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Gastrointestinal Cancer

Stage IV Gastro-Entero-Pancreatic Neuroendocrine Neoplasms: A Risk Score to Predict Clinical Outcome

Francesco Panzuto,[a] Elettra Merola,[a] Marianne Ellen Pavel,[b] Anja Rinke,[c] Patrizia Kump,[d] Stefano Partelli,[f] Maria Rinzivillo,[a] Victor Rodriguez-Laval,[g] Ulrich Frank Pape,[b] Rainer Lipp,[e] Thomas Gress,[c] Bertram Wiedenmann,[b] Massimo Falconi,[f] Gianfranco Delle Fave[a]

[a]Department of Digestive and Liver Disease, Sapienza University of Rome – Sant'Andrea Hospital, Rome, Italy; [b]Department of Hepatology and Gastroenterology, Charité Campus Mitte and Virchow Clinic, Charité University Medicine, Berlin, Germany; [c]Department of Gastroenterology, Philipps-University of Marburg, Germany; Clinical Divisions of [d]Gastroenterology and [e]Oncology, Medical University Graz, Austria; [f]Division of Pancreatic Surgery, Vita-Salute University, San Raffaele Scientific Institute, Milan, Italy; [g]Department of Radiology Charité University, Campus Virchow Klinikum, Berlin, Germany

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Neuroendocrine tumors • Prognosis • Risk score • Disease progression • Ki67 • Metastases

Abstract

Background. Several risk factors predict clinical outcome in gastro-entero-pancreatic neuroendocrine neoplasms (GEP-NENs); however, the impact of their combination has not been investigated so far.

Patients and Methods. A retrospective analysis of stage IV GEP-NENs was performed. Multivariate analysis for progression of disease (PD) was performed by Cox proportional hazards method to obtain a risk score. Area under the curve obtained by receiver operating characteristic analysis was used to assess the score performance. Progression-free survival analysis was performed by Kaplan-Meier method.

Results. Two hundred eighty-three stage IV GEP-NENs were evaluated, including 93 grade 1 neuroendocrine tumors (32.9%), 153 grade 2 neuroendocrine tumors (54%), and 37 grade 3 neuroendocrine carcinomas (13.1%). Independent risk factors for PD were Ki67, proportion of metastatic liver involvement, and presence of extra-abdominal metastases. The risk score was calculated as follows: (0.025 × Ki67) + [(0 if no liver metastases or liver involvement <25%) OR (0.405 if liver involvement 25%–50%) OR (0.462 if liver involvement >50%)] + [(0 if no extra-abdominal metastases) OR (0.528 if extra-abdominal metastases present)]. The risk score accuracy to predict PD was superior compared with the G grading system (area under the curve: 0.705 and 0.622, respectively). Three subgroups of patients with low, intermediate, and high risk of PD according to risk score were identified, median progression-free survival being 26 months, 19 months, and 12 months, respectively.

Conclusion. In stage IV GEP-NENs, a risk score able to predict PD was obtained by combining Ki67, proportion of metastatic liver involvement, and presence of extra-abdominal metastases. The score may help to discriminate patients with different progression risk level to plan tailored therapeutic approaches and follow-up programs. ***The Oncologist*** 2017;22:409–415

Implications for Practice: Clinical outcome of patients with advanced gastro-entero-pancreatic neuroendocrine neoplasms is affected by several risk factors, including the proliferative index Ki67, extension of liver metastases, and the presence of distant extra-abdominal lesions. A risk score that combines these variables may help physicians dealing with these diseases to plan the optimal therapeutic approach and follow-up program.

Introduction

Clinical outcome of patients with gastro-entero-pancreatic neuroendocrine neoplasms (GEP-NENs) is affected by several factors, including primary tumor's site, grading expressed by proliferative Ki67 index, and disease staging [1–6].

The explicit role of distant metastases in neuroendocrine neoplasms (NENs) has been recently reported in a number of studies, all suggesting that their presence and extension are associated with worse prognosis [7–9]. Furthermore, recent randomized controlled trials have highlighted different responses to medical therapies according to metastatic dissemination, thus suggesting that this parameter needs to be considered more carefully when approaching patients' treatment [10–13].

Correspondence: Gianfranco Delle Fave M.D., Digestive and Liver Disease Unit, Sapienza University of Rome – Sant'Andrea Hospital, Via di Grottarossa 1035, 00189, Rome, Italy. Telephone: 39-0633775691; e-mail: gianfranco.dellefave@uniroma1.it Received September 14, 2016; accepted for publication November 12, 2016; published Online First on February 23, 2017. http://dx.doi.org/10.1634/theoncologist.2016-0351

However, the prognostic role of the combination of the above-mentioned risk factors in GEP-NENs has not been investigated so far. Thus, this study aims at identifying, in a multi-center international series of advanced GEP-NENs, factors that can predict poor clinical outcome and combining them in order to obtain a risk score to quantify the risk of progression in these patients.

Subjects, Materials, and Methods

In this multicenter study, a retrospective analysis on institutional databases from five participating international centers was performed. The study included consecutive patients with sporadic stage IV GEP-NENs (according to the European Neuroendocrine Tumor Society [ENETS] tumor-node-metastasis staging system) [14, 15] diagnosed at the participating centers (i.e., Rome, Milan, Berlin, Marburg, and Graz) from 2000 to 2015.

Patients with familial syndromes (type I multiple endocrine neoplasia, von Hippel–Lindau syndrome), as well as patients without measurable advanced disease or without available radiological or histological data (Ki67 index) required to assess the ENETS grading and staging, were excluded. The time of inclusion in the study was at first diagnosis of stage IV disease such as (a) at initial histological diagnosis for patients with metastatic disease and (b) the time of first evidence of distant metastases identified during follow-up in patients without previous metastases. Data were prospectively collected at the centers that treated the patients with metastatic disease, a uniform computerized datasheet was created, and data were analyzed retrospectively.

Therapeutic approaches were not standardized, and thus different treatments were used at each center. However, at all participating centers, the therapeutic approaches and their sequence were always discussed within a multidisciplinary team. Therefore, patients were enrolled independently from the therapeutic protocol that had been performed. Moreover, no prospectively planned follow-up programs were standardized at the participating centers, but they all followed the ENETS standards of care for advanced GEP-NENs follow-up as appropriate in each respective center [16].

Histological diagnosis was confirmed in all tumors, which were classified according to the WHO 2010 classification [17]. Specimens were revised in those tumors diagnosed before the WHO 2010 classification introduction and examined by an experienced referral pathologist handling NEN specimens at each participating center's pathological institute. Patients were arbitrarily classified into three different categories according to the proportion of metastatic liver involvement, as assessed by conventional radiological examinations (computed tomography or magnetic resonance imaging) by measuring hepatic tumor volume: no liver metastases present or metastatic liver involvement $<$25%; metastatic liver involvement 25%–50%; metastatic liver involvement $>$50%.

According to the relevant local legislation, the study protocol was approved by the ethics committees of each participating center, and informed consent for data collection was obtained from all patients.

The primary end point considered was progression-free survival (PFS), which was defined as the interval between diagnosis of stage IV GEP-NENs and time of progressive disease (PD), or patient death, whichever occurred first. Disease progression during follow-up was assessed by conventional radiological examinations, and evaluated according to Response Evaluation Criteria in Solid Tumors 1.0 [18]. When appropriate, additional data from functional imaging procedures (somatostatin receptors scintigraphy, 68-Gallium positron emission tomography) were also evaluated to assess the disease behavior.

The distribution of continuous variables was reported as the median and interquartile range (IQR; 25th–75th percentiles). A comparison between the subgroups was carried out using the Fisher exact test or the chi-square test for noncontinuous variables, whereas the Mann–Whitney *U* test was used to compare the continuous variables, as appropriate.

PFS analysis was performed by using the Kaplan-Meier method, and results were compared by log-rank test. The analysis of risk factors for PD prediction was performed by univariate and multivariate analysis by Cox proportional hazards method. All variables with significant results by univariate analysis ($p < .05$) were included in the multivariate model, which was constructed by stepwise method. A specific risk score, expressed as a prognostic index, was calculated for each patient by summing the b coefficients for the variables that were reported to be statistically significant at the multivariate analysis. Receiver operating characteristic (ROC) analysis was performed to identify the ability of the score to discriminate between patients who did and patients who did not experience PD. Area under the curve (AUC) was used to express the predictive ability. Furthermore, patients were categorized by their scores into three different groups according to quantiles distribution in order to classify those at low, intermediate, or high risk of PD. The statistical analysis was performed using a dedicated software (Medcalc 16, Belgium, www.medcalc.org).

Results

Patient Population

A total of 283 patients were evaluated, including 147 males (51.9%), with a median age at time of stage IV GEP-NEN of 56 years (IQR 48–66). Patients' main clinical and pathologic features are summarized in Table 1. Overall, primary tumor site was the pancreas in 140 patients (49.5%), small bowel in 121 patients (42.7%), and other digestive sites in the remaining 22 patients (7.8%; rectum 8 patients, colon 6 patients, duodenum 5 patients, stomach 2 patients, appendix 1 patient). A total of 224 patients (79.1%) had stage IV disease at the time of initial NEN diagnosis, whereas the remaining 59 patients (20.9%) developed distant metastases during follow-up at a median interval of 22 months (IQR 12–48) from initial NEN diagnosis. A total of 54 patients (19.1%) had distant extra-abdominal lesions at the time of stage IV diagnosis, most frequent metastatic sites being bones (29 patients, 10.2%), peritoneum (15 patients, 5.3%), lung (12 patients, 4.2%). Among the 203 patients with nonfunctioning NENs (71.7%), 106 patients (52.2%) had an incidental diagnosis, because no symptoms were present at the time of disease onset.

Median primary tumor size was 35 mm (IQR 22–53). A total of 182 patients (64.3%) had the primary tumor surgically removed (pancreatic NEN in 69 patients, 24.3%). Specifically, it had been resected before the onset of metastatic disease in 51 patients (18%), whereas it had been removed when metastases were already present in the remaining 131 patients (46.3%).

Overall, 89 patients (31.4%) underwent surgery to resect metastatic lesions. Of these, 34 patients had a pancreatic NEN

Table 1. Patients' general features

Characteristic	Total ($n = 283$)	Pancreatic NENs ($n = 140$)	Non-Pancreatic NENs ($n = 143$)	p value
Functional status	*n* (%)	*n* (%)	*n* (%)	
Non-Functioning	203 (71.7%)	123 (60.5%)	80 (39.5%)	$< .0001$
Functioning	80 (28.3%)	17 (21.2%)	63 (78.8%)	
Grading				
G1	93 (32.9%)	25 (26.9%)	68 (73.1%)	$< .0001$
G2	153 (54%)	84 (54.9%)	69 (45.1%)	
G3	37 (13.1%)	31 (83.8%)	6 (16.2%)	
Median % Ki67 (IQR)	5 (2–12)	10 (4–20)	3 (2–7.7)	$< .0001$
Tumor liver involvement				
0%–25%	163 (57.6%)	66 (40.5%)	97 (59.5%)	.001
25%–50%	79 (27.9%)	50 (63.3%)	29 (36.7%)	
>50%	41 (14.5%)	24 (58.5%)	17 (41.5%)	
Extra abdominal metastases present	54 (19.1%)	27 (50%)	27 (50%)	1.000

Abbreviations: IQR, interquartile range; NENs, neuroendocrine neoplasms.

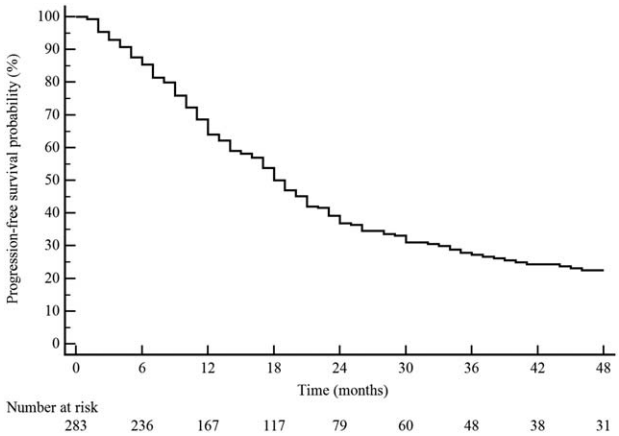

Figure 1. Progression-free survival (PFS) in 283 patients with stage IV gastro-entero-pancreatic neuroendocrine neoplasms. Median PFS: 18 months.

(12%). In most cases (58 patients, 20.5%), surgery for metastases was performed together with primary resection, whereas in 26 patients (9.2%) it was done afterwards during follow-up. In 4 patients (1.4%), the metastatic disease was operated without performing primary tumor resection. A total of 19 patients (6.7%) underwent metastatic resection, with radical intent achieving cure (R0 resection with no further disease recurrence) in only 4 patients (1.4%). As far as medical treatment after stage IV diagnosis is concerned, a total of 210 patients (74.2%) received somatostatin analogs, 101 patients (35.7%) received peptide receptors radionuclide therapy, 87 patients (30.7%) received systemic chemotherapy, and 72 patients (25.4%) received targeted therapies (everolimus, $n = 56$; sunitinib, $n = 16$).

PFS

A total of 211 patients (74.5%) showed PD at a median interval of 14 months (IQR 8–24) after stage IV GEP-NEN diagnosis. Overall, median PFS was 18 months (Fig. 1). The variables considered as risk factors for PD at the time of stage IV diagnosis evaluated by univariate analysis are summarized in Table 2. The major risk factors for PD were primary tumor site (pancreas versus non-pancreas), tumor proliferative activity (expressed either by G grading system or Ki67 as a continuous variable), and disease extension (expressed either by proportion of liver involvement or presence of distant extra-abdominal metastases). When multivariate analysis was performed, the proliferative index Ki67, the proportion of liver involvement, and the presence of distant extra-abdominal metastases were confirmed to be independent risk factors for PD (Table 3), whereas the pancreatic primary site was excluded from the model due to loss of statistical significance.

Risk Score for Tumor Progression

A risk score was generated for each patient by using the b coefficients of the variables confirmed by the multivariate analysis in order to grade the risk of PD after diagnosis of stage IV GEP-NENs. As a result, the risk may be calculated as follows: (0.025 $\times$ Ki67 value) + [(0 if no liver metastases present or liver involvement <25%) OR (0.405 if liver involvement 25%–50%) OR (0.462 if liver involvement >50%)] + [(0 if extra-abdominal metastases absent) OR (0.528 if extra-abdominal metastases present)]. The value of 0.179 was identified by ROC analysis to have the utmost ability of discriminating between patients at high (>0.179, $n = 197$ patients, median PFS 14 months) versus low ($\leq$0.179, $n = 86$ patients, median PFS 41 months) risk of PD during follow-up ($p < .0001$). An additional analysis was performed by dividing patients into three different groups according to risk score quantiles distribution to obtain "low-" (risk score <0.308, $n = 106$ patients), "intermediate-" (risk score 0.308 to 0.642, $n = 84$ patients), and "high-risk" patients (risk score >0.642, $n = 93$ patients), median PFS being 26 months, 19 months, and 12 months, respectively ($p < .0001$; Fig. 2).

As far as the primary tumor site is concerned, similar findings were obtained when PFS was analyzed according to the three risk categories in pancreatic ($p = .001$; supplemental online Fig. 1) and non-pancreatic NENs ($p < .0001$; supplemental online Fig. 2).

Overall, the risk score model ability to discriminate between patients who did and who did not experience PD was good, AUC being 0.705. This accuracy level was higher than that of the G grading system tested by ROC analysis in the

Table 2. Risk factors for tumor progression (univariate analysis)

Variable	b coefficient	HR	95% CI	*p* value
Age (year)[a]	0.001	1.00	0.98–1.01	.864
Functional status				
Non-Functioning vs Functioning	0.103	1.10	0.82–1.49	.493
Previous primary resection	0.059	1.06	0.74–1.51	.743
Primary tumor size (mm)[a]	0.003	1.003	0.99–1.00	.280
Primary tumor site				
Pancreas vs Non-pancreas	0.380	1.46	1.10–1.92	.006
Grading[b]				
G2 vs G1	0.590	1.80	1.30–2.48	.0003
G3 vs G1	1.513	4.54	2.92–7.04	< .0001
Ki67 (%)[a]	0.025	1.02	1.01–1.03	< .0001
Proportion of liver involvement[c]				
25%–50% vs. 0%–25%	0.403	1.49	1.10–2.03	.009
>50% vs. 0%–25%	0.461	1.58	1.06–2.36	.023
Extra-abdominal metastases present	0.519	1.68	1.21–2.31	.001

[a]Continuous variable.
[b]Categorical variable (G1 used as reference category).
[c]Categorical variable (0%–25% used as reference category).
Abbreviations: CI, confidence interval; HR, hazard ratio.

Table 3. Risk factors for tumor progression (multivariate analysis)

Variable	b coefficient	HR	95% CI	*p* value
Ki67 (%)[a]	0.025	1.02	1.01–1.03	< .0001
Proportion of liver involvement[b]				
25%–50% vs. 0%–25%	0.405	1.50	1.10–2.03	.009
>50% vs. 0%–25%	0.462	1.58	1.06–2.37	.024
Extra-abdominal metastases present	0.528	1.69	1.22–2.34	.001

[a]Continuous variable. Pancreatic primary site was excluded from the model (stepwise method) due to loss of significance.
[b]Categorical variable (0%–25% used as reference category).
Abbreviations: CI, confidence interval; HR, hazard ratio.

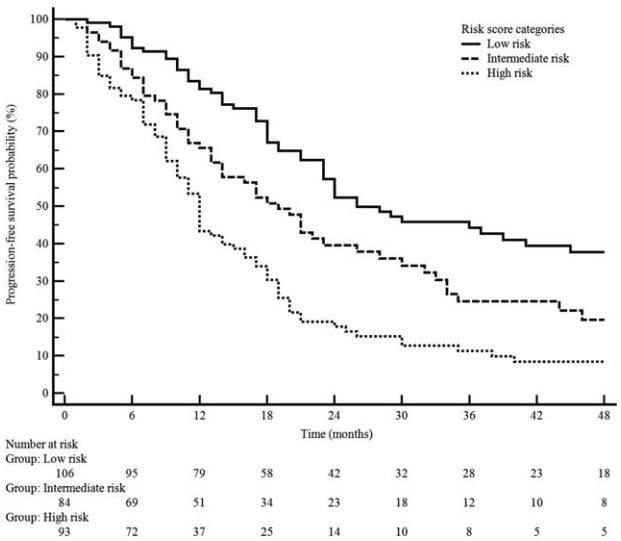

Figure 2. Progression-free survival (PFS) in 283 patients with stage IV gastro-entero-pancreatic neuroendocrine neoplasms according to risk score categories. Low risk: score <0.308; intermediate risk: score 0.308 to 0.642; high risk: score >0.642. Median PFS: 26 months, 19 months, and 12 months, respectively ($p < .0001$).

same set of patients, which was 0.622 ($p = .013$; supplemental online Fig. 3). A slightly higher predictive ability of the risk score was observed in pancreatic NENs than in non-pancreatic NENs, AUC being 0.728 and 0.662, respectively.

Patients' Survival

A total of 80 patients died during a median follow-up time of 27 months (IQR 17–49 months), with a mortality rate of 28.2%. Overall, median survival time was 90 months, and 5-year survival rate was 68%. Patients with pancreatic primary tumors had a worse survival in comparison with GEP-NENs from other sites, median survival being 86 months (5-year survival rate 58.2%) and 101 months (5-year survival rate 77.3%), respectively ($p = .005$). The variables that were statistically significant predictors for PD were also independent risk factors for patients' death at the multivariate analysis: Ki67 as continuous variable (hazard ratio [HR] 1.04, $p < .0001$), proportion of metastatic liver involvement (25%–50% versus 0%– 25%, HR 2.83, $p = .0001$; >50% versus 0%–25%, HR 6.91, $p < .0001$), and presence of distant extra-abdominal metastases (HR 1.76, $p = .027$).

Discussion

The present study shows that, when diagnosing stage IV GEP-NENs, it is possible to obtain a score to quantify the risk of PD by combining the predictive role of Ki67, the extension of liver metastases, and the presence of extra-abdominal lesions. This tool is able to provide a graded measure of the likelihood for each individual patient to experience PD and may thus help physicians dealing with GEP-NENs to plan the therapeutic sequence and follow-up program.

Over the last decade, few papers have investigated the possible impact of combined risk factors on NENs clinical outcome. An immunohistochemical prognostic score has been recently proposed by combining Ki67 with other biomarkers to predict the risk of recurrence in pancreatic NENs after radical resection, suggesting that the combination of these factors may have a higher predictive ability in comparison with each single factor alone [19]. However, different from this study, that analysis was based on a panel of immunohistochemical factors (N-myc downstream-regulated gen-1, O6-methylguanine DNA methyltransferase, and Pleckstrin homology-like domain family A member 3), thus being difficult to apply to the daily clinical practice. Furthermore, it was performed in a different setting and included a lower number of patients ($n = 92$) with pancreatic primaries only who had previously undergone radical surgery with the intent to predict the risk of recurrence.

An additional attempt to provide a mathematical-based predictive model was done in small intestine NENs by Modlin et al. [20] by a retrospective analysis of previously published literature regarding risk factors and gastrointestinal NENs and the National Cancer Institute (NCI) SEER database (1977–2007). That analysis identified several demographic, pathological, biochemical, and clinical variables that, if combined together in a nomogram tool, were proposed to be able to quantify the risk of death. Nevertheless, there are several differences as compared with the present study: (a) the risk factor analysis was performed by pooling data from other studies, published during a long period of time (1997–2010); (b) the NCI SEER database was used to assess survival data; (c) it was performed on small intestine NENs only; and (d) the main aim was to assess the risk of death, instead of the risk of progression. Finally, a different methodological approach was used (nomogram model versus prognostic index model). Consequently, a reliable comparison between the two studies is not feasible.

Another study suggested to stratify metastatic GEP-NENs into different subgroups according to the coexistence of clinical and pathological features, such as age, number of liver metastases, tumor slope, and initial surgery [8]. Based on the number of these prognostic factors, a different probability of survival was reported, again suggesting to consider more than a single variable when approaching risk factors analysis in GEP-NENs. Nevertheless, this finding was again drawn from a relatively small population ($n = 118$), before the actual NEN WHO 2010 classification was published [17], and with few data on Ki67 (available in 50 patients only), which is to date widely considered the most important risk factor for poor prognosis in NENs. On the contrary, as a result of the cooperation of five referral centers for NEN management, a large population including 283 patients with stage IV GEP-NENs with available data on Ki67 and accurate disease staging was collected in the present study, allowing us to obtain an easy-to-use tool that was effective in stratifying the risk of PD based on data that are usually available, such as Ki67 and disease extension.

According to the literature, Ki67 was confirmed to be a strong independent predictor for poor clinical outcome in terms of both PD and survival [1–3]. Ki67, as continuous variable instead of categorical variable as in the G grading system, was chosen in order to keep its predictive power and to overcome the limitations of the cut-off levels used to discriminate between different categories, as well as that of different origin of the neoplasm. Another expected risk factor was the presence of distant extra-abdominal metastases, which, again, correlated with a worse prognosis, as previously reported by several studies [7–9].

As a novel additional finding, the degree of liver involvement expressed as the proportion of liver metastatic disease (0%–25% versus 25%–50% versus >50%) was able to significantly stratify patients into three different subgroups, with an increasing risk of progression (25%–50% HR 1.50 and >50% HR 1.58 versus 0%–25% in the multivariate model). Because a standardized stratification of liver tumor burden in NENs is lacking, different percentage values have been used by several studies investigating response to therapies and patients' survival, with some of them arbitrarily proposing 25% to define limited disease [11, 21, 22] and others suggesting the alternative value of 10% [10, 23]. However, this feature represents a major issue in the clinical practice and should also be considered in clinical trial designs. In fact, most of the recent randomized control trials [10–13] have confirmed the importance of hepatic tumour load as a prognostic factor in subgroup analyses, but the proportion of liver involvement has not been a stratification factor so far. Also, the updated ENETS guidelines suggest to consider the tumor burden when approaching NEN patients with unresectable metastatic disease [24]. On these bases, a risk score based on the combination of Ki67 and the tumor burden could help select the patients in whom an early aggressive therapeutic approach is recommended.

In this study, the choice of using PD instead of survival as the main outcome is based on the evidence that PFS is a more practical and recommended end point commonly used in recent trials, as previously suggested [25]. The ability of the proposed risk score to discriminate between patients who did and did not experience PD was higher in comparison with that obtained by using the G grading stratification alone in the same set of patients, as confirmed by the ROC analysis, AUCs being 0.705 and 0.622, respectively ($p = .013$). This confirms the good accuracy of the risk score in comparison with a well-defined prognostic tool such the G grading system.

As far as the primary tumor is concerned, a trend towards a higher predictive ability of the risk score was observed in pancreatic NENs in comparison with non-pancreatic NENs (AUC 0.728 and 0.662, respectively), confirming the well-known difference, in terms of tumor behavior, deriving from the different primary tumor site [1, 2]. However, the pancreatic site did not retain its independent role when multivariate model was performed, and thus it was not included in the score. This figure, which seems to disagree with a number of previous observations, may be due to the heterogeneity of primary tumors in the group of non-pancreatic NENs, which also included NENs that, when metastatic, are usually related to worse outcome, such as gastric (type III), duodenal, and colorectal primaries.

Furthermore, it has been reported that the impact of the primary tumor site seems to decrease in the setting of advanced disease, when other factors might play a major prognostic role [2, 7, 23, 26]. Finally, the loss of statistical significance of the variable "pancreatic primary site" may be related to its correlation with the distribution of patients according to the grading system (73.1% of grade 1 neuroendocrine tumors were nonpancreatic, 83.8% of grade 3 neuroendocrine carcinomas were pancreatic).

The present study has some limitations, mainly related to the study design. Although data were collected by referral centers for the management of NENs, they were analyzed retrospectively. This may represent an inherent limitation in terms of therapeutic approaches received by the patients and possible different timing and method of follow-up programs performed by each center, which was limited by involving only referral centers with documented long-term experience for NEN patients' management. For these reasons, the direct impact of medical treatments on disease progression could not be assessed. Furthermore, as with any prognostic score, the one proposed in the present study needs to be validated in a population different from the one from which it was derived. An internal validation in the same data set by identifying different subgroups and/or by performing cross validation does not seem feasible due to the relatively small sample size and the likely risk to lose accuracy. Thus, an external validation, ideally in a prospective setting, is required to provide the evidence that the proposed risk score is transportable or generalizable to other NEN populations.

Conclusion

The present study shows that in the setting of advanced, stage IV GEP-NENs, it is possible to obtain a risk score able to predict PD by combining the specific prognostic weight of the following three factors: Ki67 value, proportion of metastatic liver involvement, and presence of extra-abdominal metastases. The score is an easy-to-use tool that may help physicians dealing with GEP-NENs to discriminate subgroups of patients with different risk of progression in order to plan tailored therapeutic approaches and specific follow-up programs as well as to select homogeneous groups of patients for future clinical trials. A validation in a prospective setting is needed to understand the real impact of the risk score in the management of GEP-NENs patients with advanced disease.

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Author Contributions

Conception/Design: Francesco Panzuto, Marianne Ellen Pavel, Anja Rinke, Patrizia Kump, Stefano Partelli, Ulrich Frank Pape, Rainer Lipp, Thomas Gress, Bertram Wiedenmann, Massimo Falconi, Gianfranco Delle Fave

Provision of study material or patients: Francesco Panzuto, Elettra Merola, Marianne Ellen Pavel, Anja Rinke, Patrizia Kump, Stefano Partelli, Maria Rinzivillo, Gianfranco Delle Fave

Collection and/or assembly of data: Francesco Panzuto, Elettra Merola, Anja Rinke, Maria Rinzivillo, Victor Rodriguez-Laval

Data analysis and interpretation: Francesco Panzuto, Massimo Falconi

Manuscript writing: Francesco Panzuto, Massimo Falconi

Final approval of manuscript: Francesco Panzuto, Elettra Merola, Marianne Ellen Pavel, Anja Rinke, Patrizia Kump, Stefano Partelli, Maria Rinzivillo, Victor Rodriguez-Laval, Ulrich Frank Pape, Rainer Lipp, Thomas Gress, Bertram Wiedenmann, Massimo Falconi, Gianfranco Delle Fave

Disclosures

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See http://www.TheOncologist.com for supplemental material available online.

For Further Reading:

Romain Coriat, Thomas Walter, Benoît Terris et al. Gastroenteropancreatic Well-Differentiated Grade 3 Neuroendocrine Tumors: Review and Position Statement. ***The Oncologist*** 2016;21:1191–1199.

Implications for Practice:

Neuroendocrine tumors presenting a number of mitoses or a Ki-67 index higher than 20% and a well-differentiated morphology have been identified and named well-differentiated grade 3 neuroendocrine tumors (NET G-3). The main localizations of NET G-3 are the pancreas, stomach, and colon. The prognosis is worse than that for NET G-2. In nonmetastatic NET G-3, surgery appeared to be the first option. The chemotherapy regimen in pancreatic NET G-3 should be in line with that implemented in NET G-1/2 when the Ki-67 index is below 55% and should be in line with that implemented for neuroendocrine carcinoma when Ki-67 is above 55%.