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ORIGINAL ARTICLE – PANCREATIC TUMORS

Impact of Tumor Grade on Pancreatic Cancer Prognosis: Validation of a Novel TNMG Staging System

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ABSTRACT

Background. Pancreatic ductal adenocarcinoma (PDAC) patients demonstrate highly variable survival within each stage of the American Joint Committee on Cancer (AJCC) staging system. We hypothesize that tumor grade is partly responsible for this variation. Recently our group developed a novel tumor, node, metastasis, grade (TNMG) classification system utilizing Surveillance Epidemiology and End Results (SEER) data in which the presence of high tumor grade results in advancement to the next higher AJCC stage. This study's objective was to validate this TNMG staging system utilizing single-institution data.

Methods. All patients with PDAC who underwent resection at UCLA between 1990 and 2009 were identified. Clinicopathologic data reviewed included age, sex, node status, tumor size, grade, and stage. Grade was redefined as a dichotomous variable. The impact of grade on survival was assessed by Cox regression analysis. Disease was restaged into the TNMG system and compared to the AJCC staging system.

Results. We identified 256 patients who underwent resection for PDAC. Patients with low-grade tumors experienced a 13-month improvement in median survival compared to those with high-grade tumors. On multivariate analysis, tumor grade was the strongest predictor of survival with a hazard ratio of 2.02 ($p = 0.0005$). Restaging disease according to the novel TNMG staging system resulted in improved survival discrimination between stages compared to the current AJCC system.

Conclusions. We were able to demonstrate that grade is one of the strongest independent prognostic factors in PDAC. Restaging with our novel TNMG system demonstrated improved prognostication. This system offers an effective and convenient way of adding grade to the current AJCC staging system.

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Tumor grade is a measure of the degree of differentiation of the tumor. Roughly, grade measures how closely the malignant cells resemble the morphologic and functional characteristics of the tissue of origin.[1] Epithelial malignancies can range from well-differentiated tumors that closely resemble the tissue of origin to poorly differentiated or undifferentiated tumors where the tissue of origin is difficult to discern.[2] In pancreatic ductal adenocarcinoma (PDAC), tumor grade has been identified as a significant independent prognostic indicator of overall survival after resection.[3–10] This is likely because less differentiated tumors possess a more aggressive biology, leading to earlier local and distant metastasis.[11] Despite this robust association of tumor grade with survival, the impact of grade on the staging system for PDAC is curiously absent.

The American Joint Committee on Cancer (AJCC) produces the *AJCC Cancer Staging Manual,* currently in its seventh edition, released in 2010. This manual determines PDAC stage on the basis of primary tumor size (T stage), regional lymph node status (N stage), and distant metastasis (M stage).[2] The AJCC stage for PDAC patients is utilized by health professionals to determine stage-appropriate cancer treatment. Moreover, it is an invaluable tool with which providers can temper patient expectations utilizing correlative outcomes of previous patients with similar stage disease.[2] Additionally, staging is utilized for patient stratification during experimental design to assess treatment effect.

The AJCC updates the staging manual as newly acquired knowledge of cancer pathology and biology becomes available, and when new markers have sufficient independent impact, they are incorporated into the staging system. The Gleason score, a measure of the tumor grade in prostate cancer, is a notable example of a new marker to be included in the *AJCC Cancer Staging Manual*.[2] In a previous *Annals of Surgical Oncology* publication, our group, utilizing Surveillance Epidemiology and End Results (SEER) data, proposed a novel staging system for PDAC that accounts for the significant independent impact of tumor grade on overall survival.[3] This novel TNMG (tumor, node, metastasis, grade) staging classification system divided grade into a dichotomous variable, where well-differentiated and moderately differentiated tumors were combined to form a low-grade group, and poorly differentiated and undifferentiated tumors were combined into a single high-grade group. The occurrence of a high-grade tumor resulted in the patient being advanced to the next higher AJCC stage.

The aim of this study was to utilize our single-institution, prospectively maintained PDAC database to assess the impact of tumor grade on overall survival after resection. We hypothesized that tumor grade would be a significant predictive factor of prognosis independent of other known factors with adverse effects on survival. We also sought to validate a novel TNMG staging system as a mechanism to incorporate tumor grade into the existing TNM system in a simple and convenient way without introducing excessive complexity. Validation with institutional-level data addresses some of the limitations of SEER data, including stage accuracy, margin status, and inter-observer pathologist variability.[12]

MATERIALS AND METHODS

Patient Selection

All patients who were diagnosed with PDAC and underwent operative resection at UCLA between 1990 and 2009 were identified. Selection criteria for resection included medical fitness for major laparotomy, no evidence of disseminated disease, and no evidence of tumor involvement of mesenteric vessels. Patients who underwent surgical exploration and whose disease was found to be unresectable as a result of locally advanced or metastatic disease were excluded. Our UCLA PDAC database was constructed under the approval of the UCLA institutional review board and is maintained prospectively. Clinicopathologic data were collected from medical records. Data collected included demographics (age, gender), primary tumor characteristics [size, grade, perineural involvement (PNI), lymphovascular invasion (LVI)], nodal staging, margin status, AJCC staging, type of resection (pancreaticoduodenectomy, distal pancreatectomy), adjuvant therapy (radiotherapy, chemotherapy), and survival.

Statistical Analysis

Kaplan–Meier curves and log-rank tests were used to identify differences in overall survival, defined as duration of survival from the time of diagnosis. Predictors of survival after surgical resection were identified by univariate analysis. Variables identified on univariate analysis that were associated with survival were then evaluated utilizing proportional hazard regression modeling. Variables included in the model were tumor size, lymph node status, margin status, and tumor grade. Of note, grade was redefined as a dichotomous, categorical variable: well-differentiated and moderately differentiated tumors were combined into a low-grade group, and poorly differentiated and undifferentiated tumors became a high-grade group. Differences between categorical variables were compared between low-grade and high-grade groups by Chi square or Fisher's exact test where appropriate, while differences between continuous variables were compared by t test. Differences were considered significant at $p = 0.05$, and confidence intervals are reported at 95 %. All statistical analysis was performed by SPSS 16.0 statistical software (IBM, Armonk, NY).

RESULTS

Patient Demographics

Our study population consisted of 256 patients who underwent resection for PDAC between 1990 and 2009. There were 132 male and 124 female subjects. The median age at diagnosis was 67. One hundred ninety-five patients had died at the time of last follow-up, with the median time to death from diagnosis of 21 months. The median follow-up of survivors was 48 months.

Tumor Characteristics

The median tumor size for the cohort was 2.6 cm (range 1–9 cm). Tumor grade was reported for 253 (98.8 %) patients, and there were 37 (14.5 %) well-differentiated tumors, 120 (46.9 %) moderately differentiated tumors, and 96 (37.5 %) poorly differentiated tumors.

Surgical Resection

The distribution of surgical resections were as follows: 228 pancreaticoduodenectomies, 1 middle pancreatectomy,

23 distal pancreatectomies, and 4 total pancreatectomies. Margin status was positive in 43 (16.8 %) patients. Metastasis to the locoregional lymph nodes was discovered in 136 (53.1 %) patients. The median number of lymph nodes reviewed was 12.

Demographic, tumor, and treatment characteristics for the entire cohort as well as the low-grade and high-grade groups are detailed in Table 1. Significant differences between the low-grade and the high-grade groups were found with regard to occurrence of metastasis to the regional lymph nodes and margin positivity, while all other factors considered were not significantly different between the two groups.

Univariate Predictors of Outcome

Age, sex, and tumor size were not associated with differences in survival. Lymph node status was predictive of outcome, with node-negative patients having a median survival of 37 months and node-positive patients having a median survival of 21 months. Additionally, tumor grade was a significant predictor of outcome, with patients with low-grade tumors experiencing a median survival of 34 months and those with high-grade tumors having a median survival of 21 months (Table 2). Other tumor characteristics such as PNI and LVI also demonstrated significant associations with decreased survival. Patients with PNI had a median survival of 26 versus 30 months for those without. Patients with LVI had a median survival of 23 versus 30 months for those without. The major surgical factor that influenced long-term survival was margin status; margin-positive patients had a median survival of 19 versus 29 months for those with a negative margin. Patients who received adjuvant chemotherapy had significantly greater median survival (31 months) versus those patients who did not receive chemotherapy (8 months); however, most patients (91 %) received adjuvant chemotherapy. There was no significant difference in survival between the groups that received adjuvant radiotherapy and those that did not.

Multivariate Predictors of Outcome

Multivariate analysis of tumor grade, lymph node status, tumor size, margin status, PNI, and LVI identified the following independent predictors of adverse outcome: lymph node positivity and high-grade tumors (Table 2). There was no collinearity of variables measured between the variables included in the analysis. The hazard ratio (HR) associated with high-grade tumors (HR 2.2) was of an even greater magnitude and significance when compared to lymph node positivity (HR 1.58).

Impact of Tumor Grade

Tumor grade was a significant predictor of outcome: patients with low-grade tumor had a median survival of 34 months, while patients with high-grade tumor had a median survival of 21 months ($p \leq 0.0001$) (Fig. 1). When patients were stratified on the basis of lymph node status, both lymph node–negative ($p \leq 0.0001$) and lymph node–positive patients ($p = 0.02$) had significantly worse overall survival with high-grade versus low-grade tumor. Tumor grade was then incorporated into the current AJCC (TNM) staging system to generate a novel TNMG staging system, as previously described utilizing SEER data by Wasif et al.[3] This TNMG staging system differs from the AJCC system by the inclusion of tumor grade, whereby a patient with a high-grade tumor is advanced to the next higher stage and a patient with a low-grade tumor continues with the same stage. For example, if a patient is AJCC stage IIa (tumor extends beyond the border of the pancreas; lymph node negative) and additionally is found to be high grade, that patient would be advanced to stage IIb in the proposed TNMG system. By restaging patients in this manner, the impact of grade on survival can be realized—for example, by advancing the high-grade tumor patients in stage Ia to stage Ib, the median survival for the Ia patients increases from 45 to 56 months (Fig. 2). Additionally, the advancement of high-grade stage IIb patients to stage III results in significant discrimination; the IIb patients have a median survival of 21 versus 17 months for the stage III patients ($p = 0.04$). Restaging results in improved discrimination in overall survival between stages compared to the current AJCC system (Fig. 3). Figure 2 presents the current AJCC staging system and the novel TNMG staging system plotted against median survival. On linear regression analysis, the AJCC and TNMG staging systems correlate similarly with median survival ($r^2 = 0.99$ and 0.97, respectively); however, the slope of the TNMG correlation is much steeper then the AJCC correlation ($m = -9.8$ vs. -7.9). This indicates that the TNMG scoring system is able to distribute patients over a wider range of survival; for each increase in stage category, the TNMG staging system results in a greater decrease in median survival.

DISCUSSION

The aim of this study was to utilize our UCLA experience from a prospectively maintained PDAC database to assess the impact of tumor grade on prognosis after operative resection and, we hoped, validate our previously published novel TNMG staging system.[3] We believe that some of the variability in survival within each AJCC stage may be influenced by factors that are not currently included in the staging system, primarily tumor grade. Our data

TABLE 1 Demographic, tumor, and treatment characteristics

Demographic	All patients ($n = 256$)	Low grade ($n = 157$)	High grade ($n = 96$)	p
Sex				
Male	132 (51.6 %)	81 (51.6 %)	49 (51.0 %)	0.932
Female	124 (48.4 %)	76 (48.4 %)	47 (49.0 %)	
Age (years)				
Mean ± SD	65.3 ± 11.1	65.2 ± 11.8	65.3 ± 10.0	0.949
Median	66	65	67	
Type of surgery				
Whipple	228 (89.1 %)	143 (91.1 %)	82 (85.4 %)	0.384
Middle	1 (0.4 %)	1 (0.6 %)	0 (0.0 %)	
Distal	23 (9.0 %)	11 (7.0 %)	12 (12.5 %)	
Total	4 (1.6 %)	2 (1.3 %)	2 (2.1 %)	
Tumor size (cm)				
Mean ± SD	3.0 ± 1.6	3.0 ± 1.6	3.0 ± 1.4	0.729
Median	2.6	2.7	2.5	
Lymph node status				
Positive	136 (53.1 %)	75 (47.8 %)	60 (62.5 %)	0.023
Negative	120 (46.9 %)	82 (52.2 %)	36 (37.5 %)	
Positive lymph nodes, mean ± SD	1.7 ± 2.8	1.6 ± 3.0	2.0 ± 2.7	0.246
No. of lymph nodes reviewed				
Mean ± SD	13.7 ± 9.3	13.3 ± 8.7	14.4 ± 10.3	0.372
Median	12	12	13	
AJCC stage				
Ia	32 (12.0 %)	23 (14.6 %)	6 (6.3 %)	0.06
Ib	44 (16.5 %)	31 (19.7 %)	13 (13.5 %)	
IIa	45 (16.9 %)	28 (17.8 %)	17 (17.7 %)	
IIb	136 (51.5 %)	75 (47.8 %)	60 (62.5 %)	
Margin status				
Negative	213 (83.2 %)	136 (86.6 %)	74 (77.1 %)	0.05
Positive	43 (16.6 %)	21 (13.4 %)	22 (22.9 %)	
Chemotherapy				
Negative	18 (7.0 %)	13 (8.3 %)	5 (5.2 %)	0.49
Positive	172 (67.2 %)	109 (69.4 %)	61 (63.5 %)	
Radiotherapy				
Negative	84 (32.8 %)	62 (39.5 %)	22 (22.9 %)	0.158
Positive	63 (24.6 %)	39 (24.8 %)	23 (24.0 %)	

Significant differences between the low-grade and high-grade subgroups include lymph node positivity, and margin status

SD standard deviation, *AJCC* American Joint Committee on Cancer

demonstrate that high-grade tumors are independent and significant predictors of decreased overall survival. When patients are restaged according to the novel TNMG staging system, we are able to generate improved survival discrimination between the stages when compared to the AJCC system. The impact of grade on survival in PDAC has previously been elucidated in a number of single-institution studies, with published multivariate HRs of between 1.14 and 2.56.[9,10,13] Our single-institution data correlate well with these previously published results; we were able to demonstrate a HR of 2.16 on multivariate survival analysis.

The impetus of this study was to demonstrate that tumor grade (HR 2.16), which carries at least as much influence over prognosis as lymph node status (HR 1.58), should be added to the AJCC staging system for PDAC. We believe that we have made a strong case for the addition of grade, and we have validated a novel TNMG staging system to conveniently and easily support the addition of grade. The TNMG system is able to identify those patients with the

Table 2 A Univariate analysis of overall survival indicating that high-grade tumors, lymph node positivity, margin positivity, chemotherapy, PNI, and LVI were all associated with worse median survival, (B) Cox regression multivariate analysis indicating that high-grade tumors and lymph node positivity are the only significant independent predictors of worse overall survival

	Patients	Median survival	Significance
(A) Univariate analysis			
Tumor grade			
Low	157	34.3	<0.0001
High	96	20.6	
Lymph node status			
Negative	120	37.2	0.0001
Positive	136	21.1	
Tumor size			
<2cm	57	30.4	0.39
>2cm	196	25.7	
Age			
<65	122	29.2	0.26
>65	134	25.4	
Sex			
Male	132	28.3	0.54
Female	124	25.4	
Margin			
Negative	213	29.0	0.01
Positive	43	19.4	
Chemotherapy			
Negative	18	8.3	0.0001
Positive	172	31.1	
Radiation			
Negative	84	30.2	0.62
Positive	63	30.4	
PNI			
Negative	84	29.5	0.013
Positive	163	25.7	
LVI			
Negative	143	30.1	0.014
Positive	103	22.7	
	HR	Significance	95% CI
(B) Multivariate analysis			
Grade			
Low	1.0	<0.0005	1.55–3.01
High	2.16		
Lymph node status			
Negative	1.0	0.007	1.13–2.23
Positive	1.58		
Tumor size			
<2cm	1.0	0.258	0.56–1.17
>2cm	0.81		
Margin status			
Negative	1.0	0.624	0.74–1.67
Positive	1.11		

TABLE 2 continued

	HR	Significance	95% CI
PNI			
Negative	1.0	0.438	0.81–1.64
Positive	1.15		
LVI			
Negative	1.0	0.774	0.67–1.35
Positive	0.95		

most favorable prognosis: stage Ia patients with low-grade tumors. These patients had a median survival of 56 months in the TNMG system—an 11-month increase compared to stage Ia patients in the AJCC system. We are also able to identify those patients who may have a worse prognosis as a result of the presence of a high-grade tumor and move them to a stage that more accurately reflects their survival; for example, AJCC stage IIa (node negative) disease with high-grade tumors behaves more similarly to current AJCC stage IIb (node positive) disease. Upstaging these high-grade IIa patients results in a 5-month improvement in median survival for the remaining IIa patients (29 vs. 34 months), reflective of a less aggressive tumor biology.

Tumor stage is utilized in randomized controlled trials to stratify patients into proper treatment groups, and the lack of inclusion of grade in the AJCC staging system could potentially lead to unequal distribution of high-grade tumor patients. For example, the CONKO-001 trial

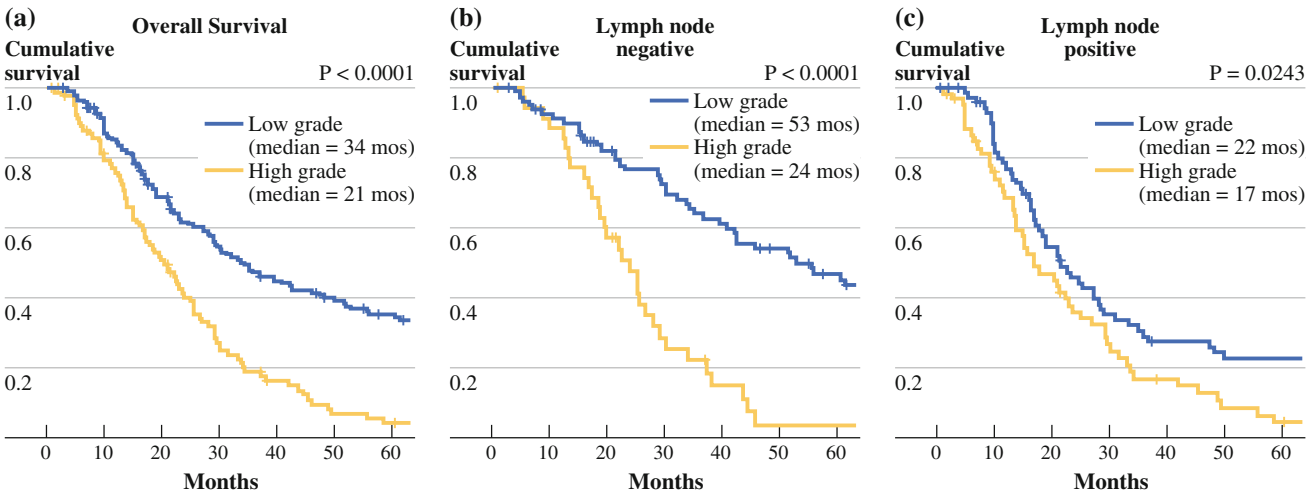
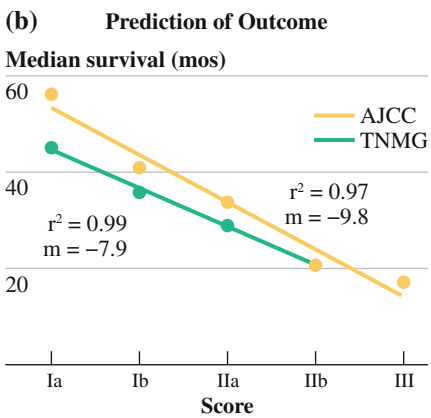


FIG. 1 Kaplan–Meier survival curves according to tumor grade **a** for the entire cohort, and stratified by lymph node status: **b** lymph node negative and **c** lymph node positive

FIG. 2 **a** Restaging according to TNMG classification. **b** Prediction of overall survival. Linear regression correlation of TNMG and AJCC staging systems to median survival are similar; however, the TNMG correlation is steeper, indicating distribution of patients over a wider range of survivals

(a)

TNM stage	Median survival (mos)	Tumor grade	TNMG stage	Median survival (mos)
IA	45	low	IA	56
		high	IB	41
IB	36	low		
		high	IIA	34
IIA	29	low		
		high	IIB	21
IIB	21	low		
		high	III	17



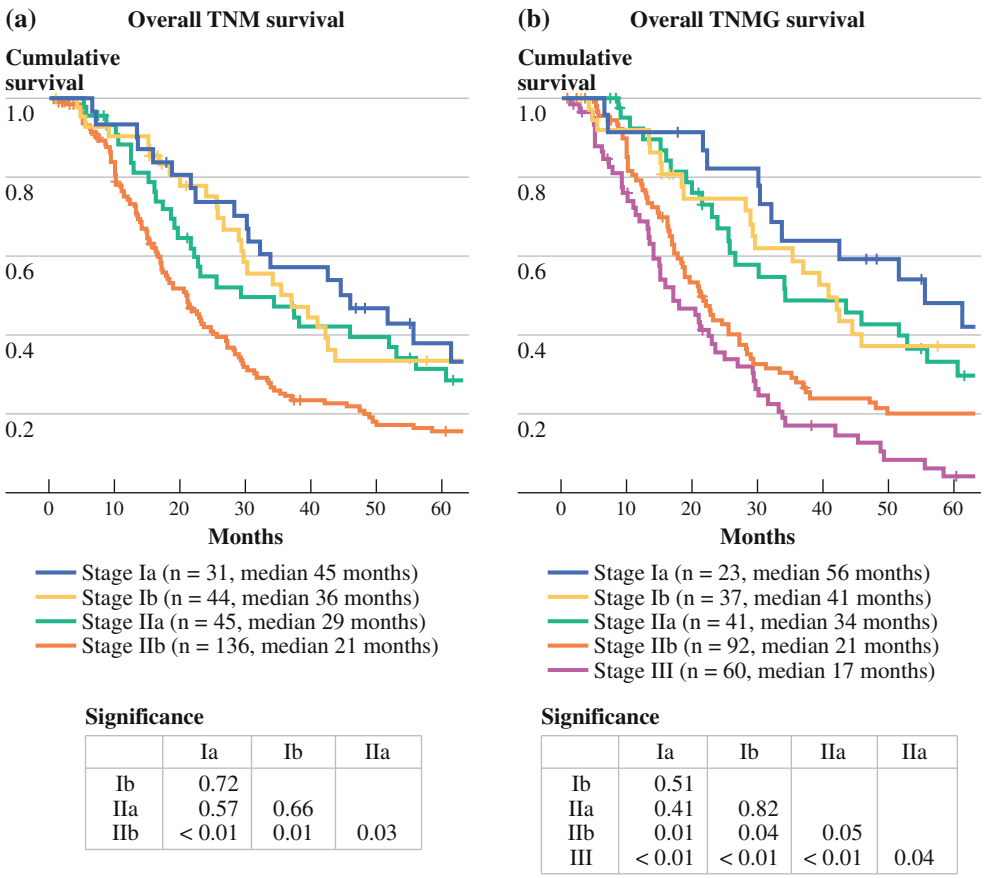


FIG. 3 Kaplan–Meier survival curves based on **a** TNM and **b** TNMG classification showing improved discrimination between stages in the TNMG system versus TNM system

Significance

	Ia	Ib	IIa
Ib	0.72		
IIa	0.57	0.66	
IIb	< 0.01	0.01	0.03

Significance

	Ia	Ib	IIa	IIa
Ib	0.51			
IIa	0.41	0.82		
IIb	0.01	0.04	0.05	
III	< 0.01	< 0.01	< 0.01	0.04

demonstrated an increase in median survival from 20.2 to 22.1 months with the addition of gemcitabine after resection.[14] However, the ESPAC-1 trial demonstrated an increase in median survival from 16.9 to 21.6 months with the addition of leucovorin and fluorouracil after resection.[15] Neither study stratified by grade. Our data demonstrate a 13-month difference in survival between patients with low-grade and high-grade tumors, indicating that when evaluating survival differences on the scale of 2–5 months, stratification by grade merits consideration. Stratification of future clinical trials by grade was also advocated by Vanderveen et al.[16] when they demonstrated that the benefit of adjuvant therapy on survival is more pronounced in high-grade tumors. The inclusion of grade in the *AJCC Cancer Staging System* for PDAC would be a mechanism to account for the significant impact of tumor grade on outcome in future clinical trials.

Perhaps the most significant attribute of the novel TNMG system is the ease with which it can be added to the existing AJCC staging system. Extensive work has been dedicated to the creation of pancreatic cancer staging nomograms that can provide more accurate prognostication of survival for PDAC patients, such as the nomogram developed and validated by the group from Memorial Sloan-Kettering Cancer Center.[4,5] These nomograms have not been widely accepted by practitioners as a result of their cumbersome nature and inherent complexities, coupled with the universally accepted nature of the *AJCC Cancer Staging Manual.* The novel TNMG staging system developed from SEER data and validated with our single-institution series data does not propose the creation of a new staging system, but rather builds on the current AJCC system in a manner that can fully account for the more aggressive biology of a high-grade tumor and its impact on survival. The simplicity with which this system could be incorporated and provide more accurate prognostication for patients is its greatest attribute. Tumor grade has already been accepted as part of the AJCC staging system for prostate cancer and sarcoma on the basis of the ability to discriminate differences in overall survival within those diseases.[2] Our analysis has demonstrated that tumor grade in PDAC is capable of doing the same and should therefore be strongly considered for addition to the AJCC staging system.

In summary, we used single-institution data to evaluate the impact of tumor grade as a significant and independent prognostic factor for survival after operative resection for PDAC. We demonstrated that tumor grade has a greater impact on survival then other, better-known factors, such as tumor size and lymph node status, which form the basis

of our current staging system. We believe that the incorporation of grade into the AJCC staging system would enhance the system's ability to provide more accurate prognostication that reflects the aggressive biology of high-grade tumors. The importance of these findings not only allows for more accurate patient education regarding prognosis and possibly adjuvant therapy decisions, but also may also have significant implications for patient stratification in future clinical trials.

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