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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-α), 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 recommendations 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 (Oberg *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 ($2mm^2$) 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 & Oberg 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_2-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 humoural 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 case 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*. 1996*a*).

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 mesenterial 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) (Dousset *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 antiproliferative 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, Ruszniewski *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-α (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) (Oberg 1997, 2000, Faiss *et al*. 2003). Synergistic effects with combination therapy of somatostatin analogues with interferon-α have been reported and prospective trials have been designed to confirm these results (Joensuu *et al*. 1992, Janson & Oberg 1993, de Herder *et al*. 1996*b*, Lamberts *et al*. 1996, Frank *et al*. 1999, Oberg 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*. 2001*a*, 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

^{123}I- and ^{131}I-meta-iodobenzylguanidine (MIBG) may accumulate in digestive endocrine tumour cells. Scintigraphy with this radiopharmacon 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 ^{131}I-MIBG (Taal *et al*. 1996).

Somatostatin receptor-mediated endocytosis is of particular importance when radiotherapy or chemotherapy of somatostatin receptor subtype $(sst)_2$- and sst_5-positive metastatic carcinoids and pancreatic neuroendocrine tumours with α- or β-emitting radionuclides or chemotherapeuticals 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 chemotherapeutical is necessary, as non-neoplastic tissues expressing somatostatin receptors should not be exposed to the toxic effects of the radioligand or cytotoxic analogue. [^{111}In-DTPA^{0}, D-Phe^{1}]octreotide (^{111}In-pentetreotide) emits both Auger electrons (which have a tissue penetration of only 0.02–10 μm) as well as conversion electrons, with a tissue penetration of 200–500 μm. High doses of ^{111}In-pentetreotide inhibited growth of sst_2-positive tumour cells *in vitro* (Slooter *et al*. 1999). It has also been shown that ^{111}In-pentetreotide can inhibit the growth of liver metastases after injection of sst_2-positive tumour cells into the portal vein of rats (Slooter *et al*. 1999). In patients with progressive metastatic neuroendocrine tumours, therapy with ^{111}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 β-emitting radionuclides, such as ^{90}Y and ^{177}Lu, is potentially more effective, as higher tumour radiation doses can be achieved and the longer range of the β-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 [^{90}Y-DOTA^{0},Tyr^{3}]octreotide (^{90}Y-DOTATOC or ^{90}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 [^{177}Lu-DOTA^{0},Tyr^{3}]-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}In-DOTA^{0}]lanreotide and [^{90}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 β-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 α-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 β-emitting radiolabelled peptides and microscopic lesions with Auger or α-particle-emitting peptides. It is also conceivable to use ^{111}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}In-pentetreotide and one in a phase I study with [^{90}Y-DOTA^{0},Tyr^{3}]octreotide and delayed renal insufficiency in a phase I study with [^{90}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}In-, ^{90}Y- and ^{177}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}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

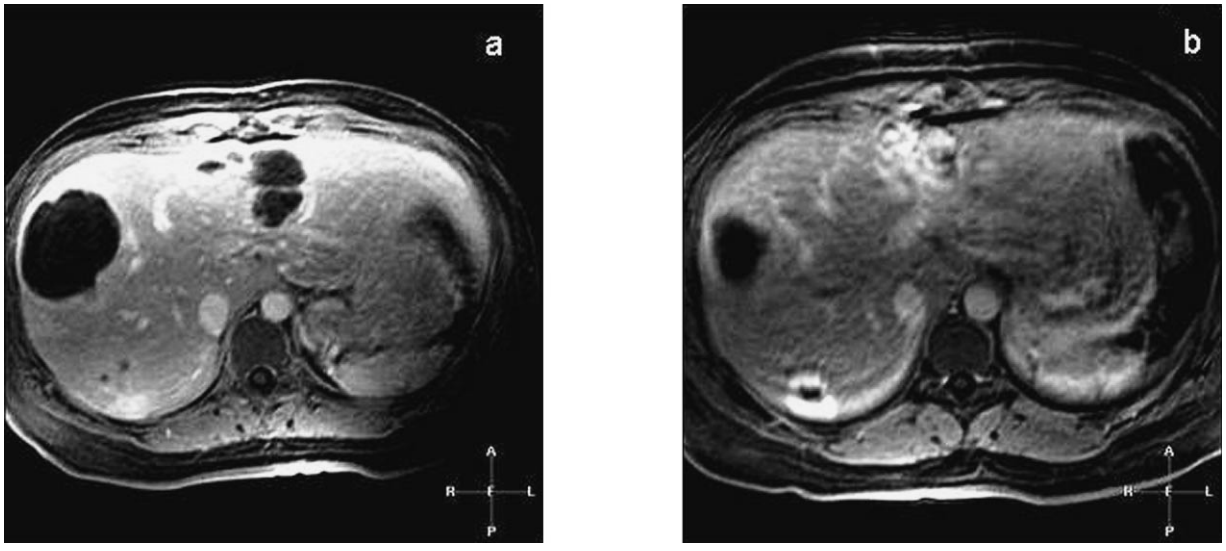

Figure 1 A 31-year old woman with metastatic gastrinoma treated with four courses of [^{177}Lu-DOTA^{0},Tyr^{3}]-octreotate, cumulative dose 29.8 GBq. T1-weighted images with fat suppression after the administration of Gd-DTPA, arterial phase. a, baseline studies; b, studies performed after 7 months. 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 therapeutical 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 ($sst_{1–5}$), whereas the octapeptide analogues octreotide and lanreotide only bind with a high affinity to sst_2 and sst_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 sst_2 and sst_5. A new so-called 'universal' somatostatin analogue, named SOM230, with high affinity for sst_1, sst_2, sst_3 and sst_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*. 2000*a*,*b*, Pfeiffer *et al*. 2001, 2002).

Powerful β-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 sst_2 and sst_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 regiments as well (Drevs *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 chemotherapeuticals and anti-angiogenesis agents, or new trials with presently available chemotherapeuticals?
- 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?

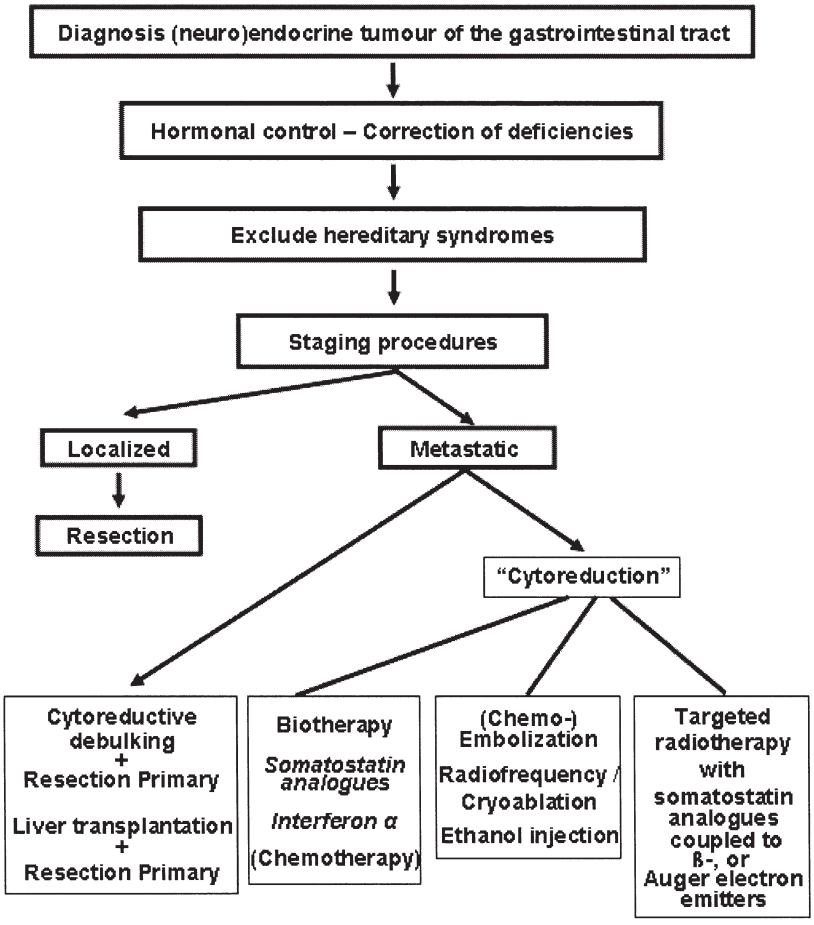

Figure 2 Subsequent steps in the diagnosis and management of patients with endocrine tumours of the pancreas and gastrointestinal tract.

- 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?

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