Neuroendocrine tumors of the small bowels are on the rise: Early aspects and management

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Abstract

Neuroendocrine tumors of the small bowel are on the rise. In the US they have increased by 300%-500% in the last 35 years. At the same time their prognosis is much improved. Today, most neuroendocrine tumors (NETs) of the duodenum are detected “incidentally” and therefore recognized at an early stage. Duodenal NETs which are well differentiated, not larger than 10 mm and limited to the mucosa/submucosa can be endoscopically resected. The management of duodenal NETs ranging between 10 and 20 mm needs an interdisciplinary discussion. Endoscopic ultrasound is the method of choice to determine tumor size and depth of infiltration. Surgery is recommended for well-differentiated duodenal NET tumors greater than 20 mm, for localized sporadic gastrinomas (of any size) and for localized poorly differentiated NE cancers. Surgery is recommended for any ileal NET. Advanced ileal NETs with a carcinoid syndrome are treated with long-acting somatostatin analogs. This treatment significantly improves (progression-free) survival in patients with metastatic NETs of the ileum. For optimal NET management, tumor biology, type, localization and stage of the neoplasm, as well as the patient’s individual circumstances have to be taken into account.

INTRODUCTION

Gastrointestinal neuroendocrine tumors (NETs) are being diagnosed more and more frequently. The latest figures from the US's Surveillance Epidemiology and End Results (SEER) Register show that in the past 35 years, the number of neuroendocrine tumors/carcinomas of the small...
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intestine has increased 300%-500% (Figure 1). Similar trends have been observed in Sweden[9] and Norway[10]. The cause of this striking increase is unknown[9]; it is often attributed to the fact that high-resolution imaging and endoscopy are being used more commonly in everyday clinical practice and immunohistochemistry more often in pathology. Other risk factors for small intestinal carcinoids include alcohol and smoking in one study[11], but not in another[9], female gender[9] and a positive family history of cancer[9]. Small intestinal carcinoids also occur with increased frequency in a few inherited syndromes[9,10]. Specifically with the autosomal dominant disorder, Multiple Endocrine Neoplasia type 1 (MEN1), there is an increased occurrence of duodenal gastrinomas and with von Recklinghausen’s disease (VRD) (neurofibromatosis 1) (NF-1) an increased occurrence of duodenal somatostatinomas, characteristically in the periampullary region[9,11]. Furthermore, in a few studies, evidence has been provided that rarely a familial form of gastrointestinal carcinoid disease may exist, including those of the small intestine[9,10].

Fortunately today, NETs of the small intestine, particularly those located in the duodenum, are increasingly detected in early, easily treatable stages (with a tumor diameter of ≤ 10 mm)[7,9,12]. These small tumors are mostly non-functional (hormone inactive) and usually do not cause any discomfort. Duodenal NETs are often diagnosed during a gastroduodenoscopy that is being carried out for other reasons[7,9,12]. If duodenal NETs present with a hormonal hypersecretion syndrome (Zollinger-Ellison or carcinoid syndrome), the situation is different. These functionally presenting duodenal NETs have generally metastasized at the time of diagnosis[9,13,14]. Currently, about 22% of all NETs of the small bowel arise from the duodenum[9] while the ileum remains the most frequent site of NETs in the small intestine (> 70%).

On the whole, increased earlier detection of NETs of the small intestine has led to improved prognosis[15,16]. The five year survival rate of patients with NETs of the small intestine in the SEER Register has gone up from 51.9% in the 1970s and 1980s to 60.5% in the 1990s[17]. In a current analysis of the years 1999-2004, Strosberg et al[18] have observed a five year survival rate of 75%. The proportion of advanced disease (at the time the diagnosis) has fallen from 31.3% in the 1970s and 1980s to 22.4% in the 1990s and finally to < 18.9% between 2002-2004[17,19].

The management of advanced NETs of the small bowel has received much attention; however the clinical management of NETs of the small bowel detected early in their course has received little attention even though it is becoming clinically more important. Treatment is based on a reliable classification of the small intestinal NET[9,12,20-23]. In many countries, well-differentiated, intestinal neuroendocrine tumors/carcinomas are classified as carcinoids of the small bowel (“duodenal carcinoids”, “jejunal carcinoids”, “ileal carcinoids”, “midgut carcinoid syndrome”). The terminology often serves to subcategorize the small intestinal tumors into NETs of the foregut (duodenal) and NETs of the midgut (ileal).

**CLINICAL PRESENTATION AND DIAGNOSIS**

Most duodenal NETs are asymptomatic and are detected during upper gastrointestinal (UGI) endoscopy study for symptoms unrelated to the carcinoid tumor[7,9,12,24,25]. The most common symptoms that lead to the detection of the duodenal carcinoid and the UGI endoscopy are vague abdominal pain (37%), UGI bleeding (21%), anemia (21%) and jaundice (18%)[7]. In contrast to other duodenal NETs, duodenal NETs located either in the periampullary region or at the ampulla of Vater more frequently cause symptoms, with up to 60% developing jaundice in some studies[7]. Duodenal NETs are usually hormonal silent tumors (60%-98% of patients in different series)[7]. However, a review of seven series demonstrates 10% ± 3% of duodenal NET patients develop the Zollinger-Ellison syndrome (ZES), 4% ± 2% Cushing’s syndrome and rare cases develop acromegaly due to a growth hormone factor releasing NET (GRFoma) and rare patients have a functional duodenal NET that is an insulinoma or a glucagonoma[9]. Patients with Zollinger-Ellison syndrome present with heartburn, gastroduodenal ulcer disease and/or chronic diarrhea[9,30].

In contrast, most ileal NETs present with symptoms either due to the ileal carcinoid itself or secondary to the development of carcinoid syndrome[11,13,31]. These symptoms include chronic diarrhea, flushing attacks, abdominal discomfort or pain, ischemia, gastrointestinal bleeding, sub ileus and weight loss[13,14,31].

With NETs of the small bowel, 6%-30% of patients develop carcinoid syndrome, characterized by the presence of diarrhea, flushing attacks, carcinoid heart disease, bronchial constriction and abdominal pain/cramps[13,14,32]. A life-threatening exacerbation of carcinoid syndrome can occur and is called a carcinoid crisis. A carcinoid crisis can be triggered by anesthesia, certain drugs or by surgery. Its
clinical pattern includes prolonged flush attack, hypo- or hypertension, heart arrhythmias, severe pulmonary spasm and diarrhea.

Serum gastrin and serum chromogranin A levels should be determined in patients with duodenal NETs. If hypergastrinemia and a hyperacidity stomach (basal gastric pH ≤ 2 or gastric acid output ≥ 10 mmol/h) are found, a secretin stimulation test should be carried out to establish ZES[13,14]. Before performing the secretin stimulation test, proton pump inhibitors should be stopped for 5-8 d; if needed, an H2 blocker can be given temporarily. An increase of gastrin levels of ≥ 120 pg/mL or higher is considered a positive test result with a recent study showing it has a sensitivity of 94% and specificity of 100%[15]. In ileal NETs, 5-HIAA (in 24 h urine) and serum chromogranin A should be measured. In 4% of patients carcinoid syndrome may be present with duodenal carcinoids[16].

The algorithm of diagnostic imaging starts with endoscopy (duodenoscopy, ileo-colonoscopy) and a tissue sample for histological diagnosis[7,13,34,35]. In the case of duodenal NETs, endoscopic ultrasound (endosonography) should follow. Endosonography allows the size and depth of infiltration of duodenal NET to be determined and also assesses the loco-regional lymph nodes[36]. Endosonography (EUS) also accurately determines the lesion’s layer of origin and internal echo pattern (low or high) which also adds to the differential diagnosis. Interestingly to note, NETs of the terminal ileum can be evaluated by EUS using high frequency miniprobes passed through the biopsy channel of the colonoscope.

Double balloon enteroscopy and capsule endoscopy[34,37,38] are two new techniques of jejunum and ileum endoscopy (Figure 2). Their use in patients whose intestinal NET disease has already been established by clinical, radiological or biochemical means is not generally required. However, recent studies show that both capsule endoscopy and balloon enteroscopy localize small intestinal NETs not yet detected by other modalities[37,38]. Besides CT scanning, CT enteroclysis or MRI enteroclysis are the most widely used radiological imaging techniques specifically used to localize NETs of the small bowel[39].

CT scanning of the abdomen and thorax as well as somatostatin receptor scintigraphy are the major imaging modalities used to establish tumor staging and localization initially[13,14,40,41]. 68-Gallium-DOTATOC-PET/CT is a new, very sensitive method for visualizing (metastatic) intestinal NETs[42-44], however, this costly technique is not available everywhere. Due to frequent carcinoid heart disease (in up to 30%-60% of patients with carcinoid syndrome), every patient with carcinoid syndrome or with elevated urinary 5-HIAA levels should be echocardiographed[13,16].

PATHOLOGY, CLASSIFICATION AND PROGNOSIS

NETs of the small bowel are, like the NETs at other sites, categorized according to the WHO classification into well-differentiated NET, well-differentiated neuroendocrine carcinoma (defined by the presence of metastases or the infiltration into the muscularis propria or angioinvasion) and poorly differentiated neuroendocrine carcinoma (NEC)[23,25,26]. The well-differentiated NETs and well-differentiated neuroendocrine carcinomas (NECs) stain for synaptophysin and usually also for chromogranin A while the poorly differentiated NECs, subtyped into small cell and large cell neoplasms, stain for synaptophysin but only infrequently and sparsely for chromogranin A. The term “carcinoid” is used both for well-differentiated NET and well-differentiated NEC.

In recent years, a TNM classification based on tumor size, depth of invasion and presence of lymph node metastases and/or distant metastases has been proposed and has been combined with a three tiered grading system (see Tables 1 and 2)[13,23,25,26]. Both G1 and G2 NETs are considered well-differentiated NETs whereas G3 characterizes the poorly differentiated NEC. Well-differentiated NETs and NECs are far more common than poorly differentiated NECs.

NETs and NECs of the small bowel usually occur in the duodenum or the ileum. The jejunal and the diverticulum of Meckel are rare locations.

Nonfunctional NETs of the duodenum

In the duodenum most NETs are nonfunctional (i.e. tumors without any clinical hormonal syndrome), sporadic (not inherited) and well-differentiated slow-growing tumors[24]. Among these NETs, those producing gastrin are most common (62%) followed by somatostatin producing tumors (18%-21%), gangliocytic paragangliomas (9%) and tumors that may produce various hormones such as serotonin or calcitonin (5.6%). Poorly differentiated neuroendocrine carcinomas (NECs) are very rare (1.8%)[40].

Gastrin-producing NETs are usually located in the proximal duodenum, are smaller than 20 mm and are limited to the mucosa-submucosa. In these NETs, lymph node metastases are found in 11%-50%[26,48], distant metastases are observed in less than 6%-10% of cases[12,19,27,28,48]. Somatostatin-producing NETs occur predominantly in the ampullary and periampullary region. If they involve the muscularis propria, have a size greater than 2 cm and an increased proliferation rate, the metastatic risk is greater than 50%[40,41]. However, even tumors with a diameter between 1 and 2 cm and smaller may show metastases in the paraduodenal lymph nodes[40,47]. Liver metastases are rare. In case of recurrence, the liver is the most common site of metastasis. Approximately 20%-30% of somatostatin producing tumors are associated with neurofibromatosis type 1. In none of the cases of somatostatin-cell tumors reported so far did the patients develop ‘somatostatinoma’ syndrome (diabetes mellitus, diarrhea, steatorrhea, hypoor achlorhydria, anemia and gallstones) that has been described in association with some pancreatic somatostatin-cell tumors[46].

Gangliocytic paragangliomas are characterized by their triphasic cellular differentiation consisting of neuroen-
Figure 2 Endoscopic images of well-differentiated (G1), small intestinal neuroendocrine tumors. A: 8 mm measuring neuroendocrine tumor (NET) in the duodenal bulb (A1). Endoscopic ultrasound shows the infiltration of mucosa and submucosa (A2). The duodenal NET exhibits a low echogenic pattern on endosonography (EUS); B: Duodenal NET of 21 mm size (B1), the muscularis propria is not infiltrated endosonographically (B2). The tumor shows a low echogenic pattern on EUS. The tumor (B3) shows a good arterial perfusion (by Doppler sonography); C: 10 mm-sized duodenal NET (C1). The chromoendoscopy (with indigo carmine) (C2) and the zoom endoscopy (C3) show an intact villous pattern and a crater-like retraction of the mucosa at the center of the tumor (modified from reference [77]); D: Sporadic gastrinoma of the duodenal bulb; E: Sporadic gastrinoma of the second part of the duodenum; F: Multiple duodenal gastrinomas in a patient with multiple endocrine neoplasia type 1 disease; G: 12 mm-sized NET of the distal ileum. Both tumor localisation and histological diagnosis were established using double balloon enteroscopy [34]. Ileal NETs present multifocally in 26%-30% of patients; H-I: 14 mm-sized NET of the terminal ileum. The primary tumor was located 8 cm proximal to the ileocecal valve. Ileocolonoscopy allowed not only tumor localization, but also histological verification of ileal NET disease (modified from reference [77]).
Table 1  Grading proposal for neuroendocrine tumors of the small bowels\cite{12,25,26}.

| Grade | Mitotic count (10 HPF) \(^1\) | Ki-67 index (%) \(^2\) |
|-------|-------------------------------|------------------------|
| G1    | < 2                           | ≤ 2                    |
| G2    | 2-20                          | 3-20                   |
| G3    | > 20                          | > 20                   |

\(^1\): 10 HPF: high power field = 2 mm\(^2\), at least 40 fields (at 40 × magnification) evaluated in areas of highest mitotic density; \(^2\): MIB1 antibody, % of 2000 tumor cells in areas of highest nuclear labeling.

Table 2  Therapy of duodenal neuroendocrine tumors

| Size      | No risk factors     | Risk factors \(^1\)          |
|-----------|---------------------|-----------------------------|
| < 1 cm    | EMR                 | Surgery (in case of surgical risk: EMR followed by surveillance) |
| 1-2 cm    | Surgery             | Surgery (or PPI therapy combined with surveillance in G1 gastrinomas and/or surgical risk) |

\(^1\): Risk factors for metastatic disease are angioinvasion or G2-G3 histological grading or infiltration of the muscularis propria or size > 2 cm or metastatic spread to lymph nodes; Surgery is the therapy of choice for sporadic gastrinoma (without distant metastases). In (very) elderly patients conservative management may, however, be preferred to surgery. NET: neuroendocrine tumor; EMR: endoscopic mucosal resection; PPI: proton pump inhibitor; MEN1: multiple endocrine neoplasia type1; G1 and G2: well differentiated; G3: poorly differentiated (histological grading: Ki-67 index of 0%-2%: G1; Ki-67 index of 3%-20%: G2; Ki-67 index of > 20%: G3).

Neuroendocrine cells (producing somatostatin and/or pancreatic polypeptide), spindle-shaped Schwann-like cells and ganglion cells. They usually occur in the periamppullary region and follow a benign course. However, occasional, large tumors (size > 2cm) may spread to local lymph nodes, mainly attributable to the endocrine component of the lesion\(^5\).

Poorly differentiated NECs occur primarily in or close to the ampullary region. They usually present in advanced stages, i.e. with lymph node, liver and other remote metastases\(^3\). The mean survival time in patients with metastases is 14.5 months\(^48,49\).

**Functional NETs of the duodenum**

Approximately 50% of sporadic (non-inherited) gastrin producing tumors are functioning and associated with the Zollinger-Ellison syndrome (ZES). These clinically functional NETs are called gastrinomas. They are well differentiated slowly growing NETs which are mostly (60% to 75%) located in the duodenum and only rarely in the pancreas\(^24\). Twenty to 30% of patients with ZES have MEN1 and in this condition most, if not all patients, have their gastrinomas in the duodenum\(^30,32\). An important difference between sporadic and MEN1-associated gastrinomas is that the latter are invariably multiple. Metastases in regional lymph nodes have been reported in 50%-90% of duodenal gastrinomas. These lymph node metastases may be much larger than the primary which may be less than 1 mm in size and may erroneously be considered pancreatic tumors, especially if they are located at the upper margin of the head of the pancreas or as primary lymph node gastrinomas\(^35\). Local lymph node metastases seem to have little influence on survival of patients with ZES. The 10 year survival rate of patients with duodenal gastrinomas (59%) is significantly better than for patients with pancreatic gastrinomas (9%), probably because metastases to the liver are more frequent in pancreatic than in duodenal gastrinomas\(^34\). Serotonin-producing NETs are unusual in the duodenum. It follows that duodenal NETs only exceptionally give rise to the classical carcinoid syndrome, associated with liver metastases of the tumor\(^50\).

**Ileal NETs**

These NETs usually present in the distal ileum. They occur sporadically and are associated neither with MEN1 nor with neurofibromatosis type 1 (although familial cases may occur). In 26%-30% they are multiple and in 15%-29% they are associated with other non-carcinoid malignancies\(^18\). Ileal NETs are well differentiated serotonin-producing tumors that usually have a low proliferation rate (Ki-67 ≤ 2%; G1). Depending on size, the rate of loco-regional lymph node metastases at the time of diagnosis varies from 30% (size 1 cm) to 100% (size > 2 cm); however, lymph node metastases may be observed in ileal NETs as small as 5 mm. Peritoneal seeding and/or distant metastases occur in 19%-64% of patients. Literature from the 1980s and 1990s indicated a five year survival rate of 65%-75% for limited tumor disease, a survival rate of 50% in cases with peritoneal carcinosis and 5 year survival of 18%-32% when liver metastases had occurred\(^13,29\).

Only 23% of the patients that were operated for ileal NET disease were tumor-free 5 years after surgery.

**Carcinoid syndrome (seen with functional ileal NETs, very rarely with duodenal NETs)**

The carcinoid syndrome with chronic diarrhea, flush attacks, carcinoid heart disease, bronchial constriction and abdominal pain/complaints is nowadays observed in 6%-30% of patients with ileal NETs and is associated with hepatic metastases in > 95% of cases with ileal NETs\(^13,18\). It occurs when the NET’s secreted products (serotonin, tachykinins, prostaglandins) reach the systemic circulation and are not inactivated by the liver\(^13,25,26\). Abdominal pain due to the desmoplastic reaction that can occur from the ileal NET and metastases in the proximal lymph nodes is also a common feature of carcinoid syndrome\(^13,25,26\). Because carcinoid syndrome is almost invariably a feature of advanced small intestinal NETs, it is...
rarely seen in early small intestinal NETs, the subject of this review.

Poorly differentiated, neuroendocrine carcinomas comprise less than 5% of all NET of the small bowel and occur mainly in the ampulla region\[^{20,57}\]. Primarily, men over 60 years are affected. Histologically, these are solid carcinomas that are reminiscent of small or large cell bronchial carcinomas and exhibit numerous mitoses as well as angioinvasion. The proliferation rate is over 20% (G3 NET). These carcinomas are clinically aggressive\[^{20,57}\].

**THERAPY**

Histological differentiation, tumor localization, type of tumor, tumor biology, tumor stage and individual circumstances must be taken into consideration when planning therapy\[^{33,34,41}\].

**Management of non-functional, well-differentiated duodenal NETs without risk factors for metastases**

Well-differentiated (G1), non-functional duodenal NETs that are limited to the mucosa/submucosa, up to 10 mm in size and grow non-angioinvasively can be endoscopically removed. These NETs carry a low risk for lymphatic or distant metastasis\[^{7,27,28}\]. The recent increased use of endoscopic ultrasound to assess duodenal NET invasion and the presence of possible lymph node metastases is particularly important in establishing the NET is in this category\[^{7}\].

Since many of the duodenal NETs infiltrate the submucosa, various therapeutic endoscopic approaches have been considered. Nowadays, endoscopic mucosal resection (EMR) is most widely performed\[^{38}\]. The aim of the endoscopic resection is to remove the tumor completely (R0-resection). Until now, no tumor recurrences have been observed after polypectomy/mucosectomy which affected the overall prognosis of the patient.

Therapy is controversial for NETs of the duodenum that are non-functional, well-differentiated (G1), limited to the mucosa/submucosa, 10-20 mm in size, grow non-angioinvasively and have not metastasized. Both endoscopic therapies and surgery are considered in this situation\[^{7,27,28}\]. Controlled studies on the different approaches are lacking\[^{13}\]. On the other hand, there is wide consensus that in operable patients, non-functional, duodenal NETs > 20 mm as well as all sporadic gastrinomas are to be subjected to surgical therapy\[^{8,9,61}\].

**Management of non-functional duodenal NETs with risk factors for metastatic disease**

Duodenal NETs which show good differentiation (G1, G2) histologically but which extend beyond the submucosa (T2-T4) or have spread to locoregional lymph nodes and/or show angioinvasion represent NETs with prognostically relevant risk factors; therefore they should be managed surgically\[^{7,27,28}\]. However, many patients at the time of the diagnosis are (very) elderly and suffer from significant comorbidity. For this reason, the decision about whether to go for surgery in well-differentiated NET disease in an elderly patient (with significant comorbidity) needs an interdisciplinary discussion and individual therapy is advised.

Poorly differentiated neuroendocrine carcinomas are rare with < 30 cases reported\[^{37}\]. These are highly invasive tumors (G3), regional lymph node and/or distant metastases are usually present at diagnosis and the majority of patients die from the tumor disease\[^{37}\]. In the uncommon patient where no distant metastases are present on careful imaging studies, surgical resection should be considered\[^{37}\].

**Management of duodenal gastrinomas**

**Sporadic gastrinoma:** Sporadic duodenal gastrinomas (i.e. without MEN1) metastasize in 40%-70% of cases and even gastrinomas less than 10 mm can already exhibit paraduodenal and peripancreatic lymph node metastasis\[^{9,59,64}\]. With this in mind, surgical tumor resection depending on tumor size plus lymphadenectomy is the therapy of choice with sporadic duodenal gastrinoma\[^{9,61}\]. ZES can be treated long-term and effectively with proton pump inhibitors should the patient decide against an operation in the high surgical risk-patient and (optionally) in advanced disease\[^{7,9,61}\]. Because the doubling time of well-differentiated gastrinoma cells is > 180 d, patients older than 65 years nowadays often die of another disease rather than of well-differentiated duodenal gastrinoma even if they have not been operated on.

**MEN1 gastrinoma:** Around 25% of duodenal gastrinomas are due to MEN1 disease\[^{7,9,61}\]. Because the duodenal NETs are almost invariably multiple, frequently small, and 40%-70% have metastasized at diagnosis, without aggressive surgery which is not recommended, MEN1 patients can generally not be cured by surgery\[^{9,60}\]. Therefore, the ZES in MEN1 has to be treated long-term and effectively with a proton pump inhibitor\[^{64}\]. Furthermore, the presence of hyperparathyroidism in these patients can make medical control of the gastric hypersecretion more difficult with more frequent and higher PPI doses needed\[^{64,65}\]. It is therefore recommended that the hyperparathyroidism be treated appropriately (surgical resection of at least 3.5 glands) and the patient followed carefully because it can relapse\[^{64,65}\]. With this in mind, MEN1/ZES patients should be treated in specialized clinics; the surgical option should be considered only in specialized centers and only after an interdisciplinary discussion of the individual patient.

**Management of NETs of the ampulla of vater**

The 20% of periampullary/ampullary NETs frequently require different treatment because they may have a different clinical course and biological activity than other duodenal NETs\[^{7,47}\]. Large NETs of the ampulla of Vater (papilla of Vater) frequently cause jaundice; however, early, small ampullary NETs are increasingly being diagnosed incidentally in asymptomatic patients. Unfortunately, there...
are no controlled studies on the optimal management of early ampullary NETs. Both endoscopic papilllectomy and surgical tumor resection can be curative approaches in early disease whereas in patients with ampullary carcinoids > 2 cm a Whipple resection or pylorus preserving pancreatico-duodenectomy is considered the treatment of choice[66]. Endoscopic therapy for early, small ampullary NETs is characterized by low morbidity and minimal hospital lethality. The obvious limitation of endoscopic endoluminal tumor resection is that possibly affected lymph nodes which are deemed “inconspicuous” in pre-interventional imaging are not removed. The situation is the opposite for surgical procedures. Surgical lymph node dissection not only allows an optimal local staging but also removes possible lymph node metastases. The disadvantage of surgical tumor resection plus lymph node dissection is higher morbidity and lethality. The optimal management of isolated loco-regional lymph node metastases of well-differentiated (G1) NET disease has not been evaluated and is therefore not known.

Ideally, once an interdisciplinary discussion has taken place, elective interventions for ampullary NETs should be carried out in specialized surgical centers with documented, very low hospital lethality for operations of ampullary and pancreatic carcinomas. If endoscopic resection is preferred for an early, small, well differentiated (G1) ampullary NET, the patient should be referred to a specialized endoscopic center. Due to the favorable tumor biology of well-differentiated NETs, patients whose well-differentiated (G1) ampullary NET of < 10-20 mm in diameter was completely (R0) resected endoscopically have a good or excellent prognosis. If lymph node metastases are detected during follow-up, (radical) surgery has to be considered then.

In the preoperative work-up, underlying VRD (neurofibromatosis type 1) or MEN1 disease should be sought for[7,8,46]. Some patients with well-differentiated ampullary NETs are (very) elderly and suffer from significant comorbidities. In such a high-risk situation, a conservative or endoscopic approach is preferred in well-differentiated NET disease.

The therapeutic approach for localized, poorly differentiated (G3) ampullary NETs involves aggressive surgical resection if possible and/or systemic chemotherapy (e.g. with cisplatin and etoposide)[51].

Management of ileal NETs

Surgery is the therapy of choice for early NETs of the jejunum or ileum[53]. Often lymphatic, peritoneal or hepatic spreading has already taken place at the time of diagnosis[11]. Diffuse peritoneal or systemic spreading characterizes the palliative situation. Due to the favorable tumor biology of well-differentiated (G1) NETs of the ileum, an elective, palliative operation performed in a specialized center should be discussed as part of a multimodal approach. Please refer to recent review papers for multimodal therapy of neuroendocrine liver metastases[18,67-72].

Palliative medical therapy

6%-30% of patients with small intestinal NETs develop carcinoid syndrome[13,19]. Stable, long-acting somatostatin analogs (octreotide-LAR, lanreotide autogel) are the initial agents of choice to control the symptoms of carcinoid syndrome[14]. They are effective in 60%-90% of patients[14], however, with time they may become ineffective and treatment with interferon-2α may be considered[14]. Treatment with somatostatin analogues or interferon primarily causes a cytostatic tumor response and rarely a decrease in tumor size[13,14].

Palliative cytoreductive chemotherapy has no proven survival benefit in advanced, well-differentiated NET disease of the small bowel[31,48]. In contrast, palliative medical therapy with octreotide-LAR significantly prolongs progression-free survival in patients with low intestinal tumor burden in their liver, as recently shown by the interim analysis of a prospective phase III study (PROMID study)[79]. These prospectively collected data confirm earlier retrospective reports. Thus, Strosberg et al[80] observed a five-year survival rate of 75% in patients that were treated multimodally for hepatic metastatic midgut NETs in addition to a long-term octreotide-LAR therapy. Medical therapy appears to be particularly effective if liver-directed locoregional treatment modalities (liver resection, chemoembolisation, radiofrequency thermal ablation, selective internal radiotherapy) are applied too.

Interferon-2 is considered, at least in Scandinavia, for second line therapy, particularly in functional NET disease. Objective radiological responses are observed in <15%-20% of the patients treated with interferon-2[53]. Innovative, targeted therapies are being tested in ongoing clinical trials[73,74].

Peptide receptor radionuclide therapy (PRRT) will not be discussed here because it is rarely used in early small bowel NET disease. For more information on PRRT please refer to current reviews[83]. The controlled prospective comparison of peptide receptor radionuclide therapy with medical therapy is the topic of a recently initiated phase III study. Peptide receptor radionuclide therapy, however, is only suitable for the prognostically favorable subgroups of patients with well-differentiated NETs showing a (high) expression of somatostatin receptors and is not recommended in early disease[60].

Poorly differentiated neuroendocrine carcinomas of the small bowel are both biologically and morphologically on par with the small and large cell neuroendocrine carcinomas of the lungs[70]. Therefore, patients are usually advised to go for a cytoreductive chemotherapy that corresponds to the medical treatment of small cell carcinoma of the lungs[20,71]. Although controlled studies are lacking, the outlined cytoreductive chemotherapy is the standard treatment for advanced neuroendocrine carcinomas of the small intestine. The objective response rate is 50% and higher for neuroendocrine carcinomas. In the rare situation that the poorly differentiated neuroendocrine carcinoma presents as limited disease, the tumor is resected surgically.

Early diagnosis and improved prognosis

In contrast to the situation in Japan[74], there is no screen-
ing esophagogastroduodenoscopy in Western countries. Nevertheless, NETs of the duodenum and the ampulla of Vater are increasingly being diagnosed in earlier tumor stages. This early detection has significantly changed the localization, distribution and the stages of the small intestinal NETs: in the 1970s the proportion of duodenal NETs was 3.6%; now they comprise 22% of all small intestinal NETs in the SEER registry\[13,17,20\]. In the 1970s and 1980s still 31.3% of the small intestinal NETs (in the SEER registry) were diagnosed in the advanced stage. This proportion decreased to 22.4% in the 1990s\[17\]. Today in Japan, distant metastases are found in fewer than 18.9% of newly diagnosed patients\[19\]. Advanced disease at diagnosis is particularly rare in duodenal NETs, making up less than 6%-10% of patients\[1,3,13,17,19,20\]. It is probable with the increased use of sensitive methods of examining the small bowel (capsule endoscopy, balloon enteroscopy) and increased use of very sensitive NET imaging methods (such as 68-Gallium-DOTATOC-PET/CT) that in the future there will be increased earlier detection of jejunal and ileal carcinoids.

At the same time, the 5 year survival rate of patients with small intestinal NETs (of the SEER registry) has risen from 51.9% in the 1970s and 1980s to 60.5% in the 1990s\[17\]. According to a recent report from Strosberg et al\[19\], 5 year survival increased in the US to about 75% between 1999 and 2004.

Similar observations have been reported from Sweden’s national cancer registry. In Sweden the 5 year survival rate of small intestinal NETs stepped up from 49%-50% in the 1960s and 1970s to 55% in the 1980s and finally to 65% in the 1990s\[16\].

PROSPECTS
NETs of the small bowel will be diagnosed much more frequently in the future. The rapid technological advances in describing molecular tumor profiles will identify molecular biomarkers which correctly predict NET biology in the near future. Reliable predictive biomarkers will be of major clinical significance, particularly in the management of “incidental” early NETs of the duodenum and the ampulla of Vater. Patients with NET disease should be monitored for secondary cancers (colon, stomach, prostate in men, breast in women) which develop in 15%-25%.

REFERENCES
1 Modlin IM, Oberk G, Chung DC, Jensen RT, de Herder WW, Thakker RV, Caplin M, Delle Fave G, Kalsbas GA, Krenning EP, Moss SF, Nilsson O, Rindi G, Salazar R, Ruszniewski P, Sundin A. Gastroenteropancreatic neuroendocrine tumours. Lancet Oncol 2008; 9: 61-72
2 Yao J, Hassam M, Phan A, Dagohoy C, Leary C, Mares JE, Abdalla EK, Fleming JB, Vaughtey JN, Rashid A, Evans DB. One hundred years after “carcinoid”: epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 2008; 26: 3063-3072
3 Hemminki K, Li X. Incidence trends and risk factors of carcinoid tumors: a nationwide epidemiologic study from Sweden. Cancer 2001; 92: 2304-2210
4 Hauso O, Gustafsson BI, Kidd M, Waldum HL, Drozdov I, Chan AK, Modlin IM. Neuroendocrine tumor epidemiology: contrasting Norway and North America. Cancer 2008; 113: 2655-2664
5 Hassan MM, Phan A, Li D Dagohoy CG, Leary C, Yao J. Risk factors associated with neuroendocrine tumors: A U.S.-based case-control study. Int J Cancer 2008; 123: 867-873
6 Chen CC, Neugut AI, Rotterdam H. Risk factors for adenocarcinomas and malignant carcinoids of the small intestine: preliminary findings. Cancer Epidemiol Biomarkers Prev 1994; 3: 205-207
7 Hoffmann KM, Furukawa M, Jensen RT. Duodenal neuroendocrine tumors: Classification, functional syndromes, diagnosis and medical treatment. Best Pract Res Clin Gastroenterol 2005; 19: 675-697
8 Jensen RT, Berna MJ, Bingham MD, Norton JA. Inherited pancreatic endocrine tumor syndromes: advances in molecular pathogenesis, diagnosis, management and controversies. Cancer 2008; 113 (7 suppl): 1807-1843
9 Jensen RT, Niederle B, Mitry E, Ramage JK, Steinmuller T, Lewington V, Scarpa A, Sundin A, Perren A, Gross D, O’Connor JM, Pauwels S, Kloppele G. Gastrinoma (duodenal and pancreatic). Neuroendocrinology 2006; 84: 173-182
10 Hiripi E, Bernejo JL, Sundquist J, Hemminki K. Familial gastrointestinal carcinoid tumours and associated cancers. Ann Oncol 2009; 20: 950-954
11 Hemminki K, Li X. Familial carcinoid tumors and subsequent cancers: a nation-wide epidemiologic study from Sweden. Int J Cancer 2001; 94: 444-448
12 Jensen RT, Rindi G, Arnold R, Lopes JM, Brandi ML, Behrstein WO, Christ E, Taal BG, Knigge U, Ahlman H, Kwekkeboom DJ, O’Toole D. Well-differentiated duodenal tumor/carcinoma (excluding gastrinomas). Neuroendocrinology 2006; 84: 165-172
13 Eriksson B, Klöppel G, Krenning E, Ahlman H, Pölöckinger U, Wiedenmann B, Arnold R, Auernhammer C, Körner M, Rindi G, Wildi S. Consensus guidelines for the management of patients with digestive neuroendocrine tumors--well-differentiated jejunal-ileoal tumors. Neuroendocrinology 2008; 87: 8-19
14 Scherübl H, Faiss S, Zeitz M. Neuroendocrine gastrointestinal tumours: Diagnostik und Therapie. Dtsch Med Wochenschr 2003; 128: 891-893
15 Bilimoria KY, Bentrom DJ, Wayne JD, Ko CY, Bennett CL, Talamonti MS. Small bowel cancer in the United States: changes in epidemiology, treatment, and survival over the last 20 years. Ann Surgery 2009; 249: 63-71
16 Zar N, Garmo H, Holmberg L, Rastad J, Hellman P. Long-term survival of patients with small intestinal carcinoid tumors. World J Surgery 2004; 28: 1163-1168
17 Modlin I, Lye K, Kidd M. A 5-decade analysis of 13715 carcinoid tumors. Cancer 2003; 97: 954-959
18 Strosberg J, Gardner N, Kvols L. Survival and prognostic factor analysis of 146 metastatic neuroendocrine tumours of the mid-gut. Neuroendocrinology 2009; 89: 471-476
19 Ito T, Tanaka M, Sasano H, Osamura YR, Sasaki I, Kimura W, Takano K, Obara T, Ishibashi M, Nakao K, Doi R, Shimatsu A, Nishida T, Komoto I, Hirata Y, Imamura M, Kawabe K, Nakamura K. The neuroendocrine tumor workshop of Japan. preliminary results of a Japanese nationwide survey of neuroendocrine gastrointestinal tumors. J Gastroenterol 2007; 42: 497-500
20 Ahlman H, Nilsson O, McNicol AM, Ruszniewski P, Niederle B, Ricke J, Jensen R, Kos-Kudla B, Oberk G, O’Connor JM, Pavel M, Vuillerme MP. Poorly-differentiated endocrine carcinomas of midgut and hindgut origin. Neuroendocrinology 2008; 87: 40-46
21 Grabowski P, Scherübl H. Expression of neuroendocrine tumors.
markers in undifferentiated carcinomas of the gastrointestinal tract. J Clin Oncol 2005; 23: 4795-4797

22 Solcia E, Klöppel G, Sobin LH. (In collaboration with 9 pathologists from 4 countries). Histological typing of endocrine tumours. Second Edition. WHO international histological classification of tumours. Berlin: Springer, 2000

23 Klöppel G, Heitz PU, Capella C, Solcia E. Pathology and nomenclature of human gastrointestinal neuroendocrine (carcinoid) tumors and related lesions. World J Surg 1996; 20: 132-141

24 Klöppel G, Rindi G, Anlauf M, Schmitt A, Polettini E, Casciani E, Bertini L, Vecchioli A, Mönkemüller K, Scherübl H, Moser E, Nitzsche E. Whole-body 18F dota PET for detection of gastrointestinal carcinoid tumors. Radiology 2001; 220: 373-381

25 Rindi G, Klöppel G, Allman H, Caplin M, Couvelard A, de Herder WW, Eriksson B, Falchetti A, Falconi M, Komminoth P, Körner M, Lopes JM, McNicol AM, Nilsson O, Perren A, Scarpa A, Scoazec JY, Wiedenmann B. TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. Virchows Arch 2006; 459: 395-401

26 Rindi G, Klöppel G, Couvelard A, Komminoth P, Körner M, Lopes JM, McNicol AM, Nilsson O, Perren A, Scarpa A, Scoazec JY, Wiedenmann B. TNM staging of midgut and hindgut (neuro) endocrine tumors: a consensus proposal including a grading system. Virchows Arch 2007; 451: 757-762

27 Soga J. Endocrinocarcinomas (carcinoids and their variants) of the duodenum. An evaluation of 927 cases. J Exp Clin Cancer Res 2003; 22: 349-363

28 Soga J. Early-stage carcinoids of the gastrointestinal tract: An analysis of 1914 reported cases. Cancer 2005; 103: 1587-1595

29 Modlin IM, Champaneria MC, Chan AK, Kidd M. A three-decade analysis of 3,911 small intestinal neuroendocrine tumors: the rapid pace of no progress. Am J Gastro 2007; 102: 1464-1473

30 Scherübl H, Schaaf L, Raue F, Faisst S, Zeitz M. Hereditäre neuroendokrine gastrintestinale Tumore und (carcinoid) tumors and related lesions. Berlin: Springer, 2000: 295-322

31 Berna MJ, Hoffmann KM, Long SH, Serrano J, Garbrecht N, Anlauf M, Scherübl H, Moser E, Nitzsche E. Whole-body 18F dota PET for detection of gastrointestinal carcinoid tumors. Radiology 2001; 220: 373-381

32 Rindi G, Klöppel G, Couvelard A, Komminoth P, Körner M, Lopes JM, McNicol AM, Nilsson O, Perren A, Scarpa A, Scoazec JY, Wiedenmann B. TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. Virchows Arch 2006; 459: 395-401

33 Modlin IM, Champaneria MC, Chan AK, Kidd M. A three-decade analysis of 3,911 small intestinal neuroendocrine tumors: the rapid pace of no progress. Am J Gastro 2007; 102: 1464-1473

34 Scherübl H, Schaaf L, Raue F, Faisst S, Zeitz M. Hereditäre neuroendokrine gastrintestinale Tumore und (carcinoid) tumors and related lesions. Berlin: Springer, 2000: 295-322

35 Berna MJ, Hoffmann KM, Long SH, Serrano J, Gilbril F, Jensen RT. Zollinger-Ellison syndrome: clinical presentation in 261 patients. Medicine (Baltimore) 2000; 79: 379-411

36 de Herder WW. Tumours of the midgut (jejunum, ileum and ascending colon, including carcinoid syndrome). Best Pract Res Clin Gastroenterol 2005; 19: 705-715

37 Bellutti M, Fry LC, Schmitt J, Seemann M, Klose S, Mallerfehner P, Mönkenmüller K. Detection of neuroendocrine tumors of the small bowel by double balloon enteroscopy. Dig Dis Sci 2009; 54: 1050-1058

38 van Tuyl SA, van Noorden JT, Timmer R, Stolk MF, Kuipers EJ, Taal BG. Detection of small-bowel neuroendocrine tumors by video capsule endoscopy. Gastrointest Endosc 2006; 64: 66-72

39 Masselli G, Poletti E, Casciani E, Bertini L, Vecchioli A, Gualdi G. Small-bowel neoplasms: prospective evaluation of MR enteroclysis. Radiology 2009; 251: 743-750

40 Wiedenmann B, Bäder M, Scherübl H, Fett U, Zimmer T, Hamn B, Koppenhögen K, Riecken EO. Gastroenteropancreatic neuroendocrine tumor imaging with somatostatin-receptor scintigraphy. Sem. Oncology 1994; 21: 29-32

41 Akerstrom G, Hellman P, Hessman O, Osmak L. Management of midgut carcinoids. J Surg Oncol 2005; 89: 161-169

42 Hoegele S, Altveehof C, Ghanem N, Koehler G, Waller CF, Scherübl H, Moser E, Nitzsche E. Whole-body 18F dota PET for detection of gastrointestinal carcinoid tumors. Radiology 2001; 220: 373-381

43 Koompans K, Neels O, Kema I, Elsinga PH, Sluiter WJ, Vanghillee E, Brouwers AH, Jager PL, de Vries EG. Improved staging of patients with carcinoid and islet cell tumors with 18F-dihydroxy-phenyl-alanine and 11C-5-hydroxy-trypophan positron emission tomography. J Clin Oncol 2008; 26: 1489-1495

44 Baum RP, Paedal V, Hommann M, Hörsch D. Receptor PET/ CT imaging of neuroendocrine tumors. Recent Results Cancer Res 2008; 170: 225-242

45 Solcia E, Capella C, Fiocca R, Sessa F, La Rosa S, Rindi G. Disorders of the endocrine system. In: Pathology of the Gastrointestinal Tract. Ming SC, Goldman H, editors. Williams and Wilkins: Baltimore, 1998: 295-322

46 Garbrecht N, Anlauf M, Schmitt A, Henoppe T, Sipos B, Raffel A, Eisenberger CF, Knooeel WT, Pavel M, Fottner C, Musholt TJ, Ringe A, Arnold R, Berndt U, Pöckinger U, Wiedenmann B, Moh H, Heitz PU, Komminoth P, Perren A, Klöppel G. Somatostatin-producing neuroendocrine tumors of the duodenum and pancreas: incidence, types, biological behavior, association with inherited syndromes, and functional activity. Endocr Relat Cancer 2008; 15: 229-241

47 Makhoul HR, Burke AP, Sobin LH. Carcinoid tumors of the ampulla of Vater. A comparison with duodenal carcinoid tumors. Cancer 1999; 85: 1241-1249

48 Sata N, Tskakahara M, Koizumi M, Yoshizawa K, Kurihara K, Nagai H, Someya T, Saito K. Primary small-cell neuroendocrine carcinoma of the duodenum - a case report and review of literature. World J Surg Oncol 2004; 2: 28

49 Zamboni G, Franzin G, Bonetti F, Scarpa A, Chilosi M, Colombani R, Menestrina F, Pea M, Iacono C, Serio G. Small cell neuroendocrine carcinoma of the ampulla region. A clinicopathological, immunohistochemical, and ultrastructural study of three cases. Am J Surg Pathol 1990; 14: 703-713

50 Donow C, Pipeleers MM, Schroder S, Stamm B, Heitz PU, Klöppel G. Surgical pathology of gastrinoma. Site, size, multicentricity, association with multiple endocrine neoplasia type 1, and malignancy. Cancer 1991; 68: 1329-1334

51 Pipeleers MM, Somers G, Willems G, Foulis A, Imrie C, Bishop AP, Polak JM, Hacki WH, Stamm B, Heitz PU. Gastrinomas in the duodenum of patients with multiple endocrine neoplasia type 1 and the Zollinger-Ellison syndrome. N Engl J Med 1990; 322: 723-727

52 Anlauf M, Garbrecht N, Henoppe T, Schmitt A, Schlenger R, Raffel A, Krausch M, Gimm O, Eisenberger CF, Knoeefel WT, Dralle H, Komminoth P, Heitz PU, Perren A, Klöppel G. Sporadic versus hereditary gastrinomas of the duodenum and pancreas: distinct clinico-pathological and epidemiological features. World J Gastroenterol 2006; 12: 5440-5446

53 Anlauf M, Erosawa T, Henoppe T, Schmitt A, Gimm O, Brauckhoff M, Dralle H, Mysil A, Hauptmann S, Perren A, Klöppel G. Primary lymph node gastrinoma or occult duodenal microgastrinoma with lymph node metastases in a MEN1 patient: the need for a systematic search for the primary tumor. Am J Surg Pathol 2008; 32: 1101-1105

54 Weber HC, Venzon DJ, Lin JT, Fishbein VA, Orbuch M, Strader DB, Gibril F, Metz DC, Fraker DL, Norton JA. Determinants of metastatic rate and survival in patients with
Scherübl H et al. Neuroendocrine tumors of the small bowel

Zollinger-Ellison syndrome: a prospective long-term study. *Gastroenterology* 1995; 108: 1637-1649

55 Capella C, Riva C, Rindi G, Sessa F, Usellini L, Chiaravalli A, Carnevali L, Solcia E. Histopathology, hormone products and clinicopathologic profile of endocrine tumours of the upper small intestine. A study of 44 cases. *Endocr Pathol* 1991; 2: 92-110

56 Druce M, Rockall A, Grossman AB. Fibrosis and carcinoid syndrome: from causation to future therapy. *Nat Rev Endocrinol* 2009; 5: 276-283

57 Nilsson O, Van Cutsem E, Dele Fave G, Yao JC, Pavel ME, McNicol AM, Sevilla Garcia MI, Knapp WH, Kelaştımur F, Sauvanet A, Pauwels S, Kwekkeboom DJ, Caplin M. Poorly differentiated carcinomas of the foregut (gastric, duodenal and pancreatic). *Neuroendocrinology* 2006; 84: 212-215

58 Shimizu N, Kaminishi M. Management of patients with neuroendocrine tumors of the esophagus, stomach, and duodenum. *Nippon Geka Gakki Zasshi* 2008; 109: 147-151

59 Norton JA, Alexander HR, Fraker DL, Venzon DJ, Jensen RT. Does the use of routine duodenotomy (DUODX) affect rate of cure, development of liver metastases or survival in patients with Zollinger-Ellison syndrome (ZES)? *Ann Surg* 2004; 239: 617-626

60 Thom AK, Norton JA, Axiotis CA, Jensen RT. Location, incidence and malignant potential of duodenal gastrinomas. *Surgery* 1991; 110: 1086-1093

61 Gibril F, Jensen RT. Advances in evaluation and management of gastrinomas in patients with Zollinger-Ellison syndrome. *Curr Gastroenterol Rep* 2005; 7: 114-121

62 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 patients from the literature. *Medicine (Baltimore)* 2004; 83: 43-83

63 Norton JA, Fraker DL, Alexander HR, Venzon DJ, Doppman JL, Serrano J, Goebel SU, Pehgini PL, Roy PK, Gibril F, Jensen RT. Surgery to cure the Zollinger-Ellison syndrome. *N Engl J Med* 1999; 341: 635-644

64 Jensen RT. Management of the Zollinger-Ellison syndrome in patients with multiple endocrine neoplasia type 1. *J Intern Med* 1998; 243: 477-488

65 Norton JA, Venzon DJ, Berna MJ, Alexander HR, Fraker DL, Libutti SK, Marx SJ, Gibril F, Jensen RT. Prospective study of surgery for primary hyperparathyroidism (HPT) in Multiple Endocrine Neoplasia type 1 (MEN1), and Zollinger-Ellison syndrome (ZES): longterm outcome of a more virulent form of HPT. *Ann Surgery* 2008; 247: 501-510

66 Hartel M, Wente MN, Sido B, Friess H, Buchler MW. Carcinoid of the ampulla of Vater. *J Gastroenterol Hepatol* 2005; 20: 676-681

67 Eriksson J, Stålberg P, Nilsson A, Krause J, Lundberg C, Skogseid B, Granberg D, Eriksson B, Åkerström G, Hellman P. Surgery and radiofrequency ablation for treatment of liver metastases from midgut and foregut carcinoids and endocrine pancreatic tumors. *World J Surgery* 2008; 32: 950-958

68 Kwekkeboem DJ, de Herder WW, Kam BL, van Eijck CH, van Essen M, Koool PF, Feelders RA, van Aken MO, Krenning EP. Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0, Tyr3] octreotate: toxicity, efficacy, and survival. *J Clin Oncol* 2008; 26: 2124-2130

69 Kennedy AS, Dezarn WA, McNeillie P, Coldwell D, Nutting C, Carter D, Murthy R, Rose S, Warner RR, Liu D, Palmedo H, Overton C, Jones B, Salem R. Radioembolization for unresectable neuroendocrine hepatic metastases using resin 90Y-microspheres: early results in 148 patients. *Am J Clin Oncol* 2008; 31: 271-279

70 Steinmüller T, Kianmansesh R, Falconi M, Scarpa A, Taal B, Kwekkeboom DJ, Lopes JM, Perzen A, Nikou G, Yao J, Delle Fave GF, O’Toole D. Consensus guidelines for the management of patients with liver metastases from digestive (neuro)endocrine tumours: foregut, midgut, hindgut, and unknown primary. *Neuroendocrinology* 2008; 87: 47-62

71 Swärd C, Johanson V, Nierven van Dijkum E, Jansson S, Nilsson O, Wängberg Å, Ahlman H, Kölby L. Prolonged survival after hepatic artery embolization in patients with midgut carcinoid syndrome. *Br J Surg* 2009; 96: 517-21

72 Rinke A, Müller H, Schade-Brittinger C, Kloese KJ, Barth P, Wied M, Mayer C, Aminossadati B, Pape UF, Bläker M, Harder J, Arnold C, Gress T, Arnold R; PROMID Study Group. PROMID Study Group. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *J Clin Oncol* 2009; 27: 4656-4663

73 Höpfner M, Schuppan D, Scherübl H. Treatment of gastrointestinal neuroendocrine tumours with inhibitors of growth factor receptors and their signaling pathways: recent advances and future perspectives. *World J Gastroenterology* 2008; 14: 2461-2473

74 Yao JC, Phan AT, Chang DZ, Wolff RA, Hess K, Gupta S, Jacobs C, Mares JE, Landgraf AN, Rashid A, Meric-Bernstam F. Efficacy of RAD001 (everolimus) and octreotide LAR in advanced low- to intermediate-grade neuroendocrine tumors: results of a phase II study. *J Clin Oncol* 2008; 26: 4311-4318

75 Yao JC, Phan A, Hoff PM, Chen HX, Charnsangavej C, Yeung SC, Hess K, Ng C, Abbruzzese JL, Ajani JA. Targeting vascular endothelial growth factor in advanced carcinoid tumor: a random assignment phase II study of depot octreotide with bevacinumab and pegylated interferon alpha-2b. *J Clin Oncol* 2008; 26: 1316-1323

76 Hosokawa O, Miyanaga T, Kaizaki Y, Hattori M, Dohden K, Ohta K, Itou Y, Aoyagi H. Decreased death from gastric cancer by endoscopic screening: association with a population-based cancer registry. *Scand J Gastroenterol* 2008; 43: 1112-1115

77 Scherübl H, Schwertner C, Steinberg J, Stölzel U, Pohl J, Dralle H, Köppel G. Neuroendokrinne Tumoren des Dünndarms sind auf dem Vormarsch: Frühe Tumoren und deren Management. *Z Gastroenterol* 2010; 48: 406-413

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