Somatostatin-producing neuroendocrine tumors of the duodenum and pancreas: incidence, types, biological behavior, association with inherited syndromes, and functional activity

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Abstract

Somatostatin-producing neuroendocrine tumors (SOM-NETs) of the duodenum and pancreas appear to be heterogeneous. To determine their clinicopathological profiles, respective data were analyzed on a series of 82 duodenal and 541 pancreatic NETs. In addition, the clinical records of 821 patients with duodenal or pancreatic NETs were reviewed for evidence of a somatostatinoma syndrome. Predominant or exclusive expression of somatostatin was found in 21 (26%) duodenal and 21 (4%) pancreatic NETs. They were classified as sporadic ($n=31$) or neurofibromatosis type 1 (NF1)-associated duodenal NETs ($n=3$), gangliocytic paragangliomas (GCPGs; $n=6$), or poorly differentiated neuroendocrine carcinomas (pdNECs; $n=2$). In addition, five duodenal and four pancreatic SOM-NETs were found in five patients with multiple endocrine neoplasia type 1 (MEN1). Metastases occurred in 13 (43%) patients with sporadic or NF1-associated SOM-NETs, but in none of the duodenal or pancreatic MEN1-associated SOM-NETs or GCPGs. Sporadic advanced (stage IV) SOM-NETs were more commonly detected in the pancreas than in the duodenum. None of the patients (including the 821 patients for whom only the clinical records were reviewed) fulfilled the criteria of a somatostatinoma syndrome. Our data show that somatostatin expression is not only seen in sporadic NETs but may also occur in GCPGs, pdNECs, and hereditary NETs. Surgical treatment is effective in most duodenal and many pancreatic SOM-NETs. MEN1-associated SOM-NETs and GCPGs follow a benign course, while somatostatin-producing pdNECs are aggressive neoplasms. The occurrence of the so-called somatostatinoma syndrome appears to be extremely uncommon.

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Introduction

Neuroendocrine tumors (NETs) of the stomach, intestine, and pancreas are heterogeneous, as far as their morphology, function, and biology are concerned. The WHO classification therefore distinguishes the gastroenteropancreatic NETs according to their location, histopathology, proliferative activity, extension, functional activity, and hereditary background (Klöppel *et al*. 2004). Recently, a tumor node metastases (TNM) disease staging system was proposed (Rindi *et al*. 2006) in order to facilitate the standardization of the diagnosis and therapy of NETs.

NETs producing mainly somatostatin (SOM-NETs) have been observed in the duodenum, pancreas, bile ducts, and ovaries (Larsson *et al*. 1977, Chamberlain & Blumgart 1999, Gregersen *et al*. 2002, Klöppel *et al*. 2004, Bastian *et al*. 2005). In the duodenum, SOM-NETs have been reported in the setting of both the multiple endocrine neoplasia type 1 (MEN1; Anlauf *et al*. 2007) and the neurofibromatosis type 1 (NF1) syndromes. Somatostatin expression was also found in gangliocytic paragangliomas (GCPGs; Hamid *et al*. 1986, Tischler *et al*. 2004). All of these tumors are uncommon. Our knowledge of their incidence, histopathology, biology, hereditary background, and functional activity is therefore based on reports of single or small series of patients and reviews (Hamid *et al*. 1986, Tomic & Warner 1996, Soga & Yakuwa 1999).

In this study, we analyzed a series of 623 resected duodenal and pancreatic NETs by identifying their immunophenotype and the relevant clinical symptoms at the time of diagnosis. In particular, the following questions were addressed: (1) what is the relative frequency of duodenal and pancreatic SOM-NETs and GCPGs, (2) do these tumors differ in their histopathology and biology from other NETs, (3) how many are associated with hereditary syndromes, and (4) do they cause a somatostatinoma syndrome? With regard to the last question, several clinical centers specializing in the diagnosis and the treatment of gastroenteropancreatic NETs were asked to retrospectively screen their series of patients with duodenal and pancreatic NETs for the occurrence of a somatostatinoma syndrome according to the WHO definition: (1) markedly elevated somatostatin levels in the plasma and/or tumor, (2) diabetes mellitus of recent onset, (3) hypochlorhydria, (4) gallbladder disease (cholelithiasis), (5) diarrhea and steatorrhea, and (6) anemia and weight loss (Dayal *et al*. 2004).

Materials and methods

Patients and tissues

Paraffin-embedded tissue blocks from duodenal ($n=82$) and pancreatic ($n=541$) resection specimens from 623 patients collected between 1975 and 2006 in the NET consultation archives of the departments of pathology of the universities of Kiel, Germany and Zurich, Switzerland were analyzed. Entrance diagnostic criteria were a neuroendocrine cytology and a homogeneous immunoreactivity for synaptophysin defining these tumors as neuroendocrine. In addition, five patients with MEN1 were included. Some of the patients were included in earlier studies investigating the histopathology and genetics of NETs (Pipeleers *et al*. 1983, Ohike *et al*. 2004, Sipos *et al*. 2004, Anlauf *et al*. 2005, 2006, Kapran *et al*. 2006).

From paraffin-embedded tissue blocks, 3–4 μm thin sections were cut and fixed in 4% formaldehyde (or individual cases in Bouin's solution). The sections were stained with hematoxylin and eosin and periodic acid-Schiff. Preparation of tissues and immunohistochemical expression analysis were performed as described previously in detail (Anlauf *et al*. 2006). Duodenal NETs were immunostained for chromogranin A (CGA, MAB, Ventana Medical systems, Tucson, AZ, USA, 1:2), synaptophysin (polyclonal antibody, DakoCytomation, Glostrup, Denmark, 1:50), somatostatin (polyclonal, DakoCytomation, 1:200), gastrin (polyclonal, Paesel, Frankfurt, Germany, 1:3000), and serotonin (monoclonal, DAKO, Hamburg, Germany, 1:20). Pancreatic NETs were immunostained for chromogranin A, synaptophysin, insulin (monoclonal, Biogenex, San Ramon, CA, USA, 1:40), glucagon (polyclonal, Biogenex, 1:60), somatostatin, and pancreatic polypeptide (PP, polyclonal, DakoCytomation, 1:5000). Additional immunohistochemical staining for gastrin (polyclonal, Paesel, 1:3000), vasoactive intestinal polypeptide (VIP, polyclonal, Zymed, San Francisco, CA, USA, 1:10), GH-releasing hormone (GRH, polyclonal, Biotrend, Cologne, Germany, 1:100), adrenocorticotropic hormone (ACTH, monoclonal, DakoCytomation, 1:500), calcitonin (polyclonal, DAKO, 1:500), and serotonin (monoclonal, DAKO, 1:20) was performed on tumors that were associated with specific syndromes, i.e., the Zollinger–Ellison syndrome, Verner–Morrison syndrome, acromegaly, or Cushing's syndrome or in special tumor entities such as the GCPGs. Immunostaining was carried out using the avidin–biotin peroxidase complex method, as described previously (Sipos *et al*. 2003). The slides were subjected to pressure cooker treatment for 3.5 min

prior to synaptophysin and VIP immunostaining. The number of somatostatin-immunoreactive cells within the NETs was scaled semiquantitatively: 5–10% (1+), >10–20% (2+), >20–40% (3+), >40–60% (4+), >60–80% (5+), >80–100% (6+).

Classification

Tumors were considered to be SOM-NETs if they were composed either exclusively (somatostatin being the only peptide hormone expressed in at least 5% of tumor cells) or predominantly (further peptide hormones only in a minor subset of tumor cells) of somatostatin-immunoreactive cells (Dayal *et al*. 2004). According to the WHO criteria (site, size, angioinvasion, infiltration level, proliferation index, immunohistochemical phenotype, and evidence of metastatic spread), NETs were classified as well-differentiated NETs (wdNETs), wdNETs of uncertain biological behavior (wdNE-Tubs), well-differentiated neuroendocrine carcinomas (wdNECs), or poorly differentiated neuroendocrine carcinomas (pdNECs; Klöppel *et al*. 2004). Proliferative activity was determined by counting Ki-67/MIB-1 positive cells, as described (Rindi *et al*. 2006). For TNM staging and tumor grading, the recently proposed systems were applied (Rindi *et al*. 2006).

Hereditary background

All patients were carefully screened for the occurrence of endocrine tumor disease outside of the duodenum and pancreas. Special attention was paid to an association with NF1, MEN1, and the Von-Hippel–Lindau (VHL) syndrome. The analysis was performed according to the published criteria for inherited endocrine tumor syndromes by the WHO (Calender *et al*. 2004, Evans *et al*. 2004, Maher *et al*. 2004, Marx & Simonds 2005).

Follow-up and clinical review of SOM-NETs

Surgical and/or cytostatic treatment and survival were recorded. Follow-up data for a period ranging from 0.1 to 17 years were available for 39 patients (83.0%).

Questionnaire regarding somatostatinoma syndrome

In order to obtain information on the occurrence of a somatostatinoma syndrome in a large series of patients, a questionnaire was sent to several clinical centers in Austria and Germany specializing in the diagnosis and treatment of NETs. The following questions were included: (1) how many patients with duodenal and pancreatic NETs were diagnosed and treated within a period of at least 10 years until the end of June 2006 and (2) how many patients presented with symptoms or signs of a somatostatinoma syndrome (i.e., at least three of the six WHO criteria) at the time of diagnosis and/or during follow-up? (Dayal *et al*. 2004).

Five centers were able to provide the appropriate data: (1) the Department of General, Visceral and Pediatric Surgery, University of Düsseldorf (5 duodenal NETs and 196 pancreatic NETs seen within a period of 32 years), (2) the Department of Gastroenterology and Endocrinology, University of Erlangen (4 duodenal NETs and 70 pancreatic NETs/15 years), (3) the Department of General and Visceral Surgery and the Department of Endocrinology, University of Mainz (4 duodenal NETs and 124 pancreatic NETs/10 years), (4) the Department of Gastroenterology and Endocrinology, University of Marburg (18 duodenal NETs and 202 pancreatic NETs/23 years), and (5) the Department of Hepatology and Gastroenterology, Charité, Berlin (28 duodenal NETs and 157 pancreatic NETs/20 years).

Ethics

The project was approved by the Ethics Committee of the University of Kiel (D430/2005) and by the German NET Register.

Results

Duodenum

Of 82 (26%) non-MEN1-associated duodenal NETs, 21 were classified as SOM-NETs (Fig. 1), including 12 sporadic SOM-NETs (57%), 3 NF1-associated SOM-NETs (14%), 5 GCPGs (24%), and 1 pdNEC (4.8%). In addition, five tiny SOM-NETs were detected in three patients with MEN1 (Table 1). The mean age of the

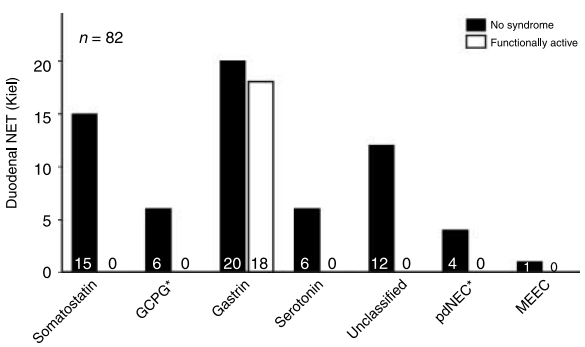

Figure 1 Immunophenotypes and endocrinological activity in duodenal non-MEN1-associated neuroendocrine tumors. Except for some gastrin-producing NETs, all other duodenal NETs were non-functioning. The asterisk indicates somatostatin expression in five of the six gangliocytic paragangliomas (GCPG) and in one of the poorly differentiated neuroendocrine carcinomas (pdNEC).

Table 1 Clinicopathological data on patients with duodenal somatostatin-producing neuroendocrine tumors

No.	Age /sex[a]	Initial symptoms[b]	Localization[c]	Surgery[d]	Size (mm)	SOM[e] IR	Ki-67 (%)[f]	Psammoma bodies	Invasion level[g]	Metastases[h]	WHO	TNM	Stage	Follow-up period (years)	Relapse	Other treatment[i]	Disease-free survival (years)
Sporadic SOM-NETs																	
1	33 M	GI bleeding	Pars desc	Duodenectomy	23	6+	3.0	Yes[j]	Muc, musc	No	wdNEC	T2N0M0	IIa	11.25	No	None	11.25
2	49 F	Jaundice	Ampulla	Whipple	Nk	6+	2.9	Yes[j]	Musc	No	wdNEC	T2N0M0	IIa	6.0	No	None	6.0
3	59 M	Jaundice	Ampulla	Papillectomy	20	4+	1.2	Yes[j]	Muc, musc	No	wdNEC	T2N0M0	IIa	5.7	No	None	5.7
4	67 M	Abd pain	Pars desc	Excision	16	6+	2.3	No	Muc	No	wdNETub	T2N0M0	IIa	0.8	No	None	0.8
5	81 F	Incidental	Ampulla	AUT	15	6+	1.7	Yes[j]	Musc	No	wdNEC	T2N0M0	IIa	AUT	AUT	No	AUT
6	41 M	Abd pain	Ampulla	Whipple	25	6+	6.6	No	Muc, musc	Ln	wdNEC	T2N1M0	IIIb	6.1	No	None	6.1
7	45 F	Incidental	Ampulla	Whipple	75	4+	3.8	Yes	Muc, panc	Ln	wdNEC	T3N1M0	IIIb	6.1	Yes	Surgery	2.2
8	51 M	Vomiting	Ampulla	Whipple	13	5+	10.6	No	Muc, musc	Ln	wdNEC	T2N1M0	IIIb	0.8	No	None	0.8
9	71 M	Abd pain	Ampulla	Whipple	15	6+	1.6	Yes[j]	Muc, musc	Ln	wdNEC	T2N1M0	IIIb	0.75	No	None	0.75
10	34 M	Abd pain	Ampulla	Whipple, liv res	20	6+	34	No	Muc, musc, panc	Ln, liv	wdNEC	T3N1M1	IV	0.75	No	Chemo	0.75
11	50 F	Nk	Ampulla	Nk	16	6+	1.8	Yes[j]	Muc, musc	Nk	wdNEC	T2NxMx	≥IIa	Nk	Nk	Nk	Nk
12	93 F	GI bleeding Jaundice	Ampulla	Stent	Nk	6+	31.4	No	Muc, musc	Nk	wdNEC	T2NxMx	≥IIa	Nk	Nk	Nk	Nk
Neurofibromatosis type 1-associated SOM-NETs																	
13	35 F	Incidental	Pars desc	Duodenectomy	7	6+	3.9	Yes[j]	Muc	No	wdNET	T1N0M0	I	0.25	No	None	0.25
14	60 M	Abd pain	Ampulla	Whipple	15	6+	0.7	Yes[j]	Muc, musc, panc	No	wdNEC	T3N0M0	IIb	4.4	No	None	4.4
15	37 F	Jaundice	Ampulla	Whipple	55	6+	1.6	Yes[j]	Muc, musc, panc	Ln	wdNEC	T3N1M0	IIIb	5	No	None	5
Multiple endocrine neoplasia type 1-associated SOM-NETs																	
16	41M	ZES	Bulbus	Whipple	1, 0.5	6+	0.8	No	Subm	Ln[k]	wdNET	T1(m)N1M0	IIIb	8	No	None	8
17	50 M	ZES	Pars desc	Duodenectomy	4, 1.5	6+	0.5	No	Subm	Ln[k]	wdNET	T1(m)N1M0	IIIb	11	No	None	11
18	54 M	ZES	Bulbus	Whipple	0.4	6+	0.7	No	Subm	Ln[k]	wdNET	T1(m)N1M0	IIIb	17	No	None	17
Gangliocytic paragangliomas																	
19	43 F	Abd pain	Ampulla	Polypectomy	10	2+	1.6	Yes	Subm	No	wdNET	T1N0M0	I	5	No	None	5
20	50 M	GI bleeding	Pars horiz	Polypectomy	25	4+	2.2	No	Musc	No	wdNEC	T2N0M0	IIa	0.33	No	None	0.33
21	70 F	Abd pain, jaundice	Pars desc	Papillectomy	13	6+	1.3	Yes	Muc, musc	No	wdNEC	T2N0M0	IIa	2.9	No	None	2.9
22	62 F	GI bleeding	Pars desc	Nk	17	4+	0.61	No	Muc	No	wdNETub	Nk	Nk	Nk	Nk	Nk	Nk

Table 1 *continued*

No.	Age /sex[a]	Initial symptoms[b]	Localization[c]	Surgery[d]	Size (mm)	SOM[e] IR	Ki-67 (%)[f]	Psammoma bodies	Invasion level[g]	Metastases[h]	WHO	TNM	Stage	Follow-up period (years)	Relapse	Other treatment[i]	Disease-free survival (years)
23	28 F	Nk	Ampulla	Nk	17	4+	1.5	No	Nk	Nk	Nk	Nk	Nk	Nk	Nk	Nk	Nk
Sporadic pdNEC																	
24	88 M	Nk	Ampulla	Whipple	12	6+	36.7	No	Musc	Ln, liv, bm	pdNEC	T2N1M1	IV	0.9	No	None	0.9

[a]Age (years); F, female; M, male.
[b]GI bleeding, gastrointestinal bleeding; Abd pain, abdominal pain; ZES, Zollinger–Ellison syndrome; Nk, not known.
[c]Pars desc, Pars descendens duodeni.
[d]Liv res, partial liver resection; AUT, autopsy.
[e]SOM IR, somatostatin immunoreactivity: 1+ > 5–10%, 2+ > 10–20%, 3+ > 20–40%, 4+ > 40–60%, 5+ > 60–80%, 6+ > 8–100%.
[f]Ki-67 immunoreactive cells counted in 20 hot spots.
[g]Muc, lamina mucosae; musc, lamina muscularis propria; panc, pancreas; Subm, submucosa.
[h]Ln, regional lymph nodes; liv, liver; bm, bone marrow.
[i]Chemo, chemotherapy.
[j]Pseudoglandular growth pattern in parts of the tumor.
[k]Gastrin-positive metastases.

patients was 54 years, the male to female ratio 1:0.8. Fifteen of the non-MEN1-associated tumors (71%) were located in the ampulla of Vater (Table 1). There was no significant difference in tumor volume between sporadic SOM-NETs (median 18 mm; ranges 13–75 mm) and NF1-associated SOM-NETs (median 15 mm; ranges 7–55 mm) and GCPGs (median 17 mm; ranges 10–25 mm). All tumors were solitary. By contrast, MEN1-associated SOM-NETs were multiple, very small, and incidental findings in patients suffering from ZES (median 1 mm; ranges 0.4–4 mm; Table 1). In one of the NF1 patients, a SOM-NET was an incidental finding next to a gastrointestinal stromal tumor (GIST).

The majority (60%) of the sporadic and NF1-associated duodenal SOM-NETs showed a trabecular pattern with a pseudoglandular component; one had a solid pattern with oncocytic differentiation. Psammoma bodies were present in 58% of the sporadic SOM-NETs, in all NF1-associated SOM-NETs, and in two out of five GCPGs (Table 1 and Fig. 2). The GCPGs revealed the typical triphasic differentiation, consisting of epithelioid endocrine cells, spindle-shaped Schwann-like cells, and ganglion cells (Fig. 3). The SOM-NETs in the MEN1 patients were associated with somatostatin cell hyperplasia of the non-tumorous mucosa, while all other types of SOM-NETs lacked such lesions.

All tumors expressed chromogranin A and synaptophysin. In addition to somatostatin, a minor cell population expressing gastrin was found in two sporadic SOM-NETs; single serotonin positive cells were detected in four sporadic SOM-NETs. Two GCPGs stained in addition to somatostatin for PP, VIP, and gastrin, two for PP, and one for VIP.

Figure 2 Duodenal somatostatin-producing neuroendocrine tumor with glandular growth pattern and numerous psammoma bodies.

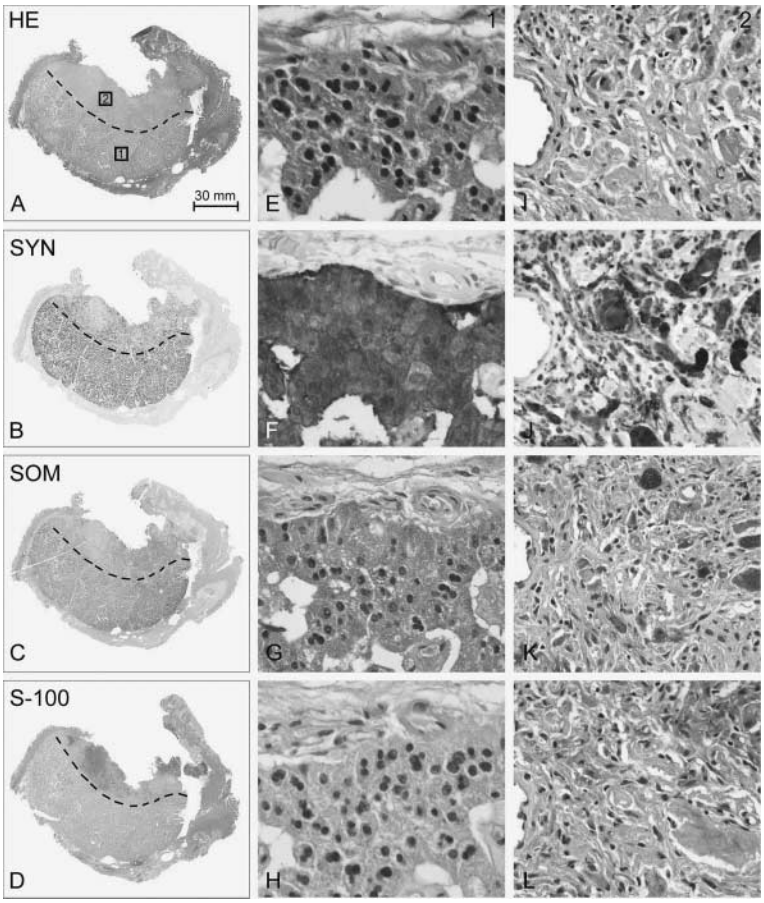

Figure 3 Duodenal gangliocytic paraganglioma with somatostatin expression. Serial-scanned sections of a GCPG (A–D). Microscopy of area 1 showing a large neuroendocrine component (E–H) positive for synaptophysin (SYN, F) and somatostatin (SOM, G) but not for S-100 protein (S-100, H). The area 2 reveals neuronal differentiation (I–L) with scattered ganglion cells expressing synaptophysin (J) and somatostatin (K), while dense aggregates of Schwann cells stain for synaptophysin (J) and S100 protein (L).

In stage IIa–IV, 13 out of the 15 sporadic and NF1-associated SOM-NETs were wdNECs. Five of these patients had lymph node metastases and one had lymph node and liver metastases (stage $\geq$IIIb). The MEN1 tumors were associated with gastrin but not somatostatin-positive lymph node metastases and were therefore related to the synchronous duodenal gastrinomas (Table 1). Two out of four somatostatin-expressing GCPGs, for which such information was available, infiltrated the smooth muscle layer but did not metastasize (Table 1). The patient with a pdNEC had lymph node, liver, and bone marrow metastases (Table 1).

None of the 24 patients met the criteria for a somatostatinoma syndrome, either at diagnosis or during follow-up (Table 1). The initial symptoms in the patients with sporadic and NF1-associated SOM-NETs and GCPGs were jaundice (28%), abdominal pain (39%), gastrointestinal bleeding 22%), and vomiting (6%; Table 1). In addition, six patients (33%) were found to have cholelithiasis and five (28%) anemia. In three patients (18%), the tumors were found during a checkup or at autopsy. All MEN1-associated SOM-NETs were incidental findings in surgical specimens from patients undergoing surgery for ZES.

All patients with sporadic or NF1-associated SOM-NETs and disease stage $\leq$IIa/b are alive and well (medium follow-up time 4.7 years). One of the five patients with regional lymph node metastases (stage IIIb) had a tumor recurrence after surgery (Whipple resection; medium follow-up time 3.7 years). Another patient had lymph node and liver metastases at the time of diagnosis (stage IV) and was treated by Whipple resection, partial liver resection, and chemotherapy. All patients with GCPGs are alive and well after local surgical or endoscopical excision (follow-up time:

4 months to 5 years; Table 1). The patient with a SOM-pdNEC exhibited lymph node, liver, and bone marrow metastases at the time of diagnosis and died of pneumonia 11 months after surgery (Table 1).

Pancreas

Figure 4 shows the immunophenotypes and hormonal syndromes of the 541 analyzed non-MEN1-associated pancreatic NETs. A total of 21 (4%) tumors expressed somatostatin predominantly or exclusively, including 19 sporadic NETs, 1 GCPG, and 1 poorly differentiated NEC. All the tumors were solitary (Table 2). Two additional MEN1-associated pancreatic endocrine tumors produced somatostatin, one associated with a macrotumor (>5 mm) and two microadenomas; the other was solitary. The mean age of all patients was 53 years (ranges: 17–79 years), the male to female ratio was 1:1.3. Most SOM-NETs were located in the head of the pancreas (Table 2). Their median size was 42.5 mm.

Most pancreatic SOM-NETs revealed a trabecular growth pattern. In a minor subset of cases (22%), a pseudoglandular component was present as well (Table 2). Three sporadic SOM-NETs additionally had a paraganglioma-like appearance (Fig. 5). Psammoma bodies were seen in 37% of the sporadic SOM-NETs, in one of the four MEN1-associated SOM-NETs, and in the GCPG, but not in the pdNEC (Table 2).

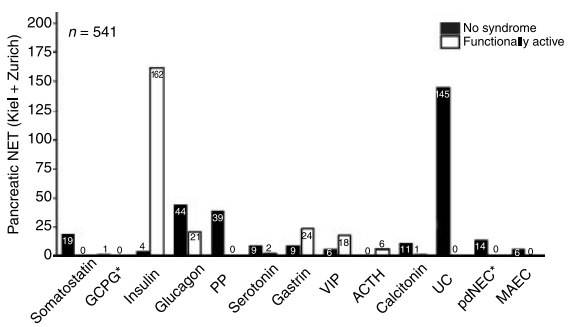

Figure 4 Immunophenotypes and endocrinological activity in pancreatic non-MEN1-associated neuroendocrine tumors. Predominant somatostatin expression in a subset of non-functioning pancreatic endocrine tumors, in one gangliocytic paraganglioma (GCGP; asterisk) and one poorly differentiated neuroendocrine tumor (pdNEC; asterisk). None of these tumors met the criteria of a somatostatinoma syndrome. Furthermore, peptide hormones being predominantly expressed by pancreatic NET were: insulin, glucagon, pancreatic polypeptide (PP), serotonin, gastrin, vasoactive intestinal polypeptide (PP), ACTH, calcitonin, and NET with no evidence for hormone expression (unclassified tumors; UC).

Chromogranin A was expressed in 16 out of 19 (84%) sporadic pancreatic SOM-NETs. Three tumors were completely negative. Synaptophysin was expressed homogeneously in all tumors. In eight tumors, somatostatin was the only hormone detected; scattered cells stained for insulin in one tumor, for PP in five, and for glucagon in eight tumors. The GCPG was completely negative for PP, but scattered tumor cells stained for VIP.

Of 17 (41%) sporadic SOM-NETs, 7 were wdNECs due to the presence of metastases, 9 (53%) were classified as tumors of uncertain behavior (wdNETubs) because of their size and/or high proliferative activity. One patient had a wdNET (stage I; Table 2). Two of the patients revealed lymph node metastases only (stage IIIb). Five patients showed additional distant metastases (stage IV; Table 2).

None of the 17 patients with sporadic SOM-NETs for whom appropriate data were available met the criteria for a somatostatinoma syndrome according to their clinical records. They suffered from non-specific symptoms at the time of diagnosis, most commonly abdominal pain (53%). In six additional patients (35%), the tumors were found incidentally during the course of a general checkup or at autopsy. One patient had a palpable abdominal tumor. Three patients showed cholelithiasis, one patient presented with weight loss, another gallstones and diarrhea. All but one of the patients with sporadic SOM-NETs (stage I-IIIb) are alive and well (mean follow-up time 5.7 years; Table 2). All five patients with sporadic SOM-NETs and distant metastasis (disease stage IV) showed progressive disease. Two patients died of disease 3 and 24 months after diagnosis respectively. The patient with the GCPG was treated by enucleation of the tumor and is alive and well after 4 months. In the patient with the pdNEC, the disease progressed despite surgery, and he was treated with chemotherapy. He died of multiple liver metastases 1 year after diagnosis.

None of the 59 patients with duodenal NETs and 749 patients with pancreatic NETs collected from the above-mentioned five centers presented evidence of a somatostatinoma syndrome.

Discussion

In our present series of 82 duodenal and 541 pancreatic NETs (excluding MEN1-associated NETs), 26 and 4% respectively were identified as SOM-NETs. Most SOM-NETs were solitary, sporadic, and showed criteria of malignancy. None was found to be associated with a so-called somatostatinoma syndrome, but a small proportion occurred in patients

Table 2 Clinicopathological data on patients with pancreatic somatostatin-producing neuroendocrine tumors

No.	Age/ sex[a]	Initial symptoms[b]	Localization	Surgery[c]	Size (mm)	SOM[d] IR	Ki-67 (%)[e]	Psammoma bodies	Metastases[f]	WHO	TNM	Stage	Follow-up period (years)	Relapse[g]	Other treatment[h]	Disease-free survival (years)
Sporadic SOM-NETs																
1	53 F	Incidental	Body	LSPR	14	6+	1.1	No	No	wdNET	T1N0M0	I	0.8	No	None	0.8
2	55 M	Incidental	Nk	Whipple	15	3+	3.1	No	No	wdNETub	T1N0M0	I	12	No	None	12
3	35 F	Abd pain	Head	Whipple	21	4+	0.8	No	No	wdNETub	T2N0M0	IIa	7	No	None	7
4	67 F	Abd pain	Head	Whipple	20	6+	3.5	Yes[i]	No	wdNETub	T2N0M0	IIa	5	No	None	5
5	45 F	Incidental	Tail	LSPR	80	3+	4.3	No	No	wdNETub	T3N0M0	IIb	0.5	No	None	0.5
6	48 F	Abd pain	Head	Whipple	50	5+	1	No	No	wdNETub	T3N0M0	IIb	16	No	None	16
7	65 F	Abd pain	Head	Whipple	45	4+	3.5	Yes	No	wdNETub	T3N0M0	IIb	4	No	None	4
8	61 M	Incidental	Tail	LSPR	50	2+	3.9	Yes[i]	No	wdNETub	T3N0M0	IIb	5	No	None	5
9	46 F	Palp tumor	Head	EN	60	4+	16.3	Yes[i]	No	wdNETub	T3N0M0	IIb	1	No	None	1
10	50 M	Abd pain	Body	LSPR	55	3+	5.8	No	No	wdNETub	T3N0M0	IIb	11	Liv, bm	Surg, rad., chemo	4.5
11	49 F	Abd pain	Tail	LSPR	25	4+	2.8	Yes	Ln	wdNEC	T3N1M0	IIIb	0.1	No	None	0.1
12	41 M	Abd pain	Tail	LSPR	140	6+	9.1	Yes[i]	Ln, liv	wdNEC	T3N1M1	IV	3.8	Liv, bm	Liv res	1.25
13	50 F	Ascites	Tail	LSPR	40	4+	7.1	No	Ln, liv, lung, thyroid	wdNEC	T3N1M1	IV	2	Yes	Chemo	0
14	57 F	Incidental	Head	Whipple, LA	50	1+	5.2	No	Ln, liv	wdNEC	T2N1M1	IV	1.7	Liv	Embolization	0
15	64 F	Abd pain	Tail	LSPR	22	3+	Nu	No	Ln, liv	wdNEC	T3N1M1	IV	0.25	Yes	None	0
16	79 M	Abd pain	Whole pancreas	Embolization	150	3+	10.3	Yes[i]	Ln, liv	wdNEC	T4N1M1	IV	2.4	Liv	Embolization	0
17	17 F	Nk	Nk	Nk	Nk	3+	Nu	No	Nk	Nk	Nk	Nk	Nk	Nk	Nk	Nk
18	38 F	Nk	Nk	Nk	15	1+	2.3	No	Nk	Nk	Nk	Nk	Nk	Nk	Nk	Nk
19	61 M	Incidental	Nk	Whipple	35	6+	1.6	No	Ln	wdNEC	Nk	Nk	Nk	Nk	Nk	Nk
Multiple endocrine neoplasia type 1-associated SOM-NETs																
20	38 M	Abd pain	Tail	LSPR	8.3, 0.7	4+	0.8	Yes	No	wdNET	T1(m) N0M0	I	4	No	None	4
21	64 M	Abd pain	Head	Whipple	50	4+	5.2	No	Ln	wdNEC	T3(m) N1M0	IIIb	3	No	None	3
Gangliocytic paraganglioma																
22	78 M	Incidental	Body	EN	21	1+	1.1	Yes	No	wdNETub	T2N0M0	IIa	0.3	No	None	0.3
Sporadic pdNEC																
23	48 M	Ascites, abd pain	Head	Hemihep, LA	>50	4+	50.3	No	Ln, liv	pdNEC	T3N1M1	IV	1	Liv	Chemo	0

[a]Age (years); F, female; M, male.
[b]Abd pain, abdominal pain; Nk, not known.
[c]LSPR, left-sided pancreas resection; Whipple, Whipple OP; EN, enucleation; LA, lymphadenectomy; Embolization, tumor embolization; Hemihep, hemihepatectomy.
[d]Som IR, somatostatin immunoreactivity: 1+ > 5–10%, 2+ > 10–20%, 3+ > 20–40%, 4+ > 4–60%, 5+ > 60–80%, 6+ > 8–100%.
[e]Ki-67 immunoreactive cells counted in ten hot spots; Nu, Not usable.
[f]Ln, regional lymph nodes; liv, liver.
[g]Liv, liver metastases; bm, bone marrow metastases.
[h]Surg, surgery; rad, radiation; Chemo, chemotherapy.
[i]Pseudoglandular growth pattern in parts of the tumor.

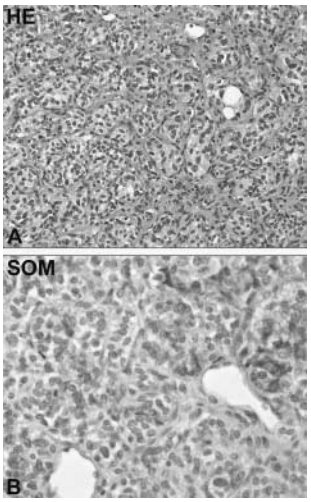

Figure 5 Paraganglioma-like growth pattern of a somatostatin-expressing pancreatic neuroendocrine carcinoma.

with MEN1 or NF1. Both the sporadic SOM-NETs of the duodenum and those of the pancreas did not appear to differ in their clinical behavior from other non-functioning NETs in the duodenum and pancreas.

The relative frequency of duodenal SOM-NETs was six times higher than that of pancreatic SOM-NETs, but the patients with duodenal and pancreatic SOM-NETs did not differ in age or sex distribution. These data are in accordance with those described earlier for duodenal (Dayal *et al*. 1983, Burke *et al*. 1989, Capella *et al*. 1991) and pancreatic SOM-NETs (Soga & Yakuwa 1999). Sporadic and NF1-associated duodenal SOM-NETs frequently show a pseudoglandular pattern including psammoma bodies and are commonly localized at the ampulla of Vater (Burke *et al*. 1989). Our data confirm these observations. ~60% of the sporadic and all NF1-associated duodenal SOM-NETs displayed glandular structures and psammoma bodies. In the pancreas, SOM-NETs did not show any particular localization nor did they consistently exhibit a glandular pattern or psammoma bodies. If, however, these features or a peculiar paraganglioma-like pattern were present, they were considered suggestive of a SOM-NET, since such findings have so far been absent from other pancreatic NETs. Three of the pancreatic SOM-NETs did not express chromogranin A, one of the most frequently used markers of neuroendocrine differentiation. The reason for the chromogranin A negativity in these tumors is not known. Interestingly, a similar lack of chromogranin A positivity is also seen in rectal NETs (Fahrenkamp *et al*. 1995).

The expression of somatostatin as predominant hormone in peculiar tumors of the duodenum and pancreas, i.e., GCPGs and pdNECs, is interesting, but remains unexplained so far. In addition to somatostatin most GCPGs also contained VIP and PP (Perrone *et al*. 1985, Burke & Helwig 1989). As we found a similar immunohistochemical pattern in the one GCPG that we observed in the pancreas, it seems that the expression of somatostatin, VIP, and PP characterizes most GCPGs.

Using the WHO classification, we found that more than half (59%) of the sporadic and NF1-associated SOM-NETs in the pancreas and the duodenum revealed criteria of malignancy. Benign tumors or tumors of uncertain biological behavior occurred more often in the pancreas than in the duodenum. Though most sporadic and NF1-associated duodenal SOM-NETs (87%) showed infiltration of the smooth muscle layers, not all of them were associated with metastases. The seven malignant sporadic pancreatic SOM-NETs showed metastases, either only lymph node metastases (2/7) or lymph node and distant metastases (5/7). When the sporadic and NF1-associated duodenal SOM-NETs were staged according to the proposed TNM classification (Rindi *et al*. 2006), stages IIa and IIIb were most frequent. In patients with pancreatic SOM-NETs stage IIb predominated, followed by stage IV. However, despite the fact that many patients with duodenal or pancreatic SOM-NETs had advanced disease (stages IIIb and IV), follow-up revealed that many of them survived without disease progression. Even the patient who suffered from relapsing distant metastases of a duodenal SOM-NET, which were removed surgically, has survived for more than 6 years so far. These data suggest that complete surgical removal of sporadic and NF1-associated duodenal and pancreatic SOM-NETs is effective and ensures prolonged survival in many patients. Our results for the pancreatic SOM-NETs are in accordance with those recently reported for malignant pancreatic non-functioning NETs (Fendrich *et al*. 2006). In this study, a 10-year survival rate of 72% after aggressive surgical treatment was observed.

The two patients with poorly differentiated SOM-NETs had distant metastases at the time of diagnosis (stage IV disease). They did not survive for more than 1 year, despite the extensive surgery and chemotherapy. This observation confirms previously published results (Pipeleers *et al*. 1983, Zamboni *et al*. 1990, Berkel *et al*. 2004, Capella *et al*. 2004, Ohike *et al*. 2004, Nassar *et al*. 2005).

SOM-NETs may be associated with hereditary syndromes, e.g., NF1, MEN1, and VHL. In NF1, the SOM-NETs typically occur in the duodenum (Mao *et al*. 1995, Soga & Yakuwa 1999, Capella *et al*. 2000,

Hamilton & Aaltonen 2000, Castoldi *et al*. 2001, Cappelli *et al*. 2004, Fendrich *et al*. 2004). In a review, the reported occurrence of duodenal and pancreatic SOM-NETs in NF1 was 43.2 and 20.8% respectively (Soga & Yakuwa 1999). We can confirm the occurrence of duodenal SOM-NETS in NF1 patients, but with a lower frequency, and were unable to confirm the high rate of NF1-associated pancreatic SOM-NETs reported by Soga & Yakuwa (1999). None of our pancreatic SOM-NETs was associated with NF1.

Pancreatic SOM-NETs have also been described in patients with MEN1 (Calender *et al*. 2004, Levy-Bohbot *et al*. 2004), but an association of duodenal SOM-NETs with MEN1 and ZES caused by multiple duodenal gastrinomas has only recently been observed (Anlauf *et al*. 2007). In contrast to the MEN1-associated duodenal gastrinomas, the MEN1-associated duodenal SOM-NETs have not so far been identified as a source of lymph node metastases.

Pancreatic and duodenal NETs have been described in VHL patients (Maki *et al*. 1995, Mount *et al*. 1995, Karasawa *et al*. 2001, Chetty *et al*. 2004). In the present series, none of the patients with a SOM-NET suffered from a *bona fide* VHL syndrome, nor did the tumors display the clear cell cytology usually observed in VHL-associated pancreatic NETs (Lubensky *et al*. 1998).

Larsson *et al*. (1977) described the first case of pancreatic SOM-NET presenting with hypochlorhydria, steatorrhea, and diabetic glucose tolerance. Later case reports and reviews described further patients with or without a somatostatinoma syndrome (Krejs *et al*. 1979, Anene *et al*. 1995, Sessa *et al*. 1998, Soga & Yakuwa 1999, Green & Rockey 2001). However, the existence of such a syndrome was challenged first by Stacpoole *et al*. (1983) in 1983. In an overview by Tanaka *et al*. (2000) and the report by House *et al*. (2002), none of the patients showed any symptoms of the somatostatinoma syndrome. In a series of five patients with SOM-NETs, Pipeleers *et al*. (1983) described three patients with an incomplete somatostatinoma syndrome. These authors considered the extreme variation to be due to marked differences in the circulating levels of biologically active somatostatin. In 2004, Lévy-Bohbot *et al*. (2004) described two functionally active pancreatic SOM-NETs in patients with MEN1. In the present series of 49 patients with SOM-NETs, we failed to identify any SOM-NET that met three or more of the criteria of the so-called somatostatinoma syndrome (Larsson *et al*. 1977, Krejs *et al*. 1979, Dayal *et al*. 2004). Even in an extended series of 821 patients (with either duodenal or pancreatic NETs) from five centers specializing in NETs, no patients with a *bona fide* somatostatinoma syndrome could be identified. The fact that we were unable to identify a somatostatinoma syndrome in the present series may be related to the retrospective nature of the study, i.e., incomplete recording of the symptoms of the patients. To clarify this issue, prospective studies are needed. However, given that our data may be confirmed, the failure to detect a somatostatinoma syndrome may be explained by the very short biological half-life of (monomeric) somatostatin (Brazeau *et al*. 1974, Tragl 1987, Pless 2005), making it almost unable to affect its target cells via the circulation. It can therefore be anticipated that only an exceptional tumor is able to produce and release somatostatin in sufficiently large amounts to cause a full-blown syndrome.

In summary, SOM-NETs were found to be a frequent tumor type in the duodenum, but rare in the pancreas. Somatostatin expression was not restricted to typical NETs, but also occurred in GCGPs and pdNECs. NF1-associated SOM-NETs only occurred in the duodenum, particularly in the ampullary region, while MEN1-associated SOM-NETs occurred in both the duodenum and the pancreas. According to the WHO criteria, most duodenal and pancreatic SOM-NETs were malignant, but surgical treatment resulted in long-term survival in many patients. A somatostatinoma syndrome was not observed; it appears to be uncommon.

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References

Anene C, Thompson JS, Saigh J, Badakhsh S & Ecklund RE 1995 Somatostatinoma: atypical presentation of a rare pancreatic tumor. *American Journal of Gastroenterology* **90** 819–821.

Anlauf M, Perren A, Meyer CL, Schmid S, Saremaslani P, Kruse ML, Weihe E, Komminoth P, Heitz PU & Klöppel G 2005 Precursor lesions in patients with multiple endocrine neoplasia type 1-associated duodenal gastrinomas. *Gastroenterology* **128** 1187–1198.

Anlauf M, Schlenger R, Perren A, Bauersfeld J, Koch CA, Dralle H, Raffel A, Knoefel WT, Weihe E, Ruszniewski P *et al.* 2006 Microadenomatosis of the endocrine pancreas in patients with and without the multiple endocrine neoplasia type 1 syndrome. *American Journal of Surgical Pathology* **30** 560–574.

Anlauf M, Perren A, Henopp T, Rudolph T, Garbrecht N, Schmitt A, Raffel A, Gimm O, Weihe E, Knoefel WT *et al.* 2007 Allelic deletion of the MEN1 gene in duodenal gastrin and somatostatin cell neoplasms and their precursor lesions. *Gut* **56** 637–644.

Bastian PJ, Eidt S, Koslowsky TC, Wulke AP & Siedek M 2005 Duodenal somatostatinoma: clinical and immunohistochemical patterns – difficult differential diagnosis in regard to gangliocytic paraganglioma: report of a case. *European Journal of Medical Research* **10** 135–138.

Berkel S, Hummel F, Gaa J, Back W, Hofheinz R, Queisser W, Singer MV & Lohr M 2004 Poorly differentiated small cell carcinoma of the pancreas. A case report and review of the literature. *Pancreatology* **4** 521–526.

Brazeau P, Vale W, Burgus R & Guillemin R 1974 Isolation of somatostatin (a somatotropin release inhibiting factor) of ovine hypothalamic origin. *Canadian Journal of Biochemistry* **52** 1067–1072.

Burke AP & Helwig EB 1989 Gangliocytic paraganglioma. *American Journal of Clinical Pathology* **92** 1–9.

Burke AP, Federspiel BH, Sobin LH, Shekitka KM & Helwig EB 1989 Carcinoids of the duodenum. A histologic and immunohistochemical study of 65 tumors. *American Journal of Surgical Pathology* **13** 828–837.

Calender A, Morrison CD, Komminoth P, Scoazec JY, Sweet KM & Teh BT 2004 Multiple endocrine neoplasia type 1. In *Pathology and Genetics: Tumours of Endocrine Organs. WHO Classification of Tumors*, pp 218–227. Eds RA DeLellis, RV Lloyd, PU Heitz & C Eng. Lyon: IARC Press.

Capella C, Riva C, Rindi G, Sessa F, Usellini L, Chiaravalli A, Carnevali L & Solcia E 1991 Histopathology, hormone products, and clinicopathological profile of endocrine tumors of the upper small intestine: a study of 44 cases. *Endocrine Pathology* **2** 92–110.

Capella C, Solcia E, Sobin LH & Arnold A 2000 Endocrine tumours of the small intestine. In *Pathology and Genetics. Tumours of the Digestive System. WHO Classification of Tumours*, pp 77–82. Eds SR Hamilton & LA Aaltonen. Lyon: IARC Press.

Capella C, Öberg K, Papotti M, Volante M & Bordi C 2004 Mixed exocrine–endocrine carcinomas. In *Pathology and Genetics: Tumours of Endocrine Organs. WHO Classification of Tumors*, pp 205–206. Eds RA DeLellis, RV Lloyd, PU Heitz & C Eng. Lyon: IARC Press.

Cappelli C, Agosti B, Braga M, Cumetti D, Gandossi E, Rizzoni D & Agabiti RE 2004 Von Recklinghausen's neurofibromatosis associated with duodenal somatostatinoma. A case report and review of the literature. *Minerva Endocrinologica* **29** 19–24.

Castoldi L, De Rai P, Marini A, Ferrero S, De LV & Tiberio G 2001 Neurofibromatosis-1 and ampullary gangliocytic paraganglioma causing biliary and pancreatic obstruction. *International Journal of Gastrointestinal Cancer* **29** 93–98.

Chamberlain RS & Blumgart LH 1999 Carcinoid tumors of the extrahepatic bile duct. A rare cause of malignant biliary obstruction. *Cancer* **86** 1959–1965.

Chetty R, Kennedy M, Ezzat S & Asa SL 2004 Pancreatic endocrine pathology in von Hippel–Lindau disease: an expanding spectrum of lesions. *Endocrine Pathology* **15** 141–148.

Dayal Y, Doos WG, O'Brien MJ, Nunnemacher G, DeLellis RA & Wolfe HJ 1983 Psammomatous somatostatinomas of the duodenum. *American Journal of Surgical Pathology* **7** 653–665.

Dayal Y, Öberg K, Perren A & Komminoth P 2004 Somatostatinoma. In *Pathology and Genetics: Tumours of Endocrine Organs. WHO Classification of Tumors*, pp 189–190. Eds RA DeLellis, RV Lloyd, PU Heitz & C Eng. Lyon: IARC Press.

Evans DGR, Komminoth P, Scheithauer BW & Peltonen J 2004 Neurofibromatosis type 1. In *Pathology and Genetics: Tumours of Endocrine Organs. WHO Classification of Tumors*, pp 243–248. Eds RA DeLellis, RV Lloyd, PU Heitz & C Eng. Lyon: IARC Press.

Fahrenkamp AG, Wibbeke C, Winde G, Ofner D, Bocker W, Fischer-Colbrie R & Schmid KW 1995 Immunohistochemical distribution of chromogranins A and B and secretogranin II in neuroendocrine tumours of the gastrointestinal tract. *Virchows Archiv* **426** 361–367.

Fendrich V, Ramaswamy A, Slater EP & Bartsch DK 2004 Duodenal somatostatinoma associated with Von Recklinghausen's disease. *Journal of Hepato-Biliary-Pancreatic Surgery* **11** 417–421.

Fendrich V, Langer P, Celik I, Bartsch DK, Zielke A, Ramaswamy A & Rothmund M 2006 An aggressive surgical approach leads to long-term survival in patients with pancreatic endocrine tumors. *Annals of Surgery* **244** 845–851.

Green BT & Rockey DC 2001 Duodenal somatostatinoma presenting with complete somatostatinoma syndrome. *Journal of Clinical Gastroenterology* **33** 415–417.

Gregersen G, Holst JJ, Trankjaer A, Stadil F & Mogensen AM 2002 Case report: somatostatin producing teratoma, causing rapidly alternating extreme hyperglycemia and hypoglycemia, and ovarian somatostatinoma. *Metabolism* **51** 1180–1183.

Hamid QA, Bishop AE, Rode J, Dhillon AP, Rosenberg BF, Reed RJ, Sibley RK & Polak JM 1986 Duodenal gangliocytic paragangliomas: a study of 10 cases with immunocytochemical neuroendocrine markers. *Human Pathology* **17** 1151–1157.

Hamilton SR & Aaltonen LA 2000 *Pathology and Genetics of Tumours of the Digestive System. WHO Classification of Tumours*. Lyon: IARC Press.

House MG, Yeo CJ & Schulick RD 2002 Periampullary pancreatic somatostatinoma. *Annals of Surgical Oncology* **9** 869–874.

Kapran Y, Bauersfeld J, Anlauf M, Sipos B & Klöppel G 2006 Multihormonality and entrapment of islets in pancreatic endocrine tumors. *Virchows Archiv* **448** 394–398.

Karasawa Y, Sakaguchi M, Minami S, Kitano K, Kawa S, Aoki Y, Itoh N, Sakurai A, Miyazaki M, Watanabe T *et al.* 2001 Duodenal somatostatinoma and erythrocytosis in a patient with von Hippel–Lindau disease type 2A. *Internal Medicine* **40** 38–43.

Klöppel G, Perren A & Heitz PU 2004 The gastroenteropancreatic neuroendocrine cell system and its tumors. The WHO classification. *Annals of the New York Academy of Sciences* **1014** 13–27.

Krejs GJ, Orci L, Conlon JM, Ravazzola M, Davis GR, Raskin P, Collins SM, McCarthy DM, Baetens D, Rubenstein A *et al.* 1979 Somatostatinoma syndrome. Biochemical, morphologic and clinical features. *New England Journal of Medicine* **301** 285–292.

Larsson LI, Hirsch MA, Holst JJ, Ingemansson S, Kuhl C, Jensen SL, Lundquist G, Rehfeld JF & Schwartz TW 1977 Pancreatic somatostatinoma. Clinical features and physiological implications. *Lancet* **i** 666–668.

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

Lubensky IA, Pack S, Ault D, Vortmeyer AO, Libutti SK, Choyke PL, Walther MM, Linehan WM & Zhuang Z 1998 Multiple neuroendocrine tumors of the pancreas in von Hippel–Lindau disease patients: histopathological and molecular genetic analysis. *American Journal of Pathology* **153** 223–231.

Maher ER, Nathanson K, Komminoth P, Neumann HPH, Plate KH, Bohling T & Schneider K 2004 Von Hippel–Lindau syndrome (VHL). In *Pathology and Genetics: Tumours of Endocrine Organs. WHO Classification of Tumors*, pp 230–237. Eds RA DeLellis, RV Lloyd, PU Heitz & C Eng. Lyon: IARC Press.

Maki M, Kaneko Y, Ohta Y, Nakamura T, Machinami R & Kurokawa K 1995 Somatostatinoma of the pancreas associated with von Hippel–Lindau disease. *Internal Medicine* **34** 661–665.

Mao C, Shah A, Hanson DJ & Howard JM 1995 Von Recklinghausen's disease associated with duodenal somatostatinoma: contrast of duodenal versus pancreatic somatostatinomas. *Journal of Surgical Oncology* **59** 67–73.

Marx SJ & Simonds WF 2005 Hereditary hormone excess: genes, molecular pathways, and syndromes. *Endocrine Reviews* **26** 615–661.

Mount SL, Weaver DL, Taatjes DJ, McKinnon WC & Hebert JC 1995 Von Hippel–Lindau disease presenting as pancreatic neuroendocrine tumour. *Virchows Archiv* **426** 523–528.

Nassar H, Albores-Saavedra J & Klimstra DS 2005 High-grade neuroendocrine carcinoma of the ampulla of Vater. A clinicopathologic and immunohistochemical analysis of 14 cases. *American Journal of Surgical Pathology* **29** 588–594.

Ohike N, Kosmahl M & Klöppel G 2004 Mixed acinar-endocrine carcinoma of the pancreas. A clinicopathological study and comparison with acinar-cell carcinoma. *Virchows Archiv* **445** 231–235.

Perrone T, Sibley RK & Rosai J 1985 Duodenal gangliocytic paraganglioma. An immunohistochemical and ultrastructural study and a hypothesis concerning its origin. *American Journal of Surgical Pathology* **9** 31–41.

Pipeleers D, Couturier E, Gepts W, Reynders J & Somers G 1983 Five cases of somatostatinoma: clinical heterogeneity and diagnostic usefulness of basal and tolbutamide-induced hypersomatostatinemia. *Journal of Clinical Endocrinology and Metabolism* **56** 1236–1242.

Pless J 2005 The history of somatostatin analogs. *Journal of Endocrinological Investigation* **28** (suppl 11) 1–4.

Rindi G, Klöppel G, Ahlman H, Caplin M, Couvelard A, de Herder WW, Eriksson B, Falchetti A, Falconi M, Komminoth P *et al.* 2006 TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. *Virchows Archiv* **449** 395–401.

Sessa F, Arcidiaco M, Valenti L, Solcia M, Di Maggio E & Solcia E 1998 Metastatic psammomatous somatostatinoma of the pancreas causing severe ketoacedotic diabetes cured by surgery. *Endocrine Pathology* **8** 327–333.

Sipos B, Möser S, Kalthoff H, Török V, Löhr M & Klöppel G 2003 A comprehensive characterization of pancreatic ductal carcinoma cell lines: towards the establishment of an *in vitro* research platform. *Virchows Archiv* **442** 444–452.

Sipos B, Klapper W, Kruse ML, Kalthoff H, Kerjaschki D & Klöppel G 2004 Expression of lymphangiogenic factors and evidence of intratumoral lymphangiogenesis in pancreatic endocrine tumors. *American Journal of Pathology* **165** 1187–1197.

Soga J & Yakuwa Y 1999 Somatostatinoma/inhibitory syndrome: a statistical evaluation of 173 reported cases as compared to other pancreatic endocrinomas. *Journal of Experimental & Clinical Cancer Research* **18** 13–22.

Stacpoole PW, Kasselberg AG, Berelowitz M & Chey WY 1983 Somatostatinoma syndrome: does a clinical entity exist? *Acta Endocrinologica* **102** 80–87.

Tanaka S, Yamasaki S, Matsushita H, Ozawa Y, Kurosaki A, Takeuchi K, Hoshihara Y, Doi T, Watanabe G & Kawaminami K 2000 Duodenal somatostatinoma: a case report and review of 31 cases with special reference to the relationship between tumor size and metastasis. *Pathology International* **50** 146–152.

Tischler AS, Komminoth P, Kimura N, Young WF Jr, Chetty R, Albores-Saavedra J & Kleihues P 2004 Extra-adrenal paraganglioma: gangliocytic, cauda equina, orbital, nasopharyngeal. In *Pathology and Genetics: Tumours of Endocrine Organs. WHO Classification of Tumors*, pp 162–163. Eds RA DeLellis, RV Lloyd, PU Heitz & C Eng. Lyon: IARC Press.

Tomic S & Warner T 1996 Pancreatic somatostatin-secreting gangliocytic paraganglioma with lymph node metastases. *American Journal of Gastroenterology* **91** 607–608.

Tragl KH 1987 Somatostatin (Article in German). *Acta Medica Austriaca* **5** 80–84.

Zamboni G, Franzin G, Bonetti F, Scarpa A, Chilosi M, Colombari R, Menestrina F, Pea M, Iacono C & Serio G 1990 Small-cell neuroendocrine carcinoma of the ampullary region. A clinicopathologic, immunohistochemical, and ultrastructural study of three cases. *American Journal of Surgical Pathology* **14** 703–713.