Defining Biological Borderline Resectable Non-functioning Pancreatic Neuroendocrine Tumors (NF-PanNETs)

A Predictive Model for Preoperative Assessment of Early Recurrence Risk

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Objective: This study aimed to develop and validate a preoperative predictive model to identify patients at high risk of early recurrence (ER), with a view to establish a framework for biological borderline resectability of non-functioning pancreatic neuroendocrine tumors (NF-PanNETs).

Background: Radical surgery is curative for most localized NF-PanNETs, but a subset of patients experiences ER. No standardized criteria define preoperative high-risk disease.

Methods: A retrospective multicentric study was conducted at 3 tertiary centers. Patients undergoing curative resection for localized NF-PanNETs were included, and preoperative clinicopathologic and imaging variables were analyzed. ER was defined as a recurrence within 24 months. A classification tree model was developed, and performance was assessed using the area under the curve (AUC) of the receiver operating characteristic curve.

Results: A total of 496 patients were analyzed, with 290 in the derivation cohort and 206 in the validation cohort. ER occurred in 55 patients (11%), including 26 (9%) in the derivation and 29 (14%) in the validation cohort. The median disease-free survival for ER patients was 16 months (interquartile range: 10–20 months). Neoplastic venous thrombosis was the strongest predictor of ER, with an ER probability of 71%. Among patients without venous thrombosis, those with a Ki-67 index $\geq 5\%$ and tumor size ≥ 3 cm had an ER probability of 41% in case of adenopathy and 19% otherwise. The model achieved an AUC of 0.91 in the derivation cohort and 0.84 in the validation cohort.

Conclusions: This externally validated model provides a reliable preoperative tool to identify NF-PanNETs at high risk of ER and introduces the concept of biological borderline resectable NF-PanNETs.

Key Words: biological borderline resectable, disease-free survival, early recurrence, Ki-67 index, non-functioning pancreatic neuroendocrine tumors, preoperative predictive model, venous thrombosis

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In recent years, surgical indications for localized and nonmetastatic non-functioning pancreatic neuroendocrine tumors (NF-PanNETs) have been refined due to a better understanding of their biological behavior.[1] Although radical surgery remains the cornerstone of treatment for localized disease, recurrence rates range from 20% to 30%.[2–7] A subset of those patients experiences early recurrence (ER) despite radical resection, highlighting aggressive tumor biology and the need for improved risk stratification to better tailor management to improve outcomes.[8] To date, there are no established indications for perioperative therapy in NF-PanNETs. This is mostly owing to limited understanding of which patients would benefit from it, whether as preoperative therapy to test biology or downstage to resectability, or to reduce risk of recurrence. Identifying patients at high risk of ER could pave the way for personalized treatment strategies and sequencing, such as the use of neoadjuvant therapies (such as peptide receptor radionuclide therapy or cytotoxic chemotherapy).[9–12] Overall, an aggressive surgical approach is often adopted for NF-PanNETs, even for locally invasive disease involving adjacent structures.[13–16] To get there, current surgical decision-making often relies on a classification system derived from pancreatic ductal adenocarcinoma, categorizing tumors as "resectable", "borderline resectable", or "locally advanced".[17] However, this classification has never been validated for NF-PanNETs, and no definition currently exists for "biological borderline resectable" NF-PanNETs. NF-PanNETs differ widely from pancreatic adenocarcinoma; NF-PanNETs generally do not show

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rapid progression (even in more aggressive tumors), are less likely to invade blood vessels, and do not necessarily warrant extensive R0 resection for disease control.[5,18] Therefore, a specific classification of resectability, including a definition of borderline resectable tumors, is needed. The aim of this study was to develop a preoperative predictive model for ER after surgery for localized, nonmetastatic NF-PanNETs, integrating diagnostic and clinical factors to refine risk assessment, with a view to developing a disease-specific framework for resectability in NF-PanNETs.

METHODS

Study Design and Participants

This is a retrospective multicentric study conducted at IRCCS San Raffaele Hospital, Milan, Sunnybrook Health Sciences Centre, Toronto, and Beaujon Hospital, Paris. The Milan and Toronto series formed the training cohort, whereas the Paris series served as the validation cohort. The present study was conducted in accordance with the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines.[19]

Inclusion and Exclusion Criteria

All consecutive patients who underwent pancreatectomy, with curative intent, for localized NF-PanNETs at IRCCS San Raffaele Hospital, Milan, Sunnybrook Health Sciences Centre, Toronto, and Beaujon Hospital, Paris, between 2015 and 2022 were retrospectively screened.

Exclusion criteria included the presence of a functioning tumor, poorly differentiated morphology, diagnosis of mixed neuroendocrine–non-neuroendocrine neoplasms, distant metastases, preoperative oncological treatment, lack of preoperative imaging performed within 60 days of surgery, and lack of preoperative biopsy.

Data Collection and Candidate Predictors

Data were retrieved from institutional databases at each site, including demographics, pathologic findings, and follow-up information. Preoperative variables considered included age, sex, and the presence of symptoms. Tumor size was defined as the maximum tumor diameter measured on preoperative imaging. All patients had a preoperative diagnostic workup including at least one morphologic imaging [computed tomography (CT) or magnetic resonance imaging (MRI)], and endoscopic ultrasound with fine needle aspiration/biopsy (EUS-FNA/B). A ^{68}[Ga]-Gallium-DOTA-PET was not routinely performed in the 3 centers. The radiologic report and the imaging in each participating center were reviewed for the following data: tumor dimension, vascular infiltration, neoplastic venous thrombosis (defined as absence of flow, evidence of hypervascularisation at the arterial phase of the thrombus, enlargement of the venous diameter), surrounding organ infiltration, evidence of necrosis, evidence of adenopathy, and main pancreatic duct (MPD) dilatation.

Tumor staging (T, N, and M) was classified according to the current European Neuroendocrine Tumor Society (ENETS) classification.[20] According to this classification local nodal involvement defines N+ disease. The definitive Ki-67 proliferative index was obtained from pathologic reports. Tumor grade was classified according to the 2017 World Health Organization (WHO) classification as G1 (Ki-67 $<3\%$), G2 (Ki-67 between 3% and 20%), and G3 (Ki-67 $>20\%$).[21] Pathology at each center was reported by pathologists specialized in NETs. Predictors considered for inclusion in the predictive were those available at the time of decision-making, that is, before surgery.

Definition of Follow-up and Outcomes

The primary outcome of interest was ER, defined as disease-free survival (DFS) of ≤ 24 months. DFS was defined as the time from surgery to the first documented disease recurrence, as detected by morphologic or functional imaging, or confirmed by EUS-guided FNA/B. Censoring occurred at the time of first recurrence or at the last available follow-up. Overall survival (OS) was examined as an indicator, defined as the time from surgery to death from any cause. For OS, patients were censored at the last available follow-up. All patients had a minimum follow-up of 24 months. No patients received postoperative adjuvant treatment. All patients underwent postoperative clinical and radiologic follow-up, although different protocols were adopted across the 3 institutions. In general, a follow-up every 6 months, including at least one high-quality imaging examination (CT and/or MRI), was recommended for the first 2 years, followed by annual assessments for a minimum of 5 years after surgery. Oncological treatment was offered in case of any evidence of recurrence. In this cases, treatment was chosen according to multidisciplinary team evaluation.

Statistical Analysis

Descriptive statistics were used to summarize patient characteristics, with categorical variables presented as absolute numbers and percentages, and continuous variables reported as median and interquartile range (IQR). Comparisons between groups were performed using the χ^2 test or Fisher exact test for categorical variables, and the Mann-Whitney U test or Student t test for continuous variables, as appropriate. Survival analyses were conducted through Kaplan-Meier curves and different subpopulation were compared with the log-rank test, to describe DFS and OS.

To develop a predictive model for ER, a classification tree analysis was performed, ensuring that each risk group contained at least 10 patients. The variables included in the model were sex, age at surgery (≥ 70 vs <70 years), presence of symptoms, tumor size (≥ 3 vs <3 cm), Ki-67 index ($\geq 5\%$ vs $<5\%$), adenopathy, vascular invasion, invasion of other organs, venous thrombosis, necrosis, and MPD dilatation. For tumor size and Ki67 index the best cutoff was assessed through receiver operating characteristic-curve analysis (Supplemental Digital Content 1, http://links.lww.com/SLA/F569 and 2, http://links.lww.com/SLA/F570). The probability of ER was calculated for each identified risk group and selected patient characteristics. The goodness of fit and predictive ability of the model were evaluated by generating a receiver operating characteristic curve and computing the corresponding area under the curve (AUC). Variables used for the model derivation and validation cohorts. For the sample description, missing data were excluded from the analysis of the corresponding variable. A P-value <0.05 was considered statistically significant for all analyses. CIs were set at 95%. Statistical analyses were performed using R software version 3.6.2 (http://www.R-project.org/).

TABLE 1. Characteristics of Patients Affected by NF-PanNET in Different Cohorts

	Training cohort Milan and Toronto n = 290	Validation cohort Paris n = 206	*P*
Demographics			
Age	58 [49–67]	55 [46–64]	0.005
Male sex, n (%)	174 (60.0)	94 (46)	0.002
Incidental diagnosis, n (%)	174 (60.2)	103 (50)	0.024
Preoperative assessment			
Necrosis, n (%)	31 (10.7)	15 (7)	0.197
Vascular infiltration, n (%)	39 (13.4)	28 (14)	0.963
Venous thrombosis, n (%)	14 (4.8)	18 (9)	0.095
Splenic vein	13 (4.5)	6 (2.9)	
Superior mesenteric vein-portal vein	1 (0.3)	6 (2.9)	
Both	0 (0)	6 (2.9)	
Other organs infiltration, n (%)	7 (2.4)	5 (2)	0.992
Adenopathy, n (%)	67 (23.1)	30 (15)	0.021
MPD dilatation > 3 mm, n (%)	81 (27.9)	34 (16.5)	0.003
Tumor size, median (mm)	30 [22–41]	25 [17–40]	0.003
Ki67 ≥ 5% at biopsy, n (%)	78 (26.9)	59 (28.5)	0.669
Surgery			< 0.001
Pancreaticoduodenectomy, n (%)	100 (34.5)	61 (30)	
Distal pancreatectomy, n (%)	158 (54.5)	73 (35)	
Total pancreatectomy, n (%)	5 (1.7)	0 (0)	
Other, n (%)	27 (9.2)	72 (35)	
Vascular resection, n (%)	13 (4.5)	27 (13)	< 0.001
Pathology			
Grading*			0.227
G1, n (%)	142 (49.0)	117 (57)	
G2, n (%)	140 (48.3)	84 (41)	
G3, n (%)	8 (2.8)	5 (2)	
T-status†			0.001
T1, n (%)	75 (25.9)	83 (40)	
T2, n (%)	128 (44.1)	78 (38)	
T3, n (%)	84 (29.0)	39 (19)	
T4, n (%)	3 (1.0)	6 (3)	
Nodal status†			0.068
N0, n (%)	172 (59.3)	130 (63)	
N1, n (%)	98 (33.8)	53 (26)	
Nx, n (%)	20 (6.9)	23 (11)	
Harvested nodes, median	19 [11-29]	10 [3-20]	< 0.001
R status			0.472
R0, n (%)	271 (93.4)	189 (92)	
R1, n (%)	19 (6.6)	17 (8)	
Perineural invasion, n (%)‡	71 (24.7)	68 (33)	0.021
Microvascular invasion, n (%)	116 (40.0)	95 (46)	0.175
Necrosis, n (%)§	13 (5.0)	11 (5)	0.687

*According to WHO classification.[21]
†According to ENETS TNM staging system.[20]
‡Missing data in 11 patients,
§Missing data in 52 patients.

RESULTS

A total of 496 patients with localized NF-PanNETs who underwent curative resection were included in the study. Among them, 290 patients belonged to the derivation cohort (227 patients in the Milan cohort and 63 patients in the Toronto one), whereas 206 patients were assigned to the validation cohort (Paris).

Patient Characteristics

Characteristics of the training and validation cohorts are presented in Table 1. The median age of patients in the training cohort was 58 years (IQR: 49–67 years) whereas in the validation cohort, it was 55 years (IQR: 46–64 years) ($P = 0.005$). A predominance of male patients was noted in the training cohort (n = 174, 60%), whereas in the validation cohort, female patients were more frequently observed (n = 112, 54%) ($P = 0.002$). Differences in preoperative factors were detected between 2 cohorts. Neoplastic venous thrombosis was identified in 5% of patients (n = 14) in the training cohort and 9% (n = 18) in the validation one, with comparable rates across cohorts ($P = 0.095$). Adenopathy was present in 23% of patients (n = 67) in the derivation cohort, and 15% (n = 30) in the validation cohort ($P = 0.021$). Tumor size also varied, with median diameters of 30 mm (IQR: 122–141 mm) in the training cohort compared with 25 mm (IQR 12–141 mm 8) in the validation one ($P = 0.003$). A Ki-67 index of ≥ 5% on preoperative biopsy was found in 27% of patients (n = 78) in the first

TABLE 2. Preoperative Factors According to the Risk of Early Recurrence (Within 24 Months) After Surgery for NF-PanNETs

	Early recurrence		
	No n = 264	Yes n = 26	*P*
Demographics			
Age, median [IQR]	58 [49–66]	63 [54–68]	0.147
Age ≥ 70 yrs, n (%)	39 (14.8)	5 (19.2)	0.545
Sex			0.502
Male, n (%)	160 (61)	14 (54)	
Female, n (%)	104 (39)	12 (46)	
Incidental diagnosis, n (%)	162 (61)	12 (46)	0.192
Preoperative assessment			
Necrosis, n (%)	27 (10)	4 (15)	0.417
Vascular infiltration, n (%)	28 (11)	11 (42)	< 0.001
Venous thrombosis, n (%)	4 (1.5)	10 (38.5)	< 0.001
Other organs infiltration, n (%)	4 (1.5)	3 (11.5)	0.001
Adenopathy, n (%)	54 (20.5)	13 (50.0)	0.001
MPD dilatation > 3 mm, n (%)	71 (27)	10 (38.5)	0.210
Tumor size ≥ 3 cm, n (%)	127 (48)	22 (85)	< 0.001
Ki67 at biopsy ≥ 5%, n (%)	57 (22)	21 (81)	< 0.001

cohort, and 28.5% (n = 59) in the second one ($P = 0.669$). A vascular resection was performed in 40 patients (8%) in the overall cohort: 13 patients (4%) in the derivation cohort and 27 (13%) in the validation one. Among the patients undergoing vascular resection, 16 (40%) also presented a neoplastic thrombosis.

Outcome – Early Recurrence

ER was observed in 55 patients (11%) overall, with 26 (9%) and 29 (14%) patients in the training and validation cohorts, respectively ($P = 0.074$). The median DFS for patients who experienced ER was 16 months (IQR: 10–20 months). The 3-year and 5-year OS was 100% and 99%, respectively, in patients without ER compared with 98% and 89%, respectively, in patients experiencing ER ($P < 0.001$).

Preoperative Predictors of Early Recurrence

As shown in Table 2, significantly higher rates of preoperative neoplastic venous thrombosis (n = 10, 38.5% vs n = 4, 1.5%, $P < 0.001$), vascular infiltration (n = 11, 42% vs n = 28, 11%, $P < 0.001$), adenopathy (n = 13, 50% vs n = 54, 20.5%, $P = 0.001$), tumor size ≥ 3 cm (n = 22, 85% vs n = 127, 48%, $P < 0.001$), and Ki-67 ≥ 5% (n = 21, 81% vs n = 57, 22%, $P < 0.001$) were observed in patients who developed ER.

The classification tree model (Fig. 1) identified neoplastic venous thrombosis, Ki-67 ≥ 5%, tumor size ≥ 3 cm, and adenopathy on preoperative imaging as key preoperative predictors associated with ER. The estimated probability of ER varied across different risk groups. The highest probability of ER was observed in patients with neoplastic venous thrombosis (71%). Among patients without neoplastic venous thrombosis, those with a Ki-67 index ≥ 5% and a tumor size ≥ 3 cm showed an ER probability of 41% in the presence of adenopathy and 19% in its absence. In cases where the Ki-67 index was ≥ 5% but the tumor size was < 3 cm, the probability of ER was 7.7%. When none of the aforementioned risk factors were present, the probability was reduced to 0.97% (Fig. 1).

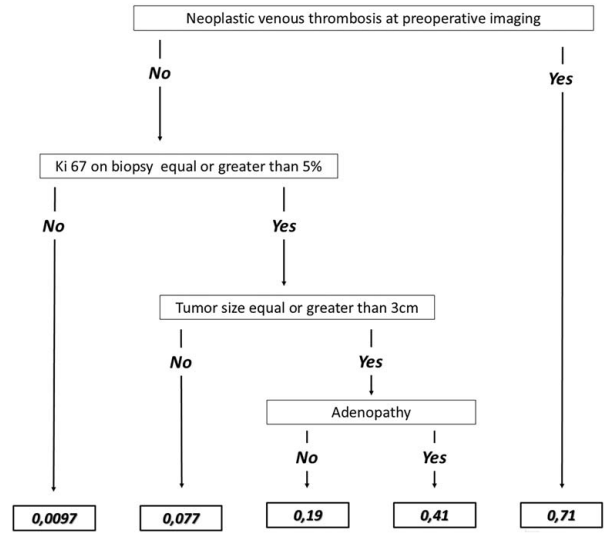


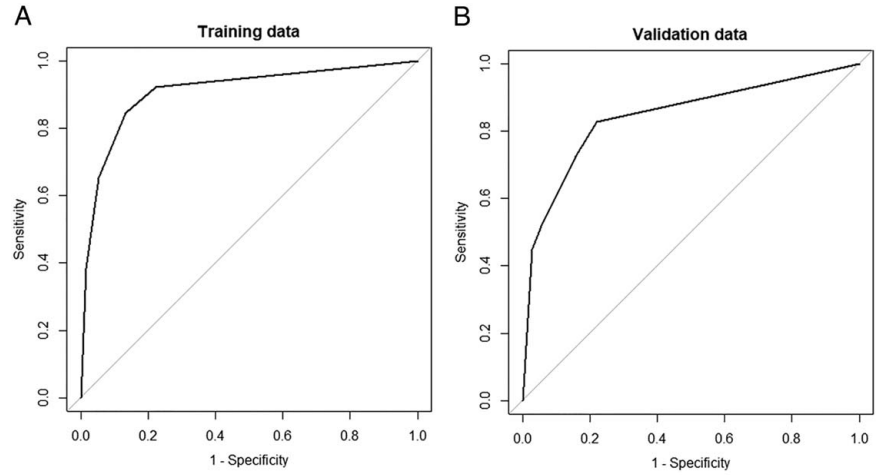
FIGURE 1. Classification tree. The numbers in the last leaves represent the estimated probabilities of early recurrence in the corresponding group.

Model Performance and External Validation

The predictive model demonstrated strong discriminatory ability, with an AUC of 0.91 (95% CI: 0.83–0.99, $P < 0.001$) in the training cohort and an AUC of 0.84 (95% CI: 0.75–0.94, $P < 0.001$) in the validation cohort (Fig. 2).

DISCUSSION

Using multicenter data of resected NF-PanNETs, preoperative predictive model for ER after surgical resection was developed and validated. Neoplastic venous thrombosis, tumor size ≥ 3 cm, a Ki-67 index ≥ 5% on preoperative EUS-FNA/B, and the presence of adenopathy on preoperative imaging were identified as main predictors of ER and included in the model. The model demonstrated excellent discriminatory ability in the derivation and validation cohorts, outlining the ability to distinguish between patients at high and low risk of ER. This model can provide accurate risk assessment of ER in patients considered for resection of NF-PanNETs, using information readily available before surgery. Beyond risk prediction, this is an important step towards defining resectability for NF-PanNETs. PanNETs are often considered relatively indolent, which has justified an aggressive surgical approach even in cases where tumors infiltrate adjacent structures, particularly vascular ones.[16] However, ER remains a concern. In the present study, an ER rate of 11% (within 2 years of surgery) was observed. Although this may seem low, patients with ER had lower OS than those without. Several predictive models have been proposed for recurrence after NF-PanNET resection, primarily based on pathologic findings.[2] However, none of these models relies exclusively on preoperative variables, making them unsuitable for presurgical risk stratification. In contrast, the present model focuses solely on preoperative predictors, enabling the identification of patients at high risk of ER before surgery and facilitating consideration of alternative treatment strategies. The current predictive score relies on routine preoperative workup, including CT or MRI for tumor size, adenopathy, and venous involvement, as well as EUS-FNA/B for Ki-67 index evaluation. Therefore, this information is readily available, use of the model is likely



	Training data	Validation data
AUC [95% CI]	0.909 [0.832; 0.986]	0.844 [0.752; 0.936]
p-value on AUC	<0.0001	<0.0001

FIGURE 2. Receiver operating characteristic curves showing the performance of the model in the training cohort (A) and in the validation cohort (B).

cost-effective, and it ultimately is easily implementable in most clinical settings. One of the most significant findings of this study is the strong association between neoplastic venous thrombosis and ER, with an observed probability exceeding 70%. Although neoplastic venous thrombosis is relatively rare in NF-PanNETs, its presence seems to be a hallmark of aggressive tumor biology.[22] Importantly, neoplastic venous thrombosis, along with the other predictors found in the present study, does not affect the technical feasibility of achieving an R0 resection but rather defines a subset of tumors that, despite being anatomically resectable, have a high likelihood of ER. Overall, the model developed and validated herein represents a novel addition to the care of NF-PanNETs. Understanding and assessing the risk of NF-PanNETs considered for resection is a key gap in NETs care. The findings of this study suggest that preoperatively retrievable factors such as neoplastic venous thrombosis, Ki-67 index, tumor size, and adenopathy on preoperative imaging can identify a high-risk group of potentially resectable NF-Pan-NETs. These could potentially be considered biologically borderline resectable NF-PanNETs. Unlike technical resectability, which is determined by anatomic feasibility for surgery, this concept focuses on tumor biology and recurrence risk, offering a more refined approach to patient selection and treatment planning. These findings have important clinical implications. First, the risk of ER ought to be balanced against the risk of the proposed resection, in the context of patient factors such as comorbidities. In that setting, the current data can support risk communication and counseling. Second, it may identify patients who could benefit from preoperative therapy, whether as a biology testing or as a downstaging attempt. Currently, no established role exists for preoperative or neoadjuvant therapy in NF-PanNETs. The first step in defining the role of such therapies in NF-PanNETs is to establish what patients should be targeted. The current study provides important data to do so, such that new neoadjuvant studies can be developed using rigorous inclusion criteria. Such data would add to the single prospective clinical trial evaluating neoadjuvant peptide receptor radionuclide therapy for resectable NF-PanNETs, which demonstrated the feasibility of such an approach.[11] Finally, identifying high-risk of ER can support tailored surveillance strategies. Refinement in risk assessment can help tailor postoperative surveillance protocols, ensuring that high-risk patients receive closer monitoring and earlier intervention in case of recurrence.

Another implication of the present is the key role of Ki-67 before surgery. In many centers tumor biopsy is not considered mandatory before surgery. However, given its important prognostic role a preoperative biopsy should always be considered in high-risk cases (ie, large tumor, adenopathy). Despite its strengths, this study has limitations. Its retrospective nature introduces the possibility of selection bias. Considerable heterogeneity across cohorts was observed, primarily due to differences in surgical indications and operative strategies among institutions. Although this may be perceived as a limitation due to variations in care, it actually represents a strength in terms of external validity of the results derived from different practices and settings. Indeed, the model performed well in both the derivation and validation cohorts, indicating its robustness across different clinical settings. Moreover, it is acknowledged that the clinical implications of this model apply to a limited subset of patients. However, with the increasing prevalence of NF-PanNETs due to earlier diagnoses and the growing trend of selecting patients with larger and more aggressive tumors for surgery, the proportion of patients at risk may significantly rise in the future. Finally, the candidate predictors did not include biomarkers such as mutation status or serological markers.

In particular, Chromogranin-A dosages were not available as they are not routinely assessed, as Chromogranin-A level can be influenced by multiple factors (ie, proton-pump inhibitors usage), severally affecting its specificity. For these reason there is a substantial lack of preoperative biomarkers which could be useful in stratifying the risk of ER. Although some have been associated with

outcomes in early studies, none is currently integrated in routine practice.[23,24] As new prospective studies explore the value of genetic and molecular markers, this predictive model can be updated as appropriate.

Another limitation is represented by the lack of data on functional imaging. The uptake of radioactive glucose is a well-known marker of aggressive behavior. In the present study, this examination was performed in only a small proportion of patients in the overall cohort, too limited to draw any conclusion. Moreover, possible radiomic features associated to 68 [Ga]-Gallium-DOTA-PET could represent novel signatures of aggressiveness that were not possible to investigate in the present study.

Finally, as the excellent disease-specific survival of these patients, recurrence-free survival could not be the most appropriate endpoint for future trials investigating the role of preoperative treatments in high-risk patients. Nevertheless, this endpoint represents an accurate surrogate for overall survival.[25] In the present study, the median follow-up of 54 months was probably too short for accurately evaluating the disease-specific survival in this population.

CONCLUSIONS

Neoplastic venous thrombosis, tumor size ≥ 3 cm, Ki-67 index $\geq 5\%$, and presence of adenopathy on preoperative imaging are independent preoperative predictors of ER after surgery for NF-PanNETs, which when combined in a predictive model, show excellent discrimination. The developed model allows for preoperative risk stratification, which can aid with risk communication and counseling, and defining populations to examine for preoperative therapy. This model also sets the stage to define biologically borderline resectable NF-PanNETs, questioning the traditional paradigm that all localized NF-PanNETs should undergo immediate surgery. This model provides the foundation to develop consensus-based definitions of resectability for NF-PanNETs and for future studies exploring preoperative therapeutic strategies, ultimately aiming to improve long-term outcomes for patients at high risk of ER.

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DISCUSSANTS

Andrea Frilling (London, United Kingdom)

I would like to thank the Association for giving me the privilege to discuss this very interesting paper. The authors have developed a predictive model for the preoperative

assessment of technically resectable non-functioning pancreatic neuroendocrine tumors regarding their risk of early recurrence. A high-risk profile would characterize a tumor as biologically borderline resectable, and consecutively, serve as a selection criterion for neoadjuvant treatment.

Neoadjuvant and adjuvant treatment concepts are considered as an unmet need in the field of neuroendocrine tumors. The authors should be congratulated on their efforts to enhance knowledge on this topic and provide evidence that could inform future guidelines.

All patients underwent EUS-guided FNAB for the assessment of the Ki67 index and tumor grading. Ki67 $\geq 5\%$ was identified as one of the risk factors predictive of early recurrence. The value of the Ki67 index in a tumor biopsy is heavily burdened by intra-tumoral heterogeneity. Since peripancreatic lymph node metastases were present in about one-third of the patients in the 3 study cohorts, intra-tumoral heterogeneity as well as inter-lesional heterogeneity would have to be considered. How was this problem approached? The Ki67 analysis was performed in 3 participating institutions. Was the interobserver agreement, as well as interlaboratory reproducibility for the Ki67 reading, assessed?

The predictive value of functional imaging, which plays a central role in the management of patients with neuroendocrine tumors, was not investigated in this study. Numerous groups have shown that information extracted from 68Ga-DOTA-somatostatin analog PET/CTs and PET/MRIs, respectively, such as standard uptake values (SUV) or dual functional imaging combining somatostatin receptor-based PET/CTs with 18F FDG PET/CTs, can predict histologic grade and the risk of recurrence. Furthermore, it can predict the response to therapies, including mTor inhibitors or peptide receptor radionuclide therapy, both potentially applicable in the neoadjuvant setting. Texture analysis on anatomic imaging accounts for another novel non-invasive strategy for the prediction of grading and prognosis of neuroendocrine tumors. Why were preoperative imaging features not investigated?

While still emerging, there is a growing body of reports that radiomics enhanced by artificial intelligence may have the potential to translate radiologic features into histologic information, and thus, avoid invasive procedures to obtain tissue samples.

The neoadjuvant treatment of patients with resectable pancreatic NET is not discussed in current guidelines. Do the authors have their own experience with neoadjuvant treatment in this clinical scenario?

Response From Stefano Partelli (Milano, Italy)

Thank you for your questions. This is a retrospective study, so we were limited to the data available within the records. The biopsy was performed at each institution using endoscopic ultrasound-guided fine needle aspiration or biopsy. The concordance between the biopsy and the final histology was high across all 3 institutions, and it has also been well-documented in the literature. Therefore, we consider the biopsy data to be reasonably accurate.

Regarding the issue of heterogeneity, I agree with you, especially in cases of very large masses or when different types of lesions (eg, lymph nodes) are present. This aspect was not directly assessed in this study because the biopsy was focused solely on the primary tumor. However, in clinical practice, this is something we take into account. For example, in selected cases with high FDG PET uptake, we perform targeted biopsies in different areas of the tumor or metastatic sites. This is certainly an approach worth exploring in future studies.

We encountered 2 main limitations in the study. First, there was some heterogeneity among institutions, particularly regarding the use of 68Gallium PET: not all the centers adopted it as a standard preoperative imaging modality. Second, in many cases, SUV values were not reported. This reflects the ongoing skepticism among nuclear medicine physicians about the reliability and reproducibility of SUV measurement. That said, I fully agree with your comment on the value of investigating radiomic features to predict tumor biology. Several studies have demonstrated that radiomics can play an important role in this area, and I believe this represents a very promising direction for future research.

As you know very well, one of the current challenges is that radioligand therapy is not yet widely available as a first-line treatment. Once both radioligand and chemotherapy are available as upfront options, the choice will likely depend on a combination of factors, particularly the Ki67 index and the imaging profile (eg, 68Ga vs FDG PET). For example, for patients with high Ki67 and strong FDG uptake, chemotherapy may be more appropriate than radioligand therapy.

Elisabeth Nieveen Van Dijkum (Amsterdam, The Netherlands)

Congratulations to the authors on this very interesting and important study on a rare tumor, especially given the size of the cohort. I have a question regarding the next steps in managing these patients, particularly in light of newer diagnostic tools that may not be available in retrospective analyses.

For example, we now have access to molecular profiling, including ATRX/DAXX status and ALT, which can provide valuable prognostic information. In addition, image-guided punctures or biopsies allow us to more accurately assess recurrence risk.

How do these advancements relate to your ongoing studies? Are you planning to incorporate molecular data into future research, and if so, how do you envision integrating this information into clinical decision-making?

Response From Stefano Partelli (Milano, Italy)

I strongly agree. We need to conduct prospective studies and identify more accurate and sophisticated signatures to better define tumor profiles. However, our preliminary data show that this predictive model is simple-yet-effective, demonstrating, for example, that neoplastic venous thrombosis is a key determinant of the risk of recurrence. Building on this finding, we believe such tools could already be useful for designing prospective studies on neoadjuvant treatments, or for guiding decisions on whether to pursue therapy instead of upfront surgery. Of course, as diagnostic technologies continue to evolve, we expect to refine our stratification strategies even further using more advanced tools.

Inne Borel-Rinkes (Utrecht, The Netherlands)

Congratulations on a nice study. I have a very brief question regarding the percentage or subgroup of patients with MEN1. Did you look at those, and if so, did it change the outcome?

Response From Stefano Partelli (Milano, Italy)

Patients with MEN1 were excluded; only sporadic cases were considered for analysis.

Giuseppe K. Fusai (London, United Kingdom)

Congratulations on this excellent study. Stratifying the risk of early recurrence in this group of patients is crucial. You have shown that venous invasion is associated with early recurrence of up to 70%. Does this apply to patients who have distortion and involvement of the splenic vein, as shown in the clinical case, or does it apply to venous involvement in the portal mesenteric venous axis as well? We have shown, together, that the resection or reconstruction of the portal vein is associated with a decent survival benefit in this cohort. If this is the case, do you anticipate that we are moving towards an algorithm for the management of patients with a borderline non-function and sporadic neuroendocrine tumor of the pancreas similar to what we already have for patients with pancreatic cancer?

Response From Stefano Partelli (Milano, Italy)

The data refers exclusively to patients with venous thrombosis. As expected, we observed a higher recurrence rate in patients with suspected vein infiltration; however, this variable did not remain an independent predictor in the multivariable analysis during the development of the predictive model. I believe the main reason lies in the fact that we relied on preoperative imaging. In other words, what had appeared to be vein infiltration on imaging may not have been performed histologically. Indeed, histologic vein infiltration is likely a strong predictor of recurrence, but its accuracy is limited when assessed through preoperative imaging alone. On the other hand, the presence of neoplastic venous thrombosis was clearly detectable on a CT scan, providing a more reliable and reproducible radiologic marker.