A New Scoring System to Predict Recurrent Disease in Grade 1 and 2 Nonfunctional Pancreatic Neuroendocrine Tumors

Cansu G. Genç, MD, Anneke P. Jilesen, MD, PhD,* Stefano Partelli, MD, PhD,† Massimo Falconi, MD, PhD,† Francesca Muffatti, MD,† Folkert J. van Kemenade, MD, PhD,‡ Susanne van Eeden, MD, PhD,§ Joanne Verheij, MD, PhD,§ Susan van Dieren, PhD,¶ Casper H. J. van Eijck, MD, PhD,|| and Elisabeth J. M. Nieveen van Dijkum, MD, PhD**

Objective: The aim of this study was to predict recurrence in patients with grade 1 or 2 nonfunctioning pancreatic neuroendocrine tumors (NF-pNET) after curative resection.

Background: Surgical resection is the preferred treatment for NF-pNET; however, recurrence occurs frequently after curative surgery, worsening prognosis of patients.

Methods: Retrospectively, patients with NF-pNET of 3 institutions were included. Patients with distant metastases, hereditary syndromes, or grade 3 tumors were excluded. Local or distant tumor recurrence was scored. Independent predictors for survival and recurrence were identified using Cox-regression analysis. The recurrence score was developed to predict recurrence within 5 years after curative resection of grade 1 to 2 NF-pNET.

Results: With a median follow-up of 51 months, 211 patients with grade 1 to 2 NF-pNET were included. Thirty-five patients (17%) developed recurrence. The 5- and 10-year disease-specific/overall survival was 98%/91% and 84%/68%, respectively. Predictors for recurrence were tumor grade 2, lymph node metastasis, and perineural invasion. On the basis of these predictors, the recurrence score was made. Discrimination [c-statistic 0.81, 95% confidence interval (95% CI) 0.75–0.87] and calibration (Hosmer Lemeshow Chi-square 11.25, $P = 0.258$) indicated that the ability of the recurrence score to identify patients at risk for recurrence is good.

Conclusions: This new scoring system could predict recurrence after curative resection of grade 1 and 2 NF-pNET. With the use of the recurrence score, less extensive follow-up could be proposed for patients with low recurrence risk. For high-risk patients, clinical trials should be initiated to investigate whether adjuvant therapy might be beneficial. External validation is ongoing due to limited availability of adequate cohorts.

Keywords: nomogram, pancreatic neuroendocrine tumors, recurrence

(*Ann Surg* 2018;267:1148–1154)

In patients with curative resected nonfunctional pancreatic neuroendocrine tumor (NF-pNET), the overall prognosis is usually favorable. The main focus during follow-up is to detect recurrence at an early stage.[1–3] However, follow-up regimens after resection of pNET are generally the same and no distinction is made between patients on the basis of the presence or absence of specific tumor characteristics. Reliable recurrence rates are difficult to deduct from literature because of the rarity of the disease and the inhomogeneous group of patients with resected pNETs. Most studies include patients with hereditary syndromes, hormonal overproduction, incidentally detected pNET, and patients with metastases or locally advanced disease.[4–8] All these patients have a different probability of tumor recurrence and survival.

In general practice, knowledge about the prognosis of a patient provides support when determining the frequency of the follow-up visits. Better estimation of long-term prognosis of curable patients is therefore desirable. With this knowledge, postoperative management can be customized on the basis of the expected risk of recurrence, as is common in some other malignancies.[9] This approach can have advantages for the patient as well as the hospital and the health care system. Despite international guidelines,[10,11] there is still much uncertainty about the frequency of follow-up visits and radiological imaging. Current European Neuroendocrine Tumor Society (ENETS) and North American Neuroendocrine Tumor Society (NANETS) guidelines provide recommendations on the management of pNET but do not include statements on postoperative follow-up regimens. Moreover, the latest guidelines propose a conservative approach in the surgical management of small tumors <2 cm. This opinion is based on retrospective analyses and the indolent nature of these tumors. This strategy could be adopted for a select group of patients after surgical resection of tumors without unfavorable characteristics.

In comparison with other types of cancer, including pancreatic cancer, adjuvant treatment after surgical resection is not recommended for patients with NF-pNET.[4] In metastatic patients, different treatment options are available in order to reduce tumor load, to inhibit tumor growth, or to alleviate these symptoms.[12] These include chemotherapy,[13,14] Long-acting somatostatin analogues,[15,16] mammalian target of rapamycin or tyrosine kinase inhibitors (everolimus, sunitinib),[17,18] and peptide receptor radionuclide therapy (PRRT).[19] Theoretically, one or more of these treatment options could serve as an adjuvant therapy in patient swith a risk of recurrent disease after curative resection. Clinical trials are needed to evaluate this benefit. However, it is difficult to identify high-risk patients, most likely explaining why this has never been investigated before.

Until now, it is unclear which combination of risk factors for recurrence matter most in patients with grade 1 or 2 NF-pNETs in daily practice. A recent study by Birnbaum et al[20] reported tumor size and tumor grade to be independent predictors for recurrence in patients with sporadic NF-pNET without distant metastases. However, studies on predictive factors are scarce and frequently include patients with distant metastasis present during surgical resection,

From the *Department of Surgery, Academic Medical Center, Amsterdam, the Netherlands; †Pancreatic Surgery Unit, Pancreas Translational & Research Institute, Scientific Institute San Raffaelle Hospital & University Vita e Salute, Milano, Italy; ‡Department of Pathology, Erasmus Medical Center, Rotterdam, the Netherlands; §Department of Pathology, Academic Medical Center, Amsterdam, the Netherlands; ¶Department of Methodology and Statistic CRU, Academic Medical Center, Amsterdam, the Netherlands; and ||Department of Surgery, Erasmus Medical Center, Rotterdam, the Netherlands.

C.G. Genc and A.P.J. Jilesen contributed equally to this work and are therefore shared first authors.

Funding for C.G. Genç was provided by Ipsen.

The authors report no conflict of interest, no disclaimers.

Reprints: Elisabeth J.M. Nieveen-van Dijkum, MD, Department of Surgery, Academic Medical Center, Meibergdreef 9; PO Box 22660, 1105 AZ Amsterdam, the Netherlands. E-mail: e.j.nieveenvandijkum@amc.uva.nl.

ISSN: 0003-4932/17/26706-1148

DOI: 10.1097/SLA.0000000000002123

hereditary syndromes, or high-grade carcinoma. The aim of this study was to analyze the long-term outcome in a very selective group of patients with low- to intermediate-grade NF-pNET without hereditary syndromes, grade 3 tumors, or distant metastasis at time of diagnosis. Recurrence rates and significant predictors for recurrence were analyzed. With these predictors, the recurrence score was developed to calculate the risk of recurrence of the individual patient and to identify high-risk patients after curative resection.

PATIENTS AND METHODS

Retrospectively, all NF-pNET with a curative resection from 1992 to 2015 of 3 academic institutions were included: the Erasmus Medical Center in Rotterdam and the Academic Medical Center in Amsterdam, both in the Netherlands, and the Ospedale San Raffaele in Milano, Italy. All institutions are high-volume centers for pancreatic surgery and specialized in the treatment of neuroendocrine tumors. The pathology reports of all pancreas resections in the selected period were reviewed for the diagnosis of pNET. Patients were included if a histopathology-proven pNET was present. Inclusion criteria for this study were adults with a curative resected grade 1 or 2 NF-pNET without distant metastases at the time of diagnosis. Patients with ampullary or duodenal NETs and all patients with (unresectable) locally advanced disease or distant metastases, successfully treated or not, were excluded. Patients with hereditary syndromes, such as multiple endocrine neoplasia type 1 (MEN-1) or Von Hippel-Lindau syndrome (VHL) or with grade 3 NF-pNET, even if diagnosed after resection of the pNET, were also excluded.

NF-pNET was defined as a pNET without clinical syndrome based on symptoms associated with hormone overproduction. The medical records, radiological imaging reports, and operation reports were reviewed for the demographics and clinical data, including age of surgery, sex, tumor size (based on preoperative radiological imaging), tumor location, and type of surgery. Radiological imaging consisted of abdominal computed tomography (CT) scan and in some patients of endoscopic ultrasonography and/or octreotide scintigraphy (Octreoscan/^{68}Ga PET-CT).

Depending on tumor location, pancreatoduodenectomy, distal, or total pancreatectomy was performed. Central pancreatectomy or tumor enucleation was performed in patients with small pNET far enough from the pancreatic duct. Lymphadenectomy was not routinely performed in patients with tumor enucleation. All included NF-pNET were reassessed with an emphasis on for tumor grade, lymph node involvement, vascular, or perineural invasion by 3 experienced pathologists (FJ van K, S van E, and JV). Mitotic count and histological grade were based on the World Health Organization (WHO) classification of 2010 in grade 1 to 3.[21] Resection margins were classified according the Royal College of Pathologists.[22] Completely excised tumors were classified as R0, and tumors with microscopic margin involvement <1 mm were classified as R1. Pathology was performed according to the local protocols.

Major complications after surgery were defined as pancreatic fistula grade B/C, delayed gastric emptying grade B/C, or postoperative bleeding grade B/C, scored according to the ISGPF classifications.[23–25]

As small pNET may show a more indolent recurrence pattern, separate analyses were performed concerning patient with NF-pNET <2 cm.

Besides routine control of physical symptoms, the follow-up program consisted of physical examination, laboratory tests, and radiological imaging. The first year after surgery, patients were seen every 6 months. Thereafter, follow-up was annually or in case of elevated chromogranin A or dubious radiology results continued every 6 months. Follow-up was indicated for 10 years after surgery. Recurrence was defined as local recurrence in the pancreas, new localization in lymph nodes, or the development of distant metastases. Recurrence-free survival was defined as the percentage of patients without recurrence after resection. Disease-specific survival was the percentage of patients who have not died due to pNET.

Statistical Analysis

Statistical analyses were performed using SPSS Statistics for Windows version 23.0 (IBM Corp., Armonk, NY) and R for Windows version 3.3.1 via the R-studio interface (2016 The R Foundation For Statistical Computing, platform i386-w64-mingw32/i386 [32-bit]) (cran-Rproject.org). On the basis of the distribution, the data were described with mean and standard deviation (SD) or median and interquartile range (IQR). For categorical data, the number and proportion (%) were displayed. Kaplan-Meier curves were used to determine the median time for recurrence and survival. To identify predictors for survival within 10 years after curative surgery, a Cox proportional hazard regression was performed. This was repeated for predictors for recurrence within 5 years. The assumption of proportional hazard regression was tested by visually inspecting the log minus log plots. No violations were detected for any of the variables included in the model. The results were presented with the hazard ratio (HR) and the 95% confidence interval (95% CI). To determine predictors for recurrence, a backwards selection with a P value of <0.05 was used to select the variables one by one from the multivariable Cox regression analysis. On the basis of the HRs of the significant predictors of the multivariable Cox regression, a scoring system was made. The HR was translated into a score (the recurrence score) for each predictor and multiplied by 10 to prevent loss of information due to rounding. The overall recurrence score corresponds to the risk for recurrence within 5 years after a curative resection. Receiver operating characteristic (ROC) analysis was performed to determine the most suitable cut-off of the recurrence score. Both the Youden index and the Log rank method were used to determine the recurrence score with the most appropriate sensitivity and specificity. Model performance was assessed by measurements of discrimination and calibration. Discrimination is the ability to separate the persons who will have recurrence from the persons who will not have recurrence. Calibration is the ability to correctly quantify the observed absolute risk. The discriminative ability of the model was examined by calculating Harrel c-statistic[26] with 95% CI and the calibration of the model was assessed by calculating the goodness of fit Hosmer-Lemeshow Chi-square test. Moreover, we examined the discrimination of the WHO grade model and compared the c-statistics of the 2 models using a z-test. The c-statistic may vary from 0.5 to 1.0. A discriminative value of 0.5 was considered as good as chance and a value above 0.9 was excellent. Calibration was not significant; the prediction of the model was comparable with the actual outcome. A 2-sided P value <0.05 was considered significant. The Medical Ethics Review Committee has approved the study.

RESULTS

With a mean age of 60 years (range 19 to 83) at diagnosis, 211 patients were included in the analysis. Patient and tumor characteristics are listed in Table 1. In total, 139 patients had a G1 tumor. Median tumor size was 25 mm (IQR 15 to 44) and most frequently located in the pancreatic head (40%). Pancreatoduodenectomy was performed in 64 (30%), left pancreatectomy in 101 (48%), tumor enucleation in 29 (14%), central pancreatectomy in 11 (5%), and total pancreatectomy in 5 (2%) patients. Postoperatively, major complications were seen in 58 patients (27%) and consisted of pancreatic fistula grade B/C in 46 patients (22%), delayed gastric

TABLE 1. Patient and Tumor Characteristics (n = 211), n (%)

Age, median	60 (IQR 50–66)
Male	103 (48.8%)
Tumor location	
Head	80 (37.9%)
Body	59 (28%)
Tail	72 (34.1%)
Tumor grade	
G1	139 (65.9%)
G2	72 (34.1%)
Tumor size, median (mm)	25 (IQR 15–44)
Major complications	58 (26.5%)
Resection margin	
R0	179 (84.8%)
R1	32 (15.2%)
Positive lymph nodes	51 (24.2%)
Perineural invasion	28 (13.3%)
Vascular invasion	50 (23.7)
Mortality	19 (9%)
Disease related deaths	9 (4.3%)
Tumors <2 cm	84 (39.8%)
Size, median	14 (IQR 11–17)
G2	14 (16.7%)
R1 resection margin	11 (13.1%)
Positive lymph nodes	10 (11.9%)
Recurrence	4 (4.8%)
Mortality	7 (8.3%)
Recurrence	35 (16.6%)
G2	24 (68.6%)
R1 resection margin	10 (28.6%)
Positive lymph nodes	20 (57.1%)
Local recurrence	24 (68.6%)
<5 years after surgery	32 (91.4%)

emptying grade B/C in 7 patients (3%), and postoperative bleeding grade B/C in 2 patients (1%). One patient experienced a pancreatic fistula and postoperative bleeding. Complete resection (R0) was performed in 179 patients (85%), whereas the remaining 32 (15%) showed either microscopic tumor cells at the resection margin or within 1 mm (R1). R1 resections were found in 12 (18.8%) patients who underwent pancreatoduodenectomy, 8 (7.9%) patients who underwent left pancreatectomy, 6 (20.7%) patients who underwent enucleation, 4 (36.4%) patients with central pancreatectomy, and 2 (40%) with a total pancreatectomy.

Long-term Follow-up

Median follow-up time was 51 months (IQR 29 to 72). Recurrence was seen in 35 patients (17%): 16 (46%) after pancreatoduodenectomy, 14 (40%) after left pancreatectomy, 3 (9%) after enucleation, 1 after central pancreatectomy, and 1 after total pancreatectomy. In 24 patients (69%), the recurrence was located in the pancreatic remnant, whereas 5 patients (14%) developed recurrence as distant metastases and 1 had lymph node metastasis. Mean tumor size of patients with recurrence was 36.8 versus 32.9 mm for patients without recurrence ($P > 0.05$). Grade 1 was seen in 11 (31.4%) patients and grade 2 in 24 (68.6%) patients. Ten (28.6%) patients with recurrence had R1 resection and 20 (57.1%) had lymph node metastases in the resected specimen of the initial surgery. Median time to recurrence was 43 months (IQR 23 to 62). Mean survival of patients without recurrence was 163 months, compared with 139 months for patients with recurrence ($P = 0.011$), Fig. 1. Overall, 19 patients (9%) deceased, including 9 patients due to tumor progression. The 5- and 10-year disease-specific survival was 98% and 84%, respectively. Overall survival was 91% within 5 years and 68% within 10 years. Recurrence free survival of all patients is presented in Fig. 1.

Tumor Size <2 cm

On the basis of the latest ENETS guidelines, a subanalysis for tumors <2 cm was performed. In this cohort, 84 of the 211 patients had a tumor smaller than 2 cm. Thirty-seven patients were male (44%) and 47 female (56%), with a median tumor size of 14 mm. Tumor location was equally distributed between the head, corpus, and tail of the pancreas (28.6%, 36.9%, and 34.5%, respectively). Enucleations were performed in 23 cases (27.4%); the remaining 51 patients underwent pancreatic resection. Eleven patients had a R1 resection (13.1%) and 14 patients had a grade 2 tumor (16.7%). Lymph node metastases were present in 10 patients (11.9%) and perineural invasion was seen in 8 patients (9.5%). Recurrence was seen in 4 of 84 patients (4.8%). Seven patients died, of whom 2 were related to pNET. From univariable analysis, tumor grade (HR 18.5, 95% CI 1.91–179.13, $P = 0.012$), positive lymph nodes in the resected specimen (HR 7.8, 95% CI 1.09–55.16, $P = 0.041$), perineural invasion (HR 30.7, 95% CI 3.19–295.74, $P = 0.003$), and vascular invasion (HR 6.9, 95% CI 0.97–49.03, $P = 0.05$) were predictors of recurrence within 5 years after curative surgery. Multivariable analysis was not performed due to patient numbers. Disease-specific survival was 97% in 5 years and the same for 10 years. The 5- and 10-year overall-survival was 91% and 79%, respectively.

Predictors for Survival and Recurrence

A Cox regression analysis was performed to identify risk factors for mortality within 10 years after surgery (Table 2). pNET-related death was associated with perineural invasion (HR 3.8, 95% CI 1.51–9.63) and recurrence (HR 2.7, 95%CI 1.4–6.56). Cox regression analysis was repeated for predictors for recurrence within 5 years after surgery (Table 3). Univariable analysis was significant for tumor size, R1 resection, tumor grade, positive lymph nodes in the resected specimen, and perineural invasion. With a backwards selection, tumor grade (HR 4.07, 95% CI 1.87–8.84), positive lymph nodes in the resected specimen (HR 2.44, 95% CI 1.17–5.09), and perineural invasion (HR2.38, 95% CI 1.11–5.10) were significant to predict recurrence in the multivariable analysis. Recurrence within 5 years after curative resection was seen in 25% of patients with only tumor grade 2, in 30% of patients with only positive lymph nodes, and in 14% of patients with perineural invasion. In the presence of 2 predictive factors, recurrence was seen in 38% of patients with a grade 2 tumor and positive lymph nodes, 40% of patients with positive lymph nodes and perineural invasion, and in 33% of patients with a grade 2 tumor and perineural invasion. When all predictive factors were present, 60% of the patients showed recurrence. Of the 107 patients with none of these factors present, only 2 developed recurrent disease.

The Recurrence Score

A scoring system was made on the basis of the independent predictors from the multivariable Cox regression analysis (Fig. 2). The recurrence score predicts the probability to develop recurrence within 5 years after curative resection in patients with a grade 1 or 2 NF-pNET. For each patient, a total recurrence score was calculated on the basis of the presence or absence of these factors. Patients with recurrent disease showed significantly higher recurrence scores (49.3) than the recurrence scores of patients without recurrence (17.7, $P < 0.001$).

The recurrence score was internally validated. The discriminative ability of the recurrence score was good, with a Harrel c-statistic of 0.81 (95% CI 0.75–0.87) and a Hosmer Lemeshow Chi-square test of 11.25 ($P = 0.258$). In practice, the WHO grading is used to predict recurrence.[15] The discrimination of the WHO grading

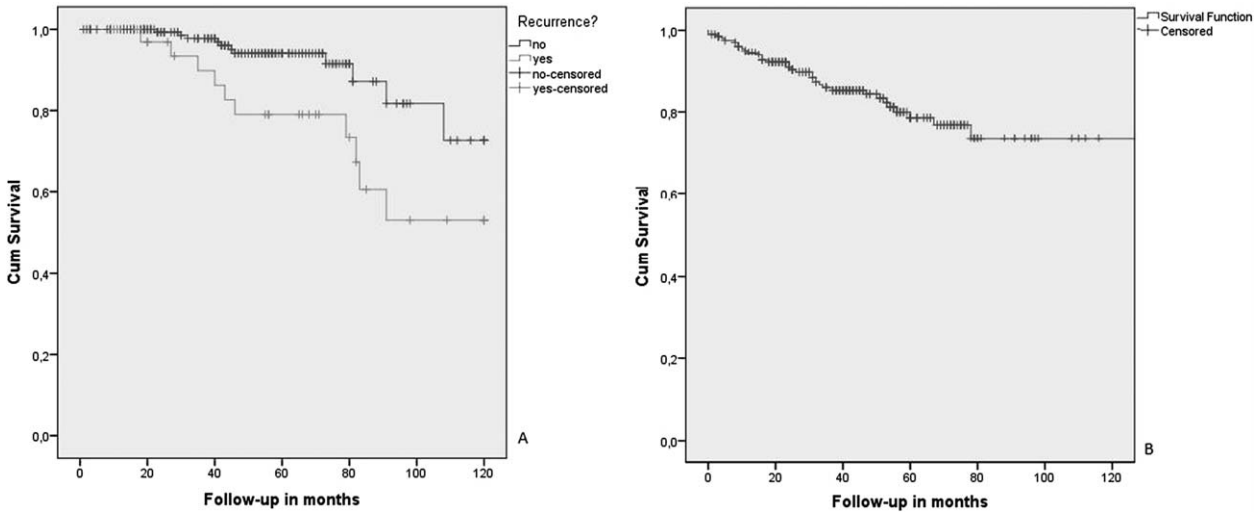

FIGURE 1. Kaplan-Meier analysis of patients with a grade 1 or 2 NF-pNET. A, Ten-year overall survival of patients with and without recurrent disease. B, Ten-year recurrence-free survival of all patients.

was lower than the recurrence score with a c-statistic of 0.72 (95% CI 0.64–0.79). However close, this was not significant ($P = 0.059$). Calibration of this model was not examined because it only consists of 2 variables, grade 1 and grade 2.

To determine the appropriate cut-off to identify high-risk patients for recurrence within 5 years after surgery, an ROC analysis of the recurrence score was performed, Fig. 3. This resulted in an optimal recurrence score cut-off of 24, with a sensitivity of 91% and specificity of 62%. Kaplan-Meier analysis showed a significant difference in recurrence within 5 years after surgery for patients with a recurrence score below 24 with a mean time to recurrence of 59 months, compared with patients with a recurrence score of 24 and higher and mean time to recurrence of 46.9 months ($P < 0.001$). Mean 10-year disease-specific and overall survival was 181.3 months (95% CI 178.0–184.6) and 110.3 months (95% CI 103.4–117.3), respectively, for patients with a recurrence score below 24, compared with 167.0 months (95% CI 140–193.6) and 99.4 months (95% CI 90.3–108.6), respectively, for patients with a recurrence score of 24 and higher (DSS $P = 0.008$, OS $P = 0.038$).

TABLE 2. Predictors for Mortality Within 10 Years

	Univariable Cox Regression			Multivariable Cox Regression		
	HR	**95% CI**	***P***	**HR**	**95% CI**	***P***
Male sex	1.218	0.515–2.877	0.654			
Age, y						
<40	ref	ref	ref			
40–50	0.307	0.019–4.919	0.404			
51–60	1.276	0.153–10.610	0.822			
61–70	1.949	0.247–15.412	0.527			
>70	2.300	0.256–20.624	0.457			
Tumor location						
Head	ref	ref	ref			
Body	0.684	0.248–1.884	0.463			
Tail	0.629	0.214–1.846	0.399			
Tumor size						
<2 cm	ref	ref	ref			
2–4 cm	1.249	0.464–3.361	0.659			
>4 cm	1.088	0.345–3.431	0.885			
Major complication	0.660	0.244–1.787	0.414			
R1 resection	2.439	0.980–6.072	0.055			
Tumor grade 2	1.816	0.768–4.291	0.174			
Positive lymph nodes	2.105	0.872–5.085	0.098			
Perineural invasion	4.130	1.644–10.375	0.003	3.813	1.510–9.627	0.005
Vascular invasion	1.755	0.723–4.263	0.214			
Recurrence	2.977	1.237–7.169	0.015	2.730	1.137–6.554	0.025

Ref indicates reference.

TABLE 3. Predictors for Recurrence Within 5 Years

	Univariable Cox Regression			Multivariable Cox Regression		
	HR	95% CI	*P*	HR	95% CI	*P*
Male sex	1.149	0.573–2.3	0.696			
Age						
<40	ref	ref	ref			
40–50	0.249	0.05–1.236	0.089			
51–60	0.775	0.213–2.818	0.699			
61–70	0.830	0.238–2.891	0.769			
>70	0.294	0.049–1.763	0.181			
Tumor location						
Head	ref	ref	ref			
Body	1.969	0.842–4.605	0.118			
Tail	1.099	0.412–2.929	0.851			
Tumor size						
<2 cm	ref	ref	ref	—	—	—
2–4 cm	3.957	1.302–12.028	0.015			
>4 cm	5.920	1.946–18.008	0.002			
Major complication	0.932	0.531–1.636	0.806			
R1 resection	2.722	1.286–5.763	0.009	—	—	—
Tumor grade 2	5.625	2.653–11.927	<0.001	4.066	1.871–8.835	<0.001
Positive lymph nodes	4.039	2.014–8.102	<0.001	2.439	1.17–5.085	0.017
Perineural invasion	4.088	1.970–8.485	<0.001	2.380	1.111–5.097	0.026
Vascular invasion	3.518	1.759–7.037	<0.001	—	—	—

Ref indicates reference.

DISCUSSION

Patients with pancreatic neuroendocrine tumors generally have a favorable prognosis. However, in case of recurrence, these patients have a poor survival. Assessment of risk factors for recurrence could therefore be of importance. In this study, the recurrence score is presented that can identify patients at risk to develop recurrence within 5 years after curative surgery of a grade 1 or grade 2 NF-pNET. For these patients, adjuvant therapy after curative resection might improve prognostic outcomes. For these patients, postoperative follow-up regimens can be customized on the basis of their risk profile. Further research is warranted to investigate whether adjuvant therapy after curative resection might improve prognostic outcomes.

The recurrence score can be calculated from the presented scoring-system based on the presence or absence of predictors for recurrence. The predictors presented in this study correspond to the ones reported in the literature and can be translated into a probability

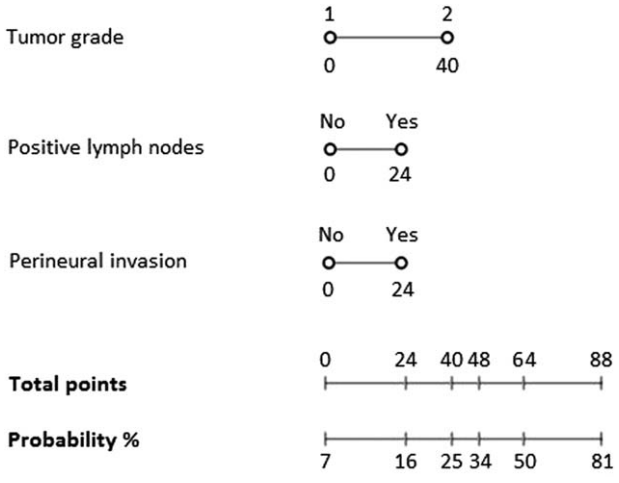

FIGURE 2. The recurrence score to predict recurrent disease within 5 years after curative resection. Patients score points for the presence or absence of each of the tumor characteristics. The total points can be translated into the probability of recurrent disease within 5 years after curative surgery.

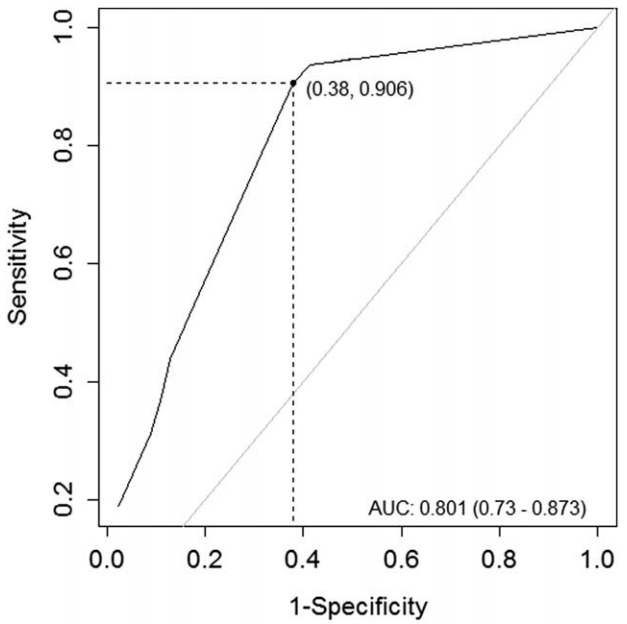

FIGURE 3. ROC analysis of recurrence scores to determine the most appropriate cut-off to identify high-risk patients for recurrence within 5 years after curative surgery.

to develop recurrence.[20,27–29] With the recurrence score, a selection of patients who have a high or low risk for recurrence after curative resection can be made. For example, patients with a recurrence score of 0 have a 7% risk of recurrence within 5 years. Cost-effectiveness of follow-up with imaging should be evaluated for this group of patients. On the contrary, patients with a recurrence score of 40 or higher have a 25% or more risk of recurrence, which will be a clear indication for follow-up with imaging techniques and possibly even adjuvant treatment to reduce this recurrence risk. To our knowledge, no literature exists that describes the role and effects of adjuvant therapy for patients after curative surgery of pNET. On the basis of the treatment of patients with advanced pNET, different treatment options are available that can serve as adjuvant treatment.[30] The presented recurrence score sets a basis for future trials to select patients to investigate the role of adjuvant therapy based on risk stratification for recurrent pNET.

According to the new ENETS guidelines, patients with NF-pNET smaller than 2 cm of size no longer have to undergo surgery to achieve optimal oncologic outcomes. Evidence for these changes in the management of this disease is based on retrospective analyses only.[31–33] Prospective cohorts are necessary to confirm this assumption. Theoretically, the same strategy could be translated to low-risk patients without unfavorable characteristics after surgical resection of pNET.

In this cohort, the recurrence score was a better predictor of recurrence within 5 years than tumor grade of the WHO classification, with an almost statistically significant lower c-statistic of 0.72 ($P = 0.058$). This effect may be explained by the comparison of a model with 2 extra independent predictors in comparison with 1 in the model of the WHO. However, in the recurrence score, grading is the strongest independent predictor with an HR of 4.01.

Most studies on risk factors for recurrence after resection of pNET include patients with distant metastases present at resection, functional and nonfunctional tumors combined or patients with familial syndromes.[28,34–36] By including these patients, the results are difficult to interpret and sometimes misleading, as the risk of recurrence and survival is different for these patients. In this study, a very selective group of NF-pNET was included and analyzed on risk factors for recurrent disease. These strict criteria limit the amount of patients suitable for inclusion considerably. To overcome this problem, cohorts from experienced international academic centers with close relations to the European Neuroendocrine Tumor Society (ENETS) were combined to increase the sample size and therefore reliability of the recurrence score. However, the same limitations were experienced in finding an adequate validation cohort. External validation is needed in order to investigate whether the recurrence score is useful in another population. Because the relevance of the recurrence score can be of clinical value, we have decided to publish these data while external validation is ongoing.

The majority of the patients in this study showed recurrence located in the pancreatic remnants (69%) as opposed to distant metastases. In the literature, there is inconsistency on the definition of recurrence. Some studies only score recurrence when it is diagnosed as distant metastases,[20,37,38] whereas new localization of tumor tissue in the remnant pancreas or regional lymph nodes should also be considered as recurrence. In addition, it is not yet known if recurrence occurs more frequently locally or as distant metastases. Therefore, it is unclear whether these results are influenced by selection bias.

There are some limitations in this study. First is the extended inclusion period. In the beginning of the study, the follow-up program was not standardized for every patient. For example, in patients with elevated chromogranin A, radiological imaging was more frequently performed. On the contrary, in patients with a grade 1 tumor without positive lymph nodes, a less strict follow-up program was followed. This may bias the time to detect recurrence. However, until now, there is no exact follow-up program in the guidelines[4,10,39] Furthermore, it has been a challenge to obtain a cohort of this size. An unrealistic large cohort is needed to meet up to the standard recommendations for Cox regression analysis. As this study investigated a rare disease with a recurrence rate that corresponds to the literature, Cox regression analysis has been performed nevertheless and 3 predictors have been included in the recurrence score.[1–3]

In this cohort of 211 NF-pNET patients, microscopic positive resection margins were seen in 15% after pancreatic resection. Similar results have been reported in studies with comparable patient populations.[38,40] However, it is noteworthy that in this cohort, incomplete resections were seen in 17.4% of the patients that underwent a surgical resection before 2012, whereas this was 8.9% from 2012 to 2015. The proportion of patients with an incomplete resection might therefore be explained by the period in which they underwent surgery. In previous years, it was generally assumed that oncologic outcome was not affected by positive resection margins, due to the indolent nature of pNET. Even in the present day, the role of resection margins remains unclear. Without this knowledge, surgeons balance the risk of postoperative complications against the prognostic value of an extensive resection.

Our future goal in the treatment of grade 1 or 2 NF-pNET is adjuvant treatment for high-risk patients with NF-pNET based on the recurrence score. External validation with a different cohort is needed in order to investigate whether this scoring system is valid for worldwide use. Furthermore, clinical trials are needed to investigate whether these high-risk patients may benefit from adjuvant treatment after curative resection. It is beyond the topic of this study to discuss the most optimal design for future research.

Conclusion

Tumor grade, positive lymph nodes, and perineural invasion are independent predictors for tumor recurrence. On the basis of these risk factors, the recurrence score is presented to predict recurrence after surgical resection of grade 1 and 2 NF-pNETs. External validation is required to investigate whether this scoring system can be used in the clinical practice. Patients with a recurrence score $\geq$24 are considered to be high-risk and may benefit from adjuvant therapy.

REFERENCES

1. Bettini R, Partelli S, Boninsegna L, et al. Tumor size correlates with malignancy in nonfunctioning pancreatic endocrine tumor. *Surgery*. 2011;150:75–82.
2. Cherenfant J, Stocker SJ, Gage MK, et al. Predicting aggressive behavior in nonfunctioning pancreatic neuroendocrine tumors. *Surgery*. 2013;154:785–791; discussion 791–793.
3. Wong J, Fulp WJ, Strosberg JR, et al. Predictors of lymph node metastases and impact on survival in resected pancreatic neuroendocrine tumors: a single-center experience. *Am J Surg*. 2014;208:775–780.
4. Falconi M, Bartsch DK, Eriksson B, et al. ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms of the digestive system: well-differentiated pancreatic non-functioning tumors. *Neuroendocrinology*. 2012;95:120–134.
5. Fischer L, Bergmann F, Schimmack S, et al. Outcome of surgery for pancreatic neuroendocrine neoplasms. *Br J Surg*. 2014;101:1405–1412.
6. Mehrabi A, Fischer L, Hafezi M, et al. A systematic review of localization, surgical treatment options, and outcome of insulinoma. *Pancreas*. 2014;43:675–686.
7. Modlin IM, Oberg K, Chung DC, et al. Gastroenteropancreatic neuroendocrine tumours. *Lancet Oncol*. 2008;9:61–72.
8. Vagefi PA, Razo O, Deshpande V, et al. Evolving patterns in the detection and outcomes of pancreatic neuroendocrine neoplasms: the Massachusetts General Hospital experience from 1977 to 2005. *Arch Surg*. 2007;142:347–354.

9. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*. 2016;26:1–133.
10. Falconi M, Eriksson B, Kaltsas G, et al. ENETS consensus guidelines update for the management of patients with functional pancreatic neuroendocrine tumors and non-functional pancreatic neuroendocrine tumors. *Neuroendocrinology.* 2016;103:153–171.
11. Kunz PL, Reidy-Lagunes D, Anthony LB, et al. Consensus guidelines for the management and treatment of neuroendocrine tumors. *Pancreas*. 2013;42:557–577.
12. Castellano D, Grande E, Valle J, et al. Expert consensus for the management of advanced or metastatic pancreatic neuroendocrine and carcinoid tumors. *Cancer Chemother Pharmacol*. 2015;75:1099–1114.
13. Moertel CG, Lefkopoulo M, Lipsitz S, et al. Streptozocin-doxorubicin, streptozocin-fluorouracil or chlorozotocin in the treatment of advanced islet-cell carcinoma. *N Engl J Med*. 1992;326:519–523.
14. Ramirez RA, Beyer DT, Chauhan A, et al. The role of capecitabine/temozolomide in metastatic neuroendocrine tumors. *Oncologist*. 2016;21:671–675.
15. Caplin ME, Pavel M, Ruszniewski P. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med*. 2014;371:1556–1557.
16. Rinke A, Muller HH, Schade-Brittinger C, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *J Clin Oncol*. 2009;27:4656–4663.
17. Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med*. 2011;364:501–513.
18. Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med*. 2011;364:514–523.
19. Bergsma H, van Vliet EI, Teunissen JJ, et al. Peptide receptor radionuclide therapy (PRRT) for GEP-NETs. *Best Pract Res Clin Gastroenterol*. 2012;26:867–881.
20. Birnbaum DJ, Gaujoux S, Cherif R, et al. Sporadic nonfunctioning pancreatic neuroendocrine tumors: prognostic significance of incidental diagnosis. *Surgery.* 2014;155:13–21.
21. Bosman FT, Carneiro F, Hruban RH, Theise ND. International Agency for Research on Cancer (IARC), volume 3. WHO Classification of Tumors, fourth edition. Lyon; 2010;13.
22. Stephenson TJ, Cross SS, Chetty R. Standards and datasets for reporting cancers dataset for neuroendocrine tumors of the gastrointestinal tract including pancreas (3rd edition). *R Coll Pathol*. 2013;12–13. http://ukeps.com/docs/gimds.pdf.
23. Bassi C, Dervenis C, Butturini G, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery.* 2005;138:8–13.
24. Welsch T, Eisele H, Zschabitz S, et al. Critical appraisal of the International Study Group of Pancreatic Surgery (ISGPS) consensus definition of postoperative hemorrhage after pancreatoduodenectomy. *Langenbecks Arch Surg*. 2011;396:783–791.
25. Wente MN, Bassi C, Dervenis C, et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery.* 2007;142:761–768.
26. Newson R. Confidence intervals for rank statistics: percentile slopes, differences, and ratios. *Stata J*. 2006;6:497–520.
27. Tsutsumi K, Ohtsuka T, Fujino M, et al. Analysis of risk factors for recurrence after curative resection of well-differentiated pancreatic neuroendocrine tumors based on the new grading classification. *J Hepatobiliary Pancreat Sci*. 2014;21:418–425.
28. Hamilton NA, Liu TC, Cavatiao A, et al. Ki-67 predicts disease recurrence and poor prognosis in pancreatic neuroendocrine neoplasms. *Surgery.* 2012;152:107–113.
29. Strosberg JR, Cheema A, Weber JM, et al. Relapse-free survival in patients with nonmetastatic, surgically resected pancreatic neuroendocrine tumors: an analysis of the AJCC and ENETS staging classifications. *Ann Surg*. 2012;256:321–325.
30. Pavel M, Baudin E, Couvelard A, et al. ENETS Consensus Guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hindgut, and unknown primary. *Neuroendocrinology.* 2012;95:157–176.
31. Crippa S, Partelli S, Zamboni G, et al. Incidental diagnosis as prognostic factor in different tumor stages of nonfunctioning pancreatic endocrine tumors. *Surgery.* 2014;155:145–153.
32. Cheema A, Weber J, Strosberg JR. Incidental detection of pancreatic neuroendocrine tumors: an analysis of incidence and outcomes. *Ann Surg Oncol*. 2012;19:2932–2936.
33. Gaujoux S, Partelli S, Maire F, et al. Observational study of natural history of small sporadic nonfunctioning pancreatic neuroendocrine tumors. *J Clin Endocrinol Metab.* 2013;98:4784–4789.
34. Boninsegna L, Panzuto F, Partelli S, et al. Malignant pancreatic neuroendocrine tumour: lymph node ratio and Ki67 are predictors of recurrence after curative resections. *Eur J Cancer.* 2012;48:1608–1615.
35. Oh TG, Chung MJ, Park JY, et al. Prognostic factors and characteristics of pancreatic neuroendocrine tumors: single center experience. *Yonsei Med J*. 2012;53:944–951.
36. Zagar TM, White RR, Willett CG, et al. Resected pancreatic neuroendocrine tumors: patterns of failure and disease-related outcomes with or without radiotherapy. *Int J Radiat Oncol Biol Phys*. 2012;83:1126–1131.
37. Ferrone CR, Tang LH, Tomlinson J, et al. Determining prognosis in patients with pancreatic endocrine neoplasms: can the WHO classification system be simplified? *J Clin Oncol*. 2007;25:5609–5615.
38. Solorzano CC, Lee JE, Pisters PW, et al. Nonfunctioning islet cell carcinoma of the pancreas: survival results in a contemporary series of 163 patients. *Surgery.* 2001;130:1078–1085.
39. Kulke MH, Anthony LB, Bushnell DL, et al. NANETS treatment guidelines: well-differentiated neuroendocrine tumors of the stomach and pancreas. *Pancreas*. 2010;39:735–752.
40. Ballian N, Loeffler AG, Rajamanickam V, et al. A simplified prognostic system for resected pancreatic neuroendocrine neoplasms. *HPB (Oxford)*. 2009;11:422–428.