Incidence and survival of neuroendocrine tumors: a population-based study of the Lower Saxony Cancer Registry, Germany

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Introduction

Neuroendocrine tumors (NET) are rare neoplasms that originate from neuroendocrine tissues localized in numerous different organ systems. They are more common in the gastro-intestinal tract (GIT) and the broncho-pulmonary system. The latest WHO classification guideline (2010) takes into account biological behavior, in order to apply risk stratification. Increasing incidence of NET has been observed in the US and in some European countries [1, 2]. Clear causative factors have not yet been described. Epidemiological data on NET in Germany is rare. This study describes the incidence and relative survival (RS) of NET in Lower Saxony.

Methods

Patients of all ages diagnosed in 2004 - 2014 with NET of all cancer sites were included and classified in G1NET, G2NET, G3-LCNEC and G3-SCNEC (ICD-O-3 morphology codes see Table 1). Composite carcinoids, medullary carcinoma and merkel cell carcinoma were excluded. Age-standardized (Europe) incidence rates per 100,000 persons were estimated by sex, topography and WHO 2010 classification. For survival calculations, only patients with malignant NET aged 15-99 years (n=14,242) were analyzed. DCO cases were excluded. Patients still alive at the end of 2014 were censored. The cohort approach was employed to derive 5-years RS by sex, topography, stage (following ENETS*) and WHO 2010 classification of NET.

Results

Table 1: Included morphology codes (ICD-O-3) and classification of WHO groups, adapted and modified from Korse et al. [2]

G1NET	well-differentiated, grade 1	G2NET	well-differentiated, grade 2
8150/3	Pancreatic endocrine tumor	8246/32	Neuroendorcrine carcinoma, NOS (grade 2)
8151/3	Insulinoma (C25._)	8249/3	Neuroendocrine tumor, grade 2*
8152/3	Glucagonoma, NOS (C25._)	**G3-LCNEC**	**poorly differentiated, large cell**
8153/3	Gastrinoma	8013/3	Large cell neuroendocrine carcinoma
8155/3	Vipoma	8245/3	Adenocarcinoid tumor
8156/3	Somatostatinoma	8246/33	Neuroendorcrine carcinoma, NOS (grade 3)
8157/3* (8152/3)	Enteroglucagonoma	8246/39	Neuroendorcrine carcinoma, NOS (unknown grade)
8240/1* (8240/3)	Carcinoid tumor of uncertain malignant potential	**G3-SCNEC**	**poorly differentiated, small cell**
8240/3	Carcinoid tumor, NOS	8041/3	Small cell carcinoma, NOS
8241/3	Enterochromaffin cell carcinoid	8042/3	Oat cell carcinoma (C34._)
8242/3	Enterochromaffin-like cell tumor	8043/3	Small cell carcinoma, fusiform cell
8246/31	Neuroendorcrine carcinoma, NOS (grade 1)	8044/3	Small cell carcinoma, intermediate cell
		8045/3	Combined small cell carcinoma

code or term change 2012

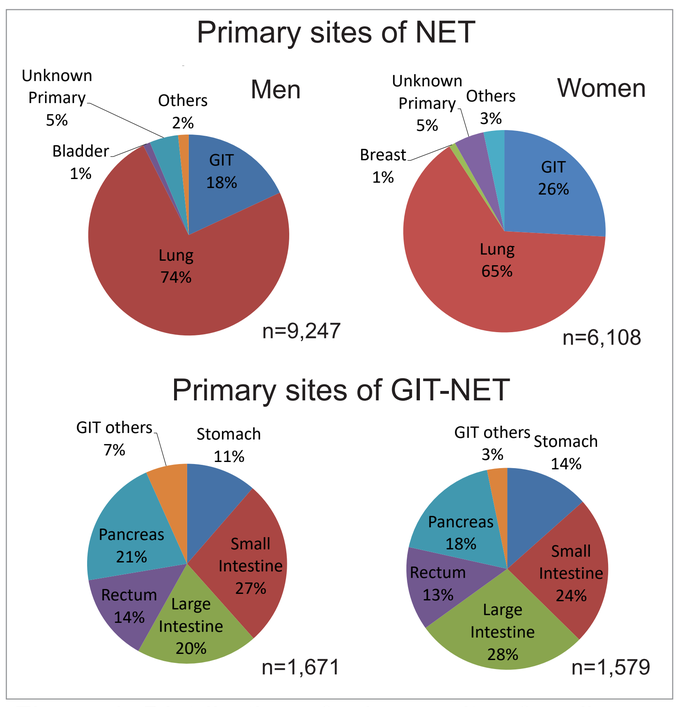

Figure 1: Distribution of primary sites for all NET and NET of the gastrointestinal tract (GIT-NET) for men and women in Lower Saxony

A total of 15,355 incident cases were analyzed, 9,247 men (60.2%) and 6,108 women (39.8%). Median age was 67 years for men and 65 years for women. Lung was the predominant primary site of NET in men and in women, followed by GIT (Figure 1). Overall, the age-standardized incidence rate was 15.7 per 100,000 men and 10.0 per 100,000 women (for GIT 3.0 vs. 2.7). Without NET of the lung, the incidence rate increased from 3.5 in 2004 to 5.8 in 2014 for men and almost doubled for women from 2.6 to 5.0 (Figure 2a). An increase in the incidence of NET was observed for all GIT sites (except oesophagus; data not shown) and for all of the WHO-groups (except G3-SNEC, see Figure 2b).

Five-year RS for NET was better for women compared to men overall and in all subgroups: overall excluding lung 58.4% vs. 48.5% and lung 15.3% vs. 8.4% (Table 2). Five-year RS was dependent on tumor site, stage and WHO group (histological grade).

Table 2: Overall, site-, stage- and WHO group-specific 5-year relative survival (RS) for patients with malignant NET in Lower Saxony 2004 - 2014

	Male		Female		Both sexes	
Variable	N	RS (SE)	N	RS (SE)	N	RS (SE)
Overall[a]	2,069	48.5 (1.4)	1,774	58.4 (1.6)	3,843	53.1 (1.1)
Topography						
GIT [b]	1,126	62.7 (1.9)	992	74.3 (1.9)	2,118	68.1 (1.4)
Pancreas	327	46.7 (3.7)	272	54.2 (3.9)	599	50.1 (2.7)
Lung	6,590	8.4 (0.4)	3,809	15.3 (0.7)	10,399	10.9 (0.4)
Others	616	24.0 (2.2)	510	31.3 (2.6)	1,126	27.3 (1.7)
Stage[c]						
Stage I	136	72.1 (6.2)	167	85.2 (4.3)	303	79.4 (3.7)
Stage II	199	54.1 (5.0)	145	79.6 (4.9)	344	65.0 (3.7)
Stage III	882	25.4 (1.9)	596	33.9 (2.5)	1,478	28.9 (1.6)
Stage IV	2,049	7.0 (0.7)	1,232	11.0 (1.1)	3,281	8.5 (0.6)
Unknown	5,393	17.5 (0.6)	3,443	28.8 (0.9)	8,836	21.9 (0.5)
WHO-group [de]						
G1NET	976	79.0 (2.0)	1,060	85.4 (1.7)	2,036	82.3 (1.3)
G2NET	268	63.9 (4.5)	287	71.4 (4.1)	555	67.8 (3.1)
G3-LCNEC	1,168	22.2 (1.5)	807	30.1 (2.0)	1,975	25.4 (1.2)
G3-SCNEC	6,192	5.9 (0.4)	3,405	8.6 (0.6)	9,597	6.9 (0.3)

SE=standard error, [a] excluding lung, [b] excluding pancreas, [c] including lung; Stage I: T1N0M0, Stage II: T2/3N0M0, Stage III: T4N0M0 or anyT N+M0, Stage IV: anyT anyN M+, [d] including all primary sites, [e] excluding 79 cases with morphology code M8246/3, grading 4 (5-year RS (SE) = 14.7 (4.9))

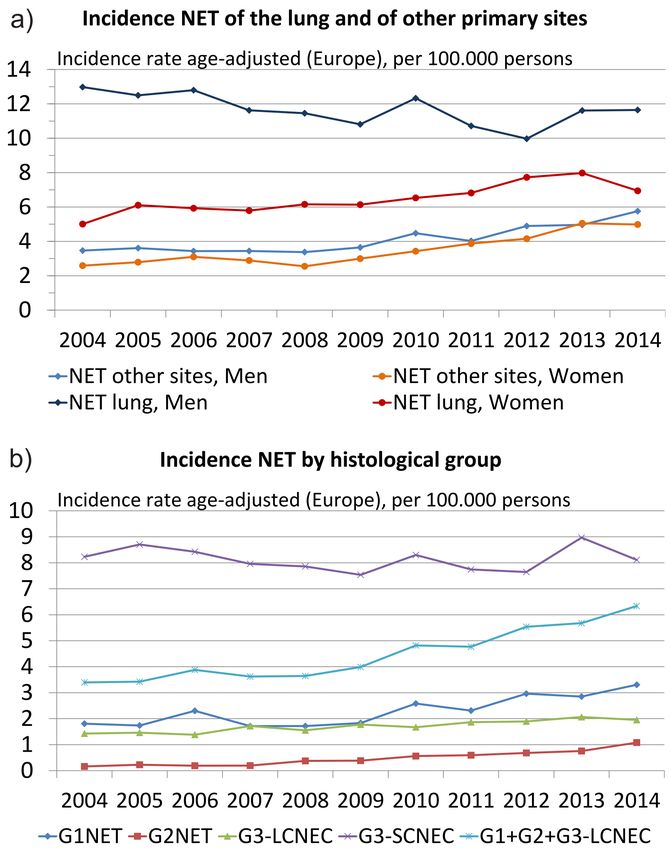

Figure 2: Incidence of NET a) by sites for men and women, b) by histological group (WHO) for Lower Saxony

Table 3: Comparison with published results for the Netherlands by Korse et al. [2]

	Lower Saxony (2004-2014)	Netherlands [2] (2001-2010)
N	15,355	24,759
Incidence (ASR/100.000 persons)		
All	12.6	13.2
G1+G2NET	2.8	2.5
G3-LCNEC	1.7	1.4
G3-SCNEC	8.1	9.3
Survival (5-year RS %)		
G1NET	82	80
G2NET	68	63
G3-LCNEC	25	20
G3-SCNEC	7	6

Conclusions

The observed increasing incidence of NET in both sexes concurs with published results from North America, Norway and the Netherlands [1, 2, 3]. Changing classifications, better quality of cancer registration, increased awareness of NET by clinicians, advanced diagnostic technology and increased prevalence could be the reasons. Tumor site, stage and the WHO most recent classification could be confirmed to be strong prognostic factors [2, 3].

The prognosis of NET of the lung in women is comparable to other lung cancers, but far poorer in men. The survival differences between women and men are not yet understood. Possible explanations: A skewed distribution of the more favorable tumours in women than in men, men may likely suffer more comorbid conditions than women or a possible role of hormonal differences. This findings should be further investigated.

References

[1] Hauso et al. (2008): Neuroendocrine tumor epidemiology: contrasting Norway and North America. Cancer 113(10):2655-64

[2] Korse et al. (2013): Incidence and survival of neuroendocrine tumours in the Netherlands according to histological grade: Experience of two decades of cancer registry. Eur J Cancer 49(8):1975-83

[3] Yao et al. (2008): One Hundred Years After “Carcinoid”: Epidemiology of and Prognostic Factors for Neuroendocrine Tumors in 35,825 Cases in the United States. J Clin oncol 26:3063-72

*ENETS: European Neuroendocrine Tumor Society

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