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Reference

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Rare neuroendocrine tumours: Results of the surveillance of rare cancers in Europe project [☆]

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KEYWORDS

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Abstract Because of the low incidence, and limited opportunities for large patient volume experiences, there are very few relevant studies of neuroendocrine tumours (NETs).

A large population-based database (including cancer patients diagnosed from 1978 to 2002 and registered in 76 population-based cancer registries [CRs]), provided by the project ‘surveillance of rare cancers in Europe’ (RARECARE) is used to describe the basic indicators of incidence, prevalence and survival of NETs, giving a unique overview on the burden of NETs in Europe. NETs at all cancer sites, excluding lung, were analysed in this study. In total over 20,000 incident cases of NETs were analysed and a data quality check upon specific NETs was performed. The overall incidence rate for NETs was 25/1,000,000 and was highest in patients aged 65 years and older with well differentiated endocrine carcinomas (non-functioning pancreatic and gastrointestinal) (40 per 1,000,000). We estimated that slightly more than 100,000 people were diagnosed with NETs and still alive in EU27 at the beginning of 2008. Overall, NETs had a 5 year relative survival of 50%; survival was low (12%) for poorly differentiated endocrine carcinoma, and relatively high (64%) for well differentiated carcinoma (not functioning of the pancreas and digestive organs). Within NETs, endocrine carcinoma of thyroid gland had the best 5-year relative survival (82%).

Because of the complexity and number of the different disciplines involved with NETs (as they arise in many organs), a multidisciplinary approach delivered in highly qualified reference centres and an international network between those centres is recommended.

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1. Introduction

Neuroendocrine tumours (NETs) can develop in most organs.¹ NETs are usually slow growing tumours with behaviour ranging from relatively benign to highly malignant.^{2–4} Due to their heterogeneous embryological origin, NETs are ubiquitous and because of their rarity can be difficult to distinguish by biologic and histopathologic features.^{5–7}

NETs are widely regarded as a rare tumour, with an incidence of 1–5 cases per 100,000 person-years.^{3,8,9} The low incidence rate has resulted in only a few relevant studies, and makes a large experience for any single healthcare professional unlikely.^{10–12} A high quality database with reliable diagnoses, which needs large clinical experience, is a condition sine qua non for epidemiological research on any rare disease.¹³

A major step forward in predicting the biological behaviour of NETs was made in 2000 by the development of a new World Health Organization (WHO) morphological classification, including NETs, based on histopathological and biological characteristics.^{6,10,14} Later, a Tumour-Node and Metastases (TNM) classification and the European Neuroendocrine Tumour Society (ENETS) grading system for NETs became available.^{10,15}

Multiple systems of nomenclature, grading and staging have been proposed, however, none has achieved universal acceptance. In general, the current WHO guidelines divide neuroendocrine neoplasms into two clinically distinct pathologic classes: well- and poorly differentiated.

The well-differentiated NETs can be classified as either grade 1 or grade 2 depending on proliferation

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Table 1

Data quality indicators for neuroendocrine cancers diagnosed 1995–2002 and archived in 76 surveillance of rare cancers in Europe (RARECARE) cancer registries.

Entity	Number malignant cancers 1995–2002 (76 CRs)		Data quality indicators				International Classification of Diseases for Oncology third edition (ICD-O3) codes	
			DCO* only	Autopsy	Microscopic verification	Cases 1995–1998 censored before 5 years	Topography	Morphology
	Tier	N	(%)	(%)	(%)	(%)		
Neuroendocrine tumours	1	20,994	0.34	1.7	97	1.2		
Well diff endocrine carcinoid tumours (skin and GI tract excluded)	2	3202	0.81	0.84	96	0.69	All cancer sites except C15–C26, C34, C44	8240–8246
Well diff endocrine atypical carcinoid tumours (skin and GI tract excluded)	2	6	0.00	0.00	100	0.00	All cancer sites except C15–C26, C34, C44	8249
Well diff endocrine carcinoma of the pancreas and digest organs (non-functioning) Carcinoid tumours, NOS/islet cell carcinoma	2	10,276	0.17	2.5	98	1.5	C15–26	8240–8246, 8249, 8150
Well diff endocrine carcinoma of pancreas and of digest tract (functioning) Malignant insulinoma, glucagonoma, somatostatinoma, gastrinoma/other ectopic hormone producing tumours	2	200	1.0	1.5	85	2.5	C15–26	8151–8153, 8155–8157
Poorly diff endocrine carcinoma (skin and thyroid excluded) Small cell endocrine carcinoma/large cell endocrine carcinoma	2	4429	0.56	1.3	97	0.40	All cancer sites except C34, C44, C73	8013, 8041–8045
Mixed endocrine–exocrine carcinoma	2	18	5.6	0.00	89	0.00	All cancer sites except C34, C44	8154
Endocrine carcinoma of thyroid gland Medullary carcinoma/mixed medullary-follicular carcinoma	2	1784	0.00	1.3	98	2.4	C73	8013, 8041–8045, 8510, 8345–8347
Endocrine carcinoma of skin Merkel cell carcinoma	2	1018	0.09	0.00	100	1.1	C44	8041–8044, 8240–8247

* DCO: death certificate only; NOS: not otherwise specified.

and histology. Well-differentiated grade 1 and grade 2 NETs have traditionally been referred to as carcinoids, regardless of grade or site of origin. The WHO 2010 guidelines apply the term ‘carcinoid’ to grade 1 NETs only.

The poorly differentiated grade 3 neuroendocrine carcinomas are characterised by rapid dissemination, resistance to therapeutic interventions and a highly aggressive course.

A comprehensive analysis of NETs in Europe is lacking within the available literature. This paper delineates the burden of NETs in Europe, providing estimates of the incidence, prevalence and survival of these tumours diagnosed from 1988 to 2002, based on the definition and list provided by the project surveillance of rare cancers in Europe (RARECARE). Although the recent improvements regarding pathologic diagnosis and grading of NET are a major step forward, the RARECARE list, and therefore our analysis, are based on the nomenclature during the time of our study period 1995–2002.

2. Materials and methods

2.1. Tumour grouping

The present analyses are based on the list of cancers provided by the RARECARE project. RARECARE included data between 1978 and 2002 and followed the 2000 WHO guidelines that distinguished NETs in four main groups: well differentiated endocrine tumours; well differentiated endocrine carcinoma; poorly differentiated endocrine carcinoma and mixed endocrine–exocrine carcinoma.

The RARECARE list of NETs is organised in two hierarchical tiers and based on the International Classification of Diseases for Oncology third edition (ICD-O3).¹⁶ Tier 1 consists of cancers that require the same clinical expertise and patient referral structure, created by grouping tier 2 entities. Tier 2 includes cancers that are similar from the point of view of clinical management and research, and is based on the combination of topographical and morphological ICD-O3 codes.

For NETs described in this paper (Table 1), there is one tier 1: ‘neuroendocrine tumours’ and eight tiers 2 (including: well differentiated endocrine tumours [identified in the ICD-O3 as carcinoids]; well differentiated endocrine carcinoma [identified in the ICD-O3 as atypical carcinoids]; well differentiated endocrine carcinomas of the pancreas and digestive organs [non-functioning]; well differentiated endocrine carcinomas of the pancreas and digestive tract [functioning]; poorly differentiated endocrine carcinomas [skin and thyroid excluded]; mixed endocrine–exocrine carcinomas; endocrine carcinomas of thyroid gland and endocrine carcinomas of the skin). Table 1 presents the ICD-O3 morphology

and topography codes of NETs considered in the present study.

The RARECARE list grouped NETs from all anatomic sites. In this study well differentiated endocrine carcinomas of the pancreas and digestive organs are divided according to WHO grouping into functioning and non-functioning endocrine carcinomas. Well differentiated endocrine carcinomas (functioning) produce hormones and other local mediators and are associated with syndromes related to this hormone over secretion. Well differentiated endocrine carcinomas (non-functioning) exhibit immuno-positivity for endocrine markers but are not related to any hyperfunctional clinical syndrome.¹⁷ This differentiation results in grouping them separately from well differentiated endocrine tumours and well differentiated endocrine carcinomas of other sites.

We included two separate tiers for thyroid and skin NETs: endocrine carcinoma of the thyroid gland and endocrine carcinoma of the skin. Including these two specific tiers results in the exclusion of skin and thyroid from poorly differentiated endocrine carcinomas, and from well differentiated endocrine tumours and well differentiated endocrine carcinomas.

The morphology codes for thyroid endocrine carcinomas include medullary carcinomas, poorly differentiated thyroid endocrine tumours and mixed medullary-follicular carcinoma. Endocrine carcinomas of the skin include Merkel cell carcinoma. Finally, poorly differentiated endocrine carcinomas include small cell endocrine carcinoma and large cell endocrine carcinoma of all sites except skin and thyroid. NETs of the lung will not be described in this article as their European incidence rate was 7.3 per 100,000 person-years, and therefore not considered to be rare.¹⁸

2.2. CRs selection and population coverage

RARECARE gathered data on cancer patients diagnosed from 1978 to 2002, registered in 89 population-based CRs, all of which had information on follow-up available up to at least 31st December 2003. However this paper considered data from 76 CRs, excluding CRs which did not classify cancers according to the ICD-O3, and also those which collected data on childhood cancers only.

2.3. Data selection for incidence analysis

The incidence analysis considered incident cases between 1995 and 2002. We excluded twelve specialised CRs, as those registered data on specific cancer sites only. As a result, the incidence analyses were restricted to 64 CRs. Incidence rates were estimated as the number of new cases occurring between 1995 and 2002 divided by the total person-years in the general population (male

and female) in the CR areas considered, over the same period. For age-standardised rates, the European standard population was used.¹⁹

For estimating the number of cases that arises per year in all 27 European member states (EU27), the observed RARECARE incidence rates 1995–2002 were multiplied to the total 2008 EU27 population (497,455,033 at 2nd April 2008) provided by EUROSTAT. In providing NET burden estimates, we assumed that the population covered by the CRs included was representative of the population of the EU27 as a whole.

2.4. Data selection for prevalence analyses

The observed prevalence of cases within 2, 5 and 15 years before the index date of 1st January 2003 was estimated by applying the counting method.²⁰ Only 22 CRs had incidence and follow-up data available for the 15 year period 1988–2002, choosing January 2003 as index date.

The completeness index method²¹ was used to estimate the EU complete prevalence, which involved adding the estimated surviving cases diagnosed prior to 1988 to those observed in 1988–2002. The completeness index was obtained on the basis of a parametric approach, by modelling 1985–1999 incidence data with a logistic exponential or polynomial function on age, and 1988–1999 survival with mixture cure models.²²

The expected number of prevalent cases in EU27 was estimated by multiplying the prevalence estimates to the 2008 European population (497,455,033 at 2nd April 2008 provided by EUROSTAT).

2.5. Data selection for survival analyses

Period survival indicators for the years 2000–2002 were estimated using the Brenner algorithm.²³ Period analysis provides more up-to-date survival experience by considering survival experience in 2000–2002. Forty-six CRs out of the 76 European CRs had data available for this period, and could be included for survival analyses.

2.6. Data quality analysis

International standards for CRs set by the International Association for Cancer Registries (IACR) and the European Network of Cancer Registries (ENCR) attempt to secure the quality of the CRs, but consideration must be given to constraints on their activity placed by local health care systems.²⁴ In summary, during the registration process there was access to comprehensive sources including pathologic reports, diagnostic examinations and clinical dossiers. Especially for NETs, it is important to have access to, and use of all sources provided by multidisciplinary teams

(including experienced pathologists) to come to a correct definition of NETs.

The main data quality indicators for the 21,066 NETs are shown in Table 1. These cases were diagnosed between 1995 and 2002 and archived by the 76 CRs considered in the study. Overall, 0.34% of the cases were Death Certificate Only (DCO), ranging from 0.00% for well differentiated endocrine tumours (atypical carcinoid) ($N = 6$ in four CRs) and endocrine carcinomas of thyroid gland ($N = 1784$ in 64 CRs) to 5.6% for the mixed endocrine–exocrine carcinomas of the pancreas ($N = 18$ in 16 CRs).

Nearly 97% of all NETs included in the RARECARE database were histologically verified (MV), however the proportion of MV cases ranged from 100% for the six cases of well differentiated endocrine tumours (atypical carcinoid) to 85% for the well differentiated endocrine carcinoma (functioning of pancreas and of digestive tract).

The proportion of cases diagnosed between 1995–1998 and censored before 5 years of follow-up (lost to follow-up) was 1.2%, ranging from 0.00% for the well differentiated endocrine tumours to 2.5% for the well differentiated endocrine carcinomas (functioning pancreas and digestive tract).

2.7. EU regions

Differences among European regions have been established by grouping the RARECARE participating cancer registries by country and grouping the countries into 5 main European regions following the European cancer registry-based study on survival and care of cancer patients (EUROCORE) study:²⁵ Northern Europe (Iceland, Norway, Sweden), United Kingdom and Ireland (England, Scotland, Wales, Northern Ireland, Republic of Ireland), Central Europe (Belgium, Austria, France, Germany, the Netherlands, Switzerland), Eastern Europe (Poland, Slovakia), and Southern Europe (Italy, Malta, Portugal, Slovenia, Spain). For 11 countries, CRs covered the entire national population (Austria, Iceland, Ireland, Malta, Norway, Slovakia, Slovenia, Sweden, Northern Ireland, Scotland, Wales and England). The other 10 countries were represented by regional CRs, covering variable proportions of their respective national populations.

3. Results

3.1. Incidence

The incidence rate is presented per 1,000,000 person-years in Europe (crude rate) in Table 2. Table 2 shows also rates by sex (age adjusted rate), age group and the estimated number of new cases expected in EU27 every year. Well differentiated endocrine carcinomas of

Table 2

Observed cases with crude incidence (rate per million/year) and standard errors (SE) for neuroendocrine tumours in Europe. Rates and SE by sex and age, with estimated incident cases in Europe (EU27). Cases diagnosed 1995–2002 in 64 European CRs.

Entity	EU overall* (64 CRs)			Sex**		Age*								Estimated number of cases arising in EU27 per year
	Observed cases 1995–2002	Rate	SE	Male		Female		0–24 yrs		25–64 yrs		65 + yrs		
				Adj. rate	SE	Adj. rate	SE	Rate	SE	Rate	SE	Rate	SE	
Neuroendocrine tumours	20,357	25	0.18	24	0.24	19	0.20	2.0	<0.10	20	0.22	88	0.83	12,586
Well diff endocrine carcinoid tumours (skin and GI tract excluded)	2956	3.7	<0.10	3.4	0.09	2.8	<0.10	0.10	<0.10	3.0	<0.10	13	0.32	1826
Well diff endocrine atypical carcinoid tumours(skin and GI tract excluded)	6	<0.10	<0.10	<0.10	<0.10	<0.10	<0.10	0.00	~	<0.10	<0.10	<0.10	<0.10	5
Well diff endocrine carcinoma of the pancreas and digest organs (non-functioning)	10,099	13	0.13	12	0.17	9.7	0.15	1.14	<0.10	11	0.16	40	0.57	6243
Carcinoid tumours, NOS/islet cell carcinoma														
Well diff endocrine carcinoma of pancreas and of digest tract (functioning)	197	0.25	<0.10	0.25	<0.10	0.21	<0.10	0.08	<0.10	0.29	<0.10	0.6	<0.10	119
Malignant insulinoma, glucagonoma, somatostatinoma, gastrinoma/other ectopic hormone producing tumours														
Poorly diff endocrine carcinoma (skin and thyroid excluded)	4181	5.2	<0.10	5.4	0.10	3.3	<0.10	0.13	<0.10	3.3	<0.10	22	0.41	2587
Small cell endocrine carcinoma/Large cell endocrine carcinoma														
Mixed endocrine–exocrine carcinoma	17	<0.1	<0.10	<0.10	<0.10	<0.10	<0.10	<0.10	<0.10	<0.10	<0.10	<0.1	<0.10	10
Endocrine carcinoma of thyroid gland	1771	2.2	<0.10	1.8	<0.10	2.3	<0.10	0.55	<0.10	2.6	<0.10	4.2	0.18	1094
Medullary carcinoma/mixed medullary-follicular carcinoma														
Endocrine carcinoma of skin	1079	1.3	<0.10	0.99	<0.10	0.87	<0.10	<0.10	<0.10	0.35	<0.10	7.3	0.24	667
Merkel cell carcinoma														

~ Statistic could not be calculated.

NOS: not otherwise specified.

* Crude rate.

** Age standardised rate.

Table 3

Observed cases for neuroendocrine tumours per main localisation in 1995–2002 in 64 European CRs.

Entity	All tumours	Head and neck	Thyroid	Stomach	Small Intestine	Appendix	Colon	Rectum	Pancreas	Skin	Male genital	Female genital	Others
	<i>N</i>	<i>N</i>	<i>N</i>	<i>N</i>	<i>N</i>	<i>N</i>	<i>N</i>	<i>N</i>	<i>N</i>	<i>N</i>	<i>N</i>	<i>N</i>	<i>N</i>
Neuroendocrine tumours	20,357	136	1753	1400	3669	1126	1425	1072	1635	1028	282	524	6307
Well diff endocrine carcinoid tumours (skin and GI tract excluded)	2956	41	9	0	0	0	0	0	0	0	67	227	2612
Well diff endocrine atypical carcinoid tumours (skin and GI tract excluded)	6	0	0	0	0	0	0	0	0	0	0	0	6
Well diff endocrine carcinoma of the pancreas and digest organs (non- functioning)	10,099	0	0	1245	3636	1124	1337	986	1313	0	0	0	458
Carcinoid tumours, NOS/islet cell carcinoma													
Well diff endocrine carcinoma of pancreas and of digest tract (functioning)	197	0	0	9	9	0	1	0	177	0	0	0	1
Malignant insulinoma, glucagonoma, somatostatinoma, gastrinoma/other ectopic hormone producing tumours													
Poorly diff endocrine carcinoma (skin and thyroid excluded)	4184	91	0	143	24	2	86	86	128	0	211	289	3121
Small cell endocrine carcinoma/ large cell endocrine carcinoma													
Mixed endocrine–exocrine carcinoma	17	0	0	1	0	0	0	0	15	0	0	0	1
Endocrine carcinoma of thyroid gland	1771	0	1771	0	0	0	0	0	0	0	0	0	0
Medullary carcinoma/mixed medullary-follicular carcinoma													
Endocrine carcinoma of skin	1097	0	0	0	0	0	0	0	0	1018	0	0	63
Merkel cell carcinoma													
Percentage of the total		0.67	8.6	6.9	18	5.5	7.0	5.3	8.0	5.0	1.4	2.6	31

Table 4

Age-standardised (Adj) incidence rates (per 1,000,000) for neuroendocrine cancers in 1995–2002, with standard errors (SE) by European Region.

Entity	European region										EU Overall (64 CRs)	
	Northern Europe		Central Europe		Eastern Europe		Southern Europe		UK and Ireland		Adj. rate	SE
	Adj. rate	SE	Adj. rate	SE	Adj. rate	SE	Adj. rate	SE	Adj. rate	SE		
Neuroendocrine tumours	32	0.51	27	0.36	7.5	0.33	18	0.32	19	0.24	21	0.15
Well diff endocrine carcinoid tumours (skin and GI tract excluded)	4.7	0.19	4.1	0.14	0.42	<0.10	2.1	0.11	3.0	0.10	3.1	<0.10
Well diff endocrine atypical carcinoid tumours (skin and GI tract excluded)	0.00	~	<0.10	<0.10	<0.10	<0.10	0.00	~	0.00	~	<0.10	<0.10
Well diff endocrine carcinoma of the pancreas and digest organs (non-functioning)	18	0.39	13	0.26	3.5	0.22	8.3	0.22	9.2	0.17	11	0.10
Carcinoid tumours, NOS/islet cell carcinoma												
Well diff endocrine carcinoma of pancreas and of digest tract (functioning)	0.33	<0.10	0.21	<0.10	0.22	<0.10	0.20	<0.10	0.21	<0.10	0.23	<0.10
Malignant insulinoma, glucagonoma, somatostatinoma, gastrinoma/other ectopic hormone producing tumours												
Poorly diff endocrine carcinoma (skin and thyroid excluded)	4.7	0.19	5.7	0.16	1.2	0.13	2.9	0.12	4.4	0.11	4.2	<0.10
Small cell endocrine carcinoma/large cell endocrine carcinoma												
Mixed endocrine–exocrine carcinoma	<0.10	<0.1	<0.10	<0.10	<0.10	<0.10	<0.10	<0.10	<0.10	<0.10	<0.10	<0.10
Endocrine carcinoma of thyroid gland	1.9	0.13	2.7	0.12	2.0	0.2	3.1	0.1	1.2	<0.10	2.1	<0.10
Medullary carcinoma/mixed medullary-follicular carcinoma												
Endocrine carcinoma of skin	1.6	0.10	0.86	<0.10	0.13	<0.10	1.0	<0.10	0.77	<0.10	0.91	<0.10
Merkel cell carcinoma												

~ Statistic could not be calculated. NOS: not otherwise specified.

Table 5
Two, 5, 15-year prevalence proportions (per 100.000) and estimated complete prevalence in Europe.

Entity	Observed prevalence									Estimated prevalence		
	Two years after diagnosis			Five years after diagnosis			Fifteen years after diagnosis			Complete		EU27 2008
	Prev.	SE	N of cases	Prev.	SE	N of cases	Prev.	SE	N of cases	Prev.	SE	N of cases
Neuroendocrine tumours	4.1	<0.10	20,262	7.9	0.11	39,717	13	0.14	66,133	20	0.25	100,003
Well diff endocrine carcinoid tumours (skin and GI tract excluded)	0.56	<0.10	2786	0.95	<0.10	4734	1.2	<0.10	6239	1.6	<0.10	7791
Well diff endocrine atypical carcinoid tumours (skin and GI tract excluded)	<0.10	<0.10	15	<0.10	<0.10	23	<0.10	<0.10	23	<0.10	<0.10	35
Well diff endocrine carcinoma of the pancreas and digest organs (non-functioning)	2.3	<0.10	11,693	4.9	<0.10	24,294	8.4	0.11	41,801	13	0.20	63,691
Carcinoid tumours, NOS/islet cell carcinoma												
Well diff endocrine carcinoma of pancreas and of digest tract (functioning)	<0.10	<0.10	210	<0.10	<0.10	413	0.15	<0.10	747	0.22	<0.10	1070
Malignant insulinoma, glucagonoma, somatostatinoma, gastrinoma/other ectopic hormone producing tumours												
Poorly diff endocrine carcinoma (skin and thyroid excluded)	0.34	<0.10	1681	0.54	<0.10	2695	0.90	<0.10	4495	1.3	<0.10	6679
Small cell endocrine carcinoma/large cell endocrine carcinoma												
Mixed endocrine–exocrine carcinoma	<0.10	<0.10	23	<0.10	<0.10	31	<0.10	<0.10	55	<0.10	<0.10	96
Endocrine carcinoma of thyroid gland	0.47	<0.10	2370	<0.10	<0.10	4866	1.8	<0.10	9028	3.2	0.11	16,164
Medullary carcinoma/mixed medullary-follicular carcinoma												
Endocrine carcinoma of skin	0.28	<0.10	1414	0.51	<0.10	2528	0.70	<0.10	3506	0.86	<0.10	4273
Merkel cell carcinoma												

N of cases: number of cases; SE: standard error; Prop.: proportion; NOS: not otherwise specified.

the pancreas and digestive organs (non-functioning) were the most common tumours among NETs, with a crude incidence rate of 13 per 1,000,000 person-years, followed by poorly differentiated endocrine carcinomas (skin and thyroid excluded), with a crude rate of 5.2 per 1,000,000 person-years. For all other entities the crude incidence rate was below 4.0 per 1,000,000 person-years (Table 2).

The localisation of NETs was 65% at 8 different sites: small intestine (18%), thyroid gland (8.6%), pancreas (8.0%), colon (7.0%), stomach (6.9%), appendix (5.5%), rectum (5.3%) skin (5.0%). The other 35% were located at sites such as female and male genital organs, head and neck and other sites. Within these 35% we found that there was no specific site registered for 19% of all NETs, which accounted for 60% of the column included 'others' (Table 3).

NETs were more common in men, except for endocrine carcinoma of the thyroid gland. The incidence rate was highest in patients aged 65 years and older, ranging from <0.10 up to 40 per 1,000,000 person-years. We estimated 12,600 new cases per year for EU27, of which 6250 (50%) were well differentiated endocrine carcinomas of the pancreas and digestive organs (non-functioning) (Table 2).

Table 4 shows the age standardised incidence rate by European region between 1995 and 2002. There was a geographical variation in age standardised incidence, with the highest rates in Northern Europe (32 per 1,000,000) and the lowest in Eastern Europe (7.5 per 1,000,000) (Table 4).

3.2. Prevalence

Table 5 shows the estimated complete prevalence in Europe and the observed prevalence proportion of those diagnosed 2, 5 and 15-years before the index date (1st January 2003). Over 100,000 people (last column of

Table 5) were estimated to be alive in EU at the beginning of 2008 with a diagnosis of NET.

Of these, 20% (20,262 over 100,003) and 40% (39,717 over 100,003) were diagnosed within 2 and 5 years before the index date, respectively. The difference (20%) between these two proportions represents the proportion of cases diagnosed 3–4 years before the index date, and therefore presumably still undergoing clinical follow-up. The remaining 60% represents those surviving over 5 years after diagnosis, 34,200 of those (34% of the total) surviving more than 15 years after their initial diagnosis.

Well differentiated endocrine carcinomas of the pancreas and digestive organs (non-functioning) were estimated for the year 2008 to be the most prevalent endocrine tumours (63,700 cases), followed by endocrine carcinomas of thyroid gland (16,200 cases), well differentiated endocrine carcinoid tumours (7800 cases), and poorly differentiated endocrine carcinomas (skin and thyroid excluded) (6700 cases). The remaining second tier entities of NETs accounted for less than 6000 prevalent cases.

The distribution of prevalent cases by time since diagnosis varied between the different tumour entities depending on the prognosis of the specific tumour type and the mean age of incidence (Table 5).

Endocrine carcinomas of the thyroid gland had the highest proportions of very long term survivors who survived over 15 years following diagnosis (44%). Around 70% of endocrine carcinoma of the thyroid gland occurred in the age groups under 65 years of age.

3.3. Survival

Fig. 1 shows 5-year relative survival for the different NET entities. Within NETs, endocrine carcinoma of thyroid gland had the best 5-year relative survival, with a rate of 82% ($N = 599$). The most frequent NETs, well

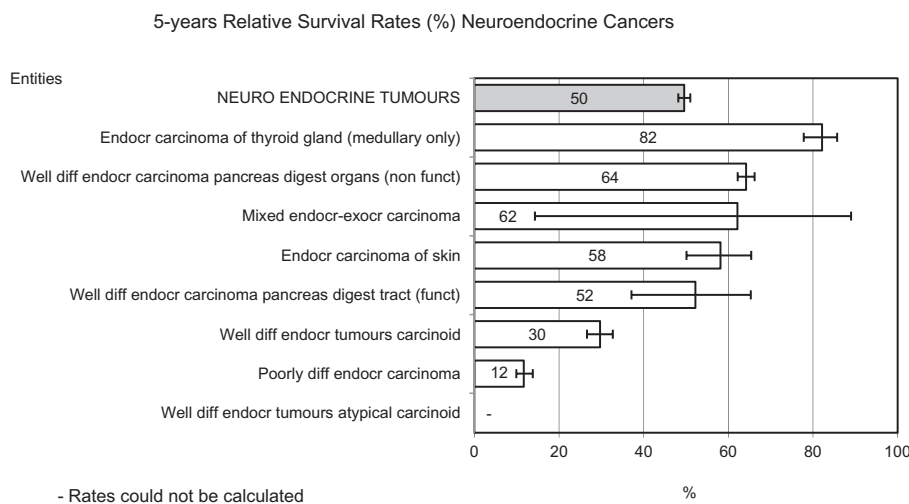


Fig. 1. Five year relative survival (%) for neuroendocrine tumours in Europe 2000–2002. Error bars are 95% confidence interval.

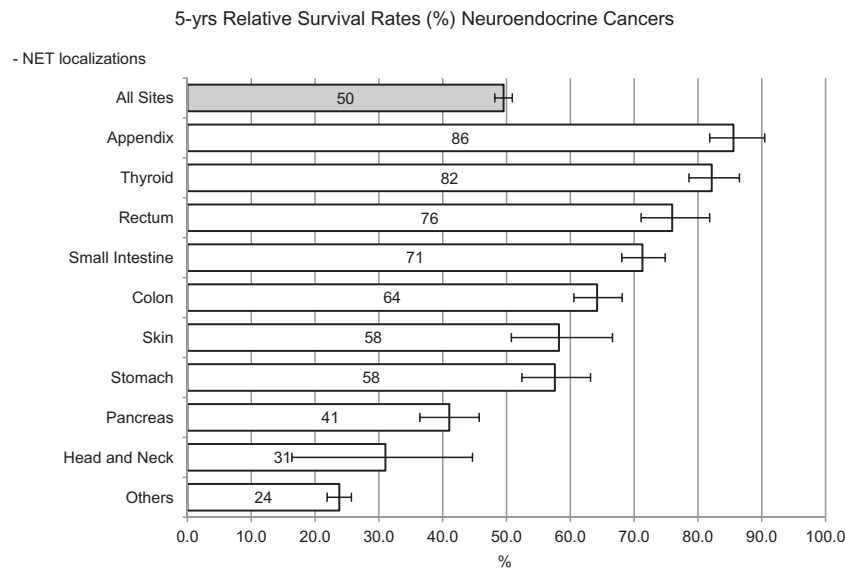


Fig. 2. Five year relative survival (%) for the main localisations of neuroendocrine tumours in Europe 2000–2002. Error bars are 95% confidence interval.

differentiated endocrine carcinomas of the pancreas and digestive organs (non-functioning) had the second best 5-year relative survival with a rate of 64% ($N = 3540$). Well differentiated endocrine tumours, and poorly differentiated endocrine carcinomas (skin and thyroid excluded) had the poorest 5-year relative survival: 30% ($N = 1144$) and 12% ($N = 1543$) respectively (N not in tables). The 5 year relative survival for mixed endocrine–exocrine carcinomas was 62% but based on only seven cases. The number of cases ($N = 6$) was too little to calculate the 5-year relative survival with the period survival method²³ for well differentiated endocrine tumours atypical carcinoid.

Fig. 2 shows that NETs of appendix and thyroid gland had the highest survival, followed by NETs diagnosed in the rectum and the small intestine. NETs of the pancreas and the Head and Neck had the poorest survival with a 5-year relative survival rate of 41% ($N = 564$) and 31% ($N = 54$). Survival was consistently lower for patients of 65 years or over than for younger patients (data not shown).

4. Discussion

The availability of a high quality European database has given us the opportunity to obtain a large scale European study on NETs. This study gives a unique possibility to compare our large scale EU data on NETs with already existing small cohort studies, reviews, case reports and large cohort studies from other countries and continents.^{8,26,27}

The major indicators of data quality (Table 1) indicate a high quality dataset with 97% of cases histologically confirmed. However, the main concern when studying such rare tumours, relates to the accuracy of

diagnosis and the completeness of registration. The recent improvements regarding pathologic diagnosis and grading of NETs are a major step forward, however we had to use the nomenclature at the time of our study period 1995–2002, and we had to rely on the diagnosis reported in the clinical records.

The RARECARE group assessed the quality of data and the extent of registration bias undertaking a dedicated study in collaboration with CRs providing the data. RARECARE reviewed the original data of a selected sample ($N = 3000$) focusing on undifferentiated (ICD-O3 code 8020/3) and anaplastic (ICD-O3 code 8021/3) carcinomas of the digestive tract (ICD-O3 code C15 to C25).²⁸ The objective of this review was to identify additional cases, if any. This check led to only 10 additional cases out of 929 cases of undifferentiated and anaplastic carcinomas identified. Also, all carcinoids (ICD-O3 codes 8240–8244) of the digestive tract were reviewed to assess their behaviour. Pathological reports were reviewed looking for information on depth of invasion, tumour size and Ki67 labelling index. Unfortunately, most prognostic information regarding so called carcinoids of the digestive tract were missing in the majority of pathological reports. This finding suggests that the quality of diagnosis was high, although major concerns can be raised regarding the completeness of prognostic parameter evaluation. Our data clearly indicate that the referral of NETs to an expert pathologist would greatly impact on diagnostic accuracy, as well as on evaluation of prognosis across the EU. Where ENETS is giving practical guidelines for diagnosis and treatment of NETs, no information is available on the criteria for expert pathologists.

Our data confirm results presented by other small sets of population based studies that report an incidence rate

for NETs (NETs of the lung excluded) of around 2 per 100,000 person-years.^{3,8,9} The overall survival rate shown is broadly in line with the literature²⁷, which seems to relate to anatomic sites, i.e. 86% in the appendix, 71% in the small intestine, and 41% in the pancreas (Fig. 2). A population based study included potential prognostic parameters in their study model including disease stage, primary tumour site, histology, age, sex, race and period of diagnosis, and found all parameters to be significant.²⁷

Regarding well differentiated endocrine tumours, our analysis describes four different subgroups of neuroendocrine tumours: (1) well differentiated endocrine tumours, (2) well differentiated endocrine carcinoma, (3) endocrine carcinoma of the pancreas and digestive organs (non-functioning) and (4) the endocrine carcinoma of the pancreas and digestive tract (functioning) (Table 1).

Well differentiated endocrine tumours are less aggressive than poorly differentiated endocrine tumours, indicated by their lower Ki67 index.²⁹

The age standardised incidence rates within the well differentiated endocrine tumours showed a difference between the different EU regions (Table 5). The difference for the well differentiated endocrine carcinoma of the pancreas and digestive tract (non-functioning) was most marked. The highest age adjusted rate was found in the Northern Europe and the lowest rate was found for the Eastern Europe region. Unfortunately, we could not find studies confirming this result. For both regions the percentage of histologically verified cases was similar. The difficulties in reaching a diagnosis (by non-expert pathologists or limited diagnostic mean available), the availability of organised NET centres, the use of endoscopic surveillance or the existence of national hereditary screening programs could all contribute to explain the observed difference in incidence. Differences in incidence could also be due to different distribution of risk factors in the population, however, limited information is available on NET risk factors. An important limitation of this study is that the Eastern region is represented by only four CRs, in contrast to the Northern EU region, represented by National CRs including the whole population of those countries.

Our data are consistent with the literature for the majority of well differentiated endocrine tumours.³⁰ The literature for carcinoids shows a wide variation in survival rates, related to the different sites in which carcinoids have been found.³¹ In our study, the survival for well differentiated endocrine tumours of the digestive tract was 52% for the functioning tumours and 64% for non-functioning, respectively. For the other sites, 5 year relative survival was of 30% (Fig. 1). This low survival can be explained by two facts. Most carcinoids are diagnosed having already metastasised,³⁰ resulting in limited possibilities for potentially curative treatment.³¹

For example, surgery is considered an effective treatment in early stage NETs, but once metastasised there are limited options for potentially curative treatment. Single agent chemotherapy, results in very low response rates of about 10%.³¹

Secondly, the majority of the carcinoids with poor prognosis are those of unknown primary site (ICD-O3 code C80.9).

Results on incidence, prevalence and survival for the endocrine atypical carcinoid tumours should be interpreted with caution as they were based on a very limited number of cases ($N = 6$ in three differentiated sites). However, this is the first time these outcomes are reported.

The poorly differentiated endocrine carcinomas are characterised by a high grade of malignancy and poor prognosis.³² Our study reported a 5-year relative survival of 12%. As the expected number of incident cases covers over 20% of all expected cases of NETs in EU27 this observation seriously affects the overall 5 year relative survival of NETs. We found a predominance in men (1:0.6) and a peak incidence in people older than 65 years. This male predominance was also found by other studies.^{33,34}

Endocrine carcinoma of the thyroid, mainly including medullary carcinomas with amyloid stroma, represented just over 8.5% of the total number of NETs. A female predominance and an increase in age standardised incidence rate through age was found, confirming results seen elsewhere in the literature.^{35,36} A pooled analysis of 14 different case control studies in different continents found a relationship between having a first child after the age of 25 years and a significantly increased risk for developing medullary thyroid cancer.³⁶ This could partly explain the rise in incidence for the female gender through age.

The survival analyses showed better survival following diagnosis at a younger age (ranging from 100% for the age group 0–14 to 70% for the age group >65). This higher survival in age 0–14 might be affected by standardised surveillance programmes, which allows the early detection of micro carcinomas and the possibilities for a complete cure.³⁷ These cases of early detection are included in our analyses. The literature reports 25% of all medullary thyroid carcinomas being familial.^{38,39} These results found are in line with a population based study which included the SEER population for the period 1973–1991.³⁵

The 5 year relative survival of the endocrine carcinoma of the thyroid gland (82%) was by far the best seen within NETs (Fig. 1). It is well known that surgery after early detection of thyroid medullary carcinomas offers a near 100% cure rate.⁴⁰

Mixed endocrine–exocrine carcinomas are rare pancreatic neoplasms and most arise as a single type cell, either from the endocrine or exocrine pancreas. To make

an accurate diagnosis of these tumours is difficult, because a lesion is only categorised to be a mixed endocrine–exocrine carcinoma when the endocrine cells exceed 25–30% of the tumour⁴¹ and complete resection of the tumour is needed for the final diagnosis. We only identified 18 cases of mixed endocrine–exocrine carcinoma, so no conclusions can be drawn. However, for the mixed endocrine–exocrine carcinomas 89% of the cases included were microscopically verified. We found similar results on survival compared to the study done by Yao et al.,²⁷ who report a median survival of 135 months. Both, Yao et al. and our study found that mixed forms have a survival similar to well differentiated carcinoid tumours.²⁷

Endocrine carcinoma of the skin mainly includes the Merkel cell carcinoma which has an aggressive behaviour.⁴² We found an annual incidence rate of 1.3/1,000,000, resulting in an estimated number of 600 Merkel cell carcinomas each year in the EU27, with a highest incidence in the age category 65+. The 5 year relative survival of 58% was consistent with the 59% reported in previous studies.^{43–46} The Finnish cancer registry found a small predominance in female and a mean age of 76 years at time of diagnosis.⁴⁵ This small discrepancy in relation to our study might be caused by the fact that the Finnish cancer registry only included 181 cases of Merkel cell carcinomas, while we observed 1079 Merkel cell carcinomas within our study.

Classifying NETs is an on-going debate.⁴⁷ In 2010 the WHO has presented a new classification of NETs in the digestive tract,⁴⁸ while the classification for NETs of the lung has already existed since 1994.⁴⁹ The evolution of the classification of NETs is still incomplete, for example different anatomic site (such as lung) still use different terminologies. This paper, far from trying to resolve such issues, may contribute to improve data quality on this important subset of cancers. We would encourage this debate by publishing population based data collected by CRs all over Europe, showing results based on a relatively large number of cases for a relatively rare tumour.

From the quality check conducted by the RARE-CARE study we can conclude that despite 97% of the cases being histologically confirmed, the completeness of case ascertainment of NETs is still not always being achieved.⁵⁰ It is extremely important that in future classification nomenclatures become homogenous for all anatomic sites. In addition strong educational efforts should be made in order to familiarise with punctual registration of key prognostic factors such as mitotic count as well as ki67 labelling index.

In contrast to previous studies, usually based on small numbers of cases, our study is based on a large series of patients. Because of the complexity and lack of knowledge of the different disciplines involved in the management of NETs, a multidisciplinary approach

on NETs is desirable.⁵¹ To support this multidisciplinary approach, highly qualified reference centres, guidelines and an international network between those centres is recommended.¹⁸

Conflict of interest statement

The authors declare no conflicts of interest. The founding sources had no role in study design, data collection, data analysis, data interpretation, in writing this report, or in the decision to submit for publication.

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