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Original Research

Long-term survival in patients with gastroenteropancreatic neuroendocrine neoplasms: A population-based study

Iris N. Poleé [a], Bregtje C.M. Hermans [b], Jan Maarten van der Zwan [c], Stefan A.W. Bouwense [d], Marcus W. Dercksen [b], Ferry A.L.M. Eskens [e], Bastiaan Havekes [f], Johannes Hofland [g], Thomas M.A. Kerkhofs [h], Heinz-Josef Klümpen [i], Loes M. Latten-Jansen [h], Ernst-Jan M. Speel [j], Frederik A. Verburg [k], Annemiek M.E. Walenkamp [l], Sandra M.E. Geurts [h], Judith de Vos-Geelen [h,*]

[a] *Department of Pulmonology, Zuyderland Medical Center, Heerlen, the Netherlands*
[b] *Department of Medical Oncology, Maxima Medical Center, Veldhoven, the Netherlands*
[c] *Department of Research and Development, Netherlands Comprehensive Cancer Organization (IKNL), Utrecht, the Netherlands*
[d] *Department of Surgery, Maastricht University Medical Center, Maastricht, the Netherlands*
[e] *Department of Internal Medicine, Division of Medical Oncology, Erasmus Medical Center, Rotterdam, the Netherlands*
[f] *Department of Internal Medicine, Division of Endocrinology, Maastricht University Medical Center, Maastricht, the Netherlands*
[g] *Department of Internal Medicine, Division of Endocrinology, Erasmus Medical Center, Rotterdam, the Netherlands*
[h] *Department of Internal Medicine, Division of Medical Oncology, GROW - School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, the Netherlands*
[i] *Department of Medical Oncology, Amsterdam University Medical Center, Location AMC, Amsterdam, the Netherlands*
[j] *Department of Pathology, GROW - School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, the Netherlands*
[k] *Department of Radiology&Nuclear Medicine, Erasmus Medical Center, Rotterdam, the Netherlands*
[l] *Department of Internal Medicine, Division of Medical Oncology, University Medical Center Groningen, Groningen, the Netherlands*

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KEYWORDS
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Abstract ***Background:*** Gastroenteropancreatic (GEP) neuroendocrine neoplasms (NENs) comprise a group of rare malignant tumours with heterogeneous behaviour. This study aimed to assess long-term survival and prognostic factors associated with survival, in order to

* *Corresponding author*: Department of Internal Medicine, Division of Medical Oncology, Maastricht University Medical Center, P. Debyelaan 25, Maastricht, 6202 AZ, Netherlands.
E-mail address: judith.de.vos@mumc.nl (J. de Vos-Geelen).

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Carcinoid;
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optimise counselling.
Patients and methods: This population-based study included all GEP-NENs diagnosed between 1989 and 2016 in the Netherlands, selected from the Netherlands Cancer Registry. Overall survival (OS) and relative survival (RS) were calculated. A Cox Proportional Hazard analysis was used to identify prognostic factors (gender, age, tumour stage, location and treatment) for OS. Analyses were stratified by metastatic disease status and tumour grade.
Results: In total, 9697 patients were included. In grade 1, 2 and 3 non-metastatic GEP-NENs (N = 6544), 5-year OS and RS were 81% and 88%, 78% and 83%, and 26% and 30%, respectively. In grade 1 non-metastatic GEP-NENs 10-year OS and RS were 68% and 83%. In grade 1, 2 and 3 metastatic GEP-NENs (N = 3153), 5-year OS and RS rates were 47% and 52%, 38% and 41%, and 5% and 5%, respectively. The highest (relative) survival rates were found in appendicular and rectal NENs, demonstrating 10-year OS and RS of 87% and 93%, and 81% and 95%, respectively.
Conclusions: These long-term follow-up data demonstrate significant differences in survival for different grades, tumour stage, and primary origin of GEP-NENs, with the most favourable overall and RS rates in patients with non-metastatic grade 1 appendicular and rectal NENs. This study demonstrates unique long-term OS and RS rates using combined stratification by tumour site, grade and stage.

1. Introduction

Gastroenteropancreatic (GEP) neuroendocrine neoplasms (NENs) are rare tumours with a combined age-adjusted incidence of 3.56–3.65 per 100,000 person-years [1,2]. Even though NENs can originate in almost every organ throughout the body, they are located in the gastrointestinal tract in approximately 60% of all neuroendocrine tumours (NETs) [1,3], and in 27% of all neuroendocrine carcinomas (NECs) [4]. GEP-NENs generally show a better prognosis than the corresponding adenocarcinomas, but particularly high-grade GEP-NENs can be very aggressive and resistant to systemic therapies [5]. The most important predictor of behaviour and prognosis is tumour grade [1].

In 2010, the World Health Organization (WHO) published guidelines on the classification of tumours of the digestive system, introducing a new grading system and nomenclature [5]. Together with guidelines from the European Neuroendocrine Tumour Society (ENETS) [6–8], this created more clarity on diagnosis, nomenclature, classification and treatment of GEP-NENs. This classification system's differentiation grade is based on Ki-67 and mitotic index proliferation markers, resulting in grade 1 (G1) NETs, grade 2 (G2) NETs, and grade 3 (G3) NECs. In 2019, WHO guidelines added morphology to the grading system for G3 NENs, resulting in well-differentiated G3 NETs and poorly differentiated G3 NECs [9]. Apart from this grading system, tumour-node-metastasis (TNM) classifications for tumour staging were specified for NENs of different sites of origin by both the ENETS and the Union for International Cancer Control (UICC) [10]. Besides tumour grade and stage, the location of the primary tumour is among the most relevant prognostic factors for survival [3]. As a consequence, most guidelines base their treatment strategy mainly on the primary origin of the NEN [3–6].

Little is known about long-term survival and prognostic factors in GEP-NENs. Numerous studies have underlined the prognostic importance of stage and grade to predict survival [1,11–13]. However, none of these studies combined stratification by the tumour grade, stage and primary origin for survival analysis. However, these data are essential for patient counselling and prediction of treatment outcome.

This study aimed to assess long-term overall survival (OS) and relative survival (RS) in a nationwide cohort of patients diagnosed with GEP-NENs per grade, stage and tumour location.

2. Methods

2.1. Patients

All GEP-NENs in the GEP tract (oesophagus, stomach, small intestines, pancreas, appendix, colon and rectum) and diagnosed between January 1989 and December 2016 in the Netherlands were selected from the Netherlands Cancer Registry (NCR). The NCR is a population-based cancer registry including patients with a diagnosed malignancy, with a nationwide coverage >95%, based on the notification by the Netherlands nationwide network and registry of histo- and cytopathology (PALGA) and the National Registry of Hospital Discharge Diagnoses. A yearly linkage between the

NCR and the municipality registry (GBA) ensured the completeness of follow-up, identifying all deceased citizens in the Netherlands. Data were requested on tumours registered under the morphological codes listed in Supplementary Table S1, matching the paper published by Korse *et al.* [14].

Patient informed consent was waived by the Medical Ethics Board AZM/UM due to the study's retrospective nature (METC 2018-0584). The reporting of this study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [15].

2.2. Definitions

Since there have been four different versions of the UICC TNM classification from 1989 to 2016, tumours were re-staged according to the UICC 7th edition [10]. Pathologic tumour stage was assessed for stage distribution, or if not available, clinical tumour stage was noted. Patients with an unknown metastatic status (Mx) were defined as having no distant metastasis (M0). If TNM staging was not determined, the extent of disease was registered, which was classified as either tumour limited to organ, nodal involvement or distant metastases. Tumours with nodal involvement were re-staged as stage III. However, since no differentiation between stage I and stage II disease could be made for tumours limited to the organ, these were categorised as 'stage unknown'. Tumour grade was based on the ICD-O-3 morphological codes, which provide information on the histological term, tumour behaviour (e.g. malignant, benign) and histological grading, in which a separate one-digit code provides the histological grading (Supplementary Table 1) [14].

Treatment was categorised as either surgery, surgery with (neo)adjuvant treatment (radiotherapy and/or systemic therapy), radiotherapy (including external radiotherapy, internal radiotherapy and (peptide receptor) radionuclide therapy (PRRT)), chemotherapy, endocrine therapy (including somatostatin analogues), concurrent chemotherapy and radiotherapy, or combined endocrine therapy and radiotherapy. In metastatic disease, induction therapy before surgery or postoperative treatment, independent of intention of treatment (curative or palliative), is listed under 'surgery with (neo) adjuvant treatment'.

2.3. Survival analysis

OS was defined as the time from diagnosis until death or censored on February 1st 2019, or at the emigration date. RS was used to approximate the disease-specific survival (DSS) by correcting OS for the expected survival of subjects of the same sex and age in the general population at the time of diagnosis.

The median duration of follow-up was calculated using the reverse Kaplan–Meier method, censored at death. Starting at the time of diagnosis, survival curves for OS were created and displayed using Kaplan–Meier analyses. Log rank tests were performed to assess statistically significant differences in patient OS. Five and 10-year OS rates were calculated using survival analyses, and RS rates were calculated using the Ederer II method. Univariable and multivariable Cox Proportional Hazard Analyses were used to analyse the impact of gender, age, tumour stage, tumour location and treatment on OS. Variables were included in the multivariable model if they were statistically significantly associated with OS in univariable analysis ($P < 0.05$) and after testing for multicollinearity. All analyses were performed per tumour grade and stratified by metastatic disease status. Results were considered statistically significant at $P < 0.05$. Statistical analyses were performed using IBM SPSS Statistics 25 and STATA 14.

3. Results

3.1. Patient characteristics

A total of 9697 patients with GEP-NENs were included. The median age at diagnosis was 63 years, and 50% were male (Table 1). In 67% of patients, the disease was non-metastatic. Of all NENs, 21% were located in the jejunum or ileum, 18% in the pancreas, 15% in the appendix, 14% in the rectum, 12% in the colon and 21% in either the oesophagus, stomach, duodenum or Papil of Vater. GEP-NENs were classified as stage I in 20%, stage II in 10%, stage III in 16%, stage IV in 33% and in 22% the stage was unknown.

In patients with non-metastatic NENs (N = 6544, 30% stage I, 14% stage II, 24% stage III, 32% stage unknown), 83% were diagnosed with G1, 5% with G2 and 12% with G3. In patients with metastatic NENs (N = 3153), 48% were G1, 11% G2 and 41% G3 NENs (Table 1). Details on treatment are described in Supplemental Figs. S1 and S2.

3.2. Overall and relative survival

The median duration of follow-up was 98 months (95% confidence interval (CI): 94–102 months). Five-year OS was 81% (95%CI: 79–83), 78% (95%CI: 72–84) and 26% (95%CI: 22–30) in patients with non-metastatic G1, G2 and G3 NENs, respectively (Table 2 and Figs. 1 and 2). Five-year RS was respectively 88% (95%CI: 87–90), 83% (95%CI: 77–89) and 30% (95%CI: 27–34). In patients with non-metastatic G1 NENs, 10-year OS and RS were 68% (95%CI: 66–70) and 83% (95%CI: 81–85). For non-metastatic G2 and G3 NENs, 10-year survival estimates should be interpreted with caution due to the low number of patients remaining beyond five years.

In G1 NENs, 5-year OS and RS were 87% (95%CI: 85–89) and 93% (95%CI: 91–95) for stage I, 86% (95%

Table 1
Patient and tumour characteristics in non-metastatic and metastatic neuroendocrine neoplasms.

	Total	Non-metastatic			Metastatic		
		Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
Patient total	9697	5419	345	780	1501	361	1291
Age (year)							
Median	63	59	62	70	65	64	67
Range	12–102	12–95	13–92	25–95	15–94	19–92	22–102
	N (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)
Age (year)							
<50	2244 (23)	1755 (32)	76 (22)	77 (10)	189 (13)	47 (13)	100 (8)
50-75	5825 (60)	2919 (54)	230 (67)	470 (60)	1062 (71)	261 (72)	883 (68)
>75	1628 (17)	745 (14)	39 (11)	233 (30)	250 (17)	53 (15)	308 (24)
Gender							
Male	4890 (50)	2526 (47)	181 (53)	455 (58)	761 (51)	174 (48)	793 (61)
Female	4807 (50)	2893 (53)	164 (48)	325 (42)	740 (49)	187 (52)	498 (39)
Tumour location							
Oesophagus	547 (6)	5 (0)	0 (0)	214 (27)	5 (0)	0 (0)	323 (25)
Stomach	957 (10)	558 (10)	48 (14)	123 (16)	56 (4)	11 (3)	161 (13)
Duodenum	392 (4)	298 (6)	10 (3)	18 (2)	45 (3)	11 (3)	10 (1)
Papil of Vater	82 (1)	39 (1)	5 (1)	26 (3)	5 (0)	0 (0)	7 (1)
Pancreas	1727 (18)	689 (13)	109 (32)	126 (16)	357 (24)	141 (39)	305 (24)
Jejunum/ileum	2055 (21)	1124 (21)	82 (24)	24 (3)	672 (45)	125 (35)	28 (2)
Appendix	1409 (15)	1322 (24)	28 (8)	7 (1)	44 (3)	2 (1)	6 (1)
Colon	1154 (12)	390 (7)	33 (10)	138 (18)	267 (18)	45 (13)	281 (22)
Rectum	1374 (14)	994 (18)	30 (9)	104 (13)	50 (3)	26 (7)	170 (13)
T classification							
T1	1923 (20)	1698 (31)	84 (24)	70 (9)	32 (2)	12 (3)	27 (2)
T2	1066 (11)	548 (10)	88 (26)	107 (14)	102 (7)	75 (21)	146 (11)
T3	1592 (16)	662 (12)	101 (29)	249 (32)	232 (16)	92 (26)	256 (20)
T4	854 (9)	177 (3)	27 (8)	138 (18)	201 (13)	71 (20)	240 (19)
Unknown	4262 (44)	2334 (43)	45 (13)	216 (28)	934 (62)	111 (31)	622 (48)
N classification							
N0	3376 (35)	2543 (47)	170 (49)	225 (29)	189 (13)	88 (24)	161 (13)
N+	3014 (31)	990 (18)	146 (42)	417 (54)	475 (32)	204 (57)	782 (61)
Unknown	3307 (34)	1886 (35)	29 (8)	138 (18)	837 (56)	69 (19)	348 (27)
TNM stage							
Stage I	1945 (20)	1744 (32)	106 (31)	95 (12)	–	–	–
Stage II	938 (10)	715 (13)	78 (23)	145 (19)	–	–	–
Stage III	1564 (16)	1052 (19)	127 (37)	385 (49)	–	–	–
Stage IV	3153 (33)	–	–	–	1501 (100)	361 (100)	1291 (100)
Stage unknown	2097 (22)	1908 (35)	34 (10)	155 (20)	–	–	–
Treatment							
Surgery	5884 (61)	4604 (85)	298 (86)	290 (37)	515 (34)	65 (18)	112 (9)
Surgery + (neo)adjuvant treatment	579 (6)	85 (2)	18 (5)	110 (14)	234 (16)	55 (15)	77 (6)
Radiotherapy	210 (2)	11 (0)	3 (1)	50 (6)	51 (3)	17 (5)	78 (6)
Chemotherapy	557 (6)	9 (0)	3 (1)	80 (10)	63 (4)	13 (4)	389 (30)
Endocrine therapy	416 (4)	22 (0)	9 (3)	4 (1)	230 (15)	128 (35)	23 (2)
Chemotherapy + radiotherapy	189 (2)	1 (0)	1 (0)	86 (11)	9 (1)	4 (1)	88 (7)
Endocrine therapy + radiotherapy	28 (0)	2 (0)	2 (1)	0 (0)	12 (1)	9 (2)	3 (0)
No treatment	1449 (15)	581 (11)	8 (2)	117 (15)	289 (19)	39 (11)	415 (32)
Unknown	385 (4)	104 (2)	3 (1)	43 (6)	98 (7)	31 (9)	106 (8)

Percentages may not add up to 100% because of rounding.

CI: 84–88) and 93% (95%CI: 89–95) for stage II, and 74% (95%CI: 72–76) and 83% (95%CI: 80–86) for stage III tumours (Table 2, Figs. 1 and 2). In G1 NENs, 10-year OS and RS were 76% (95%CI: 72–80) and 87% (95%CI: 82–91) for stage I, 76% (95%CI: 72–80) and 88% (95%CI: 83–92) for stage II, and 58% (95%CI: 54–62) and 74% (95%CI: 69–78) for stage III tumours. In G2 NENs 5-year OS and RS were 90% (95%CI: 84–96) and 96% (95%CI: 86–100) for stage I, 77% (95% CI: 65–89) and 84% (95%CI: 68–94) for stage II, and 70% (95%CI: 60–80) and 75% (95%CI: 63–85) for stage III tumours. In G3 NENs, 5-year OS and RS rates were 49% (95%CI: 37–61) and 57% (95%CI: 44–69) for stage I, 27% (95%CI: 19–35) and 33% (95%CI: 25–43) for stage II, and 22% (95%CI: 18–26) and 25% (95%CI: 20–30) for stage III tumours (Table 2, Figs. 1 and 2).

Considering tumour location, the highest survival rates were found in non-metastatic G1 appendicular and rectal NENs, demonstrating 10-year OS of 87% (95%CI: 85–89) and 81% (95%CI: 77–85), and 10-year RS of

Table 2
Survival and prognostic factors associated with survival in patients with non-metastatic GEP-NENs, stratified by tumour grade.

	N	5-year OS (%) (95%CI)	5-year RS (%) (95%CI)	10-year OS (%) (95%CI)	10-year RS (%) (95%CI)	Multivariable HR OS (95%CI)	*P*-value
Grade 1	5419	81 (79–83)	88 (87–90)	68 (66–70)	83 (81–85)		
Gender							
Male	2526	78 (76–80)	88 (86–89)	65 (63–67)	82 (79–85)	Ref.	
Female	2893	83 (81–85)	89 (88–91)	71 (69–73)	83 (81–86)	0.80 (0.73–0.88)	**<0.001**
Age							
<50 year	1755	97 (95–99)	98 (97–98)	95 (93–97)	96 (94–97)	Ref.	
50–75 year	2919	80 (78–82)	87 (85–88)	64 (62–66)	77 (75–80)	6.74 (5.55–8.16)	**<0.001**
>75 year	745	44 (40–48)	71 (95–77)	20 (16–24)	69 (57–81)	21.86 (17.70 –27.00)	**<0.001**
TNM stage							
Stage I	1744	87 (85–89)	93 (91–95)	76 (72–80)	87 (82–91)	Ref.	
Stage II	715	86 (84–88)	93 (89–95)	76 (72–80)	88 (83–92)	1.11 (0.91–1.35)	0.317
Stage III	1052	74 (72–76)	83 (80–86)	58 (54–62)	74 (69–78)	1.29 (1.09–1.53)	**0.004**
Unknown	1908	77 (75–79)	86 (84–88)	66 (64–68)	82 (79–84)	1.24 (1.08–1.44)	**0.003**
Location							
Oesophagus	5	40 (0–88)[a]	57 (7–97)[a]	0[a]	0[a]	2.19 (0.75–6.83)	0.175
Stomach	558	69 (65–73)	79 (74–84)	55 (51–59)	74 (68–80)	0.91 (0.75–1.11)	0.349
Duodenum	298	72 (66–78)	83 (76–89)	55 (47–63)	71 (62–80)	1.00 (0.78–1.24)	0.902
Papil of Vater	39	79 (65–93)	86 (67–96)	67 (47–87)	79 (51–97)	1.22 (0.69–2.15)	0.487
Pancreas	689	82 (78–86)	89 (85–92)	67 (63–71)	78 (72–83)	Ref.	**0.012**
Jejunum/ileum	1124	69 (67–71)	82 (78–85)	52 (48–56)	73 (69–78)	1.26 (1.05–1.50)	**0.023**
Appendix	1322	92 (90–94)	95 (93–96)	87 (85–89)	93 (91–96)	0.78 (0.63–0.94)	**0.003**
Colon	390	71 (67–75)	81 (75–86)	54 (48–60)	70 (62–78)	1.37 (1.11–1.70)	**<0.001**
Rectum	994	91 (89–93)	97 (95–99)	81 (77–85)	95 (91–98)	0.59 (0.48–0.73)	
Treatment							
Surgery	4604	84 (82–86)	91 (90–92)	72 (70–74)	86 (84–87)	Ref.	
Surgery + (neo)adjuvant treatment	85	63 (51–75)	67 (53–77)	54 (40–68)	61 (45–76)	1.61 (1.14–2.27)	**0.007**
Radiotherapy	11	73 (47–99)[a]	78 (40–97)[a]	62 (32–92)[a]	73 (33–99)[a]	1.79 (0.67–4.80)	0.247
Chemotherapy	9	50 (14–86)[a]	55 (16–86)[a]	34 (0–70)[a]	40 (7–79)[a]	2.76 (1.09–6.98)	**0.032**
Endocrine therapy	22	76 (58–94)	91 (62–100)	50 (22–78)[a]	69 (29–100)[a]	1.25 (0.64–2.41)	0.514
Chemotherapy + radiotherapy	1	100[a]	100[a]	[b]	[b]	–	–
Endocrine therapy + radiotherapy	2	100[a]	100[a]	[b]	[b]	2.03 (0.28–14.54)	0.481
No treatment	581	57 (53–61)	71 (65–75)	44 (40–48)	65 (58–72)	1.85 (1.60–2.14)	**<0.001**
Unknown	104	78 (68–88)	86 (74–95)	63 (49–77)	78 (59–93)	1.06 (0.73–1.52)	0.776
Grade 2	345	78 (72–84)	83 (77–89)	66 (56–76)	77 (64–88)		
Gender							
Male	181	78 (70–86)	84 (75–91)	59 (43–75)[a]	70 (49–86)[a]	Ref.	
Female	164	78 (70–86)	83 (73–90)	73 (61–85)	85 (70–96)	0.91 (0.54–1.54)	0.722
Age							
<50 year	76	97 (93–100)	98 (90–100)	97 (93–100)[a]	99 (91–100)[a]	Ref.	
50–75 year	230	75 (67–83)	80 (72–87)	60 (46–74)	71 (54–84)	4.12 (1.44–11.78)	**0.008**
>75 year	39	52 (30–74)	72 (40–98)	52 (30–74)[a]	100 (60–100)[a]	7.28 (2.23–23.79)	**0.001**
TNM stage							
Stage I	106	90 (84–96)	96 (86–100)	90 (84–96)[a]	100 (90–100)[a]	Ref.	
Stage II	78	77 (65–89)	84 (68–94)	51 (9–93)[a]	66 (14–100)[a]	2.11 (0.87–5.10)	0.098
Stage III	127	70 (60–80)	75 (63–85)	64 (50–78)[a]	77 (59–91)[a]	3.95 (1.61–9.73)	**0.003**
Unknown	34	73 (57–89)	79 (59–92)	58 (40–76)	67 (45–85)	3.07 (1.24–7.61)	**0.015**
Location							
Oesophagus	0	–	–	–	–	–	–
Stomach	48	69 (53–87)	78 (58–92)	69 (53–85)[a]	85 (64–100)[a]	1.60 (0.70–3.69)	0.267
Duodenum	10	100[a]	100[a]	[b]	[b]	–	–
Papil of Vater	5	60 (16–100)[a]	64 (13–93)[a]	60 (16–100)[a]	66 (14–97)[a]	1.42 (0.32–6.42)	0.646
Pancreas	109	79 (69–89)	84 (71–92)	65 (45–85)[a]	74 (46–92)[a]	Ref.	0.216
Jejunum/ileum	82	78 (66–90)	84 (68–94)	64 (42–86)[a]	73 (45–93)[a]	0.58 (0.25–1.37)	0.389
Appendix	28	93 (83–100)[a]	96 (77–100)[a]	93 (83–100)[a]	98 (79–100)[a]	0.52 (0.12–2.30)	0.456
Colon	33	80 (66–94)	88 (67–99)	63 (39–87)[a]	77 (42–99)[a]	0.70 (0.27–1.80)	0.081
Rectum	30	60 (38–82)	67 (40–87)	60 (38–82)[a]	77 (46–99)[a]	2.08 (0.91–4.73)	
Treatment							
Surgery	298	81 (75–87)	87 (80–92)	68 (56–80)	79 (64–90)	Ref.	
Surgery + (neo)adjuvant treatment	18	77 (57–97)[a]	83 (53–97)[a]	77 (57–97)[a]	89 (58–100)[a]	0.80 (0.28–2.29)	0.678
Radiotherapy	3	33 (0–87)[a]	35 (1–81)[a]	[b]	[b]	3.53 (0.80–15.55)	0.096

Table 2 (*continued*)

	N	5-year OS (%) (95%CI)	5-year RS (%) (95%CI)	10-year OS (%) (95%CI)	10-year RS (%) (95%CI)	Multivariable HR OS (95%CI)	*P*-value
Chemotherapy	3	[b]	[b]	[b]	[b]	3.79 (0.84–17.01)	0.082
Endocrine therapy	9	53 (0–100)[a]	59 (4–99)[a]	[b]	[b]	1.17 (0.27–5.18)	0.834
Chemotherapy + radiotherapy	1	[b]	[b]	[b]	[b]	9.21 (1.02–83.17)	**0.048**
Endocrine therapy + radiotherapy	2	[b]	[b]	[b]	[b]	5.30 (0.65–43.19)	0.119
No treatment	8	50 (14–86)[a]	59 (18–92)[a]	50 (14–86)[a]	81 (25–100)[a]	1.36 (0.38–4.90)	0.638
Unknown	3	[b]	[b]	[b]	[b]	7.66 (0.91–64.47)	0.061
Grade 3	780	26 (22–30)	30 (27–34)	19 (15–23)	25 (21–30)		
Gender							
Male	455	23 (19–27)	27 (23–32)	17 (13–21)	24 (18–29)	Ref.	
Female	325	30 (24–36)	34 (29–40)	20 (14–26)	28 (22–36)	0.87 (0.73–1.03)	0.104
Age							
<50 year	77	42 (30–54)	42 (31–53)	35 (23–47)	35 (23–47)	Ref.	
50–75 year	470	30 (26–34)	32 (28–37)	22 (18–26)	28 (23–33)	1.38 (1.01–1.88)	**0.041**
>75 year	233	14 (10–18)	22 (15–31)	4 (0–8)[a]	14 (5–31)	2.04 (1.47–2.84)	**<0.001**
TNM stage							
Stage I	95	49 (37–61)	57 (44–69)	46 (34–58)	67 (50–83)	Ref.	
Stage II	145	27 (19–35)	33 (25–43)	18 (10–26)	26 (16–39)	2.39 (1.69–3.36)	**<0.001**
Stage III	385	22 (18–26)	25 (20–30)	16 (12–20)	21 (16–27)	2.22 (1.62–3.05)	**<0.001**
Unknown	155	20 (14–26)	25 (18–33)	11 (5–17)	16 (9–24)	1.91 (1.34–2.70)	**<0.001**
Location							
Oesophagus	214	13 (7–19)	15 (10–21)	10 (4–16),[a]	14 (8–21),[a]	2.31 (1.73–3.09)	**<0.001**
Stomach	123	22 (14–30)	27 (18–37)	17 (9–25)	25 (15–37)	1.44 (1.06–1.94)	**0.018**
Duodenum	18	21 (1–41)[a]	24 (7–49)[a]	21 (1–41)[a]	28 (8–57)[a]	1.49 (0.84–2.64)	0.169
Papil of Vater	26	18 (2–34),[a]	22 (7–44)[a]	12 (0–26)[a]	17 (3–44)[a]	1.42 (0.88–2.29)	0.152
Pancreas	126	38 (30–46)	42 (33–52)	24 (16–34)	29 (19–40)	Ref.	
Jejunum/ileum	24	54 (43–74)	59 (35–78)	54 (34–74)	65 (39–86)	0.86 (0.46–1.62)	0.639
Appendix	7	86 (60–100)[a]	95 (37–100)[a]	43 (0–100)[a]	50 (1–99)[a]	0.27 (0.07–1.08)	0.064
Colon	138	37 (21–53)	44 (35–54)	21 (11–31)	31 (19–45)	1.67 (1.20–2.33)	**0.003**
Rectum	104	21 (13–29)	25 (16–35)	18 (10–26),[a]	25 (15–37)[a]	2.26 (1.62–3.16)	**<0.001**
Treatment							
Surgery	290	41 (35–47)	47 (40–54)	33 (27–39)	44 (36–53)	Ref.	
Surgery + (neo)adjuvant treatment	110	27 (17–37)	30 (20–41)	17 (7–27),[a]	25 (13–40)[a]	1.07 (0.80–1.41)	0.659
Radiotherapy	50	9 (1–17),[a]	11 (4–23),[a]	3 (0–9)[a]	4 (0–16)[a]	1.69 (1.16–2.46)	**0.006**
Chemotherapy	80	6 (0–14)[a]	7 (2–15),[a]	4 (0–8)[a]	6 (2–15),[a]	1.94 (1.42–2.66)	**<0.001**
Endocrine therapy	4	38 (0–96)[a]	42 (1–91)[a]	0[a]	0[a]	1.52 (0.47–4.92)	0.484
Chemotherapy + radiotherapy	86	32 (22–42)	35 (24–47)	21 (9–33),[a]	26 (13–41)[a]	0.83 (0.58–1.17)	0.279
Endocrine therapy + radiotherapy	0	–	–	–	–	–	–
No treatment	117	12 (6–18)	16 (9–25)	4 (0–8)[a]	7 (2–16),[a]	3.93 (2.92–5.29)	**<0.001**
Unknown	43	6 (0–14)[a]	8 (1–22),[a]	0[a]	0[a]	4.21 (2.88–6.17)	**<0.001**

OS = overall survival; CI = confidence interval; RS = relative survival; HR = hazard ratio; Ref. = reference.
Bold font indicates significant prognostic factors of overall survival.
[a] Note, low patient numbers.
[b] No follow-up data available.

93% (95%CI: 91–96) and 95% (95%CI: 91–98), respectively (Table 2, Figs. 1 and 2). Across G1 NENs and G3 NENs, age, stage, location of the primary tumour and treatment were independent prognostic factors for OS (Table 2). In G2 NENs, age, stage and treatment were independently associated with survival.

In metastatic disease, 5-year OS and RS rates were 47% (95%CI: 45–49) and 52% (95%CI: 49–54) for G1, 38% (95%CI: 30–46) and 41% (95%CI: 34–49) for G2, and 5% (95%CI: 3–7) and 5% (95%CI: 4–7) for G3 NENs, respectively (Table 3 and Figs. 1 and 2). Across all grades, the highest 10-year OS rates were achieved by G1 primary tumours located in the duodenum and the jejunum or ileum (53% (95%CI: 35–71) and 38% (95%CI: 34–43), respectively) (Table 3). Age and primary tumour location were independent prognostic factors associated with OS in patients with G1 and G3 NENs, but not in G2 NENs (Table 3). Across all grades, patients who received any modality of anti-tumour treatment had superior survival compared with those who did not undergo anti-tumour treatment.

Overall, 5-year OS was best in patients diagnosed in 2012–2016 (63% (95%CI 61–95%)) and similar in the

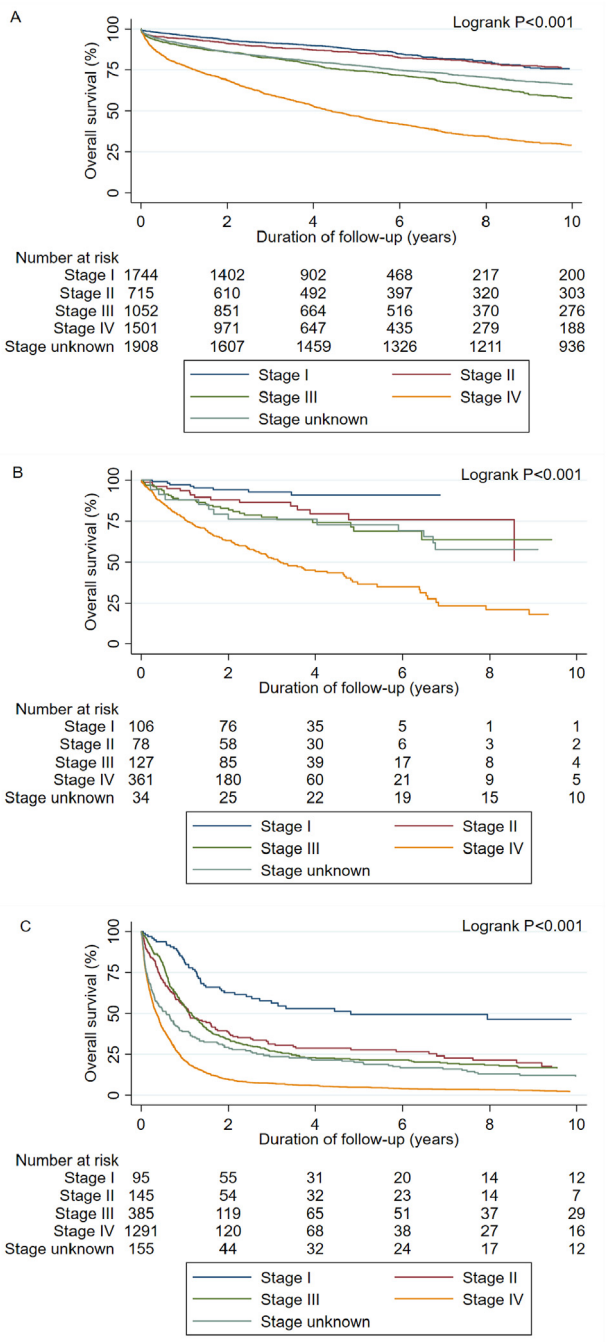

Fig. 1. Overall survival of patients with (A) grade 1 NEN (B) grade 2 NEN and (C) grade 3 NEN, stratified by stage.

period 1989–2011 (range: 57%–59%) (logrank $P < 0.001$) (Supplementary Fig. S3).

4. Discussion

This population-based nationwide study demonstrates long-term overall and RS and prognostic factors in 9697 patients with GEP-NENs. To the best of our knowledge, this is the most extensive European study on GEP-NENs to date, providing data to support the individual counselling on the prognosis of patients with GEP-NENs, stratified by grade, stage and primary origin of the tumour.

This study underlines the heterogeneity within GEP-NENs, demonstrating great variety in 10-year survival rates. Not unexpectedly, non-metastatic NENs G1 show the best outcome. Almost seven out of ten patients were alive ten years after diagnosis, with an even higher survival rate for tumours in the appendix or rectum. This outcome contrasts sharply with G3 NENs demonstrating 10-year OS rates of only 19% and 2% for non-metastatic and metastatic disease, respectively. These data are comparable with a large (N = 35618) study by Yao *et al.* [3] including patients with NENs registered in the Surveillance, Epidemiology, and End Results (SEER) reporting 10-year OS rates of 69% for well to moderately differentiated localised tumours and only 2% for patients with metastatic, poorly differentiated tumours. Another SEER-based study by Modlin *et al.* [16] (N = 13715) describes 5-year OS rates of 76% in patients with localised G1 NENs and 41% in patients with metastatic G1 (N = 3370). However, these SEER studies do not provide information on RS.

The current study includes long-term RS data, which provides meaningful real-life and disease-specific knowledge. After correcting OS for the expected survival of the general population, RS data demonstrated 10-year survival rates of 30–88% in non-metastatic disease and 10-year RS rates ranging from 5% in G3 NENs to 52% in G1 NENs in metastatic disease. These results are highly relevant for patient counselling in this heterogeneous malignancy, indolent in a large subset of patients. A study by McMullen *et al.* [17] using the Canadian Cancer Registry (N = 530) showed a 5-year DSS of 97% for localised disease, 90% for regional disease and 58% for metastatic gastrointestinal NENs. These survival rates are significantly higher than the RS rates reported in our study, explained by the exclusion of NECs and oesophageal and pancreatic NENs, which had the worst survival rates in our cohort. Chi *et al.* [18] used the SEER database to analyse 20-year DSS in 13,348 patients with non-metastatic GEP-NENs diagnosed between 1988 and 2009 after undergoing surgical resection. This study reported 20-year DSS rates of 80%, 68% and 35% in well-, moderately and poorly differentiated tumours, respectively. Though the current study did not analyse 20-year RS, these survival rates seem to be higher than reported in our study, related to the inclusion of patients who had undergone surgical resection only.

Furthermore, one must be cautious in comparing RS and DSS data since RS is a proxy for DSS. The RS rates might be lower if the disease is associated with risk factors or comorbidities, resulting in a poorer prognosis. Several meta-analyses demonstrated (hereditary) malignancies, metabolic syndrome, obesity, smoking and alcohol abuse to be associated with the development of GEP-NENs, which might result in a lower RS compared

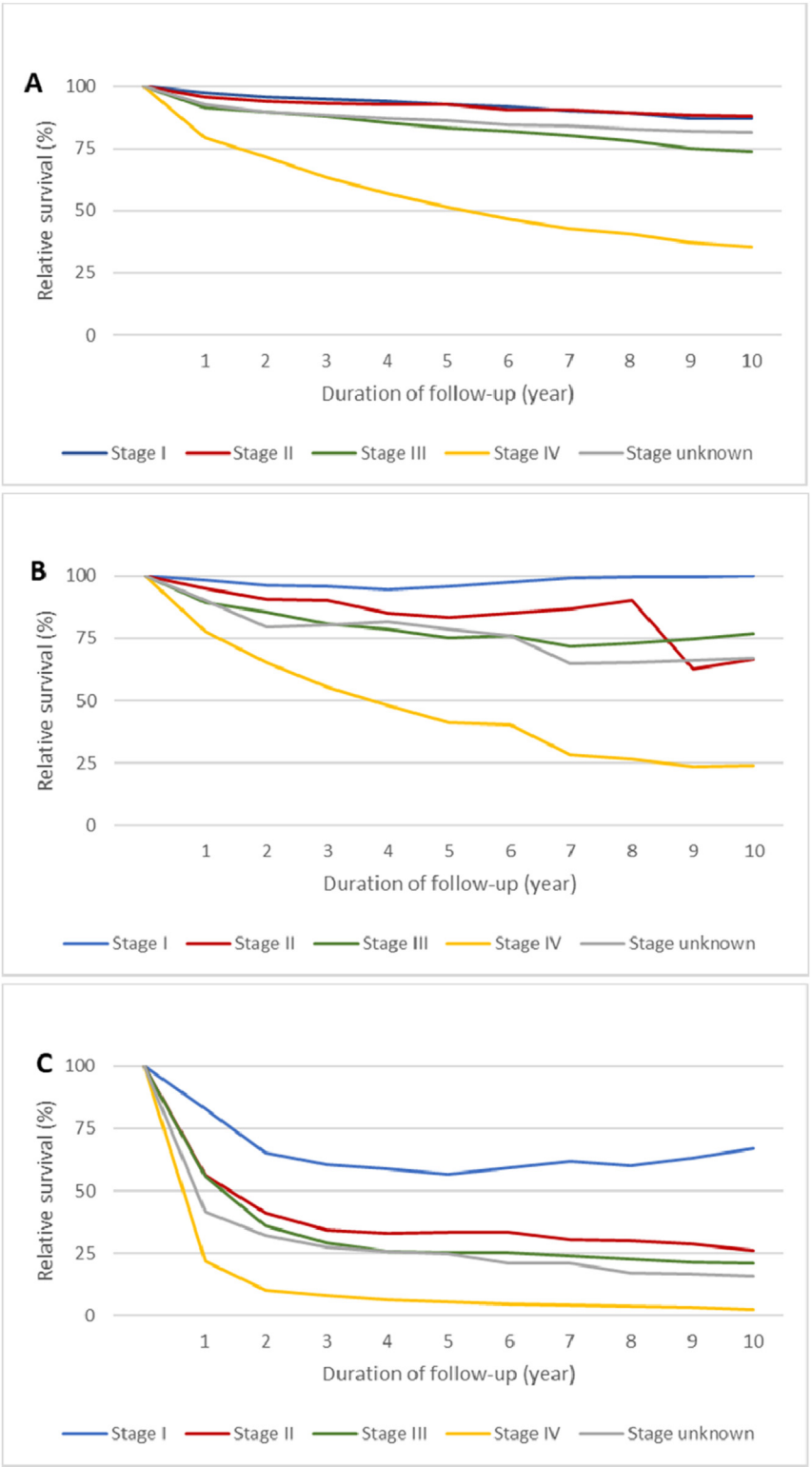

Fig. 2. Relative survival of patients with (A) grade 1 NEN (B) grade 2 NEN, and (C) grade 3 NEN, stratified by stage.

with DSS [19–21]. Unfortunately, DSS could not be calculated since the cause of death was not registered in the NCR database.

The current study shows that age, tumour location and TNM stage are independent prognostic factors associated with survival in G1 and G3 NENs in patients with both non-metastatic and metastatic disease. Applied treatment was shown to be a prognostic factor across all stages and grades. However, the decision to perform a specific treatment is multifactorial,

Table 3
Survival and prognostic factors associated with survival in patients with metastatic GEP-NENs, stratified by tumour grade.

	N	5-year OS (%) (95%CI: %)	5-year RS (%) (95%CI: %)	10-year OS (%) (95%CI: %)	10-year RS (%) (95%CI: %)	HR OS (95%CI)	*P*-value
Grade 1	1501	47 (45–49)	52 (49–54)	29 (27–31)	36 (32–39)		
Gender							
Male	761	46 (42–50)	51 (47–56)	29 (25–33)	37 (32–42)	Ref.	
Female	740	48 (44–52)	52 (47–56)	29 (25–33)	34 (30–39)	0.94 (0.83–1.07)	0.367
Age							
<50 year	189	63 (55–71)	64 (57–71)	52 (44–60)	53 (45–62)	Ref.	
50–75 year	1062	50 (46–54)	53 (50–57)	30 (26–34)	36 (32–40)	1.86 (1.48–2.35)	**<0.001**
>75 year	250	21 (15–27)	31 (24–40)	6 (2–10),[a]	15 (7–30),[a]	4.02 (3.07–5.25)	**<0.001**
Location							
Oesophagus	5	0[a]	0[a]	0[a]	0[a]	2.30 (0.93–5.69)	0.072
Stomach	56	18 (8–28)	20 (10–34)	11 (1–21),[a]	13 (4–26),[a]	1.54 (1.13–2.10)	**0.006**
Duodenum	45	65 (51–79)	73 (55–86)	53 (35–71)	70 (46–90)	0.40 (0.26–0.64)	**<0.001**
Papil of Vater	5	60 (16–100)[a]	62 (13–91)[a]	60 (16–100)[a]	62 (13–91)[a]	0.84 (0.21–3.40)	0.803
Pancreas	357	34 (28–40)	36 (31–42)	19 (15–23)	22 (17–28)	Ref.	
Jejunum/ileum	672	59 (55–63)	65 (61–69)	38 (34–42)	47 (42–53)	0.76 (0.64–0.91)	**0.003**
Appendix	44	42 (26–58)	45 (27–61)	33 (15–51)[a]	38 (19–57)[a]	1.31 (0.87–1.97)	0.191
Colon	267	43 (37–49)	48 (41–55)	23 (17–29)	28 (21–36)	1.10 (0.90–1.34)	0.349
Rectum	50	25 (13–37)	28 (15–42)	13 (3–23),[a]	17 (6–34),[a]	1.30 (0.93–1.82)	0.129
Treatment							
Surgery	515	56 (52–60)	63 (58–67)	39 (35–43)	49 (43–54)	Ref.	
Surgery + (neo)adjuvant treatment	234	69 (63–55)	74 (66–80)	50 (42–58)	58 (47–67)	0.74 (0.58–0.93)	**0.011**
Radiotherapy	51	45 (31–59)	48 (34–62)	19 (7–31),[a]	22 (10–37)[a]	1.39 (0.98–1.97)	0.066
Chemotherapy	63	10 (2–18)	10 (4–19)	4 (0–10)[a]	4 (1–13),[a]	2.96 (2.02–3.97)	**<0.001**
Endocrine therapy	230	53 (45–61)	57 (49–65)	26 (18–34)	31 (22–41)	1.07 (0.86–1.32)	0.559
Chemotherapy + radiotherapy	9	22 (0–50)[a]	23 (4–54)[a]	0[a]	0[a]	2.27 (1.10–4.69)	**0.027**
Endocrine therapy + radiotherapy	12	50 (18–82)	53 (20–80)	24 (0–56)[a]	29 (4–68)[a]	1.05 (0.49–2.23)	0.903
No treatment	289	23 (17–29)	27 (21–33)	11 (7–15)	15 (10–21)	2.19 (1.82–2.62)	**<0.001**
Unknown	98	29 (10–39)	33 (23–43)	17 (9–25)	21 (12–32)	1.96 (1.52–2.52)	**<0.001**
Grade 2	361	38 (30–46)	41 (34–49)	19 (9–29),[a]	24 (14–37)		
Gender							
Male	174	39 (29–49)	44 (32–55)	24 (10–38)[a]	30 (15–48)[a]	Ref.	
Female	187	36 (26–46)	40 (30–50)	15 (1–29),[a]	18 (5–38)[a]	0.88 (0.65–1.19)	0.403
Age							
<50 year	47	44 (26–62)	44 (25–61)	31 (5–57)[a]	32 (11–57)	Ref.	
50–75 year	261	40 (32–48)	43 (34–52)	25 (13–37)[a]	29 (16–44)	1.01 (0.63–1.61)	0.973
>75 year	53	18 (4–32),[a]	29 (12–52)[a]	0[a]	0[a]	1.73 (0.95–3.16)	0.075
Location							
Oesophagus	0	–	–	–	–	–	0.476
Stomach	11	[b]	[b]	[b]	[b]	1.32 (0.61–2.86)	0.136
Duodenum	11	44 (2–86)[a]	58 (17–90)[a]	[b]	[b]	0.45 (0.16–1.29)	–
Papil of Vater	0	–	–	–	–	–	0.071
Pancreas	141	38 (8–68)	30 (20–42)	15 (0–31)[a]	16 (4–36)[a]	Ref.	0.218
Jejunum/ileum	125	57 (45–69)	63 (49–76)	26 (6–46)[a]	33 (12–59)[a]	0.67 (0.44–1.03)	**0.023**
Appendix	2	[b]	[b]	[b]	[b]	3.67 (0.46–29.11)	0.086
Colon	45	22 (8–36)[a]	25 (11–42)[a]	13 (0–29)[a]	18 (3–44)[a]	1.80 (1.08–3.00)	
Rectum	26	29 (19–39)[a]	42 (13–71)[a]	26 (0–56)[a]	31 (6–67)[a]	0.58 (0.31–1.08)	
Treatment							
Surgery	65	71 (57–85)	80 (61–93)	38 (2–74)[a]	53 (11–97)[a]	Ref.	
Surgery + (neo)adjuvant treatment	55	54 (36–72)	56 (36–74)	[b]	[b]	1.97 (1.02–3.82)	**0.044**
Radiotherapy	17	37 (7–67)[a]	41 (14–68)[a]	0[a]	0[a]	3.14 (1.40–7.08)	**0.006**
Chemotherapy	13	0[a]	0[a]	0[a]	0[a]	6.19 (2.69–14.27)	**<0.001**
Endocrine therapy	128	35 (21–49)	39 (25–53)	19 (3–35),[a]	24 (9–46)[a]	2.51 (1.43–4.43)	**0.001**
Chemotherapy + radiotherapy	4	0[a]	0[a]	[b]	[b]	7.19 (2.30–22.52)	**0.001**
Endocrine therapy + radiotherapy	9	38 (0–82)[a]	42 (5–82)[a]	[b]	[b]	2.56 (0.82–7.94)	0.104
No treatment	39	6 (0–14)[a]	7 (1–19),[a]	6 (0–14)[a]	7 (1–20),[a]	7.70 (4.16–14.24)	**<0.001**
Unknown	31	25 (5–45)[a]	26 (9–48)[a]	25 (5–45)[a]	27 (9–50)[a]	3.17 (1.55–6.50)	**0.002**
Grade 3	1291	5 (3–7)	5 (4–7)	2 (0–4)	3 (2–4)		
Gender							
Male	793	5 (3–7)	6 (4–7)	2 (0–4)	3 (2–5)	Ref.	
Female	498	5 (3–7)	5 (4–7)	2 (0–4)[a]	2 (1–5),[a]	0.94 (0.84–1.06)	0.306
Age							
<50 year	100	14 (8–20)	14 (8–22)	7 (1–13),[a]	7 (3–13),[a]	Ref.	
50–75 year	883	5 (3–7)	5 (4–7)	2 (0–4)	2 (1–4)	1.28 (1.03–1.59)	**0.026**

Table 3 (*continued*)

	N	5-year OS (%) (95%CI: %)	5-year RS (%) (95%CI: %)	10-year OS (%) (95%CI: %)	10-year RS (%) (95%CI: %)	HR OS (95%CI)	*P*-value
>75 year	308	2 (0–4)[a]	3 (1–6)	0[a]	0[a]	1.73 (1.36–2.22)	**<0.001**
Location							
Oesophagus	323	3 (1–5)	3 (2–6)	2 (0–4)[a]	2 (1–5),[a]	1.80 (1.50–2.16)	**<0.001**
Stomach	161	2 (0–4)[a]	2 (1–6),[a]	1 (0–3)[a]	1 (0–5)[a]	1.70 (1.38–2.09)	**<0.001**
Duodenum	10	10 (0–28)[a]	11 (1–38)[a]	[b]	[b]	0.86 (0.44–1.69)	0.661
Papil of Vater	7	14 (0–40)[a]	15 (1–49)[a]	14 (0–40)[a]	16 (1–53)[a]	0.90 (0.40–2.05)	0.804
Pancreas	305	10 (6–14)	10 (7–15)	4 (2–6)	4 (2–8)	Ref.	0.650
Jejunum/ileum	28	31 (13–49)[a]	36 (18–55)[a]	14 (0–30)[a]	18 (4–43)[a]	0.90 (0.57–1.41)	0.468
Appendix	6	17 (0–47)[a]	17 (1–53)[a]	17 (0–47)[a]	18 (1–54)[a]	1.40 (0.56–3.48)	**<0.001**
Colon	281	2 (0–4)[a]	3 (1–5),[a]	1 (0–3)[a]	2 (0–6)[a]	2.85 (2.34–3.47)	**<0.001**
Rectum	170	2 (0–4)[a]	2 (1–6),[a]	0[a]	0[a]	2.53 (2.05–3.12)	
Treatment							
Surgery	112	15 (9–21)	17 (10–25)	8 (2–14),[a]	9 (4–17),[a]	Ref.	
Surgery + (neo)adjuvant treatment	77	13 (5–21),[a]	14 (7–24),[a]	9 (1–17),[a]	11 (4–24),[a]	0.61 (0.45–0.83)	**0.002**
Radiotherapy	78	5 (1–9),[a]	6 (2–13),[a]	4 (0–8)[a]	4 (1–11),[a]	1.17 (0.85–1.61)	0.347
Chemotherapy	389	2 (0–4)[a]	2 (1–4),[a]	0[a]	0[a]	1.07 (0.84–1.37)	0.570
Endocrine therapy	23	13 (0–27)[a]	15 (4–35),[a]	13 (0–27)[a]	17 (4–38)[a]	0.83 (0.50–1.36)	0.452
Chemotherapy + radiotherapy	88	11 (5–18)	11 (6–20)	6 (0–12)[a]	7 (2–15),[a]	0.63 (0.45–0.87)	**0.005**
Endocrine therapy + radiotherapy	3	0[a]	0[a]	0[a]	0[a]	1.11 (0.35–3.53)	0.866
No treatment	415	2 (0–4)[a]	2 (1–4),[a]	0[a]	0[a]	4.28 (3.35–5.47)	**<0.001**
Unknown	106	5 (1–9),[a]	6 (2–12),[a]	0[a]	0[a]	2.31 (1.72–3.10)	**<0.001**

OS = overall survival; CI = confidence interval; RS = relative survival; HR = hazard ratio; Ref. = reference.
Bold font indicates significant prognostic factors of overall survival.
[a] < 10 cases, insufficient follow-up data for a reliable estimation of prognosis.
[b] No follow-up data available.

considering performance status and comorbidities, including second primary tumours, which might influence patient survival. Furthermore, it should be noted that treatment intent (curative or palliative) was unknown. Therefore, no conclusion on the best course of treatment could be made based on these data.

Several retrospective studies confirmed age, tumour location, tumour grade, and TNM stage as independent prognostic factors [1,11,12,22–28]. In addition, these studies demonstrated that the size of the primary tumour, N-classification, M-classification and year of diagnosis are independent factors associated with survival. A study performed in Germany and France by Jann *et al.* emphasises the importance of grade and stage as prognostic factors for survival and considers grade based on Ki-67 or mitotic index proliferation markers superior to tumour differentiation [26]. The relevance of tumour grade was confirmed by several other European studies, describing hazard ratios of 2.21–24.8 in tumours with a Ki-67 of >20 versus ≤2 [22,27,28]. Now our study has analysed prognostic factors for survival per tumour grade, creating a further understanding of the prognosis of GEP-NENs.

The data reported in this study are crucial in clinical practice to counsel patients on the survival rates of GEP-NENs, by combining the information on tumour stage, grade and primary tumour location. These data are more specific than any survival data reported on GEP-NENs so far. This study contributed to define long-term outcome in GEP-NENs, whereas it is crucial to recognise advancements in outcome over time (Supplementary Fig. S3). The positive effect on survival in the most recent years is to be expected, anticipating progress in several fields of GEP-NEN care. Diagnostics and staging have improved using 68Ga/64Cu-DOTA-somatostatin analogue (SSA) positron emission tomography (PET) in combination with CT, providing high sensitivity for imaging of most types of NET lesions [29]. The 2013 Dutch guideline for NENs included DOTA-PET-CT for patients suspected of NETs. Furthermore, progress in treatments for metastatic disease leads to improved outcomes (e.g. SSAs [30], 177Lu-Dotatate [31,32] and everolimus [33–35]). Hence, one could anticipate that contemporary care might result in slightly better survival. Furthermore, some subgroups constitute only a limited number of patients and data should be used with great caution. Though the strength of this study is providing a large population of patients with GEP-NENs and long median follow-up of eight years, its retrospective nature also results in limitations. Limited data were available on symptoms (i.e. functional or non-functional tumours), performance status, Ki-67 proliferation index, exact treatment regimens and cause of death. The lack of data on Ki-67 and mitotic index proliferation markers disallowed grading according to the WHO and ENETS grading system, therefore a surrogate grading system using the ICD-O-3 coding was applied, approximating WHO and ENETS grading. Moreover, we were unable to revise the pathology of this large

dataset. Hence, there could be a great inter-observer variation in morphological coding, grading and staging.

In conclusion, GEP-NENs are a heterogeneous group of tumours with differences in survival rates and prognostic factors. The data reported in this study demonstrate unique long-term OS and RS rates which can be used in clinical practice to counsel patients using combined stratification by tumour site, grade and stage.

Statement of ethics

This study was approved by the Medical Ethics Board MUMC+/UM (Maastricht University Medical Center/ Maastricht University) (METC 2018-0584).

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Author contributions

I.N. Poleé: conceptualization, methodology, formal analysis, investigation, resources, data curation, writing – original draft, writing – review & editing, visualization, project administration. **B.C.M. Hermans**: conceptualization, methodology, writing – original draft, writing – review & editing. **J.M. van der Zwan**: conceptualization, methodology, validation, formal analysis, investigation, resources, data curation, writing – review & editing, visualization. **S.A.W. Bouwense**: writing – review & editing. **M.W. Dercksen**: writing – review & editing. **F.A.L.M. Eskens**: writing – review & editing. **B. Havekes**: writing – review & editing. **J. Hofland**: writing – review & editing. **T.M.A. Kerkhofs**: writing – review & editing. **H.J. Klümpen**: writing – review & editing. **L.M. Latten-Jansen**: writing – review & editing. **E.J.M. Speel**: writing – review & editing. **F.A. Verburg**: writing – review & editing. **A.M.E. Walenkamp**: writing – review & editing. **S.M.E. Geurts**: conceptualization, methodology, validation, formal analysis, investigation, writing – original draft, writing – review & editing, visualization. **J. de Vos-Geelen**: conceptualization, methodology, investigation, resources, data curation, writing – original draft, writing – review & editing, visualization, supervision.

Conflict of interest statement

The authors declare the following financial interests/ personal relationships which may be considered as potential competing interests:

AMEW reports institutional research grants and study funding from IPSEN, Novartis, Abbvie, BMS, Genzyme, Karyopharm Therapeutics, Roche and Polyphor. All outside the submitted work.

BCMH reports personal fees from Ipsen, Pfizer and Novartis Pharma. All outside the submitted work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.06.003.

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