Occurrence of second primary malignancies in patients with neuroendocrine tumors of the digestive tract and pancreas (GEP-NET)

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Abstract

An increased association between neuroendocrine tumors of the gastro-intestinal tract and pancreas (GEP-NET) and other second primary malignancies has been suggested. We determined whether there is indeed an increased risk for second primary malignancies in GEP-NET patients as compared to an age- and sex matched control group of patients with identical malignancies. The series comprised 243 men and 216 women, diagnosed with a GEP-NET between 2000 and 2009 in a tertiary referral centre. The timeline, before-at-after diagnosis, and type of other malignancies were studied using person-year methodology. Poisson distributions were used for testing of statistical significance. All data were crosschecked with the national cancer registry. Out of 459 patients with GEP-NET, 63 (13.7%) had a second primary cancer diagnosis: 25 previous cancers (5.4%), 13 synchronous cancers (2.8%) and 29 metachronous cancers (6.3%). The most common types of second primary cancer were breast cancer (n=10), colorectal cancer (n=8), melanoma (n=6) and prostate cancer (n=5). The number of patients with a cancer history was lower than expected, although not significant (n=25 versus n=34.5). The diagnosis of synchronous cancers, mainly colorectal tumors, was higher than expected (n=13 versus n=6.1, p<0.05). Metachronous tumors occurred as frequent as expected (n=29 versus n=25.2, NS). In conclusion, our results are in contrast with previous studies and demonstrate that only the occurrence of synchronous second primary malignancies, mainly colorectal cancers, is increased in GEP-NET patients as compared to the general population.
Introduction

Neuroendocrine tumors (NETs) are a heterogeneous group of tumors with various clinical manifestations and biological behavior (Modlin et al. 2008). The primary localizations of the majority of metastatic NETs are the gastrointestinal (GE), bronchopulmonary (BP) tracts and pancreas (P). In addition, these tumors can also be found in other more rare primary localizations like: ovaries, liver and kidneys. NETs that originate from cells of the diffuse neuroendocrine system of the GI tract and the pancreas, gastroenteropancreatic NETs (GEP-NETs) are considered relatively rare tumors. However, more recent studies on NET epidemiology demonstrate an increasing GEP-NET incidence and prevalence over the past 30 years. According to the United States Surveillance Epidemiology and End Results (SEER) database and several other European databases, current estimates of GEP-NET incidence vary between 2.5 and 5 cases per 100,000 population (Yao et al. 2007, Yao et al. 2008, Halfdanarson et al. 2008a, Halfdanarson et al. 2008b, Niederle et al. 2010, Lawrence et al. 2011). It is not yet evident whether this is a true increase in NET incidence, or the result of increased use of diagnostic procedures, or a combination of both.

Previous published studies have reported an association between GEP-NETs and second primary malignancies (Gerstle et al. 1995, Schneider et al. 1995, Habal et al. 2000). Unfortunately these studies were either small case series or autopsy studies (Gerstle, Kauffman, Jr., & Koltun 1995, Schneider, Wittekind, & Kockerling 1995, Habal, Sims, & Bilchik 2000). Most studies also did not differentiate between previous, synchronous and metachronous lesions. The absence of age- and sex correlations between the investigated populations and national cancer registries are also major
drawbacks in the reported series. Etiologic explanations ranged from incidental
discovery to stimulation of cancer growth by neuroendocrine factors.

The aim of the present study was to determine whether there was indeed a true
increased risk for a second primary malignancy in a GEP-NET patient group as
compared to an age- and sex matched control group of patients with identical
malignancies.

Patients and Methods

Patients

Patients with GEP-NETs were identified from the Erasmus MC NET database.
Patients diagnosed with the multiple endocrine neoplasia type 1 (MEN-I) syndrome
were excluded from the study. The medical histories of 459 (non-MEN-I) patients with
GEP-NET, evaluated between 2000 and 2009 in the Erasmus MC, Rotterdam, the
Netherlands, were reviewed. All GEP-NET patients treated in the Erasmus MC, Rotterdam (as described in the present manuscript) gave written informed consent
before inclusion in the studies, which were approved by the Medical Ethics
Committee of the Erasmus MC, Rotterdam. Data were collected from medical
records and cross-checked with the Dutch National Cancer Registry. The diagnosis
of associated second primary malignancies was made by chart review - including
pathology reports -, the medical history, physical examination of the patient, clinical
notes and the correspondence of the referring physician, documenting and cross-
checking the previous diagnosis of malignancy.

Associated malignancies were assigned as “previous” (diagnosed > 6 months before
GEPNET diagnosis), “synchronous” (diagnosed within 6 months before or after
GEPNET diagnosis) or “metachronous” second primary malignancies (diagnosed > 6 months after GEPNET diagnosis).

Non-invasive, benign tumors (adenomas), carcinoma *in situ* of the cervix and non-melanoma tumors of the skin (basaliomas & basal cell cancers) were excluded from this study.

**Statistical methods**

The expected number of second primary malignancies was calculated with age- and gender-specific reference tables, using actuarial calculations (Breslow & Day 1987). Confidence intervals were constructed using Poisson tables for the observed number of malignancies.

For previous cancers, the age- and gender-specific distribution of the NET cohort was multiplied with a prevalence table, derived from the Dutch National Cancer Registry. The prevalence table describes the proportion of patients living with a previous diagnosis of cancer at a given age and stratified by gender.

For synchronous tumors, person-years at risk were calculated in a similar fashion up to 6 months after diagnosis, and then multiplied by two. The expected number of tumors was obtained by multiplying these person-years at risk with corresponding age- and gender-specific incidence rates for the Dutch population, derived from the Dutch National Cancer Registry.

For metachronous tumors, person-years at risk were calculated from 6 months after the date of diagnosis of the first GEP-NET until the censored date of metachronous cancer, date of death or end of follow-up (01-01-2010). For the total number of previous, synchronous and metachronous tumors, differences between observed and expected numbers were tested for significance using Poisson tables. To avoid post-
hoc bias, subgroup analyses were only performed for the most prevalent previous, synchronous or metachronous second primary malignancies (n>3 per group).

Results

From 2000 to 2009, 459 consecutive patients - 243 men and 216 women (female to male ratio: 1.1:1) - with GEP-NETs were evaluated at the Erasmus MC, Rotterdam, the Netherlands. The median age of the patients at the time of the GEP-NET diagnosis was 62.3 years (range: 23.8 - 89.1 years). The mean follow-up of the study population was 44 months (range: 0.4 – 118.6 months). Table 1 gives the clinical characteristics of the individuals in the analysis. Metastases were demonstrated in 432 patients (94.1%). The great majority of patients (88.2%) was diagnosed with ENETS stage IV disease (Table 1). (6)

Sixty-three (13.7%) GEP-NET patients had 67 second primary cancers. Table 2 shows the occurrence of the most prevalent second primary malignancies in 459 patients diagnosed with GEP-NETs divided into previous, synchronous and metachronous cancers. The 67 second primary malignancies could be divided over 25 previous cancers (5.4%), 13 synchronous cancers (2.8%) and 29 metachronous cancers (6.3%). (The most common types of second primary cancer were breast cancer (n=10), colorectal cancer (n=8), melanoma (n=6) and prostate cancer (n=5) (Table 2). Other second primary malignancies tumors which are not included in the table, because of their small numbers, were: bronchial carcinoma (n=2), small intestinal carcinoma (n=2), renal cell carcinoma (n=4), lung carcinoma (n=2), gynecological malignancies (n=3), myelodysplastic syndromes (n=2) and leukemia (n=2).
The number of patients with a cancer history was lower than expected but not significantly (n=25 versus n=34.5). Diagnosis of synchronous cancers was higher than expected (n=13 versus n=6.1, p<0.05). Synchronous cancers were colorectal cancer (n=4), small intestinal cancer (n=2), bronchial carcinoma (n=2), renal cell cancer (n=2), breast cancer (n=1), prostate cancer (n=1) and bladder cancer (n=1). Metachronous tumors occurred as frequent as expected (n=29 versus n=25.2, NS).

**Discussion**

We have evaluated the occurrence of second primary malignancies in a large cohort of patients with GEP-NETs, who were followed in a single, academic, tertiary referral institution. We have only found a significant increased risk of synchronous second primary malignancies, mainly colorectal cancers, in patients with GEP-NET.

We have chosen not to use GEP-NET data from a national registry since it occurred to us that the GEP-NET registration in the Dutch national cancer registry is incomplete. Reasons for this decision were: some GEP-NETs were not considered malignant and, therefore, not reported. Variability’s in GEP-NET nomenclature occurred over time. Also variability’s in classification systems were noted over time.

In our study group, the great majority of patients was diagnosed with ENETS stage IV disease. Patients were not randomized.

The Netherlands has an estimated population of 16.6 million people. Our centre covers approximately one fifth of this population. Until now, there is no national GEP-NET registry in the Netherlands. Therefore, we cannot give an impression on the proportion of Dutch GEP-NET patients who are treated in our centre.

In historical series, the incidence of second primary malignancies in patients with GEP-NETs (carcinoids) ranged from 12-46%, with an average of 17% (Habal, Sims, &
Bilchik 2000). In our series, the incidence of second malignancies in patients with GEP-NETs is 13.7%, which is in line with the findings in these historical GE-NET series.

A different distribution of GE-NETs (carcinoids) was noted in Taiwanese patients. In comparison to Western patients with GE-NETs, the Taiwanese patients presented with significantly more carcinoid tumors located in the rectum (Li et al 2008). This study showed that Taiwanese GE-NET patients had a high probability of developing associated, non-carcinoid, tumors mainly in the gastrointestinal tract, lungs and the genitourinary system. However, a statistical quantification of risk using a national reference group was not performed (Li et al 2008).

It still remains questionable whether there is a true increased incidence of second primary malignancies in GEP-NET patients. The historical series did not correct for age, sex, period of diagnosis and time from diagnosis and did not provide standardized incidence/mortality ratios, nor used data obtained from national cancer registries for comparison. Population-based cancer registries can provide high quality, long-term, national data, with histological confirmation in the majority of cases (Tulinius et al 1992). The major strength of our study is the use of an age- and sex national reference group by using linkage to the Dutch National Cancer Registry.

In a study on NETs (carcinoids) and adenocarcinomas of the small intestine, Zar and co-workers corrected their analyses for sex, age, period of diagnosis and time from diagnosis (Zar et al 2008). These authors concluded that second primary malignancies were generally diagnosed within the first year after the diagnosis of a tumor in the small intestine. This was possibly due to the extensive clinical work-up and follow-up of their patients (Zar, Garmo, Holmberg, & Hellman 2008).
In a study with a similar design in patients with primary lung carcinoids, Cote and co-workers reported an increased risk of breast cancer in females within the first 5 years after the diagnosis of the lung carcinoid (Cote et al 2006). However, after that period, the risk of breast cancer was lower than expected (Cote, Wenzlaff, Philip, & Schwartz 2006). These authors also reported on increased risks of breast and prostate cancer in males who had an earlier diagnosis of a lung carcinoid. In these studies, other types of second primary malignancies in lung carcinoid patients were not more prevalent than in the general population (Cote, Wenzlaff, Philip, & Schwartz 2006). Statistical quantification of risk using a population-based reference group has not yet been used for analyzing second primary cancer risks in GEP-NET patients. Therefore, we have conducted an analysis in this group of patients, using the same methodology as the study in patients with lung carcinoids (Cote, Wenzlaff, Philip, & Schwartz 2006). Our methodology was also similar to the methodologies used in two large studies analyzing second primary cancer risks in patients with Merkel cell carcinomas, which are neuroendocrine skin tumors (Kaae et al 2010, Bzhalava et al 2011).

In conclusion, our results are refining conclusions obtained in previous studies and demonstrate that mainly the occurrence of synchronous second primary (intestinal) malignancies is increased in GEP-NET patients as compared to the general population. This is probably due to incidental findings obtained at radiological, or surgical examination, or gastroenterology work-up. Surveillance bias after diagnosis should always be considered as an explanation for excess risk of second primary malignancies, as medical attention is intensified immediately after a cancer diagnosis. Due to the rarity of GEP-NET and the diversity of the other cancer types, collaborative international studies will be required to study this issue in further detail.
The present study does not support extensive screening programs for second primary malignancies in GEP-NET patients.

**Declaration of interest**

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

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**Author contribution statement**

Richard A Feelders, Wouter W de Herder &, Kimberly Kamp: collection patients group data, manuscript writing.

Kimberly Kamp & Ronald AM Damhuis: collection control group data, data analysis/statistics.

Kimberly Kamp: data registry.

Part of the data was presented as a poster at the 8th Annual ENETS Conference for the Diagnosis and Treatment of Neuroendocrine Tumor Disease, in Lisbon, Portugal, 9-11 March 2011.
References


Table 1:
Characteristics of 459 consecutive patients with gastro-entero-pancreatic neuroendocrine tumors (GEP-NETs), diagnosed from 2000-2009 in the Erasmus MC, Rotterdam, the Netherlands.

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<th>N</th>
<th>%</th>
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<tr>
<td><strong>Total</strong></td>
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<td>100</td>
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<td><strong>Gender</strong></td>
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<td>Male</td>
<td>243</td>
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<tr>
<td>Female</td>
<td>216</td>
<td>47.1</td>
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<tr>
<td><strong>Age</strong></td>
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<tr>
<td>&lt; 50</td>
<td>63</td>
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<td>50-69</td>
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<td>59.3</td>
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<td>&gt; 70</td>
<td>124</td>
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<td><strong>Primary localization</strong></td>
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<td>Non-functioning</td>
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<tr>
<td>VIPoma</td>
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<td>1.1</td>
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<td>Small intestine</td>
<td>140</td>
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<tr>
<td>Colorectal</td>
<td>57</td>
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<tr>
<td>Stomach</td>
<td>12</td>
<td>2.6</td>
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<td>IIIB</td>
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<td>IV</td>
<td>405</td>
<td>88.2</td>
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Table 2:


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<th></th>
<th>Observed</th>
<th>Expected</th>
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<th>SIR (O/E)</th>
<th>95% CI (SIR)</th>
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<td><strong>Prev</strong></td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>Total</td>
<td>25</td>
<td>34.5</td>
<td>16.2-36.9</td>
<td>0.72</td>
<td>0.47-1.07</td>
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<tr>
<td>Prostate</td>
<td>5</td>
<td>6.7</td>
<td>1.6-11.7</td>
<td>0.75</td>
<td>0.24-1.75</td>
</tr>
<tr>
<td>Breast</td>
<td>5</td>
<td>7.5</td>
<td>1.6-11.7</td>
<td>0.67</td>
<td>0.21-1.56</td>
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<tr>
<td>Melanoma</td>
<td>4</td>
<td>2.3</td>
<td>1.1-10.2</td>
<td>1.74</td>
<td>0.48-4.43</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Total</td>
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<td>6.9-22.2*</td>
<td>2.13</td>
<td>1.13-3.64</td>
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<tr>
<td>Colorectal</td>
<td>4</td>
<td>0.9</td>
<td>1.1-10.2*</td>
<td>4.44</td>
<td>1.22-11.33</td>
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<td><strong>Metachr</strong></td>
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<td>19.4-41.7</td>
<td>1.15</td>
<td>0.77-1.65</td>
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<tr>
<td>Breast</td>
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<td>1.6-11.7</td>
<td>1.92</td>
<td>0.62-4.50</td>
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<tr>
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<td>4.0</td>
<td>1.1-10.2</td>
<td>1.00</td>
<td>0.28-2.55</td>
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<tr>
<td><strong>Total</strong></td>
<td>67</td>
<td>65.8</td>
<td>51.9-85.0</td>
<td>1.02</td>
<td>0.79-1.29</td>
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</tbody>
</table>

**Prev** (previous second primary malignancies) = diagnosed >6 months before GEP-NET diagnosis

**Synchr** (synchronous second primary malignancies) = diagnosed within 6 months before, or after GEP-NET diagnosis

**Metachr** (metachronous second primary malignancies) = diagnosed >6 months after GEP-NET diagnosis

**CI** = confidence interval

**SIR** = standardized incidence ratio

* = p<0.05