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Short title: Grading pancreatic neuroendocrine neoplasms.

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ABSTRACT

Background: the World Health Organization (WHO) and the American Joint Cancer Committee (AJCC) modified the grading of pancreatic neuroendocrine neoplasms from a three-tiers (WHO-AJCC 2010) to a four-tiers system by introducing the novel category of NET G3 (WHO-AJCC 2017).

Objectives: This study aims at validating the WHO-AJCC 2017 and identifying the most effective grading system.

Method: 2102 patients were enrolled; entry criteria were i) performed surgery; ii) at least two years of follow-up; iii) observation time up to 2015. Data from 34 variables were collected; grading was assessed and compared for efficacy by statistical means including Kaplan Meier method, Cox regression analysis, Harrell's C statistics and Royston's explained variation in univariable and multivariable analyses.

Results: At descriptive analysis, the two grading systems demonstrated statistically significant differences for the major category sex but not for age groups. At Cox regression analysis, both grading systems showed statistically significant differences between grades for OS and EFS, however no statistically significant difference was observed between the two G3 classes of WHO-AJCC 2017. At multivariable analysis for the two models fitted to compare efficacy, the two grading systems performed equally well with substantially similar optimal discrimination and well-explained variation for both OS and EFS. The WHO-AJCC 2017 grading system retained statistically significant difference between the two G3 classes for OS but not for EFS.

Conclusions: the WHO-AJCC 2017 grading is at least equally performing as the WHO-AJCC 2010 but allows the successful identification of the most aggressive PanNET subgroup. Grading is confirmed as probably the most powerful tool for patient survival prediction.

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INTRODUCTION

Today there are two World Health Organization (WHO) - American Joint Cancer Committee (AJCC) classification grading systems for pancreatic neuroendocrine neoplasms (PanNENs), the old in three tiers (AJCC-WHO 2010) and the novel one in four tiers (AJCC-WHO 2017), also meant for the tubular gastrointestinal tract by AJCC 2017 only [1-3].

WHO-AJCC 2017 emphasizes differentiation, thus effectively separating G3 poorly differentiated neuroendocrine carcinomas (PanNEC), which run fast and appear to respond to platinum-based chemotherapy, from G3 neuroendocrine tumors (PanNET G3), which appear to behave more alike PanNET G2 [4-9]. Recognized problems exist however and refer to the absence of validation on large series and the absence of exclusive parameters separating PanNET G3 from PanNEC [10, 11].

Aims of the present study were: i) to test the efficacy of the WHO-AJCC 2017 grading system with the novel PanNET G3 category and ii) to competitively test the WHO-AJCC 2010 vs the WHO-AJCC 2017 grading systems to assess which is more efficient for stratification of patients.

MATERIALS AND METHODS

Data were collected from 2102 patients. The cohort was exclusively surgical and obtained from 18 European hospitals, nine of which Centers of Excellence (CoE) for the diagnosis and cure of NENs as certified by the European Neuroendocrine Tumor Society (ENETS), five referral centers for pancreas cancer and four referral centers for neuroendocrine tumor disease (for details see supplementary data, Table S1). The internal ethics committees of each center gave their approval for the study. The study enrolment criteria were: i) performed open surgery; ii) at least two years of follow-up at study entry in 2015; iii) observation time up to 2015. 34 relevant clinical-pathological variables (see supplementary Table S2) were collected including the grading according to the definitions by both WHO-AJCC 2010 and 2017 (Table 1) [1-3, 12]. Particular attention was paid to grading variables which included five overlapping parameters of: i) NET and NEC definition, ii)

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poorly differentiated morphology, iii) G1-G3 definition, iv) Ki67 index and v) mitotic count index. PanNET-G3 were defined as "not poorly differentiated G3" where poor differentiation and G3 variables were defined as from WHO 2010 and WHO 2017 (Table 1) [13, 14]. In brief, the morphological criteria for poorly differentiated neuroendocrine carcinoma include: i) solid or organoid (large trabeculae) structure; ii) extensive (geographical chart) necrosis; iii) severe cytological atypia, frequent mitoses often atypical; iv) small size cell with a thin rim of cytoplasm (small cell type); v) abundant eosinophilic cytoplasm (large cell type); vi) large nuclei with salt and pepper chromatin; vii) inconspicuous nucleoli in most cells (small cell type); conspicuous nucleoli, sometimes prominent, in most cells (large cell type). The G3 proliferation grade was defined by Ki67>20%. Based on such morphological and proliferative criteria, the "not poorly differentiated G3" was defined as "a neuroendocrine neoplasia with Ki67 index >20% and void of the above-defined poorly differentiated morphological criteria" and equalized the NET G3 (well differentiated neuroendocrine tumor of high proliferative grade). NET G3 were separated from small cell and large cell NEC based on the above-detailed morphological criteria. Each center reassessed each case for morphological criteria of differentiation, provided the original NET or NEC report definition, the grade and the mitotic and Ki67 indexes. Progression was defined as evidence of stage modification or of cancer relapse after curative (R0) surgery, and death as related to the underlying cancer, based on patient medical charts as assessed by each center. Tumor-related death was defined as death directly or indirectly (e.g. therapy-related mortality) associated with the tumor. Empty electronic datasheets with compilation instructions were provided to participating Centers and, upon completion, centralized to GR and CK. Data collection started in June 2015 and was completed by December 2016 after multiple runs of data assessment and verification per each contributing center. Every effort was applied to minimize the number of missing/incomplete data.

Statistics

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Continuous data were described as the mean and standard deviation (SD) or median and 25th to 75th percentiles and were compared by Kruskall–Wallis tests. Categorical data were described as counts and percentages and were compared by chi-squared test. Median follow-up was calculated by the inverse Kaplan–Meier method. Event-free survival and tumor-related death were calculated and follow-up time was determined from the date of diagnosis to the date of first progression event and tumor-related death or the last follow-up for survivors. Event-free and tumor-related death-free survivals were estimated with the Kaplan–Meier method. The Cox model was used to assess the prognostic value of a series of patient and tumor characteristics (univariable analysis). Hazard ratios (HRs) and 95% confidence intervals (CIs) were also calculated. The proportional hazard assumption (Schoenfeld residuals) was always satisfied. A multivariable Cox model was fitted for each of the grading systems, while adjusting for sex, age, curative surgery, site of tumor, presence of multiple metastatic sites and stage. Huber-White robust standard errors were computed while clustering on center to account for intra-center correlation.

The performance of the two grading systems was compared through Royston explained variation and Harrell's C discrimination statistics (the closer to 1, the better). With this purpose, the model was fitted in a training sample (n.1468 cases) and validated in a testing sample (n. 634 cases), after a random 2:1 split of the case series [15, 16]. Only cases with data for both grading systems were used for head to head comparative tests.

ROC curve analysis was performed to identify the optimal cut-off for predicting 5-year tumor-related mortality for tumor size, number of positive lymph nodes, mitotic count and Ki67 index. Cox models for these variables, dichotomized at these optimal cut-offs, were fitted (over the entire follow-up) in the training sample discovery cohort, and the performance of the dichotomized variable was assessed on the testing sample validation cohort by means of the Harrell's c statistic.

Data were analyzed with Stata (version 15; Stata Corporation, College Station, TX, USA). A two-sided *P* value of less than .05 was considered statistically significant. All statistical tests were two-sided. The Bonferroni correction was applied for paired post-hoc comparisons.

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RESULTS

Cohort description

All clinical-pathological features and differences by sex and age are described in Supplementary Results and detailed in Supplementary Tables S2 and S3. The cohort showed a slight prevalence of Caucasian, female patients (1085, 52%) of the 6th decade and slightly younger than males (median 54 years vs 57, P=0.001). The two grading systems showed statistically significant differences for sex, with female prevalence for G1, equal distribution for G2 and male prevalence for G3 grades. No statistically significant difference was observed for age between the two grading systems (supplementary Tables S2 and S3).

Profile of high grade well differentiated neuroendocrine neoplasms (PanNET G3)

PanNET G3 were identified as high grade, "*not poorly differentiated G3*" neuroendocrine neoplasms (Table 2). At cohort analysis by grade, PanNET G3 accounted for 2% of the cohort (41 out of 2018 available cases) and showed statistically significant differences vs G1-G2 PanNETs and PanNECs for all variables except age and ethnicity. PanNET G3 were most often seen in males (66%), void of genetic predisposition, mostly non-functioning (82%), surgically cured only in about half of cases (46%), most often treated with chemotherapy (56%) rather than biotherapy (40%) and PRRT (20%). Most PanNET G3 were solitary, large lesions (median 47 mm) of the head and body-tail (43% at each site, total 86%) and usually high staged (29% at stage III and 61% at stage IV, total 90%), with higher frequency of node and distant metastases vs PanNET G1-G2 (P<0.001) and a quote of positive lymph-node deposits similar to PanNEC but significantly different versus G1-G2 (median 3, P<0.001). All PanNET G3 showed a well differentiated morphology (nonetheless 50% of them were classified as PanNEC according to WHO 2010), 46% showed necrosis and displayed a median Ki67 index of 29% and a median mitotic count of 9 per 2mm^2, in all cases with a statistically significant difference vs both PanNET G1-2 and PanNEC (P<0.001).

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Survival analysis

Information on survival was available for 2047 subjects, with an observed median follow-up of 64 months (25^{th}-75^{th}, 35-110), 333 tumor-related deaths, a mortality of 2.85 (95%CI 2.56-3.17) per 100-person year (Figure 1a) and 684 events with an event rate of 7.27 (95%CI 6.65-7.84) (Figure 1b). Overall survival (OS, tumor-related death) and event-free survival (EFS) (Table 3) showed a similar statistically significant increased risk by stage (with the exception of I vs II and I vs III after Bonferroni adjustment for EFS; Figures 1c and 1d), sex (higher in male), age group (higher in 30-60 and >60 years), no curative surgery, tumor site (higher in body-tail and head), absence of hormonal function, WHO NEC class, presence of necrosis, poor differentiation morphology, increase of grade (with the exception of G3 PanNET vs PanNEC, after Bonferroni adjustment for both OS and EFS; Figures 2a-d), T, N (with the exception of NX for OS and NX vs N0 for EFS after Bonferroni adjustment), M and presence of multiple metastases (Table 3). At sub-analysis of the M site (lung, liver, bone, mesentery and other sites), none of them posed any statistically significant increased risk for tumor-related death, while increased risk for EFS was observed for bone metastases and multiple sites deposits (bone EFS HR 2.43, P<0.000; multiple site EFS HR 3.13, P<0.000).

Cutoff identification for continuous variables

The empirical cutoff associated with increased risk of death due to cancer were: mitotic count=1.5 (sensitivity 85%; specificity 65%), Ki67=4.85 (sensitivity 80%; specificity 73%); size=30 mm (sensitivity 70%; specificity 59%). Similar ROC areas under the curve, high NPV and low PPV were observed for all the three variables for both OS and EFS (see Supplementary Table S4 for details). An increased risk was observed for mitotic count, Ki67 and size values above the optimal cutoff identified by ROC curve analysis (P<001; Table 3). Substantially similar incidence rate

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(mitotic count=15.30; Ki67=15.38) and HR (mitotic count 3.2; Ki67 3.32) were observed for both mitotic count and Ki67 index (Table 3).

Comparing efficacy of grading systems at multivariable analysis modelling

Models were built using the grade definitions according to WHO-AJCC 2010 and WHO-AJCC 2017 for prediction capacity for OS and EFS. Since both grading systems were collinear with several other variables including Ki67 and mitotic count, the two models were fitted adjusting for the following clinically relevant variables: gender, age, genetics (in three categories, MEN1, other and sporadic), tumor site, stage, curative surgery and multiple metastases sites. In the two models, statistically independent predictors of OS and EFS were both 2010 and 2017 grading systems, age and stage; statistically independent predictor of OS only was multisite metastases; and statistically independent predictor of EFS only was curative surgery (Table 4). Both models performed well and showed substantially similar high optimal discrimination and well-explained variation for OS (model #1 Harrell's C 0.87 and Royston R2 0.72; model #2 Harrell's C 0.87 and Royston R2 0.74), and lower discrimination and explained variation for EFS (model #1 Harrell's C 0.75 and Royston R2 0.45; model #2 Harrell's C 0.74 and Royston R2 0.44) (Table 4). After Bonferroni correction, statistically significant differences between grades were observed in both models, with the exception for G1 vs G2 (model #1, OS P= 0.051, EFS P= 0.089; model #2 OS P=0.103, EFS P=0.182) and, in model 2, for PanNET G3 vs PanNEC but for EFS only (P= 1.000; Table 4).

DISCUSSION

Our data validate the novel WHO-AJCC 2017 grading system and indicate that when competitively tested versus the previous WHO-AJCC 2010, performed with equal efficacy in predicting both overall (tumor-related death, OS) and event-free survival (EFS), efficiently stratifying patients.

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The present surgical cohort was collected from 18 high-volume European centers, all with vast and well-documented clinical practice of pancreatic neuroendocrine neoplasms (see Table S1). As such it reflects the current European standards following the European Neuroendocrine Tumor Society (ENETS) guidelines [17-19]. This was solid ground for consistently structured clinical-pathological features and guarantee of high quality and comparable data. The size of this cohort provided statistical power unprecedented for pancreatic neuroendocrine neoplasms surgical series [20, 21], guarantee of clinical relevance.

The emerging picture indicates that patients with surgically treated pancreatic neuroendocrine neoplasms are slightly more female, belong to the sixth decade of life and rarely are also treated with bio and chemotherapy (Supplementary Table S2). The low number of PRRT treatments here observed likely reflects the low access to this option, bound to change following recent evidence [22]. Pancreatic neuroendocrine neoplasms were usually non-functioning, sporadic, single lesion of 2.5 mm in median size, non-metastatic with homogenous stage distribution, well differentiated PanNETs of low grade, with one mitosis per 2 mm^2 and 2% Ki67 index (Supplementary Table S3). All of the above is substantially in line with previous reports and confirms the dataset quality [20, 21].

This study was designed to test the efficacy of the WHO-AJCC 2017 grading system and its novel PanNET G3 class [3, 14]. Its basis was the reported evidence of neuroendocrine neoplasms with high Ki67 values in absence of poorly differentiated morphology [4, 7, 9], following the wide application of the ENETS grading system as endorsed by WHO and AJCC [1, 12, 23]. Published PanNET G3 series had pre-defined features (Ki67 values above the G3 threshold and differentiated morphology) and were from different anatomical sites. Cases however proved somehow heterogeneous, the diagnosis being sometimes challenging and often difficult to direct to the two NET and NEC high grade classes [7, 9-11, 24].

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The present series was built independently by any pre-defined features and from a single anatomical site, the pancreas, thus responding as much as possible to an unbiased approach and truly reflecting the current European clinical and surgical pathology practice. The novel PanNET G3 class resulted from the cross-definition of multiple somehow redundant variables which included the WHO NET and NEC class definition, the grade, the mitotic count, the Ki67 absolute values and the poorly differentiated morphology as defined by WHO 2000, 2010 and 2017 [13, 14, 25]. As such, the "*not poorly-differentiated G3"* class solidly identified the PanNET G3 class. In this series the G3 cases represented about 7% of the entire cohort (141 out of 2023 available cases), NEC cases 6% (93 out of 1454 available cases) and poorly differentiated cases 5% (108 out of 2020 available cases). PanNET G3 were about one third of the G3 cases, corresponding to 2% of the cohort (41 out of 2018 available cases). Overall PanNET G3 proved to be a minority of this cohort, indicating that in the current clinical practice, even of referral centers, PanNET G3 are rare. A note of caution is however mandatory, since our data may underestimate the G3 class overall, usually directed to medical therapy only, when high-staged and especially with poorly-differentiated morphology.

At descriptive analysis, both grading systems demonstrated statistically significant differences for the major category sex but not for age groups, indicating that the very same disease may occur at any age. The PanNET G3 profile observed here was unique for the three variables necrosis (46% of cases), mitotic count (median 9 per $2mm^2$) and Ki67 index (median 29%), similar to PanNEC for six variables (sex, age, stage, size, curative surgery and chemotherapy), similar to PanNET G1-G2 for two (function, biotherapy) and in line with PanNET G1-G2 and PanNEC for four (sporadic, tumor site, single lesion and PRRT) (Table 2). Overall, this tumor class appear unique vs both PanNET G1-G2 and NEC for biology parameters, which is partly in line with previous reports [7, 9].

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Despite increasing twice the mortality rate and 1.5 times the event rate vs G2, PanNET G3 were not statistically different vs PanNEC for both the overall and the event-free survival after Bonnferroni correction at univariable analysis (P=0.7; Table 3). This may well reflect the low statistical power associated to the relatively low numbers of the two categories in this cohort. However, the profile of the survival curves overlaps for several months, as particularly evident for EFS, suggesting a substantially similar aggressive behavior (Fig. 2 c, d). Our data may mirror the actual clinical behavior of the two high grade WHO classes at least in pancreas, as in part suggested by previous findings [6-9]. Larger prospective series are needed to unquestionably address this issue.

When competitively tested at multivariable modelling, similar Harrell's C and Royston R2 model values as well similar HR for the other independent confounders showed that both grading systems are equally effective, or none is superior (Table 4). This indicates that diagnoses made in previous years with the WHO-AJCC 2010 can still be used with confidence by clinicians for prognosis assessment, especially when the classification parameters (namely Ki67% and mitotic count) are clearly reported. However, since poor response to platinum-based chemotherapy was proposed as a key feature of PanNET G3 [4, 5, 8], somehow underlining significant biological differences vs PanNEC [26], it appears wise to re-evaluate the histology of G3 cases with Ki67 index in the low side for patients' tailored therapy. This appears relevant also in light of the DNA damage repair pathway impairment recently described in PanNETs [27]. For such cases, clinicians are advised to plan the management strategy based on proliferative parameters that consistently proved effective in predicting overall and event-free survival.

Finally, at multivariable analysis PanNET G3 proved statistically different vs PanNEC after Bonferroni correction for overall (P<0.001) but not for event-free survival (P=1.000) (Table 6). These observations suggest PanNET G3 to be a similarly aggressive, but less deadly disease when compared to PanNEC. Most importantly, our data at both univariable and multivariable analysis

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show that PanNET G3 are statistically different vs PanNET G2 for both overall and event free survival (Tables 3 and 4). These data clearly indicate that PanNET G3 are the most aggressive form of well differentiated pancreatic neuroendocrine neoplasms, and as such should be carefully identified and taken care of.

The multi-institutional nature of this study is an important limit. Collecting data from different Institutions may expose to potential differences at multiple levels, including surgical treatment, pathology assessment and patient management. In addition, the collection of retrospective data is source of potential time-dependent variations, including those related to the change in therapy which may affect patient survival. Nonetheless nine Institutions here enrolled were ENETS Centers of Excellence and adhering to the current ENETS standard guidelines, thus reducing the chance of different overall approach. The collection of information for rare disease is per se a challenge, and this vast retrospective cohort appears a reasonable surrogate to gather significant data. Ideally variables for any single clinical item should be pre-defined and a study on a prospective series so defined should be planned to confirm the present findings.

In conclusion, our data indicate that the current WHO-AJCC 2017 grading system is, if not superior, at least equally performing as the WHO-AJCC 2010. Most importantly, the current WHO-AJCC 2017 classification filled a classification gap by identifying the most aggressive fraction of PanNETs. The detailed picture of the novel PanNET G3 class here portrayed will be an effective reference and help for better tailoring the management of patients for personalized therapy. Grading is confirmed as probably the most powerful tool for patient survival prediction.

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STATEMENT OF ETHICS

The internal ethics committees of each center gave their approval for this study.

DISCLOSURE STATEMENT

The authors have no conflicts of interest to declare.

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AUTHOR CONTRIBUTIONS

GR, MF and CK designed the study, prepared the datasheet and the work plan; data were collected by all Authors; GR and CK checked and cleaned all data according to various Authors' indication; CK performed the statistical analyses; GR wrote the paper; all authors contributed to and revised the text.

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FIGURE LEGEND

Figure 1. Overall (**a**, **c**) and event-free (**b**, **d**) survival of the cohort (OS **a**, EFS **b)** and according to stage (OS, **c**; EFS, **d**).

Figure 2. Overall (**a**, **c**) and event-free (**b**, **d**) survival of the cohort according to grading WHO-AJCC 2010 (OS, **a**; EFS, **b**) and WHO-AJCC 2017 (OS, **c**; EFS, **d**).

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Table 1. Grading of pancreatic neuroendocrine neoplasms according to WHO-AJCC 2010 and WHO-AJCC 2017; differences are highlighted in **bold**.

		Mitotic count (10 HPF)*		Ki-67 index (%)**	
Definition	Grade	2010	2017	2010	2017
NET	G1	<2	<2	≤2	**<3**
NET	G2	2-20	2-20	3-20	3-20
NET	**G3**	**na**	**>20**	**na**	**>20**
NEC	G3	>20	>20	>20	>20

* 10 HPF: High Power Field = 2mm^2, at least 50 fields (at 40x magnification) evaluated in areas of highest mitotic density; ** MIB1 antibody; % of 500-2000 tumor cells in areas of highest nuclear labeling.

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Table 2. Clinical and pathological descriptors of pancreatic neuroendocrine neoplasms by grade.

	Cases		**G1**	**G2**	**G3**	**G3 pd**	***P***
Sex	2018						**<0.001**
n (%)		F	588 (55)	411 (50)	14 (34)	30 (35)	
		M	476 (45)	416 (50)	27 (66)	57 (65)	
Age (years)	2011	median (25^{th}-75^{th})	55 (46-65)	55 (45-64)	58 (48-64)	58 (49-68)	0.177
Age	2094						0.783
		<30	60 (6)	40 (5)	2 (5)	4 (5)	
		30-60	605 (57)	494 (60)	23 (56)	45 (52)	
		>30	393 (37)	292 (35)	16 (39)	37 (43)	
Ethnicity	1601						0.844
		C	838 (98)	631 (98)	30 (97)	70 (99)	
		Other	19 (2)	11 (2)	1 (3)	1 (1)	
Genetics	1621						**0.003**
n (%)		MEN	65 (8)	36 (5.2)	0 (0)	0 (0)	
		VHL	11 (1)	18 (2.6)	0 (0)	0 (0)	
		[2]Other	4 (0.5)	2 (0.2)	0 (0)	0 (0)	
		Sporadic	755 (90.5)	631 (92)	32 (100)	67 (100)	
Function	1996						**<0.001**
n (%)		NF	711 (67)	667 (82)	33 (82)	80 (98)	
		F	346 (33)	150 (18)	7 (18)	2 (2)	
Site	1877						**<0.001**
n (%)		Body	236 (24)	86 (11)	5 (14)	6 (9)	
		Body/Tail	399 (40)	359 (47)	16 (43)	22 (32)	
		Head	358 (35)	301 (40)	16 (43)	40 (59)	
		Head/Body/Tail	15 (1)	18 (2)	0 (0)	0 (0)	
Surgery	2018						**<0.001**
n (%)		C	959 (90)	610 (74)	22 (46)	44 (51)	
		NC	105 (10)	217 (26)	19 (34)	42 (49)	
Biotherapy	1570						**<0.001**
n (%)		Y	106 (12)	207 (34)	12 (40)	7 (12)	
		N	762 (88)	406 (66)	18 (60)	52 (88)	
Chemotherapy	1589						**<0.001**
n (%)		Y	66 (8)	217 (35)	18 (55)	48 (68)	
		N	805 (92)	398 (65)	14 (45)	23 (32)	
PPRT	1584						**<0.001**
n (%)		Y	41 (7)	91 (15)	6 (8)	1 (2)	
		N	834 (93)	529 (85)	24 (92)	58 (98)	
Stage	1948						**<0.001**
n (%)		I	502 (49)	80 (10)	1 (3)	1 (1)	
		II	241 (24)	168 (21)	3 (7)	7 (9)	
		III	142 (14)	226 (28)	12 (29)	27 (32)	
		IV	132 (13)	332 (41)	25 (61)	49 (58)	
T	1937						**<0.001**
n (%)		1	564 (54)	115 (15)	2 (6)	3 (4)	
		2	266 (26)	252 (32)	6 (16)	14 (18)	
		3	158 (15)	324 (41)	26 (70)	42 (54)	
		4	47 (5)	96 (12)	3 (8)	19 (24)	
Size (mm)	1933	median (25^{th}-75^{th})	18 (12-30)	35 (23-56)	47 (32-65)	45 (35-65)	**<0.001**

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No. lesions	2018						**0.002**
n (%)		single	791 (74)	610 (74)	28 (68)	60 (70)	
		multiple	76 (7)	47 (6)	1 (2)	0 (0)	
		na	*197 (19)*	*170 (20)*	*12 (30)*	*26 (30)*	
N	1878						**<0.001**
n (%)		N0	657 (68)	336 (42)	9 (23)	15 (19)	
		N1	216 (22)	427 (54)	29 (74)	62 (80)	
		NX	92 (10)	33 (4)	1 (3)	1 (1)	
number of N+	1399	median (25^{th}-75^{th})	0 (0-0)	1 (0-2)	3 (1-5)	3 (1-5)	**<0.001**
M	1914						**<0.001**
n (%)		M0	847 (86)	471 (58)	15 (37)	36 (43)	
		M1	134 (14)	337 (42)	26 (63)	48 (57)	
Multiple M	2018						**<0.001**
n (%)		N	1056 (99)	796 (96)	40 (98)	83 (97)	
		Y	8 (1)	31 (49)	1 (2)	3 (3)	
Morphology	1973						**<0.001**
n (%)		WD	1050 (100)	776 (97)	41 (100)	0 (0)	
		PD	0 (0)	20 (3)	0 (0)	86 (100)	
WHO Class	1416						**<0.001**
n (%)		NET	689 (100)	630 (99)	14 (50)	0 (0)	
		NEC	0 (0)	6 (1)	14 (50)	63 (100)	
Necrosis	1517						**<0.001**
n (%)		N	824 (98)	482 (83)	15 (54)	8 (12)	
		Y	21 (2)	98 (17)	13 (46)	56 (88)	
Mitotic count	1390	median (25^{th}-75^{th})	0 (0-1)	2 (1-4)	9 (5-16)	27 (12-54)	**<0.001**
Ki67	1953	median (25^{th}-75^{th})	1 (1-2)	5 (3-10)	29 (22-34)	50 (30-70)	**<0.001**

Legend
In bold, statistically significant values; G3 pd: G3 poorly differentiated; n: number; F: female; M: male; C: Caucasian; [1]Other: other types of race including African, Asian, etc.; sporadic: void of any known heritable genetic background; MEN: multiple endocrine neoplasia syndrome type 1; VHL: von Hippel-Lindau; [2]Other: other types of heritable genetic background including Type I fibromatosis, etc.; NF: non-functioning; F: functioning; H: head; B: body; BT: body-tail; HBT: head-body-tail; C: curative; NC: non-curative; PRRT: peptide receptor radio-therapy; T: tumor; N: lymph-node; N+: lymph-node positive for metastasis; M: metastasis; WD: well differentiated; PD: poorly differentiated; WHO: World Health Organization; NET: neuroendocrine tumor; NEC: neuroendocrine carcinoma.

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Table 3. Univariable analysis for overall survival (OS, tumor-related death) and event free survival (EFS) of most relevant clinical-pathological features.

		Case No.	Rate (95%CI)	OS HR (95%CI)	*P*	Rate (95%CI)	EFS HR (95%CI)	*P*
Sex	F	1055	2.35 (2.00-2.76)	1		6.65 (5.98-7.41)	1	
	M	992	3.42 (2.97-3.96)	1.45 (1.17-179)	**0.001**	7.99 (7.19-8.87)	1.17 (1.04-1.30)	**0.007**
Age (years)					**<0.001**			**0.001**
	<30	106	0.90 (0.43-1.88)	1		3.37 (2.24-5.07)	1	
	30-60	1191	2.80 (2.44-3.22)	3.09 (1.89-5.06)	**<0.001**	7.57 (6.88-8.33)	2.05 (1.30-3.22)	**0.002**
	>60	742	3.39 (2.85-4.04)	3.70 (2.02-6.80)	[1]**<0.001**	7.68 (6.76-8.72)	2.00 (1.21-3.30)	[1]**0.007**
Site					**<0.001**			**<0.001**
	B	330	1.47 (1.00-2.15)	1		4.33 (3.42-5.50)	1	
	BT	811	2.97 (2.52-3.51)	2.04 (1.09-3.83)	[2]**0.026**	7.98 (7.11-8.96)	1.83 (1.22-2.74)	**0.003**
	H	730	2.68 (2.22-3.22)	1.84 (1.22-2.79)	**0.004**	7.49 (6.62-8.47)	1.74 (1.25-2.42)	**0.001**
	HBT	32	2.16 (0.81-5.76)	1.45 (0.48-4.35)	0.508	4.82 (2.41-9.63)	1.10 (0.47-2.57)	0.818
Curative Surgery	y	1655	1.70 (1.46-1.98)	1		6.08 (5.55-6.65)	1	
	n	392	8.47 (7.28-9.85)	5.00 (4.35-5.55)	**<0.001**	12.74 (11.15-14.56)	2.06 (1.18-3.59)	**0.011**
Functioning tumor	y	528	1.95 (1.54-2.48)	1		6.04 (5.17-7.06)	1	
	n	1503	3.23 (2.86-3.64)	1.64 (1.06-2.56)	**0.027**	7.74 (7.10-8.43)	1.22 (0.64-2.63)	0.611
WHO class	NET	1328	2.54 (2.22-2.90)	1		7.45 (6.83-8.14)	1	
	NEC	90	17.42 (12.97-23.42)	6.86 (5.90-7.98)	**<0.001**	34.66 (27.13-44.28)	3.69 (2.35-5.81)	**<0.001**
Necrosis	n	1343	1.91 (1.63-2.22)	1		5.74 (5.20-6.33)	1	
	y	143	9.09 (7.26-11.39)	4.72 (3.19-6.97)	**<0.001**	20.97 (17.56-25.04)	3.12 (1.69-5.74)	**<0.001**
Poor differentiation	n	1859	2.28 (2.01-2.58)	1		6.32 (5.82-6.87)	1	
	y	106	17.78 (13.75-23.00)	7.62 (6.19-9.38)	**<0.001**	29.68 (23.70-37.16)	4.10 (2.84-5.92)	**<0.001**
Grade					**<0.001**			**<0.001**
	G1	1030	0.98 (0.76-1.26)	1		3.70 (3.22-4.25)	1	
	G2	809	4.32 (3.74-4.99)	4.44 (2.35-8.38)	**<0.001**	10.75 (9.69-11.94)	2.74 (.05)1.32-5.67)	**0.007**
	G3	40	12.25 (7.50-19.99)	13.19 (8.83-19.71)	**<0.001**	27.69 (18.85-40.67)	6.09 (2.17-13.05)	**0.001**
	G3 pd	84	26.93 (20.46-35.43)	28.28 (15.64-51.14)	[3]**<0.001**	43.50 (34.12-55.48)	9.47 (3.83-23.42)	[3]**<0.001**
T					**<0.001**			**0.002**
	T1	686	0.59 (0.39-0.88)	1		2.60 (2.11-3.20)	1	
	T2	550	2.51 (2.03-3.11)	4.31 (2.45-7.56)	**<0.001**	7.03 (6.10-8.10)	2.74 (1.39-5.40)	**0.003**

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	T3	547	4.72 (4.00-5.57)	8.05 (4.12-15.73)	**<0.001**	11.76 (10.43-13.27)	4.38 (4.38-10.79)	**0.001**
	T4	177	6.09 (4.71-7.88)	10.36 (7.18-14.95)	[4]**<0.001**	13.72 (11.25-16.75)	4.98 (1.93-12.86)	[4]**0.001**
N					**<0.001**			**<0.001**
	N0	1029	1.52 (1.24-1.88)	1		4.00 (3.48-4.58)	1	
	N1	756	4.94 (4.31-5.66)	3.24 (2.34-4.49)	**<0.001**	13.00 (11.78-14.33)	3.15 (2.20-4.52)	**<0.001**
	NX	132	1.37 (0.78-2.42)	0.90 (0.32-2.54)	0.845	1.64 (0.97-2.76)	0.42 (0.20-0.90)	[5]**0.026**
M	M0	1364	1.07 (0.86-1.33)	1		3.38 (2.97-3.84)	1	
	M1	579	7.47 (6.58-8.48)	6.96 (5.07-9.55)	**<0.001**	17.14 (15.50-18.95)	4.88 (2.92-8.17)	**<0.001**
Multisite metastases	N	1995	2.80 (2.51-3.13)	1		6.97 (6.45-7.53)	1	
	Y	52	4.50 (2.75-7.34)	1.63 (0.55-4.78)	0.376	23.57 (17.29-32.13)	3.13 (1.95-5.04)	**<0.001**
Stage					**<0.001**			**0.002**
	I	582	0.18 (0.08-0.41)	1		1.87 (1.43-2.44)	1	
	II	419	0.89 (0.59-1.33)	4.81 (2.22-10.46)	**<0.001**	3.91 (3.17-4.82)	2.17 (0.88-5.31)	[6]0.091
	III	407	2.78 (2.18-3.56)	15.05 (9.20-24.59)	**<0.001**	9.01 (7.72-10-52)	4.72 (1.16-19.17)	[6]**0.030**
	IV	573	7.55 (6.64-8.57)	40.75 (24.66-63.33)	**<0.001**	17.33 (15.67-19.17)	8.84 (2.00-39.07)	**0.004**
*Mitotic count	≤1.5	870	1.31 (1.04-1.66)	1		4.29 (3.73-4.94)	1	
	>1.5	495	6.53 (5.59-7.63)	4.94 (4.13-5.91)	**<0.001**	15.30 (13.59-17.22)	3.20 (1.59-6.46)	**0.001**
*Ki67	≤4.85	1286	1.25 (1.02-1.53)	1		4.30 (3.82-4.83)	1	
	>4.85	640	7.59 (6.65-8.67)	6.13 (4.28-8.77)	**<0.001**	15.38 (13.82-17.12)	3.32 (1.85-5.96)	**<0.001**
*Size	≤30	1167	1.26 (1.02-1.55)	1		4.26 (3.76-4.83)	1	
	>30	781	5.05 (4.42-5.77)	4.00 (2.47-6.49)	**<0.001**	11.73 (10.62-12.97)	2.67 (1.68-4.24)	**<0.001**

Legend
In bold, statistically significant values; No.: number; EFS: event free survival; OS: overall survival; HR: hazard ratio; 95%CI: 95% confidence interval; F: female; M: male; Y: yes; N: no; B: body, BT: body-tail; H: head; HBT: head-body-tail; WHO: World Health Organization; NET: neuroendocrine tumor; NEC: neuroendocrine carcinoma; G3pd: G3 poorly differentiated; T: tumor; N: lymph-node; M: metastasis; after Bonferroni correction: [1]*P*=0.48 OS, and =1.00 EFS for 30-60 vs >60; [2]*P*=0.159 OS when BT vs B; [3]*P*=0.71 OS and *P*=0.72 EFS when G3 vs G3 pd; [4]*P* =0.72 OS and *P*=1.00 EFS when T3 vs T4; [5]*P*=0.078 EFS when NX vs N0; [6]*P*=0.548 EFS when I vs II EFS and *P*=0.179 EFS when I vs III. *Cutoff identified at ROC analysis. The variables ethnicity and genetics were excluded due to low observation numbers.

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Table 4. Multivariable analysis modelling for overall survival (OS, tumor-related death) and event free survival (EFS).

		Model #1 OS HR (95%CI)	***P***	**Model #2 OS HR (95%CI)**	***P***	**Model #1 EFS HR (95%CI)**	***P***	**Model #2 EFS HR (95%CI)**	***P***
		Model p<0.001 Harrell's C 0.87 (95%CI 0.84-0.90) Royston R2 0.72 (95%CI 0.57-0.82)		Model p=<0.001 Harrell's C 0.87 (95%CI 0.84-0.90) Royston R2 0.74 (95%CI 0.64-0.83)		Model p=<0.001 Harrell's C 0.75 (95%CI 0.70-0.78) Royston R2 0.45 (95%CI 0.34-0.52)		Model p=<0.001 Harrell's C 0.74 (95%CI 0.70-0.78) Royston R2 0.44 (95%CI 0.36-0.53)	
Grade WHO 2010			**<0.001**		**-**		**<0.001**		**-**
	G1	1		-		1		-	
	G2	2.13 (1.15-3.96)	**[1]0.017**	-		1.59 (1.05-2.41)	**[1]0.030**	-	
	G3	8.14 (5.02-13.20)	**<0.001**	-		4.28 (2.41-7.62)	**<0.001**	-	
Grade WHO 2017			**-**		**<0.001**		**-**		**<0.001**
	G1	**-**		1		**-**		1	
	G2	-		2.12 (1.14-3.93)	**[2]0.017**	-		1.59 (1.04-2.41)	**[2]0.030**
	G3	-		5.71 (3.74-8.74)	**<0.001**	-		3.54 (1.78-7.04)	**<0.001**
	G3 pd	-		10.99 (6.47-18.67)	**<0.001**	-		4.68 (2.71-8.09)	**<0.001**
Sex	F	1	0.625	1	0.676	1	0.548	1	0.538
	M	1.06 (0.83-1.37)		1.06 (0.80-1.42)		1.97 (088-1.03)		0.97 (0.87-1.07)	
Age (years)			**<0.001**		**<0.001**		**0.001**		**0.001**
	<30	1		1		1		1	
	30-60	2.46 (1.62-3.37)	**<0.001**	2.48 (1.55-3.97)	**<0.001**	1.54 (1.03-2.30)	**0.035**	1.54 (1.02-1.32)	**0.040**
	>60	3.49 (2.10-5.78)	**<0.001**	3.51 (2.18-5.63)	**<0.001**	1.83 (1.25-2.69)	**0.002**	1.81 (1.24-2.65)	**0.002**
Curative surgery	Y	1	0.158	1	**0.097**	1	**0.009**	1	**0.012**
	N	1.40 (0.88-2.24)		1.44 (0.94-2.23)		0.63 (0.44-0.89)		0.63 (0.44-0.90)	
Site			0.280		0.581		0.509		0.652
	B	1		1		1		1	
	BT	0.93 (0.53-1.62)		0.92 (0.46-1.81)		1.12 (0.84-1.49)		1.10 (0.80-1.51)	
	H	1.01 (0.70-1.45)		0.97 (0.60-1.57)		1.11 (0.84-1.48)		1.09 (0.80-1.49)	
	HBT	1.16 (0.30-4.53)		1.15 (0.27-4.97)		0.93 (0.40-2.17)		0.92 (0.39-2.17)	
Multisite metastases	N	1		1		1		1	
	Y	0.38 (0.22-066)	**0.001**	0.39 (0.22-0.67)	**0.001**	1.17 (0.92-1.48)	0.204	1.17 (093-1.48)	0.176
Stage			**<0.001**		**<0.001**		**<0.001**		**<0.001**

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	I	1		1		1		1	
	II	3.84 (1.19-12.39)	**0.024**	3.81 (1.19-12.22)	**0.024**	1.84 (0.75-4.53)	0.183	1.85 (0.75-4.55)	0.182
	III	8.55 (3.24-22.59)	**<0.001**	8.20 (3.02-22.27)	**<0.001**	3.56 (1.13-11.18)	**0.030**	3.55 (1.12-11.24)	**0.032**
	IV	20.03 (7.67-52.34)	**<0.001**	20.05 (7.78-51.63)	**<0.001**	7.70 (2.25-26.34)	**0.001**	7.67 (2.23-26.34)	**0.001**

Legend
In bold, statistically significant values; No.: number; OS: overall survival; EFS: event free survival; HR: hazard ratio; 95%CI: 95% confidence interval; WHO: World Health Organization; G3 pd: G3 poorly differentiated; F: female; M: male; Y: yes; N: no; B: body, BT: body-tail; H: head; HBT: head-body-tail. After Bonferroni correction: [1]for OS G1 vs G2, *P*=0.051, G2 vs G3 *P*<0.001; for EFS G1 vs G2 *P*=0.089, G2 vs G3 *P*<0.001; [2]for OS G1 vs G2, *P*=0.103, G2 vs G3 *P*<0.001, G3 vs G3pd *P*<0.001; for EFS G1 vs G2 *P*=0.182, G2 vs G3 *P*<0.001 and G3 vs G3pd *P*=1.000.

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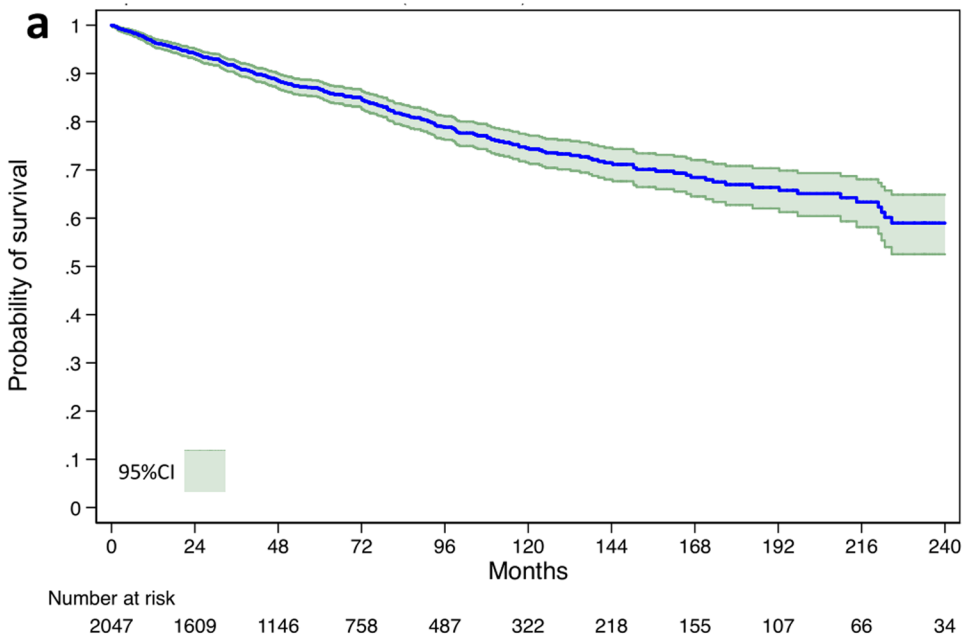
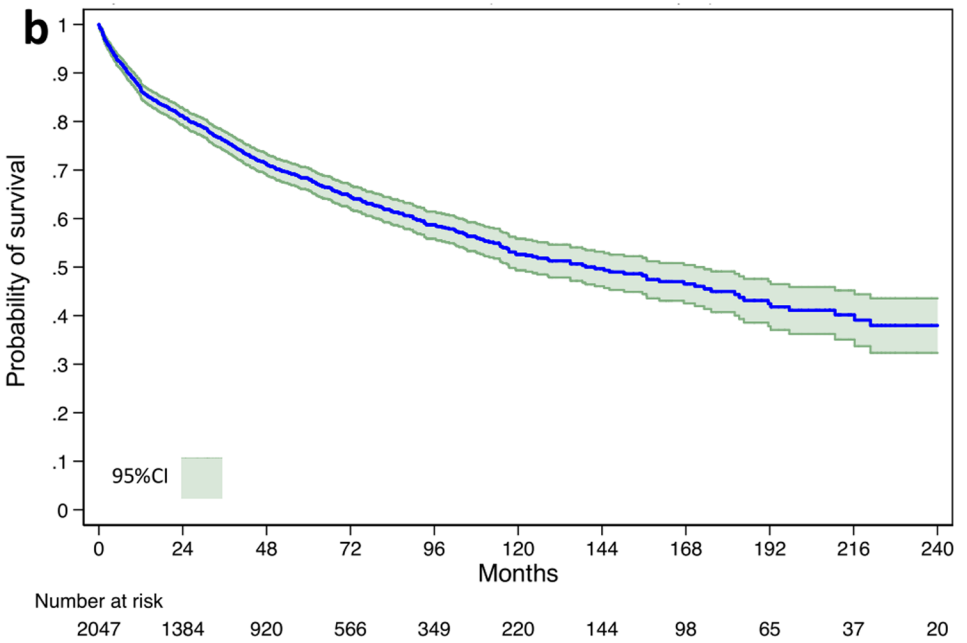
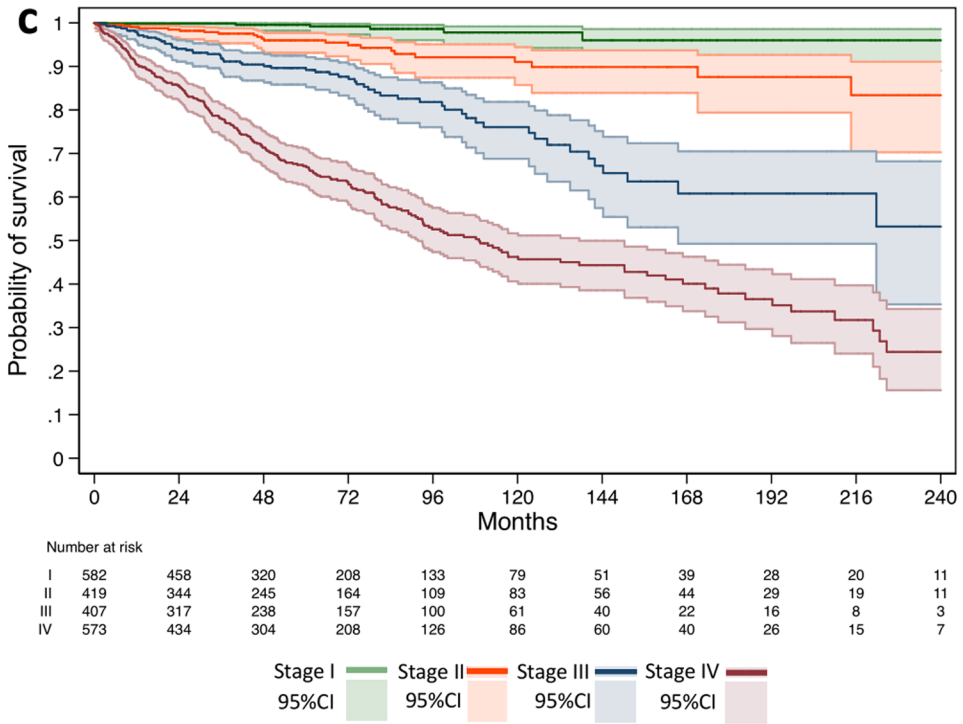
Figure 1







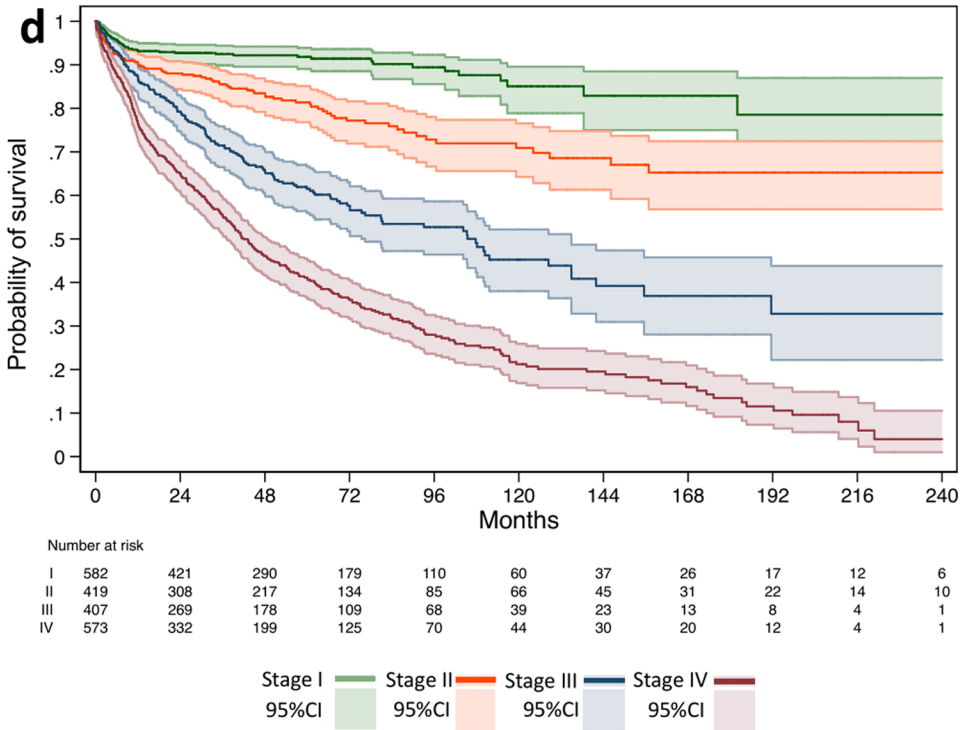


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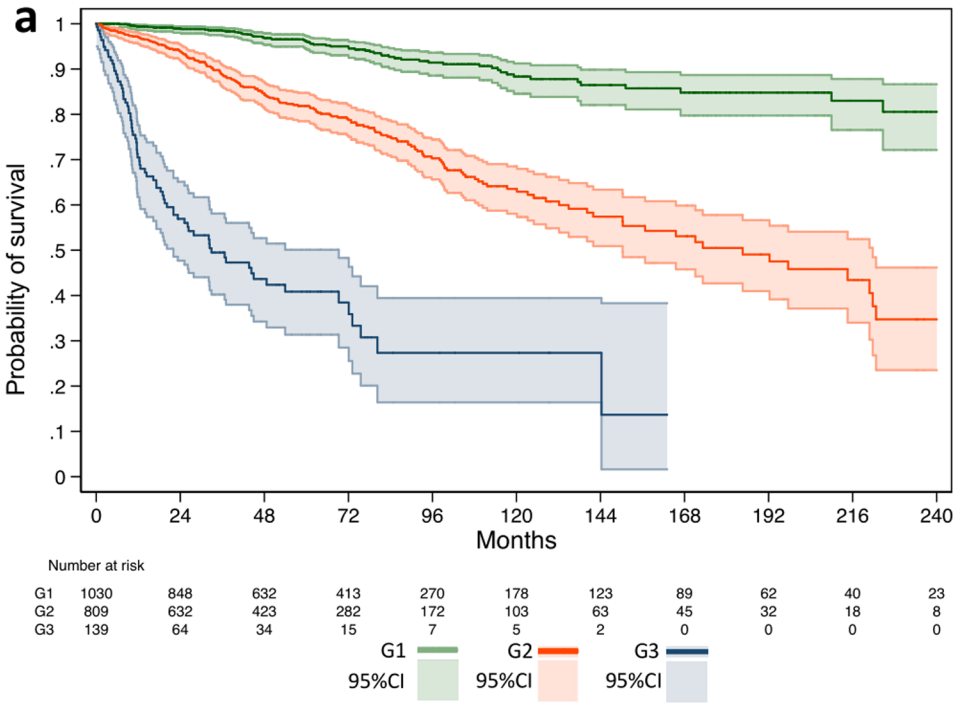
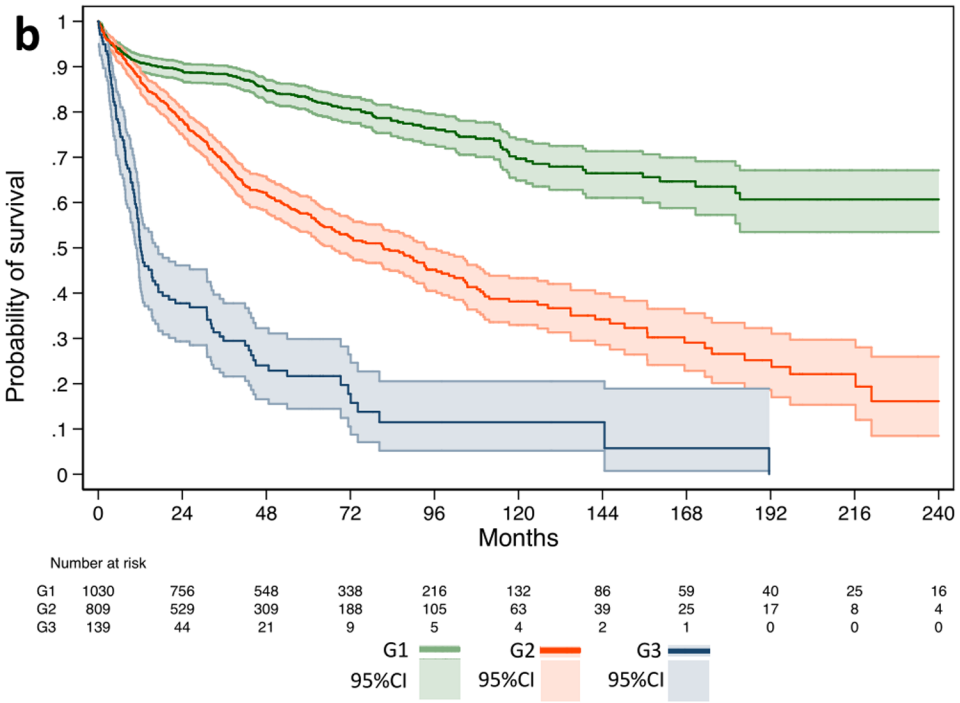
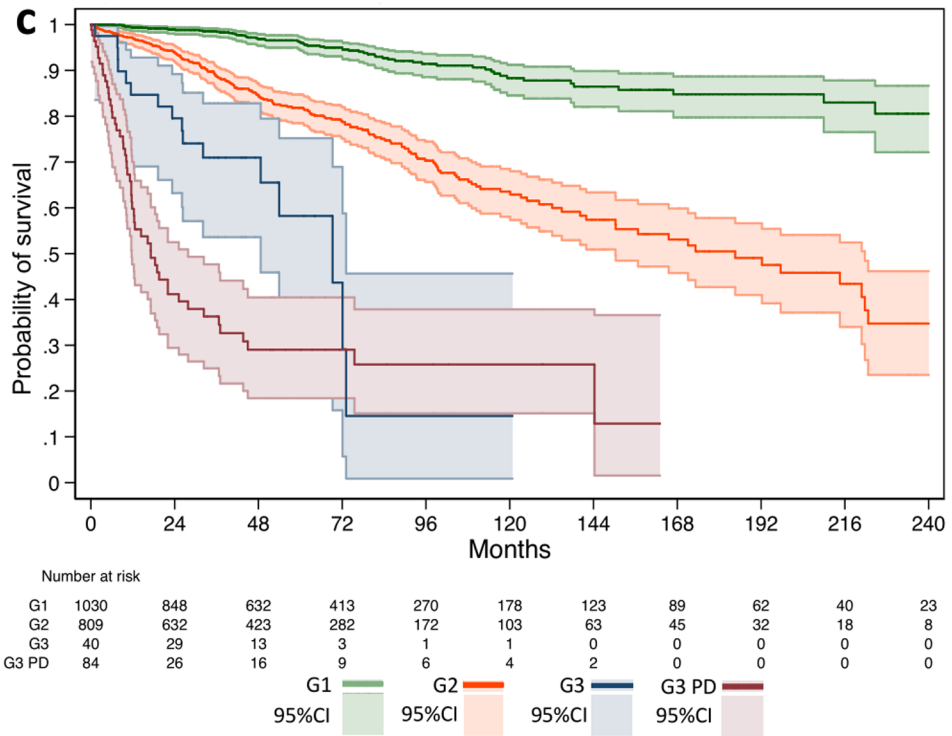
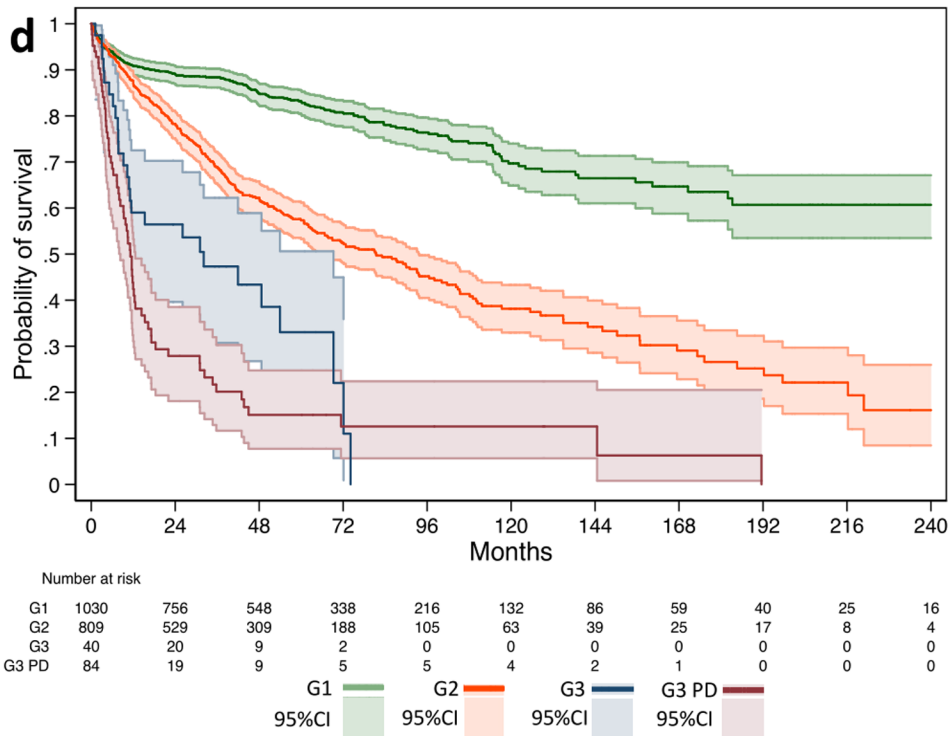
Figure 2









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SUPPLEMENTARY DATA

MATERIALS AND METHODS

Investigated Variables

The 34 analyzed variables were: age, sex, ethnicity, date of first diagnosis, date of first relapse, date of last follow-up, time of follow-up, status, curative surgery, genetics, site number of lesions, functioning tumor, type of syndrome, WHO 2010 class, WHO 2017 grade, mitotic count per $2mm^2$, Ki67 index, necrosis, poorly differentiated morphology (WHO 2000), size, stage ENETS/UICC 8^{th} Edition, T, N, number of lymph-nodes, M, site of distant metastases (liver, lung, mesentery, bone and other sites), Stage UICC 7th edition, T UICC 7th Edition, number of assessed lymph-nodes, type of surgery, therapy chemo (cytotoxic chemo, any; temozolomide; 5FU; STZ), therapy bio (somatostatin analogs [SSA], interferon, tyrosine kinase inhibitors [TKI], mTOR inhibitors), peptide receptor radionuclide therapy (PRRT).

RESULTS

Descriptive data

Most patients (81%) were treated by curative surgery rather than other therapy (biotherapy 21%, chemotherapy 21% and PRRT 10%). PanNENs were mostly single, sporadic (91%) lesions of the head and body-tail (81%), 25mm in median size, non-functioning (74%) and almost equally distributed in four stages (Table S3). In less than half of patients, metastases were observed in lymph-node (40%) and at distant sites (30%). More than 90% of PanNENs were NET G1 or G2. Differences for sex were observed for all variables except for ethnicity, genetics, site, PRRT, number of lesions, M and multiple M (Tables S2 and S3). Differences for age were observed for all variables except for ethnicity, curative surgery, chemotherapy, T, size and well differentiated morphology (Tables S2 and S3).

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Table S1: Participating Centers, number of cases provided and Center features

Institution	**EU Nation**	**Number of Cases**	**Center feature**
Ancona, University Hospital	Italy	32	Pancreas Cancer Referral Center
Bern, University Hospital	Switzerland	99	NE tumors referral center
Berlin, Charité University Hospital	Germany	195	ENETS CoE
Copenhagen, University Hospital	Denmark	58	ENETS CoE
Heidelberg, University Hospital	Germany	309	Pancreas Cancer Referral Center
London, Royal Free Hospital	Great Britain	67	ENETS CoE
Milan-Humanitas, University Hospital	Italy	49	ENETS CoE
Milan-San Raffaele University Hospital	Italy	162	Pancreas Cancer Referral Center
Paris Clichy, University Hospital	France	310	ENETS CoE
Pavia, University Hospital	Italy	50	NE tumors referral center
Roma, Sant'Andrea Hospital & Policlinico A. Gemelli	Italy	104	ENETS CoE
Rotterdam, Erasmus University Hospital	The Netherlands	134	ENETS CoE
Varese, University Hospital	Italy	106	NE tumors referral center
Verona-Negrar, Hospital	Italy	104	Pancreas Cancer Referral Center
Verona, University Hospital	Italy	56	ENETS CoE
Villejiuif, Gustave Roussy Hospital	France	168	Pancreas Cancer Referral Center
Zurich, Stadtspital Triemli	Switzerland	99	NE tumors referral center

Legend
EU: Europe; NE: neuroendocrine; ENETS: European Neuroendocrine Tumor Society; CoE: Center of Excellence

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Table S2. Major demographic and clinical descriptors of the cohort by sex and age groups.

Variable	**Cases**	**Type**	**N (%)**	**Sex F n. (%)**	**M n. (%)**	***p***	**Age Cases**	**<30 n. (%)**	**30-60 n. (%)**	**>60 n. (%)**	***p***
Sex	2102	F	1085 (52)	-	-	-	-	-	-	-	-
		M	1017 (48)								
Age*	2094	-	55 (45-65)	54 (44-64)	57 (46-66)	**0.001**	-	-	-	-	-
Age	2094	<30	108 (5)	70 (6)	38 (4)	**0.001**					
		30-60	1220 (58)	646 (60)	574 (57)		-	-	-	-	-
		>60	766 (37)	366 (34)	400 (39)						
Ethnicity	1684	C	1648 (98)	832 (98)	816 (98)	1.00	1676	85 (5)	940 (57)	615 (38)	0.637
		[1]Oth	36 (2)	18 (2)	18 (2)			1 (3)	23 (64)	12 (33)	
Genetics	1702	Spo	1561 (92)	813 (91)	748 (92)	0.317	1694	63 (4)	897 (58)	593 (38)	**<0.001**
		MEN	104 (6)	53 (6)	51 (6.6)			20 (19)	74 (71)	10 (10)	
		VHL	30 (1.5)	20 (2.5)	10 (1.2)			7 (23)	21 (70)	2 (7)	
		[2]Oth	7 (0.5)	5 (0.5)	2 (0.2)			1 (14)	5 (72)	1 (14)	
Function	2079	NF	1542 (74)	762 (71)	780 (78)	**<0.001**	2071	53 (3)	880 (58)	601 (39)	**<0.001**
		F	537 (26)	313 (29)	224 (22)			54 (10)	128 (61)	155 (29)	
			Ins 358 (67)								
			[3]Oth 179 (33)								
Site	1949	B	341 (17)	197 (19)	144 (15)	0.182	1945	21 (6)	177 (52)	141 (42)	**0.015**
		BT	822 (42)	423 (41)	399 (43)			38 (5)	496 (60)	287 (35)	
		H	753 (39)	384 (38)	369 (40)			41 (5)	448 (60)	263 (35)	
		HBT	33 (2)	17 (2)	16 (2)			4 (12)	24 (73)	5 (15)	
Surgery	2102	C	1699 (81)	916 (84)	783 (77)	**<0.001**	2094	93 (6)	984 (58)	615 (36)	0.321
		NC	403 (19)	169 (16)	234 (23)			15 (4)	236 (59)	151 (37)	
Biotherapy	1640	N	1291 (79)	688 (81)	603 (76)	**0.030**	1651	76 (6)	735 (57)	477 (37)	**0.015**
		Y	349 (21)	163 (19)	186 (24)			12 (3)	234 (65)	117 (32)	
Chemotherapy	1659	N	1296 (78)	701 (82)	595 (74)	**<0.001**	1632	74 (6)	739 (57)	470 (37)	0.185
		Y	363 (22)	156 (18)	207 (26)			13 (4)	215 (62)	121 (35)	
PRRT	1654	N	1487 (90)	780 (91)	707 (89)	0.221	1646	83 (6)	852 (57)	545 (37)	**0.043**
		Y	167 (10)	79 (9)	88 (11)			5 (3)	11 (67)	50 (30)	

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Legend
In bold, statistically significant values; N: number; F: female; M: male; INS: insulinoma; [1]Oth : other types of race including African, Asian, etc. ; Spo: sporadic, i.e. void of any known heritable genetic background ; MEN: multiple endocrine neoplasia syndrome type 1 ; VHL : von Hippel-Lindau ; [2]Oth: other types of heritable genetic background including Type I fibromatosis, etc. ; [3]Oth: other types of hormonal syndromes including carcinoid, glucagonoma, Verner-Morrison, Zollinger-Ellison and other very rare as ACTH, etc. ; NF: non-functioning ; F: functioning; H: head; B: body; BT: body-tail; HBT: head-body-tail; C: curative; NC: non-curative; Chemo: chemotherapy; Bio: biotherapy; PRRT: peptide receptor radio-therapy.

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Table S3. Major pathological descriptors of the cohort by sex and age groups.

Variable	**Cases**	**Type n. (%)**	**Sex F n. (%)**	**M n. (%)**	***p***	**Age Cases n. (%)**	**<30 n. (%)**	**30-60 n. (%)**	**>60 n. (%)**	***p***
Stage	2028	I 601 (30)	354 (34)	247 (25)	**<0.001**	599 (30)	40 (37)	344 (29)	215 (29)	**0.001**
		II 428 (21)	230 (22)	198 (20)		427 (21)	32 (30)	223 (20)	172 (24)	
		III 417 (20)	189 (18)	228 (23)		413 (20)	16 (15)	240 (20)	157 (21)	
		IV 582 (29)	278 (26)	304 (31)		581 (29)	19 (18)	373 (31)	189 (26)	
T	2008	1 709 (35)	408 (39)	301 (31)	**<0.001**	706 (35)	44 (41)	413 (35)	249 (35)	0.180
		2 558 (28)	300 (29)	258 (27)		557 (28)	36 (34)	330 (28)	191 (26)	
		3 562 (28)	264 (25)	298 (31)		562 (28)	20 (18)	327 (28)	215 (30)	
		4 179 (9)	77 (7)	102 (11)		175 (9)	6 (7)	106 (9)	63 (9)	
Size (mm)*	1999	25 (15-45)	25 (14-40)	28 (16-45)	**<0.001**	1991	23 (13-35)	25 (15-45)	25 (15-45)	0.055
No. lesions*	1684	1 (1-1)	1 (1-1)	1 (1-1)	0.811	1678	1 (1-18)	1 (1-16)	1 (1-7)	**<0.001**
N	1961	N0 1057 (54)	581 (58)	476 (50)	**0.001**	1053 (54)	62 (61)	594 (52)	397 (56)	**0.021**
		N1 771 (39)	354 (35)	417 (44)		767 (39)	31 (30)	482 (42)	254 (36)	
		NX 133 (7)	71 (7)	62 (6)		133 (7)	9 (9)	69 (6)	55 (8)	
number of N+*	1450	0 (0-2)	0 (0-1)	0 (0-2)	**<0.001**	1442	0 (0-1)	0 (0-2)	0 (0-1)	**0.007**
M	1993	0 1405 (70)	744 (72)	661 (68)	0.055	1398 (70)	83 (81)	777 (67)	538 (74)	**<0.001**
		1 588 (30)	283 (28)	305 (32)		587 (30)	19 (19)	379 (33)	189 (26)	
multiple M	2102	0 2050 (98)	1058 (98)	992 (98)	1.000	2042 (98)	108 (100)	1185 (97)	749 (98)	**0.041**
		1 52 (2)	27 (2)	25 (2)		52 (2)	0 (0)	35 (3)	17 (2)	
Morphology	2020	WD 1912 (95)	1011 (97)	901 (93)	**<0.001**	1905 (95)	100 (95)	1114 (95)	691 (94)	0.530
		PD 108 (5)	35 (3)	73 (7)		108 (5)	5 (5)	58 (5)	45 (6)	
WHO Class	1454	NET 1361 (94)	741 (95)	620 (91)	**0.002**	1361 (94)	71 (95)	821 (95)	469 (91)	**0.048**
		NEC 93 (6)	35 (5)	58 (9)		93 (6)	4 (5)	45 (5)	44 (9)	
Necrosis	1570	N 1375 (88)	743 (90)	632 (85)	**0.007**	1367 (88)	83 (94)	812 (87)	472 (86)	0.078
		Y 195 (12)	85 (10)	110 (15)		195 (12)	5 (6)	116 (13)	74 (14)	
Grade 2010	2033	G1 1064 (52)	588 (56)	476 (49)	**<0.001**	1058 (52)	60 (57)	605 (52)	393 (53)	0.502

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		G2 827 (41)	411 (39)	416 (42)		826 (41)	40 (38)	494 (42)	292 (39)	
		G3 142 (7)	50 (5)	92 (9)		141 (7)	6 (5)	76 (6)	59 (8)	
Grade 2017	2018	G1 1064 (53)	588 (56)	476 (49)	**<0.001**	1058 (53)	60 (57)	605 (52)	393 (53)	0.783
		G2 827 (41)	411 (39)	416 (43)		826 (41)	40 (38)	494 (42)	292 (40)	
		G3 42 (2)	14 (2)	27 (3)		41 (2)	2 (2)	23 (2)	16 (2)	
		G3 pd 86 (4)	30 (3)	56 (6)		86 (4)	4 (3)	45 (4)	37 (5)	
Mitosis*	1401	1 (0-2)	1 (0-2)	1 (0-3)	**0.009**	1395	1 (0-2)	1 (0-3)	1 (0-2)	0.360
Ki67%*	1973	2 (1-5)	2 (1-5)	2 (1-7)	**<0.001**	1965	2 (1-4)	2 (1-5)	2 (1-7)	0.652

Legend
In bold, statistically significant values for two tiers variables; N: number; F: female; M: male; T: tumor; N: lymph-node; N+: lymph-node positive for metastasis; M: metastasis; WHO: World Health Organization; WD: well differentiated; PD: poorly differentiated; NET: neuroendocrine tumor; NEC: neuroendocrine carcinoma; Grade 2010: grade according to WHO 2010; Grade 2017: grade according to WHO 2017; G3 pd: G3 poorly differentiated; *median (25^{th}-75^{th}).

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Table S4. ROC curve analysis data of continuous variables for mortality and event.

	Variables		
	mitotic count (95%CI)	Ki67 % (95%CI)	Size, mm, (95%CI)
Mortality at 5 years			
Optimal cutoff	1.5	4.85	30
ROC area	0.73 (0.70-0.77)	0.75 (0.72-0.84)	0.67 (0.63-0.70)
Sensitivity	77.2 (69.6-83.7)	76.5 (70.0-82.1)	73.1 (66.3-79.2)
Specificity	69.7 (65.9-73.3)	73.7 (70.6-76.7)	60.8 (57.4-64.1)
PPV	38.6 (33.0-44.4)	41.5 (36.5-46.7)	29.8 (25.7-34.0)
NPV	92.5 (89.7-94.8)	92.8 (90.6-94.6)	90.9 (88.2-93.1)
Event at 5 years			
Optimal cutoff	1.5	4.85	30
ROC area	0.69 (0.65-0.72)	0.70 (0.67-0.73)	0.64 (0.61-0.67)
Sensitivity	67.8 (61.5-73.6)	66.5 (61.0-71.6)	67.0 (61.5-72.1)
Specificity	69.7 (65.9-73.3)	73.7 (70.6-76.7)	60.8 (57.4-64.1)
PPV	47.6 (42.2-52.9)	49.1 (44.3-53.9)	38.7 (34.7-42.9)
NPV	84.2 (80.7-87.3)	85.2 (82.4-87.7)	83.3 (80.1-86.1)

Data were generated in testing sample and diagnostic ability was assessed in the testing and the validating sample; PPV: positive predictive value; NPV: negative predictive value.

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