Gastroenteropancreatic neuroendocrine tumours: the current incidence and staging based on the WHO and European Neuroendocrine Tumour Society classification: an analysis based on prospectively collected parameters

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Abstract

As incidence data on gastroenteropancreatic neuroendocrine tumours (GEP-NETs) have so far only been retrospectively obtained and based on inhomogeneous material, we conducted a prospective study in Austria collecting all newly diagnosed GEP-NETs during 1 year. Using the current WHO classification, the tumor, nodes, metastases (TNM) staging and Ki67 grading and the standard diagnostic procedure proposed by the European Neuroendocrine Tumor Society (ENETS), GEP-NETs from 285 patients (male: 148; female: 137) were recorded. The annual incidence rates were 2.51 per 100 000 inhabitants for men, 2.36 per 100 000 for women. The stomach (23%) was the main site, followed by appendix (21%), small intestine (15%) and rectum (14%). Patients with appendiceal tumours were significantly younger than patients with tumours in any other site. About 46.0% were classified as benign, 15.4% as uncertain, 31.9% as well differentiated malignant and 6.7% as poorly differentiated malignant. Patients with benign or uncertain tumours were significantly younger than patients with malignant tumours. Among the malignant tumours of the digestive tract, 1.49% arose from neuroendocrine cells. For malignant gastrointestinal NETs, the incidence was 0.80 per 100 000: 40.9% were ENETS stage I, 23.8% stage II, 11.6% stage III and 23.8% stage IV. The majority (59.7%) were grade 1, 31.2% grade 2 and 9.1% grade 3. NETs of the digestive tract are more common than previously reported; the majority show benign behaviour, are located in the stomach and are well differentiated. G3 tumours are very rare.

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Introduction

Neuroendocrine tumours (NETs) of the gastrointestinal tract are rare neoplasms and represent a heterogeneous group of tumours with distinct functional and biological behaviour depending on location, tumour size and clinical symptoms (Kloppel *et al.* 2004). NETs arise from the neuroendocrine cells of the diffuse neuroendocrine system. Located in the oesophagus, stomach, duodenum, pancreas, ileum, jejunum, appendix, colon

or rectum, these tumours are summarised as gastroenteropancreatic (GEP) NETs (Kloppel *et al.* 2004); they were formerly referred to as gastrointestinal carcinoids, a term introduced by Oberndorfer more than 100 years ago (Kloppel 2007a, Modlin *et al.* 2007).

NETs were recently classified according to standardised histopathological criteria established by the WHO (Solcia *et al.* 2000). Irrespective of the site of origin, these endocrine tumours are classified in general

as ‘well differentiated with benign’ or ‘uncertain’, ‘well differentiated with low-grade malignant’ or ‘poorly differentiated with high-grade malignant behaviour’. The classification is based on particular criteria (size, invasion, Ki67 index, etc.) and used to predict a tumour’s biological behaviour (benign, malignant) with high probability (Kloppel *et al.* 2004).

Incidence data on GEP-NETs are difficult to obtain and are mainly based on national cancer registries. These usually document malignant diseases on the basis of clinical reports, and therefore accurate and relevant analysis of the incidence of GEP-NETs may have substantial limitations since the majority of NETs with benign or uncertain clinical course may not be fully incorporated. In addition, such data have usually been collected over an extended period, during which time the definitions of the disease have evolved. Furthermore, information on the incidence of NETs in different sites is not as precisely documented in the national registries as information on adenocarcinoma of the digestive tract.

To our knowledge, the rare papers analysing the incidence of NETs are either retrospective database analyses (Godwin 1975, Hemminki & Li 2001, Taal & Visser 2004) or autopsy studies (Berge & Linell 1976), and they lack both the recently recommended standardised histopathological characterisation and the current WHO classification of NETs.

The aim of this study was to evaluate the incidence of GEP-NETs in a Middle European country (Austria) based on prospectively collected pathological reports, using a standardised histopathological protocol for initial diagnosis. The current WHO recommendations were used for classification (Kloppel *et al.* 2004), and the recently defined criteria of the European Neuroendocrine Tumour Society (ENETS) were used for staging and grading (Rindi *et al.* 2006, 2007). In addition, the incidence of malignant GEP-NETs was compared with that of other malignant tumours identified in the same parts of the digestive tract.

Methods

The objective of the prospective trial was to collect pathology reports of all tumours diagnosed and classified histologically/immunohistochemically as NETs during 1 year (01/05/2004–30/04/2005) to analyse current data on the Austrian national incidence of GEP-NETs.

Incidence

There are 41 registered departments and institutes of clinical pathology linked to public and private hospitals in Austria. All were invited, and 40 participated in this prospective 1-year study.

With regard to the study protocol, only patients with NETs located in the gastrointestinal tract and pancreas initially diagnosed within the study period were included in the analysis. Of the 40 participating pathological institutes, 31 reported NETs during the study period.

Tumour definition was initially based on typical morphological characteristics (Soga 1997). However, the detailed neuroendocrine origin of the tumours was definitively identified using staining for markers of neuroendocrine differentiation, chromogranin A and/or synaptophysin, as described recently (Kloppel *et al.* 2004). Neuron-specific enolase was not used for characterisation as it is insufficiently reliable (Kloppel 2007b).

Apart from the histopathological characteristics, additional parameters such as tumour location and the patient’s sex and age were documented by the participating institutes, and the pathology reports were sent online to the study centre.

WHO tumour classification

As published recently (Kloppel *et al.* 2004), the detected NETs were subdivided, irrespective of the site of the primary tumour, as ‘well differentiated’ tumours with either ‘benign’ or ‘uncertain’ behaviour or as ‘well differentiated’ or ‘poorly differentiated’ neuroendocrine carcinomas.

Neuroendocrine liver tumours were included in the analysis if no other neuroendocrine malignancy outside the abdomen (e.g. lung, ovary) was detected at the time of diagnosis and were therefore assessed as distant metastasis from GEP-NETs. For further evaluation of liver tumours, particularly to gain information on location of the primary tumour in the ileum or jejunum, and if adequate amounts of samples were available, tissue was stained immunohistochemically with antibodies against serotonin (Kloppel *et al.* 2009).

The pathological data were supervised by one of the authors (K K), and if questionable, additional immunohistochemical studies were conducted.

TNM staging and grading based on ENETS definitions

Based on the clinical, surgical and imaging data, the recently published TNM classification and staging system, together with the tumour grading suggested by Rindi *et al.* (2006, 2007), was used whenever possible.

Statistical analysis

A Filemaker database for documentation of patients with NETs was built up, recording all pathological and available clinical parameters. SPSS version 17.0 (Chicago, IL, USA) was used for statistical analyses.

Data are described as median and interquartile range (IQR). Age-standardised (=age-adjusted) incidence rates were calculated using Austrian population data published by Statistics Austria. The reference population was based on the World standard population, as used by the International Agency for Research on Cancer (Parkin *et al.* 2003) and modified by Doll *et al.* (1966) after Segi *et al.* (1960).

For comparison of the Austrian incidence data to those of the usually cited ‘Surveillance, Epidemiology, and End Results’ (SEER) Program of the National Cancer Institute from the USA (Modlin *et al.* 2003, Hauso *et al.* 2008, Yao *et al.* 2008), the age-adjusted incidence rate was further calculated to the 2000 US standard population (Klein & Schoenborn 2001).

The population-based Austrian cancer registry, which recorded all digestive tract cancers in 2004, was used to compare the incidence of malignant NETs with that of gastrointestinal cancer of various sites of the digestive tract. Austria, in central Europe, has about 8.3 million inhabitants, 10% of whom are foreigners mainly from other countries of the European Union, the former Yugoslavia and Turkey.

P values were calculated using Mann–Whitney *U* tests and corrected for multiple testing using the Bonferroni–Holm method. *P* values <0.05 were considered significant.

Informed consent

All the patients were asked to give informed consent for documentation of their pathological and clinical data. The full names of the patients remained unknown to the study centre.

All the patients agreed to participate in the ‘pathological analysis’, but not all agreed to participate in the ‘clinical’ part of the study; thus not all patients could be included. Information on the presence or absence of metastasis had to be available as a minimum requirement for ENETS staging.

The design of the prospective study, the manner of data collection and the retrospective analysis were approved by the ethics committee of the Medical University of Vienna (Resolution number 157/2005).

Results

Incidence

A total of 305 tumours were reported during the 12-month period. Eleven specimens were excluded because the immunohistochemistry was either negative or impossible to assess because of inadequate material; an additional five were excluded because the date of

diagnosis was not within the study period; a further three specimens were metastasis in the liver from NETs in other sites (lung: 2, ovary: 1), and one biopsy could not be related to an organ (biopsy of a NET of the abdomen). Thus, 285 NETs located in the gastrointestinal tract were selected from the database and were made available for detailed evaluation.

Incidence and biological behaviour of NETs

Adjusted to the World standard population, the overall incidence was 2.39 per 100 000 inhabitants per year: 2.36 per 100 000 for women and 2.51 per 100 000 for men. Calculated to the 2000 US standard population, the overall incidence was 2.99 per 100 000 inhabitants per year.

The age-specific incidence rate was highest between 50 and 70 years and began to increase at about 35 years.

Classification of the NETs according to the WHO criteria found that the overall incidence of tumours with benign, uncertain and malignant behaviour was 1.15, 0.43 and 0.81 per 100 000 inhabitants respectively.

Age and sex of patients

Of the 285 patients, 148 were men and 137 were women; their median ages at initial diagnosis were 63 (IQR: 22) and 59 (IQR: 27) years respectively (*P* value significant only before correction for multiple testing: *P* < 0.05, then non-significant). Patients with appendiceal NETs were significantly younger (median 38 (IQR: 45) years) than patients with NETs in any other site (*P* < 0.05).

Location

The site of the primary tumour was the stomach in 65 (22.8%) patients, followed by the appendix (*n* = 59; 20.7%), small intestine (excl. duodenum; *n* = 44; 15.4%), rectum (*n* = 40; 15.4%), pancreas (*n* = 33; 11.6%), colon (*n* = 20; 7.0%) and duodenum (*n* = 16; 5.6%). In one patient, the tumour was located in the oesophagus, and in another patient, it was located in the gallbladder and Meckel’s diverticulum (Fig. 1; for analysis of the clinical data in Part 2, these three tumours were excluded).

Liver tumours expressing neuroendocrine markers were documented in five (1.7%) patients. By definition (see above), these tumours were categorised as metastasis from NETs located in various sites of the gastrointestinal tract. Adequate amounts of tissue were available for further immunohistochemical studies in three of the tumours: all three stained negative for serotonin. The definitive location of the primary tumour remained unknown during the follow-up period of 1 year. These five tumours were excluded from further clinical analysis.

Figure 1 Number, location and biological behaviour of neuroendocrine tumours in each site.

Differentiation and biological behaviour of NETs

By definition (Kloppel *et al.* 2004), 131 (46.0%) NETs were classified as benign (incidence rate 1.15 per 100 000), 44 (15.4%) as having uncertain behaviour (incidence rate 0.43) and 110 (38.6%) as malignant (incidence rate 0.81). Among the malignant tumours, 91 (82.7%; 31.9% of all 285 tumours) were well differentiated and 19 (17.3%; 6.7% of all 285 tumours) were poorly differentiated.

Age/sex of patients and biological behaviour of tumours

The median age of patients with benign tumours was 60.0 (IQR: 26) years, with tumours of uncertain behaviour was 51.0 (IQR: 37) years and with malignant tumours was 65.5 (IQR: 18) years. Patients with benign or uncertain tumours were significantly younger than patients with malignant tumours (both $P < 0.01$); the ages of patients with benign and uncertain tumours were not significantly different from each other.

Even after excluding appendix NETs (patients with appendix NETs were significantly younger; 62.7% classified benign), patients with benign tumours were

younger than patients with malignant tumours ($P < 0.05$) (uncertain versus malignant and benign versus uncertain: P not significant). Among patients with malignant tumours, the median age of those with well differentiated tumours was 60.0 (IQR: 24) years and of those with poorly differentiated tumours was 73.0 (IQR: 17) years ($P < 0.05$; after correction for multiple testing P not significant, 0.06).

The distribution of tumours with benign, uncertain and malignant behaviour was approximately equal in male and female patients for all tumour sites.

Location and biological behaviour of tumours

Whereas NETs in the stomach (67.7%), rectum (65%) and appendix (62.7%) were mainly classified as benign, those in the small intestine (86.4%), pancreas (75.8%) and colon (70.0%) were predominantly malignant (Fig. 1).

Concerning tumour location, Fig. 2 summarises the malignant NETs after subdividing them into well differentiated and poorly differentiated. Four of five malignant rectal NETs were classified as poorly differentiated, whereas the proportions of this tumour type in all other sites except the duodenum were closely similar. Among pancreatic NETs (PNETs), 20 (80.0%) of 25 were classified as well differentiated and five as poorly differentiated endocrine carcinoma. Five of five malignant duodenal NETs were classified as well differentiated.

Figure 2 Malignant neuroendocrine tumours of the digestive tract – well differentiated and poorly differentiated neuroendocrine carcinomas.

Table 1 Site and incidence of malignant neuroendocrine tumours and other malignancies of the digestive tract

Site	Incidence in digestive tract (per 100 000 population)		Digestive malignant NETs: percentage of all malignancies
	Malignant NETs ^a	All reported malignancies ^b	
Oesophagus	0.01	2.55	0.39
Stomach	0.08	8.16	0.98
Duodenum	0.02	0.23	8.70
Pancreas	0.19	8.31	2.29
Small intestine excl. duodenum	0.29	0.56	51.79
Appendix	0.08	0.27	29.63
Colon (incl. rectosigmoid junction)	0.06	18.19	0.33
Rectum	0.03	9.73	0.31
Liver	0.05	5.48	0.91
Meckel's diverticulum	0.00	0.01	0.00
Gall bladder incl. bile duct	0.00	1.00	0.00
Total	0.81	54.49	1.49

^aStudy period: 05/2004–04/2005.^b2004: reference year.

Incidence of malignant NETs and other malignancies in the digestive tract

Table 1 summarises the incidence of malignant NETs and all reported malignancies in the digestive tract. By definition, 1.49% of all malignant tumours of the digestive tract documented in the study period arose from neuroendocrine cells. In addition, 51.79% of all malignant tumours of the small intestine, 29.63% of all carcinomas of the appendix and 8.70% of duodenal malignancies were of neuroendocrine origin. The incidence of malignant gastrointestinal NETs was 0.81 per 100 000 inhabitants, and the incidence of all reported malignancies in the digestive tract was 54.49 per 100 000 inhabitants.

Distant metastasis

A total of 110 (38.6%) of 285 tumours were classified as malignant using the WHO criteria. At the time of diagnosis, information on metastasis was available in 87 (79.1%) patients. Lymph node and distant metastases were documented in 65 (74.7%) of 87 patients. The majority of distant metastases were located in the liver ($n=35$: multiple 32, solitary 3), followed by the peritoneum ($n=11$), bone ($n=4$), lung ($n=2$), ovary ($n=2$) and brain ($n=1$). Extended lymph node and distant metastases were documented in 29 (33.3%) patients.

TNM staging based on ENETS definitions

ENETS TNM classification and staging was possible in 181 (63.5%) of 277 tumours. Localised disease (lymph node negative) was documented in 118 (65.2%) of 181 tumours, regional disease (lymph node positive) in 20 (11.0%) and distant disease in 43 (23.8%) tumours

respectively. Applying the ENETS criteria, 74 tumours (46.4%) were stage I, 43 (23.8%) were stage II, 21 (11.6%) were stage III and 43 (23.8%) were stage IV independent of their location. Details are summarised in Table 2.

Histopathological grading based on ENETS criteria

Sufficient data were available in 77 (46.8%) of 277 tumours. The majority (46; 59.7%) of the tumours were grade 1, 24 (31.2%) were grade 2 and 7 (9.1%) were grade 3. Of the seven tumours classified grade 3, one was located in the stomach, two in the pancreas, two in the colon and two in the rectum.

Discussion

This is the first study to analyse the incidence of GEP-NETs using a prospectively run database. During the 1-year period, 285 tumours were recorded, resulting in an overall annual age-adjusted incidence rate (world standardised) of digestive NETs being 2.39 per 100 000 inhabitants per year. The results of the study, in which all locations of the digestive tract were included, show a higher incidence of GEP-NETs than that in other studies analysing similar populations (Helland *et al.* 2006, Ito *et al.* 2010).

It may be assumed that nearly all newly diagnosed Austrian cases were recorded within the study period: 40 of 41 departments and institutes of clinical pathology, including four academic institutes, distributed throughout the country participated in the prospective study protocol, and 31 institutes reported tumours diagnosed within the study period. This enables the analysis to attain a high degree of completeness.

Table 2 European Neuroendocrine Tumour Society (ENETS) staging based on details of 181 of 277 (65.3%) patients

Stage	T	N	M	Stomach	Duodenum/ ampulla	Pancreas	Prox/dist jejunum/ileum	Appendix	Colon	Rectum	Σ
<i>n</i>				65	16	33	44	59	20	40	277
<i>n</i> ^a		0	0	35 (8 m)	7 (2 m)	29	31	48	10	21	181/277 (65.3%)
I	1	0	0	25 (71.4%)	3 (42.9%)	5 (17.2%)	2 (6.5%)	19 (39.6%)	1 (10%)	13 (61.9%)	74/181 (40.9%)
IA	1a ^b	0	0								
IB	1b ^c								2 (20%)	4 (19.0%)	43/181 (23.8%)
II	2	0	0	1 (2.9%)	2 (28.6%)	6 (20.7%)	1 (3.2%)	18 (37.5%)	0	1 (4.8%)	21/181 (11.6%)
IIB	3	0	0	2 (5.7%)	0	2 (6.9%)	2 (6.5%)	8 (16.7%)	0	0	
IIIA	4	0	0	0	0	0	0	1 (2.1%)	0	0	
IIIB	Any T	1	0	1 (2.9%)	0	3 (10.3%)	11 (35.5%)	1 (2.1%)	3 (30%)	1 (4.8%)	21/181 (11.6%)
IV	Any T	Any N	1	6 (17.1%)	2 (28.6%)	13 (44.8%)	15 (48.4%)	1 (2.1%)	4 (40%)	2 (9.5%)	43/181 (23.8%)

TX, primary tumour could not be assessed; T0, no evidence of primary tumour; Tis, *in situ* tumour/dysplasia (<0.5 cm) – stomach; For any T add (m) for multiple tumours. NX, regional lymph node status could not be assessed; N0, no regional lymph node metastasis; N1, regional lymph node metastasis. MX, distant metastasis could not be assessed; M0, no distant metastases; M1, distant metastasis.

^a*n* patients with ENETS TNM classification/staging (Rindi et al. 2006, 2007).
^bT1a: colon/rectum – tumour invades mucosa or submucosa. T1a size <1 cm.
^cT1b: colon/rectum – tumour invades mucosa or submucosa. T1b size 1–2 cm.

The number of patients diagnosed with GEP-NETs, on the basis of standardised histopathological criteria, and the incidence of these tumours are therefore representative for a central European country with a highly developed medical training and social framework.

Because of vague clinical presentation sometimes and low awareness among physicians, data in the literature on the real incidence of NETs are probably underestimates. Data comparisons in relation to the site of tumour origin are difficult to obtain because of the overall rarity of these neoplasms and their incomplete recognition and documentation in various national cancer registries (Gatta et al. 2006) and because of their variable and sometimes imprecise classification (Kloppel et al. 2009, Klimstra et al. 2010).

NETs were not well-defined entities before 2000 (Solcia et al. 2000), and national tumour databases offer population-based prospective documentation for malignant tumours only. The majority of these databases therefore underreport or even omit NETs classified as benign according to the WHO criteria (Newton et al. 1994, Crocetti et al. 1997) and usually correspond to grade 1 NETs according to the ENETS criteria (Rindi et al. 2006).

Recently, Hauso et al. (2008) and Yao et al. (2008) have reported a worldwide increasing incidence of NETs over the past three decades, suggesting that NETs are more prevalent than previously realised. These findings may partially reflect the more precise pathohistological definition of the neuroendocrine cells with the inclusion of those classified as benign in incidence studies. As shown in our study, NETs classified as benign are the largest group (46.0%). The higher incidence may also be associated with the incidental identification of small, asymptomatic lesions as the result of increased availability of endoscopic imaging of the upper and lower gastrointestinal tract and the broad use of early radiological imaging in addition to clinical examinations.

In discussion of the incidence of NETs, data from the SEER Program of the National Cancer Institute are usually cited (Modlin et al. 2003, Hauso et al. 2008, Yao et al. 2008). The SEER registries may underestimate the total number of patients with NETs in various locations because all cases from the SEER database are by definition denoted to be malignant. It is therefore likely that small tumours with benign appearance may not generally be included in the SEER registries. One also has to keep in mind that all studies, including the SEER database, lack a standardised histopathological protocol for diagnosis.

In analysis of the late SEER period (1992–1999), Modlin et al. (2003) presented incidence rates of 1.89

per 100 000 for White males and 1.59 per 100 000 for White females. Because of higher incidence rates in Black males and females, the number for the White population may be best compared to European population. More recently, Hauso *et al.* (2008) have compared the SEER NET data with the corresponding data of the Norwegian Registry of Cancer. The age-adjusted incidence rates extracted from 1993 to 2004 using the 2000 US standard population as reference for both databases calculated an incidence rate of 1.99 per 100 000 per year for Norway and of 2.3 for the USA (White subset of the SEER data; excluded lung/bronchus, urogenital tract, breast). The same calculation for Austria would show a higher incidence (2.99 per 100 000 per year; Fig. 3a) including all GEP-NETs independent of their presumed biological behaviour. This ‘statistical game’ underlines the importance of adjusting incidence calculations to the same (and representative) ‘reference population’.

Using the ‘World standard population’ as reference, Hemminki & Li (2001) calculated incidence rates of 1.6 per 100 000 for males and 1.9 per 100 000 for females (no data for pancreas, liver or biliary tract) for Sweden (1983–1998). The incidence rates for Canton Vaud in Switzerland (1986–1997) provided by Levi *et al.* (2000) are 2.05 per 100 000 for males and 2.17 per 100 000 for females (no data for pancreas, liver or biliary tract; Fig. 3b). The corresponding incidence data for Austria (World standard population; all gastroenteropancreatic sites) were 2.36 per 100 000 per year for females and 2.51 per 100 000 for males (Fig. 3b). In our prospective study, more males than females had GEP-NETs (1.08:1). This difference is more pronounced in the USA (1.2:1, Yao *et al.* 2008) and in Japan (2:1, Ito *et al.* 2010).

WHO classification: ENETS staging and grading

Using the WHO criteria (Solcia *et al.* 2000), 175 (61.4%) tumours were classified as well differentiated benign (131, 46.0%; WHO 1a) or uncertain (44, 15.4%; WHO 1b); a further 91 (31.9%) were well differentiated (WHO 2) and 19 (6.7%) poorly differentiated (WHO 3) neuroendocrine carcinoma.

Using the ENETS staging criteria (Rindi *et al.* 2006, 2007), 40.9% of tumours were stage I and 23.8% were stage II. ENETS stage III (IIIB) is defined as any T (except the location appendix), lymph node positive, but distant metastasis negative, and 11.0% fulfilled these criteria. In 23.8%, stage IV was diagnosed, meaning that distant metastases were diagnosed at the time of initial diagnosis.

Figure 3 (a) Incidence rates of gastroenteropancreatic neuroendocrine tumours (n/100 000 per year); age-adjusted using the 2000 US standard population comparing the recent data with Norway and the USA (Hauso *et al.* 2008). (b) Incidence rates of gastroenteropancreatic neuroendocrine tumours (n/100 000 per year); age-adjusted using the World standard population comparing the recent data with Sweden (Hemminki & Li 2001) and Switzerland (Levi *et al.* 2000).

To our knowledge, the report by Levi *et al.* (2000) is the only study distinguishing benign and malignant NETs on the basis of local infiltration and/or existence of metastasis: the incidence for benign NETs was 1.34 per 100 000 and that for malignant tumours was 0.72, the proportion of benign to malignant tumours being very similar to the data presented here (benign 1.15 per 100 000; uncertain 0.43; malignant 0.81).

Patients with malignant tumours were significantly older than patients with benign NETs, which raise the question of whether benign lesions transform into malignant tumours and therefore may be considered lesions with latent or low-grade malignancy. If this concept is accepted, the issue of early diagnosis and treatment becomes of critical clinical relevance.

In the present study, 1.49% of all malignant digestive tumours were classified as NETs. GEP-NETs are diagnosed less frequently than adenocarcinomas of the digestive tract. Among malignant tumours, GEP-NETs constitute <2% of all gastrointestinal malignancies (Maroun *et al.* 2006).

It has been widely discussed and long generally accepted that no histological grading system effectively predicts the behaviour of well differentiated endocrine tumours (Rindi *et al.* 2006). However, a grading system has been introduced by ENETS (Rindi *et al.* 2006, 2007) partly adopting the WHO criteria. In our study, G3 tumours were diagnosed only in the stomach, colon, rectum and pancreas.

Location

Stomach

The present study reveals the stomach as the preferential location (22.8% of all GEP-NETs) as suspected by Kloppel & Clemens (1996) and Kloppel *et al.* (2007). This is in contrast to other studies (Modlin *et al.* 2003, Maggard *et al.* 2004, Helland *et al.* 2006, Lombard-Bohas *et al.* 2009) describing NETs of the small intestine most frequently. Reviewing clinical single-centre studies, gastric NETs are recorded as 3.1–13.8% (Li *et al.* 2008). NETs of the stomach comprise 4.1% of all gastrointestinal NETs in the late SEER (Modlin *et al.* 2003) and 8% in the population-based study from western Norway (Helland *et al.* 2006). An explanation for the increase may be the large number and liberal use of endoscopic diagnostic procedures, with biopsies routinely taken from all, even small, gastric lesions.

By definition (Kloppel *et al.* 2004), 67.7% of the gastric lesions in our study were classified as NETs with benign behaviour, 12.3% as uncertain and 20.0% as malignant. The incidence of malignant NETs in the stomach was low, calculated as 0.08 per 100 000. In contrast to other studies (Rindi *et al.* 1996), a higher proportion of benign tumours in women with stomach NETs was not documented in our study.

Duodenum/small intestine

Even when small intestine (15.4%) and duodenal (5.6%) NETs are added together (21.0%), the stomach remains the most frequent location in our

study. Previously, duodenal NETs accounted for 3.8% of all gastrointestinal NETs and were integrated in the group of small bowel NETs in older series (total 25.2%; Modlin *et al.* 2003). It appears unjustified to sum NETs of the small intestine and duodenum since our data document that small intestine NETs are predominantly malignant (86.4%) and duodenal NETs are more often benign (62.5%). The incidence of malignant NETs in the duodenum was very low at 0.02 per 100 000, whereas the incidence of malignant NETs in the ileum/jejunum was 0.29 per 100 000.

Pancreas

In our study, the overall annual incidence of PNETs was 0.25 per 100 000, subdividing into benign, uncertain and malignant at 0.02, 0.04 and 0.19 per 100 000 respectively. The annual incidence of PNETs was reviewed recently and was described as <0.4 cases per 100 000 (Halfdanarson *et al.* 2008), accounting for only 1–3% of all pancreatic neoplasms.

Appendix

Patients with appendiceal NETs were significantly younger (median 38.0 years) than patients with tumours in all other sites: children and adults ≤20 years may be affected, as found in 5 (8.9%) of 56 patients. One may speculate that appendiceal NETs are diagnosed incidentally during appendectomy because appendicitis is diagnosed more often in younger patients. Overall appendiceal NETs accounted for 20.7% of all gastrointestinal NETs, the majority (62.7%) being classified as benign, 27.1% as uncertain and 10.2% as malignant. The incidence of malignant NETs in this location was 0.08 per 100 000 population. Although the frequency of appendiceal NETs has decreased over time (Modlin *et al.* 2003), NETs are the most frequent type of tumour in the appendix and can be expected in 1 of 200 appendectomies (Godwin 1975). They rarely reach clinical significance.

Colon and rectum

In the analysis by Modlin & Sandor (1997) and Modlin *et al.* (2003), 1481 (21.2%) of 6996 digestive NETs were localised in the rectum, comprising 1–2% of all rectal tumours, and 938 (21.2%) were in the colon. In the current study, 40 (14%) of 285 GEP-NETs were located in the rectum and 20 (7%) in the colon. Although the majority of those in the rectum were classified as benign (26 of 40, 65%), the incidence of malignant rectal NETs being only 0.03 per 100 000

population, 14 (70%) of 20 colonic NETs were classified as neuroendocrine carcinoma (well differentiated 10, 71%; poorly differentiated 4, 29%; 0.13 per 100 000).

Conclusion

Standard cancer registries do not reflect the real incidence because benign tumours are omitted from many national registries. Using strict pathohistological/immunohistochemical criteria, the incidence of benign and malignant gastrointestinal NETs has been demonstrated for the first time in a middle European country. As presumed, NETs are most frequently located in the stomach followed by the sites appendix, small intestine, rectum, pancreas and colon. Subdividing them into groups as recommended by the WHO, 46% of NETs were classified as ‘benign’, 15% as showing ‘uncertain’ biological behaviour and 39% as showing ‘malignant’ behaviour. Using the ENETS TNM classification, a minority of gastrointestinal NETs were classified as stage IIIB (N positive 11.0%; regional disease) and stage IV (N and/or M positive 23.8%; distant disease) at the time of diagnosis. In the ENETS grading system, the majority of NETs were G1 (59.7%) and G2 (31.2%) independent of their staging. G3 tumours are very rare (9.1%).

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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