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ORIGINAL ARTICLE – ENDOCRINE TUMORS

Radical Resection in Entero-Pancreatic Neuroendocrine Tumors: Recurrence-Free Survival Rate and Definition of a Risk Score for Recurrence

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ABSTRACT

Background. Surgery with radical intent is the only potentially curative option for entero-pancreatic neuroendocrine tumors (EP-NETs) but many patients develop recurrence even after many years. The subset of patients at high risk of disease recurrence has not been clearly defined to date.

Objective. The aim of this retrospective study was to define, in a series of completely resected EP-NETs, the recurrence-free survival (RFS) rate and a risk score for disease recurrence.

Patients and Methods. This was a multicenter retrospective analysis of sporadic pancreatic NETs (PanNETs) or small intestine NETs (SiNETs) [G1/G2] that underwent R0/R1 surgery (years 2000–2016) with at least a 24-month follow-up. Survival analysis was performed using the

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Kaplan–Meier method and risk factor analysis was performed using the Cox regression model.

Results. Overall, 441 patients (224 PanNETs and 217 SiNETs) were included, with a median Ki67 of 2% in tumor tissue and 8.2% stage IV disease. Median RFS was 101 months (5-year rate 67.9%). The derived prognostic score defined by multivariable analysis included prognostic parameters, such as TNM stage, lymph node ratio, margin status, and grading. The score distinguished three risk categories with a significantly different RFS ($p < 0.01$).

Conclusions. Approximately 30% of patients with EP-NETs recurred within 5 years after radical surgery. Risk factors for recurrence were disease stage, lymph node ratio, margin status, and grading. The definition of risk categories may help in selecting patients who might benefit from adjuvant treatments and more intensive follow-up programs.

Surgery with radical intent is the only potentially curative option for patients with entero-pancreatic neuroendocrine tumors (EP-NETs),[1–3] but in clinical practice recurrence can occur even after many years.

The major risk factors for disease recurrence (DR) indicated by previous studies include disease stage according to the European Neuroendocrine Tumor Society (ENETS) tumor-node-metastasis (TNM) staging system,[4,5] proliferative index (Ki67), and lymph node (LN) ratio. However, the prognostic impact of the combination of these features into a risk score for DR has been poorly investigated, with data derived from heterogeneous series, with relatively short follow-up after resection, and most studies focused exclusively on pancreatic NETs (PanNETs).[6–19]

The absence of a risk score for DR results in two major issues in post-surgical management. First, the efficacy of adjuvant treatments in radically resected EP-NETs still represents an unexplored option. The characteristics of patients at 'high risk' for DR have not yet been clearly defined, but these patients might represent a subgroup that could potentially benefit from this therapeutic strategy. Second, although the ENETS guidelines recommend follow-up after radical resection for EP-NETs at regular intervals, the lack of accurate patient stratification according to DR risk precludes the definition of precise schedules.[1–3] Consequently, intensive surveillance still represents a burden for disease-free patients at 'low risk' of DR. Based on these considerations, the primary aims of the present study were to describe the recurrence-free survival (RFS) rates for EP-NETs after radical resection and to identify risk factors for DR. The secondary endpoint was to propose a 'risk score' to enable stratification of patients with radically resected EP-NETs according to the DR risk.

METHODS

Study Population

This retrospective, multicenter analysis involved the following participating sites: Berlin (Germany), Marburg (Germany), Milan (Humanitas; Italy), Bolzano (Italy), Manchester (UK), Rotterdam (The Netherlands), Milan (IEO; Italy), Trento (Italy), Erlangen (Germany), and Naples (Italy). The data of some patients have been previously reported.[20]

Inclusion criteria were sporadic PanNETs or small intestine NETs (SiNETs) [G1 or G2] as defined by the World Health Organization (WHO) classification 2010,[21] diagnosed between 2000 and 2016, receiving upfront surgery with curative intent (R0/R1), and with a minimum follow-up time after resection for alive patients of 24 months. Exclusion criteria were the presence of genetic syndromes (i.e., von Hippel–Lindau syndrome, multiple endocrine neoplasia type 1), primary tumor site other than the small bowel or pancreas, G3 histology, R2 resection, use of neoadjuvant or adjuvant treatment, a follow-up period shorter than 24 months for alive patients, and/or a lack of follow-up information. Patients were classified according to the ENETS TNM staging system and G Grading.[4,5]

After surgery, patients were followed up with conventional imaging tests or functional imaging tests (somatostatin receptor scintigraphy or ^{68}Gallium positron emission tomography/conventional tomography) every 6–12 months after discussion in a local dedicated multidisciplinary tumor board.[22]

In accordance with local legislation, the study protocol was approved by the local ethical committee of each participating center, and informed consent was obtained from patients for data acquisition.

This study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies.

Data Acquisition

The variables were retrospectively collected from electronic and paper patient records and transferred in anonymous form to a common database. These variables included demographics, tumor features (primary site, primary size, TNM stage, presence of a clinical syndrome), type of surgery, histological features (Ki67, R status, LN involvement), DR (date, sites, first imaging test to detect recurrence), survival data, and first-line therapy after recurrence.

The LN ratio was calculated as the ratio between the number of positive LNs and the total number of removed LNs. Based on data from the literature, the cut-off values of 0.2 for PanNETs and 0.6 for SiNETs were adopted for the analysis.[23,24]

Endpoints

The gold standard for determination of DR was availability of two imaging tests in agreement and/or new histology confirming recurrence. The RFS was calculated as the interval between radical surgery and DR or last follow-up. Primary endpoints included the description of median RFS, RFS rates at 1-, 2-, and 5-years after surgery, and median time to recurrence, while the secondary endpoint was assessment of recurrence risk by application of a 'risk score' for DR able to distinguish cases at 'low', 'intermediate' and 'high' risk for DR.

Statistical Analysis

Statistical analysis was performed using a dedicated software program (Medcalc 15.6.1, www.medcalc.be).

The distribution of continuous variables was reported as the median and range. A comparison between the subgroups was carried out using the Mann–Whitney U test for continuous variables and Fisher's exact test or the Chi-square test for non-continuous variables. The *p*-value was considered statistically significant when <0.05.

Survival analysis was performed in accordance with the Kaplan–Meier method and the log-rank test.

The Cox regression model was used to investigate a possible correlation between neoplastic features and DR, and results are expressed in terms of hazard ratio (HR) and 95% confidence interval (CI). The multivariable model was constructed using the 'stepwise' method, including all variables that had shown significance in univariable analysis. A specific risk score for DR was calculated for each patient by summing the b coefficients for the significant variables in the multivariable analysis.

The area under the curve (AUC) obtained by receiver operating characteristic (ROC) analysis was adopted to express the predictive ability of the score to identify recurring patients after radical resection. Patients were then divided into three different subgroups according to the quantile distribution of the score, i.e. 'low', 'intermediate', or 'high risk' of DR.

RESULTS

Patient Characteristics at Surgery

A total of 441 patients (224 PanNETs and 217 SiNETs) met the inclusion criteria. Demographics are reported in Table 1 and are detailed according to the primary tumor site. Local disease (TNM stage I/II) was observed more often in the PanNET subgroup than among SiNET cases (43.8% vs. 13.8%; $p < 0.01$); however, data on pathological TNM stage were lacking for 42 patients who were not metastatic and did not have LN resection.

Stage IV disease was present in 36 (8.2%) patients and involved the liver in 33 cases. The other cases presented ovarian, adrenal gland, and urinary bladder metastases. Forty-seven of 441 (10.6%) cases were functioning tumors, including 14 carcinoid syndromes, 5 gastrinomas, 24 insulinomas, 2 glucagonomas, and 2 vasoactive intestinal peptide tumors. The surgical procedures for primary tumor resection are described in electronic supplementary Table 1.

Survival Analysis

Overall, DR was observed in 158 (35.8%) patients. Median RFS of the overall population was 101 months and the 5-year RFS rate was 67.9% (Fig. 1). No statistically significant differences in terms of median RFS were observed between the primary tumor sites (144 months for PanNETs vs. 95 months for SiNETs; $p > 0.05$).

Features of recurrent disease and long-term patient outcomes are described in Table 2. Recurrent lesions mostly involved the liver (23.6%). Recurrent disease was first detected by conventional imaging tests (67.7%) but in about one-third of cases functional imaging diagnosed DR. As far as post-relapse treatment is concerned, although medical therapy was adopted in the majority of recurring NETs (54.4%), surgery was the second-line approach in 18.4% of cases.

Risk Factor Analysis and Score Definition

Univariable analysis revealed the following statistically significant risk factors ($p < 0.01$) for DR: primary tumor size, TNM staging, R status, and proliferative index (Table 3). At multivariable analysis, the following variables were identified as statistically significant risk factors: TNM stage, LN ratio, margin status, and grading. A model including these variables identified the following risk score for DR: [(0 if TNM stage I) OR (1.54 if TNM stage II) OR (1.86 if TNM stage III) OR (2.44 if TNM stage IV)] + [(0 if LN ratio $\leq$0.20 for PanNETs or $\leq$0.60 for SiNETs) OR (0.44 if LN ratio $>$0.20 for PanNETs or $>$0.60 for

TABLE 1 Patient characteristics at surgery, with stratification according to primary tumor site

Characteristic	All patients [$n = 441$]	PanNETs [$n = 224$]	SiNETs [$n = 217$]	p-Value
Sex, male	230 (52.1)	113 (50.4)	117 (53.9)	0.50
Age, years [median (range)]	58 (26–87)	57 (26–83)	60 (28–87)	0.12
Primary tumor size, mm [median (range)]	20 (5–150)	23.5 (5–150)	16 (5–72)	**< 0.01**
TNM staging[4,5]				**< 0.01**
Stage I/II	128 (29.0)	98 (43.8)	30 (13.8)	
Stage III	235 (53.3)	71 (31.7)	164 (75.6)	
Stage IV	36 (8.2)	16 (7.1)	20 (9.2)	
Unknown	42 (9.5)	39 (17.4)	3 (1.4)	
N[4,5a]				**< 0.01**
N0	143 (35.8)	110 (59.5)	33 (15.4)	
N1	256 (64.2)	75 (40.5)	181 (84.6)	
Lymph node ratio[23,24b]				**< 0.01**
Ratio = 0	149 (39.7)	113 (64.6)	36 (18.0)	
Ratio 0–0.20 (PanNET) or 0–0.60 (SiNET)	172 (45.9)	34 (19.4)	138 (69.0)	
Ratio >0.20 (PanNET) or >0.60 (SiNET)	54 (14.4)	28 (16.0)	26 (13.0)	
Margin status[c]				0.41
R0	384 (90.6)	191 (89.3)	193 (91.9)	
R1	40 (9.4)	23 (10.7)	17 (8.1)	
Ki67, % [median (range)][d]	2 (1–20)	2 (1–20)	2 (1–15)	**< 0.01**
G grading[4,5d]				**< 0.01**
G1	255 (59.7)	115 (52.5)	140 (67.3)	
G2	172 (40.3)	104 (47.5)	68 (32.7)	

Data are expressed as n (%) unless otherwise specified

Bolded values indicate significance

PanNETs pancreatic neuroendocrine tumors, *SiNETs* small intestine neuroendocrine tumors

[a]Available in 399 cases

[b]Available in 375 cases (no lymphadenectomy in 42 cases, number of lymph nodes not reported in 24 cases)

[c]Available in 424 cases

[d]Available in 427 cases

SiNETs)] + [(0 if R0) OR (0.68 if R1)] + [(0 if G1) OR (0.55 if G2)].

A total of 357 patients were eligible for assessment of the prognostic impact of the risk score (in certain patients, some of the variables required to calculate the score were missing and were therefore not included).

The value of 1.86 was indicated by ROC analysis as a cut-off to distinguish between patients at 'low' and 'high risk' for DR. The AUC value was 0.73 and was associated with a higher accuracy than Ki67 in this population (0.64; $p < 0.01$). Adopting the cut-off score of 1.86, median RFS for 'low risk' EP-NETs (180 patients) was 127 months vs. 62 months for the 'high risk' subgroup (177 patients) [$p < 0.01$]. A further analysis was performed stratifying patients according to risk quantile distribution, as follows: 'low risk' (score <1.54, 97 patients), 'medium risk' (score 1.54–2.41, 199 patients) and 'high risk' (score >2.41, 61 patients).

The prognostic impact of the score in the presented population is shown in Table 3. Figure 2 shows the RFS curves for these three patient subgroups ($p < 0.01$), and survival data are summarized in Table 4.

A direct comparison between the characteristics of patients at 'low' and 'high' risk for DR according to our risk score is provided in electronic supplementary Table 2. Focusing on the 97 patients at 'low risk' for DR, all patients had stage I–II disease at surgery and the majority had G1 histology. Only one patient had received R1 resection. All 'high risk' patients had advanced disease, 47.5% had distant metastases (25/29 in the liver), and 77.0% had G2 disease.

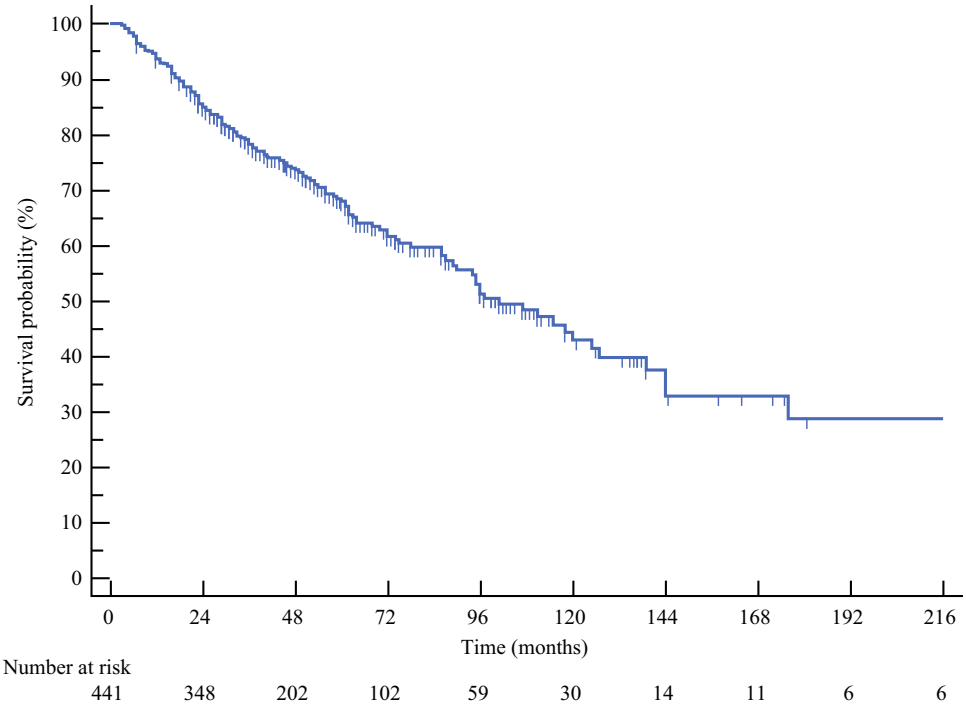

FIG. 1 Recurrence-free survival of the overall population. Median recurrence-free survival was 101 months; the 1-year rate was 93.6%, 2-year rate was 84.9%, and the 5-year rate was 67.9%

DISCUSSION

In this retrospective multicenter series of radically resected EP-NETs, about one-third of patients experienced DR within 5 years after surgery. The risk was higher for patients with advanced disease at surgery as well as G2 tumors with R1 resections.

Previous studies suggested these variables to be prognostic factors for resected EP-NETs;[11,20,25–32] however, the data were obtained from heterogeneous series, with a relatively short post-surgical follow-up. This current study included patients with EP-NETs, with a minimum follow-up of 24 months and ranging up to 18 years. All cases were evaluated at NET expert centers and their management was discussed in local dedicated multidisciplinary tumor boards, as recommended by the ENETS guidelines.[22] Our survival data showed a median RFS of about 8 years, which is in agreement with previous series of radically resected NETs.[29]

The results of this multivariable analysis allowed the derivation of a score to quantify the risk of DR in radically resected EP-NETs, stratifying patients into three subgroups, i.e. 'low', 'medium', and 'high risk' of DR. The prognostic impact of the score is supported by statistically significantly different RFS rates observed among the three subgroups (Fig. 2 and Table 4).

Unlike previously proposed risk scores for DR,[6–10,13–19,25,33] G3 cases were excluded from this analysis as they represent a totally different population to G1 and G2 tumors. Furthermore, we included not only PanNETs but also SiNETs. This decision was supported by results showing that primary tumor site was not a statistically significant prognostic factor in our series. In addition, subanalysis classifying patients according to primary tumor site proved the usefulness of the score not only in PanNETs but also in SiNETs, including or excluding TNM stage I disease ($p < 0.01$).

Merath et al.[17] proposed a nomogram for DR after radical surgery including Ki67 and variables related to disease extent. Their score was valid not only for PanNETs but also for other primary tumor sites, but unlike our study, the authors analyzed a very heterogeneous series of NETs, including those with poorly differentiated histology and primary sites other than the pancreas or small bowel. This feature may have had an impact on the results and may have introduced potential bias towards a less favorable outcome. Furthermore, unlike Merath et al.,[17] we did not exclude TNM stage IV disease, a decision that was supported by a subanalysis proving the validity of the score even when applied to TNM stage I–III EP-NETs alone.

The rate of functioning tumors in our population was just 10.6%, a proportion that may appear significantly lower than previously reported in the literature (20–30% of all NETs). This difference likely relates to the fact that only EP-NETs receiving upfront surgery were eligible in our project. Consequently, all cases of functioning tumors and those receiving first-line somatostatin analogs to control symptoms, or as bridging therapy to surgery, were excluded from the analysis.

TABLE 2 Characteristics of recurrent disease and long-term outcome

Characteristic	$N = 441$
Disease recurrence	158 (35.8)
Time to recurrence, months [median (range)]	30.5 (3–219)
Site of recurring disease	
Primary tumor site	15 (3.4)
Liver	104 (23.6)
Abdominal lymph nodes	43 (9.7)
Peritoneal carcinomatosis	14 (3.2)
Ovary	4 (0.9)
Adrenal gland	1 (0.2)
Chest lymph nodes	4 (0.9)
Lung	4 (0.9)
Bones	6 (1.4)
Breast	1 (0.2)
First method detecting recurrence	
Functional imaging tests[a]	49 (31.0)
Conventional imaging tests[b]	107 (67.7)
Surgery	2 (1.3)
First-line therapy for disease recurrence	
Surgery	29 (18.4)
Locoregional liver treatments	11 (7.0)
Systemic therapy	86 (54.4)
None[c]	32 (20.2)
Follow-up time, months [median (range)]	58 (7–216)
Observed death	31 (7.0)
Median overall survival, months	Not reached

Data are expressed as *n* (%) unless otherwise specified

[a]Somatostatin receptor scintigraphy or ^{68}Gallium-positon emission tomography/conventional tomography

[b]Conventional tomography, magnetic resonance imaging, or ultrasonography

[c]No oncological treatment due to poor conditions or patient's decision

The potential clinical impact of a valid risk score for radically resected EP-NETs is high. It would allow identification of 'high risk' patients requiring intensive follow-up programs and who may potentially benefit from adjuvant treatment. This therapeutic strategy has never really been explored for NETs, unlike other tumors, and our results might pave the way for prospective studies to evaluate adjuvant therapies in these patients. Likewise, the definition of a 'low risk' subgroup of patients might reduce the negative impact on quality of life related to overly intensive follow-up programs, and also optimize health care costs and hospital resources.

According to our results (electronic supplementary Table 2), patients with stage I–II disease, receiving R0 resection, and characterized by G1 tumor have the lowest risk of recurrence. With respect to outcome, just 2% of 'low risk' patients experienced a relapse within 12 months after surgery and only 3% within 24 months (Table 4). These patients might benefit from less intensive follow-up, probably with a first imaging procedure 18–24 months after resection. There is also a need to identify biomarkers beyond histopathological criteria and disease extent to capture this small proportion of patients at risk of DR within 1–2 years. On the contrary, 'high risk' patients may require a first imaging after 6 months as they have a significantly higher risk of early recurrence. The characteristics of 'medium risk' patients are less well-defined and this subgroup of patients may represent a grey zone, where a follow-up program should be started earlier than in the 'low risk' category. Since they represent a more heterogeneous category in terms of the expression of recurrence risk factors, the score may be particularly useful in assessing the 'middle risk' of this subgroup, helping in the adoption of tailored follow-up programs based on their individual risk.

About one-third of recurrent lesions were first detected by functional imaging tests. These data suggest that these diagnostic tools may have a role to play not only in NET diagnosis or for therapeutic management in metastatic NETs[34] but also in post-surgical follow-up for disease-free recurrence. The lack of a standardized follow-up protocol including these tests and common to the participating centers precludes definitive conclusions. However, to our knowledge, this result is novel and supports prospective series investigating the clinical utility of functional imaging tests in post-surgical follow-up of radically resected EP-NETs.

The limitations of the present study are its retrospective and multicenter design. In comparison with other similar projects, the bias related to this feature was nevertheless reduced and was outweighed by careful patient selection, including a population that was as homogeneous as possible, with a long follow-up time after resection.

Another possible criticism of this study might be represented by the observation of a better median RFS for PanNETs than SiNETs, although the difference was not statistically significant (144 months vs. 95 months; $p > 0.05$). Considering the higher frequency of localized disease in the PanNET subgroup as a potential bias for this result (Table 1), a subanalysis excluding cases with very limited disease (TNM stage I) was performed and showed a worse outcome for PanNETs than for SiNETs, with a median RFS of 64 vs. 94 months ($p = 0.03$).

In addition, subanalysis classifying patients according to primary tumor site and after excluding TNM stage I disease proved the usefulness of the score, in both PanNETs and SiNETs ($p < 0.01$).

TABLE 3 Risk factors for disease recurrence after radical surgery

Variable	Univariable analysis		
	HR	95% CI	*p*-Value
Sex, male vs. female	0.93	0.68–1.28	0.67
Age at surgery, years[a]	0.99	0.98–1.01	0.71
Pancreatic vs. intestinal primary tumor site	0.83	0.61–1.41	0.26
Functioning tumor	1.43	0.90–2.27	0.12
Primary tumor size, mm[a]	1.01	1.00–1.02	< **0.01**
TNM staging (ref. stage I)[4,5b]			
Stage II	5.38	1.61–17.98	< **0.01**
Stage III	8.61	2.73–27.17	< **0.01**
Stage IV	19.47	5.90–64.20	< **0.01**
Stage IV vs. other stages[4,5]	3.28	2.16–4.98	< **0.01**
N1 vs. N0[4,5]	2.06	1.32–3.01	< **0.01**
Lymph node ratio[a]	2.12	1.25–3.62	< **0.01**
Lymph node ratio (ref. ratio = 0)[23,24b]			
Ratio >0 but ≤0.20 (for PanNETs) or 0.60 (for SiNETs)	1.97	1.32–2.93	< **0.01**
Ratio >0.20 (for PanNETs) or 0.60 (for SiNETs)	2.81	1.74–4.54	< **0.01**
R1 vs. R0	3.14	2.03–4.87	< **0.01**
Ki67, %[a]	1.07	1.04–1.11	< **0.01**
G2 vs. G2[4,5]	2.44	1.76–3.70	< **0.01**

Variables	Multivariable analysis			
	b	HR	95% CI	*p*-Value
TNM staging (ref. stage I)[4,5b]				
Stage II	1.54	4.66	1.38–15.75	**0.01**
Stage III	1.86	6.37	1.99–20.37	< **0.01**
Stage IV	2.44	11.38	3.38–38.86	< **0.01**
Lymph node ratio (ref. ratio = 0)[23,24b]	0.44	1.56	1.01–2.40	**0.04**
Ratio >0.20 (for PanNETs) or 0.60 (for SiNETs)				
R1 vs. R0	0.68	1.97	1.17–3.33	**0.01**
G2 vs. G1[4,5]	0.55	1.74	1.21–2.50	< **0.01**

Variables not included in the model ($p > 0.05$)

Lymph node ratio (ref. ratio = 0)[23,24b]
Ratio >0 but ≤0.20 (for PanNETs) or 0.60 (for SiNETs)

Risk score model	HR	95% CI	*p*-Value
Risk categories (ref. low risk)			
Medium risk	4.03	2.14–7.57	< **0.01**
High risk	8.48	4.35–16.54	< **0.01**

Bolded values indicate significance

HR hazard ratio, *CI* confidence interval, *ref.* reference, *PanNETs* pancreatic neuroendocrine tumors, *SiNETs* small intestine neuroendocrine tumors

[a]Continuous variables

[b]Categorical variables

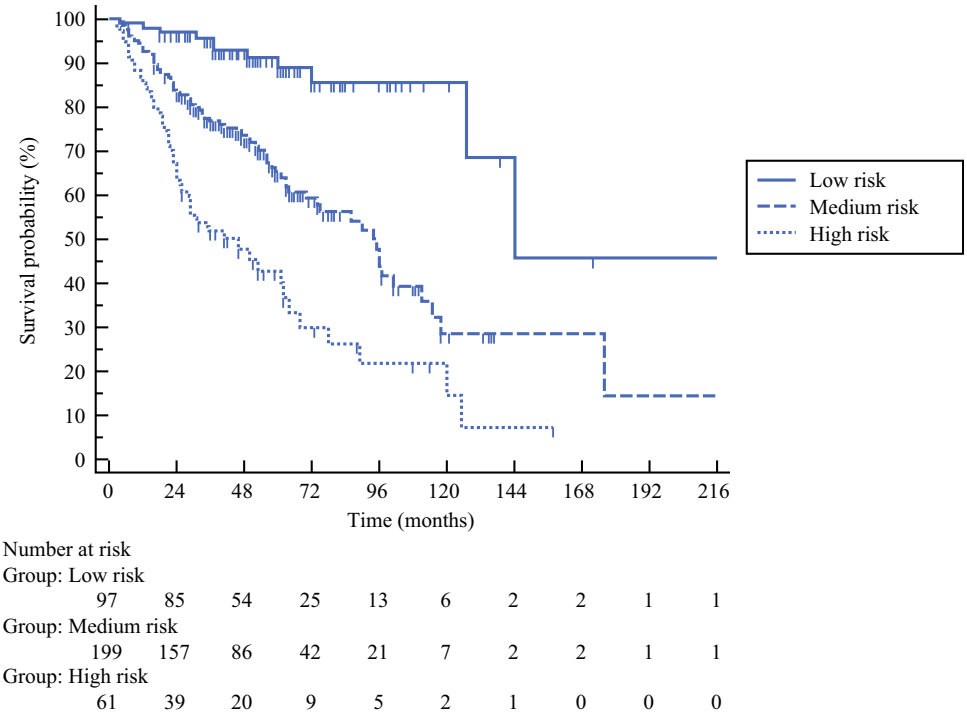

FIG. 2 Recurrence-free survival according to risk score for disease recurrence ($p < 0.01$). Survival rates are reported in Table 4

TABLE 4 Recurrence-free survival rates according to risk stratification ($p < 0.01$)

Risk category	Median RFS (months)	6-month RFS (%)	1-year RFS (%)	2-year RFS (%)	5-year RFS (%)
Low risk	144	99.0	97.9	96.9	88.9
Medium risk	94	97.5	93.5	83.3	65.1
High risk	46	93.4	85.2	63.9	42.8

RFS recurrence-free survival

A further limit of this study might be associated with the inclusion of clinical/pathological characteristics alone in the risk score. A scoring system including molecular characteristics would be novel and preferable but it would also be difficult to adopt in daily clinical practice. Rather, our aim was to provide an easy-to-use instrument to quantify risk of DR in patients with radically resected EP-NETs. The ability of our risk score to make a distinction between patients who will and will not recur after radical surgery was better than the use of Ki67 alone in this population, as proven by the ROC analysis (AUC 0.73 vs. 0.64; $p < 0.01$). An external validation will however be necessary to prove its prognostic role in clinical practice, preferably in a prospective setting, since the included population was not large enough to allow the definition of the nomogram in a subgroup of cases and its validation in another subset of patients.

An additional potential criticism of our study may be represented by the inclusion of both TNM status and LN ratio in our risk model. However, we decided to consider these variables as separate and not redundant, as in our opinion they provide different information regarding tumor extent, thus not determining a significant multicollinearity in the nomogram.

CONCLUSIONS

A risk score based on proliferative index, R status, and disease extent can accurately predict the risk of DR in radically resected G1/G2 EP-NETs. This tool might identify patients who would potentially benefit from adjuvant therapies ('high risk' patients), resulting in optimization of follow-up programs according to DR risk. Prospective studies applying this score to external populations are needed to validate its prognostic impact and to define follow-up schedules based on risk stratification.

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