F.J., McMahon,M.M., O'Brien,P.C. & Ballard,D.J. 1991. Functioning insulinoma--incidence, recurrence, and long-term survival of patients: a 60-year study. *Mayo Clin. Proc.* 66, 711-719.
- Shapiro,B. & Fig,L.M. 1989. Management of pheochromocytoma. *Endocrinol. Metab Clin. North Am.* 18, 443-481.
- Shojamanesh,H., Gibril,F., Louie,A., Ojeaburu,J.V., Bashir,S., Abou-Saif,A. & Jensen,R.T. 2002. Prospective study of the antitumor efficacy of long-term octreotide treatment in patients with progressive metastatic gastrinoma. *Cancer* 94, 331-343.
- Soga,J. 1997. Gastric carcinoids: a statistical evaluation of 1,094 cases collected from the literature. *Surg. Today* 27, 892-901.
- Soga,J., Suzuki,T., Yoshikawa,K., Katoh,H., Tsuno,Y. & Muto,T. 1990. Carcinoid somatostatinoma of the duodenum. *Eur. J. Cancer* 26, 1107-1108.
- Soga,J. & Yakuwa,Y. 1998. Vipoma/diarrheogenic syndrome: a statistical evaluation of 241 reported cases. *J. Exp. Clin. Cancer Res.* 17, 389-400.
- Soga,J. & Yakuwa,Y. 1999. Somatostatinoma/inhibitory syndrome: a statistical evaluation of 173 reported cases as compared to other pancreatic endocrinomas. *J. Exp. Clin. Cancer Res.* 18, 13-22.
- Soga,J., Yakuwa,Y. & Osaka,M. 1999. Carcinoid syndrome: a statistical evaluation of 748 reported cases. *J. Exp. Clin. Cancer Res.* 18, 133-141.
- Solcia,E., Klöppel G & Sobin H ,2000. Histological typing of endocrine tumours. World Health Organization International Histological Classification of Tumours.

- Solcia,E., Rindi,G., Paolotti,D., La Rosa,S., Capella,C. & Fiocca,R. 1999. Clinicopathological profile as a basis for classification of the endocrine tumours of the gastroenteropancreatic tract. *Ann. Oncol.* 10 Suppl 2, S9-15.
- Tanaka,Y., Funahashi,H., Imai,T., Naruse,T., Suzumura,K. & Oda,Y. 2000. The effectiveness of administering a minimal dose of octreotide long-term prior to surgery for insulinoma: report of a case. *Surg. Today* 30, 541-543.
- Tiensuu Janson,E.M., Ahlstrom,H., Andersson,T. & Oberg,K.E. 1992. Octreotide and interferon alfa: a new combination for the treatment of malignant carcinoid tumours. *Eur. J. Cancer* 28A, 1647-1650.
- Tiffet,O., Nicholson,A.G., Ladas,G., Sheppard,M.N. & Goldstraw,P. 2003. A clinicopathologic study of 12 neuroendocrine tumors arising in the thymus. *Chest* 124, 141-146.
- Tomassetti,P., Campana,D., Piscitelli,L., Mazzotta,E., Brocchi,E., Pezzilli,R. & Corinaldesi,R. 2005. Treatment of Zollinger-Ellison syndrome. *World J. Gastroenterol.* 11, 5423-5432.
- Tomassetti,P., Migliori,M., Caletti,G.C., Fusaroli,P., Corinaldesi,R. & Gullo,L. 2000a. Treatment of type II gastric carcinoid tumors with somatostatin analogues. *N. Engl. J. Med.* 343, 551-554.
- Tomassetti,P., Migliori,M., Corinaldesi,R. & Gullo,L. 2000b. Treatment of gastroenteropancreatic neuroendocrine tumours with octreotide LAR. *Aliment. Pharmacol. Ther.* 14, 557-560.
- Travis,W.D., Rush,W., Flieder,D.B., Falk,R., Fleming,M.V., Gal,A.A. & Koss,M.N. 1998. Survival analysis of 200 pulmonary neuroendocrine tumors with clarification of criteria for atypical carcinoid and its separation from typical carcinoid. *Am. J. Surg. Pathol.* 22, 934-944.
- Tsolakis,A.V., Portela-Gomes,G.M., Stridsberg,M., Grimelius,L., Sundin,A., Eriksson,B.K., Oberg,K.E. & Janson,E.T. 2004. Malignant gastric ghrelinoma with hyperghrelinemia. *J. Clin. Endocrinol. Metab.* 89, 3739-3744.
- Ueberberg,B., Tourne,H., Redman,A., Walz,M.K., Schmid,K.W., Mann,K. & Petersenn,S. 2005. Differential expression of the human somatostatin receptor subtypes sst1 to sst5 in various adrenal tumors and normal adrenal gland. *Horm. Metab. Res.* 37, 722-728.
- Valkema,R., de Jong,M., Bakker,W.H., Breeman,W.A., Kooij,P.P., Lugtenburg,P.J., De Jong,F.H., Christiansen,A., Kam,B.L., de Herder,W.W., Stridsberg,M., Lindemans,J., Ensing,G. & Krenning,E.P. 2002. Phase I study of peptide receptor radionuclide therapy with [In-DTPA]octreotide: the Rotterdam experience. *Semin. Nucl. Med.* 32, 110-122.
- van der Harst,E., de Herder,W.W., Bruining,H.A., Bonjer,H.J., de Krijger,R.R., Lamberts,S.W., van de Meiracker,A.H., Boomsma,F., Stijnen,T., Krenning,E.P., Bosman,F.T. & Kwekkeboom,D.J. 2001. [(123)I]metaiodobenzylguanidine and [(111)In]octreotide uptake in benign and malignant pheochromocytomas. *J. Clin. Endocrinol. Metab.* 86, 685-693.

- van Eyck,C.H., Bruining,H.A., Reubi,J.C., Bakker,W.H., Oei,H.Y., Krenning,E.P. & Lamberts,S.W. 1993. Use of isotope-labeled somatostatin analogs for visualization of islet cell tumors. *World J. Surg.* 17, 444-447.
- Vergani,D., Massironi,L., Lombardi,F. & Fiorentini,C. 1998. Carcinoid heart disease from ovarian primary presenting with acute pericarditis and biventricular failure. *Heart* 80, 623-626.
- Verschoor,L., Uitterlinden,P., Lamberts,S.W. & Del Pozo,E. 1986. On the use of a new somatostatin analogue in the treatment of hypoglycaemia in patients with insulinoma. *Clin. Endocrinol. (Oxf)* 25, 555-560.
- Vezzosi,D., Bennet,A., Rochaix,P., Courbon,F., Selves,J., Pradere,B., Buscail,L., Susini,C. & Caron,P. 2005. Octreotide in insulinoma patients: efficacy on hypoglycemia, relationships with Octreoscan scintigraphy and immunostaining with anti-sst2A and anti-sst5 antibodies. *Eur. J. Endocrinol.* 152, 757-767.
- Vinik,A.I., McLeod,M.K., Fig,L.M., Shapiro,B., Lloyd,R.V. & Cho,K. 1989. Clinical features, diagnosis, and localization of carcinoid tumors and their management. *!Lost Data* 18, 865-896.
- Vinik,A.I., Tsai,S.T., Moattari,A.R., Cheung,P., Eckhauser,F.E. & Cho,K. 1986. Somatostatin analogue (SMS 201-995) in the management of gastroenteropancreatic tumors and diarrhea syndromes. *Am. J. Med.* 81, 23-40.
- 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. *Semin. Nucl. Med.* 32, 148-155.
- Vitale,G., Tagliaferri,P., Caraglia,M., Rampone,E., Ciccarelli,A., Bianco,A.R., Abbruzzese,A. & Lupoli,G. 2000. Slow release lanreotide in combination with interferon-alpha2b in the treatment of symptomatic advanced medullary thyroid carcinoma. *J. Clin. Endocrinol. Metab* 85, 983-988.
- von Eyben,F.E., Grodum,E., Gjessing,H.J., Hagen,C. & Nielsen,H. 1994. Metabolic remission with octreotide in patients with insulinoma. *J. Intern. Med.* 235, 245-248.
- Waldherr,C., Pless,M., Maecke,H.R., Haldemann,A. & Mueller-Brand,J. 2001. The clinical value of [90Y-DOTA]-D-Phe1-Tyr3-octreotide (90Y-DOTATOC) in the treatment of neuroendocrine tumours: a clinical phase II study. *Ann. Oncol.* 12, 941-945.
- Warren,W.H. & Gould,V.E. 2002. Neuroendocrine tumors of the bronchopulmonary tract: a reappraisal of their classification after 20 years. *Surg. Clin. North Am.* 82, 525-40, vi.
- Warren,W.H., Welker,M. & Gattuso,P. 2006. Well-differentiated neuroendocrine carcinomas: the spectrum of histologic subtypes and various clinical behaviors. *Semin. Thorac. Cardiovasc. Surg.* 18, 199-205.
- Watson,J.T., Badner,N.H. & Ali,M.J. 1990. The prophylactic use of octreotide in a patient with ovarian carcinoid and valvular heart disease. *Can. J. Anaesth.* 37, 798-800.
- 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.

- Wermers,R.A., Fatourech, V., Wynne,A.G., Kvols,L.K. & Lloyd,R.V. 1996. The glucagonoma syndrome. Clinical and pathologic features in 21 patients. *Medicine (Baltimore)* 75, 53-63.
- Wymenga,A.N., Eriksson,B., Salmela,P.I., Jacobsen,M.B., Van Cutsem,E.J., Fiasse,R.H., Valimaki,M.J., Renstrup,J., de Vries,E.G. & Oberg,K.E. 1999. Efficacy and safety of prolonged-release lanreotide in patients with gastrointestinal neuroendocrine tumors and hormone-related symptoms. *J. Clin. Oncol.* 17, 1111
- Zatelli,M.C., Piccin,D., Bondanelli,M., Tagliati,F., De Carlo,E., Culler,M.D. & Uberti,E.C. 2003. An in vivo OctreoScan-negative adrenal pheochromocytoma expresses somatostatin receptors and responds to somatostatin analogs treatment in vitro. *Horm. Metab. Res.* 35, 349-354.