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RESEARCH

Distribution, Incidence, and Prognosis in Neuroendocrine Tumors: a Population Based Study from a Cancer Registry

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Abstract Neuroendocrine tumors are considered rare tumors: recently an increased incidence and an improvement in survival were described. We explore distribution, incidence and survival of neuroendocrine tumors using population based registry data. We extracted from the Tuscan Cancer Registry neuroendocrine tumors from 1985–2005, and we evaluated distribution, incidence ad survival according to sex, site of tumor, age and stage at diagnosis. 455 cases of neuroendocrine tumors were identified. The overall incidence increased over the study period from 0.7 per 100,000 per year to 1.6 among men (APC +3.6) and from 0.3 to 2.1 among women (APC +4.8). The anatomic distribution of tumors was lung 25.7%, small intestine 23.5%, appendix 10.9%, colon 10.3%, pancreas 9.4%, stomach 7.4%, and rectum 5.2%. Neuroendocrine tumors were more frequent among males and incidence rate increased with age. We observed increased incidence of neuroendocrine tumors, while survival did not change over time. Prognosis varied with age, stage and localization; females had better survival than males. The increase number of neuroendocrine tumors may be due, at least in part, to better registration and to improvement of diagnosis.

Keywords Neuroendocrine tumors · Rare tumors · Incidence · Prognosis · Survival

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Introduction

Neuroendocrine tumors (NETs) are neoplasms that originate from neuroendocrine cell, localized in different organ through the body [1, 2]. These tumors share common features, as expression of neuroendocrine markers and growth pattern [1], and they can produce peptides causing hormonal syndromes [3]. NETs comprise a spectrum of malignancies that ranges from low-grade tumors to high- grade carcinomas; although most of them are indolent tumors, they can be aggressive and resistant to therapy [4, 5].

Although neuroendocrine tumors are localized in numerous different organ systems, the bronchopulmonary and gastrointestinal system constitute the most frequent sites of tumors [6, 7].

The incidence and prevalence of these tumors has been increasing over the past decades and it is unclear whether this reflects a true rise in incidence or an increased diagnosis and recognition of these neoplasms. To evaluate distribution, incidence and survival of neuroendocrine tumors we analyzed data from a population based cancer registry from 1985 to 2005, focusing on low and intermediate grade neoplasms.

Materials and methods

All cases of neuroendocrine tumors diagnosed among residents in the provinces of Firenze and Prato during the period 1985–2005 were retrieved from the Tuscan Cancer Registry (RTT).

According to recent study on SEER data [4], cases were selected from the Tuscan Cancer Registry database using the following International Classification of Diseases for Oncology (ICD-O-3) histology codes: 8150, 8151, 8152,

8153, 8154, 8155, 8156, 8157, 8240, 8241, 8242, 8243, 8244, 8245, 8246, 8249. Small cell (8040–8045), large cell neuroendocrine carcinoma (8013), and Merkel carcinoma (8247) were excluded.

Both behavior uncertain (/1) and malignant (/3) behavior has been included in the analysis. Benign lesions were not reported to the registry and were not included.

Patients with neuroendocrine tumors were analyzed by age at diagnosis, sex, primary tumor site, stage of tumor at diagnosis. Tumor stage at diagnosis was classified as localized, regional and distant, following the registry cancer staging system: localized tumor was defined as an invasive tumor confined to the organ of origin, regional tumor as a neoplasm that extended beyond the limits of organ of origin directly into surrounding organ or tissue and/or involved regional lymph nodes, distant tumor as a neoplasm that spread to parts of the body distant from the site of origin.

Frequencies, age-adjusted incidence, relative 5 year survival were calculated for the most common sites of neuroendocrine tumors.

All incidence rates per 100.000 per year were age-adjusted using the European 2000 standard population and presented in terms of site, sex, stage at diagnosis. Confidence intervals are 95% rates and trends. Annual percent changes (APC) were calculated using weighted least squares method. The APC is significantly different from zero when $p<0.05$.

To examine trends in neuroendocrine tumors survival was calculated for separate time period (1985–1994 and 1995–2005) by the most frequent sites of tumor (stomach, pancreas, colon, rectum).

Results

From 1985 to 2005, a total of 455 neuroendocrine tumors (NETs) were recorded in cancer registry.

Of the 455 patients with NETs identified, 215 (47.3%) were women and 240 (52.7%) were men. Gastrointestinal NETs constitutes the most frequent tumors (57.5% of total NETs, 262 cases), following by lung NETs (25.7% of total,117 cases).

Incidence rate for all study period was 1.5×100.000, 1.6 for male and 1.4 for female. We also reported incidence rates by primary tumor site: the most frequent site of origin of neuroendocrine tumors was represented by lung (incidence rate 0.4), followed by small intestine (incidence rate 0.3) and colon (incidence rate 0.3). Among colon site, appendix neuroendocrine tumors incidence rate was 0.2 By stage at diagnosis, higher number of NETs were diagnosticated at regional stage (incidence rate 0.3×100.000) than at localized (0.2 cases × 100.00) or at distant stage (0.2 cases × 100.00).

The age specific incidence rates showed that incidence of NETs increased with age, reaching the peak at 65 years of age (65–69 age group, incidence rate 5.2, 6.7 for male and 3.9 for female) (Fig. 1).

The trend indicates a statistically significant increase (APC 4.2, CI 2.4-6.2) of age-adjusted incidence from 1985 (incidence rate 0.5/100.000) to 2005 (incidence rate 1.9/100.000); incidence rate increase was statistically significant both among males (APC 4.8, CI 0.3-2.1) and females (APC 3.6, CI 1.4-5.9) (Fig. 2). By behaviour, incidence rate for uncertain tumors increased from 0 to 0.3, suggesting the introduction of a different modality of registration through the study period; however, malignant tumors incidence rate also increased (APC 4.1, CI 2.2-6) (Table 1).

The incidence rate increased particularly in colon NETs (APC 5.9, CI 2–10) and, although without statistically significance, in small intestine and in lung neuroendocrine tumors. Among colon tumors, appendiceal neuroendocrine neoplasms incidence rate increased from 0 to 0.3 (data not shown).

Overall survival of patients with NETs was 77.5% and women had better survival than men (5 year survival: 80.7% and 74.4%, respectively). Age and stage at diagnosis was also prognostic of survival: patients younger than 65 years of age and with localized tumor had better prognosis (Table 2).

Primary tumor site was a predictor of survival duration: lung NETs had the best prognosis (5 year survival 90.5%), whereas the outcomes for pancreatic and stomach NETs were the worst (5-year survival 62.7% and 63.5%, respectively). Among patients with gastric tumors, women had poorer prognosis than men (74.4% and 51.1% 5 year survival in males and in females, respectively),in contrast with all other sites of tumor, particularly pancreas (5 year survival 68.8% for women, 47.1% for men) (Table 2).

Over time, survival for all NETs patients not improved (Table 2), although from 1985–1994 to 1995–2005 period an increased 5 year survival for stomach, pancreas and lung was found (Fig. 3).

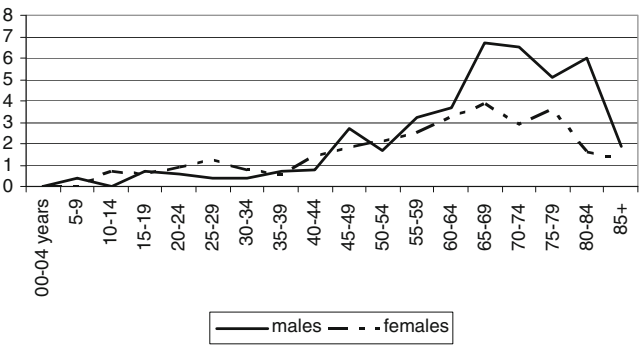

Fig. 1 Tuscan Cancer Registry 1985–2005: the age distribution of neuroendocrine tumors by sex. Rates are per 100.000 and age-adjusted to the 2000 European standard population

Fig. 2 Tuscan Cancer Registry 1985–2005: trend in neuroendocrine tumors incidence by sex Rates are per 100.000 and age-adjusted to the 2000 European standard population

Discussion

Neuroendocrine tumors are rare neoplasms: annual incidence rates vary by study from 1 to 5 per 100.000 persons [7]. Recently, incidence rate reported was 4.4 per 100.000 in United States and 3.24 in Norwegian Registry of Cancer through 1993–2004 period [1, 4].

According to multiple previous studies, our results found a significant increase in the incidence of NETs during the last years [4, 6, 8–10]. The reason of this increase has been related to an increase in awareness and an improvement in diagnosis. However, a change in collection of NETs may contributed to an increased incidence over time; in the past, the incomplete recognition and the inaccurate classification of these tumors have make difficult to obtain incident data [11]. Previously, neuroendocrine tumors were referred to as carcinoid tumors, considered as neoplasms with better behaviour than carcinomas [5]. Successively, a uniform terminology and a prognostic stratification with the WHO classification has been introduced [12], considering the biological and morphological heterogeneity typical of NETs. The last World Health Organization (WHO) classification of NETs introduced a uniform diagnosis, classifying these tumors into 3 well-distinct prognostic categories as low-, intermediate-, and high-grade [13, 14]. Currently, however, NETs are described according to their location of primary origin [3].

Difficulty in collection of data also depends on different behavior of these tumors: although NETs comprise a spectrum from benign to highly malignant tumors, some

Table 1 Tuscan Cancer Registry 1985–2005: neuroendocrine tumors incidence rates by sex Rates are per 100.000 and age-adjusted to the 2000 European standard population

	All	males	females
stage			
localized	0.2	0.2	0.2
regional	0.3	0.4	0.3
distant	0.2	0.2	0.1
unknown	0.3	0.3	0.3
age			
0–64	1.1	1.1	1.1
65+	4.3	5.9	3.1
period			
1984–1994	1.1	1.3	1.1
1995–2005	1.7	1.9	1.6
sites			
stomach	0.1	0.1	0.1
small intestine	0.3	0.5	0.2
colon	0.3	0.3	0.4
rectum	0.1	0.1	0.1
pancreas	0.1	0.1	0.2
lung	0.4	0.4	0.3

Table 2 Tuscan Cancer Registry 1985–2005: 5-year survival of neuroendocrine tumors by sex

	All	males	females
stage			
localized	91.7	89.2	91.0
regional	72.6	75.2	67.3
distant	29.4	25.6	34.2
unknown	83.3	74.4	87.6
age			
0–64	83.5	77.3	88.9
65+	71.8	74.1	68.4
sites			
stomach	63.5	69.6	51.1
small intestine	72.9	79.2	68.3
colon	86.3	87.5	84.0
rectum	76.4	65.2	84.5
pancreas	62.7	47.9	70.8
lung	90.5	87.2	93.5
Period			
1985–1994	82.6	81.4	81.9
1995–2005	78.3	74.6	81.9

Difficulty in collection of data also depends on different behavior of these tumors: although NETs comprise a spectrum from benign to highly malignant tumors, some

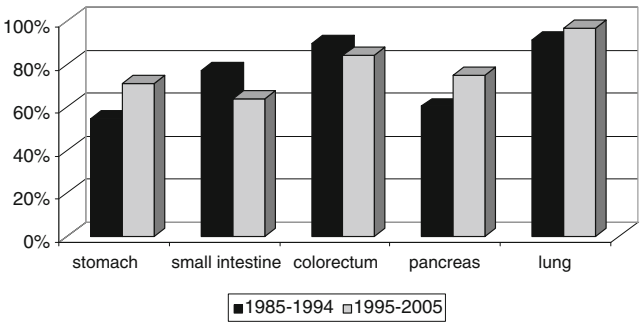

Fig. 3 Tuscan Cancer Registry 1985–2005: 5-year survival of neuroendocrine tumors by sites (1985–1994 and 1995–2005)

registries collected only malignant tumors. Thus, the real number of NETs could be underestimated and the survival rates could be more poor than the real survival [1].

For example, in cancer registry coding for appendix neurocarcinoma was 8240/1, referred to non malignant behavior, while carcinoid of other sites were code as 8240/3, as malignant tumors. Thus, in some registries the appendiceal carcinoids were not considered in analysis of neuroendocrine carcinomas; our data revealed that appendiceal neuroendocrine tumors incidence rate increased from 0 in 1985 to 0.2 in 2005, suggesting a change in registration methods.

The designation for these tumors often depends on the anatomic site in which they appear [5]. The most frequent sites of NETs in Europe and in United States are lung, rectum and small intestine [3]. Our data showed that the lung was the most common site follow by small intestine, according to data from SEER, while an analysis on Norvegian registry reported that small intestine was the most frequent location [1]. All NETs appeared to be increasing, particularly in lung and appendix, as recently reported [3], while in others studies stomach was the site of greatest increase [1].

According to the recent studies [1], our data showed that incidence rates of NETs was higher in male than in female; moreover, we found a substantially similar distribution of NETs through localized, regional, distant stages, in contrast with data from SEER, which reported an higher percentage of NETs in localized stages at diagnosis [1, 4]. Pancreatic NETs were more frequently diagnosed at distant stage than other NETs.

Incidence rates of NETs in total increased with increasing age, particularly among males; NETs were more frequently diagnosed in 60–70 age groups, according to data reported from SEER, where the median age at diagnosis was 63 years of age. Interestingly, data from SEER found low median age only for appendiceal NETs [4]. An improvement in survival was also recently described, particularly for metastatic neuroendocrine tumors, suggesting an influence from new therapeutic agents [3, 4]. Our analysis failed to show an improvement between 1985–1994 and 1995–2005 period, according to other reports [10, 15, 16]. However, in our data a slightly improvement in survival for stomach, pancreas and lung NETs was shown.

These discordant results could be due to difficulties in collection of data by registries: poor differentiated tumors that previously were diagnosed as carcinoma nas, subsequently, through immunoistochemical markers, were recognized as neuroendocrine tumors affecting survival trend. On the other hand, lead time and related effects of earlier diagnosis could have influenced survival improvement [7, 17]

Prognosis depends on site of tumor, sex, age and stage at diagnosis; as recently reported in literature, pancreas site get worse prognosis [1, 4, 7]. Generally female patients showed better survival than male and prognosis declined with increasing age, particularly among female patients.

A limit in data from registries is that probably not all tumors are collected and there are still some types of tumors not properly described and not considered NET tumors from all studies; thus, although our registry collects also uncertain behavior NETs, the incidence rate could be underestimated [4]. Moreover, clinical information such as the performance score of the patient, the medical therapy and the interventional procedures are generally lacking in the registries.

We showed an increased incidence of NETs, according to recent studies; this increase was probably due, at least in part, to a better registration and to a increase awareness [1, 8, 13, 15, 18]. Although the rising incidence may be real, it is possible that improvement in pathologic diagnosis and increasing use of diagnostic imaging techniques and of immunohistochemistry markers have influenced the observed increase in incidence of NETs [7, 17]. However, further observations on larger studies are needed to evaluate the real incidence trend and to detect changes in prognosis of NETs.

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