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Rare Functioning Pancreatic Endocrine Tumors

Dermot O'Toole[a] Ramon Salazar[b] Massimo Falconi[c] Gregory Kaltsas[d] Anne Couvelard[e] Wouter W. de Herder[f] Rudolf Hyrdel[g] George Nikou[h] Eric Krenning[i] Marie-Pierre Vullierme[j] Martin Caplin[k] Robert Jensen[l] Barbro Eriksson[m] and all other Frascati Consensus Conference participants

[a]Department of Gastroenterology, Beaujon Hospital, Clichy, France; [b]Department of Oncology, Institut Català d'Oncologia, Barcelona, Spain; [c]Department of Surgery, Verona University, Verona, Italy; [d]Department of Endocrinology and Metabolism, Genimatas Hospital, Athens, Greece; [e]Department of Gastroenterology, Beaujon Hospital, Clichy, France; [f]Department of Endocrinology, Erasmus MC University, Rotterdam, The Netherlands; [g]Department of Internal Medicine, Martin University, Martin, Slovakia; [h]Department of Propaedeutic Internal Medicine, Laiko Hospital, Athens, Greece; [i]Department of Nuclear Medicine, Erasmus MC University, Rotterdam, The Netherlands; [j]Department of Gastroenterology, Beaujon Hospital, Clichy, France; [k]Department of Gastroenterology, Royal Free Hospital, London, UK; [l]Department of Cell Biology, National Institute of Health, Bethesda, Md., USA; [m]Department of Endocrinology, University Hospital, Uppsala, Sweden

Introduction

Pancreatic endocrine tumors (PETs) represent a heterogeneous group of tumors depending on functional status and histological differentiation. Functioning tumors are defined when clinical symptoms are related to peptide/hormone overproduction. Tumors secreting pancreatic polypeptide, human chronic gonadotrophin subunits, calcitonin, neurotensin or other peptides do not usually produce specific symptoms and should be considered as non-functioning tumors. In addition, it is important to note that several of these rare functioning tumors (RFTs) may have extra-pancreatic localizations such as VIPomas (10%), somatostatinoma (~50%), GRFoma (70%) and adrenocorticotropic-secreting tumors (ACTHoma) (85%) [1].

Epidemiology and Clinicopathological Features

General

The incidence of clinically detected PETs has been reported to be 4–12 per million, which is much lower than that reported from autopsy series (about 1%) [2, 3]. Considering functioning PETs, insulinomas are the most common (17% incidence), followed by gastrinoma (15%). The remainder incorporates RFTs and includes: VIPoma (2%), glucagonoma (1%), carcinoid (1%), somatostatinoma (1%), and the rest are comprised of adrenocorticotropic-secreting tumors (ACTHoma), GRFomas, calcitonin-producing tumors, parathyroid hormone-related peptide tumors, and other exceedingly rare neoplasms [4–14].

Similar to insulinomas and gastrinomas, the majority of RFTs are well-differentiated tumors [15]. Most RFTs present as malignant disease (WHO group 2) and liver metastases are common [8, 10, 14, 16, 17]. The 5-year survival rate is reported to be 60–100% for localized disease,

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Dermot O'Toole
Department of Gastroenterology
CHU d'Angers
FR–49000 Angers (France)
Tel. +33 1 4087 5328, E-Mail deotoole@chu-angers.fr

40% for regional disease, 29% for distant metastases, and 80% for all stages [2, 3]. In a publication from 1993 [18], the 5-year survival rate for advanced PETs approached 60 months from diagnosis. RFTs can occur at any age with an equal sex distribution [10, 14, 17]. Overall, about 15–30% of patients with PETs have multiple endocrine neoplasia type 1 (MEN-1). In MEN-1 patients, multiple tumors occur either synchronously or metachronously [19]. The incidence of MEN-1 in patients with RFTs is not known but in recent studies appears to be about 2% for VIPomas and glucagonomas [20, 21]; the incidence of MEN1 in somatostatinomas and GRFomas may be higher.

Patients with malignant tumors may present with mixed syndromes, or the tumors may change clinically over time.

Minimal Consensus Statements on Epidemiology and Clinicopathological Features – Specific

RFTs represent less than 10% of all PETs. The majority of patients with RFTs of the pancreas present with metastatic disease and only some with local disease. Most RFTs are diagnosed as WHO group 2. Not enough data in the literature is currently available to give accurate estimates on survival. The average age at diagnosis is estimated to be 50–55 years, with equal gender distribution. Patients with malignant tumors may present with mixed syndromes or tumors may change clinically over time. The most frequent familial condition associated with RFT is MEN-1.

Diagnostic Procedures: Imaging, Nuclear Medicine and Laboratory Tests

Diagnostic Procedures – General

The standard imaging procedures for RFTs, like other PETs, include endoscopic ultrasonography (EUS), contrast-enhanced helical CT or MRI of the abdomen (for both primary tumor and detection of metastases) in combination with somatostatin receptor scintigraphy (SRS). Image-fusion data, combining CT and SRS (SPECT), appears promising [22] in helping to accurately locate tumoral residues and plan surgery. EUS is a proven method in detecting most PETs and can be combined with EUS-FNA [23, 24]. SRS is a routine investigation for both primary tumors and metastases [25–27] and should be performed prior to treatment planning, especially surgery [68]. Gallium-labeled somatostatin analogue PET is also a promising detection method and despite the limited experience to date, the technique appears interesting, even in the detection of small tumors [28, 29]. Standard PET with ^{18}F-glucose is not efficient in detecting well-differentiated tumors but may have some value in the detection of aggressive poorly differentiated PETs [30]. Recently, data using positron emission tomography with 5-HTP or ^{18}F-DOPA has also shown promising results and may be an option for the detection of small well-differentiated tumors [30–32].

Biological tests in the presence of RFTs should include both specific markers (VIP, glucagon, somatostatin, GRF, ACTH) and general markers (chromogranin A and pancreatic polypeptide) [14, 16, 17, 33, 34].

Minimal Consensus Statements on Diagnostic Procedures – Specific

Imaging and Nuclear Medicine

The combined use of CT scan (or MRI) and SRS is always recommended. Endosonography is not universally recommended as a first-line procedure in the investigation of RFT of the pancreas; it may be used in circumstances where CT, MRI and SRS are inconclusive, especially preoperatively; however, in patients with RFTs presenting with liver metastases, EUS is rarely necessary. Insufficient data is available to recommend PET methods on a routine basis and availability is limited. If certain circumstances in the suspicion of RFTs and all above recommended imaging are negative [68]. Gallium-labeled somatostatin analogues positron emission tomography may be performed; however, this is not universally available. Other examinations which may be useful are ^{18}F-DOPA-PET or ^{11}C-5-HTP PET (although availability and costs may have to be considered).

Laboratory Tests

The minimal biochemical work-up for RFTs includes specific biochemical analyses related to specific hormonal activity (example serum glucacon in suspicion of glucagonoma) and general markers chromogranin A and pancreatic polypeptide. Serum parathormone and calcium should also be performed as a baseline screening for MEN-1. All biochemical tests should be performed at first visit.

Pathology and Genetics

Histopathology and Genetics – General

Pathological diagnosis is mandatory in all cases and is easily obtained on tumor biopsy performed either in cases of hepatic metastases (e.g. ultrasound-guided biopsy) or of the primary tumor (preferably using EUS-FNA if locally-advanced, or at surgery). Pathological diagnosis of RFTs is performed using conventional HE staining, immunohistochemical staining with chromogranin and synaptophysin [15]. Determination of mitotic index by

counting 10 HPF and calculation of Ki-67 index by immunohistochemistry is mandatory [35]. The tumors should be classified according to WHO system knowing that the vast majority of RFTs fall within group 2 tumors. Genetic testing for hereditary tumor syndromes should be performed in case of suspected familial predisposition to MEN-1 or if the presence of other associated endocrinopathies (e.g. elevated serum calcium or PTH suggesting hyperparathyroidism and prolactinoma, respectively).

Minimal Consensus Statements on Histopathology and Genetics – Specific

Histopathology

Histology is always necessary to establish a diagnosis. Cytology may be helpful, but should be confirmed by histology. The minimal ancillary tests to support the histological diagnosis include immunohistochemistry for chromogranin A, synaptophysin and specific hormones according to the clinical setting. Both the mitotic count in 10 HPF (2 mm^2) and the Ki-67 index (the latter performed using immunohistochemistry, although the techniques and counting standards need to be established) are mandatory in all cases. Immunohistochemistry for p53 and SSR2A receptors is not routinely recommended, with the exception of staining for SSR2A if SRS is not available.

Genetics

Germline DNA testing is only recommended in the presence of a positive family history of MEN-1, if there are suspicious clinical findings or if multiple tumors or precursor lesions are present. Genetic analysis should also be performed in suspected cases of MEN-1. Genetic testing, when performed, should include mutational screening and sequencing allowing the analysis of the entire coding gene and splice sites and genetic counseling should be sought prior to testing in all patients. Informed consent is mandatory prior to genetic testing. Somatic (tumor) DNA testing is not recommended.

Surgical and Cytoablative Therapies

Curative Surgery and Cytoablation – General

Indications for surgery depend on clinical symptoms, tumor size and location, malignancy and metastatic spread. Curative surgery should be sought also in metastatic disease, including 'localized' metastatic disease to the liver [36]. The type of surgery depends on the location of the primary tumor – pancreatico-duodenal resection (Whipple's operation), distal pancreatectomy, tumor enucleation or enucleation in combination with resection. If malignancy is suspected, adequate lymph node clearance is mandatory.

In case of surgery for liver metastases, complete resection (RO) of metastases should always be considered both in functioning and non-functioning tumors. Liver surgery includes metastasis enucleation, segmental resection(s), hemi-hepatectomy or extended hemi-hepatectomy [37]. Intraoperative US should be performed for detection of all liver metastases. Prior to performing liver surgery, metastatic disease should be confined to the liver. Surgery should be undertaken only if 90% of the tumor mass can be successfully removed. Liver surgery can be done concomitantly with surgery of the primary tumor or on a separate occasion. In patients with RFTs, specific measures to avoid hormonal crisis are required during surgery (notably perioperative somatostatin analogue infusion) and specified anesthetic considerations [10]. Palliative surgery (to primary or metastases) may also be performed following multidisciplinary discussions and includes palliative or debulking resections (resection of >90% of tumor burden) to control symptoms related to hormonal hypersecretion [10, 14, 17, 33]. Bilateral adrenalectomy should be performed in selected cases with ACTH secretion resulting in Cushing syndrome [38, 39]. Liver transplantation may be indicated for a small number of patients, without extrahepatic metastases [40], in whom life-threatening hormonal symptoms persist despite maximal medical therapy and where standard surgery is not feasible.

Selective embolization alone or in combination with intra-arterial chemotherapy (chemoembolization – using streptozotocin, doxorubicin, mitomycin C, etc.) is an established procedure effective in controlling symptoms and controlling tumor progression [41]. Symptomatic responses of about 60% are reported with approximately a 40–50% tumor response [42–46]. It has not been established whether chemoembolization is more efficient than embolization alone. In experienced centers, the mortality rate is low, however, significant morbidity may occur (hepatic or renal failure). The postembolization syndrome is frequent with fever (sometimes prolonged), right upper quadrant pain, nausea, elevation of liver enzymes and a decrease in albumin and PT [41]. Adequate analgesia and hydration are recommended during and following treatment and prophylaxis with somatostatin analogues is always indicated when embolizing functioning tumors. Contraindications of TACE are complete portal vein thrombosis, hepatic insufficiency and a previous pancreaticoduodenectomy, which may expose the patient to severe complications of TACE.

Other local ablative methods which may be used alone or in combination with surgery, including radiofrequen-

cy ablation (RFA), cryotherapy and laser therapy [47–53]. Local ablative methods are usually reserved to treat limited disease (<8–10 metastases of <4–5 cm in diameter).

Minimal Consensus Statements on Surgery and Cytoablative Therapies – Specific

Curative surgery is always recommended whenever feasible after careful symptomatic control of the clinical syndrome [10]; the latter may be achieved by medical or locoregional treatments. Curative surgery should include oncological resection with lymphadenectomy. Surgery of liver metastases may be performed during treatment of the primary tumor. The best treatment option for liver metastases in RFTs is liver resection when feasible or chemoembolization. In patients with advanced stages, debulking surgical strategies have a major role. Liver transplantation may be reserved for rare circumstances in patients where extra-hepatic disease is ruled out. Bilateral adrenalectomy should be performed in selected cases with Cushing syndrome. Loco-regional ablative therapies recommended for the treatment of malignant RFTs of the pancreas include transarterial chemoembolization and radiofrequency ablation.

Medical Therapy

Medical Therapy – General

Both somatostatin analogues and interferon have been shown to be effective in the control of symptoms in functioning PETs [54] and this also includes RFTs [8, 10, 14]; in fact about 80–90% of patients with VIPoma and glucagonoma improve very promptly, overcoming diarrhea and skin rash, and 60–80% have a reduction in VIP and glucagon levels. Symptomatic relief is not always related to reduction in circulating hormone levels, indicating that somatostatin analogues have direct effects on the peripheral target organ. Escape from symptomatic control can be seen quite frequently but an increase in the dose of somatostatin analogues can help temporarily. The anti-tumor efficacy of somatostatin analogues appears less pronounced according to recent data, with objective tumor responses of <10% [55–58]; however, disease stabilization of up to 40% has been reported and these agents may be of value in subgroups of patients with slowly-progressive well-differentiated tumors expressing sst2 receptor subtype (i.e., a positive SRS) [56, 58]. In the control of symptoms, somatostatin analogue therapy should be initiated with short-acting substance (octreotide 100 μg subcutaneously ×2–3) for 1–2 days with titration according to clinical response. The patient can then be transferred to slow-release Lanreotide-SR® i.m., Lanreotide autogel® s.c. or Sandostatin–LAR® i.m. (every 4 weeks) [59]. Likewise, interferon may be indicated in metastatic low-proliferating tumors and can be effective in VIPomas not responding to somatostatin analogs [60], but this requires confirmation in a controlled manner [56, 58].

Systemic chemotherapy is indicated in patients with metastatic and progressive RFTs using combinations of streptozotcin and 5-FU and or doxorubicin with objective response rates in the order of 35% [61, 62]. This is considerably lower than the 69% reported by Moertel et al. [63] in 1992. Chemotherapy in the adjuvant setting has not been explored to date. Peptide receptor radionuclide therapy (PRRT) has been made possible due to development of chelators suitable for radiometal labeling allowing for coupling of modified somatostatin analogues with trivalent metal ions (indium, gallium, yttrium, lutetium, etc.), thus allowing for further potential in diagnostic and therapeutic applications. Limited experience is available concerning PRRT in the treatment of RFTs; however, its efficacy in other advanced PETs with positive SRS has been demonstrated [64, 65].

Minimal Consensus Statements on Medical Therapy – Specific

Somatostatin analogues are an effective treatment in the control of symptoms in RFTs, especially in patients with VIPomas and glucagonomas. They may also be indicated as an antiproliferative treatment in selected cases based on positive SRS. Interferon may also be useful in selected patients with RFTs.

Systemic chemotherapy is reserved for patients with metastatic and progressive RFTs using streptozotocin plus 5-FU and or doxorubicin. Chemotherapy is not recommended in an adjuvant setting outside of a prospective evaluation. Peptide receptor radionuclide therapy can be used for RFTs in case of inoperable metastatic disease if the tumors have a high uptake (grade 3–4) on SRS.

Follow-Up

Follow-Up – General

As in other cases of PETs, follow-up in RFTs should include careful appraisal of clinical, biological and morphological parameters at regular intervals. No formal recommendation to date has been proposed. Given the high incidence of metastatic disease in RFTs, most patients are usually followed at intervals of between 3 and 6 months with appropriate biological and imaging tests.

Minimal Consensus Statements on Follow-Up – Specific

Follow-up for patients with RFTs should be at intervals of 3 to 6 month in metastatic disease and yearly in patients without metastatic disease. Following treatment, in patients with no evidence of residual disease, pertinent biochemical assessment (i.e. hormones known to be elevated prior to treatment, both specific and non-specific) should be initially performed and, when negative, further tests are not usually required. For patients with residual disease, specific markers coupled with CT-scan and SRS should be performed.

List of Participants

H. Ahlman, Department of Surgery, Gothenburg University, Gothenburg (Sweden); R. Arnold, Department of Gastroenterology, Philipps University, Marburg (Germany); W.O. Bechstein, Department of Surgery, Johann-Wolfgang-Goethe-Universität, Frankfurt (Germany); G. Cadiot, Department of Hepatology and Gastroenterology, CHU Bichat – B. Claude Bernard University, Paris (France); M. Caplin, Department of Gastroenterology, Royal Free Hospital, London (UK); E. Christ, Department of Endocrinology, Inselspital, Bern (Switzerland); D. Chung, Department of Gastroenterology, Massachussetts General Hospital, Boston, Mass. (USA); A. Couvelard, Department of Gastroenterology, Beaujon Hospital, Clichy (France); W.W. de Herder, Department of Endocrinology, Erasmus MC University, Rotterdam (the Netherlands); G. Delle Fave, Department of Digestive and Liver Disease, Ospedale S. Andrea, Rome (Italy); B. Eriksson, Department of Endocrinology, University Hospital, Uppsala (Sweden); A. Falchetti, Department of Internal Medicine, University of Florence and Centro di Riferimento Regionale Tumori Endocrini Ereditari, Azienda Ospedaliera Careggi, Florence (Italy); M. Falconi, Department of Surgery, Verona University, Verona (Italy); D. Ferone, Department of Endocrinology, Genoa University, Genoa (Italy); P. Goretzki, Department of Surgery, Städtisches Klinikum Neuss, Lukas Hospital, Neuss (Germany); D. Gross, Department of Endocrinology and Metabolism, Hadassah University, Jerusalem (Israel); D. Hochhauser, Department of Oncology, Royal Free University, London (UK); R. Jensen, Department of Cell Biology, National Institute of Health, Bethesda, Md. (USA); G. Kaltsas, Department of Endocrinology and Metabolism, Genimatas Hospital, Athens (Greece); F. Keleştimur, Department of Endocrinology, Erciyes University, Kayseri (Turkey); R. Kianmanesh, Department of Surgery, UFR Bichat-Beaujon-Louis Mourier Hospital, Colombes (France); W. Knapp, Department of Nuclear Medicine, Medizinische Hochschule Hannover, Hannover (Germany); U.P. Knigge, Department of Surgery, Rigshospitalet Blegdamsvej Hospital, Copenhagen (Denmark); P. Komminoth, Department of Pathology, Kantonsspital, Baden (Switzerland); M. Körner, University of Bern, Institut für Pathologie, Bern (Switzerland), B. Kos-Kudła, Department of Endocrinology, Slaska University, Zabrze (Poland); L. Kvols, Department of Oncology, South Florida University, Tampa, Fla. (USA); D.J. Kwekkeboom, Department of Nuclear Medicine, Erasmus MC University, Rotterdam (the Netherlands); V. Lewington, Department of Radiology, Royal Marsden Hospital, Sutton (UK); J.M. Lopes, Department of Pathology, IPATIMUP Hospital, Porto (Portugal); R. Manfredi, Department of Radiology, Istituto di Radiologia, Policlinico GB, Verona (Italy); A.M. McNicol, Department of Oncology and Pathology, Royal Infirmary Hospital, Glasgow (UK); E. Mitry, Department of Hepatology and Gastroenterology, CHV A Pare Hospital, Boulogne (France); B. Niederle, Department of Surgery, Wien University, Vienna (Austria); O. Nilsson, Department of Pathology, Gothenberg University, Gothenberg (Sweden); K. Öberg, Department of Endocrinology, University Hospital, Uppsala, Sweden; J. O'Connor, Department of Oncology, Alexander Fleming Institute, Buenos Aires (Argentina); D. O'Toole, Department of Gastroenterology, Beaujon Hospital, Clichy (France); S. Pauwels, Department of Nuclear Medicine, Catholique de Louvain University, Brussels (Belgium); U.-F. Pape, Department of Internal Medicine, Charité, University of Berlin (Germany); M. Pavel, Department of Endocrinology, Erlangen University, Erlangen (Germany); A. Perren, Department of Pathology, Universitätsspital Zürich, Zürich (Switzerland); U. Plöckinger, Department of Hepatology and Gastroenterology, Charité Universitätsmedizin, Berlin (Germany); J. Ramage, Department of Gastroenterology, North Hampshire Hospital, Hampshire (UK); J. Ricke, Department of Radiology, Charité Universitätsmedizin, Berlin (Germany); G. Rindi, Department of Pathology and Laboratory Medicine, Università degli Studi, Parma (Italy); P. Ruszniewski, Department of Gastroenterology, Beaujon Hospital, Clichy (France); R. Salazar, Department of Oncology, Institut Català d'Oncologia, Barcelona (Spain); A. Sauvanet, Department of Surgery, Beaujon Hospital, Clichy (France); A. Scarpa, Department of Pathology, Verona University, Verona (Italy); J.Y. Scoazec, Department of Pathology, Edouard Herriot Hospital, Lyon (France); M.I. Sevilla Garcia, Department of Oncology, Virgen de la Victoria Hospital, Malaga (Spain); T. Steinmüller, Department of Surgery, Vivantes Humboldt Hospital, Berlin (Germany); A. Sundin, Department of Radiology, Uppsala University, Uppsala (Sweden); B. Taal, Department of Oncology, Netherlands Cancer Centre, Amsterdam (the Netherlands); E. Van Cutsem, Department of Gastroenterology, Gasthuisberg University, Leuven (Belgium); M.P. Vullierme, Department of Gastroenterology, Beaujon Hospital, Clichy (France); B. Wiedenmann, Department of Hepatology and Gastroenterology, Charité Universitätsmedizin, Berlin (Germany); S. Wildi, Department of Surgery, Zürich Hospital, Zürich, Switzerland; J.C. Yao, Department of Oncology, University of Texas, Houston, Tex. (USA); S. Zgliczyński, Department of Endocrinology, Bielanski Hospital, Warsaw (Poland).

References

1 Jensen R: Natural history of digestive endocrine tumors; in Mignon M, Colombel JF (eds): Recent Advances in the Pathophysiology and Management of Inflammatory Bowel Disease and Digestive Endocrine Tumors. Paris, John Libbey Eurotext, 1999, pp 192–219.

2 Eriksson B, Arnberg H, Lindgren PG, Lorelius LE, Magnusson A, Lundqvist G, Skogseid B, Wide L, Wilander E, Oberg K: Neuroendocrine pancreatic tumors: clinical presentation, biochemical and histopathological findings in 84 patients. J Intern Med 1990;228:103–113.

3 Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. Cancer 2003;97:934–959.

4 Verner JV, Morrison AB: Islet cell tumor and a syndrome of refractory watery diarrhea and hypokalemia. Am J Med 1958;25:374–380.

5 Mallinson CN, Bloom SR, Warin AP, Salmon PR, Cox B: A glucagonoma syndrome. Lancet 1974;ii:1–5.

6 Ganda OP, Weir GC, Soeldner JS, Legg MA, Chick WL, Patel YC, Ebeid AM, Gabbay KH, Reichlin S: 'Somatostatinoma': a somatostatin-containing tumor of the endocrine pancreas. N Engl J Med 1977;296:963–967.

7 Vinik AI, Moattari AR: Treatment of endocrine tumors of the pancreas. Endocrinol Metab Clin N Am 1989;18:483–518.

8 Gorden P, Comi RJ, Maton PN, Go VL: NIH conference. Somatostatin and somatostatin analogue (SMS 201-995) in treatment of hormone-secreting tumors of the pituitary and gastrointestinal tract and non-neoplastic diseases of the gut. Ann Intern Med 1989; 110:35–50.

9 Kimura W, Kuroda A, Morioka Y: Clinical pathology of endocrine tumors of the pancreas. Analysis of autopsy cases. Dig Dis Sci 1991;36:933–942.

10 Wermers RA, Fatourechi V, Kvols LK: Clinical spectrum of hyperglucagonemia associated with malignant neuroendocrine tumors. Mayo Clin Proc 1996;71:1030–1038.

11 Soga J: Statistical evaluation of 2001 carcinoid cases with metastases, collected from literature: a comparative study between ordinary carcinoids and atypical varieties. J Exp Clin Cancer Res 1998;17:3–12.

12 Soga J, Yakuwa Y: Somatostatinoma/inhibitory syndrome: a statistical evaluation of 173 reported cases as compared to other pancreatic endocrinomas. J Exp Clin Cancer Res 1999;18:13–22.

13 Chastain MA: The glucagonoma syndrome: a review of its features and discussion of new perspectives. Am J Med Sci 2001;321:306–320.

14 Nikou GC, Toubanakis C, Nikolaou P, Giannatou E, Safioleas M, Mallas E, Polyzos A: VIPomas: an update in diagnosis and management in a series of 11 patients. Hepatogastroenterology 2005;52:1259–1265.

15 Solcia E, Klöppel G, Sobin LH: Histological Typing of Endocrine Tumors. Berlin, Springer, 2000.

16 Long RG, Bryant MG, Mitchell SJ, Adrian TE, Polak JM, Bloom SR: Clinicopathological study of pancreatic and ganglioneuroblastoma tumors secreting vasoactive intestinal polypeptide (vipomas). Br Med J (Clin Res Ed) 1981;282:1767–1771.

17 Smith SL, Branton SA, Avino AJ, Martin JK, Klingler PJ, Thompson GB, Grant CS, van Heerden JA: Vasoactive intestinal polypeptide secreting islet cell tumors: a 15-year experience and review of the literature. Surgery 1998;124:1050–1055.

18 Eriksson B, Oberg K: An update of the medical treatment of malignant endocrine pancreatic tumors. Acta Oncol 1993;32:203–208.

19 Skogseid B, Eriksson B, Lundqvist G, Lorelius LE, Rastad J, Wide L, Akerstrom G, Oberg K: Multiple endocrine neoplasia type 1: a 10-year prospective screening study in four kindreds. J Clin Endocrinol Metab 1991; 73:281–287.

20 Levy-Bohbot N, Merle C, Goudet P, Delemer B, Calender A, Jolly D, Thiefin G, Cadiot G: Prevalence, characteristics and prognosis of MEN 1-associated glucagonomas, VIPomas, and somatostatinomas: study from the GTE (Groupe des Tumeurs Endocrines) registry. Gastroenterol Clin Biol 2004;28:1075–1081.

21 Gibril F, Schumann M, Pace A, Jensen RT: Multiple endocrine neoplasia type 1 and Zollinger-Ellison syndrome: a prospective study of 107 cases and comparison with 1009 cases from the literature. Medicine (Baltimore) 2004;83:43–83.

22 Gabriel M, Hausler F, Bale R, Moncayo R, Decristoforo C, Kovacs P, Virgolini I: Image fusion analysis of (99m)Tc-HYNIC-Tyr(3)-octreotide SPECT and diagnostic CT using an immobilisation device with external markers in patients with endocrine tumors. Eur J Nucl Med Mol Imaging 2005;32:1440–1451.

23 Anderson MA, Carpenter S, Thompson NW, Nostrant TT, Elta GH, Scheiman JM: Endoscopic ultrasound is highly accurate and directs management in patients with neuroendocrine tumors of the pancreas. Am J Gastroenterol 2000;95:2271–2277.

24 Gines A, Vazquez-Sequeiros E, Soria MT, Clain JE, Wiersema MJ: Usefulness of EUS-guided fine needle aspiration (EUS-FNA) in the diagnosis of functioning neuroendocrine tumors. Gastrointest Endosc 2002;56: 291–296.

25 Lebtahi R, Cadiot G, Sarda L, Daou D, Faraggi M, Petegnief Y, Mignon M, le Guludec D: Clinical impact of somatostatin receptor scintigraphy in the management of patients with neuroendocrine gastroenteropancreatic tumors. J Nucl Med 1997;38:853–858.

26 Lebtahi R, Le Cloirec J, Houzard C, Daou D, Sobhani I, Sassolas G, Mignon M, Bourguet P, Le Guludec D: Detection of neuroendocrine tumors: 99mTc-P829 scintigraphy compared with ^{111}In-pentetreotide scintigraphy. J Nucl Med 2002;43:889–895.

27 Kwekkeboom D, Krenning EP, de Jong M: Peptide receptor imaging and therapy. J Nucl Med 2000;41:1704–1713.

28 Hofmann M, Maecke H, Borner R, Weckesser E, Schoffski P, Oei L, Schumacher J, Henze M, Heppeler A, Meyer J, Knapp H: Biokinetics and imaging with the somatostatin receptor PET radioligand (68)Ga-DOTA-TOC: preliminary data. Eur J Nucl Med 2001;28:1751–1757.

29 Kowalski J, Henze M, Schuhmacher J, Macke HR, Hofmann M, Haberkorn U: Evaluation of positron emission tomography imaging using [^{68}Ga]-DOTA-D Phe(1)-Tyr(3)-octreotide in comparison to [^{111}In]-DTPAOC SPECT. First results in patients with neuroendocrine tumors. Mol Imaging Biol 2003;5: 42–48.

30 Eriksson B, Orlefors H, Oberg K, Sundin A, Bergstrom M, Langstrom B: Developments in PET for the detection of endocrine tumors. Best Pract Res Clin Endocrinol Metab 2005;19:311–324.

31 Hoegerle S, Altehoefer C, Ghanem N, Koehler G, Waller CF, Scheruebl H, Moser E, Nitzsche E: Whole-body 18F dopa PET for detection of gastrointestinal carcinoid tumors. Radiology 2001;220:373–380.

32 Orlefors H, Sundin A, Garske U, Juhlin C, Oberg K, Skogseid B, Langstrom B, Bergstrom M, Eriksson B: Whole-body (11)C-5-hydroxytryptophan positron emission tomography as a universal imaging technique for neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and computed tomography. J Clin Endocrinol Metab 2005;90:3392–3400.

33 Guillausseau PJ, Guillausseau C, Villet R, Kaloustian E, Valleur P, Hautefeuille P, Lubetzki J: [Glucagonomas. Clinical, biological, anatomopathological and therapeutic aspects (general review of 130 cases). Gastroenterol Clin Biol 1982;6:1029–1041.

34 Capella C, Polak JM, Buffa R, Tapia FJ, Heitz P, Usellini L, Bloom SR, Solcia E: Morphologic patterns and diagnostic criteria of VIP-producing endocrine tumors: a histologic, histochemical, ultrastructural, and biochemical study of 32 cases. Cancer 1983;52: 1860–1874.

35 Solcia E, Klöppel G, Sobin LH: Histological typing of endocrine tumors; in Solcia E, Klöppel G, Sobin LH (eds): Histological Typing of Endocrine Tumors (International Classification of Tumors), ed 2. Berlin, Springer, 2000.
36 Akerstrom G: Management of carcinoid tumors of the stomach, duodenum, and pancreas. World J Surg 1996;20:173–182.
37 Ahlman H, Wangberg B, Jansson S, Friman S, Olausson M, Tylen U, Nilsson O: Interventional treatment of gastrointestinal neuroendocrine tumors. Digestion 2000;62(suppl 1):59–68.
38 Maton PN, Gardner JD, Jensen RT: Cushing's syndrome in patients with the Zollinger-Ellison syndrome. N Engl J Med 1986;315:1–5.
39 Yu F, Venzon DJ, Serrano J, Goebel SU, Doppman JL, Gibril F, Jensen RT: Prospective study of the clinical course, prognostic factors, causes of death, and survival in patients with long-standing Zollinger-Ellison syndrome. J Clin Oncol 1999;17:615–630.
40 Ahlman H, Friman S, Cahlin C, Nilsson O, Jansson S, Wangberg B, Olausson M: Liver transplantation for treatment of metastatic neuroendocrine tumors. Ann NY Acad Sci 2004;1014:265–269.
41 O'Toole D, Maire F, Ruszniewski P: Ablative therapies for liver metastases of digestive endocrine tumors. Endocr Relat Cancer 2003;10:463–468.
42 Ruszniewski P, Rougier P, Roche A, Legmann P, Sibert A, Hochlaf S, Ychou M, Mignon M: Hepatic arterial chemoembolization in patients with liver metastases of endocrine tumors: a prospective phase II study in 24 patients. Cancer 1993;71:2624–2630.
43 Clouse ME, Perry L, Stuart K, Stokes KR: Hepatic arterial chemoembolization for metastatic neuroendocrine tumors. Digestion 1994;55(suppl 3):92–97.
44 Ruszniewski P, Malka D: Hepatic arterial chemoembolization in the management of advanced digestive endocrine tumors. Digestion 2000;62(suppl 1):79–83.
45 Roche A, Girish BV, de Baere T, Baudin E, Boige V, Elias D, Lasser P, Schlumberger M, Ducreux M: Trans-catheter arterial chemoembolization as first-line treatment for hepatic metastases from endocrine tumors. Eur Radiol 2003;13:136–140.
46 Gupta S, Johnson MM, Murthy R, Ahrar K, Wallace MJ, Madoff DC, McRae SE, Hicks ME, Rao S, Vauthey JN, Ajani JA, Yao JC: Hepatic arterial embolization and chemoembolization for the treatment of patients with metastatic neuroendocrine tumors: variables affecting response rates and survival. Cancer 2005;104:1590–1602.
47 Wessels FJ, Schell SR: Radiofrequency ablation treatment of refractory carcinoid hepatic metastases. J Surg Res 2001;95:8–12.
48 Hellman P, Ladjevardi S, Skogseid B, Akerstrom G, Elvin A: Radiofrequency tissue ablation using cooled tip for liver metastases of endocrine tumors. World J Surg 2002;26:1052–1056.
49 Berber E, Flesher N, Siperstein AE: Laparoscopic radiofrequency ablation of neuroendocrine liver metastases. World J Surg 2002;26:985–990.
50 Cozzi PJ, Englund R, Morris DL: Cryotherapy treatment of patients with hepatic metastases from neuroendocrine tumors. Cancer 1995;76:501–509.
51 Shapiro RS, Shafir M, Sung M, Warner R, Glajchen N: Cryotherapy of metastatic carcinoid tumors. Abdom Imaging 1998;23:314–317.
52 Dick EA, Joarder R, de Jode M, Taylor-Robinson SD, Thomas HC, Foster GR, Gedroyc WM: MR-guided laser thermal ablation of primary and secondary liver tumors. Clin Radiol 2003;58:112–120.
53 Mensel B, Weigel C, Heidecke CD, Stier A, Hosten N: Laser-induced thermotherapy (LITT) of tumors of the liver in central location: results and complications. Rofo 2005;177:1267–1275.
54 Plockinger U, Rindi G, Arnold R, Eriksson B, Krenning EP, de Herder WW, Goede A, Caplin M, Oberg K, Reubi JC, Nilsson O, Delle Fave G, Ruszniewski P, Ahlman H, Wiedenmann B: Guidelines for the diagnosis and treatment of neuroendocrine gastrointestinal tumors: a consensus statement on behalf of the European Neuroendocrine Tumor Society (ENETS). Neuroendocrinology 2004;80:394–424.
55 Aparicio T, Ducreux M, Baudin E, Sabourin JC, De Baere T, Mitry E, Schlumberger M, Rougier P: Antitumor activity of somatostatin analogues in progressive metastatic neuroendocrine tumors. Eur J Cancer 2001;37:1014–1019.
56 Faiss S, Pape UF, Bohmig M, Dorffel Y, Mansmann U, Golder W, Riecken EO, Wiedenmann B: Prospective, randomized, multicenter trial on the antiproliferative effect of lanreotide, interferon alfa, and their combination for therapy of metastatic neuroendocrine gastroenteropancreatic tumors: The International Lanreotide and Interferon Alfa Study Group. J Clin Oncol 2003;21:2689–2696.
57 Welin SV, Janson ET, Sundin A, Stridsberg M, Lavenius E, Granberg D, Skogseid B, Oberg KE, Eriksson BK: High-dose treatment with a long-acting somatostatin analogue in patients with advanced midgut carcinoid tumors. Eur J Endocrinol 2004;151:107–112.
58 Arnold R, Rinke A, Klose KJ, Muller HH, Wied M, Zamzow K, Schmidt C, Schade-Brittinger C, Barth P, Moll R, Koller M, Unterhalt M, Hiddemann W, Schmidt-Lauber M, Pavel M, Arnold CN: Octreotide versus octreotide plus interferon-alpha in endocrine gastroenteropancreatic tumors: a randomized trial. Clin Gastroenterol Hepatol 2005;3:761–771.
59 Oberg K, Kvols L, Caplin M, Delle Fave G, de Herder W, Rindi G, Ruszniewski P, Woltering EA, Wiedenmann B: Consensus report on the use of somatostatin analogs for the management of neuroendocrine tumors of the gastroenteropancreatic system. Ann Oncol 2004;15:966–973.
60 Oberg K, Alm G, Lindstrom H, Lundqvist G: Successful treatment of therapy-resistant pancreatic cholera with human leucocyte interferon. Lancet 1985;i:725–727.
61 Kouvaraki MA, Ajani JA, Hoff P, Wolff R, Evans DB, Lozano R, Yao JC: Fluorouracil, doxorubicin, and streptozocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. J Clin Oncol 2004;22:4762–4771.
62 Delaunoit T, Ducreux M, Boige V, Dromain C, Sabourin JC, Duvillard P, Schlumberger M, de Baere T, Rougier P, Ruffie P, Elias D, Lasser P, Baudin E: The doxorubicin-streptozotocin combination for the treatment of advanced well-differentiated pancreatic endocrine carcinoma; a judicious option? Eur J Cancer 2004;40:515–520.
63 Moertel CG, Lefkopoulo M, Lipsitz S, Hahn RG, Klaassen D: Streptozocin-doxorubicin, streptozocin-fluorouracil or chlorozotocin in the treatment of advanced islet-cell carcinoma. N Engl J Med 1992;326:519–523.
64 Waldherr C, Pless M, Maecke HR, Schumacher T, Crazzolara A, Nitzsche EU, Haldemann A, Mueller-Brand J: Tumor response and clinical benefit in neuroendocrine tumors after 7.4 GBq (90)Y-DOTATOC. J Nucl Med 2002;43:610–616.
65 Kwekkeboom DJ, Teunissen JJ, Bakker WH, Kooij PP, de Herder WW, Feelders RA, van Eijck CH, Esser JP, Kam BL, Krenning EP: Radiolabeled somatostatin analog [^{177}Lu-DOTA0,Tyr3]octreotate in patients with endocrine gastroenteropancreatic tumors. J Clin Oncol 2005;23:2754–2762.