Management of Neuroendocrine Tumors: A Meeting of Experts from Latin America

F. Costa^a E. Domenichini^c G. Garavito^e R. Medrano^g G. Mendez^d
J. O'Connor^c W. Rojas^f S. Torres^h R.N. Younes^{a, b} G. Delle Faveⁱ K. Öberg^j

^aHospital Sírio Libanês, ^bUniversity of São Paulo, São Paulo, Brazil; ^cInstituto Alexander Fleming, ^dHospital de Gastroenterología Dr. Carlos Bonorino Udaondo, Buenos Aires, Argentina; ^eInstituto Nacional de Cancerología, ^fHospital San Jose, Bogotá, Colombia; ^gCentro Médico Naval, Secretaría de Marina Armada de México, ^hHospital de Oncología Centro Medico Nacional Siglo XXI I.M.S.S., Mexico, Mexico; ⁱUniversita Degli Studi di Roma 'La Sapienza', Rome, Italy; ^jUppsala University, Uppsala, Sweden

Key Words

Interferon- α • Latin America • Neuroendocrine tumors • Octreotide • Radionuclide imaging • Somatostatin receptors

Abstract

A panel of experts from Latin America convened in Brazil, in May of 2007, for consensus recommendations regarding the management of neuroendocrine tumors (NETs) of the gastrointestinal tract and pancreas. The recently introduced World Health Organization classification of NETs represents a step forward, but the former classification of carcinoids into foregut, midgut and hindgut is still likely to be useful in the near future. Macroscopic description of the tumor should be followed by light microscopic examination and immunohistochemical staining, whereas other techniques might not be widely available in Latin America. Surgery remains the mainstay of treatment for patients with potentially curable tumors, and adequate selection is paramount in order to optimize treatment results. Regarding systemic therapy, patients with well-differentiated tumors or islet-cell carcinomas may be categorized as having indolent disease, while patients with poorly differentiated, anaplastic, and small-

cell carcinomas, or with atypical carcinoids, may be approached initially as having aggressive disease. Somatostatin analogues play a cytostatic role in indolent tumors, and chemotherapy may play a role against other, more aggressive NETs. Obviously, there is an urgent need for novel therapies that are effective against NETs.

Copyright © 2008 S. Karger AG, Basel

Introduction

A panel of experts from four Latin-American and two European countries convened in São Paulo, Brazil, in May of 2007, for a consensus meeting on the management of neuroendocrine tumors (NETs) of the gastrointestinal tract and pancreas. This paper presents the opinions of the panelists on subjects related to the classification, diagnosis, treatment and follow-up of patients with NETs in Latin America, a world region that currently comprises approximately 550 million inhabitants. Given the fact that prospective data from controlled trials for many of the questions discussed in the meeting are currently scarce [1], evidence-based medical data have been used by panel members whenever possible, but many of the rec-

Table 1. WHO classification of NETs of the gastrointestinal tract and pancreas

Tumor subtype
Well-differentiated endocrine tumor
Well-differentiated endocrine carcinoma
Poorly differentiated endocrine carcinoma
Mixed exocrine and endocrine carcinomas
Tumor-like lesions

ommendations were made based upon the collective experience of the authors. The panel recommendations were provided in light of the recognition that the appropriate management of patients with NETs of the gastrointestinal tract and pancreas requires close collaboration between specialists in multiple fields, including pathology, endocrinology, radiology/nuclear medicine, surgery, medical oncology and radiation oncology. In addition, the meeting was held with the underlying philosophy that it is often difficult to provide universal recommendations for adoption in Latin America, given the diversity of medical scenarios that are likely to be found in this world region. For this reason, some of the recommendations are provided in a broad sense, with their implementation calling for the consideration of the issues of local feasibility and affordability.

Classification of NETs

Although NETs of the gastrointestinal tract and pancreas comprise only about 2% of all malignancies, they include a number of different tumors derived from cells of the diffuse neuroendocrine system [2]. Such cells display the capacity to produce and store biogenic amines and peptides. Although different NETs are categorized together, their clinical behavior may be strikingly divergent in terms of molecular features, symptoms and outcome [3]. As a result of this heterogeneity, several classification schemes have been proposed in the last decades. The recent World Health Organization (WHO) classification now indicates five subtypes (table 1): well-differentiated endocrine tumor, well-differentiated endocrine carcinoma, poorly differentiated endocrine carcinoma, mixed exocrine and endocrine carcinomas, and tumor-like lesions [4]. The differentiation between tumor types in the WHO classification is based on histomorphology, tumor size and the presence of local invasion and/or me-

tastases. In the WHO classification, the term ‘carcinoid’ was retained to refer to gastrointestinal NETs that are well differentiated NETs [3]. Although this new classification of NETs is a step forward, the former classification of carcinoids into foregut, midgut and hindgut is still useful, and it will probably take some time before the new classification is widely accepted [2].

Despite the rational basis for predicting prognosis provided by the WHO classification, there is no reliable means of predicting the clinical course of patients with NETs of the gastrointestinal tract and pancreas [3]. Thus, clinicians are still left with the challenge of translating the morphologic and biologic information provided by the classification systems into clinically useful categories. Furthermore, the tumor-node-metastasis (TNM) system has not been validated for use in the overall classification of NETs of the gastrointestinal tract and pancreas. Recently, the European Neuroendocrine Tumour Society (ENETS) has proposed a TNM classification for NETs of the stomach, duodenum, and pancreas [5]. It is hoped that the WHO classification, coupled with anatomical staging systems such as TNM, and possibly incorporating molecular features [3] of NETs will provide clinicians with effective means of classification and prognostication of patients with these tumors. According to the panel, although pathologists vary significantly in their reporting of NETs, the WHO classification system should be encouraged as a useful tool in Latin-American countries. In addition, the use of the TNM classification, recently proposed by the ENETS, is also considered valuable.

Diagnostic Pathology in NETs

The pathologist plays a prominent role in the management of patients with NETs. However, the pathology report may only be as good as the material and information provided by the clinician to the pathologist. Therefore, enough tissue should be obtained for analysis, along with information regarding the clinical scenario. Fine-needle aspiration biopsy is considered insufficient in most instances to provide meaningful information about the tumor. Core biopsy should be favored over fine-needle aspiration whenever possible. In some cases, a repeat biopsy is indicated, for example when there is a change in the clinical course of the disease [1]. Clinicians and organizations in Latin-American countries may find it interesting, on a local or national level, to prepare explicit instructions for the handling of clinical specimens by surgeons and health care staff. The panel considered that

macroscopic description of the tumor should be followed by light microscopic examination and immunohistochemical staining (table 2). Other techniques, such as electron microscopy, immunofluorescent hybridization and molecular testing, should be considered when possible, but might not be widely available in Latin America. In addition, clinicians and investigators may find it useful to identify local or national referral centers for diagnosis of NETs in Latin America, such as the Argentum and GETNE working groups in Argentina and Brazil, respectively.

Among the immunohistochemical markers for NETs, chromogranin A and synaptophysin are important in delineating the neuroendocrine nature of gastrointestinal and pancreatic tumors [6], and staining for these two markers should be an integral part of pathologic evaluation. Staining for other markers, such as gastrin and glucagon, should be considered in selected patients when the clinical scenario warrants it. Immunohistochemical staining for Ki-67 is also considered an essential component of the diagnostic algorithm in NETs [7, 8]. A cutoff point of 2% has been suggested as an indication of aggressiveness [1, 7]. The panel recommends that Ki-67 staining be reported by the pathologist as a continuous variable (i.e., percent staining). Given the role of Ki-67 in terms of predicting prognosis, the ENETS has proposed a working formulation for the grading of digestive NETs based on mitotic count and on Ki-67 staining [5].

Imaging Workup

Even though close to 75% of the patients are diagnosed with localized disease, preoperative staging is important in order to identify all sites of disease and optimize treatment strategies. In some cases of NETs of the gastrointestinal tract and pancreas, the primary tumor is not found because of its small size and paucity of symptoms. Special imaging techniques should be used to identify suspected tumors, especially in the duodenum, pancreas and ileum, using dynamic computed tomography (CT) scan and magnetic resonance imaging (MRI). Endoscopic ultrasound and capsule endoscopy increase the identification of unsuspected lesions by conventional radiology, but are available only in referral centers. Colonoscopy is performed to diagnose suspected colonic and rectal tumors. The use of nuclear medicine techniques to complement tumor staging should be considered in all patients prior to treatment initiation. Somatostatin receptor scintigraphy (SRS), also known as Octreoscan, is available in many

Table 2. Proposed minimum requirements for the pathology report in cases of suspected NETs of the gastrointestinal tract and pancreas

<i>Macroscopic evaluation</i>	
Description of tumor location, size and number	
Description of solid and/or cystic components	
Description of necrotic component	
Description of invasion (with depth or extension) and metastasis	
<i>Microscopic evaluation</i>	
Description of morphologic features on routine hematoxylin and eosin staining	
Description of vascular/lymphatic invasion, perineural invasion, necrosis, fibrosis, and invasion of adjacent organs/structures	
Description of mitotic index	
<i>Immunohistochemistry</i>	
Description of intensity of staining for Ki-67 (as percent of cells), chromogranin A, synaptophysin	
If available, description of other peptides and of somatostatin receptors	

Latin-American countries and uses Indium-111 radiolabeled octreotide ([¹¹¹In-DTPA⁰]-octreotide) to identify tumors that express mainly type 2 somatostatin receptors on the cell surface. A positive result on Octreoscan can be used to select patients for treatment with somatostatin analogues, including peptide-receptor radionuclide therapy. Unfortunately, the sensitivity with this method varies according to tumor type and size. Meta-iodobenzylguanidine (MIBG) is another available method recommended for catecholamine-producing tumors such as pheochromocytoma and paragangliomas [6]. MIBG is less sensitive than Octreoscan for detecting other NETs. The use of 2-[¹⁸F]-2-deoxy-D-glucose positron emission tomography may have some benefit only in poorly differentiated NETs [7]. Currently, serotonin and levodopa labeled with carbon-11 are being used with higher sensitivity in NETs [8]. The use of PET-CT with gallium 68 as a radiotracer, available only in some European countries, seems to be more sensitive in detecting unsuspected metastasis and does not depend on tumor receptor expression [9].

Surgical Approach to Patients with NETs

Surgery is the mainstay of treatment for patients with potentially curable NETs of the gastrointestinal tract and pancreas [2, 10–13]. However, adequate selection of patients is paramount in order to optimize treatment re-

sults. Previous attempts at obtaining consensus on the surgical treatment of NETs have made it clear that management policies vary among centers, in part as a reflection of a lack of controlled studies [14]. These caveats notwithstanding, the panel recognizes that surgical treatment of NETs of the gastrointestinal tract and pancreas is important for symptom palliation and survival. Given this rationale, surgical resection may be attempted with curative or palliative intent, with the latter aiming at cytoreduction or simply at alleviating symptoms [1].

The choice of surgical technique will vary according to patient characteristics, tumor histomorphology, size and location, surgeon's preference, and local availability of resources. As a general rule, an aggressive approach seems justified in carefully selected patients, based on the results of a series of patients with duodenal or pancreatic tumors [14–17]. Wedge or segmental resection is justified in many different clinical scenarios, including when a symptomatic tumor is amenable to surgical control. Endoscopic resection may be indicated otherwise, especially in cases of small, type 1 gastric carcinoids and rectal carcinoids [18–20]. Localized gastric type 3 carcinoids, however, are best treated by radical surgery [18], whereas small- and large-cell neuroendocrine carcinomas of the colon and rectum are frequently metastatic upon diagnosis, warranting careful workup [21]. The role of lymphadenectomy in NETs of the gastrointestinal tract and pancreas is currently unclear, although it may improve staging in patients with no evidence of distant metastasis.

The panel could not reach consensus on all surgical situations, maintaining broad recommendations for surgical indications, and leaving the management of specific situations to the discretion of the local surgeons, taking into account experience and availability of specialized teams in every institution. However, the panel recommends the use of updated guidelines from ENETS or other specific guidelines to orient the management of individual cases.

At major centers, resection of liver metastases of NETs seems to be associated with the same rates of morbidity and mortality that are seen with nonneuroendocrine metastatic tumors, thus being a reasonable option for patients with good performance status who are candidates for resection [22]. Liver transplantation may be considered in selected patients with liver metastases and without extrahepatic disease [23], but it is still unclear whether patients with carcinoid tumors [24] or other histological types [25] fare better. In addition, the long-term results of this approach are still awaited [2]. In addition to conventional tumor resection, cytoreductive approaches to

NETs include radiofrequency ablation and cryotherapy [1], two treatment modalities that are not likely to be found in many Latin-American centers.

Systemic Treatment of Patients with NETs

General Principles

The panel recommends a practical approach to patients with NETs of the gastrointestinal tract and pancreas that takes into account the clinical nature of the disease. Patients with well-differentiated tumors or islet-cell carcinomas may be categorized as having indolent disease, unless proven otherwise. Similarly, patients with poorly differentiated, anaplastic, and small-cell carcinomas, or with atypical carcinoids, may be approached initially as having aggressive disease. Several systemic modalities are currently available for the treatment of patients with indolent and aggressive NETs of the gastrointestinal tract and pancreas. Although no individual drug is sufficiently active and devoid of toxicity, the panel suggests the following general conclusions regarding systemic therapy of NETs of the gastrointestinal tract and pancreas: (1) somatostatin analogues play a cytostatic role in indolent tumors; (2) interferon- α is commonly used notwithstanding its still undefined benefits; (3) chemotherapy regimens may play a role against some types of NETs, and (4) there is an urgent need for novel therapies.

Somatostatin Analogues

High-affinity somatostatin receptors are found in approximately 90% of NETs [2]. The currently available somatostatin analogues include regular octreotide as well as long-acting formulations, such as long-acting release octreotide and lanreotide. In addition, the radiolabeled somatostatin analogue [^{111}In -DPTA 0]-octreotide (Octreoscan) is available in some major Latin-American centers. Novel analogues are under development and should be available in the future, including pasireotide (SOM230) and the radioactive analogue [^{177}Lu -DOTA 0 ,Tyr 3]-octreotate [26]. The binding affinity to somatostatin receptors varies according to the somatostatin analogues [27], and some patients who become resistant to one agent may on occasion respond to another. In addition, dose escalation and temporary treatment interruption, with institution of interferon- α , may help circumvent resistance [2].

Somatostatin analogues play an important role in the treatment of patients with indolent tumors, especially carcinoids (well-differentiated endocrine carcinomas of

Table 3. Typical schedules and mode of administration of somatostatin analogues

Somatostatin analogue	Injection	Dosage	Duration of effect
Octreotide	SC	100–300 µg TID	up to 6 h
Octreotide LAR	IM	10–30 mg once a month	up to 4 weeks
Lanreotide SR	IM	30–60 mg twice a month	up to 2 weeks
Lanreotide autogel	deep SC	60–120 mg once a month	up to 4 weeks

IM = Intramuscular; LAR = long-acting release; SR = slow release; SC = subcutaneous; TID = three times a day.

the small bowel, in the WHO classification). In these tumors, somatostatin analogues may induce symptomatic, biochemical and objective responses. The former two types of responses occur in nearly two thirds of patients, while objective responses are seen in approximately 10% of cases [2]. Therefore, patients with symptomatic tumors, and those whose metastatic disease progresses even without a clinical syndrome, are candidates for therapy with somatostatin analogues. In addition, the perioperative use of somatostatin analogues is critical in the prevention of ‘carcinoid crisis’. Currently, controversial indications for somatostatin analogues include their use after debulking procedures, the adjuvant treatment with octreotide in patients who have no evidence of residual disease, and use in the asymptomatic patient at the time of diagnosis of metastatic disease.

Despite the low response rates to somatostatin analogues, most patients with indolent tumors achieve disease stabilization during treatment [28–36]. While all currently available agents seem to be similarly effective, patient convenience should be taken into account when choosing treatment. Table 3 shows the typical schedules and mode of administration of somatostatin analogues for the treatment of NETs of the gastrointestinal tract and pancreas.

Interferon- α

Interferon- α displays single-agent activity against indolent tumors, as far as symptomatic and biochemical responses are concerned. The comparative efficacy of somatostatin analogues and interferon- α has been investigated only to some extent. The combination of somatostatin analogues with interferon- α has been assessed in recent randomized trials [37–40]. Given the small size of these studies and the heterogeneity of tumors investigated, the role of combination therapy remains unclear. Also, the benefit of adding interferon- α to somatostatin analogues has not been consistent across studies [37, 40].

One of the limiting factors of treatment with interferon- α is toxicity, such as severe flu-like symptoms, mild depression and autoimmune phenomena [1, 2]. Therefore, the panel considers treatment with interferon- α an alternative in cases where somatostatin analogues are not available, not tolerable, or not effective. As a general rule, doses should be titrated individually according to tolerance and laboratory parameters such as the leukocyte count [2].

Chemotherapy

Chemotherapy has an established role in the treatment of patients with several types of NETs of the gastrointestinal tract and pancreas. However, most of the current studies suffer from the limited number of patients and variable criteria for response assessment [2]. Concerning NETs of the gastrointestinal tract and pancreas, there is currently more enthusiasm with islet-cell carcinomas [41] and small-cell carcinomas [42], although patients with poorly differentiated or anaplastic carcinomas, and with atypical carcinoids, may also benefit from chemotherapy. In addition, despite the efficacy of somatostatin analogues in carcinoid tumors, the prognosis of patients with progressive, unresectable metastases is dismal, and palliative chemotherapy may be considered in these cases. Active chemotherapeutic agents include dacarbazine, doxorubicin, etoposide, fluorouracil, ifosfamide, irinotecan, platinum compounds, streptozocin, taxanes, and temozolomide. Various combinations have been investigated along the years, and the doublet fluorouracil/streptozocin has demonstrated good results in a contemporary randomized trial [43]. Moreover, the triplet fluorouracil/streptozocin/doxorubicin is active in islet-cell carcinoma [41]. However, streptozocin is not available in all Latin-American countries, and alternative regimes, such as fluorouracil/doxorubicin, or fluorouracil/epirubicin/dacarbazine [44], will need to be considered in individual cases. Finally, novel chemotherapy

Fig. 1. Sample treatment algorithm, in this case showing the suggested management for sporadic (type III) gastric carcinoids.

regimens, such as oral temozolomide and thalidomide [45], or oral capecitabine and intravenous oxaliplatin [46], seem to be active options in some cases.

Novel Therapies

Given the genetic abnormalities found in NETs of the gastrointestinal tract and pancreas, several targeted agents are currently undergoing investigation in clinical trials [47]. Among these agents, the tyrosine-kinase inhibitors AMG 106, gefitinib, GW786034, imatinib, sorafenib and sunitinib, the mammalian target of rapamycin inhibitors everolimus (RAD001) and temsirolimus, and the antibody bevacizumab, are the ones with more encouraging early results so far.

Treatment Algorithms for NETs

One of the goals of gathering the Latin-American panel was to initiate the process of developing treatment algorithms for NETs of the gastrointestinal tract and pancreas, on the assumptions that the rarity of these tumors, the fact that only a few centers are dedicated to their management, and that new developments in diagnosis and treatment need to be rapidly disseminated in order to ensure adequate patient management. Although international guidelines are currently available [1, 48, 49], it is hoped that locally developed treatment algorithms should help expedite treatment decisions based on the best available evidence and the specific resources that are likely to be found in Latin-American countries. The panel therefore plans to develop disease- and organ-specific guidelines, a model of which is shown in figure 1.

Follow-Up of Patients with NETs

Follow-up of patients with NETs of the gastrointestinal tract and pancreas aims at detecting disease recurrence and second tumors, and may also help in the assessment of functional symptoms and the various medical aspects involved in the treatment of such patients. Despite the fact that evidence-based data on the optimal surveillance strategies are lacking, as a general rule, follow-up tests may include imaging studies, gastrointestinal endoscopies and serum or urinary markers such as chromogranin A and 5-hydroxyindoleacetic acid, all coupled with the clinical assessment. The panel suggests follow-up strategies for some of the specific clinical situations, as discussed in the following paragraphs.

In well-differentiated gastric tumors, surveillance with upper endoscopy should be performed every 2 years in type 1, or every year in type 2 lesions, and mucosal resection should be attempted in lesions measuring >10 mm. In patients with chronic atrophic gastritis, biopsies on flat mucosa should be done to rule out adenocarcinoma. In type 3 tumors resected with curative intent, imaging and chromogranin A should be performed every 6 months for the first 2 years and yearly for the next 3 years. In well-differentiated metastatic disease, follow-up with CT scan or MRI should be done every 3 months.

In well-differentiated, asymptomatic duodenal carcinoma resected with curative intent, the minimal suggested strategy includes upper endoscopy, CT scan and chromogranin A at 6, 24 and 36 months. In patients with metastatic disease, CT scan and chromogranin A should be done every 3–4 months, as dictated by the clinical scenario, and SRS, when available, should be performed every 12 months. Patients with gastrinoma and the multiple endocrine neoplasia type 1 (MEN-1)/Zollinger-Ellison syndrome (ZES) should be seen every 6–12 months, after control of the medical problems related to MEN-1. Typical patients with ZES should be seen yearly with tumor assessment (CT scan and/or SRS), and fasting gastrin determination.

Patients with benign or borderline asymptomatic pancreatic NETs should be followed every 12 months with CT scans (or ultrasound) and serum chromogranin A. Pancreatic tumors of uncertain behavior should be followed every 12 months with CT scans or MRI, and biochemical markers. When available, SRS is recommended at 6 months after surgery. Patients with malignant, asymptomatic pancreatic carcinoma require follow-up every 3–6 months with CT scans or MRI, and serum chromogranin A, according to the clinical scenario. In cases of insulinoma, the first follow-up after pancreatic

surgery for a well-differentiated tumor should take place at 3 months, followed by reassessments every 6 months for 3 years. In rare cases of symptomatic pancreatic tumors, such as VIPoma, glucagonoma, somatostatinoma, etc., the suggested follow-up includes assessment every 3–6 months in metastatic disease and yearly in patients with no metastases, using specific markers coupled with CT scan and SRS.

In poorly-differentiated NETs of the stomach, duodenum and pancreas, patients should be closely followed every 3 months with CT scans or MRI, and with biochemical markers that were positive at diagnosis. In mid-gut tumors (lower jejunum and ileum), clinical examination, ultrasound, CT scans or MRI, SRS, and chromogranin A are suggested every 4–6 months for patients with localized disease. In advanced disease, in addition to the same procedures, echocardiography once a year is considered mandatory to rule out right-sided valvular heart disease. Also, clinicians should keep in mind the risk of second tumors, including NETs, adenocarcinomas of the gastrointestinal tract, and tumors of the lung, prostate, cervix uteri, etc.

Patients who have undergone an appendectomy for a carcinoid tumor <2 cm, located in the tip of the appendix, and with no evidence of serosal invasion or lymph node metastases need no follow-up. After hemicolectomy for carcinoids or goblet cell tumors, patients should be followed annually for 5 years. The suggested follow-up immediately after surgery for patients with rectal carcinoids depends on tumor size. In tumors <1 cm, no follow-up is recommended; for tumors measuring 1–2 cm, follow-up is suggested if there is angioinvasion, muscular invasion

or an atypical histology; for tumors >2 cm, routine follow-up should include CT scan or MRI, and chromogranin A if positive at baseline. In the longer term, patients undergoing resection of a rectal carcinoid should be followed with endoscopic ultrasound and chromogranin A every 6 months until 3 years, and annually thereafter.

Finally, all patients with poorly differentiated carcinomas of the hindgut should be closely followed with CT scans every 3 months. In some instances, MRI might provide better imaging of the pelvis, and could be indicated in selected cases. Furthermore, positive biochemical markers at baseline should be followed. In metastatic disease, follow-up will vary according to symptoms and the type of treatment.

Conclusions

A final role of the panel was to determine whether a Latin-American Registry of patients with NETs of the gastrointestinal tract and pancreas is in order. Although data on NETs may originate from population-based tumor registries [50–52], no such mechanism is currently in operation in Latin America. On the other hand, previous experience of some of the panel members has shown that setting and maintaining a tumor registry is feasible. Therefore, a Latin-American Registry of patients with NETs of the gastrointestinal tract and pancreas is currently planned, and should provide valuable information regarding the epidemiology and patterns of care for these tumors in this part of the world.

References

- Oberg K, Kvols L, Caplin M, et al: Consensus report on the use of somatostatin analogs for the management of neuroendocrine tumors of the gastroenteropancreatic system. *Ann Oncol* 2004;15:966–973.
- Oberg K: Management of neuroendocrine tumours. *Ann Oncol* 2004;15(suppl 4):iv293–iv298.
- Zikusoka MN, Kidd M, Eick G, et al: The molecular genetics of gastroenteropancreatic neuroendocrine tumors. *Cancer* 2005;104:2292–2309.
- Solcia E, Kloppel G, Sobin L (eds): *Histological Typing of Endocrine Tumours*. New York, Springer, 2000, pp 38–74.
- Rindi G, Kloppel G, Alhman H, et al: TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. *Virchows Arch* 2006;449:395–401.
- Greenblatt DY, Shenker Y, Chen H: The utility of metaiodobenzylguanidine (MIBG) scintigraphy in patients with pheochromocytoma. *Ann Surg Oncol* 2008;15:900–905.
- Adams S, Baum R, Rink T: Limited value of fluorine-18 fluorodeoxyglucose positron emission tomography for the imaging of neuroendocrine tumours. *Eur J Nucl Med* 1998;25:79–83.
- Koopmans KP, de Vries EG, Kema IP: Staging of carcinoid tumours with 18F-DOPA PET: a prospective, diagnostic accuracy study. *Lancet Oncol* 2006;7:728–734.
- Koukouraki S, Strauss LG, Georgoulas V: Evaluation of the pharmacokinetics of 68Ga-DOTATOC in patients with metastatic neuroendocrine tumours scheduled for 90Y-DOTATOC therapy. *Eur J Nucl Med Mol Imaging* 2006;33:460–466.
- Oberg K: Neuroendocrine gastrointestinal tumours. *Ann Oncol* 1996;7:453–463.
- La Rosa S, Sessa F, Capella C, et al: Prognostic criteria in nonfunctioning pancreatic endocrine tumours. *Virchows Arch* 1996;429:323–333.
- Rorstad O: Prognostic indicators for carcinoid neuroendocrine tumors of the gastrointestinal tract. *J Surg Oncol* 2005;89:151–160.

- 13 Akerstrom G, Hellman P: Surgery on neuroendocrine tumours. *Best Pract Res Clin Endocrinol Metab* 2007;21:87–109.
- 14 Wiedenmann B, Jensen RT, Mignon M, et al: Preoperative diagnosis and surgical management of neuroendocrine gastroenteropancreatic tumors: general recommendations by a consensus workshop. *World J Surg* 1998;22:309–318.
- 15 Fendrich V, Langer P, Celik I, et al: An aggressive surgical approach leads to long-term survival in patients with pancreatic endocrine tumors. *Ann Surg* 2006;244:845–851; discussion 852–853.
- 16 Schurr PG, Strate T, Rese K, et al: Aggressive surgery improves long-term survival in neuroendocrine pancreatic tumors: an institutional experience. *Ann Surg* 2007;245:273–281.
- 17 Norton JA, Kivlen M, Li M, et al: Morbidity and mortality of aggressive resection in patients with advanced neuroendocrine tumors. *Arch Surg* 2003;138:859–866.
- 18 Schindl M, Kaserer K, Niederle B: Treatment of gastric neuroendocrine tumors: the necessity of a type-adapted treatment. *Arch Surg* 2001;136:49–54.
- 19 Akerstrom G: Management of carcinoid tumors of the stomach, duodenum, and pancreas. *World J Surg* 1996;20:173–182.
- 20 Wang AY, Ahmad NA: Rectal carcinoids. *Curr Opin Gastroenterol* 2006;22:529–535.
- 21 Bernick PE, Klimstra DS, Shia J, et al: Neuroendocrine carcinomas of the colon and rectum. *Dis Colon Rectum* 2004;47:163–169.
- 22 Sarmiento JM, Que FG: Hepatic surgery for metastases from neuroendocrine tumors. *Surg Oncol Clin N Am* 2003;12:231–242.
- 23 Lang H, Oldhafer KJ, Weimann A, et al: Liver transplantation for metastatic neuroendocrine tumors. *Ann Surg* 1997;225:347–354.
- 24 Le Treut YP, Delperio JR, Dousset B, et al: Results of liver transplantation in the treatment of metastatic neuroendocrine tumors. A 31-case French multicentric report. *Ann Surg* 1997;225:355–364.
- 25 Routley D, Ramage JK, McPeake J, et al: Orthotopic liver transplantation in the treatment of metastatic neuroendocrine tumors of the liver. *Liver Transpl Surg* 1995;1:118–121.
- 26 Strosberg JR, Kvols LK: A review of the current clinical trials for gastroenteropancreatic neuroendocrine tumours. *Expert Opin Invest Drugs* 2007;16:219–224.
- 27 Plockinger U, Wiedenmann B: Neuroendocrine tumors. *Biotherapy. Best Pract Res Clin Endocrinol Metab* 2007;21:145–162.
- 28 Arnold R, Trautmann ME, Creutzfeldt W, et al: Somatostatin analogue octreotide and inhibition of tumour growth in metastatic endocrine gastroenteropancreatic tumours. *Gut* 1996;38:430–438.
- 29 di Bartolomeo M, Bajetta E, Buzzoni R, et al: Clinical efficacy of octreotide in the treatment of metastatic neuroendocrine tumors. A study by the Italian Trials in Medical Oncology Group. *Cancer* 1996;77:402–408.
- 30 Ruszniewski P, Ducreux M, Chayvialle JA, et al: Treatment of the carcinoid syndrome with the longacting somatostatin analogue lanreotide: a prospective study in 39 patients. *Gut* 1996;39:279–283.
- 31 Saltz L, Trochanowski B, Buckley M, et al: Octreotide as an antineoplastic agent in the treatment of functional and nonfunctional neuroendocrine tumors. *Cancer* 1993;72:244–248.
- 32 Eriksson B, Renstrup J, Imam H, et al: High-dose treatment with lanreotide of patients with advanced neuroendocrine gastrointestinal tumors: clinical and biological effects. *Ann Oncol* 1997;8:1041–1044.
- 33 Rubin J, Ajani J, Schirmer W, et al: Octreotide acetate long-acting formulation versus open-label subcutaneous octreotide acetate in malignant carcinoid syndrome. *J Clin Oncol* 1999;17:600–606.
- 34 O'Toole D, Ducreux M, Bommelaer G, et al: Treatment of carcinoid syndrome: a prospective crossover evaluation of lanreotide versus octreotide in terms of efficacy, patient acceptability, and tolerance. *Cancer* 2000;88:770–776.
- 35 Ricci S, Antonuzzo A, Galli L, et al: Octreotide acetate long-acting release in patients with metastatic neuroendocrine tumors pretreated with lanreotide. *Ann Oncol* 2000;11:1127–1130.
- 36 Welin SV, Janson ET, Sundin A, et al: High-dose treatment with a long-acting somatostatin analogue in patients with advanced midgut carcinoid tumours. *Eur J Endocrinol* 2004;151:107–112.
- 37 Arnold R, Rinke A, Klose KJ, et al: Octreotide versus octreotide plus interferon-alpha in endocrine gastroenteropancreatic tumors: a randomized trial. *Clin Gastroenterol Hepatol* 2005;3:761–771.
- 38 Faiss S, Pape UF, Bohmig M, et al: Prospective, randomized, multicenter trial on the antiproliferative effect of lanreotide, interferon alpha, and their combination for therapy of metastatic neuroendocrine gastroenteropancreatic tumors – the International Lanreotide and Interferon Alfa Study Group. *J Clin Oncol* 2003;21:2689–2696.
- 39 Fjallskog ML, Sundin A, Westlin JE, et al: Treatment of malignant endocrine pancreatic tumors with a combination of alpha-interferon and somatostatin analogs. *Med Oncol* 2002;19:35–42.
- 40 Kolby L, Persson G, Franzen S, et al: Randomized clinical trial of the effect of interferon alpha on survival in patients with disseminated midgut carcinoid tumours. *Br J Surg* 2003;90:687–693.
- 41 Kouvaraki MA, Ajani JA, Hoff P, et al: Fluorouracil, doxorubicin, and streptozocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. *J Clin Oncol* 2004;22:4762–4771.
- 42 de Lima Lopes G Jr, Chiappori A, Simon G, et al: Phase I study of carboplatin in combination with gemcitabine and irinotecan in patients with solid tumors: preliminary evidence of activity in small cell and neuroendocrine carcinomas. *Cancer* 2007;109:1413–1419.
- 43 Sun W, Lipsitz S, Catalano P, et al: Phase II/III study of doxorubicin with fluorouracil compared with streptozocin with fluorouracil or dacarbazine in the treatment of advanced carcinoid tumors: Eastern Cooperative Oncology Group Study E1281. *J Clin Oncol* 2005;23:4897–4904.
- 44 Bajetta E, Ferrari L, Procopio G, et al: Efficacy of a chemotherapy combination for the treatment of metastatic neuroendocrine tumours. *Ann Oncol* 2002;13:614–621.
- 45 Kulke MH, Stuart K, Enzinger PC, et al: Phase II study of temozolomide and thalidomide in patients with metastatic neuroendocrine tumors. *J Clin Oncol* 2006;24:401–406.
- 46 Bajetta E, Catena L, Procopio G, et al: Are capecitabine and oxaliplatin (XELOX) suitable treatments for progressing low-grade and high-grade neuroendocrine tumours? *Cancer Chemother Pharmacol* 2007;59:637–642.
- 47 Yao JC: Neuroendocrine tumors. Molecular targeted therapy for carcinoid and islet-cell carcinoma. *Best Pract Res Clin Endocrinol Metab* 2007;21:163–172.
- 48 Clark OH, Ajani J, Benson AB 3rd, et al: Neuroendocrine tumors. *J Natl Compr Canc Netw* 2006;4:102–138.
- 49 Ramage JK, Davies AH, Ardill J, et al: Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours. *Gut* 2005;54(Suppl 4):iv1–iv16.
- 50 Hemminki K, Li X: Incidence trends and risk factors of carcinoid tumors: a nationwide epidemiologic study from Sweden. *Cancer* 2001;92:2204–2210.
- 51 Quaedvlieg PF, Visser O, Lamers CB, et al: Epidemiology and survival in patients with carcinoid disease in The Netherlands. An epidemiological study with 2391 patients. *Ann Oncol* 2001;12:1295–1300.
- 52 Maggard MA, O'Connell JB, Ko CY: Updated population-based review of carcinoid tumors. *Ann Surg* 2004;240:117–122.