J Gastrointest Surg (2013) 17:2105–2113
DOI 10.1007/s11605-013-2360-9

ORIGINAL ARTICLE

Nonfunctional Pancreatic Neuroendocrine Tumors <2 cm on Preoperative Imaging are Associated with a Low Incidence of Nodal Metastasis and an Excellent Overall Survival

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Received: 23 July 2013 / Accepted: 19 September 2013 / Published online: 8 October 2013

Abstract

Background The optimal surgical management of small nonfunctional pancreatic neuroendocrine tumors (NF-PNETs) remains controversial. We sought to identify (1) clinicopathologic factors associated with survival in NF-PNETs and (2) preoperative tumor characteristics that can be used to determine which lesions require resection and lymph node (LN) harvest.

Methods The records of all 116 patients who underwent resection for NF-PNETs between 1989 and 2012 were reviewed retrospectively. Preoperative factors, operative data, pathology, surgical morbidity, and survival were analyzed.

Results The overall 5- and 10-year survival rates were 83.9 and 72.8 %, respectively. Negative LNs ($p=0.005$), G1 or G2 histology ($p=0.033$), and age <60 years ($p=0.002$) correlated with better survival on multivariate analysis. The 10-year survival rate was 86.6 % for LN-negative patients ($n=73$) and 34.1 % for LN-positive patients ($n=32$). Tumor size ≥2 cm on preoperative

This paper was presented at the Pancreas Club, 17 May 2013, Orlando, FL.

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imaging predicted nodal positivity with a sensitivity of 93.8 %. Positive LNs were found in 38.5 % of tumors ≥2 cm compared to only 7.4 % of tumors <2 cm.

Conclusions LN status, a marker of systemic disease, was a highly significant predictor of survival in this series. Tumor size on preoperative imaging was predictive of nodal disease. Thus, it is reasonable to consider parenchyma-sparing resection or even close observation for NF-PNETs <2 cm.

Keywords Pancreatic neuroendocrine tumor · Nonfunctional pancreatic neuroendocrine tumor · Pancreatic neoplasms · Pancreatectomy

Introduction

Pancreatic neuroendocrine tumors (PNETs) are rare and account for 1–2 % of all pancreatic neoplasms.[1,2] The annual incidence of PNETs is <1 per 100,000 persons in the USA, although it has been increasing in recent years, likely a result of improved detection methods.[1,3] PNETs are subdivided into two major categories: functional and nonfunctional. Functional tumors secrete hormones and produce characteristic endocrine syndromes. Nonfunctional pancreatic neuroendocrine tumors (NF-PNETs) can secrete various products (chromogranin A, neuron-specific enolase, pancreatic polypeptide, etc.) but do not cause symptoms.[4]

Surgical resection is the treatment of choice for patients with functional tumors, and it is preferred for most NF-PNETs.[5–8] However, for small NF-PNETs, the need for resection and the appropriate operation to perform remain controversial.[5–12] Surgical options for treating small tumors include standard resection with lymph node (LN) harvest (pancreaticoduodenectomy and distal pancreatectomy) and parenchyma-sparing resection (enucleation and middle pancreatectomy). The more limited parenchyma-sparing resections typically do not include LN harvest. Although the positive impact of resection on survival in NF-PNETs has been repeatedly demonstrated,[13–17] it has also been suggested that most small tumors have an indolent course and may be amenable to observation.[9,10]

In this study, we reviewed the outcomes of patients who underwent resection for NF-PNETs at a single institution during the past two decades. The aims of the study were to identify (1) clinicopathologic factors associated with survival in NF-PNETs and (2) tumor characteristics that can be measured preoperatively and used to determine which lesions require resection and LN harvest.

Materials and Methods

Data Collection

The records of all patients who underwent resection for NF-PNET between 1989 and 2012 were reviewed retrospectively after approval from the institutional review board. Functional tumors were defined by preoperative symptoms or elevated serum hormones with histopathologic confirmation after resection, and all were excluded from this study. The review included demographics, surgical data, pathologic characteristics, postoperative morbidity, and overall survival. Histologic grade and differentiation were classified using the World Health Organization (WHO) 2010 nomenclature[18,19] based on pathology reports as well as on reviews of archived surgical pathology slides and a previously generated tissue microarray comprising 114 patients who underwent resection for PNET at this institution. Tumor size on preoperative imaging was obtained from cross-sectional imaging with computed tomography (CT) or magnetic resonance imaging (MRI). In the few cases in which cross-sectional imaging were equivocal, the size on endoscopic ultrasound (EUS) was used. For the 11 patients with no available records of preoperative imaging, the tumor size recorded in the final pathology report was used. There was a strong correlation between imaging and pathologic size in our cohort (R^2=0.86).

Morbidity analysis included the following complications: pancreatic fistula (abdominal drainage with an amylase level >3 times the upper limit of normal after postoperative day number 3), delayed gastric emptying (inability to tolerate oral intake after postoperative day number 7), wound infection (any wound that required opening or antibiotics beyond standard prophylaxis), urinary tract infection (positive urine culture), thrombotic event (deep venous thrombosis or pulmonary embolus), pulmonary (pneumonia, effusion requiring thoracentesis, or reintubation), cardiac (myocardial infarction or new arrhythmia requiring intervention), intra-abdominal abscess (fluid requiring drainage with positive cultures), small bowel obstruction, *Clostridium difficile* infection (diarrhea and positive test), bleeding (hemorrhage requiring transfusion or reoperation), and chyle leak (elevated abdominal fluid triglyceride level). Postoperative mortality was defined as death prior to hospital discharge. Overall survival was determined by review of the medical record as well as the Social Security Death Index. Survival time was calculated from the date of operation to the date of final follow-up or death.

Statistical Analysis

Differences in continuous variables were analyzed via Student's *t* test. Differences in discrete variables were analyzed via Fisher's exact test (categorical variables) or Mann–Whitney *U* test (nominal variables). Survival estimates were generated

using the Kaplan–Meier method. Differences in survival were assessed by univariate and multivariate Cox regression. All variables with $p \leq 0.05$ on univariate analysis were included in the multivariate model. The multivariate analysis was performed in a stepwise fashion with forward selection, with inclusion and exclusion probabilities of 0.05 and 0.10, respectively. Statistical significance was assumed at $p \leq 0.05$. Receiver operating characteristics (ROC) analysis was performed to evaluate the ability of tumor size to predict LN status. Sensitivity and specificity values were evaluated over the full range of possible cutpoints for tumor size. Patients with no LNs sampled were excluded from all analyses involving LN status. All analyses were performed with the SPSS statistical software, version 20 (IBM).

Results

Clinicopathologic Factors of All Patients

As summarized in Table 1, a total of 116 pancreatic resections were performed for NF-PNET between 1989 and 2012. The median age was 57.5 years (interquartile range [IQR], 46.0–67.8). Operations performed included pancreaticoduodenectomy ($n=43$), distal pancreatectomy ($n=65$), middle pancreatectomy ($n=4$), and enucleation ($n=4$). Median tumor size on preoperative imaging was 2.8 cm (IQR, 1.7–5.0). Patients treated with parenchyma-sparing resections had a median tumor size of 1.5 cm (IQR, 1.0–2.3) on imaging. The majority of tumors were low (G1 or G2) grade ($n=105$, 90.5 %). Positive LNs were found in 32 patients (30.5 %). No LNs were sampled in 4.6 % of standard resections ($n=5$) compared to 75.0 % of parenchyma-sparing resections ($n=6$). Distant metastases were present in 17 patients (14.7 %). Metastatic locations included the liver ($n=15$), spleen ($n=1$), and jejunal LN ($n=1$). The presence of metastases was known prior to operation in six cases, and complete resection of metastatic disease was accomplished in ten cases. The overall postoperative morbidity rate was 48.3 %. The most common complications included pancreatic fistula (21.6 %), delayed gastric emptying (10.3 %), pulmonary complications (9.5 %), and wound infection (8.6 %). The overall morbidity rate after parenchyma-sparing resection was 62.5 % ($n=5$), with specific complications including pancreatic fistula ($n=2$), bleeding ($n=1$), wound infection ($n=1$), and pulmonary complication ($n=1$). There were no perioperative deaths.

Patient Survival

The median overall actuarial survival for all patients undergoing resection for NF-PNETs was 17.2 years (IQR, 9.1–19.6) (Fig. 1). The overall 5- and 10-year survival rates were 85.8 and 77.9 %, respectively. The median follow-up for survivors was 3.9 years (IQR, 1.6–7.2). Univariate and multivariate

Table 1 Clinicopathologic factors of all patients

Age, median (IQR), years	57.5 (46.0–67.8)
Gender, *n* (%)	
Male	65 (44.0)
Female	51 (56.0)
Tumor size, median (IQR), cm[a]	2.8 (1.7–5.0)
Tumor location, *n* (%)	
Head	44 (37.9)
Body/tail	72 (62.1)
Operation, *n* (%)	
PD	43 (37.1)
DP	65 (56.0)
MP	4 (3.4)
Enucleation	4 (3.4)
EBL, mean±SEM, ml	398.0±63.9
Morbidity, *n* (%)	56 (48.3)
Grade, *n* (%)[b]	
1	52 (44.8)
2	53 (45.7)
3	7 (6.0)
Unknown	4 (3.4)
Differentiation, *n* (%)	
Well	110 (94.8)
Poor	6 (5.2)
T stage, *n* (%)[c]	
1	40 (34.5)
2	47 (40.5)
3	28 (24.1)
4	1 (0.9)
Margin, *n* (%)	
Positive	15 (12.9)
Negative (R0)	101 (87.1)
LVI, *n* (%)	
Present	41 (35.3)
Absent	75 (64.7)
PNI, *n* (%)	
Present	22 (19.0)
Absent	94 (81.0)
LNs, *n* (%)	
Positive	32 (27.6)
Negative	73 (62.9)
Unknown	11 (9.5)
Distant metastases, *n* (%)	
Present	17 (14.7)
Absent	99 (85.3)

IQR interquartile range, *SEM* standard error of the mean, *PD* pancreaticoduodenectomy, *DP* distal pancreatectomy, *MP* middle pancreatectomy, *EBL* estimated blood loss, *LVI* lymphovascular invasion, *PNI* perineural invasion, *LN* lymph node

[a] Size on preoperative imaging

[b] WHO 2010 classification

[c] AJCC 7th edition classification

survival analyses for various clinicopathologic variables are summarized in Table 2.

On univariate analysis, significant predictors of worse survival included positive LNs (HR, 3.1; $p=0.01$), distant metastases (HR, 3.4; $p=0.01$), positive margin (HR, 3.7; $p=0.01$), T stage 3 or 4 (HR, 2.9; $p=0.02$), G3 histology (HR, 3.7; $p=0.04$), and age ≥60 years (HR, 2.5; $p=0.05$). Poor differentiation (HR, 3.4; $p=0.06$) and tumor size treated as a continuous variable (HR, 1.2; $p=0.09$) approached significance. However, when size was coded as a dichotomous variable (<2 vs. ≥2 cm), the correlation with survival did not reach significance (HR, 1.3; $p=0.69$).

On multivariate analysis, positive LNs (HR, 4.4; $p=0.005$), G3 histology (HR, 4.1; $p=0.033$), and age ≥60 years (HR, 4.5; $p=0.002$) were associated with significantly worse survival. The overall 5- and 10-year survival rates were 90.8 and 86.6 %, respectively, for LN-negative disease compared to 68.4 and 34.1 %, respectively, for LN-positive disease (Fig. 2).

Tumor Size as a Predictor of LN-Positive Disease

Although LN status was a highly significant predictor of survival on multivariate analysis, it is not a parameter that can be assessed preoperatively. ROC analysis was conducted to evaluate the ability of tumor size to predict LN status. Size was chosen because it can be measured preoperatively in all patients. Patients who had no LNs sampled were excluded. The ROC analysis demonstrated that tumor size is a reasonable predictor of positive LNs, with an area under the curve (AUC) of 0.71 (Fig. 3). A cutpoint of ≥2 cm was associated with a sensitivity of 93.8 % for the presence of positive LNs. The negative predictive value of tumor size <2 cm was 92.6 %. Of the 35 patients with tumors <2 cm on preoperative imaging, only two had positive LNs. One of the patients also

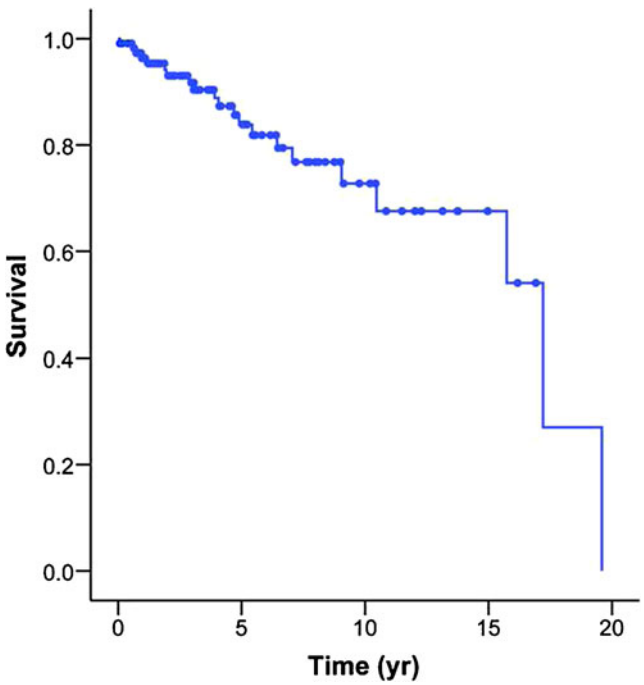

Fig. 1 Kaplan–Meier survival estimate after resection of NF-PNETs. The 5- and 10-year survival rates were 83.9 and 72.8 %, respectively

Table 2 Association of overall survival with clinicopathologic factors

	Univariate analysis		Multivariate analysis	
	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value
Age				
<60 years	1.0		1.0	
≥60 years	2.5 (1.0–6.3)	0.05	5.3 (1.8–15.3)	0.002
Gender				
Female	1.0			
Male	0.9 (0.4–2.3)	0.90		
Tumor location				
Head	1.0	0.98		
Body/tail	1.0 (0.4–2.5)			
Grade[a]				
G1+G2	1.0		1.0	
G3	3.7 (1.0–13.2)	0.04	4.1 (1.1–15.1)	0.033
Differentiation				
Well	1.0			
Poor	3.4 (0.9–12.3)	0.06		
Tumor size[b]				
<2 cm	1.0			
≥2 cm	1.3 (0.4–3.8)	0.69		
T stage[c]				
1+2	1.0			
3+4	2.9 (1.2–7.0)	0.02	–	–
Margin				
Negative	1.0			
Positive	3.7 (1.4–9.9)	0.01	–	–
LVI				
Absent	1.0			
Present	1.8 (0.7–4.7)	0.20		
PNI				
Absent	1.0			
Present	1.2 (0.4–3.5)	0.80		
LNs				
Negative	1.0		1.0	
Positive	3.1 (1.3–7.6)	0.01	4.4 (1.6–12.2)	0.005
Distant metastases				
Absent	1.0			
Present	3.4 (1.4–8.4)	0.01	–	–

HR hazard ratio, *CI* confidence interval, *LVI* lymphovascular invasion, *PNI* perineural invasion, *LN* lymph node

[a] WHO 2010 classification

[b] Tumor size on preoperative imaging

[c] AJCC 7th edition classification

had a 2-mm liver metastasis at the time of laparotomy. Overall, tumor size was a very sensitive, though not specific, indicator of LN status.

Clinicopathologic Factors Stratified by Tumor Size

On preoperative imaging, 35 patients (30.2 %) had tumors <2 cm, while 81 patients (69.8 %) had tumors ≥2 cm. The various clinicopathologic factors reviewed in this study stratified by a tumor size cutpoint of 2 cm are summarized in Table 3. Demographics between the two groups were similar with a median age of 58 years (IQR, 45.0–69.0) for tumors <2 cm and 57 years (IQR, 47.0–66.5) for tumors ≥2 cm. The estimated blood loss was significantly higher in operations for larger tumors (mean 473.9 vs. 222.4 ml, $p=0.01$). Tumors ≥2 cm on preoperative imaging were significantly more likely to have lymphovascular invasion (46.9 vs. 8.6 %, $p<0.001$), positive LNs (38.5 vs. 7.4 %, $p=0.003$), and distant metastases (19.8 vs. 2.9 %, $p=0.02$). Additionally, six of the seven tumors with G3 histology were ≥2 cm on preoperative imaging. Tumors <2 cm were more likely to have no LNs sampled (22.9 vs. 3.7 %, $p=0.003$). However, when LNs were removed, the median number sampled was 10.0 (IQR, 4.0–18.0) for tumors <2 cm and 10.5 (IQR, 5.8–16.3) for tumors ≥2 cm. Overall postoperative morbidity was 48.6 % for tumors <2 cm and 48.1 % for tumors ≥2 cm. Specific postoperative complications stratified by tumor size are summarized in Table 4.

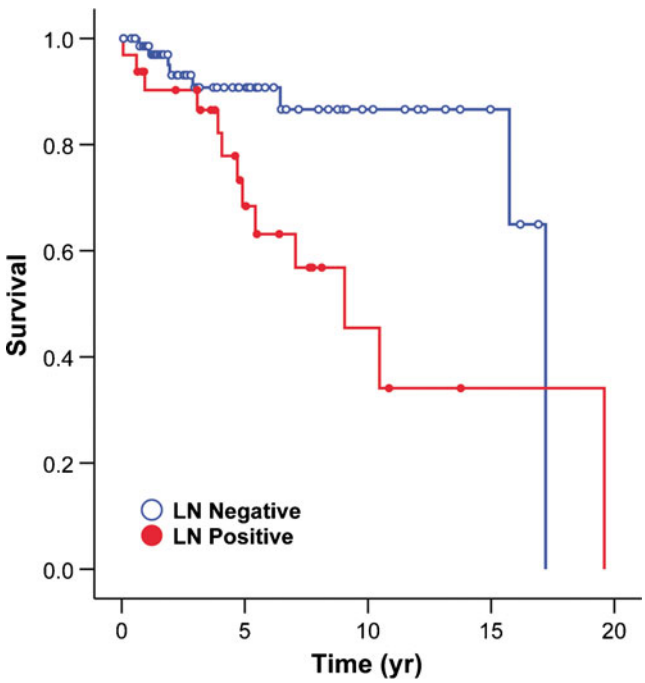

Fig. 2 Kaplan–Meier survival estimate demonstrating the relationship between LN status and survival. Univariate HR=3.1 (95 % CI=1.3–7.6), $p=0.01$. Multivariate HR=4.4 (95 % CI=1.6–12.2), $p=0.005$

Discussion

NF-PNETs are rare pancreatic neoplasms with an apparently increasing incidence. Many small NF-PNETs are discovered incidentally on cross-sectional imaging (CT/MRI) which is being performed more frequently.[1,16] This poses a significant management challenge: should all NF-PNETs, even the incidentally detected small ones, be removed? Current practice at most institutions is to resect all NF-PNETs. However, whether some can be safely observed is still not well-defined.[5–12] For those patients undergoing resection, whether a parenchyma-sparing procedure without a nodal harvest is appropriate also remains in question.[20–22] In an attempt to answer these clinical questions, we performed a retrospective analysis of resected NF-PNETs at our institution with the objectives of (1) identifying factors associated with survival as well as (2) preoperative tumor characteristics that can be used to guide treatment decisions.

Our experience confirms the excellent overall survival following resection of NF-PNETs. However, as observed in previous reports,[10–12,15,23] postoperative morbidity approached 50 %. LN status was a highly significant predictor of survival. Advanced age and high-grade (G3) histology were also associated with shorter overall survival on multivariate analysis. Furthermore, tumor size on preoperative imaging was a sensitive predictor of LN status. Tumors <2 cm were very unlikely to have positive LNs.

Previous studies have reported varying results with regards to clinicopathologic factors associated with survival. Factors that have been associated with survival include age,[17,24] tumor size,[9,11,17,25] grade/differentiation,[11,12,16,17,24,25] LN status,[11,25,26] presence of distant metastases,[14,16,17,24–26] and surgical resection.[13–17] Several of these factors were also significant predictors of survival in our analysis. Tumor size was not significantly associated with survival when coded as a dichotomized variable (<2 vs. ≥2 cm). However, T stage, a measure closely related to tumor size, was a significant predictor of survival on univariate analysis, and tumor size approached significance when coded as a continuous variable. These results indicate that there is a correlation between increasing tumor size and worse prognosis. Although a high-grade tumor (G3) was significantly associated with worse survival, we did not focus on histology as a preoperative indicator to guide treatment because there were few patients in our series with high-grade tumors. Despite the relatively small sample size, it should be noted that nearly all of the high-grade tumors were ≥2 cm.

Whether characteristics that can be measured preoperatively and are associated with shorter survival should be used to decide which patients with NF-PNETs require resection remains a point of contention. This controversy is due to the (1) excellent survival associated with the current treatment approach (all tumors resected), (2) lack of effective

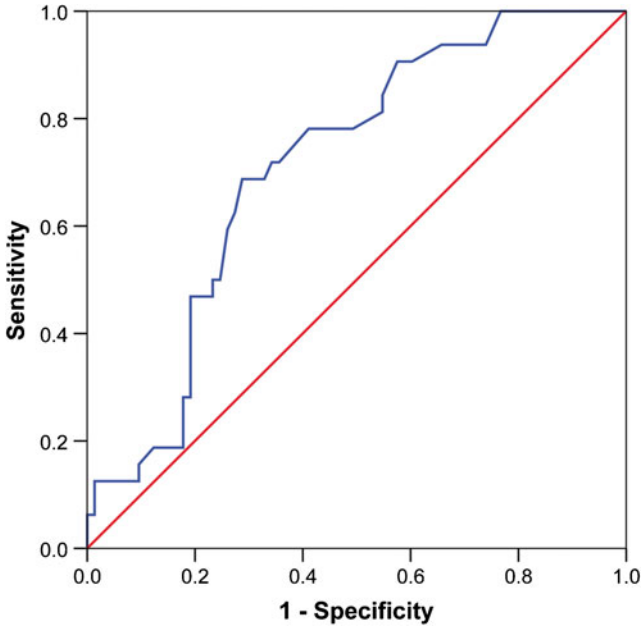

Fig. 3 ROC curve of tumor size on preoperative imaging as a predictor of LN status, AUC=0.71. At a cutpoint of 2 cm, sensitivity=93.8 %

chemotherapy or targeted therapy for patients with systemic disease, (3) absence of a prospective randomized trial examining the impact of resection on survival, and (4) inconsistent results in retrospective studies with regards to the prognostic significance of variables that can be measured preoperatively. Our study suggests that the use of preoperative prognostic factors to determine treatment may be possible, as tumor size was a highly sensitive indicator of LN status.

Although tumor size has been the most extensively studied variable to identify the need for resection, there is some disagreement as to its accuracy in predicting survival. Two well-performed studies support the use of size to identify patients with aggressive tumors that should be removed. Bettini et al.,[9] in a retrospective study of 230 patients undergoing resection for NF-PNET, demonstrated a strong correlation between increasing tumor size and higher tumor grade, positive LN status, and worse overall survival. Lee et al.[10] revealed that there was no evidence of progression or disease-specific mortality in a cohort of patients with small PNETs (median, 1.0 cm) managed nonoperatively over a mean follow-up of 45 months. Conversely, two other studies caution that tumor size may not be an accurate prognostic indicator. Haynes et al.[11] reviewed the outcomes of 139 patients with incidentally discovered NF-PNETs and found that three of 39 patients with tumors ≤2 cm developed metastases after resection and eventually died of their disease. Although a small minority of patients with tumors ≤2 cm developed metastatic disease, increased tumor size (≥2 cm) was a significant predictor of disease progression or metastasis in their study. Parekh et al.,[27] in a study evaluating predictors of nodal

Table 3 Clinicopathologic factors stratified by tumor size

	Tumor size <2 cm (n=35)[a]	Tumor size ≥2 cm (n=81)[a]	p value
Age, median (IQR), years	58.0 (45.0–69.0)	57.0 (47.0–66.5)	0.89
Gender, n (%)			
Male	21 (60.0)	44 (54.3)	0.68
Female	14 (40.0)	37 (45.7)	
Tumor location, n (%)			
Head	9 (25.7)	35 (43.2)	0.10
Body/tail	26 (74.3)	46 (56.8)	
Operation, n (%)			
PD	9 (25.7)	34 (42.0)	0.07
DP	21 (60.0)	44 (54.3)	
MP	2 (5.7)	2 (2.5)	
Enucleation	3 (8.6)	1 (1.2)	
EBL, mean±SEM, ml	222.4±28.2	473.9±89.9	0.01
Morbidity, %	48.6	48.1	0.97
Grade, n (%)[b]			
1	19 (54.3)	33 (40.7)	0.11
2	13 (37.1)	40 (49.4)	
3	1 (2.9)	6 (7.6)	
Unknown	2 (5.7)	2 (2.5)	
Differentiation, n (%)			
Well	34 (97.1)	76 (93.8)	0.67
Poor	1 (2.9)	5 (6.2)	
T stage, n (%)[c]			
1	33 (94.3)	7 (8.6)	<0.001
2	1 (2.9)	46 (56.8)	
3	1 (2.9)	27 (33.3)	
4	0 (0.0)	1 (1.2)	
Margin, n (%)			
Positive	2 (5.7)	13 (16.0)	0.23
Negative (R0)	33 (94.3)	68 (84.0)	
LVI, n (%)			
Present	3 (8.6)	38 (46.9)	<0.001
Absent	32 (91.4)	43 (53.1)	
PNI, n (%)			
Present	4 (11.4)	18 (22.2)	0.21
Absent	31 (88.6)	63 (77.8)	
LNs, n (%)			
Positive	2 (5.7)	30 (37.0)	0.003
Negative	25 (71.4)	48 (59.3)	
Unknown	8 (22.9)	3 (3.7)	
Distant metastases, n (%)			
Present	1 (2.9)	16 (19.8)	0.02
Absent	34 (97.1)	65 (80.2)	

IQR interquartile range, *SEM* standard error of the mean, *PD* pancreaticoduodenectomy, *DP* distal pancreatectomy, *MP* middle pancreatectomy, *EBL* estimated blood loss, *LVI* lymphovascular invasion, *PNI* perineural invasion, *LN* lymph node

[a] Size on preoperative imaging

[b] WHO 2010 classification

[c] AJCC 7th edition classification

Table 4 Postoperative complications stratified by tumor size

	Tumor size <2 cm (n=35)[a]	Tumor size ≥2 cm (n=81)[a]	p value
Pancreatic fistula, n (%)	10 (28.6)	15 (18.5)	0.32
Delayed gastric emptying, n (%)	2 (5.7)	10 (12.3)	0.34
Pulmonary, n (%)	4 (11.4)	7 (8.6)	0.73
Wound infection, n (%)	4 (11.4)	6 (7.4)	0.72
Intra-abdominal abscess, n (%)	5 (14.3)	3 (3.7)	0.05
Cardiac, n (%)	2 (5.7)	2 (2.5)	0.58
Bleeding, n (%)	0 (0.0)	4 (4.9)	0.31
Other complication, n (%)	7 (20.0)	5 (6.2)	0.04
Overall morbidity, n (%)	17 (48.6)	39 (48.1)	0.97

[a] Tumor size on preoperative imaging

metastases, concluded that tumor size was not a reliable indicator of LN status based on the observation that mean tumor size was similar for patients with negative and positive LNs (4.6 vs. 5.2 cm). Interestingly, only one patient in their series with a tumor <2 cm had positive LNs.

Previous reports taken together with our study suggest that smaller tumors (<2 cm) are associated with low rates of nodal metastasis, better histology, and a more indolent clinical course than larger tumors. Therefore, observation is a reasonable treatment choice for selected NF-PNETs <2 cm. This more conservative approach would be most suitable for higher-risk patients with significant medical comorbidities. This conclusion is similar to the current National Comprehensive Cancer Network (NCCN) guidelines,[8] which recommend considering observation in selected tumors <1 cm. It is important to note that our conclusions are limited by the retrospective nature of the data. A randomized trial comparing observation and resection would provide more definitive results but would be difficult to perform given the low incidence of NF-PNETs.

Even in patients who should undergo surgical resection, the appropriate extent of resection is debated. Indeed, there is accumulating evidence that parenchyma-sparing operations, without LN removal, may be appropriate for small NF-PNETs.[20–22] Compared to standard resections, they are associated with reduced overall serious morbidity.[28] Specific benefits include decreased length of hospital stay, lower operative blood loss, and less need for ICU care.[29] Furthermore, parenchyma-sparing procedures are associated with less postoperative endocrine and/or exocrine insufficiency.[20,28] Importantly, overall and disease-free survival are excellent after parenchyma-sparing resection for PNETs.[20] One argument against their use is the increased risk of pancreatic fistula reported in most series.[20,29,30] It has been suggested that parenchyma-sparing techniques are most suitable for small lesions with a low risk of systemic involvement.[20,28] Such NF-PNETs are unlikely to benefit from more extensive resections that include LN dissection. Our results indicate that it is reasonable to consider parenchyma-sparing resection without LN harvest in tumors <2 cm because of the low risk of LN involvement. Our findings are again consistent with NCCN guidelines,[8] which recommend parenchyma-sparing resection as a treatment option for tumors <2 cm and consideration of LN harvest in tumors 1–2 cm in size. When parenchyma-sparing techniques are pursued, it is essential to accomplish complete resection as positive margin was associated with worse survival in our analysis.

In addition to size, tumor grade is another variable associated with survival that can be assessed in the preoperative setting. Previous studies and our results indicate that grade and differentiation are indicators of biologic behavior in NF-PNETs and are associated with survival.[17,25] EUS can be combined with fine-needle aspiration (FNA) or core needle biopsy to evaluate tumor pathology preoperatively. FNA can demonstrate various cytopathologic features associated with high-grade histology such as nuclear pleomorphism/multinucleation, nucleoli, mitoses, and Ki67 index. Ki67 index >2 % on FNA strongly correlates with high-grade pathology at the time of resection.[31] The presence of any of these concerning features should favor an aggressive surgical approach consisting of standard resection. While core biopsies have the benefit of providing tissue architecture for the evaluation of tumor grade, they are not feasible for most patients as they are often only performed at high-volume centers, can be challenging for small masses, and are associated with a risk of pancreatitis and bleeding.[32,33] Regardless of the biopsy technique, intra-tumoral heterogeneity of PNETs is well-established, which results in potential sampling errors and limits the accuracy of preoperative tumor grading with this approach.[34,35] Our study highlights the utility of tumor size, a variable measured easily and accurately via noninvasive imaging, as a preoperative prognostic indicator. EUS with FNA

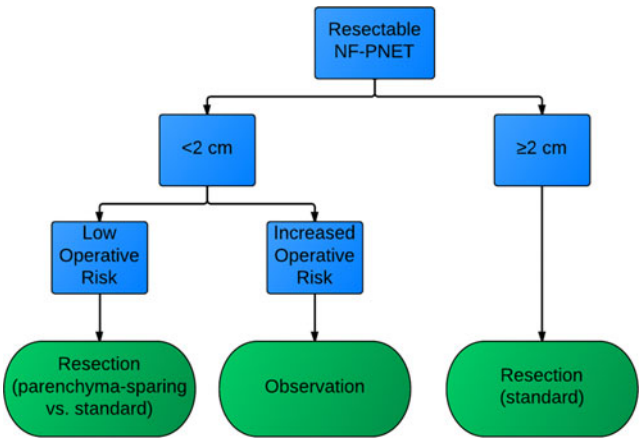

Fig. 4 Proposed treatment algorithm for NF-PNETs

or core biopsy is an additional preoperative test that could be useful, particularly when it remains unclear if resection is appropriate after tumor size and patient risk have been considered.

In conclusion, NF-PNETs represent a heterogeneous group of neoplasms with variable biologic behavior. Given the significant morbidity associated with resection of NF-PNETs, the identification of preoperative variables that can be used to decide which patients can be closely observed or have a more limited procedure is warranted. In our study, LN metastases were a significant predictor of worse survival, and tumors <2 cm on preoperative imaging were unlikely to have positive LNs. A proposed treatment algorithm for NF-PNETs based on these findings is summarized in Fig. 4. Because of the risk of LN involvement, our results suggest that standard resection with lymphadenectomy is most appropriate for NF-PNETs ≥2 cm. Parenchyma-sparing resections without lymphadenectomy or nonoperative management with close surveillance are reasonable options for selected patients with NF-PNETs <2 cm because of the low probability of LN positivity.

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