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


Department of Pathology, University of Kiel, Michaelisstr. 11, 24105 Kiel, Germany
1Department of Pathology, University Hospital of Zürich, 8091 Zürich, Switzerland
2Department of General, Visceral and Pediatric Surgery, University of Düsseldorf, 40228 Düsseldorf, Germany
3Department of Gastroenterology and Endocrinology, University of Erlangen, 91054 Erlangen, Germany
4Department of Endocrinology, University of Mainz, 55131 Mainz, Germany
5Department of General and Abdominal Surgery, University of Mainz, 55131 Mainz, Germany
6Department of Gastroenterology and Endocrinology, University of Marburg, 35033 Marburg, Germany
7Department of Hepatology and Gastroenterology, Charité, Campus Virchow Klinikum, 13353 Berlin, Germany
8Department of Pathology, Triemli Spital, 8063 Zürich, Switzerland
9Institute of Pathology, Technical University, 8165 Munich, Germany

(Correspondence should be addressed to N Garbrecht; Email: ngarbrecht@path.uni-kiel.de)

N Garbrecht and M Anlauf contributed equally to this work

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.

Endocrine-Related Cancer (2008) 15 229–241
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), GRH-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 (wdNETubs), 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 Histopathology and Endocrinology, 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
Table 1 Clinicopathological data on patients with duodenal somatostatin-producing neuroendocrine tumors

<table>
<thead>
<tr>
<th>No.</th>
<th>Age/sex</th>
<th>Initial symptoms</th>
<th>Localization</th>
<th>Surgery</th>
<th>Size (mm)</th>
<th>SOM IR</th>
<th>Ki-67 (%)</th>
<th>Psammoma bodies</th>
<th>Invasion level</th>
<th>Metastases</th>
<th>WHO</th>
<th>TNM</th>
<th>Stage</th>
<th>Follow-up period (years)</th>
<th>Re-lapse</th>
<th>Other treatment</th>
<th>Disease-free survival (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>33 M</td>
<td>GI bleeding</td>
<td>Pars desc</td>
<td>Duodenectomy</td>
<td>23</td>
<td>6+</td>
<td>3.0</td>
<td>Yes</td>
<td>Muc, musc</td>
<td>No</td>
<td>wdNEC</td>
<td>T2N0M0</td>
<td>Ila</td>
<td>11.25</td>
<td>No</td>
<td>None</td>
<td>11.25</td>
</tr>
<tr>
<td>2</td>
<td>49 F</td>
<td>Jaundice</td>
<td>Ampulla</td>
<td>Whipple</td>
<td>Nk 6+</td>
<td>2.9</td>
<td>Yes</td>
<td>Musc</td>
<td>No</td>
<td>wdNEC</td>
<td>T2N0M0</td>
<td>Ila</td>
<td>6.0</td>
<td>No</td>
<td>None</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>59 M</td>
<td>Jaundice</td>
<td>Ampulla</td>
<td>Papillotomy</td>
<td>20</td>
<td>4+</td>
<td>1.2</td>
<td>Yes</td>
<td>Muc, musc</td>
<td>No</td>
<td>wdNEC</td>
<td>T2N0M0</td>
<td>Ila</td>
<td>5.7</td>
<td>No</td>
<td>None</td>
<td>5.7</td>
</tr>
<tr>
<td>4</td>
<td>67 M</td>
<td>Abd pain</td>
<td>Pars desc</td>
<td>Excision</td>
<td>16 6+</td>
<td>2.3</td>
<td>No</td>
<td>Muc</td>
<td>No</td>
<td>wdNETub</td>
<td>T2N0M0</td>
<td>Ila</td>
<td>0.8</td>
<td>No</td>
<td>None</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>81 F</td>
<td>Incidental</td>
<td>Ampulla</td>
<td>AUT</td>
<td>15 6+</td>
<td>1.7</td>
<td>Yes</td>
<td>Musc</td>
<td>No</td>
<td>wdNEC</td>
<td>T2N0M0</td>
<td>Ila</td>
<td>AUT</td>
<td>AUT</td>
<td>No</td>
<td>AUT</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>41 M</td>
<td>Abd pain</td>
<td>Ampulla</td>
<td>Whipple</td>
<td>25 6+</td>
<td>6.6</td>
<td>No</td>
<td>Muc, musc</td>
<td>Ln</td>
<td>wdNEC</td>
<td>T2N1M0</td>
<td>Illb</td>
<td>6.1</td>
<td>No</td>
<td>None</td>
<td>6.1</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>45 F</td>
<td>Incidental</td>
<td>Ampulla</td>
<td>Whipple</td>
<td>75 4+</td>
<td>3.8</td>
<td>Yes</td>
<td>Muc, panc</td>
<td>Ln</td>
<td>wdNEC</td>
<td>T3N1M0</td>
<td>Illb</td>
<td>6.1</td>
<td>Yes</td>
<td>Surgery</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>51 M</td>
<td>Vomiting</td>
<td>Ampulla</td>
<td>Whipple</td>
<td>13 5+</td>
<td>10.6</td>
<td>No</td>
<td>Muc, musc</td>
<td>Ln</td>
<td>wdNEC</td>
<td>T2N1M0</td>
<td>Illb</td>
<td>0.8</td>
<td>No</td>
<td>None</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>71 M</td>
<td>Abd pain</td>
<td>Ampulla</td>
<td>Whipple</td>
<td>15 6+</td>
<td>1.6</td>
<td>Yes</td>
<td>Muc, musc</td>
<td>Ln</td>
<td>wdNEC</td>
<td>T2N1M0</td>
<td>Illb</td>
<td>0.75</td>
<td>No</td>
<td>None</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>34 M</td>
<td>Abd pain</td>
<td>Ampulla</td>
<td>Whipple, liv res</td>
<td>20 6+</td>
<td>34</td>
<td>No</td>
<td>Muc, musc, panc</td>
<td>Ln, liv</td>
<td>wdNEC</td>
<td>T3N1M1</td>
<td>IV</td>
<td>0.75</td>
<td>No</td>
<td>Chemo</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>50 F</td>
<td>Nk</td>
<td>Ampulla</td>
<td>Nk</td>
<td>16 6+</td>
<td>1.8</td>
<td>Yes</td>
<td>Muc, musc</td>
<td>Nk</td>
<td>wdNEC</td>
<td>T2NxMx</td>
<td>≥ Ila</td>
<td>Nk</td>
<td>Nk</td>
<td>Nk</td>
<td>Nk</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>93 F</td>
<td>GI bleeding</td>
<td>Ampulla</td>
<td>Stent</td>
<td>Nk 6+</td>
<td>31.4</td>
<td>No</td>
<td>Muc, musc</td>
<td>Nk</td>
<td>wdNEC</td>
<td>T2NxMx</td>
<td>≥ Ila</td>
<td>Nk</td>
<td>Nk</td>
<td>Nk</td>
<td>Nk</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>35 F</td>
<td>Incidental</td>
<td>Pars desc</td>
<td>Duodenectomy</td>
<td>7 6+</td>
<td>3.9</td>
<td>Yes</td>
<td>Muc</td>
<td>No</td>
<td>wdNET</td>
<td>T1N0M0</td>
<td>I</td>
<td>0.25</td>
<td>No</td>
<td>None</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>60 M</td>
<td>Abd pain</td>
<td>Ampulla</td>
<td>Whipple</td>
<td>15 6+</td>
<td>0.7</td>
<td>Yes</td>
<td>Muc, musc</td>
<td>No</td>
<td>wdNEC</td>
<td>T3N0M0</td>
<td>Illb</td>
<td>4.4</td>
<td>No</td>
<td>None</td>
<td>4.4</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>37 F</td>
<td>Jaundice</td>
<td>Ampulla</td>
<td>Whipple</td>
<td>55 6+</td>
<td>1.6</td>
<td>Yes</td>
<td>Muc, musc, panc</td>
<td>Ln</td>
<td>wdNEC</td>
<td>T3N1M0</td>
<td>Illb</td>
<td>5</td>
<td>No</td>
<td>None</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>41 M</td>
<td>ZES</td>
<td>Bulbus</td>
<td>Whipple</td>
<td>1, 0.5 6+</td>
<td>0.8</td>
<td>No</td>
<td>Subm</td>
<td>Ln</td>
<td>wdNET</td>
<td>T1(m)N1M0</td>
<td>Illb</td>
<td>8</td>
<td>No</td>
<td>None</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>50 M</td>
<td>ZES</td>
<td>Pars desc</td>
<td>Duodenectomy</td>
<td>4, 1.5</td>
<td>6+</td>
<td>0.5</td>
<td>No</td>
<td>Subm</td>
<td>Ln</td>
<td>wdNET</td>
<td>T1(m)N1M0</td>
<td>Illb</td>
<td>11</td>
<td>No</td>
<td>None</td>
<td>11</td>
</tr>
<tr>
<td>18</td>
<td>54 M</td>
<td>ZES</td>
<td>Bulbus</td>
<td>Whipple</td>
<td>0.4 6+</td>
<td>0.7</td>
<td>No</td>
<td>Subm</td>
<td>Ln</td>
<td>wdNET</td>
<td>T1(m)N1M0</td>
<td>Illb</td>
<td>17</td>
<td>No</td>
<td>None</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>43 F</td>
<td>Abd pain</td>
<td>Ampulla</td>
<td>Polyectomy</td>
<td>10 2+</td>
<td>1.6</td>
<td>Yes</td>
<td>Subm</td>
<td>No</td>
<td>wdNET</td>
<td>T1N0M0</td>
<td>I</td>
<td>5</td>
<td>No</td>
<td>None</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>50 M</td>
<td>GI bleeding</td>
<td>Pars horiz</td>
<td>Polyectomy</td>
<td>25 4+</td>
<td>2.2</td>
<td>No</td>
<td>Musc</td>
<td>No</td>
<td>wdNEC</td>
<td>T2N0M0</td>
<td>Ila</td>
<td>0.33</td>
<td>No</td>
<td>None</td>
<td>0.33</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>70 F</td>
<td>Abd pain, jaundice</td>
<td>Pars desc</td>
<td>Papillotomy</td>
<td>13 6+</td>
<td>1.3</td>
<td>Yes</td>
<td>Muc, musc</td>
<td>No</td>
<td>wdNEC</td>
<td>T2N0M0</td>
<td>Ila</td>
<td>2.9</td>
<td>No</td>
<td>None</td>
<td>2.9</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>62 F</td>
<td>GI bleeding</td>
<td>Pars desc</td>
<td>Nk</td>
<td>17 4+</td>
<td>0.61</td>
<td>No</td>
<td>Muc</td>
<td>No</td>
<td>wdNETub</td>
<td>Nk</td>
<td>Nk</td>
<td>Nk</td>
<td>Nk</td>
<td>Nk</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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.
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: 4.7 years).
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).

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>
<thead>
<tr>
<th>No.</th>
<th>Age/sex&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Initial symptoms&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Localization</th>
<th>Surgery&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Size (mm)</th>
<th>SOM&lt;sup&gt;d&lt;/sup&gt; IR</th>
<th>Ki-67 (%)&lt;sup&gt;e&lt;/sup&gt;</th>
<th>Psammoma bodies</th>
<th>Metastases&lt;sup&gt;f&lt;/sup&gt;</th>
<th>WHO</th>
<th>TNM</th>
<th>Stage</th>
<th>Follow-up period (years)</th>
<th>Relapse&lt;sup&gt;g&lt;/sup&gt;</th>
<th>Other treatment&lt;sup&gt;h&lt;/sup&gt;</th>
<th>Disease-free survival (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>53 F</td>
<td>Incidental</td>
<td>Body</td>
<td>LSPR</td>
<td>14</td>
<td>6+</td>
<td>1.1</td>
<td>No</td>
<td>No</td>
<td>wdNET</td>
<td>T1N0M0</td>
<td>I</td>
<td>0.8</td>
<td>No</td>
<td>None</td>
<td>0.8</td>
</tr>
<tr>
<td>2</td>
<td>55 M</td>
<td>Incidental</td>
<td>Nk</td>
<td>Whipple</td>
<td>15</td>
<td>3+</td>
<td>3.1</td>
<td>No</td>
<td>No</td>
<td>wdNETub</td>
<td>T1N0M0</td>
<td>I</td>
<td>12</td>
<td>No</td>
<td>None</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>35 F</td>
<td>Abd pain</td>
<td>Head</td>
<td>Whipple</td>
<td>21</td>
<td>4+</td>
<td>0.8</td>
<td>No</td>
<td>No</td>
<td>wdNETub</td>
<td>T2N0M0</td>
<td>Ila</td>
<td>7</td>
<td>No</td>
<td>None</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>67 F</td>
<td>Abd pain</td>
<td>Head</td>
<td>Whipple</td>
<td>20</td>
<td>6+</td>
<td>3.5</td>
<td>Yes&lt;sup&gt;i&lt;/sup&gt;</td>
<td>No</td>
<td>wdNETub</td>
<td>T2N0M0</td>
<td>Ila</td>
<td>5</td>
<td>No</td>
<td>None</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>45 F</td>
<td>Incidental</td>
<td>Tail</td>
<td>LSPR</td>
<td>80</td>
<td>3+</td>
<td>4.3</td>
<td>No</td>
<td>No</td>
<td>wdNETub</td>
<td>T3N0M0</td>
<td>IIb</td>
<td>0.5</td>
<td>No</td>
<td>None</td>
<td>0.5</td>
</tr>
<tr>
<td>6</td>
<td>48 F</td>
<td>Abd pain</td>
<td>Head</td>
<td>Whipple</td>
<td>50</td>
<td>5+</td>
<td>1</td>
<td>No</td>
<td>No</td>
<td>wdNETub</td>
<td>T3N0M0</td>
<td>IIb</td>
<td>16</td>
<td>No</td>
<td>None</td>
<td>16</td>
</tr>
<tr>
<td>7</td>
<td>65 F</td>
<td>Abd pain</td>
<td>Head</td>
<td>Whipple</td>
<td>45</td>
<td>4+</td>
<td>3.5</td>
<td>Yes&lt;sup&gt;i&lt;/sup&gt;</td>
<td>No</td>
<td>wdNETub</td>
<td>T3N0M0</td>
<td>IIb</td>
<td>4</td>
<td>No</td>
<td>None</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>61 M</td>
<td>Incidental</td>
<td>Tail</td>
<td>LSPR</td>
<td>50</td>
<td>2+</td>
<td>3.9</td>
<td>Yes&lt;sup&gt;i&lt;/sup&gt;</td>
<td>No</td>
<td>wdNETub</td>
<td>T3N0M0</td>
<td>IIb</td>
<td>5</td>
<td>No</td>
<td>None</td>
<td>5</td>
</tr>
<tr>
<td>9</td>
<td>46 F</td>
<td>Palp tumor</td>
<td>Head</td>
<td>EN</td>
<td>60</td>
<td>4+</td>
<td>16.3</td>
<td>Yes&lt;sup&gt;i&lt;/sup&gt;</td>
<td>No</td>
<td>wdNETub</td>
<td>T3N0M0</td>
<td>IIb</td>
<td>1</td>
<td>No</td>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>50 M</td>
<td>Abdominal pain</td>
<td>Body</td>
<td>LSPR</td>
<td>55</td>
<td>3+</td>
<td>5.8</td>
<td>No</td>
<td>No</td>
<td>wdNETub</td>
<td>T3N0M0</td>
<td>IIb</td>
<td>11</td>
<td>Liv, bm</td>
<td>Surg, rad., chemo</td>
<td>4.5</td>
</tr>
<tr>
<td>11</td>
<td>49 F</td>
<td>Abdominal pain</td>
<td>Tail</td>
<td>LSPR</td>
<td>25</td>
<td>4+</td>
<td>2.8</td>
<td>Yes</td>
<td>Ln</td>
<td>wdNEC</td>
<td>T3N1M0</td>
<td>IIIb</td>
<td>0.1</td>
<td>No</td>
<td>None</td>
<td>0.1</td>
</tr>
<tr>
<td>12</td>
<td>41 M</td>
<td>Abdominal pain</td>
<td>Tail</td>
<td>LSPR</td>
<td>140</td>
<td>6+</td>
<td>9.1</td>
<td>Yes&lt;sup&gt;i&lt;/sup&gt;</td>
<td>Ln, liv</td>
<td>wdNEC</td>
<td>T3N1M1</td>
<td>IV</td>
<td>3.8</td>
<td>Liv, bm</td>
<td>Liv res</td>
<td>1.25</td>
</tr>
<tr>
<td>13</td>
<td>50 F</td>
<td>Abdominal pain</td>
<td>Tail</td>
<td>LSPR</td>
<td>40</td>
<td>4+</td>
<td>7.1</td>
<td>No</td>
<td>Ln, liv, tu,</td>
<td>wdNEC</td>
<td>T4N1M1</td>
<td>IV</td>
<td>2</td>
<td>Yes</td>
<td>Chemo</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>57 F</td>
<td>Ascites</td>
<td>Head</td>
<td>Whipple, LA</td>
<td>50</td>
<td>1+</td>
<td>5.2</td>
<td>No</td>
<td>Ln, liv</td>
<td>wdNEC</td>
<td>T2N1M1</td>
<td>IV</td>
<td>1.7</td>
<td>Liv</td>
<td>Embolization</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>64 F</td>
<td>Abdominal pain</td>
<td>Tail</td>
<td>LSPR</td>
<td>22</td>
<td>3+</td>
<td>Nu</td>
<td>No</td>
<td>Ln, liv</td>
<td>wdNEC</td>
<td>T3N1M1</td>
<td>IV</td>
<td>0.25</td>
<td>Yes</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>79 M</td>
<td>Abdominal pain</td>
<td>Whole pancreas</td>
<td>Embolization</td>
<td>150</td>
<td>3+</td>
<td>10.3</td>
<td>Yes&lt;sup&gt;i&lt;/sup&gt;</td>
<td>Ln, liv</td>
<td>wdNEC</td>
<td>T4N1M1</td>
<td>IV</td>
<td>2.4</td>
<td>Liv</td>
<td>Embolization</td>
<td>0</td>
</tr>
<tr>
<td>17</td>
<td>17 F</td>
<td>Nk</td>
<td>Nk</td>
<td>Nk</td>
<td>Nk</td>
<td>3+</td>
<td>Nu</td>
<td>No</td>
<td>Nk</td>
<td>Nk</td>
<td>Nk</td>
<td>Nk</td>
<td>Nk</td>
<td>Nk</td>
<td>Nk</td>
<td>Nk</td>
</tr>
<tr>
<td>18</td>
<td>38 F</td>
<td>Nk</td>
<td>Nk</td>
<td>Nk</td>
<td>Nk</td>
<td>1+</td>
<td>2.3</td>
<td>No</td>
<td>Nk</td>
<td>Nk</td>
<td>Nk</td>
<td>Nk</td>
<td>Nk</td>
<td>Nk</td>
<td>Nk</td>
<td>Nk</td>
</tr>
<tr>
<td>19</td>
<td>61 M</td>
<td>Incidental</td>
<td>Nk</td>
<td>Whipple</td>
<td>35</td>
<td>6+</td>
<td>1.6</td>
<td>No</td>
<td>Ln</td>
<td>wdNEC</td>
<td>Nk</td>
<td>Nk</td>
<td>Nk</td>
<td>Nk</td>
<td>Nk</td>
<td>Nk</td>
</tr>
<tr>
<td>20</td>
<td>38 M</td>
<td>Abdominal pain</td>
<td>Tail</td>
<td>LSPR</td>
<td>8.3, 0.7</td>
<td>4+</td>
<td>0.8</td>
<td>Yes</td>
<td>No</td>
<td>wdNET</td>
<td>T1(m)</td>
<td>NOM0</td>
<td>4</td>
<td>No</td>
<td>None</td>
<td>4</td>
</tr>
<tr>
<td>21</td>
<td>64 M</td>
<td>Abdominal pain</td>
<td>Head</td>
<td>Whipple</td>
<td>50</td>
<td>4+</td>
<td>5.2</td>
<td>No</td>
<td>Ln</td>
<td>wdNEC</td>
<td>T3(m)</td>
<td>N1M0</td>
<td>3</td>
<td>No</td>
<td>None</td>
<td>3</td>
</tr>
<tr>
<td>22</td>
<td>78 M</td>
<td>Incidental</td>
<td>Body</td>
<td>EN</td>
<td>21</td>
<td>1+</td>
<td>1.1</td>
<td>Yes</td>
<td>No</td>
<td>wdNETub</td>
<td>T2N0M0</td>
<td>Ila</td>
<td>0.3</td>
<td>No</td>
<td>None</td>
<td>0.3</td>
</tr>
<tr>
<td>23</td>
<td>48 M</td>
<td>Ascites, abdominal pain</td>
<td>Head</td>
<td>Hemihep, LA</td>
<td>&gt;50</td>
<td>4+</td>
<td>50.3</td>
<td>No</td>
<td>Ln, liv</td>
<td>pdNEC</td>
<td>T3N1M1</td>
<td>IV</td>
<td>1</td>
<td>Liv</td>
<td>Chemo</td>
<td>0</td>
</tr>
</tbody>
</table>

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

Acknowledgements

The authors are grateful to Maike Pacena, Anja Bredtmann, and Sonja Schmid for their excellent technical assistance. We are indebted to Waldemar Straus for the photo documentation and Katherine Dege for carefully reading the manuscript. We thank all colleagues who supported this study: Drs A Akovbiantz, Zürich; H P Bange, Gaarding; G Baretton, Dresden; M Barten, Rostock; D B von Bassewitz, Münster; D Berger, Baden-Baden; R Beverungen, Höxter-Lüchtringen; Bode, Weener-Ems; T Bozkurt, Koblenz; J Braun, Bremen; K Buchhardt, Bremen; P Buchmann, Zürich; A Burkhardt, Reutlingen; J Caselitz, Hamburg; T Czerny, St Gallen; J Erhard, Dinslaken; S Eidt, Köln; M Gregor, Tübingen; F Hagenmüller, Hamburg; B Van den Heule, Brüssel; K and T Jatzkewitz, Kiel; De Jonge, Wilrijk; K Junke, Bremen; F Fändrich, Kiel; G Fischer, Wilhelmshaven; P Flemming, Celle; R Gützkow, Eutin; D Henne-Bruns, Ulm; S Hollerbach, Celle; M Kindler, Aachen; E Klar, Rostock; B Kremer, Kiel; J Kühne, Oldenburg; T Lehner,
Bremen; S Liebe, Rostock; R Lindenfelser, Würselen-Bardenberg; W Löffler, Stadttoldendorf; J Löhr, Oldenburg; G Mangold, Lahr; L Mantovani Löffler, Delitzsch; E Van Marck, Antwerpen; M Marichal, Brussels; T Mattfeld, Ulm; R Motz, Linz; S Mühl dorfer, Bayreuth; L Müller, Leer; H K Müller-Hermelink, Würzburg; K-J Oldhafer, Celle; E Petzsche, Aachen; J Placke, Dinslaken; C von der Planitz, Bayreuth; H-D Säger, Dresden; A Schuchert, Neumünster; M Schumacher, Düsseldorf; W Schumn, Rendsburg; N T Schwarz, Neumünster; Dr W Schweizer, Schaffhausen; A Scobel, Leer; W Senst, Frankfurt/Oder; M Sevenich, Leer; M Siedek, Köln; G Somers, Brüssel; M Sonntag, Pöritz; M Stolte, Bayreuth; A Thiede, Würzburg; R Wagner, Kiel; H Wehner, Lahr; A Weimann, Leipzig; W Schumm, Rendsburg; J Witte, Augsburg; G Wrede, Weener/Ems; U Woziwodzki, Aurich.

Supported by the Hensel Stiftung, Kiel, Germany (F370011; M A and G K), the Swiss National Foundation (SNF 31-108257; A P and P K), the German Society of Pathology (M A) and Novartis Oncology, Nürnberg, Germany. Nele Garbrecht has a fellowship sponsored by the Hensel Stiftung, Germany. Some of the results of this study are part of her MD thesis. Tobias Henopp has a fellowship sponsored by Ipsen GmbH, Ettlingen, Germany. The authors declare that there is no conflict of interest that would prejudice the impartiality of this scientific work.

References


