GEP-NET : rare tumour connections. Pathophysiological aspects of gastroenteropancreatic neuroendocrine tumours

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Chapter 3

Pathological Incidence of Duodenopancreatic Neuroendocrine Tumours in the Netherlands: a Pathologisch Anatomisch Landelijk Geautomatiseerd Archief study

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Abstract

Duodeno-pancreatic neuroendocrine tumours are rare, although current epidemiological studies worldwide suggest an incidence increase. We assessed the pathological incidence of duodeno-pancreatic neuroendocrine tumours over 18 years in The Netherlands.

Standardized excerpts from pathology reports of all patients diagnosed with duodeno-pancreatic neuroendocrine tumours from 1991 until 2009 were collected from PALGA and reviewed. This nationwide network and registry of histo- and cytopathology covers 100% of the pathology reports in The Netherlands.

We identified 905 patients with pancreatic (n=692) or duodenal (n=213) neuroendocrine tumours. The majority of these patients (69.4%) had a non-functional tumour. Functional tumours were diagnosed at a younger age compared to non-functional tumours (mean age ± s.d. 52.3 ± 17.7 years versus 60.0 ± 14.6 years, respectively, $P<0.01$). The average annual incidence per 1,000,000 persons over 1991 to 2009 was 2.54 for pancreatic and 0.81 for duodenal neuroendocrine tumours. The highest incidence was found in patients 65 to 79 years of age. The incidence of non-functional neuroendocrine tumours had increased significantly over two decades, $P<0.01$.

The incidence of duodeno-pancreatic non-functional neuroendocrine tumours in The Netherlands increased over 1991 to 2009. The etiology for this change includes improved diagnostic techniques and clinical awareness, as discussed.

Introduction

Duodeno-pancreatic neuroendocrine tumours comprise a very heterogeneous group of neoplasms, with regard to morphologic, functional and behavioral features[1]. In 2000, the World Health Organization (WHO) introduced a classification for neuroendocrine tumours (NETs) of the gastroenteropancreatic tract using histopathological characteristics and tumour behaviour to categorize these tumours per site[2]. Duodeno-pancreatic NETs are referred to as functional (or functioning) in case of the presence of a clinical syndrome resulting from ectopic hormone production, e.g., gastrin, insulin, glucagon, vasoactive intestinal peptide (VIP) or somatostatin, by the tumour, whereas non-functional NETs are not associated with a hormonal syndrome. Although these latter tumours may secrete biologic substances, like pancreatic polypeptide (PP) and chromogranin A, non-functional NETs can remain clinically silent for a relatively long time, and are only detected when morbidity is caused by tumour mass leading to biliary duct obstruction, bowel obstruction, and development of metastases or invasion into adjacent organs[3,4]. Duodeno-pancreatic NETs may be sporadic or component of the more comprehensive Multiple Endocrine Neoplasia type 1 syndrome (MEN-1), of which hyperparathyroidism and pituitary tumours are other frequent manifestations[5]. Although duodeno-pancreatic NETs have been considered as rare tumours, incidence rates have been reported to be increased substantially over the past years[6-8]. Furthermore, a high number of incidental findings of clinically silent duodeno-pancreatic NETs by autopsy studies was suggested[9,10]. Therefore, current incidence rates of duodeno-pancreatic NETs are likely to represent an underestimation. In the present study we aimed to provide insights into the epidemiology of both pancreatic and duodenal NETs in The Netherlands over a period of approximately 20 years. Therefore, we have carried out a search in the nation-wide network and registry of histo- and cytopathology in The Netherlands, abbreviated as PALGA, which is a central database for all pathology reports in our country[11].

Materials and Methods

Collection of data by PALGA

Data were collected from PALGA, the nationwide network and registry of histo- and cytopathology in The Netherlands[11]. This computerized database for pathology reports was founded in 1971, and since the participation of all pathology laboratories in 1991, national coverage was achieved. Currently, the PALGA databank contains about 50.5 million excerpts on nearly 11 million patients, with an annual addition of more than two million excerpts. A decentralized computer system collects the pathology reports from every pathology institution in The Netherlands automatically, and reports are sent to the central database on a daily basis. Reports are converted to excerpts that contain a limited number of encrypted patient data, a report identifier, (part of) the conclusions and the so called PALGA diagnosis, a coded diagnosis line based upon standard pathology terminology, containing topography (localization), morphology (nature of tissue change), etiology, function (functional abnormality), procedure and diseases. Encryption of the identifiers secures the patient's and participating laboratory's privacy.

Our search was directed to patients filed with a histological proven diagnosis of a neuroendocrine tumour in pancreas or duodenum between January 1991 and December 2008. For each excerpt, gender, date of pathology intervention, conclusion first sentences and diagnosis line were made available for retrospective analysis. Terms used for this search query were 'gastrinoma', 'insulinoma', 'glucagonoma', 'APUDoma', 'neuroendocrine tumour of digestive tract' and 'pancreas' or 'pancreatic islets' and 'duodenum' in combination with 'malignant endocrine tumour'. A query to identify patients with the MEN-1 syndrome, including hyperparathyroidism, was additionally performed under these patients.

Excerpts described several pathologic interventions, e.g., biopsies, punctures, resections autopsies or revisions of a pathologic report. Some patients had multiple excerpts included in the database, but were analyzed as one patient.

Histological proof of tumour diagnosis

The routine procedure for neuroendocrine tumours at pathology starts with the identification of the epithelial and neuroendocrine nature of the tumour by immunohistochemical staining, with markers like keratin, chromogranin A, grimelius, synaptophysin, etc. Based on the presence of clinical symptoms or syndrome, hormonal production by the tumour is evaluated, to exactly reveal the tumour type (i.e., gastrinoma, insulinoma, etc.). As a consequence, tumours are classified on immunopostivity for hormonal markers and clinical symptoms or syndrome as specific tumour type.

Incidence calculations

The incidence rates were calculated as the number of new cases per 1,000,000 persons, adjusted to general population data as obtained by the Dutch Central Bureau for Statistics (CBS)[12]. Data that were drawn from the CBS included age and sex of the total number of residents in The Netherlands per year, annual mortality rates and number of deaths caused by pancreatic malignancies. Age distribution in Table 2 was chosen referring to the distribution of the CBS, i.e., <20 years, 20-39 years, 40-64 years, 65-79 years and >80 years. The 'not reported' data refer to the use of excerpts, whereas complete pathology reports were not assessed because of privacy reasons. During the last three decades, the Leiden University Medical Centre has been the nationwide referral centre for patients with gastrinomas in The Netherlands. All patients diagnosed with or suspected of a gastrinoma, treated in our hospital, were traced and revised, to assess the extent of incidence underestimation based on pathology reports.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences version 16 (SPSS) and GraphPad version 5. Results were reported as mean ± standard deviation (s.d.) or median, when appropriate. Using linear regression analysis, trends in annual incidence rates over the study period of 18 years were analyzed. A p-value of <0.05 was considered statistically significant.

Results

Patient characteristics

As a result of the search query, 1529 excerpts of 1263 patients were found between 1991 and 2009. Patients with extrapancreatic or extraduodenal tumours were excluded, so that the final study cohort consisted of 692 patients with a pancreatic neuroendocrine tumour (PNET) and 213 patients with a duodenal neuroendocrine tumour (DNET) (Table 1).

Table 1. Patient characteristics

	Pancreatic NETs	**Duodenal NETs**
Age	**Mean ± s.d. (range)**	**Mean ± s.d. (range)**
All tumours	56.3 ± 16.3 (0-94)	62.1 ± 14.1 (25-91)
Functional tumours	52.59 ± 18.1 (0-98)	51.6 ± 10.3 (38-73)
Non-functional tumours	58.6 ± 14.7 (15-94)	63.1 ± 14.1 (25-91)
Sex	**n (%)**	**n (%)**
Male	322 (46.5%)	114 (53.5%)
Female	370 (53.5%)	99 (46.5%)
Tumour type	**n (%)**	**n (%)**
Non-functional	433 (62.6%)	195 (91.5%)
Functional	259 (37.4%)	18 (8.5%)
Insulinoma	202 (78.0%)	0
Gastrinoma	21 (8.1%)	16 (88.9%)
Glucagonoma	23 (8.9%)	0
VIPoma	6 (2.3%)	0
Somatostatinoma	3 (1.2%)	2 (11.1%)
Mixed	4 (1.5%)	0

Table 1. Characteristics of 692 patients with pancreatic neuroendocrine tumours and 213 patients with duodenal neuroendocrine tumours in the PALGA database from 1991 to 2009.

For PNETs, there was a slight female predominance, while DNETs showed a higher percentage of males. The majority of both PNETs and DNETs were non-functional tumours (Table 1). Functional PNETs comprised predominantly insulinomas (59.9% female), DNETs were mainly gastrinomas (62.5% male).

Patients with PNETs were significantly younger than patients with DNETs, $P<0.01$. This difference was largely caused by the younger age of patients with pancreatic compared to duodenal non-functional NETs, $P<0.01$. Patients with functional PNETs and DNETs were significantly younger at time of the pathologic evaluation compared to patients with non-functional PNETs and DNETs, $P<0.01$ and $P<0.01$, respectively (Table 1). Taking all PNETs and DNETs together, functional NETs were diagnosed at a younger age compared to non-functional NETs, 52.3 ± 17.7 vs 60.0 ± 14.6 years, respectively, $P<0.01$.

The MEN-1 syndrome was present in 10 patients with functional (two pancreatic glucagonomas, two insulinomas, one gastrinoma and one mixed glucagonoma/insulinoma, four duodenal gastrinomas) and 11 patients with non-functional NETs (10 pancreas, one duodenum).

Incidence rates

Using census statistics obtained from the Dutch Central Bureau of Statistics, the annual incidence rates per 1,000,000 population for PNETs and DNETs were calculated (Figures 1 and 2). The average annual incidence of PNETs per 1,000,000 from 1991 to 2009 was 2.54. The total incidence of PNETs increased over the years (slope 0.12 with a 95% c.i. of 0.07 to 0.18, $P<0.01$). Non-functional PNETs showed a higher incidence compared to functional tumours. The incidence increased with advancing age at time of the pathology diagnosis. The highest incidence of PNETs was found in patients from 65-79 years (Table 2). Remarkably, the incidence in patients under 40 years of age was higher for functional PNETs compared to non-functional tumours. We found a statistically significant increase in incidence of non-functional PNETs over two decades (slope 0.14 with a 95% c.i. of 0.09 to 0.19, $P<0.01$). In contrast, functional PNETs showed a slight but significant decrease in incidence over the study period (-0.01 with a 95% c.i. of -0.03 to -0.00, $P=0.05$). In the study period from 1991 to 2009, a total of 33,459 patients with malignant tumours in the pancreas were reported in the Dutch population. Crude incidences of functional and non-functional PNETs were therefore 0.008 and 0.013, respectively.

Figure 1. Incidence rates of pancreas neuroendocrine tumours from 1991-2008 in the Netherlands

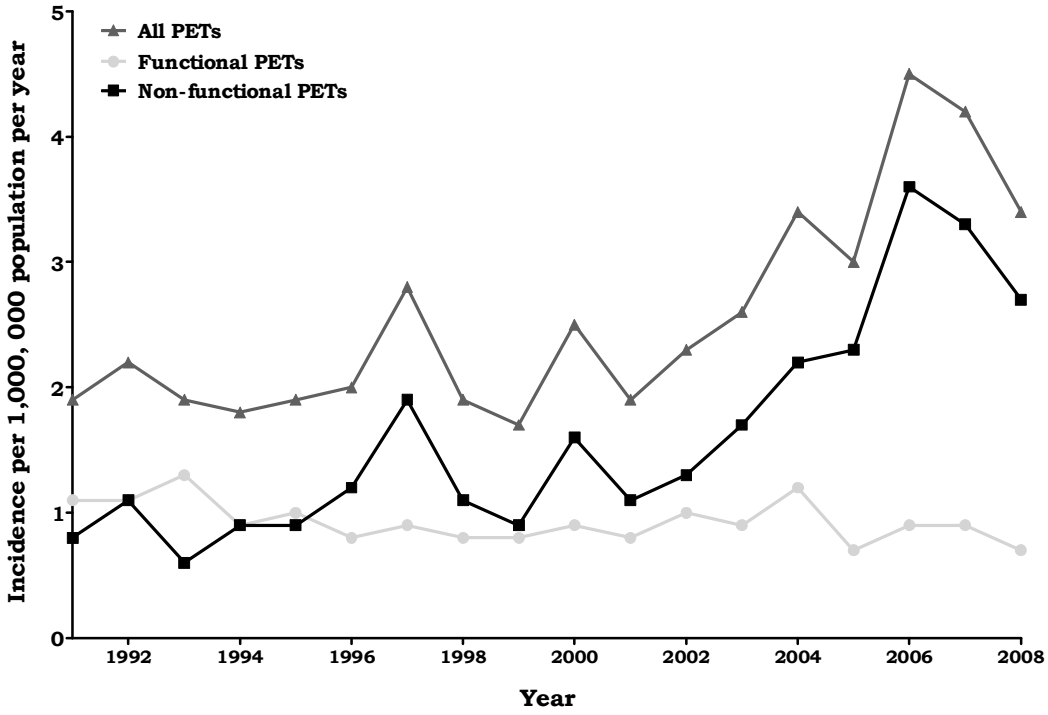

Figure 1. Annual incidence rates of pancreatic neuroendocrine tumours per 1,000,000 persons in The Netherlands from 1991 to 2009.

The average annual incidence of duodenal NETs per 1,000,000 from 1991 to 2009 was 0.81. The total incidence of these DNETs showed a similar pattern to PNETs, namely an increase over the years from 1991 to 2009 (slope 0.05 with a 95% c.i. of 0.02 to 0.07, *P*=0.003), which was mainly due to a significant increase in incidence of the non-functional duodenum NETs (slope 0.04 with a 95% c.i. of 0.02 to 0.07, *P*=0.001) while the incidence of functional tumours remained relatively stable (slope 0.00 with a 95% c.i. of -0.00 to 0.02, *P*=0.40).

Figure 2. Incidence rates of duodenal neuroendocrine tumours from 1991 - 2008 in the Netherlands

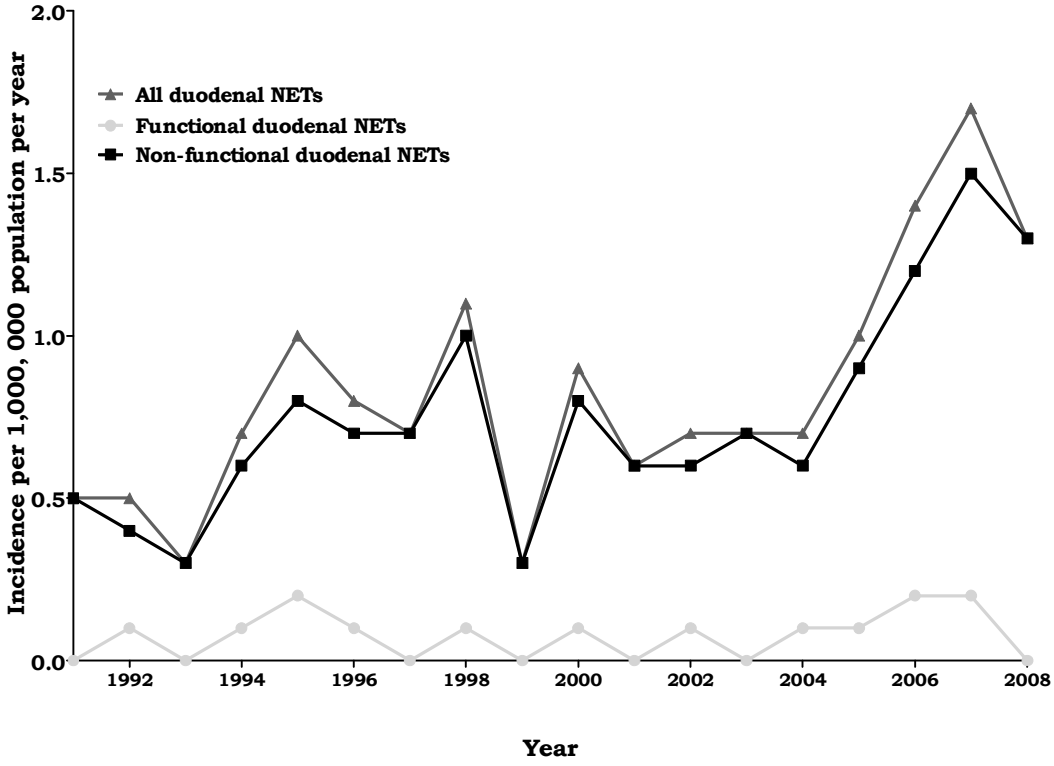

Figure 2. Annual incidence rates of duodenal neuroendocrine tumours per 1,000,000 persons in The Netherlands from 1991 to 2009.

The highest incidence of duodenal tumours was also seen in the patient group of 65-79 years of age (Table 2).

Table 2. Incidence rates

Age	All tumours			Functional tumours			Non-functional tumours		
	P	D	T	P	D	T	P	D	T
<20 yrs	0.2	0.0	0.2	0.1	0.0	0.1	0.1	0.0	0.1
20-39 yrs	1.0	0.1	1.1	0.6	0.0	0.6	0.4	0.1	0.5
40-64 yrs	4.0	1.2	5.2	1.4	0.2	1.6	2.6	1.0	3.6
65-79 yrs	6.1	2.5	8.7	2.0	0.1	2.1	4.2	2.4	6.6
>80 yrs	4.7	2.4	7.1	1.5	0.0	1.5	3.2	2.4	5.6

Table 2. Incidence of pancreatic and duodenal neuroendocrine tumours per 1,000,000 persons by age at time of pathologic intervention form 1991 to 2009. P=pancreas, D=duodenum, T=total.

When pancreatic and duodenal tumours were analyzed together, a similar trend in incidence rates was seen; the incidence of non-functional tumours increased significantly (slope 0.18 with a 95% c.i. of 0.11 to 0.24, $P<0.01$) while the incidence of functional tumours slightly decreased over time (slope -0.01 with a 95% c.i. of -0.03 to -0.01, $P=0.16$).

Furthermore, 124 autopsy reports of 35 patients with functional PNETs, 75 non-functional PNETs and 14 non-functional DNETs were included. Mean age at time of death did not differ between functional PNETs (67.4 ± 14.5 years), non-functional PNETs (67.0 ± 15.0 years) and non-functional DNETs (69.4 ± 11.8 years). Patients were all younger than the mean age at death of the general population of The Netherlands (males 72.0 ± 0.8 years and females 78.2 ± 0.6 years) over the period from 1991 to 2009. When patients who where found to have a NET by incidence at autopsy were excluded from the analysis, the average annual incidence numbers were 2.17 for PNETs and 0.76 for DNETs, respectively. Furthermore, incidence numbers were still significantly increasing over the period from 1991 to 2009 (slope 0.13 with a 95% c.i. of 0.08 to 0.17, $P<0.01$ for PNETs and slope 0.04 with a 95% c.i. of 0.01 to 0.07, $P<0.01$ for DNETs).

Tumour characteristics

Tumour characteristics are presented in Table 3. 37.8% of PNETs and 66.7% of duodenal NETs were <2 cm in diameter. All duodenal NETs were <5 cm, but only 78.4% of the PNETs were of that size. 6.2% of the pancreatic tumours had a size of >10 cm in diameter. Tumours were <2 cm, <5 cm or >10 cm in 65.2%, 91.1% and 3.6% cases of functional PNETs and in 25.5%, 72.1% and 7.3% cases of non-functional PNETs, respectively. Tumour size of non-functional PNETs (mean 3.9 ± 3.2 cm) was significantly larger compared to tumour size of patients with functional PNETs (mean 2.3 ± 2.5 cm), $P<0.01$. Non-functional DNETs had an average size of 1.6 ± 1.2 cm, while functional DNETs were on average 0.7 ± 0.5 cm, $P=0.10$. Non-functional PNETs had a larger tumour size compared to non-functional DNETs, $P<0.01$, and functional PNETs were also significantly larger compared to functional DNETs, $P<0.01$. Mainly lymph node metastases were

present in both PNETs and DNETs. The majority of tumours were described as well-differentiated. PNETs were mainly high grade malignant, while DNETs were most often reported as low grade malignant tumours. Angioinvasion was present in the majority of tumours.

Table 3. Tumour characteristics of pancreatic and duodenal neuroendocrine tumours.

Table 3. Tumour characteristics		
Tumour characteristic	**Pancreatic NETs**	**Duodenal NETs**
Tumour size	**n (%)**	**n (%)**
Reported	*259 (37.4%)*	*39 (18.3%)*
<1 cm	20 (7.7%)	16 (41.0%)
1-<2 cm	78 (30.1%)	10 (25.6%)
2-<3 cm	50 (19.3%)	6 (15.4%)
3-<4 cm	36 (13.9%)	5 (12.8%)
4-<5 cm	19 (7.3%)	2 (5.1%)
5-<10 cm	40 (15.4%)	0
>10 cm	16 (6.2%)	0
Not reported	*433 (62.5%)*	*174 (81.7%)*
Metastases	**n (%)**	**n (%)**
Reported	*239 (34.5%)*	*44 (20.7%)*
Lymph node	68 (28.5%)	24 (54.5%)
Liver	46 (19.2%)	8 (18.2%)
Lymph node and liver	12 (5.0%)	1 (2.3%)
Multiple or other	28 (11.7%)	0
No metastases	85 (35.6%)	11 (25.0%)
Not reported	*453 (65.5%)*	*169 (79.3%)*
Differentiation	**n (%)**	**n (%)**
Reported	*103 (14.9%)*	*31 (14.6%)*
Well-differentiated	83 (80.6%)	17 (54.8%)
Intermediate differentiated	17 (16.5%)	7 (22.6%)
Poorly-differentiated	3 (2.9%)	7 (22.6%)
Not reported	*589 (85.1%)*	*182 (85.4%)*

Grade	**n (%)**	**n (%)**
Reported	*120 (17.3%)*	*23 (10.8%)*
Benign	23 (19.2%)	1 (4.3%)
Low grade malignant	19 (15.8%)	10 (43.5%)
High grade malignant	64 (53.3%)	8 (34.8%)
Uncertain behaviour	14 (11.7%)	4 (17.4%)
Not reported	*572 (82.7%)*	*190 (89.2%)*
Angioinvasion	**n (%)**	**n (%)**
Reported	*111 (16.0%)*	*10 (4.7%)*
Yes	78 (70.3%)	9 (90%)
No	33 (29.7%)	1 (10%)
Not reported	*581 (83.9%)*	*203 (95.3%)*

The majority of PNETs was located in the pancreatic tail. Compared to non-functional PNETs, more functional PNETs were located in the pancreatic tail, but less in the pancreatic head (Table 4).

Table 4. Detailed information on the location of the pancreatic tumour

Pancreas location	**All tumours** **n (%)**	**Functional tumours** **n (%)**	**Non-functional tumours** **n (%)**
Reported	*312 (45.1%)*	*112 (43.2%)*	*200 (46.2%)*
Caput	105 (33.6%)	26 (23.2%)	79 (39.5%)
Corpus	19 (6.1%)	6 (5.4%)	13 (6.5%)
Cauda	164 (52.6%)	70 (62.5%)	94 (47.0%)
Overlapping	24 (7.7%)	10 (8.9%)	14 (7.0%)
Not reported	*380 (54.9%)*	*147 (56.8%)*	*233 (53.8%)*

Table 4. Detailed information on the location of the tumour in the pancreas

Clinical assessment of incidence calculations

To get an idea about the potential underestimation of the incidence calculation by this study using histocytopathological information from the PALGA database, we also assessed from our own referral centre what percentage of patients clinically suspected of or diagnosed with a gastrinoma in pancreas or duodenum, were

scored as a gastrinoma by the pathologists as well. We found that only 45.7% (16/35) of our clinical gastrinoma patients were scored accordingly by pathologists, whereas 28.6% (10/35) of the patients were scored otherwise, i.e., as undefined neuroendocrine tumour. 25.7% (9/35) of the patients had not undergone any surgery and/or other pathological evaluation for their tumour and were therefore not traceable in the PALGA database. One patient was not diagnosed in the clinical setting, but was found to have a gastrinoma by incidence at autopsy.

Discussion

Duodeno-pancreatic NETs are considered to be rare neoplasms with a relatively slow-growing nature[13]. Because of the common embryonic origin it is attractive to study both locations in one study. Although the majority of these tumours are malignant, they can remain indolent and undetected for a long period of time, leading to substantial delays in diagnosing. Specifically non-functional tumour patients often present with metastases and more advanced disease[4].

The present study describes the incidence rates of both pancreatic and duodenal NETs from 1991 to 2009 in The Netherlands. This study is not only the first to examine epidemiological features of NETs in The Netherlands, it is also unique in the analysis of the incidence of duodenal tumours.

In the evaluation period from 1991 until 2009, 905 patients with pancreatic and duodenal NETs were registered in PALGA. The majority was described as non-functional NETs, 69.4%. Similar to Fitzgerald *et al.* we found an increase in incidence over time for non-functional pancreatic and duodenal NETs[7]. We concur with their postulation that this increase is likely to be due to increased use and improved techniques of diagnostic modalities. Moreover, the WHO classification for neuroendocrine tumours of the gastroenteropancreatic tract, which was introduced in 2000[2], has most likely contributed as well. We assume that introduction of this classification not only resulted in more intelligibility for the nomenclature and categorization of GEP-NETs, but also raised the awareness for

the existence of these tumours. As feasible in Figures 1 and 2, incidence lines increased remarkably after 2000.

Furthermore, Fitzgerald *et al.* found that the incidence of functional PNETs over their study period of 16 years remained stable[7]. We found that the incidence of these tumours slightly decreased from 1991 to 2009. As a result of the hormonal secretion of this tumour type, functional NETs might be suspected and detected due to the clinical symptoms in these patients. The role of improved imaging techniques in the diagnosis of these tumours is only marginal, if any. In contrast, non-functional NETs are often only discovered at an advanced tumour stage, corresponding with the relatively older age of these patients at the first (pathological) diagnosis and the larger size of these tumours, compared to functional tumours, as suggested previously and confirmed in the present study[6-8]. Together, these findings imply that the increase in incidence numbers is most likely to represent an increase in detection, rather than a raise in occurrence of these tumours. The fact that in several autopsy studies neuroendocrine tumours are found by coincidence, confirms this implication[9-10]. We found that among the patients with duodeno-pancreatic NETs included in this study on autopsy reports, the majority of patients (117/124) were not included in the PALGA database for any pathologic evaluation related to a neuroendocrine disease. This suggests that in 12.9% patients (117/905) the pancreatic or duodenal neuroendocrine tumour might be an incidental finding at autopsy, not detected earlier during life. Furthermore, analysis of autopsy reports revealed that, unsurprisingly, patients with PNETs and DNETs die at a younger age, compared to the general Dutch population. However, no difference in age at time of death was found between functional and non-functional NETs.

We found that most PNETs were located in the pancreatic tail (52.6%), followed by the pancreatic head (33.6%), which is in contrast to others, who found the pancreatic head as preferred location of PNETs[14-16].

It is noteworthy to emphasize that we intentionally did not include any data on survival of the patients. Most studies which do report survival figures are based on information from the Surveillance, Epidemiology and End Results (SEER)

database, which collects cancer incidence and survival of the US population and includes data on clinical and pathology information on tumours. However, we have chosen to estimate incidence rates based on pathology data, because of several reasons. Firstly, The Netherlands Cancer Registry, which is comparable to the SEER database, does not include detailed data on (the type of) pancreatic and/or duodenal neuroendocrine tumours. Secondly, this cancer registry is partially based and dependent on information of the PALGA database. Furthermore, in the present study both benign and malignant neuroendocrine tumours were included, while in most other studies, based on information from the SEER database, only malignant tumours were covered. Therefore, we suffice with the estimation of epidemiological numbers, although a survival study might be an interesting future option.

Indeed, we are aware of the fact that the incidence rates calculated in our study might be an underestimation, as an unknown number of patients without pathology/surgical interventions were not retrievable in the PALGA database and therefore not included in our study. We assume that this mainly concerns functional NETs, as these tumours cause clinical symptoms, in contrast to non-functional tumours. From our own experience, we know that for example patients with gastrinomas can do well on medication and surgical intervention in these patients is not always necessary[17]. In the past three decades, our hospital has been the nationwide referral centre for gastrinomas in The Netherlands. Therefore, we approached the possible underestimation of incidence by exploring what percentage of patients with clinically detected gastrinomas was retrievable in the PALGA database. We found that 73.6% of the patients were present in PALGA, although only 45.7% was actually scored as a 'gastrinoma' by the pathologists. Thus the underestimation of PNETs and DNETs may be between 25% and 50%.

We further recognize that the pathological diagnosis of pancreatic or duodenal NETs is not always necessarily in agreement with the clinical symptoms of the patients. This was already noticed by Chetty[18]. As Mansour *et al.* illustrated using gastrinomas, a general pathological differentiation between different types of functional NETs is more based on the clinical background, as also

immunohistochemical staining does not often lead to conclusive evidence[19]. Therefore, we think that the combination of both clinical data and pathological findings is needed to establish the correct diagnosis in patients with NETs.

It is worth to iterate that our study is based on pathological reports, and therefore the incidence rates are most likely lower than the actual incidence when these would also be based on clinical records. However, the study period was depicted from 1991 to 2009, to warrant a 100% national coverage of all the pathologic institutions in The Netherlands by the PALGA database.

In conclusion, we explored the pathological incidence of duodeno-pancreatic NETs in The Netherlands, and found that the incidence of non-functional NETs has increased over the past two decades. However, although this effect may be due to the improvement of diagnostic tools in the clinical field, these tumours are still detected at a relatively late stage illustrated by the larger size and a diagnosis at an older age than in those patients affected by functional neuroendocrine tumours.

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