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EDITORIAL

Management of early gastrointestinal neuroendocrine neoplasms

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Abstract

Neuroendocrine neoplasms (NENs) of the stomach, duodenum, appendix or rectum that are small (≤ 1 cm) and well differentiated can be considered "early" tumors, since they generally have a (very) good prognosis. In the new WHO classification of 2010, these neoplasms are called neuroendocrine tumors/ carcinoids (NETs), grade (G) 1 or 2, and distinguished from poorly differentiated neuroendocrine carcinomas (NECs), G3. NETs are increasing, with a rise in the age-adjusted incidence in the U.S.A. by about 700 % in the last 35 years. Improved early detection seems to be the main reason for these epidemiological changes. Both the better general availability of endoscopy, and imaging techniques, have led to a shift in the discovery of smaller-sized (≤ 10-20 mm) intestinal NETs/carcinoids and earlier tumor stages at diagnosis. Endoscopic screening is therefore effective in the early diagnosis, not only of colorectal adenocarcinomas, but also of NETs/carcinoids. Endoscopic removal, followed up with endoscopic surveillance is the treatment of choice in NETs/carcinoids of the stomach, duodenum and rectum that are ≤ 10 mm in size, have a low proliferative activity (G1), do not infiltrate the muscular layer and show no angioinvasion. In all the other intestinal NENs, optimal treatment generally needs surgery and/or medical therapy depending on type, biology and stage of the tumor, as well as the individual situation of the patient.

Key words: Neuroendocrine tumor; Carcinoid; Stomach; Duodenum; Gut; Appendix; Rectum; Small size; Prognosis; Treatment

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INTRODUCTION

Gastrointestinal neuroendocrine neoplasms (NENs) have received much attention in recent years with regard to their diagnosis, classification, incidence, prognosis and treatment[1-3]. The most recent achievement is the new WHO classification, which appeared in the second half of 2010.

Table 1 Comparison of the WHO classification 2010 for gastroenteropancreatic neuroendocrine neoplasms with previous WHO classifications

WHO 1980	WHO 2000	WHO 2010
I Carcinoid	WDET[a]	NET G1 (carcinoid) G2[a]
	WDEC[a]	
	PDEC	NEC G3 Large cell or small cell type
	MEEC	MANEC
II Pseudotumour lesions	TLL	Hyperplastic and preneoplastic lesions

G: Grade (for definition, see text and table 2); [a]In case that the Ki67 proliferation rate exceeds 20%, this NET may be graded G3. WHO: World Health Organization; WDET: Well-differentiated endocrine tumor; WDEC: Well-differentiated endocrine carcinoma; MEEC: Mixed exocrineendocrine carcinoma; TLL: Tumour-like lesions; NET: Neuroendocrine tumor; NEC: Neuroendocrine carcinoma; MANEC: Mixed adenoneuroendocrine carcinoma.

In essence, this classification stratifies the pure gastroenteropancreatic (GEP)-NENs into three groups (Table 1): neuroendocrine tumors (NETs, equivalent to carcinoids) that are well differentiated and graded according to their proliferative activity into G1 or G2 (Table 2), and neuroendocrine carcinomas (NECs) that are poorly differentiated and graded as G3. The poorly differentiated NECs are divided into small cell and large cell neoplasms. Staging of tumor extension according to the available TNM classifications of ENETS[4,5] and AJCC/UICC[6] leads to a further stratification of NETs and NECs. The neoplasms that show non-endocrine components (usually adenocarcinoma structures) in addition to a considerable number of neuroendocrine cells (exceeding at least 30% of all tumor cells), are distinguished from the pure neuroendocrine neoplasms, and called mixed adeno-neuroendocrine carcinomas (MANEC).

Gastrointestinal NETs/carcinoids are on the rise[3]. In the U.S.A., the prevalence and the incidence of gastrointestinal NETs/carcinoids has recently been calculated to be 35/100 000 and 5/100 000, respectively[7], revealing a 7-fold increase in the last 35 years. Similar observations have been reported from England[8] and Norway[9]. The most obvious reason for this phenomenon is a better awareness of, and improved diagnostic strategies, for NENs, and an increased and more widespread use of gastrointestinal endoscopy[8-15].

The overall 5-year-survival rate for patients with gastrointestinal NETs/carcinoids has improved by almost 20% in the last 35 years[16-18]. This achievement is largely due to early detection, as gastrointestinal NETs/carcinoids are nowadays more frequently diagnosed at an early asymptomatic stage[7], notably tumors with a size below 10 mm and a G1 differentiation. Due to a lack of controlled prospective studies the management of these "early" gastrointestinal NETs/carcinoids has been a matter of debate. Here we review the retrospective data from large national registries and large hospital series, mainly from Japan, the U.S.A. and Korea.

Table 2 Grading of gastrointestinal neuroendocrine neoplasms according to proliferative activity[a]

Grade	Ki-67 index (%)[b]
G1	≤ 2
G2	3-20
G3	> 20

[a]Modified according to reference[4,5,19]; [b]MIB1 antibody, % of 100 tumor cells in areas of highest nuclear labeling.

RISK STRATIFICATION AND PROGNOSIS OF GASTROINTESTINAL NEN DISEASE

The risk of metastatic disease of gastrointestinal NENs correlates with histological differentiation (well or poorly differentiated), proliferative activity (G1-3, Table 2), tumor size, depth of tumor infiltration and angioinvasion. The recently introduced and generally accepted histological grading of gastrointestinal NENs (G1-G3) by the WHO is of major prognostic and therapeutic relevance (Table 2).

Prognosis of gastric NETs/carcinoids

At present, the most common of the gastric NENs, the type 1 (Table 3), is mostly diagnosed at an early stage, with 80%-90% of them being ≤ 1 cm in diameter[13]. These small tumors only rarely cause specific symptoms; in most instances they are found incidentally during a gastroscopy being performed for another reason, such as anemia, reflux symptoms or other non-specific abdominal symptoms. Type 2 gastric NENs, similar to type 1 (Table 3) are usually detected at an early stage, and thus have an excellent long term prognosis. For all gastric carcinoids the prognosis has much improved[3,16,20-22], with the proportion with advanced tumor stages at diagnosis decreasing from 23.8% in the 1950s and 1960s to 6.5%-7.9% in the 1990s, suggesting that early diagnosis is contributing to patients' improved survival. In Japan, the rate of advanced stages at diagnosis today is as low as 5.1%[20]. The 5-year-survival rate of patients with gastric NENs has improved from 51% in the 1970s and 1980s to 63% in the 1990s[3,20-22]. According to a recent analysis of the SEER data by Landry *et al*[21], the 5-year-survival is now up to 71%.

Small (≤ 1cm), well-differentiated (G1) carcinoids/NETs of the stomach that do not infiltrate the muscularis propria and do not show angioinvasion have been shown to have a very low risk of distant metastatic spread or carcinoid-related death; they are considered early NETs/ carcinoids of the stomach.

Prognosis of NETs/carcinoids of the small bowel

In the small bowel, ileal NETs/carcinoids are most frequently found (> 70%), but recent data show that the NE-

Table 3 Clinicopathological characteristics of gastric neuroendocrine neoplasms[4,23-26]

	Gastric NETs/carcinoids			Gastric NECs (poorly differentiated NENs)
	Type 1	Type 2	Type 3	Type 4
Relative frequency	70%-80%	5%-6%	14%-25%	6%-8%
Features	Mostly small (< 1-2 cm) and multiple	Mostly small (< 1-2 cm) and multiple	Solitary often > 2 cm	Solitary mostly exulcerated, > 2 cm
Associated conditions	CAG	MEN1/ZES	No	No
Histology	Well differentiated G1	Well differentiated G1	Well/moderate differentiated* G2[a]	Poorly differentiated G3
Serum gastrin	(Very) high	(Very) high	Normal	(Mostly) normal
Gastric pH	Anacidic	Hyperacidic	Normal	(Mostly) normal
Metastases	< 10%	10%-30%	50%-100%	80%-100%
Tumor-related deaths	no	< 10%	25%-30%	⩾ 50%

NET: Neuroendocrine tumor; NEC: Neuroendocrine carcinoma; CAG: Chronic atrophic gastritis, due to pernicious anemia or Helicobacter pylori infection; MEN1: Multiple endocrine neoplasia type1; ZES: Zollinger-Ellison syndrome; MEN1/ZES: ZES associated with MEN1; G1-3 histological differentiation: see Table 2; ENETS and NANETS nomenclature are identical for G1 and G3 grading: G1: Well differentiated; G3: Poorly differentiated. For G2 grading ENETS and NANETS nomenclature differ: *ENETS-nomenclature: G2: Well-differentiated; [a]NANETS-nomenclature: G2: Moderate differentiated (modified from Scherübl *et al*[13])

Ts of the duodenum are nowadays more common (22%) than previously noted[27]. Regarding prognosis, the 5-year survival rate has risen from 51.9% in the 1970s and 1980s to 60.5% in the 1990s[16]. In an analysis of the years 1999-2004, Strosberg *et al* reported a 5-year survival rate of about 75% in patients with metastatic NET/carcinoid disease of the small intestine, receiving multimodal therapy[17]. An earlier detection of all NETs of the small bowel may have led to improved prognosis[15,18], since the proportion of advanced disease of small intestine NETs (at the time of diagnosis) has decreased from 31.3% in the 1970s and 1980s, to 22.4% in the 1990s and finally to < 18.9% in the years between 2002-2004[7,16,20,27]. With duodenal NETs/carcinoids, distant metastases are nowadays observed in less than 6%-10% of the cases[19,20,28,29,30]. If duodenal NETs/carcinoids are ⩽ 10 mm in size, are G1, show neither angioinvasion nor infiltration of the muscular layer, and have no associated hormonal syndrome, they have a very low metastatic potential and can be considered "early" duodenal NETs/carcinoids. In contrast, duodenal gastrinomas (i.e. duodenal NETs/carcinoids associated with a Zollinger-Ellison syndrome (ZES), with or without multiple endocrine neoplasia 1) as well as jejunal/ileal NETs/carcinoids of only a few millimeters in size, may already have spread to locoregional lymph nodes and/or distant organs such as the liver. Thus, neither for jejunal/ileal NETs/carcinoids nor for duodenal ZES/gastrinomas, is the term "early" appropriate, and should not be used.

Prognosis of rectal NETs/carcinoids

Because of the introduction of colorectal cancer screening, the vast majority (85%-100%) of rectal NETs/carcinoids are nowadays detected at an early stage (Table 4). This has improved patients' 5-year-survival rate by more than 20%[14].

The 5-year-survival rate of rectal NETs/carcinoid patients with distant metastases ranges between 15%-30%[29,31,32]. For nodal-positive rectal carcinoid disease (without distant metastases detected at the time of diagnosis) the 5-year-survival rate is 54%-73%[31,32-34]. In contrast, histologically nodal-negative rectal NETs/carcinoids that are ⩽ 1 cm in size and do not show angioinvasion or infiltration of the muscular layer have an excellent 5-year-survival rate of 98.9%-100%[3,29,31,32]. These rectal NETs/ carcinoids may be regarded as "early" tumors.

Table 4 Impact of endoscopic screening on the size of detected rectal NENs/carcinoids[14]

Size of the primary	Without screening (%)	Endoscopic screening (%)
< 10 mm	65-80	93.3-100
11-20 mm	10-22	0-6.7
> 20 mm	10-15	0

The risk of lymph node metastases of rectal NETs/carcinoids is not lower than the metastatic risk of rectal adenocarcinoma of the same size[29,32,33]. Interestingly, neither is the prognosis of patients with metastatic rectal NET/carcinoid disease better than that of patients suffering from metastastic rectal adenocarcinoma of the same size[31-34].

The clinical significance of histological lymph node involvement in G1-G2 differentiated rectal NETs/carcinoids of 1-2 cm in size is not well studied and therefore not known, at least not in Western countries. Current guidelines published by NANETS do not recommend follow-up of patients with well-differentiated rectal carcinoids/NETs of 1-2 cm in size that have been completely resected and that had not invaded the muscular layer[35]. Yet ENETS recommends further surveillance of these patients when angioinvasion or invasion of the muscular layer or G2 grading have been reported[36].

DIAGNOSIS OF EARLY NETS/ CARCINOIDS OF THE STOMACH, DUODENUM OR RECTUM

Endoscopic screening and the increasingly widespread

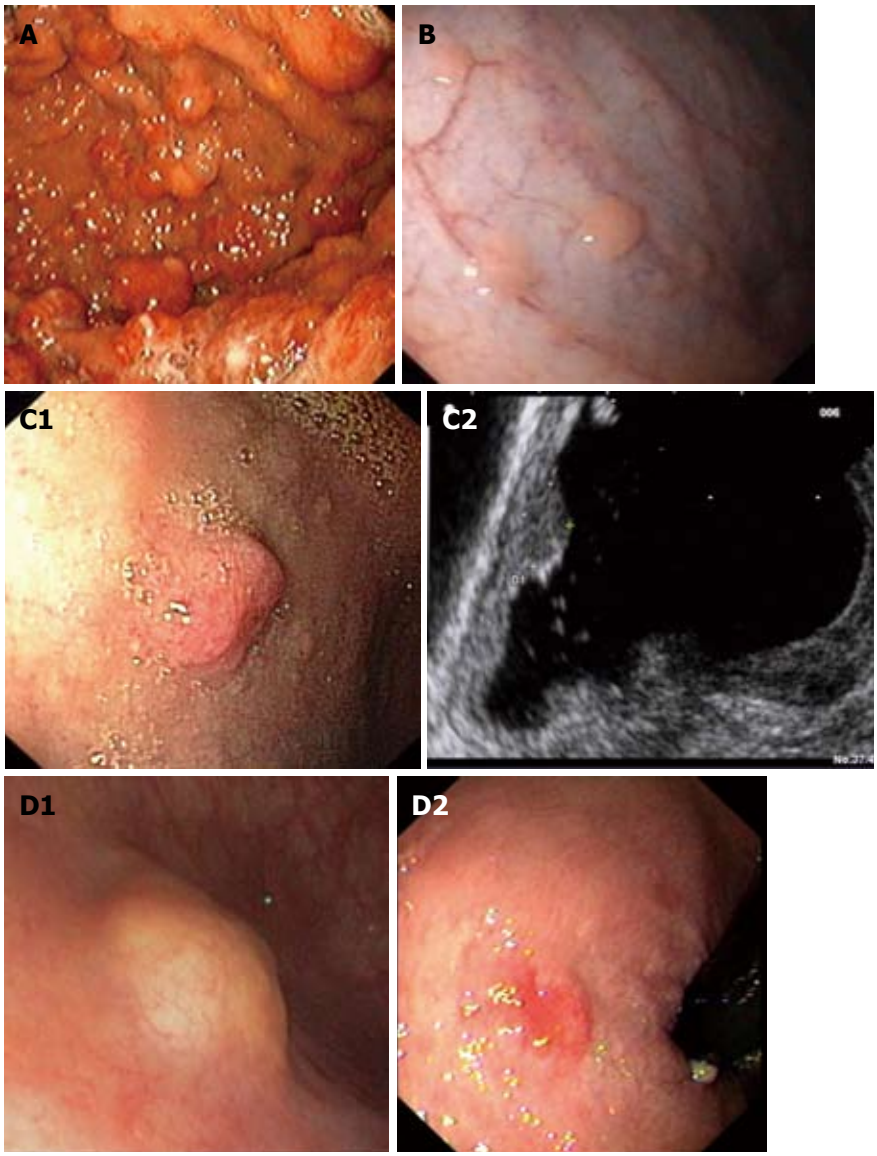

Figure 1 Endoscopic images of early gastrointestinal NETs/carcinoids. A: Multiple small (< 1 cm), well differentiated (G1) type 2 gastric NETs/carcinoids associated with Zollinger-Ellison-syndrome (ZES) and multiple endocrine neoplasia type 1 (MEN1); B: Multiple small (< 1 cm), well differentiated (G1) type 1 gastric NETs/carcinoids associated with autoimmune chronic atrophic gastritis and pernicious anemia; C: 8 mm measuring NET/carcinoid in the duodenal bulb (C1). Endoscopic ultrasound shows the infiltration of mucosa and submucosa (C2). The duodenal NET/carcinoid exhibits a low echogenic pattern on EUS; D: 10 mm measuring NET/carcinoid of the rectum (D1). 7 mm measuring NET/carcinoid of the rectum (D2). Modified from reference[13-15]. NETs: neuroendocrine tumors; EUS: Endoscopic ultrasound.

availability of gastrointestinal endoscopy have led to a shift in the discovery of smaller-sized (≤ 10-20 mm) gastrointestinal carcinoids/NETs at the time of diagnosis. Most of these tumors are asymptomatic, but occasionally they may present with abdominal discomfort, gastrointestinal bleeding, altered bowel habits or in the case of an ampullary NET with jaundice. If they present with hormonal hypersecretion syndromes, as for instance as duodenal gastrinomas associated with ZES (see above), they have often already spread to the regional lymph nodes, despite their small size. These functional intestinal NETs that almost never represent "early" tumors, will not be discussed here in detail (see recent reviews).

Endoscopy is the only method of choice to detect (asymptomatic) gastric, duodenal or rectal NETs/carcinoids at an early stage. So far there are no data available concerning the sensitivity and specificity of radiological and scintigraphic imaging techniques to visualize early gastric, duodenal or rectal NETs/carcinoids (Figure 1).

THERAPY OF EARLY GASTROINTESTINAL NETS/CARCINOIDS

For early NETs/carcinoids of the stomach, duodenum or rectum, the treatment of choice is endoscopic resection. For the treatment and management of more advanced NETs/carcinoids, all the prognostically relevant parameters (see below) have to be taken into account. Best palliative therapy is required for far advanced tumor disease.

Stomach, duodenum and rectum

Small (≤ 1 cm), well-differentiated (G1) NETs/carcinoids of the stomach, duodenum or rectum that do not infiltrate the muscularis propria and do not show angio-invasion have a very low risk of metastatic spread, i.e. they are considered early NETs/carcinoids of the stomach, duodenum or rectum. Endoscopic ultrasound is excellent for determining exact tumor size and to exclude infiltration of the NETs/carcinoids into the muscular wall (muscularis

Table 5 Therapy of gastric NENs

	No risk factors (for metastatic disease)		risk factors[a]
Size	⩽ 1 cm	1-2 cm	
Type 1	Surveillance[b] optionally EMR	EMR followed by surveillance	Surgery[c]
Type 2	Surveillance[b]	EMR followed by surveillance	Surgery[c]
Type 3	EMR	Surgery[c]	Surgery[c]
Type 4	-	-	Surgery[d]

[a]risk factors for metastatic disease are angioinvasion or G2-G3 histological grading or infiltration of the muscularis propria or tumor size > 2cm; [b]somatostatin analogs are being tested in ongoing clinical trials, they should not be used except in clinical trials; [c]followed by endoscopic surveillance of the gastric remnant. Adjuvant (medical) therapy is not established in NET/carcinoid disease; [d]surgery in localized type 4 gastric/d NEC disease (or systemic cytoreductive chemotherapy in advanced type 4 gastric NEC disease). Type 4 gastric NECs are never benign, they are neuroendocrine carcinomas. EMR: Endoscopic mucosal resection; NENs: Neuroendocrine neoplasms.

Table 6 Therapy of duodenal NENs

Type	⩽ 1 cm[a]	1-2 cm[a]	Any size but risk factors[b]
Sporadic NET (no gastrinoma, no MEN1)	EMR	Surgery (in case of surgical risk: EMR followed by surveillance)	Surgery
Sporadic gastrinoma	Surgery[c]	Surgery[c]	Surgery[c]
Gastrinoma and MEN1	PPI therapy and surveillance (or surgery)	Surgery (particularly if the gastrinoma is growing) or PPI therapy combined with surveillance	Surgery (or PPI therapy combined with surveillance in G1 gastrinomas and/or surgical risk)
NEC (G3)	-	-	Surgery or cytoreductive chemotherapy

[a]without risk factors (for metastatic disease) such as G2-G3, angioinvasion, infiltration of the muscularis propria or tumor size > 2 cm; [b]in the presence of risk factors for metastatic disease, surgery is generally indicated, regardless of tumor size; [c]Surgery is the therapy of choice for sporadic gastrinoma (without distant metastases). In (very) elderly patients conservative management may, however, be preferred to surgery. Adjuvant (medical) therapy is not established in NET/carcinoid disease. NET: Well differentiated neuroendocrine tumor; EMR: Endoscopic mucosal resection; PPI: Proton pump inhibitor; MEN1: Multiple endocrine neoplasia type 1.

propria). Endoscopic ultrasound is not mandatory for NETs/carcinoids measuring less than 1 cm, because those do generally not infiltrate the muscular layer. Early, G1-differentiated NETs/carcinoids of the stomach, duodenum or rectum should be removed by endoscopic polypectomy or by endoscopic mucosal resection (EMR). In early rectal NETs/carcinoids endoscopic submucosal dissection (ESD) may be considered, too. The resected specimen has to

Table 7 Therapy of rectal NENs

	No risk factors (for metastatic disease)		Risk factors[a]
Grade/Size	⩽ 1.0 cm	1.1 - 2 cm	Any size
G1	EMR or polypectomy or ESD	Surgery[b] (EMR or ESD in case of surgical risk or for carcinoids of 11-14 mm in diameter)	Surgery[b]
G2	EMR, ESD, surgery[b]	Surgery[b]	Surgery[b]
G3	-	-	Surgery[b]

[a]risk factors for metastatic disease are angioinvasion or infiltration of the muscularis propria, or tumor size of > 2cm; [b]surgery only in localized NET/NEC disease and systemic medical therapy in advanced tumor/cancer disease. Adjuvant medical therapy is not established for curatively resected, well-differentiated NETs/carcinoids of the rectum. G3 neuroendocrine neoplasms of the rectum are always neuroendocrine carcinomas. EMR: Endoscopic mucosal resection; ESD: endoscopic submucosal dissection; NENs: Neuroendocrine neoplasms.

be carefully evaluated for grade, angioinvasion, and infiltration of the deep resection margin. In case of angioinvasion, histological infiltration of the muscular wall or grade G2/G3, surgery is the first line therapy. The management of G1 NETs/carcinoids of 1-2 cm in size is a matter of debate[16-18]. Unfortunately, there are no controlled prospective studies available that have compared the endoscopic to the surgical approach for these 1-2 cm sized carcinoids/NETs. Due to the particular tumor biology of G1 NETs/carcinoids (of 1-2 cm in size) the endoscopic approach should be preferred to surgery in patients with significant comorbidities and, in elderly patients, a (high) surgical risk. No adjuvant therapy has been established for curatively resected, G1-G2 gastrointestinal NETs/carcinoids. Analogous to the situation of small cell or large cell neuroendocrine cancer disease of the lungs, cytoreductive chemotherapy is generally recommended for gastrointestinal NECs (G3 neuroendocrine carcinomas). G3 NENs are never "early" and almost always metastatic at diagnosis. The specific therapeutic strategies for early NETs/carcinoids of the rectum, duodenum and stomach are outlined in Table 5-7.

APPENDIX

Appendiceal NENs are usually NETs/carcinoids that are found incidentally in (young) patients undergoing appendectomy for suspected acute appendicitis. The term "early appendiceal NET/carcinoid" may be considered for the tumors that are G1, measure ⩽ 10 mm, show no angioinvasion, are confined both to the tip of the appendix and to the wall (without invasion of the mesoappendix) and have been completely (R0) removed. Such early appendiceal carcinoids have a very low risk of distant metastatic spread. Neither ENETS nor NANETS recommend further surveillance of patients with these early appendiceal tumors[38,39]. The management of other appendiceal carci-

noids/NETs is not discussed here; we refer to recent review and guideline papers[38,39].

CONCLUSION

New diagnostic techniques have led to increasingly early recognition of early gastrointestinal NETs/carcinoids. The general widespread use and availability of gastrointestinal endoscopy has led to a shift in the discovery of smaller-sized (≤ 10-20 mm) gastrointestinal NETs/carcinoids at the time of diagnosis. In the last 35 years, the overall 5-year-survival rate of patients with gastrointestinal carcinoid/NEN disease has increased by almost 20%. Most patients with early, well differentiated (G1) NETs/carcinoids of the stomach, duodenum and rectum can be treated conservatively, and be followed-up by endoscopic surveillance. It should be noted that patients with (previous) NET/carcinoid disease have a 15%-25% risk for second malignancies including breast, prostate, colorectal or gastric cancer.

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