Títol

Neuroendocrine Tumors (NETs): A population-based study of incidence and survival in Girona province, 1994-2004.

Treball de Recerca: Suficiència investigadora

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FA CONSTAR,

que el treball titulat **"Neuroendocrine Tumors (NETs): A population-based study of incidence and survival in Girona province, 1994-2004**" ha estat realitzat sota la meva direcció per la llicenciada **Maria Alsina Maqueda**, trobant-se en condicions de poder ser presentat com a treball d'investigació de 12 crèdits, dins el programa de doctorat en Medicina Interna/Diagnòstic per la Imatge (curs 2009-2010), a la convocatòria de setembre.

A Barcelona, 25 d'Agost de dos mil deu,

Joan Carles Galceran

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Índex

Resum

Els tumors neuroendocrins (TNEs) pertanyen a un grup de neoplàsies poc freqüents i heterogènies, amb un ampli espectre d'agressivitat. Hi ha molt poca informació sobre la seva incidència i supervivència a nivell mundial. L'objectiu d'aquest estudi ha estat el de reportar la incidència i la supervivència d'aquests tumors a la província de Girona.

Hem inclòs tots els codis de la ICD-O3 que codifiquen a un TNE, període 1994-2002. Les dades dels TNEs malignes provenen del Registre del Càncer de Girona, i les dels tumors benignes o de comportament incert provenen directament dels Laboratoris d'Anatomia Patològica.

Hem identificat 698 NETs, els més freqüents són els originats al sistema bronco-pulmonar (65,75%), seguits pels gastro-entero-pancreàtics (GEP) (12,75%), i els de les glàndules endocrines (9,31%). Els tumors de cèl·lula petita són els TNEs més freqüents dins els sistema bronco-pulmonar (92,59%), amb una taxa d'incidència ajustada a la població mundial (TAM) de 4,29/100.000 persones-any. Els carcinoides pulmonars tenen una TAM de 0,32/100.000 persones-any, i una supervivència relativa (SR) als 5 anys del 77%. La TAM dels TNE del GEP és el 1,07/100.000 persones-any, i la SR als 5 anys del 95%. La SR als 5 anys del pàncrees és del 43%. Els TNE del tiroides tenen una TAM de 0,17/100.000 persones-any, i una SR als 5 anys del 75%. Els feocromocitomes tenen una TAM del 0,47/100.000 persones-any, i una SR als 5 anys del 85%. El tumors de merkel tenen una TAM de 0,11/100.000persones-any.

Segons la informació que tenim, aquest és el primer estudi poblacional que reporta la incidència dels TNEs a Espanya. Els nostres resultats són consistents amb les publicacions europees. El fet d'haver reportat la incidència i supervivència dels TNEs a Girona contribueix al millor coneixement d'aquestes neoplàsies.

Abstract

Neuroendocrine tumors (NETs) belong to a rare and heterogeneous group of neoplasms with a wide range of aggressiveness. Little information is available about incidence and mortality of NETs in the World population. The objective of this study was to report the incidence and survival of these tumors in Girona province.

We include all ICD-O3 codes that codified a NET, period 1994-2004. Data from malignant NETs came directly from the Girona Cancer Registry, and data from benign or with uncertain behavior NETs directly from the Anatomic-Pathological Laboratories.

We identified 698 NETs, the most frequent were those aroused in the bronco-pulmonary system (65.75%), followed by the gastro-entero-pancreatics (GEP) (12.75%). Small cell lung carcinomas (SCLC) were the most frequent NETs of the bronco-pulmonary system (92.59%), with an adjusted world (ASWr) incidence of 4.29/100,000 person-years. Carcinoid lung tumors had an ASWr incidence of 0.32/100,000 person-years and a 5-year relative survival (RS) of 77%. The ASWr incidence of GEP NETs was 1.07/100,000 person-years, and the 5-year RS was 95%. The 5-year RS of pancreas was 43%. Thyroid NETs had an ASWr incidence of 0.17/100,000 person-years, and a 5-year RS of 75%. Pheocromocytomas had an ASWr incidence of 0.47/100,000 person-years and a 5-year RS of 85%. Merkel cell carcinonas had an ASWr incidence of 0.11/100,000 person-years.

To our acknowledge, this is the first population-based study reporting incidence of NETs in Spain. Our data was consistent with other European reports. By providing the incidence and survival of NETs in Girona province, this study contributes to a better understanding of these rare tumors.

Introduction

Neuroendocrine tumors (NETs) belong to a rare and heterogeneous group of neoplasms with a wide range of aggressiveness. They originate from neuroendocrine cells which are located in the endocrine glands and also distributed throughout the body as a part of the diffuse neuroendocrine system.

NETs may occur in any organ of the body, and their frequency correlate with the density of neuroendocrine cells in a particular organ. The World Health Organization (WHO) classification for NETs includes neoplasms that originate in endocrine glands and in the diffuse neuroendocrine system (1-4).

In general, most publications agree that the most frequent sites where NETs arise are the gastrointestinal tract and pancreas (70%) followed by the bronco-pulmonary system (20-30%). Other publications present conflicting data regarding their sites of origin. However, other sites such as head, neck, thymus, genital and urinary system and skin are very rare,<10 % (5-11).

The treatment and the prognosis of patients with a NET depend on the degree (grade) of differentiation of the NET. For example, the more differentiated NETs can be effectively treated by hormone analogues, whereas the poorly differentiated NETs generally require more aggressive treatment such as surgery and chemotherapy. New drugs, such as some tyrosine kinase inhibitors, have demonstrated a benefit on overall survival for well-differentiated NETs, but they have yet to be approved for the regulatory agencies (12-13).

Very little information is available about the incidence and mortality of NETs in the world population. In the literature (5-11,14), the world frequency of NETs is listed as only 0.5% of all malignancies. Depending on different published reports, their incidence varies from 0.65/100,000 to 8.4/100,000. This is probably because the concept of NET refers to a pool of different and few frequent neoplasms, and mainly because the concept and terminology of NET has changed greatly since the end of 1800's, which has created much confusion. It is clear but, that the incidence and the survival of NETs have increased over time, suggesting that NETs are more prevalent than previously reported (10).

The objective of this study was to contribute in the knowledge of NETs by describing the incidence and the survival of these tumors in Girona province in the period 1994-2004.

Patients and Methods

We made an exhaustive review of NETs history that allowed us to make a list of all ICD-O3 codes that codified a NET. Then, we identified which of these codes were present in the patients in the Girona Cancer Registry (GCR) from January of 1994 to December of 2004, and we calculated the incidence and survival of NETs in Girona Province.

We included the following codes: large cell neuroendocrine carcinoma 80133, small cell carcinoma NOS 80413, oat cell carcinoma 80423, adenoma NOS 81400 (parathyroid C75.0), parathyroid adenoma (parathyroid C75.0) 81400, adenocarcinoma NOS (parathyroid C75.0) 81403, islet cell adenoma (pancreas C25._) 81500, islet cell tumor NOS (pancreas C25._) 81501, islet cell carcinoma (pancreas C25._) 81503, insulinoma NOS (pancreas C25._) 81510, insulinoma malignant (pancreas C25._) 81513, glucagonoma NOS (pancreas C25._) 81521, glucagonoma malignant (pancreas C25._) 81523, gastrinoma NOS 81531, gastrinoma malignant 81533, vipoma NOS 81551, vipoma malignant 81553, somatostatinoma NOS 81561, somatostatinoma malignant 81563, enteroglucagonoma NOS 81571, enteroglucagonoma malignant 81573, carcinoid tumor of uncertain malignant potential 82401, carcinoid tumor NOS (except of appendix M-82401) 82403, enterochromaffin cell carcinoid 82413, enterochromaffin-like cell carcinoid NOS 82421, enterochromaffin-like cell carcinoid malignant 82423, goblet cell carcinoid 82433, composite carcinoid 82443, tubular carcinoid 82451, neuroendocrine carcinoma NOS 82463, merkel cell carcinoma (Skin C44._) 82473, chromophobe adenoma (pituitary C75.1) 82700, prolactinoma (pituitary C75.1) 82710, pituitary adenoma typical 82720, pituitary adenoma atypical 82721, pituitary carcinoma 82723, clear cell adenoma (parathyroid C75.0) 83100, chief cell adenoma (parathyroid C75.0) 83210, medullary carcinoma with amyloid stroma (thyroid C73.9) 83453, paraganglioma benignant 86800, paraganglioma NOS 86801, paraganglioma malignant 86803, sympathetic paraganglioma 86811, parasympathetic paraganglioma 86821, gangliocytic paraganglioma 86830, glomus jugulare tumor NOS (aortic body and other paraganglia C75.5) 86901, aortic body tumor (aortic body and other paraganglia C75.5) 86911, carotid body tumor (carotid body C75.4) 86921, extra-adrenal paraganglioma NOS 86931, extra-adrenal paraganglioma malignant 86933, pheochromocytoma NOS (medulla of adrenal gland C74.1) 87000, pheochromocytoma malignant (medulla of adrenal gland C74.1) 87003, pinealoma (pineal gland C75.3) 93601, pineocytoma (pineal gland C75.3) 93611, pineoblastoma (pineal gland C75.3) 93623, ganglioneuroma 94900, ganglioneuroblastoma 94903, gangliocytoma 94920, neuroblastoma NOS 95003, olfactory neurocytoma (nasal cavity C30.0) 95213, olfactory neuroblastoma (nasal cavity C30.0) 95223, olfactory neuroephithelioma (nasal cavity C30.0) 95233. We excluded cases that were not classified precisely and those of mixed endocrine/exocrine type of neoplasm because their biological behavior is not clearly defined.

Data from all ICD-O3 malignant NET codes (ending with "3") came directly from the GCR. The GCR is a population-based cancer registry located the northeast Spain that covers Girona Province except Cerdanya with a population approximately of 700,000 inhabitants. The information sources of the cancer are the regional and community hospitals, the hematology and pathology departments, and death certificates. Tumors registered were those considered malignant or borderline. The completeness of the registry is 96.3% (15).

In contrast, data of NETs classified as benign or uncertain (ICD-O3 codes ended by "0" or "1") came from an exhaustive revision of all cases that Anatomic Pathological Laboratories diagnosed from 1994 to 2004. ICD-O3 code ended by "2" do not exist.

Incidence was calculated as crude rate (CR) and also as world age-standardized rate (ASWr) (16). Survival was obtained by active follow-up, and was calculated from the date of biopsy until December of 2006 or last follow-up. Record linkage to the Catalan Mortality Registry was made in the case of incomplete follow-up. Relative survival (RS) was set as the ratio between observed survival and expected survival, and was calculated to express the probability of cancer survival after adjustment for competing causes of death (17). RS rates at 5 years were calculated using the Hakulinen method (18) by means of WAERS (19), a web-assisted application developed by the Catalan Institute of Oncology, which permits the estimation of the relative survival of a cohort of patients.

Results

For an eleven-year period from January of 1994 to December of 2004, we identified 698 NETs, which are listed in table 1. The most of them had a pathological diagnostic, mainly by biopsy (543, 77.8%), but the others by cytology 149 (21.3%), and only 6 cases (0.9%) by other non-histological methods. Of the 698 NETs, 549 (78.7%) were males and 149 (21.3%) females, with a median age at diagnoses of 60.89 years, ranging from one month to 92 years (figure 1).

We divided these tumors into five groups as follows: gastro-entero-pancreatic tumors (GEP), bronco-pulmonary tumors, skin tumors (merkel cell carcinoma), endocrine glands tumors and other sites. The most frequent ones were the NETs aroused in the bronco-pulmonary system (65.75%), followed by GEP NETs (12.75%) and endocrine gland NETs (9.31%).

There were 459 NETs of the bronco-pulmonary system. The median age at diagnoses was 64.78 years (range from 9 up to 90 years), 430 (93.68%) were males. There were 425 (92.59%) small cell carcinomas (SCLC), 7 (1.52%) large cell neuroendocrine carcinomas (LCNC), and 27 (5.88%) carcinoids (table 2).

There were 89 GEP NET, but only the 6% of them were poorly differentiated neuroendocrine carcinomas. The median age at diagnoses was 52.65 years (range from 13 to 89 years), 45 (50.56%) of them were males. The most frequent location was the appendix in 34 cases (38.2%), followed by the pancreas, small bowels, colorectal, and stomach (table 3).

There were 65 NET of the endocrine glands. The median age at diagnoses was 47.22 years (ranging from one month to 77 years), with and excess of females. There were 23 (35.4%) NETs of the adrenal gland (pheocromocytomas), 22 (33.8%) NETs of the parathyroid gland, 11 (16.9%) NETs of the thyroid gland, and 9 (13.8%) paragangliomas (table 4).

There were 16 (2.29%) merkel cell carcinomas, 10 (62.5%) males and 6 (37.5%) females, with a median age at diagnoses of 77.38 years (range from 66 to 92 years) (table 5).

The rest of the NET tumors were mainly tumors with an unknown primary site (33, 4.72%), and the 66% of them with a histology of small cell carcinoma. Other less frequent NETs were those aroused in the laryngologist area, central and peripheral system, and genital and urinary system.

The ASWr incidence of SCLC was 4.29/100,000 person-years, of LCNC was 0.07/100,000 person-years, and of carcinoids (typical and atypical) was 0.32/100,000 person-years. The 5-year RS of SCLC was 4%, of LCNEC was 0%, and of carcinoids was 77% (table 6).

The ASWr incidence of GEP NETs, excluding the ones with small cell carcinoma histology, was 1.07/100,000 person-years. The ASWr incidence of different GEP NETs is listed in table 7. The 5-year RS of GEP NETs except pancreas was 95%, whereas was 43% for pancreas (table 6).

The ASWr incidence of thyroid gland NETs was 0.17/100,000 person-years, of pheocromocytomas was 0.47/100,000 person-years, of parathyroid gland NETs was 0.27/100,000 person-years, and of paragangliomas was 0.11/100,000 person-year. The 5-year RS of thyroid gland NETs was 76%, of pheocromocytoma was 85%, and of parathyroid NETs was 100% (table 6).

The ASWr incidence of Merkel cell carcinoma was 0.11/100,000 person-years, and the 5 year RS was 50.4% (table 6).

Discussion

The terminology of NET refers to a wide variety of different and infrequent neoplasms, and the concept and terminology of NET has significantly changed over years, mainly during the last three decades. This fact has hampered the collection and publication of epidemiological data. In addition, the incidences of NETs have been underestimated in most of the publications: the population registers of cancer do not normally consider neoplasm with a benign behavior. Whereas histological evidence of invasion of a basement membrane defines malignant behavior for most epithelial malignancies, the definition of malignant behavior classifying a NET is more difficult.

Oberndorfer was the first person to describe a NET in 1907 when he reported on benign tumors of small intestines. He called them “karzinoide tumoren” (carcinoid tumors) (20). Later, carcinoid tumors were recognized in other organs of the body, and it was observed that not all of them were benign, but some were malignant.

In 1963, Sandler and Williams classified carcinoids based upon their site of origin. They separated foregut carcinoids (the ones arising from the bronchus, stomach and pancreas) from midgut carcinoids (the ones arising from small intestines in the mid-duodenum, caecum and colon as far as the mid-transverse colon), and from hindgut carcinoids (those arising from descending colon and rectum) (21). The WHO adopted this classification for many years, and then in 1999 the WHO adopted the currently accepted classification.

During the last two decades, there have been many efforts to establish a NET classification that would discriminate between the true benign behaviors (low risk of metastasis) from low-grade malignant well-differentiated NET (high risk of metastasis).

For lung NET, Travis and colleagues presented a classification in 1999 which was adopted by WHO (22) to predict the behavior of the tumor (23-25). This classification separated lung NET in four groups: 1) Typical carcinoid, 2) Atypical carcinoid, 3) Small cell lung cancer (SCLC) and 4) Large cell neuroendocrine carcinoma (LCNC).

For GEP NET, Solcia and colleagues (26) presented a classification in 1999 which was adopted by WHO in 2000. Their classification was based on a series of histopathological and biological tumor characteristics (site, size, cellular grading, cell proliferation index, local or vascular invasion, and the production of biologically active substances). Their classification was the first to have prognostic value (3-4,27-28). This classification separated GEP NET in three groups: 1) Well-differentiated neuroendocrine tumor (including the differentiation among the ones with benign

behavior and the others with uncertain malignant potential) 2) Well-differentiated neuroendocrine carcinoma, and 3) Poorly-differentiated neuroendocrine carcinoma.

Poorly differentiated neuroendocrine carcinomas, SCLC and LCNC have high proliferation indices, which indicate a high grade of malignancy, a poor patient prognosis, and they usually should be treated with chemotherapy. Well-differentiated GEP NET and typical carcinoids have low proliferation indices, which indicate a low grade of malignancy, so they can be treated successfully with biotherapy. Atypical carcinoids have an intermediate aggressiveness behavior.

In 2005 the European Neuroendocrine Tumor Society (ENETS) organized a Consensus Conference and proposed a tumor-node-metastasis (TNM) classification for foregut NET, and in 2006 for midgut and hindgut NET (29-30). Both proposals included the grade of the tumor to better define the behavior. This last TNM classification provided a dependable means of prognosis, but the WHO has not accepted it yet. Recently, a new TNM classification proposed by the American Joint Committee on Cancer (AJCC) has been published with significant differences compared with the European ENETS classification. An international meeting is planned in the near future to try to reach a consensus. (31).

We listed all ICE-O-3 codes that codify a NET, including the malignant and also the benign and the ones with uncertain behavior, diagnosed in Girona province from January of 1994 to December of 2004. The aim of our study was to report their incidence and survival.

We reported 698 NETs, 459 (65.75%) were originated in the lung. This high figure is due to the inclusion of SCLC, as accepted by the last WHO classification (22). If we had omitted these tumors, we would have found that the 14% of the NETs were originated in the lung, similarly from what was reported in other European countries: from 9% (Sweden), up to 18% (Switzerland, England) and 22% (Netherlands) (5, 8, 6, 32).

We found an ASWr incidence of SCLC of 4.29 /100,000 person-years. An incidence of 14.4 /100,000 person-years for men and 8.8 /100,000 person-years for women in the same period of time was reported in Denmark (33). And in US, taking into account that SCLC represented the 15% of all lung cancers (34), the incidence would have been 10.5 /100,000 person-years (35). That differences could be explained because the populations where incidences had been adjusted were different: if we adjusted our cases to the European population, the incidence would have been 5.98 /100.000 person-years, a figure closer than the results from Denmark and US, and also to the reported Spanish SCLC incidence of 12.32 /100,000 person-years (36).

The ASWr incidence of carcinoids tumors was 0.32 /100,000 person-years, which did not differ extremely than other reports. In Denmark, an incidence of 0.52 /100,000 person-years for men and 0.46 /100,000 person-years for woman was reported (33), but in Italy it was only of 0.20 /100,000 person-years (11). In contrast, a much higher incidence of these tumors was reported in US: 1.35 /100,000 person-years (10). We should have a special mention about the incidence comparisons between United States and other European countries. Technically, these comparisons are not statistically correct. While in the US an adjustment of the incidence to the American population is used, in Europe usually is to the world population. This fact could jeopardize the final incidence of rare tumors due to the several reasons mentioned above that have been conditioned the underestimation of this tumors in certain countries.

The 5-year RS of lung NETs range from almost 0% of SCLC to 77% of lung carcinoids. The reported 5-year RS for SCLC in Europe and US was consistent with ours: 2% in Denmark (33), and 10% in US, but for limited stage SCLC, which were the 20% of their cases (35). For typical and atypical carcinoids, our data was consistent with other European countries: 82% in Switzerland, 80% in Netherlands, 95% in Italy, and 44% for atypical carcinoid and 87% for typical carcinoid in Denmark (6,11,32-33).

Eighty-nine GEP NETs were described, with an ASWr incidence of 1.07 /100,000 person-years. Our data was consistent with the European reports, ranging from 0.35 /100,000 person-years in Italy, 0.55 /100,000 person-years in England, 0.63 /100,000 person-years in France, 1.21 /100,000 person-years in Netherlands, 1.75 /100,000 person-years in Sweden, and to 1.79 /100,000 person-years in Switzerland (5-6,8,11,32,37). In contrast, the US incidence was higher: 2.89 /100,000 person-years (10).

The appendix was the most common site of origin between GEP NETs, representing the 38.20% of the cases. In the recent study published in Spain, from the National Cancer Registry for Gastroenteropancreatic Neuroendocrine Tumors (RGETNE), the appendix NETs only represented the 9% of the GEP NETs (38). This difference was probably due to the bases of the patient recruitment. The main recruiters of the RGETNE database were oncologists and endocrinologists which usually do not see patients with operated NETs of the appendix. Only 4% of the investigators involved in the REGETNE database were surgeons, which are the usual specialists that follow-up these patients. Interestingly, and as mentioned above, the main information included in our database came from the anatomo-pathological reports, reducing to the minimum the risk of biases. We found an ASWr incidence of appendix NETs of 0.50 /100,000 person-years, similar to the reported 0.52 /100,000 person-year in Netherlands, and 0.60 /100,000 person-years in Sweden; but higher than the 0.09 /100,000 person-years reported in Italy, and 0.15 /100,000 person-years reported in US (5-6,10-11).

We calculated the prognosis for GEP NETs except pancreas and appendix, both because their different behavior, finding a 5-years RS of 76%, which is very similar to the 75% reported by the RGETNE (38). Other European countries reported similar data: 75% for men and 83% for woman in Switzerland (6), 70% in Italy (11), and 61% in Netherlands (32). The survival data in France was given including pancreatic NETs, so it is understandable the lower figure: 49% (37). Appendix NETs had better prognosis, with a 5-years RS of 95%, which was similar to the 100% reported by the RGETNE (38) and in other Europe countries: 95% in Netherlands (32), and 100% in Italy (11).

We found 33 NETs from unknown origin; the 33% of them were carcinoids. Carcinoids with an unknown origin are though to come from the gastrointestinal system because their behavior. If we classified them inside GEP NETs, they would represent the 12% of GEP NETs. The RGETNE reported a 20% of unknown origin carcinoids. This difference was also probably due to different recruiters (38). Similarly, in Netherlands was reported a 12% of unknown origin carcinoids (32). Comparisons with other European and American studies was impossible because they grouped unknown origin carcinoids and other (less frequent) carcinoids as an unique set. The ASWr incidence of unknown origin carcinoids was 0.11 /100,000 person-years.

Very few studies reported incidences of endocrine gland NETs, which made difficult to compare our results. We found an ASWr incidence of medullary thyroid cancer of 0.17 /100,000 person-years, similar to the reported in Europe between 0.1-0.2 /100,000 person-years (39). The 5-year RS of medullary thyroid cancer was 75%, where it was 85% in other European reports (39). We found 22 cases of parathyroid carcinoma, which resulted in an extremely high incidence of 0.27 /100,000 person-years, compared with the incidence reported in US of 0.015 /100,000 person-years (34). In addition, we found a parathyroid carcinoma 5-year RS of 100%, which did differ from the 55.5% reported in US (40). These findings suggested that maybe an overestimate incidence and survival of parathyroid carcinoma was found due to an inclusion of false tumors.

Pheocromocytomas are intra-adrenal paragangliomas, closely related tumors of extra-adrenal sympathetic or parasympathetic paraganglia, the extra-adrenal paragangliomas. We found an ASWr incidence of pheocromocytoma of 0.47 /100,000 person-years, and of paragangliomas of 0.11 /100,000 person-years. The annual incidence in US of both tumors together was between 500 to 1600 cases per year, which would represent an incidence of 0.32 /100,000 person-years, similar to ours (41). Pheocromocytoma was found to have a 5-year RS of 85%, when in US a 34% was reported for the malignant ones, and a 97% for the benign ones, defining the malignant ones those which had done metastases at the diagnoses (42).

We found a merkel cell carcinoma incidence of 0.11 /100,000 person-years, lower than the 0.22 /100,000 person-years reported in Denmark (43), and the 0.24 /100,000 person-years reported in the US (30). The 5-year RS was

50%, similar to the 62% reported in US (44). Vilar-Coromina et al. published the incidence of this tumor in Girona province in a similar period than us, between 1995 to 2005, finding a ASWr incidence rate of 0.13 /100,000 person-years; but when they adjusted the incidence to the American population, the found rate was 0.23 /100,000 person-years, which was the same as the reported in US (45).

Conclusions

There are few epidemiological reports of NETs published. This is probably because NETs are rare neoplasms and because their nomenclature and classification have significantly changed making difficult their registration. Another point to be considered is that most publications underestimate the total number of NETs because the majority of population registries do not include benign NETs. We emphasize the effort in order to obtain data from all NETs recruiting the information of the benign NETs from every anatomical laboratory of Girona province.

To our acknowledge, this is the first population-based study with incidence of NETs in Spain. Our results are consistent with other reported in European countries. Comparisons with data coming from US are difficult due to different population used to adjust the incidence.

This study provides data of the incidence and survival of NETs in Girona area, which is a very important step towards to a better understanding of these infrequent tumors.

Tables

Table 1.

NETs identified in Girona province, from January 1994 to December 2004.

Histology	Frequency	Percentage
Large cell neuroendocrine carcinoma	11	1,6
Small cell carcinoma	288	41,3
Oat cell carcinoma	172	24,6
Adenoma	7	1,0
Islet cell carcinoid	1	,1
Insulinoma	1	,1
Malignant insulinoma	3	,4
Malignant gastrinoma	2	,3
Carcinoid tumor with uncertain behavior	33	4,7
Carcinoid tumor	60	8,6
Enterocromafin cell carcinoid	2	,3
Neuroendocrine carcinoma	26	3,7
Merkel cell carcinoma	15	2,1
Prolactinoma	2	,3
Clear cell adenoma	3	,4
Chief cell adenoma	14	2,0
Medular carcinoma with amyloid stroma	11	1,6
Paraganglinoma	6	,9
Malignant Paragangliona	1	,1
Jugular corpuscle tumor	2	,3
Pheocromocytoma	11	1,6
Malignant pheocromocitoma	2	,3
Pinealoma	2	,3
Pineocytoma	2	,3
Ganglioneuroma	6	,9
Ganglioneuroblastoma	2	,3
Neuroblastoma	12	1,7
Estesioneuroblastoma	1	,1
Total	698	100,0

Table 2

Bronco-pulmonary NETs.

Bronco-pulmonary NETs	Males	Females	Total	Percentage (%)
SCLC	405	20	425	92.6
LCNC	7	0	7	1.5
Carcinoid	18	9	27	5.9
Total	430 (93.7%)	29 (6.3%)	459 (100.0%)	100.0

Table 3

GEP NETs

GEP NETs	Males	Females	Total	Percentage (%)
Stomach	5	2	7	7.9
Small bowels	8	8	16	18.0
Appendix	16	18	34	38.2
Colon and rectum	9	6	15	16.9
Pancreas	7	10	17	19.1
Total	45 (50.6%)	44 (49.4%)	89 (100.0%)	100.0

Table 4

Endocrine gland NETs.

Endocrine gland NETs	Males	Females	Total	Percentage (%)
Thyroid gland	5	6	11	16.9
Adrenal gland	12	11	23	35.4
Parathyroid gland	8	14	22	33.8
Paraganglioma	2	7	9	13.8
Total	27 (41.5%)	38 (58.5%)	65 (100.0%)	100.0

Table 5

Merkel cell carcinomas.

Skin NETs	Males	Females	Total	Percentage (%)
Merkel cell carcinoma	6 (37.5%)	10 (62.5%)	16 (100.0%)	100.0

Table 6

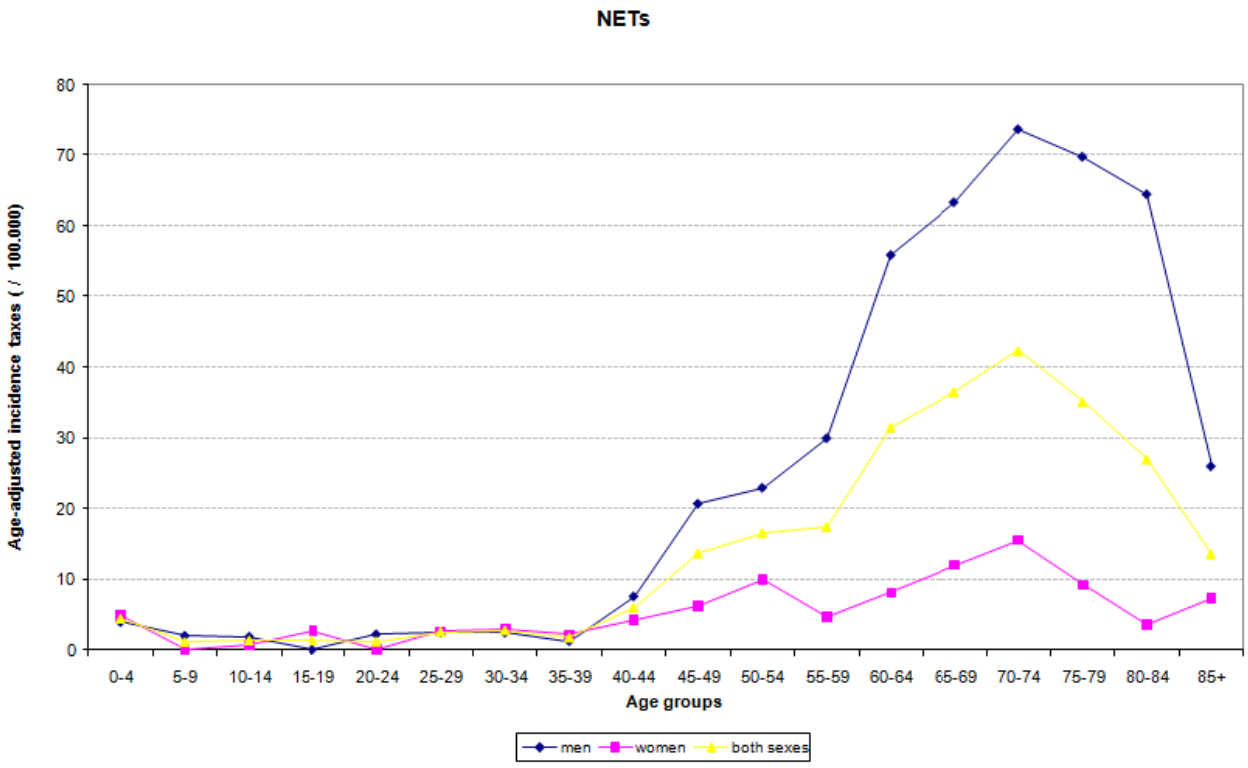
Incidence and survival of NETs. CR: crude rate. ASWr: adjusted world incidence. 95% CI: 95% confidence interval. 5-year RS: 5-year relative survival.

Site of tumor	CR	ASWr Incidence	95% CI	5-year RS
LUNG NETs				
SCLC	7.10	4.29	3.86-4.73	0.04
LCNC	0.10	0.07	0.01-0.12	0.00
Carcinoid	0.50	0.32	0.18-0.46	0.77
GEP NETs				
ALL	1.40	1.07	0.83-1.31	
Stomach	0.08	0.05	0.00-0.09	
Small bowels	0.25	0.15	0.07-0.24	0.95
Appendix	0.57	0.50	0.32-0.67	
Colo-rectum	0.22	0.16	0.07-0.25	
Pancreas	0.28	0.21	0.11-0.31	0.43
SKIN NETs				
Merkel cell carcinoma	0.30	0.11	0.05-0.16	0.50
ENDOCRINE GLAND NETs				
Thyroid	0.20	0.17	0.06-0.28	0.76
Parathyroid	0.40	0.27	0.16-0.39	1.00
Pheocromocytoma	0.40	0.47	0.24-0.69	0.85
Paraganglioma	0.20	0.11	0.04-0.19	
UNKNOWN ORIGINE NETs				
Small cell histology	0.40	0.17	0.09-0.24	
Carcinoid histology	0.20	0.11	0.04-0.18	

Figures

Figure 1

Distribution of the diagnostic age for men, women, and both.



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