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ORIGINAL ARTICLE – PANCREATIC TUMORS

Redefining the Ki-67 Index Stratification for Low-Grade Pancreatic Neuroendocrine Tumors: Improving Its Prognostic Value for Recurrence of Disease

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ABSTRACT

Background. The Ki-67 index is an established prognostic marker for recurrence after resection of pancreatic neuroendocrine tumors (PanNETs) that groups tumors into three categories: low grade (< 3%), intermediate grade (3–20%), and high grade (> 20%). Given that the majority of resected PanNETs have a Ki-67 less than 3%, this study aimed to stratify this group further to predict disease recurrence more accurately.

Methods. The Ki-67 index was pathologically re-reviewed and scored by a pathologist blinded to all other clinicopathologic variables using tissue microarray blocks made in triplicate. All patients who underwent curative-intent resection of non-metastatic PanNETs at a single institution from 2000 to 2013 were included in the study. The primary outcome was recurrence-free survival (RFS).

Results. Of 113 patients with well-differentiated PanNETs resected, 83 had tissue available for pathologic re-review. The Ki-67 index was lower than 3% for 72 tumors (87%) and between 3 and 20% for 11 tumors (13%). Considering only Ki-67 less than 3%, the tumors were further stratified by Ki-67 into three groups: group A (< 1%, $n = 43$), group B (1–1.99%, $n = 23$), and group C (2–2.99%, $n = 6$). Compared with group A, groups B and C more frequently had advanced T stage (T3: 44% and 67% vs 12%; $p = 0.003$) and lymphovascular invasion (50% and 83% vs 23%; $p = 0.007$). Groups B and C had similar 1- and 3-year RFS, both less than group A. After combining groups B and C, a Ki-67 of 1–2.99% was associated with decreased RFS compared with group A (< 1%). This persisted in the multivariable analysis (hazard ratio [HR] 8.6; 95% confidence interval [CI] 1.0–70.7; $p = 0.045$), with control used for tumor size, margin-positivity, lymph node involvement, and advanced T stage.

Conclusions. PanNETs with a Ki-67 of 1–2.99% exhibit distinct biologic behavior and earlier disease recurrence than those with a Ki-67 lower than 1%. This new stratification scheme, if externally validated, should be incorporated into future grading systems to guide both surveillance protocols and treatment strategies.

Pancreatic neuroendocrine tumors (PanNETs) are rare, accounting for only 1–2% of all pancreatic neoplasms, with approximately 1000 new cases diagnosed annually in the United States.[1,2] These tumors are typically indolent in nature, can be hormonally functional or nonfunctional, and can have low or high malignant potential. Many are discovered incidentally on cross-sectional imaging for other diagnoses.[3] Heterogeneity in the clinical presentation of PanNETs creates unique challenges for their management, particularly in deciding on the extent of surgical resection or on surgical resection versus surveillance.[4,5]

The World Health Organization (WHO) classifies pancreatic neuroendocrine lesions into two main categories: well-differentiated neuroendocrine tumors (NETs) and

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poorly differentiated neuroendocrine carcinomas (NECs).[4,6] Grading of NETs is based on mitotic count and the Ki-67 index.[4,6] The Ki-67 index stratifies PanNETs into low-grade tumors (Ki-67 < 3%), intermediate-grade tumors (Ki-67 3–20%), and high-grade carcinomas (Ki-67 > 20%).[1,7] Findings have shown the Ki-67 index, in particular, to be highly correlated with clinical outcome, perhaps more so than other known histopathologic features.[8–11]

Approximately 90% of diagnosed PanNETs are considered well-differentiated tumors (low-to-intermediate grade) and primarily treated with surgical resection.[2,4,12] However, the clinical behavior of these well-differentiated tumors is heterogeneous, with recurrences reported for 10–54% of patients, and the median overall survival (OS) ranges from 51 to 79 months.[3,12–14] With the majority of resected PanNETs (80%) well-differentiated, and with the Ki-67 index lower than 3% all grouped together, the current WHO stratification scheme is limited in its ability to differentiate outcomes within this low-grade PanNET subset.[13,15,16] Thus, our study aimed to further risk-stratify patients with well-differentiated, low-grade PanNETs (Ki-67 index < 3%), with the intent of using Ki-67 to discriminate outcomes better by predicting disease recurrence and biologic behavior.

METHODS

Study Population and Pathologic Assessment

All patients with primary, non-metastatic PanNETs who underwent surgical resection at Emory University from 1 January 2000 to 31 December 2013 were identified. Pathologic re-review was undertaken. Only patients who had surgery with curative intent and with available tissue samples for pathologic re-review were included in the study. For the purpose of this study, only patients with well-differentiated tumors and a Ki-67 lower than 3% (low grade) were included in the analysis. Patients with distant metastases or other malignancies, multifocal disease, R2 resections, or mortality within 30 days after surgery were excluded from the analysis.

For this study, tissue microarrays were created in triplicate from the archived formalin-fixed, paraffin-embedded archived tissue blocks. Standard immunohistochemistry was performed. The slides were stained for Ki-67 (clone MIB-1; DAKO Agilent Pathology Solutions, Santa Clara, CA, USA) using antigen retrieval and the Leica Bond Autostainer (Leica Biosystems, Wetzlar, Germany) and counterstained with hematoxylin. The tissue microarray slides were scanned at × 40 magnification on the Leica Aperio AT2 bright field instrument (Leica Biosystems) for computerized quantitation image analysis. The Ki-67 proliferation index was determined as the percentage of tumor cells with Ki-67 immunoreactive nuclei. Depending on the tumor cellularity, the number of total cells counted ranged from 600 to 1800. An overall score for each sample was calculated as the sum of the expression percentage of each triplicate divided by 3. An experienced and dedicated gastrointestinal pathologist at Emory University, blinded to all other clinicopathologic variables for each tissue sample, supervised the analysis. Only the results from re-review of Ki-67 expression were used for analysis.

Study Variables

Retrospective chart review captured pertinent demographic, preoperative, intraoperative, pathologic, and postoperative data. Preoperative comorbidities were defined using the Charlson Comorbidity Scoring System, and staging was assigned as per the American Joint Committee on Cancer 7th edition guidelines.[5] Data regarding neoadjuvant and adjuvant therapy, disease recurrence, and survival were additionally collected. Recurrence of disease was specifically determined according to review of patient medical records, radiographic reports on surveillance imaging, and/or biopsy results. Institutional review board approval was obtained before data collection.

Statistical Analyses

Descriptive and comparative analyses were performed on the entire cohort. Recurrence-free survival (RFS) was calculated from the date of operation to the date of recurrence diagnosis. All statistical analyses were performed using SPSS version 23.0 (Armonk New York Software, IBM Inc., Armonk, New York, USA). Chi square analyses and Fisher's exact tests were used to compare categorical variables, and Student's t test was used for continuous variables, where indicated. Uni- and multivariable Cox regression analyses were performed to assess the association of individual pathologic factors with RFS. Kaplan–Meier survival plots for RFS were created, and variables were compared using log-rank tests. Statistical significance was predefined as a p value lower than 0.05.

RESULTS

Patient Variables

Of 265 patients with gastrointestinal/pancreatic neuroendocrine tumors and tissue available for pathologic re-review, 98 (37%) had primary PanNETs, and 83 (31%) had

well-differentiated, non-metastatic pancreatic tumors that underwent curative-intent resection. After exclusion of 11 patients with a Ki-67 index of 3% or higher, 72 (27%) patients who had primary resected PanNETs with a Ki-67 index lower than 3% were available for analysis.

The baseline demographics and clinicopathologic features of this study cohort are summarized in Table 1. The mean age was 55 years. Nearly half of the patients (46%, $n = 33$) were male, and 74% ($n = 53$) were white. The mean tumor size was 3.2 cm, and 26% ($n = 19$) of the PanNETs were considered functional tumors. The location for 51% of the tumors ($n = 37$) was in the body or tail of the pancreas, and 71% ($n = 51$) were resected via an open procedure. Whereas 64 (89%) underwent R0 resections, only 8 (11%) underwent R1 resections. No R2 resections were performed in our study cohort, and 90% of all recurrences were at distant sites. Only 5 of the 72 patients received systemic therapy, 3 of which were treated neoadjuvantly.

Pathologic Re-review and Ki-67 Data

Among the 72 well-differentiated PanNETs with a Ki-67 index lower than 3%, Ki-67 was further stratified into three initial groups after pathologic re-review: group A (< 1%: $n = 43$, 60%), group B (1–1.99%: $n = 23$, 32%), and group C (2–2.99%: $n = 6$, 8%) (Table 2). Representative immunohistochemical KI-67 slides for this grouping are shown in Fig. 1. These groups were well-matched in terms of baseline demographic and operative variables including age, race, comorbidities, location of PanNET, tumor size, and operative blood loss ($p > 0.05$). However, the groups displayed key pathologic differences. Groups B and C were characterized by advanced T stage (44 and 67%, respectively) compared with group A (12%) ($p = 0.003$), as well as by an increased incidence of lymphovascular invasion (LVI) (83% in group C vs 23% in Group A) ($p = 0.007$) (Table 2).

Recurrence-Free Survival Analysis

The median follow-up period was 39 months (interquartile range [IQR] 7.1–60.3). In the Kaplan-Meir analysis, the 3-year RFS was 97% for group A, 71% for group B, and 67% for C ($p = 0.018$) (Fig. 2a).

Ki-67 Index as a Guide for Re-stratification

Given the similarity in pathologic characteristics and RFS between groups B and C, these groups were combined to form two final subsets of patients with well-differentiated, low-grade PanNETs for subsequent survival analysis: group A with a Ki-67 lower than 1% ($n = 43$, 60%) and

TABLE 1 Baseline demographics and clinicopathologic variables of patients with primary pancreatic neuroendocrine tumors who underwent curative-intent resection at a single institution from 2000 to 2013 ($n = 72$)

Baseline variables	*n* (%)
Mean age (years)	55 ± 13
Male	33 (46)
Mean BMI	29 ± 8
Comorbidities[a]	
0	39 (54)
1	24 (33)
≥ 2	9 (13)
Race	
White	53 (74)
Black	14 (19)
Other	4 (7)
ASA class	
1	3 (4)
2	33 (46)
3	30 (42)
4	2 (3)
Functional tumor	19 (26)
Insulinoma	17 (24)
Glucagonoma	1 (1)
Gastrinoma	1 (1)
Mean CgA (ng/L)	125 ± 183
Operative/pathologic data	
Mean tumor size (cm)	3.2 ± 3.0
Location of tumor in pancreas	
Head/uncinate	28 (39)
Neck	7 (10)
Body/tail	37 (51)
Surgical technique	
Open	51 (71)
Laparoscopic	9 (13)
Other	12 (17)
Type of resection	
Enucleation	10 (14)
Classic pancreatoduodenectomy	6 (8)
Pylorus-preserving pancreatoduodenectomy	14 (19)
Central pancreatectomy	6 (8)
Distal pancreatectomy	36 (50)
Mean EBL (mL)	216 ± 162
Ki-67 Index (%)	
< 1	43 (60)
1–1.99	23 (32)
2–2.99	6 (8)

BMI body mass index, *ASA* American Society of Anesthesiologists, *CgA* chromogranin A, *EBL* estimated blood loss

[a]Comorbidities are defined as any concurrent medical condition, including, but not limited to, heart disease, chronic pulmonary disease, diabetes, renal disease, and liver disease as per the Charlson Comorbidity Scoring System

TABLE 2 Distribution of covariates among patients with low-grade non-metastatic primary pancreatic neuroendocrine tumors who underwent curative-intent resection from 2000 to 2013 at a single institution, stratified by the Ki-67 index

Covariates	Group A Ki-67 < 1% ($n = 43$) n (%)	Group B Ki-67 1–1.99% ($n = 23$) n (%)	Group C Ki-67 2–2.99% ($n = 6$) n (%)	p value[a]
Mean age (years)	57 ± 14	52 ± 12	50 ± 10	0.261
Male	18 (42)	12 (52)	3 (50)	0.709
Race				0.522
White	30 (71)	19 (83)	4 (67)	
Black	9 (21)	4 (17)	1 (17)	
Other	3 (71)	0 (0)	1 (17)	
Mean BMI (kg/m^2)	30 ± 8	27 ± 6	28 ± 8	0.498
Comorbidities				0.591
0	22 (51)	13 (57)	4 (67)	
1	14 (33)	9 (39)	1 (17)	
≥ 2	7 (16)	1 (4)	1 (17)	
Mean tumor size (cm)	2.8 ± 2.6	3.7 ± 3.7	4.4 ± 1.9	0.327
Location of PanNET				0.418
Head/uncinate	15 (35)	11 (48)	2 (33)	
Neck	3 (7)	4 (17)	0 (0)	
Body/tail	25 (58)	8 (35)	4 (67)	
Surgical technique				0.065
Open	28 (65)	19 (83)	4 (67)	
Laparoscopic	6 (14)	2 (9)	1 (17)	
Other	9 (21)	2 (9)	1 (17)	
Type of resection				0.629
Enucleation	5 (12)	5 (22)	0 (0)	
Classic PD	3 (7)	2 (9)	1 (17)	
PPPD	8 (19)	5 (22)	1 (17)	
Central pancreatectomy	2 (5)	3 (13)	1 (17)	
Distal pancreatectomy	25 (58)	8 (35)	3 (50)	
Mean EBL (mL)	188 ± 124	257 ± 213	300 ± 265	0.417
AJCC T stage				0.003
T1	18 (43)	10 (44)	0 (0)	
T2	19 (45)	2 (9)	2 (33)	
T3	5 (12)	10 (44)	4 (67)	
Mitotic rate				0.480
< 2	17 (85)	10 (77)	5 (100)	
2–20	3 (15)	3 (23)	0 (0)	
Final resection status				0.099
R0[b]	41 (95)	18 (78)	5 (83)	
R1[b]	2 (5)	5 (22)	1 (17)	
LVI				0.007
Negative	27 (77)	9 (50)	1 (17)	
Positive	8 (23)	9 (50)	5 (83)	
PNI				0.391
Negative	26 (77)	12 (71)	5 (100)	
Positive	8 (24)	5 (29)	0 (0)	
Lymph node positive	6 (21)	6 (32)	1 (25)	0.696

BMI body mass index, *PanNET* pancreatic neuroendocrine tumor, *PD* pancreatoduodenectomy, *PPPD* pylorus-preserving pancreatoduodenectomy, *EBL* estimated blood loss, *AJCC* American Joint Committee on Cancer, *LVI* lymphovascular invasion, *PNI* perineural invasion

[a]Statistical significance is indicated by a p value lower than 0.05

[b]R0 resection refers to negative margins on pathologic review of the specimen, whereas R1 resection refers to positive margins on pathologic review of the specimen

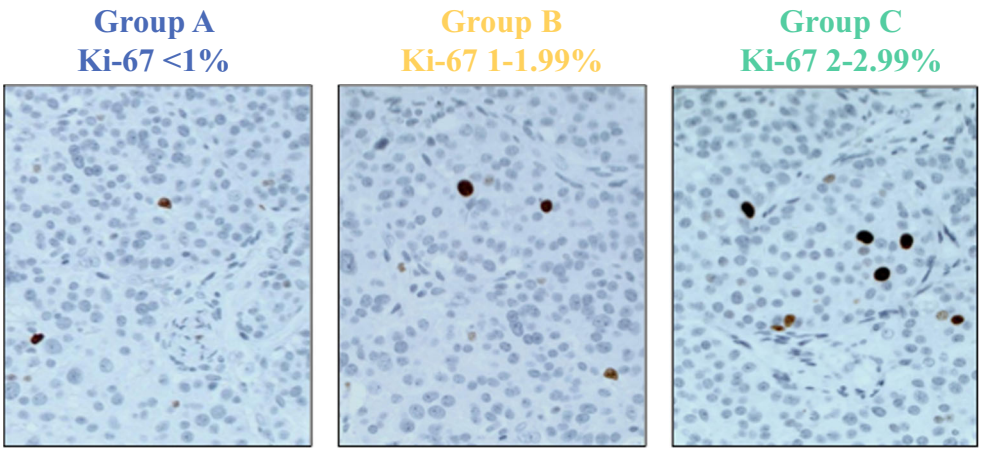

FIG. 1 Re-stratification of Ki-67 based on histologic analysis by a pathologist blinded to all other clinicopathologic variables using tissue microarray blocks made in triplicate. Patients with low-grade, Ki-67 < 3% were further stratified into 3 initial groups based on immunohistochemical expression: Group A (Ki-67 < 1%), Group B (Ki-67 1–1.99%), and Group C (Ki-67 2–2.99%)

groups B and C with a Ki-67 of 1–2.99% ($n = 29$, 40%). Analysis showed that group A had a 3-year RFS of 97%, whereas groups B and C had a decreased 3-year RFS of 70% ($p = 0.005$) (Fig. 2b).

A subgroup analysis also was performed excluding the 20 patients of the study group with functional and syndromic PanNETs. The results indicated a 23% decrease in 3-year RFS (96% vs 73%) for the combined groups B and C compared with group A ($p = 0.017$) (Fig. 2c).

Predictors for Recurrence-Free Survival

In the univariable Cox regression analysis, a Ki-67 index of 1% to 2.99% (HR 7.1; 95% CI 1.5–33.8; $p = 0.014$), tumor size, final resection status, perineural invasion (PNI), lymph node positivity, and advanced T stage each was associated with worse RFS (Table 3). In the multivariable analysis, R1 resection and Ki-67 (HR 8.6; 95% CI 1.0–70.7; $p = 0.045$) remained independently significant, even when these other adverse clinicopathologic factors were taken into account (Table 3).

DISCUSSION

Although well-differentiated, low-grade PanNETs are uniformly noted to have improved recurrence and overall survival compared with high-grade PanNETs (i.e., pancreatic NECs), significant heterogeneity in outcomes among these well-differentiated tumors remains.[12,13] The absence of a reliable risk stratification scheme to discriminate among well-differentiated, low-grade PanNETs has hindered ability to predict disease recurrence adequately after surgical resection.[13,17] Furthermore, grouping up to 80% of resected PanNETs as well-differentiated (grade 1 or 2) limits ability to guide individualized postoperative management and surveillance.[2,13,18,19]

Findings have shown the Ki-67 index to be a particularly sensitive histopathologic marker for a more aggressive clinical course.[9,20] However, the current method of using broad Ki-67 categories to define PanNETs may obscure the true prognostic value of this variable, particularly for the low-grade cohort.[10] Indeed, our findings suggest that even among well-differentiated, low-grade PanNETs, a Ki-67 index of 1–2.99% is independently associated with an eightfold increase in risk of disease recurrence compared with tumors that have a Ki-67 index lower than 1%, even after the study has accounted for other adverse clinicopathologic variables.

Previous studies have attempted to determine the optimal Ki-67 index cutoff point to predict outcomes for low-to-intermediate grade PanNETs.[21] For example, Lowe et al.[9] demonstrated that a Ki-67 index above 10% rather than above 3% better predicts lymph node metastases and poor overall survival (OS). Another study by Hamilton et al.[22] found that a Ki-67 index higher than 9% predicts a higher likelihood of disease recurrence and worse OS. Finally, a Ki-67 index cutoff of 7.5% was the recommendation of Goodell et al.[23] However, these studies included both low- and intermediate-grade PanNETs in their analyses instead of focusing solely on the well-differentiated, low-grade subset. Because our findings suggest heterogeneity in disease recurrence when the Ki-67 index is used for stratification, even for such low-grade PanNETs, it may be inappropriate to increase the Ki-67 cutoff to classify more patients into the low-grade group. Partly due to the rarity of PanNETs, studies that focus on this subset with a Ki-67 lower than 3% currently are limited.

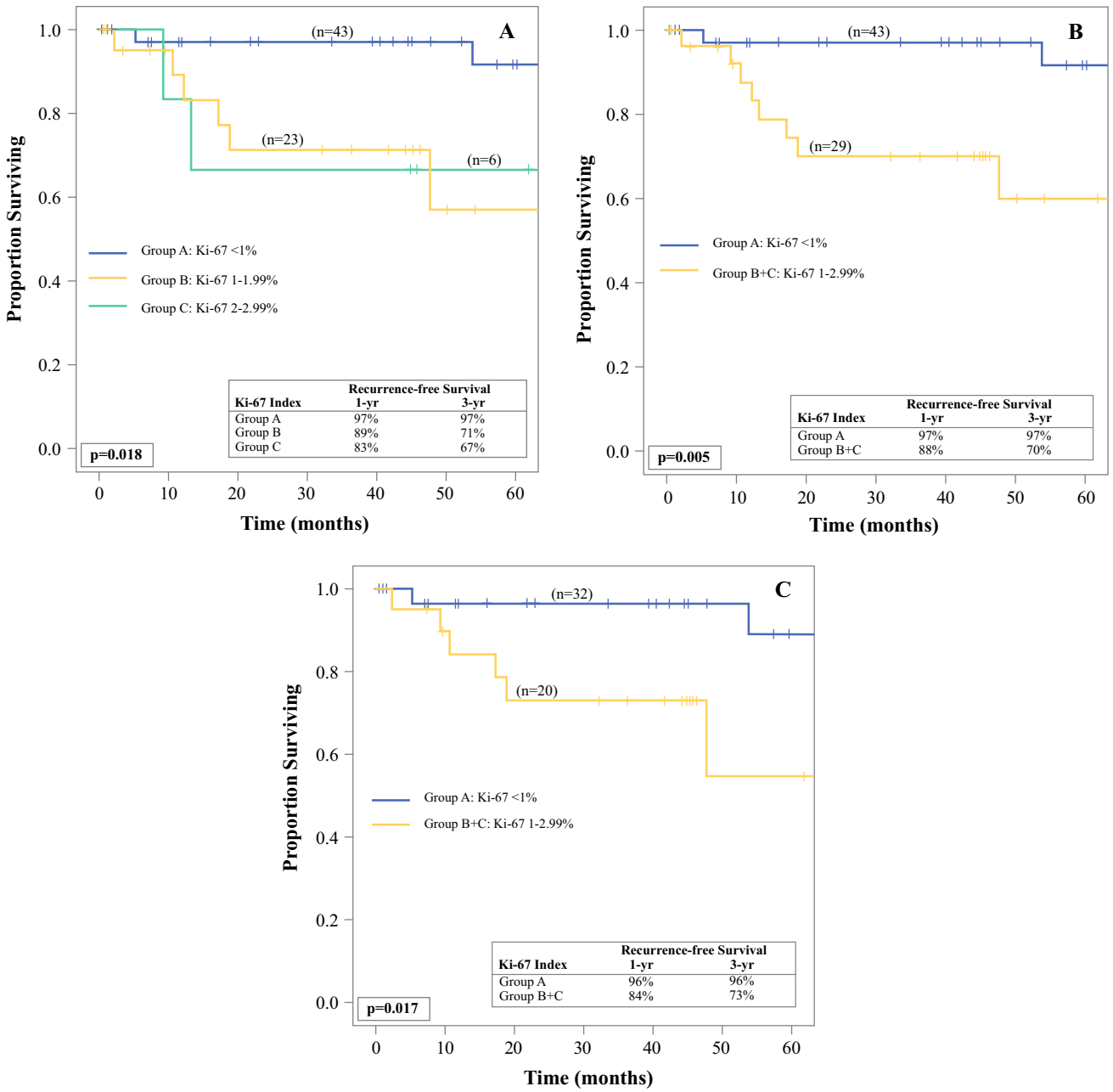

FIG. 2 Kaplan-Meier survival curve for recurrence-free survival in re-stratified Ki-67 index groups. **a** There is no statistically significant difference between Group B (Ki-67 1–1.99% ($n = 23$)) and Group C (Ki-67 2–2.99% ($n = 6$)), but both are associated with worse RFS compared to Group A (Ki-67 $< 1\%$ ($n = 43$)). Log-rank p value $= 0.018$; **b** The combined Groups B and C (Ki-67 1–2.99% ($n = 29$)) show a 27% decrease in 3-year RFS compared with Group A (Ki-67 $< 1\%$ ($n = 43$)). Log-rank p value $= 0.005$. **c** After excluding functional and syndromic PanNETs ($n = 20$), the combined Groups B and C (Ki-67 1–2.99% ($n = 20$)) show a 23% decrease in 3-year RFS compared with Group A (Ki-67 $< 1\%$ ($n = 32$)). Log-rank p value $= 0.017$

In our study, the PanNET patients with a Ki-67 lower than 1% had improved RFS compared with the patients who had a Ki-67 index of 1–2.99%, with an RFS of 97% at 3 years versus 70%, respectively. Although no studies to our knowledge have focused on the effect of the Ki-67 index on RFS in well-differentiated, low-grade PanNETs, a study by Boyar Cetinkaya et al.[3] did show a significant difference in 5-year OS for patients who had PanNETs with a Ki-67 lower than 2% (75.2%) versus a Ki-67 of 3–20% (55.8%) ($p = 0.04$).[3] This difference continued in the analysis of 10-year OS in this study, with a Ki-67 lower than 2% related to a 68.9% survival compared with a 46.5% survival for a Ki-67 of 3–20% ($p = 0.03$).

TABLE 3 Association of clinicopathologic factors with recurrence of disease in patients with non-metastatic primary pancreatic neuroendocrine tumors who underwent curative-intent resection from 2000 to 2013 at a single institution

Variables	Univariable analysis RFS		Multivariable analysis[a] RFS	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age	1.0 (0.9–1.0)	0.078	–	–
Gender			–	–
Male	Reference			
Female	1.8 (0.5–6.6)	0.343		
Race			–	–
White	Reference			
Black	1.8 (0.5–6.9)	0.407		
Other	0.0 (0.0–0.0)	0.986		
BMI (kg/m^2)	0.9 (0.8–1.1)	0.309	–	–
Comorbidities			–	–
0	Reference			
1	1.2 (0.3–4.2)	0.817		
≥ 2	0.0 (0.0–0.0)	0.980		
Functional tumor	0.05 (0.0–2.4E+28)	0.931		
Type of resection			–	–
Enucleation	Reference			
Pancreatoduodenectomy	1.3 (0.1–14.2)	0.842		
Pylorus-preserving pancreatoduodenectomy	0.9 (0.1–8.9)	0.940		
Central pancreatectomy	0.0 (0.0–0.0)	0.985		
Distal pancreatectomy	0.4 (0.0–3.8)	0.442		
EBL (mL)	1.0 (1.0–1.0)	0.064	–	–
Ki-67 index				
< 1	Reference		Reference	
1–2.99	7.1 (1.5–33.8)	0.014	8.6 (1.0–70.7)	0.045
Tumor size (cm)	1.1 (1.0–1.3)	0.032	1.0 (0.9–1.2)	0.695
Final resection status				
R0[b]	Reference		Reference	
R1[b]	5.1 (1.3–20.2)	0.019	9.3 (1.3–66.8)	0.026
Mitotic rate (per 10 HPF)			–	–
< 2	Reference			
2–20	1.9 (0.4–10.5)	0.451		
Lymphovascular invasion			–	–
Negative	Reference			
Positive	133.3 (0.2–89,108)	0.140		
Perineural invasion			–	–
Negative	Reference			
Positive	6.3 (1.1–34.8)	0.035		
Lymph node-positive	5.9 (1.6–21.5)	0.007	6.1 (1.0–38.0)	0.054
Advanced T stage				
T1/T2	Reference		Reference	
T3	25.1 (3.2–199.9)	0.002	3.9 (0.4–39.3)	0.249

RFS recurrence-free survival, *HR* hazard ratio, *CI* confidence interval, *BMI* body mass index, *EBL* estimated blood loss, *HPF* high-power fields

[a]Variables were included in the multivariable analysis based on statistical significance in the univariable analysis. Perineural invasion was not included in the final multivariable model due to small numbers to allow adequate analysis

[b]R0 resection refers to negative margins on pathologic review of the specimen, whereas R1 resection refers to positive margins on pathologic review of the specimen

Another study by Miller et al.[19] also analyzed OS for patients whose NETs were graded on the basis of the WHO/European Neuroendocrine Tumor Society (ENETS) stratification scheme. In this study, those classified as having low-grade tumors had an OS of 87% compared with 83 and 50% for the patients with intermediate- and high-grade tumors, respectively.[19] However, this study did not focus solely on PanNETs, but rather on all gastrointestinal NETs.

Finally, a study by Panzuto et al.[24] also identified the Ki-67 index as a risk factor for disease progression in PanNETs. In their study, compared with low-grade PanNETs, intermediate-grade (Ki-67 3–20%) and high-grade (Ki-67 $>$ 20%) PanNETs were associated respectively with 3.43-fold ($p < 0.001$) and 1.5-fold ($p = 0.074$) increases in risk for progression (Ki-67 $\leq$ 2%).[24]

To our knowledge, this study is the first to evaluate the use of the Ki-67 index to further risk stratify and predict outcomes for well-differentiated, low-grade PanNETs. These findings may be used to guide future management of low-grade PanNETs given the unclear current National Comprehensive Cancer Network (NCCN) guidelines regarding surgical resection versus observation for small well-differentiated, low-grade PanNETs.[15] These results could perhaps be extrapolated to support surgical resection of PanNETs 2 cm in size or smaller if the measured Ki-67 index is higher than 1% on a preoperative biopsy because tumors with a Ki-67 index higher than 1% may display more aggressive behavior. Specifically, this study demonstrated higher recurrence rates after resection for such tumors compared with those smaller than 1%. Moreover, postoperative surveillance could be increased to include imaging at shorter intervals rather than intervals of 1 year or longer, as per the current standard of care.[15] Ultimately, this proposed stratification scheme could be included in future adjuvant trials for the development of targeted postoperative therapy, as the armamentarium for PanNETs continues to improve.

This study had various limitations, including its retrospective design using data from a single institution with a relatively small number of patients who had tissue available for analysis. Pathologic re-review was performed only for Ki-67, which left data on other important histopathologic factors such as lymphovascular and perineural invasion dependent on the original surgical pathology reports, from which they were frequently missing. Moreover, the creation of tissue microarrays from random areas in each tumor may have underestimated the Ki-67 index because hot-spot analysis generally is used in the clinical setting. The applicability of our findings is further limited by the numerous and unstandardized methods that currently exist for measuring Ki-67 proliferation and their variable reported accuracy and reliability.[23,25]

In conclusion, our data suggest that even within well-differentiated, low-grade PanNETs, the Ki-67 index is a strong predictor of disease recurrence. This may have implications for its incorporation into future grading systems, treatment recommendations, and surveillance protocols as the management for PanNETs continues to evolve.

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