NEUROENDOCRINE TUMOURS

100%
OF NEUROENDOCRINE TUMOURS ARE RARE

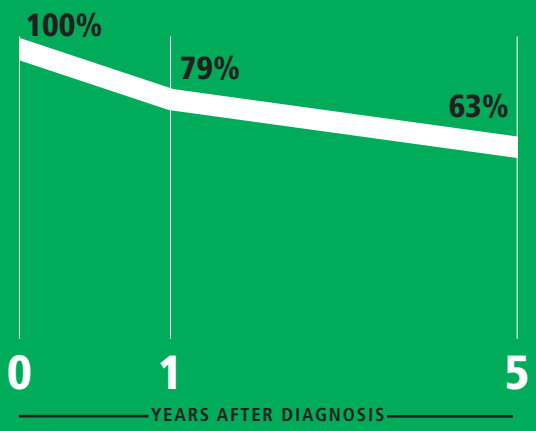
INCIDENCE

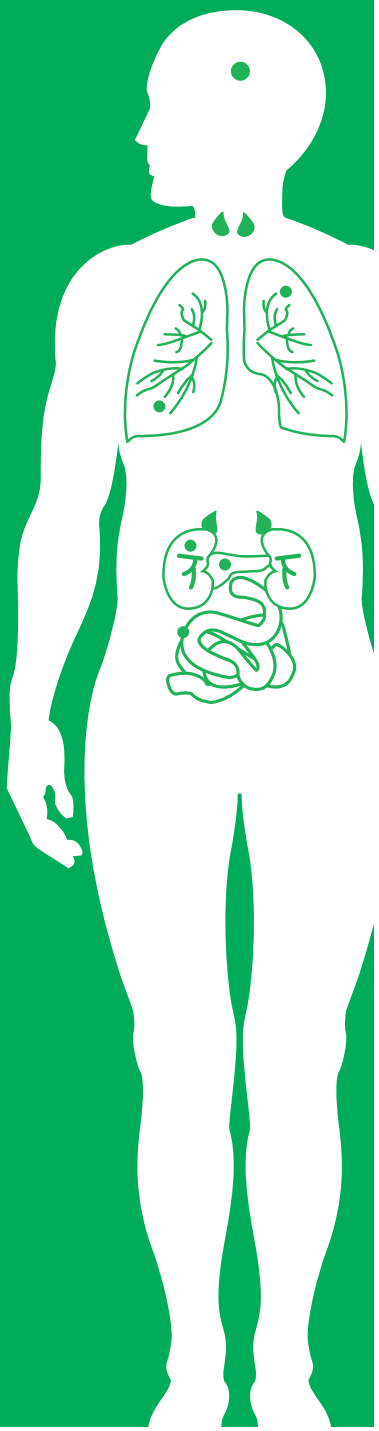
2 697
ESTIMATED NEW CASES
ITALY, 2015

PREVALENCE

23 937
ESTIMATED PREVALENT CASES
ITALY, 2010

SURVIVAL

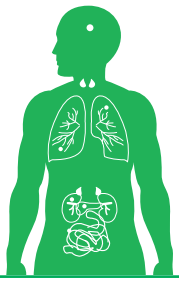




SOURCE: AIRTUM. ITALIAN CANCER FIGURES–REPORT 2015

NEUROENDOCRINE TUMOURS

INCIDENCE



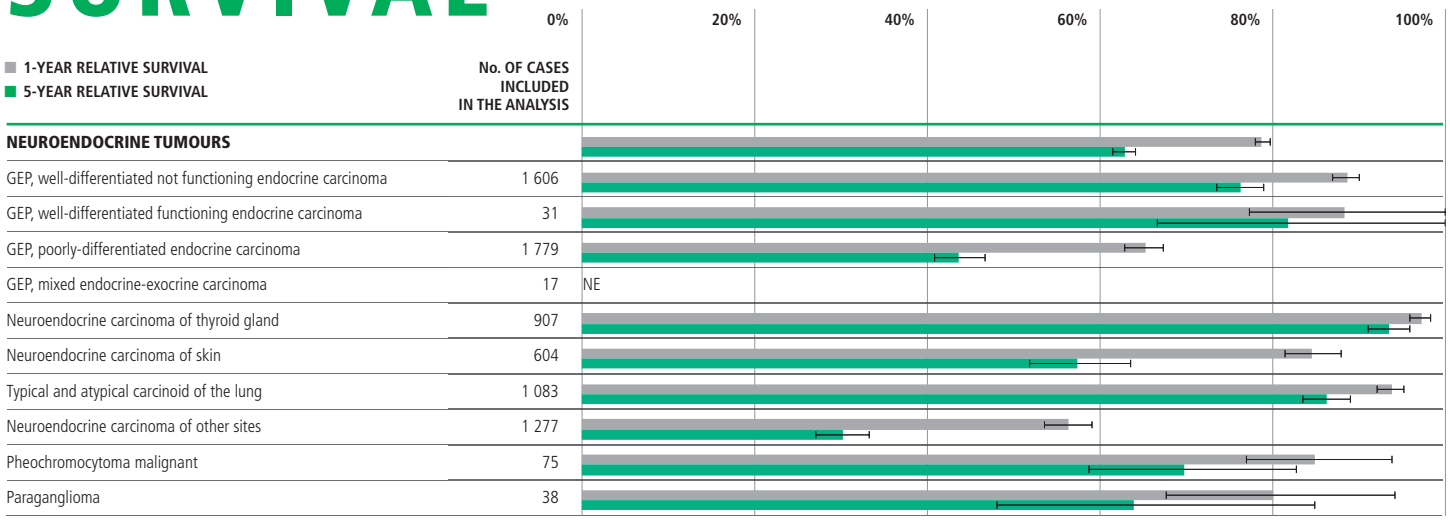
NEUROENDOCRINE TUMOURS. Crude incidence (rate per 100,000/year) and 95% confidence interval (95% CI), observed cases and proportion of rare cancers on all (common + rare) cancers by site. Rates with 95% CI by sex and age. Estimated new cases at 2015 in Italy.

	AIRTUM POOL (period of diagnosis 2000-2010)														ITALY
					SEX				AGE						
					MALE		FEMALE		0-54 yrs		55-64 yrs		65+ yrs		
	RATE	95% CI	OBSERVED CASES (No.)	RARE CANCERS BY SITE (%)	RATE	95% CI	RATE	95% CI	RATE	95% CI	RATE	95% CI	RATE	95% CI	ESTIMATED NEW CASES 2015
NEUROENDOCRINE TUMOURS	**4.15**	**4.06-4.23**	**9 196**	**NA**	**4.31**	**4.18-4.43**	**4.00**	**3.88-4.12**	**1.49**	**1.42-1.55**	**7.37**	**7.05-7.70**	**11.27**	**10.95-11.58**	**2 697**
GEP, well-differentiated not functioning endocrine carcinoma	0.89	0.85-0.93	1 970		0.97	0.91-1.03	0.81	0.76-0.87	0.34	0.31-0.37	1.58	1.44-1.74	2.34	2.20-2.49	576
GEP, well-differentiated functioning endocrine carcinoma	0.02	0.01-0.03	41		0.02	0.01-0.03	0.02	0.01-0.03	<0.01	0.01-0.02	0.06	0.03-0.09	0.03	0.01-0.05	12
GEP, poorly-differentiated endocrine carcinoma	1.01	0.97-1.05	2 233		1.20	1.13-1.26	0.83	0.78-0.89	0.31	0.28-0.34	1.87	1.72-2.04	2.85	2.69-3.01	655
GEP, mixed endocrine-exocrine carcinoma	<0.01	0.00-0.01	17		<0.01	0.00-0.01	<0.01	0.00-0.02	<0.01	0.00-0.01	<0.01	0.00-0.03	0.01	0.01-0.03	5
Neuroendocrine carcinoma of thyroid gland	0.51	0.48-0.54	1 125		0.38	0.34-0.42	0.63	0.58-0.67	0.30	0.27-0.33	1.05	0.93-1.18	0.88	0.80-0.97	320
Neuroendocrine carcinoma of skin	0.34	0.32-0.37	759		0.33	0.30-0.37	0.35	0.32-0.39	0.03	0.02-0.04	0.34	0.28-0.42	1.42	1.31-1.54	238
Typical and atypical carcinoid of the lung	0.60	0.57-0.63	1 328		0.56	0.51-0.60	0.64	0.59-0.68	0.27	0.24-0.30	1.17	1.05-1.31	1.37	1.26-1.49	378
Neuroendocrine carcinoma of other sites	0.71	0.68-0.75	1 585		0.77	0.72-0.83	0.66	0.61-0.71	0.18	0.16-0.21	1.16	1.03-1.29	2.26	2.12-2.41	474
Pheochromocytoma, malignant	0.04	0.03-0.05	94		0.04	0.03-0.06	0.04	0.03-0.05	0.03	0.02-0.04	0.08	0.05-0.12	0.07	0.05-0.10	27
Paraganglioma	0.02	0.01-0.03	44		0.02	0.02-0.03	0.02	0.01-0.03	0.01	0.01-0.02	0.05	0.03-0.08	0.03	0.02-0.05	13

NA: not applicable **GEP:** gastroenteropancreatic tract

SURVIVAL

NEUROENDOCRINE TUMOURS. One and 5-year relative survival. Error bars are 95% confidence interval. Cohort approach (complete analysis), period of diagnosis 2000-2008.



	No. OF CASES INCLUDED IN THE ANALYSIS
NEUROENDOCRINE TUMOURS	
GEP, well-differentiated not functioning endocrine carcinoma	1 606
GEP, well-differentiated functioning endocrine carcinoma	31
GEP, poorly-differentiated endocrine carcinoma	1 779
GEP, mixed endocrine-exocrine carcinoma	17
Neuroendocrine carcinoma of thyroid gland	907
Neuroendocrine carcinoma of skin	604
Typical and atypical carcinoid of the lung	1 083
Neuroendocrine carcinoma of other sites	1 277
Pheochromocytoma malignant	75
Paraganglioma	38

NE: not estimable

NE: not estimable because 30 or less incident cases were observed **GEP:** gastroenteropancreatic tract

PREVALENCE

NEUROENDOCRINE TUMOURS. Observed prevalence (proportion per 100,00 and 95% confidence interval - 95% CI) by duration (≤2, 2-5, ≤15 years) prior to prevalence date (1st January 2007), and complete prevalence. Estimated prevalent cases in 2010 in Italy.

	AIRTUM POOL								ITALY
	OBSERVED PREVALENCE BY DURATION						COMPLETE PREVALENCE		
	≤2 YEARS		2-5 YEARS		≤15 YEARS				
	PROPORTION	95% CI	PROPORTION	95% CI	PROPORTION	95% CI	PROPORTION	95% CI	ESTIMATED PREVALENT CASES 2010
NEUROENDOCRINE TUMOURS	**7.38**	**6.82-7.97**	**7.65**	**7.08-8.25**	**28.18**	**27.07-29.31**	**40.73**	**38.95-42.50**	**23 937**
GEP, well-differentiated not functioning endocrine carcinoma	1.70	1.43-1.99	2.08	1.78-2.40	8.54	7.94-9.18	12.89	11.96-13.82	7 427
GEP, well-differentiated functioning endocrine carcinoma	NE	–	0.03	0.01-0.10	0.20	0.11-0.31	0.33	0.16-0.49	195
GEP, poorly-differentiated endocrine carcinoma	1.35	1.11-1.61	1.30	1.07-1.56	3.43	3.05-3.84	3.49	3.09-3.89	2 140
GEP, mixed endocrine-exocrine carcinoma	0.02	0.00-0.08	0.01	0.00-0.06	0.05	0.01-0.12	0.09	0.01-0.18	51
Neuroendocrine carcinoma of thyroid gland	1.24	1.01-1.49	1.48	1.24-1.76	4.93	4.47-5.42	9.45	8.51-10.39	5 455
Neuroendocrine carcinoma of skin	0.76	0.59-0.96	0.48	0.35-0.65	1.90	1.62-2.21	2.34	1.98-2.70	1 369
Typical and atypical carcinoid of the lung	1.33	1.10-1.60	1.38	1.14-1.65	6.07	5.57-6.61	8.34	7.62-9.06	4 995
Neuroendocrine carcinoma of other sites	0.96	0.77-1.19	0.76	0.59-0.96	2.77	2.43-3.14	3.16	2.76-3.56	1 932
Pheochromocytoma, malignant	0.02	0.00-0.08	0.08	0.03-0.17	0.28	0.18-0.41	0.47	0.28-0.66	275
Paraganglioma	NE	–	0.05	0.01-0.12	0.09	0.04-0.18	0.17	0.05-0.28	98

NE: not estimable in observed prevalence if no cases were observed within ≤2, 2-5, ≤15 years prior to prevalence date, in complete prevalence if the 15-year prevalence is NE **GEP:** gastroenteropancreatic tract

The list of rare cancers proposed by the European RARECARE project (www.rarecare.eu) is based on a combination of ICD-O-3 morphologies and topographies. This is appropriate for all rare cancers and especially for neuroendocrine tumours. Morphologic analyses, immunohistochemical studies, and, more recently, molecular studies have attempted to classify this family of neoplasms. These classifications properly group neuroendocrine tumours (NETs) according to grading, but diagnosis, treatment, and prognosis also depend on the site of origin. Thus, in addition to grading, the site of origin should always be considered to understand the different behaviour, clinical presentations, and prognosis of these tumours and to properly describe them.

The NET grouping proposed by RARECARE combines morphologies (as a proxy of the grading) and topographies as follows:

- gastroenteropancreatic (GEP), well-differentiated non functioning endocrine carcinoma;
- GEP, well-differentiated functioning endocrine carcinoma;
- GEP, poorly differentiated endocrine carcinoma;
- GEP, mixed endocrine-exocrine carcinoma;
- neuroendocrine carcinoma of thyroid gland;
- neuroendocrine carcinoma of skin;
- typical and atypical carcinoid of the lung;
- neuroendocrine carcinoma of other sites;
- malignant pheochromocytoma;
- paraganglioma.

Poorly differentiated endocrine carcinoma of the lung is not considered in this monograph, because it is not considered rare by the RARECARE cancer list (since its incidence is >6 per 100,000 at EU level).

WHAT DO WE KNOW ABOUT THESE CANCERS?

NETs are neoplasms that originate from the diffuse neuroendocrine cell system which is in many different organs, sharing common expression of neuroendocrine markers and characterised by amine, neuropeptide, or hormone production. NETs are rare tumours and aetiological factors are unknown, apart from familial syndromes like multiple endocrine neoplasia (MEN) and the reported familial risk for gastrointestinal carcinoids.[1] About 20% of thyroid neuroendocrine carcinomas are related to MEN. No association was found with smoking for lung NETs, which are associated with MEN in 8% of cases.[2] **Neuroendocrine carcinoma of the skin** is mostly represented by Merkel carcinoma, which is characterised by an aggressive behaviour. Ultraviolet radiation exposure plays an important role for the development of this cancer. Patients with AIDS have a higher risk to develop this tumour.[3] Polyomavirus infection has been detected in Merkel carcinoma and seems to be a contributing factor to its development.[4] **Pheochromocytoma and paraganglioma** are both very rare and have similar basic histopathological characteristics, but pheochromocytoma arises from the adrenal medulla and paraganglioma from nerve ganglia, mainly located in the head and neck. About 24%-27% of pheochromocytoma or paraganglioma are associated with known genetic mutations, which in children reach a prevalence of 40%.[5] NETs have in general been considered indolent tumours with low metastatic potential; however, some NET subtypes are highly malignant and carry a bad prognosis with the possibility to metastasise to regional lymph nodes and distant organs. In general, the current WHO guidelines divide NETs into well-differentiated, traditionally referred to as carcinoids and pancreatic islet cell tumours, and poorly differentiated tumours, with different prognosis.[6,7] Most poorly differentiated NETs (about 50%) have metastatic disease at diagnosis, in contrast with well-differentiated NETs (20%).[8]

NET incidence is in constant, gradual increase in the Western populations.[7-9] Improvement in classification and new immunohistochemical techniques could have contributed to this increase, but it is still unclear if this trend is due to an increased awareness among physicians and pathologists, improved diagnostic tools, or an actual real increase in NET incidence.[8] Furthermore, increasing clinical and biological knowledge has led to changes in the classification of these tumours, which could be responsible for the geographical differences in incidence reported in the literature, together with different awareness of clinicians, different expertise of pathologists, and availability of markers to identify these tumours across countries.[9] It should also be considered that registration is based on a morphology code of the ICD-O-10 with a malignant behaviour, so data may partly vary between clinical trial and population-based cancer registries.

Incidence rate and distribution by anatomic site are widely variable in the literature, depending on the specific code included in the studies, so it is very difficult to compare the results. As the pathology report is the basis for a correct diagnosis and for a correct identification and classification of NETs, it is essential that the pathological report contains all the necessary information to identify the NET and their different subtypes. Despite the lack of some clinical and histopathological variables, such as associated syndromes (ICD-O does not include any code for secretor function) or proliferation index or grading, the association of ICD-O-3 codes with the different sites proposed in this report properly captures the different clinical behaviours of these tumours and thus represents the first unselected study from a large population in Italy to describe the burden of these heterogeneous neoplasms in Italy.

THE EPIDEMIOLOGICAL DATA IN ITALY

Incidence

NETs included in this monograph are all rare cancers. In Italy 9,197 cases were registered in the period 2000-2010 leading to an incidence rate (IR) of 4.15 per 100,000 (incidence table, p. 91). The incidence of all NETs is slightly higher in Italy than in the European RARECAREnet database (IR 3.5) (www.rarecarenet.eu), mainly due to a slightly higher incidence in Italy than in Europe of poorly differentiated GEP carcinoma, thyroid NETs, and well-differentiated carcinoids of the lung. NETs occur with similar frequency in males and females, except for neuroendocrine carcinoma of the thyroid, which has higher incidence in females than males, with an IR of 0.63 vs. 0.38, respectively (see table p. 91) and poorly differentiated GEP carcinoma, which is more frequent in males than females. The IR of NETs increases with age. In Italy about 2,700 new cases are expected in 2015. About 46% of NETs are in the GEP system with a marked heterogeneity in terms of biologic behaviour and histological differentiation.

Tumours can be functioning, causing a specific syndrome, or non-functioning. For tumours that arise mostly from the pancreas it is possible to attribute a specific code of functioning tumours, for other NETs it is not possible to identify syndrome-affected patients

(about 10%, variable in relation to the stage and primary site).
The most frequent primary GEP sites are the small intestine (25%), pancreas (22%), colon (19%), stomach (17%), and rectum (10%). NETs of the appendix comprise only 5% of all GEP NETs (data not shown). It is important to stress that carcinoid tumours of uncertain malignant potential of the appendix are not included in the data presented here. The most frequent morphologies of GEP NETs are poorly differentiated carcinoma (52%) and well-differentiated non functioning endocrine carcinoma (46%); well-differentiated functioning endocrine carcinomas are very rare, probably in part because of the lack of a code for functioning NETs arising in sites other than the pancreas. Typical and atypical carcinoids of lung are the second in order of frequency (14% of NETs). These tumours occur mainly in the over-54-year age group, with only a slight increase in those aged over 65 years, with an IR of 1.2 and 1.4, respectively (see table p. 91). Other lung NETs are not rare, and are therefore not included in this report. Neuroendocrine carcinoma of thyroid (12% of NETs) is mostly represented by medullary carcinoma, and occurs mainly in the fourth and fifth decade of life, with an IR of 1.1 (see table p. 91). NETs of skin (8% of NETs) typically occur in people over 64 years of age, with an IR of 1.4 (see table p. 91). Pheochromocytoma and paraganglioma are very rare tumours, with 94 and 44 cases observed over 11 years of observation in Italy. Neuroendocrine carcinoma of other sites is a very heterogeneous group including various primary sites, but also NETs of unknown origin, and represent in total about 18% of NETs, with an IR of 0.7 (see table p. 91). Of these, 13% are from the bladder, 11% from the breast, 9% from the female genital tract, 9% from the respiratory tract, 7% from head and neck, 3% from the prostate, 2% from the thymus, and 46% unknown origin. About 90% of all NETs of other sites have poorly differentiated morphology (data not shown).

Survival

In Italy, 1- and 5-year relative survival (RS) of NETs is 79% and 63%, respectively (survival figure, p. 91); slightly higher than the European RARECAREnet database (71% and 54% at 1 and 5-year, respectively). Five-year RS is slightly higher in Italy than in the European RARECAREnet database for GEP poorly differentiated, well-differentiated functioning and non-functioning, for NETs of thyroid, and for typical and atypical carcinoids of the lung. For the others, no major differences are observed between Italy and Europe. For GEP NETs a great difference in 5-year RS is observed between well-differentiated non functioning carcinoma (RS: 76%) and poorly differentiated tumours (RS: 44%) (see figure p. 91). This result is due to the aggressiveness of poorly differentiated NETs. The small intestine is the NET site with the best prognosis, as reported in the literature,[8] which shows only a slight difference in RS between well-differentiated NETs (1-year RS: 90%; 5-year RS: 77%) and poorly differentiated NETs (1-year RS: 85%, 5-year RS: 71%) (data not shown). Absence of symptoms in non functioning GEP NETs can lead to a delay in diagnosis and increased probability of metastatic disease, which make surgical treatment with curative intent impossible. The very complex treatment, requiring multidisciplinary integration, may lead to a heterogeneous care of these patients that could partially explain the geographical difference in survival observed across European countries. One- and 5-year RS of typical and atypical carcinoids of the lung is high (1-year RS: 94%, 5-year RS: 84%) see figure p. 91), reflecting the good prognosis of these tumours. Survival is strongly influenced by the possibility of receiving surgery, since surgery is the only curative approach.[11] Neuroendocrine carcinoma of thyroid gland has a good prognosis, with 1- and 5-year RS >90% (see figure p. 91). Age and stage at diagnosis are strictly correlated with survival. NETs of skin have an RS of 85% at 1 year, which drops to 57% at five years (see figure p. 91) This could be attributed to the aggressiveness of this tumour.
Diagnosis of metastasised disease in elderly patients could limit treatments.[12] Pheochromocytoma has an RS of 85% at 1 year and 70% at 5 years from diagnosis (see figure p. 91). Therapy of choice is surgical resection after appropriate preoperative preparation. Radiotherapy with MIBG could have a role in diffuse metastatic disease.[13] Paraganglioma has a relatively good survival, although estimates are based on 38 cases only. The worst RS is observed for NETs of other sites (RS 56% at one year and 30% at five years) (see figure p. 91), slightly better than European data (RS 48% and 24%, respectively). The large proportion of NETs of unknown primary site and of poorly differentiated NETs in this group can contribute to explain their low RS.

Prevalence

About 25,000 persons were estimated to be living with a NET diagnosis in Italyin 2010. GEP, well-differentiated, non functioning endocrine carcinomas are the most prevalent NETs, followed by neuroendocrine carcinomas of the thyroid gland, typical and atypical carcinoid of the lung, GEP, poorly differentiated endocrine carcinoma, and NETs of the skin. The remaining NETs accounted for a limited number of prevalent cases. The distribution of prevalent cases by time since diagnosis varied between the different tumour entities, depending on the prognosis of the specific histotype, site of origin, and mean age of incidence.

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