Original Paper

Neuro
-endocrinology

Neuroendocrinology 2018;107:50–59
DOI: 10.1159/000488987

Received: October 3, 2017
Accepted after revision: April 2, 2018
Published online: April 14, 2018

Extra-Pulmonary Neuroendocrine Carcinomas: A Population-Based Study in the Netherlands

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Keywords
Extra-pulmonary neuroendocrine carcinoma · Incidence · Cancer registry · Population based study

Abstract
Background: Extra-pulmonary neuroendocrine carcinomas (EP-NEC) are rare tumours that require expertise for correct and timely diagnosis, which is essential for clinical decision making. The number of patients affected, treatment given, and the proportion surviving the disease is based on limited evidence. The aim of this study is to retrospectively analyse the incidence, treatment, and relative survival (RS) of EP-NEC patients in the Netherlands. ***Methods:*** Patients diagnosed between 2008–2012 with EP-NEC or NEC with unknown primary site (UP-NEC) were selected from the Netherlands Cancer Registry based on combinations of tumour localisation and morphology code. Incidence was studied using the European standardised (ESR) and world standardised rates, and RS was calculated using the Ederer II method. ***Results:*** In total, 1,544 cases were analysed, 1,045 EP-NEC and 499 UP-NEC. For EP-NEC, the incidence was 1.0 per 100,000 person-years (ESR), the mean age was 68 years, and the male to female ratio was 1:0.6. Most frequent EP-NEC localisations were the bladder and the gastrointestinal tract, and the treatment most frequently given was surgery in combination with chemotherapy. The overall 5-year RS was 38% for patients with local/regional disease ($n = 447$), and 7% for patients with extensive disease ($n = 582$). For UP-NEC patients ($n = 499$), the 5-year RS was 6%. ***Conclusions:*** This study is the first nationwide study presenting an increase in the incidence of EP-NEC patients from 196 to 260 cases annually in the Netherlands. The best 5-year RS was found for EP-NEC patients with local disease located in the bladder, where the worst 5-year RS was found for patients with disease located in the oesophagus.

Introduction

Neuroendocrine carcinomas (NEC) are fast-growing tumours, characterised by expression of neuroendocrine proteins, which have the ability to secrete peptide hormones or bio-amines [1]. Morphologically and clinically

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distinct from well-differentiated neuroendocrine tumours (NET), NEC are classified according to the World Health Organization (WHO) and the European Neuroendocrine Tumor Society (ENETS) grading systems [2–4]. While both these grading systems are based on the mitotic rate and Ki67 labelling index, they differ in numbers and percentages for neuroendocrine malignancies found in the lung or thymus and the gastroenteropancreatic tract [4]. Grade is considered to be the most important prognostic factor for patients with a neuroendocrine malignancy [3, 4]. Making a correct and timely diagnosis needs expertise, which is difficult due to the low incidence. In addition, the low incidence results in few studies which affect the level of evidence available. This could be improved through joint efforts, for example, developing information networks or centres of expertise [5–7].

In this paper, we focus on extra-pulmonary neuroendocrine carcinomas (EP-NEC), located in a range of different organs, including the gastrointestinal tract, bladder, cervix, and prostate [8], and are very rare compared to the majority of NEC, which originate from the lung [8]. According to the international definition, small and large cell NEC of the lung are not rare cancers [7]. Although accurate information about the incidence of EP-NEC is unavailable, the number of new cases of NEC in the gastrointestinal tract is estimated to be 1–3% of all neuroendocrine malignancies per year [8–10]. Since patients with EP-NEC often present with metastatic disease at the moment of diagnosis [11, 12], treatment is limited to palliative chemotherapy [10–13]. While EP-NEC patients diagnosed with local disease can be cured by surgery [12, 14], the median survival is rather poor, ranging from 5 months in metastatic disease, to 38 months for local disease [12].

Little is known about the numbers of the patients with EP-NEC, the treatment given, and the survival rates of several subgroups. The aim of this population-based study is therefore to gain insight into the incidence and relative survival (RS) for EP-NEC patients in the Netherlands, using data from the nationwide Netherlands Cancer Registry (NCR).

Material and Methods

Study Population

Retrospective data from the population-based NCR for the period 2008–2012 were used for this study. The NCR receives notifications of newly diagnosed malignancies from the nationwide Automated Pathology Archive (Palga).

A high level of data quality is guaranteed by trained data managers who gather patient, tumour, and treatment characteristics directly from the patient files. The completeness of follow-up is ensured by a yearly linkage between the NCR and the municipality registry (GBA), identifying all deceased citizens in the Netherlands. An additional check to confirm and review the correctness of NCR data was done by an expert data manager and researcher; this was based on updated pathology report conclusions. In case the pathology report was inconclusive, the data manager contacted the pathologist for clarification. Clinical and pathological expertise was ensured by the involvement of expert clinicians, including an expert pathologist, all working in an ENETS Centre of Excellence. For this study, tumour cases were selected using the International Classification of Disease for Oncology Third Edition (ICD-O3) [15] codes, following the NCR guideline for registrars, including large cell NEC not otherwise specified (NOS) (M8013), small cell carcinoma NOS (M8041), combined small cell carcinoma (M8045), mixed acinar-endocrine carcinoma (M8154), and NEC NOS (M8246). Patients with unknown primary location, UP-NEC (ICD-O3 code C80.9), were reported separately as, by definition, most patients presented with metastatic disease [16]; so, neither TNM classification nor exclusion of lung localisation was possible.

The TNM Classification of Malignant Tumours, following the Union for International Cancer Control (UICC), was used [16] for staging EP-NEC. We grouped stages defined as local disease (TNM stage I and II), regional disease (TNM Stage III), and extensive disease (TNM stage IV). Due to differences in the nomenclature for EP-NEC through time, registering EP-NEC patients into the NCR was complex. To cross check diagnosis, the NCR data were linked to Palga, reviewing all NEC NOS and large cell NEC. The number of cases diagnosed per university hospital (including the National Cancer Institute) (n = 9 hospitals) and non-university hospitals (n = 83) are presented. These as centres of expertise for EP-NEC do not exist in the Netherlands.

Methods of Statistical Analysis

Newly diagnosed EP-NEC and UP-NEC cases were scored per year for the selected period. In addition, the crude, European standardised (ESR), and world standardised (WSR) incidence rates were calculated for the EP-NEC patients and expressed per 100,000 person-years. The RS, which is a proximate of the disease-specific survival, was calculated using the Ederer II method [17]. The independent t test and the χ^2 test were used to calculate the p value for significance. STATA version 13 was used for analyses.

Results

Diagnosis

Of the 1,544 NEC cases identified, 499 cases were UP-NEC. The 1,045 cases with a known primary tumour outside the lung (EP-NEC) had a male to female ratio of 1: 0.6, resulting in, for the total population, an ESR and WSR of 1.0 and 0.7 per 100,000, respectively. For males, the ESR and WSR were 1.3 and 0.9 per 100,000, and 0.8 and 0.6 per 100,000 for females. The incidence increased by 28%, from 189 cases in 2008 to 242 cases in 2012. Males were older than females at the time of diagnosis, 69 versus

66 years ($p < 0.001$). Overall, 10% were diagnosed in university hospitals (Table 1).

Prognosis

Overall, 56% of all EP-NEC patients had extensive disease at diagnosis (Fig. 1). The highest percentage of extensive disease was found in the prostate (85%) and pancreas (73%), and the lowest in the bladder (40%) and other organs (48%). For the gastrointestinal tract and oesophagus, 66 and 59% were diagnosed with extensive disease.

The patients with EP-NEC in "other organs" and patients diagnosed with an EP-NEC in the bladder had the best prognosis, with a 5-year RS of 33% (95% CI 25.2–

Table 1. Characteristics of patients with EP-NEC

	Year of diagnosis					
	2008	2009	2010	2011	2012	Total
Age						
Mean, years	68	68	67	68	68	68
Median, years	69	70	68	69	68	69
Range, years	19–99	27–91	32–92	32–93	29–93	19–99
Age cat. 18–60, *n*	44	43	67	50	64	268
Age cat. 61–74, *n*	88	73	86	89	102	438
Age cat. 75+, *n*	57	63	70	73	76	339
Gender						
Male	125	109	138	133	145	650
Female	64	70	85	79	79	395
TNM staging						
Local disease	51	55	57	50	59	272
Regional disease	35	27	34	41	38	175
Extensive disease	101	89	132	121	144	587
Not available	2	8	0	0	1	11
Hospital of diagnosis						
Non-university	166	165	205	183	221	940
University	23	14	18	29	21	105
Histological type						
Small cell EP-NEC	102	95	115	113	112	537
Large cell EP-NEC	27	37	45	54	79	242
NEC EP-NOS	25	26	27	18	20	116
Mixed EP-NEC	1	2	0	1	0	4
Combined EP-NEC	34	19	36	26	31	146
Localisation						
Gastrointestinal tract[a]	40	44	48	53	61	246
Bladder	58	54	61	70	58	301
Pancreas	19	19	17	19	29	103
Oesophagus	30	24	31	20	29	134
Prostate	13	9	19	13	15	69
Other organs[b]	29	29	47	37	50	192
Total number of EP-NEC patients	189	179	223	212	242	1,045

[a] Excl. oesophagus and pancreas. [b] Other organs (n >10) include: breast, ovary, larynx, and biliary tract.

Fig. 1. a Relative survival in EP-NEC patients differentiated for localisation. **b** Relative survival in EP-NEC patients with local disease differentiated for localisation. **c** Relative survival in EP-NEC patients with regional disease differentiated for localisation. **d** Relative survival in EP-NEC patients with extensive disease differentiated for localisation.

(For figure see next page.)

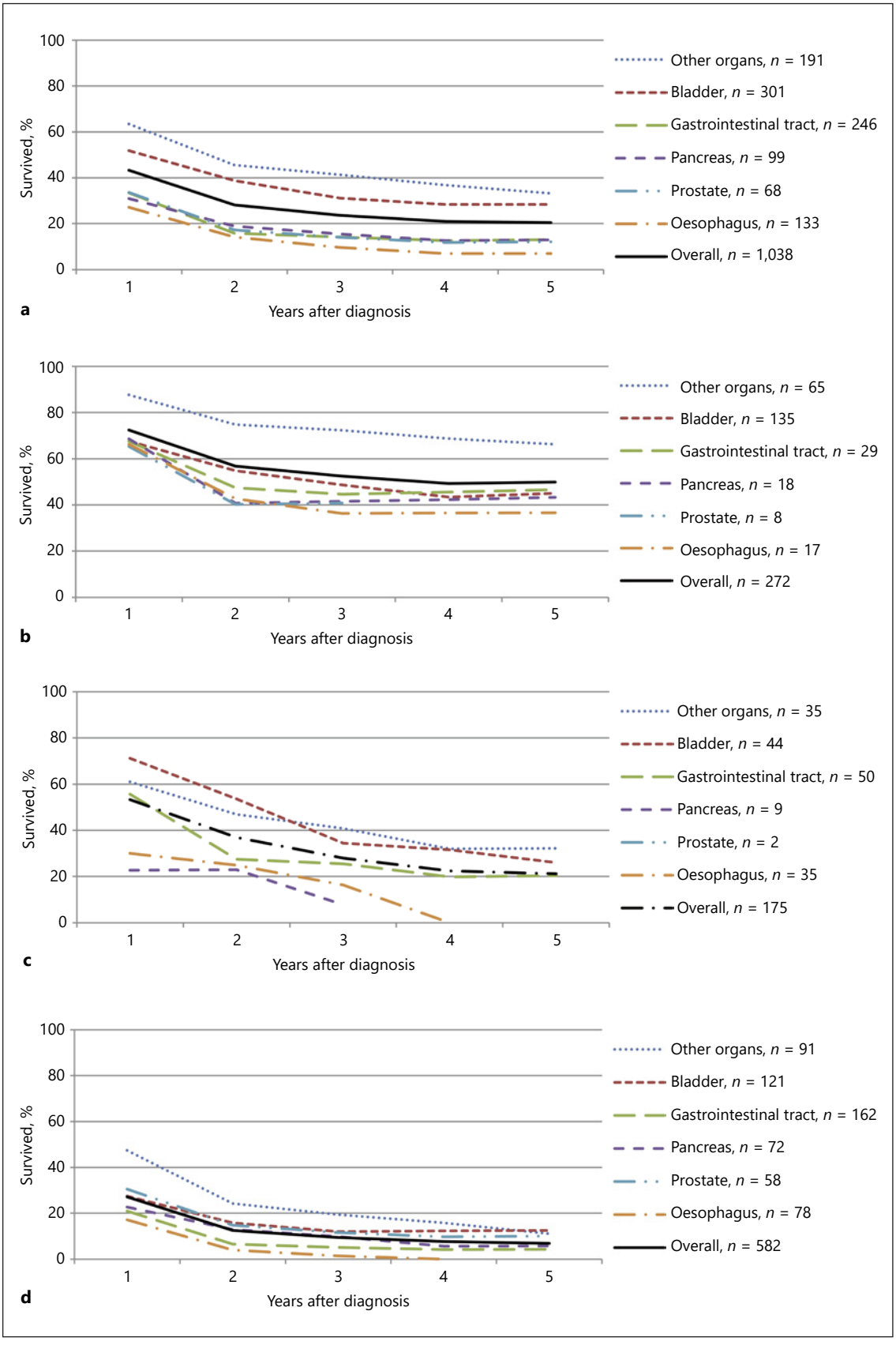

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Table 2. Treatment overview: number of treated EP-NEC patients

	Surgery only	Surgery + chemo	Surgery + chemo and radio	Chemo only	Chemo + radio	Radio only	No treatment	Other treatment
Age, years								
Mean	70	65	62	63	62	74	74	71
Median	70	68	63	63	62	77	76	71
Range	27–93	19–89	32–84	29–83	28–87	43–91	36–99	32–91
Gender								
Male	102	76	43	123	73	49	143	41
Female	73	39	31	63	46	32	84	27
Localisation								
Gastrointestinal tract[a]	64	31	3	55	15	18	54	6
Bladder	72	61	47	26	37	11	33	14
Pancreas	16	3	0	25	3	4	49	3
Oesophagus	4	0	3	41	25	20	41	0
Prostate	0	0	0	14	10	6	17	22
Other organs[b]	19	20	21	25	29	22	33	23
Total cases, *n*	175	115	74	186	119	81	227	68

[a] Excl. oesophagus and pancreas. [b] Other organs (n >10) include: breast, ovary, larynx, and biliary tract.

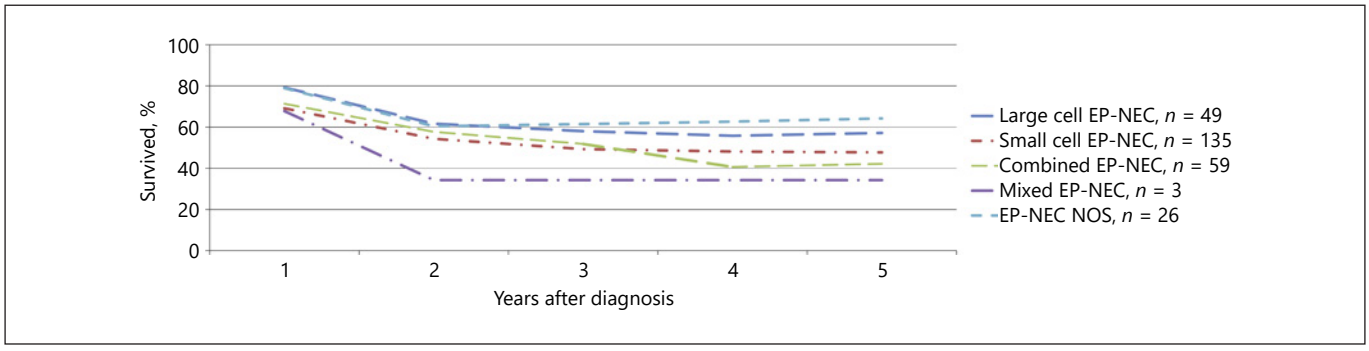

Fig. 2. Relative survival in EP-NEC patients differentiated for histology type.

41.5) and 28% (95% CI 22.6–34.6), respectively. EP-NEC of the gastrointestinal tract had a 5-year RS of 13% (95% CI 8.8–18.0), of the pancreas 13% (95% CI 6.7–21.3), and of the prostate 12% (95% CI 4.9–23.3). EP-NEC diagnosed in the oesophagus, mostly small cell EP-NEC, had the worst 5-year RS, 7% (95% CI 3.0–13.2) (Fig. 1a).

Presenting the 5-year RS per histology type (Fig. 2), we observe the best RS in the group of EP-NEC NOS 64% (95% CI 64.2–82.2). The worst survival was observed in the group of patients diagnosed with a mixed EP-NEC; however, the number of cases (n = 3) is too small to draw any conclusions.

Treatment

Table 2 presents age and treatment of patients with EP-NEC. Patients receiving chemotherapy alone or in combination with other treatment modalities were significantly younger than those receiving treatment modalities without chemotherapy. Among all EP-NEC patients, 818 (78%) received any type or a combination of therapies. Of the 227 patients who received no therapy, the majority had extensive disease (n = 178). The group of other treatment modality included hormonal therapy (n = 41), and surgery combined with radiotherapy (n = 27). Patients diagnosed with prostate NEC accounted for 32% of the cases of other treatment, all related to hormonal therapy.

Table 3. Stage overview: number of EP-NEC patients treated

	TNM staging			
	local disease	regional disease	extensive disease	no stage available
Age, years				
Mean	67.5	67.6	68.0	73.6
Median	69	68	68	81
Range	19–92	28–99	32–93	45–87
Gender, *n* (%)				
Male	167 (61)	100 (57)	378 (64)	5 (45)
Female	105 (39)	75 (43)	209 (36)	6 (55)
Therapy, *n* (%)				
Surgery only	78 (29)	45 (26)	50 (9)	2 (18)
Surgery + chemo	47 (17)	25 (14)	43 (7)	0 (–)
Surgery + chemo and radio	46 (17)	13 (7)	15 (3)	0 (–)
Chemo only	8 (3)	15 (9)	162 (28)	1 (9)
Chemo + radio	33 (12)	26 (15)	60 (10)	0 (–)
Radio only	13 (5)	20 (11)	47 (8)	1 (9)
No treatment	18 (7)	25 (14)	178 (30)	6 (55)
Other treatment	29 (11)	6 (3)	32 (5)	1 (9)
Localisation, *n* (%)				
Gastrointestinal tract[a], %	29 (11)	50 (29)	162 (28)	5 (45)
Bladder	135 (50)	44 (25)	121 (21)	1 (9)
Pancreas	18 (7)	9 (5)	75 (13)	1 (9)
Oesophagus	17 (6)	35 (20)	79 (13)	3 (27)
Prostate	8 (3)	2 (1)	58 (9)	1 (9)
Other organs[b]	65 (24)	35 (20)	92 (16)	0 (–)
Total cases, *n*	272 (100)	175 (100)	587 (100)	11 (100)

[a] Excl. oesophagus and pancreas. [b] Other organs (*n* >10) include: breast, ovary, larynx, and biliary tract.

Treatment given differed according to the stage of disease (Table 3). For the 272 EP-NEC cases with localised disease, surgery with or without any other therapy was applied most frequently (63%). In EP-NEC patients with extensive disease, the most frequent treatment of choice was chemotherapy alone (28%), which is considered to be of palliative intent. Stage of disease at diagnosis was different, depending on localisation (Fig. 1; Table 3).

Survival of EP-NEC Patients

In Figure 3, an overview on the 5-year RS for EP-NEC patients in relation to treatment is given. Irrespective of the stage of disease, the 5-year RS was best in the group of patients treated with surgery plus chemotherapy and radiotherapy, (53%, 95% CI 38.9–65.8) (Fig. 3a). Figure 3b–d shows the survival with each type of therapy given according to the stage of disease. Patients with local disease treated with surgery combined with chemotherapy had the best 5-year RS, 61% (95% CI 42.1–76.6), with similar 5-year RS rates being found for EP-NEC patients receiving chemotherapy in combination with radiotherapy and EP-NEC patients receiving surgery in combination with chemotherapy and radiotherapy (59% [95% CI 38.5–75.2] and 55% [95% CI 37.1–71.3], respectively). When only surgery was applied in EP-NEC patients with local disease, the 5-year RS was 46% (95% CI 33.0–58.1) (Fig. 3b). For EP-NEC patients with regional disease, the best 5-year RS, of 52% (95% CI 19.4–79.7), was for the patients receiving surgery in combination with chemotherapy and radiotherapy (Fig. 3c).

Overall, EP-NEC patients with extensive disease had a 5-year RS below 15% (Fig. 1d), but when receiving surgery in combination with chemotherapy and radiotherapy, a much better survival was observed (48%, 95% CI 20.6–72.1). Of these, 15 cases, the minority ($n = 7$), had distant metastasis. This contrasts with other patients with extensive disease who were treated with different modalities, 76% of whom had distant metastasis. All results should be inter-

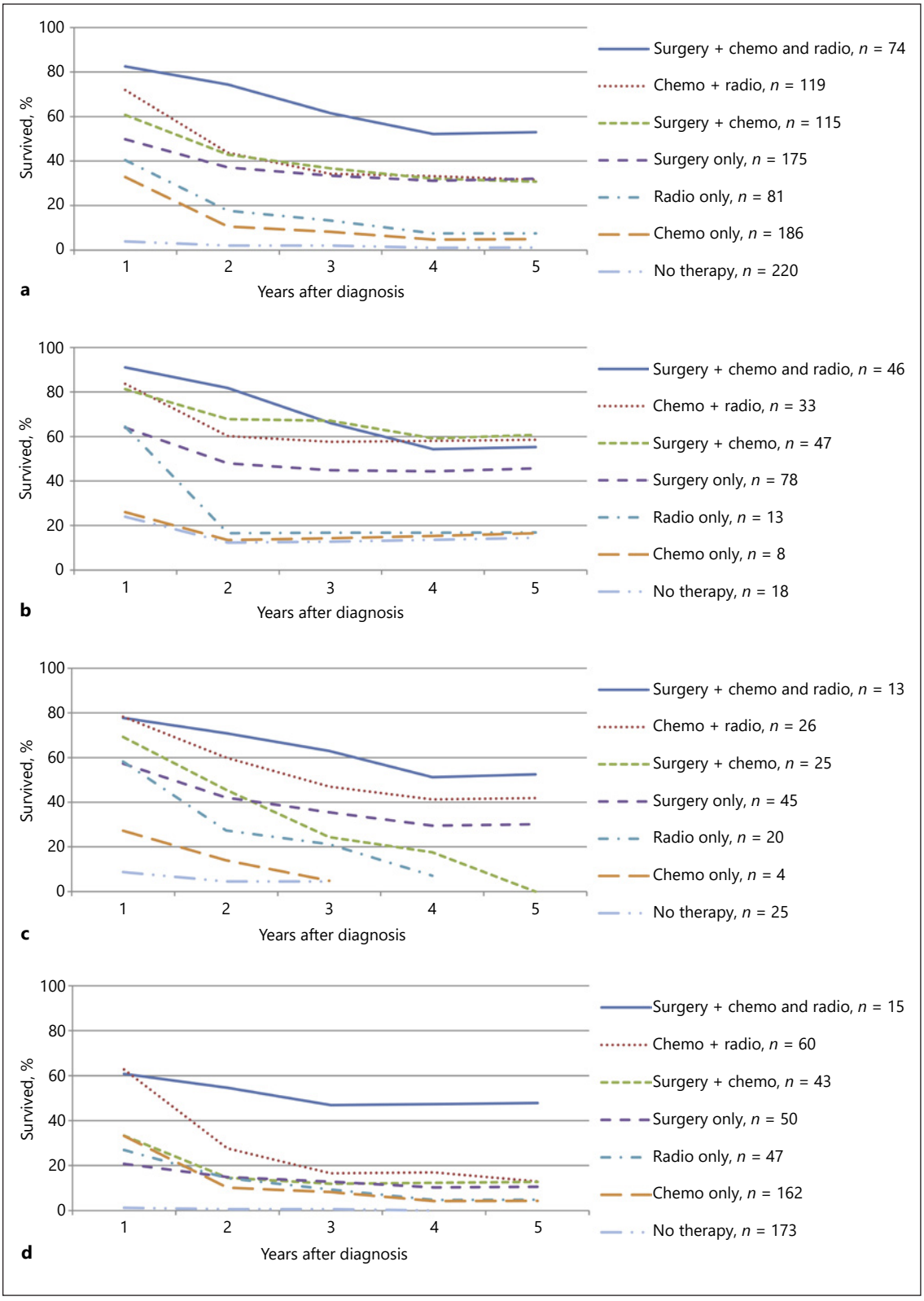

Fig. 3. a Relative survival per therapy type for all EP-NEC patients. **b** Relative survival per therapy type for all EP-NEC patients with local disease. **c** Relative survival per therapy type for all EP-NEC patients with regional disease. **d** Relative survival per therapy type for all EP-NEC patients with extensive disease.

Neuroendocrinology 2018;107:50–59
DOI: 10.1159/000488987

Table 4. Characteristics of NEC with unknown localisation

	Year of diagnosis				
	2008	2009	2010	2011	2012
Age					
Mean, years	67	72	69	70	70
Median, years	71	75	71	72	70
Range, years	28–86	32–96	34–96	19–93	37–91
Age cat. 18–60, *n*	29	20	20	20	12
Age cat. 61–74, *n*	45	35	38	35	41
Age cat. 75+, *n*	33	56	39	41	35
Gender					
Male	56	52	54	58	49
Female	51	59	43	38	39
Hospital of diagnosis					
Non-university	92	93	87	87	79
University	15	18	10	9	9
Histological type					
Small cell carcinoma	75	68	66	52	49
Large cell NEC	17	20	20	25	24
NEC NOS	11	20	8	18	12
Combined NEC	4	3	3	1	3
Therapy given[a]					
Surgery only	2	3	2	5	2
Surgery + chemo	2	0	0	0	0
Surgery + chemo and radio	1	1	0	0	0
Chemo only	32	20	23	23	23
Chemo and radio	6	3	7	4	4
Radio only	10	9	11	5	9
No treatment	51	70	52	56	49
Other therapy	3	5	2	3	1
Total cases, *n*	107	111	97	96	88

[a] Based on year of incidence.

preted with caution because of the small numbers and wide confidence intervals. Furthermore, no information on the intention of treatment was taken into account, as this information was not available. The results as presented cannot be interpreted as the effect of the treatment given solely.

NEC with Unknown Primary Site

UP-NEC diagnosed were predominantly small cell NEC (Table 4), with 41% of the UP-NEC patients ≥75 years, compared to 32% of EP-NEC patients. EP-NEC patients with extensive disease were significantly younger ($p = 0.007$) than patients with an UP-NEC, 68 versus 70 years.

Survival of UP-NEC Patients

The 1-year RS in patients diagnosed with an UP-NEC was 17.4% (95% CI 14.2–21.0). The 5-year RS for patients with an UP-NEC was 5.8% (95% CI 3.7–8.6) (Fig. 4). For both groups of patients, EP-NEC patients with extensive disease and UP-NEC patients, most metastases were found in the liver.

Discussion

The aim of this study was to provide better insight into the burden of EP-NEC, reporting the incidence and survival rates. In this first nationwide population-based study of the incidence of EP-NEC, we found an annual incidence increasing from 179 EP-NEC patients in 2009 to 242 in 2012. Stage at diagnosis and histology were major prognostic factors and expected to be of importance for clinical decision making.

To estimate the true incidence of EP-NEC patients in the Netherlands, we identified an additional 499 cases with an UP-NEC. Pathologically confirmed UP-NEC are based mostly on biopsy samples from metastases [18]. In the Netherlands, the group of UP-NEC is relatively large compared to number of unknown primary tumours in general (www.cijfersoverkanker.nl). Due to the poor prognosis, performing further diagnostics to identify the primary localisation of an UP-NEC is unlikely to result in different treatment options [19–24]. To estimate the number of UP-NEC cases that might be EP-NEC, we used the study of Korse et al. [8], which shows that 48% of the large cell NEC and 90% of the small cell NEC originate from the lung. With these results we speculate that approximately 10% of the small cell UP-NEC and 52% of the large cell UP-NEC can be considered as an EP-NEC. Based on these assumptions, we speculate that in total, this increases the number of cases suspected to be EP-NEC by 86 cases (31 small cell UP-NEC and 55 large cell UP-NEC), so the incidence of all EP-NEC may actually range from 196 cases in 2009 to 260 cases in 2012.

Consistent with other studies [7, 8, 25], our data confirm the predominance of males in EP-NEC. With an ESR of 1.3 per 100,000 in the Dutch population, the number of EP-NEC patients is more than two-fold greater than that reported in the RARECARE study for the 1995–2002 period [7]. The overall increase in cancer cases, the improved standardisation of grading neuroendocrine malignancies, and the more frequent use of tissue staining might explain this trend in an increasing number of EP-NEC cases detected. Therefore, the increase in EP-NEC patients is expected not to be an actual increase in patients but is the result of improved diagnostics. Since we included the study period 2008–2012 and used the WHO 2010

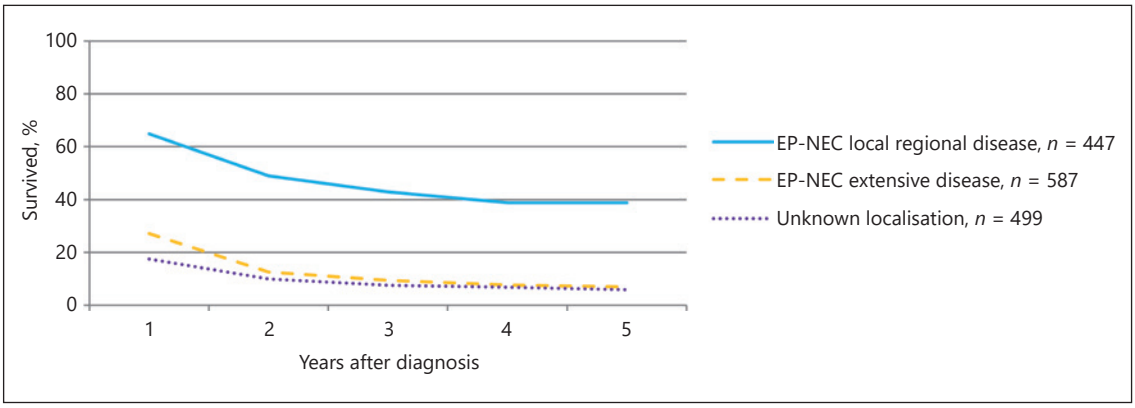

Fig. 4. Relative survival differentiated for UP-NEC.

classification, with the recent introduction of NET grade 3 [3], we hypothesise that NEC patients will shift to grade 3 NET, making the disease even rarer.

In terms of the origin of the EP-NEC, we found most EP-NEC originated in the bladder. With 60 cases annually, this accounts for 2% of all cases of bladder cancer in the Netherlands per year. Overall, patients with EP-NEC of the bladder had the best RS (28.4%), while the 5-year RS for bladder cancer in the Netherlands is 52% (www.cijfersoverkanker.nl) Annually, we observed 97 cases of all EP-NEC found in the gastrointestinal tract, including the pancreas and oesophagus combined. The worst survival was found in patients with an EP-NEC primarily originating in the oesophagus, regardless of the stage of disease. While Lv et al. [26] reported a 5-year overall survival of 12.2% in 126 small cell oesophagus cases, in our study this was 6.9%. Whereas our study took into account the age distribution of the study population by presenting RS, Lv et al. [26] used absolute survival. Besides, our study presents results based on population-based data, while the study by Lv's group was a single-centre study including 32.5% of the patients with extensive disease. In our population, this was 56%. Also, the difference in ethnicity between both study populations could lead to differences in survival, as 5-year RS for oesophagus cancer in the Netherlands was 16% for the 2006–2010 period (www.cijfersoverkanker.nl).

For EP-NEC patients with local disease and no treatment given ($n = 17$) (Fig. 3b), the number of cases was low and was potentially based on the circumstances of the individual patient. The poor prognosis for EP-NEC patients with local disease receiving surgery only (Fig. 3b) confirms the findings in the literature that surgery alone is rarely curative in patients with local disease [12]. Chemotherapy and radiotherapy combined with surgery was given mostly to patients with local disease (Table 3). Sørbye et al. [11] conclude that, for patients with limited disease, a combination of systemic platinum-based chemotherapy and local treatment consisting of radiotherapy and/or surgery has the best prognosis. This is in line with our findings (Fig. 3b, c). For EP-NEC patients with extensive disease, surgery in combination with radiotherapy and chemotherapy ($n = 15$) led to a 5-year RS of around 50%. In the group of EP-NEC patients with extensive disease receiving other types of therapy, we observed worse survival rates. Irrespective of the stage of disease, EP-NEC patients not receiving any type of treatment or chemotherapy alone had the worst RS (Fig. 3).

Our study has limitations. This study relies on the diagnoses made by the local pathologist. The additional check to confirm and review the correctness of the NCR is based on updated pathology report conclusions only. A further limitation concerns the treatment-related survival outcome. The treatment of choice is expected to be correlated with the patients' specific characteristics and general condition. We did not have information available concerning the patients' performance status and co-morbidities. More patient characteristics are needed to better explain and draw firm conclusions concerning the findings in survival. Still, this is the first study ever that attempts to give an overview on patients diagnosed with an EP-NEC based on the information already available.

In conclusion, this study is the first nationwide population-based study presenting an increase in incidence from 196 to 260 cases annually in the Netherlands during the 2008–2012 study period, taking into account 499 cases with an unknown primary. We found that the best

5-year RS was for EP-NEC patients with local disease receiving surgery in combination with chemotherapy. For EP-NEC patients with extensive disease, the 5-year RS was 15%. Since the numbers at a national level are low, making it difficult to draw firm conclusions, an international population-based study on EP-NEC is necessary.

Acknowledgement

We thank all NEC patients and their families and the Stichting NET groep and their sponsor for making this research possible.

Disclosure Statement

The authors declare that they have no conflicts of interest.

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