National Cancer Registry Ireland **Cancer Trends**

Neuroendocrine Cancers

Case numbers and groups

Neuroendocrine tumours (NETs) are cancers formed by cells that release hormones in response to signals from the nervous system. They occur at various sites in the body but are most commonly diagnosed in the digestive system, particularly the pancreas and small bowel, and in the lung. Many NETs are benign i.e. do not invade surrounding tissue or spread to other parts of the body. This article focuses on invasive NETs as defined by RARECARE[1], but also includes invasive pheochromocytomas and non-invasive NETs (carcinoids) of the appendix. Due to large numbers of unspecified cancer subtypes in the lung, NETs at this site are excluded, in accordance with the RARECARE definition.

1927 invasive NETs were diagnosed in Ireland from 1994 to 2010, representing an annual average of 113 cases (Table 1). Almost all cases (97%) were histologically confirmed. Similar numbers of men and women were diagnosed, although cancers located in the small intestine and thyroid were more frequent in men and cancers of the skin and appendix (invasive and non-invasive) were more common in women. NETs represented just 0.5% of all invasive tumours but they comprised almost one-third of tumours of the small intestine and appendix (invasive). Almost one in five adrenal cancers were NETs (pheochromocytomas). An average of 27 non-invasive NETs of the appendix (carcinoids) was diagnosed per year.

Table 1. Annual average numbers of neuroendocrine tumours (NETs) by cancer site, 1994–2010

	total	annual average	M/F ratio	% all cancers at this site
Total invasive	1927	113.4	1.0	0.5%
mouth & pharynx	29	1.7	1.2	0.4%
upper GI#	276	16.2	0.9	2.0%
pancreas	155	9.1	1.1	2.3%
hepato-biliary	25	1.5	0.8	0.6%
small intestine	257	15.1	1.6	32.5%
colorectal (excluding appendix)	215	12.6	1.2	0.6%
appendix (invasive)	89	5.2	0.5	32.2%
skin	231	13.6	0.7	0.2%
breast	23	1.4	0.0	0.1%
genito-urinary	99	5.8	0.8	0.1%
thyroid	91	5.4	1.4	5.2%
adrenal	41	2.4	1.1	19.4%
other/unspecified*	396	23.3	1.2	
appendix (non-invasive)	*453*	*26.6*	*0.6*	
TOTAL CASES	2380	140	0.9	

 # stomach & oesophagus **90% were cases where tumour site was not specified (most diagnosed from liver biopsies of metastases but no detail was provided in medical notes on the original site of the tumour – almost all cases were described as M-8041/3 "small cell neuroendocrine carcinoma", M-8240/3 "carcinoid, NOS" or M-8246/3 "neuroendocrine carcinoma, NOS"). Other specified sites included thymus, mediastinum and peritoneum.*

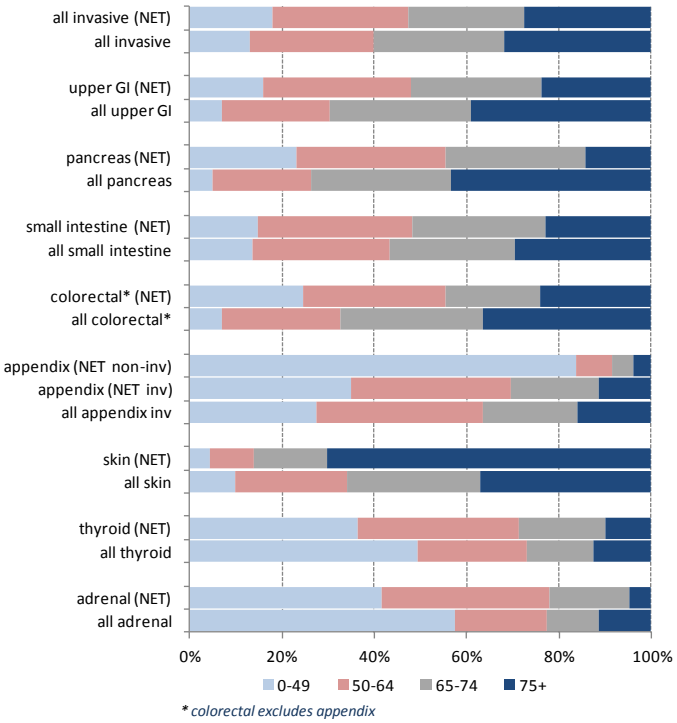
A note on subtypes

RARECARE identified 8 NET subgroups, depending on cell type and function as well as tumour site. Almost half of the 1927 invasive NETs described here were categorised as "well differentiated non-functioning endocrine carcinomas of the pancreas and digestive tract". This subgroup represented 100% of NETs sited in the small intestine and appendix and over 90% of those in the pancreas, hepato-biliary, colorectum (excluding appendix) and stomach. 93% of NETs of the skin were Merkel cell carcinomas and all but 1 NET sited in the adrenal gland was pheochromocytoma. Almost 60% of thyroid NETs were specified as medullary carcinomas with amyloid stroma but 40% were unspecified.

Age profile

Patients with NETs of the upper GI, pancreas and colorectum were generally diagnosed at a younger age than those with other tumours at the same sites (Figure 1). In contrast, patients with skin NETs had a much older age profile (median age 79) than patients with other non-melanoma skin cancers (NMSC) (median age 70). Patients diagnosed with carcinoid tumours of appendix (non-invasive) were considerably younger than those with malignant disease.

Figure 1. Percentage age distribution of NETs and all invasive tumours at specified cancer sites, 1994-2010

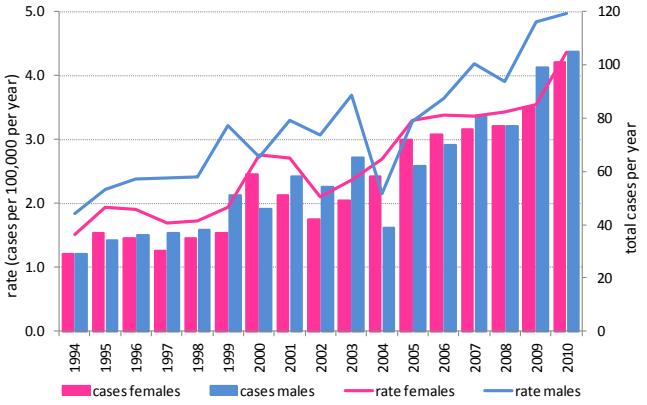


Time trends in incidence

The incidence of invasive NETs (excluding those of lung) in Ireland between 1994 and 2010 inclusive was 3.0 cases per 100,000 per year (2.7 in females and 3.3 in males), which is close to rates reported elsewhere[2 3]. Since 1994, there has been a fairly steady

increase in numbers, from 29 males and 29 females in 1994 to 101 males and 105 females in 2010, an annual percentage increase of 8% (Figure 2). Current incidence rates are 4.6 per 100,000 per year (4.4 in females and 5.0 in males).

Figure 2. Total number of cases and incidence rates for invasive NETs (all subtypes combined), 1994-2010



Annual average case numbers and incidence rates for the 6 most common NETs are shown in Table 2 and Figure 3 (a & b) respectively. Annual percentage change (APC) in case numbers for these sites ranged from 7% to 15%. While incidence rates have been very variable, overall annual percentage increase in rates of between 5% and 13% have been observed. Numbers of pancreatic NETs have increased from less than 5 cases per year during the 1990's to 24 cases diagnosed in 2010 alone. This probably reflects the increase in the proportion of histologically diagnosed pancreatic cancers since 1994[4]. Tumours in the upper GI (80% of which were located in the stomach) were the commonest digestive NETs diagnosed and had the highest incidence rates in most years.

Table 2. Annual average numbers of the 6 commonest NETs diagnosed between 1996 and 2010

	upper GI	pancreas	small intestine	*colo-rectal	appen-dix	skin
1996 - 2000	11	4	10	9	2	11
2001 - 2005	15	8	15	12	5	13
2006 - 2010	25	17	22	20	9	19
APC	8%	15%	7%	10%	15%	8%

** colorectal excludes appendix*

Figure 3a. Variation in incidence rate for the 6 commonest NETs diagnosed between 1994 and 2010: upper GI, pancreas & small intestine.

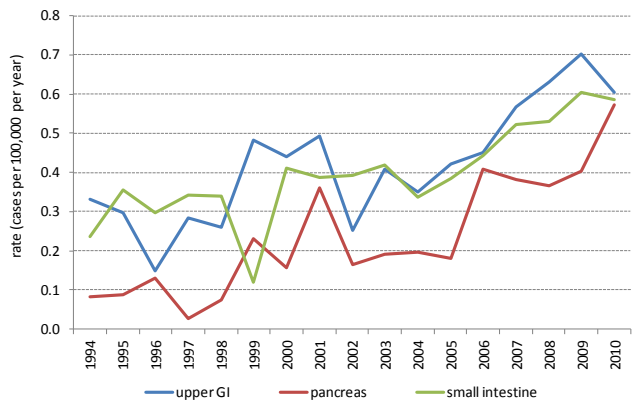
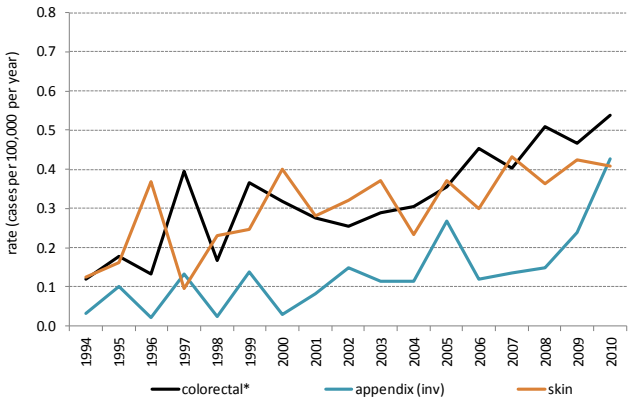


Figure 3b. Variation in incidence rate for the 6 commonest NETs diagnosed between 1994 and 2010: colorectal, appendix & skin



** colorectal excludes appendix*

Method of detection

The method in which patients presented was known for over 90% of all NETs diagnosed between 1996 and 2010. Of these, many patients, particularly those with digestive cancers, were diagnosed incidentally, where the tumour was detected while the patient was undergoing investigations or treatment for an unrelated illness. One-third of adrenal NETs and 22% of invasive NETs of the appendix were detected in this way between 2006 and 2010 (Table 3). A large proportion of NETs of the digestive system, particularly the small intestine, are carcinoid tumours. These tumours frequently do not cause symptoms, even when they have metastasized[5]. Non-digestive NETs, such as those of the mouth & pharynx, skin and breast were almost all diagnosed symptomatically.

Table 3. Percent of NETs patients whose tumours were diagnosed incidentally (not symptomatic#), 1996–00, 2001-05 & 2006-10

	1996-2000	2001-2005	2006-2010
Total invasive*	17 (4%)	42 (8%)	71 (8%)
upper GI	2 (4%)	5 (7%)	8 (6%)
pancreas	3 (14%)	4 (10%)	7 (8%)
small intestine	5 (10%)	7 (10%)	15 (13%)
colorectal (excluding appendix)	3 (6%)	5 (9%)	11 (11%)
appendix (invasive)	2 (17%)	5 (19%)	10 (22%)
genito-urinary	0 (0%)	3 (9%)	5 (14%)
thyroid	1 (5%)	1 (4%)	4 (11%)
adrenal	0 (0%)	3 (20%)	4 (29%)
appendix (non-invasive)	*24 (20%)*	*46 (34%)*	*44 (30%)*

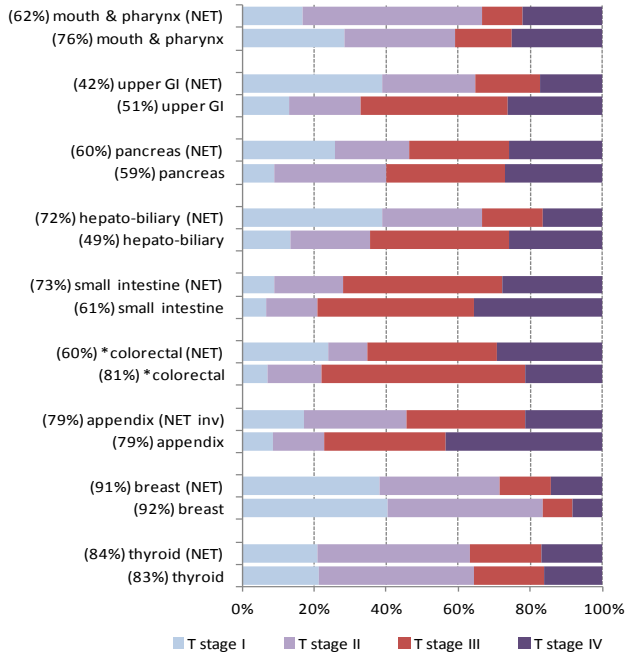
 # includes small number of cases diagnosed through screening or autopsy
** includes some groups not shown*

Tumour stage

Tumour T stage provides a description of the size or level of invasion of the tumour. Although there is no standard staging system for neuroendocrine tumours and tumour T stage normally applies only to carcinomas, a significant proportion of NETs were defined by T stage categories similar to those of non-NET/ carcinomas at particular sites. Figure 4 illustrates the distribution of tumour T stage for NET and non-

NETs at a range of sites. NET and non-NET tumours had a fairly similar T stage distribution generally, although upper GI and hepato-biliary NETs tended to be smaller/less extensive that the non-NET tumours at these sites.

Figure 4. Percentage distribution of tumour T stage I-IV for NETs and all tumours at specified sites

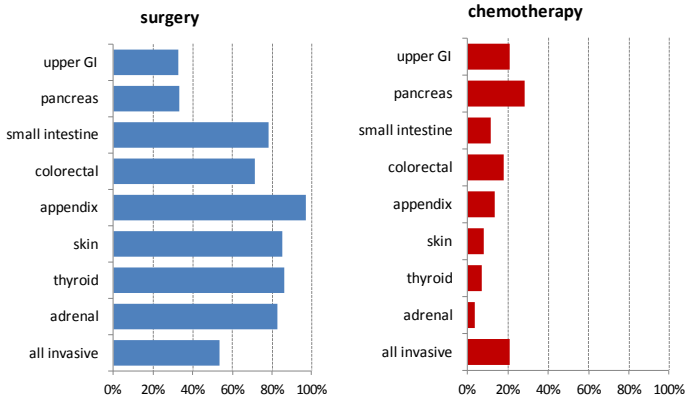


*percentages indicate the proportion of all tumours that were allocated T stage. *colorectal excludes appendix*

Treatment

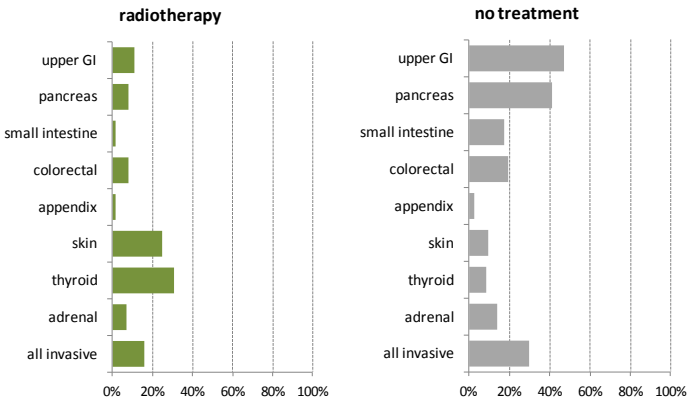
Surgical removal of the tumour was the main treatment for patients with lower gastrointestinal NETs and with NETs of the skin, thyroid and adrenal glands (Figure 5a). Far fewer patients with NETs of the upper GI and pancreas had surgery. 47% of upper GI and 41% of pancreatic NET patients had no tumour-directed treatment (Figure 5b), although many of these patients had other procedures to relieve symptoms, such as the insertion of stents. Relatively few patients had chemotherapy or radiotherapy. With the exception of patients with skin and thyroid NETs, less than 10% of patients had radiotherapy.

Figure 5a. Percentage of the most common NETs having had tumour-directed surgery or chemotherapy, 2001-2010 inclusive



colorectal excludes appendix

Figure 5b. Percentage of the most common NETs having had radiotherapy or no tumour directed treatment, 2001-2010 inclusive

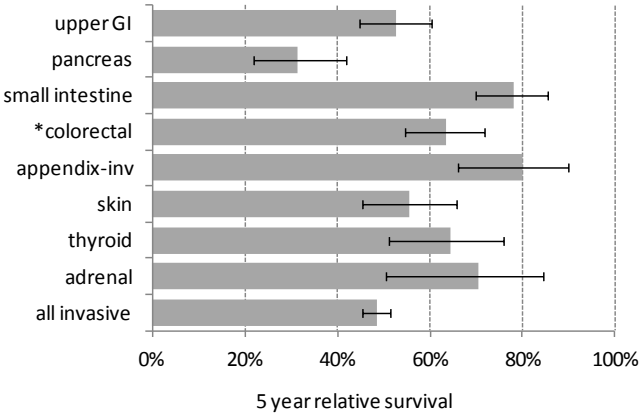


colorectal excludes appendix

Survival

Five year relative survival estimates for the most common NET groups are shown in Figure 6 and for males and females separately in Table 4. 5 year relative survival (RS) for all invasive NETs was 49% (Figure 6). Although NETs of the small intestine and appendix (invasive) had the best survival, with rates close to 80%, poor relative survival rates for pancreatic (32%), upper GI (53%) and skin (56%), which together make up over one-third of all the invasive NETs included here, resulted in a low RS for the group overall. The poor survival rates for skin NETs (93% Merkel cell subtypes) are worth noting when compared to the excellent prognosis for other non-melanoma skin cancers (BCC and SCC), where 5 year RS is close to 100%.

Figure 6. Five year relative survival (with 95% confidence intervals) for invasive NET cancer patients[6]



* *colorectal excludes appendix*

Survival was generally better for women, statistically significantly so for upper GI and pancreas patients (Table 4). Males had higher RS than females for invasive appendix and skin tumours, although this was not significant.

Table 4. Five year relative survival (RS) estimates for females and male NET cancer patients[6]

	females	males
	RS (95% CI)	RS (95% CI)
all invasive	53.8 (48.5-56.9)	44.3 (40.1-48.5)
upper GI	65.1 (54.3-74.6)	38.7 (28.1-49.8)
pancreas	47.2 (32.7-60.8)	14.3 (5.1-28.4)
small intestine	78.9 (65.3-89.6)	77.9 (67.1-87.0)
colorectal*	67.4 (53.7-79.1)	60.3 (47.9-71.5)
appendix-invasive	78.0 (59.9-90.1)	84.3 (58.9-97.8)
skin	50.9 (38.3-63.7)	63.0 (46.3-79.0)
thyroid	79.8 (60.3-91.2)	51.3 (32.8-68.0)
adrenal	84.2 (53.1-97.6)	58.0 (30.1-78.8)

**colorectal excludes appendix*

There is little international information available on NET incidence and survival compared to other cancer sites. Variation in definitions and sub-groupings makes it difficult to find comparable international data. Recent results from Spain[7] indicate 5 year RS (males & females combined) of 50% for Merkel cell skin NETs, similar to results shown here. However reported 5 year RS of 43% for pancreas, 76% for thyroid and 85% for pheochromocytoma (adrenal NETs) are somewhat higher than RS found here (32%, 65% and 71% respectively).

Prevalence

Currently the vital status of all registered cancer patients is known to the end of 2010. Using this information, it is possible to examine the number of patients alive in the population (at end 2010) that have ever had a diagnosis of neuroendocrine cancer. In all, a total of 830 patients that were ever diagnosed since January 1994 were still alive at end 2010 (17 year prevalence, Table 5). The bulk of these patients are those that had a diagnosis of small intestine, upper GI and colorectal NETs. The distribution of prevalent cancers changed fairly little over time, although the relative proportion of pancreas NETs declined, from representing 12% of prevalent cancers at 1 year (ie all patients still alive within 1 year of their diagnosis) to 7% at 17 years, reflecting their poor survival rates. In contrast, patients with NETs of the small intestine made up a greater proportion of the prevalent population at 17 years (18%) compared to 1 year (14%), illustrating their overall better survival rates.

Table 5. Prevalence of neuroendocrine tumours (NETs) as known at end 2010, by cancer site

	17 years[a]	5 years[b]	3 years[c]	1 year[d]
Total invasive	830	488	361	170
mouth & pharynx	9	6	3	1
upper GI (oesophagus & stomach)	133	77	59	25
pancreas	61	47	36	21
hepato-biliary	11	8	7	4
small intestine	153	92	64	23
colorectal (excluding appendix)	117	65	46	20
appendix (invasive)	67	37	32	18
skin	93	49	34	19
breast	9	3	3	1
genito-urinary	30	21	15	5
thyroid	57	25	18	8
adrenal	28	10	8	5
other/unspecified*	62	48	36	20

**90% were cases where tumour site was unspecified. Other specified sites included thymus, mediastinum and peritoneum. (a) 17 year prevalence=all patients registered (diagnosed since Jan 1994) that were still alive at end 2010 (b) 5 year prevalence=all patients still alive diagnosed 2006-2010 inclusive, (b) 3 year prevalence=all patients still alive diagnosed 2008-2010 inclusive and (c) 1 year prevalence=all patients still alive diagnosed 2010 only*

References and notes

1. RARECARE. The surveillance of rare cancer in Europe. Website: http://www.rarecare.eu/rarecancers/rarecancers.asp
2. Gatta G et al, 2011. Rare cancers are not so rare, the rare cancer burden in Europe. Eur J Cancer. 17:2493-2511
3. Kulke MH et al, 2012. Neuroendocrine tumours. J Natl Compr Canc Netw. 10:724-764
4. NCRI, 2012. Cancer trends No 13 – Cancer of the pancreas. http://www.ncri.ie/pubs/pubfiles/Pancreas.pdf
5. Frilling A, et al 2012: Neuroendocrine tumor disease: an evolving landscape. Endocrine related cancer, 19:R163-R185
6. Cases diagnosed 1994-2009, followed up to 31/12/2010.
7. Alsina M, et al 2011. Neuroendocrine tumors: a population based study of incidence and survival in Girona province, 1994-2004. CancerEpidemiology 35: e49-e54

