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Tumor grade as significant prognostic factor in pancreatic cancer: validation of a novel TNMG staging system

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Aim of the study was to asses the tumor grade prognostic value in the Czech pancreatic cancer patients and to evaluate the accuracy of TNMG prognostic model. Retrospective analysis of 431 pancreatic cancer patients undergoing pancreatic resection in seven Czech oncological centers between 2003 and 2013 was performed. The impact of tumor grade and the accuracy of TNMG prognostic model were evaluated. Lymph node status, tumor size, tumor stage and grade were proved as statistically significant survival predictors. The lower tumor differentiation (grade 3 and 4) was associated with poorer prognosis in all stages (stage I: HR 2.23 [1.14; 4.36, CI 95%] p=0.019, stage II: HR 3.09 [2.01; 4.77, CI 95%] p=0.001, stage III and IV: HR 3.52 [1.73; 7.18, CI 95%] p=0.001). Kaplan-Meier analysis verified statistically significant impact of new TNMG stages on survival after resection for pancreatic cancer (p=0.001). In conclusion, we can state that the tumor grade was confirmed as statistically significant prognostic factor in pancreatic cancer. Its incorporation into the current TNM classification enables more accurate prognosis prediction within particular clinical stages. That is why an inclusion of the grade to the standard TNM classification should be discussed.

Key words: pancreatic cancer, grade, TNM classification, prognosis

The main role of TNM staging systems is to predict patient survival and to determine the method of treatment. The current staging system in pancreatic ductal adenocarcinoma (PDAC) determines tumor stage on the basis of primary tumor size (T stage), regional lymph node status (N stage) and distant metastasis (M stage) [1, 2]. Because of the high survival variability within a particular stage, novel more complex systems incorporating other parameters to predict survival more precisely were created [3, 4]. Several multivariate analyses have shown tumor grade as one of the most important prognostic indicators [5–9]. That is why some authors suggest that inclusion of the tumor grade into AJCC staging for pancreatic cancer would enhance the current system and provide better survival prognostication reflective of the aggressive biology associated with high-grade tumors [4]. The goal of this retrospective multicenter study was to assess the prognostic value of tumor grade in PDAC patients using data from seven Czech complex oncological centers and to evaluate the accuracy of the prognostic TNMG nomogram designed by Wasif et al. [4].

Patients and methods

The study was designed as retrospective multicenter analysis of patients who underwent pancreatic resection due to PDAC in seven Czech oncological centers between 2003 and 2013. This study has been approved by the institutional Review Board at University Hospital Brno with No 01-5.4.2017. The retrospective data of 464 patients were obtained from local hospital registries separately. Due to incomplete demographic characteristics, 33 (7.1%) cases had to be excluded. In total, 431 patients were included in the study. Descriptive statistics with demographic and treatment characteristics are displayed in Table 1a.

Clinical stages were assessed using the 7th edition of AJCC staging system [1]. The tumor grade was determined using the College of American Pathologists four degree classification. The tumors were classified as: well differentiated (G1), when more than 95% of the tumor was composed of glands, moderately differentiated (G2), where the glands formed from 50% to 95% of the tumor, poorly differentiated (G3), when 49% or less of the tumor was composed of glands and dedifferentiated (G4) with no or minimal differentiation that was discernible only in rare, tiny foci. Clinical stages and tumor grade distribution are shown in Table 1b.

Radicality of the surgery was evaluated before the implementation of the Leeds protocol using pancreatic neck and common bile duct resection margins assessment. The histopathological examination of the other resection margins (circumferential, ventral, dorsal) was not standardized. Due to the possibility of the bias, R status was not taken into account in the study.

Statistical analysis. Standard descriptive statistics (relative and absolute frequencies) were used to describe the data. Statistical significance of differences between patient groups according to the tumor grade was assessed using the Fisher's exact test. Median survival time was used to describe differences in overall survival after resection. Modeling of the simultaneous effect of observed factors on overall survival was carried out by both, univariate and multivariate Cox regression model. Two procedures taking the tumor grade into account were carried out. The first based on multivariate Cox regression model, the second using algorithm published by Wasif et al. [4]. Kaplan-Meier curves, median survival time and log-rank tests were used to identify differences in overall survival after resection of pancreatic carcinoma according to the TNM and TNMG classification. Standard level of statistical significance α=0.05 was used.

Results

Patients' treatment. Most frequent procedure (83.1%) was pancreatoduodenectomy. In 53 (12.3%) cases splenopancreatectomy and in 20 (4.6%) cases total pancreatectomy were performed. Regarding adjuvant oncological treatment, 287 (66.6%) patients were treated with gemcitabin based adjuvant chemotherapy. Ninety-eight (22.7%) patients did not received any chemotherapy (CHT). In 46 cases (10.7%) retrospective data about CHT were not available. Similarly, adjuvant radiotherapy (RT) was applied in 59 (13.7%) and not applied in 328 (76.1%) patients. In 44 (10.2%) cases retrospective data were not available.

Patients' survival. The median overal survival for stages I, II and III+IV was 25 months, 17 months and 15 months, respectively. The longest median survival time was noticed in patients with pancreatic body or tail tumor after splenopancreatomy (20 months, min 6, max 90). Median survival of the patients after pancreatoduodenectomy and total pancreatectomy was shorter (16 months; min 4, max 129) and (14 months; min 5, max 47), respectively.

Table 1a. Demographic and treatment characteristics of patients with pancreatic carcinoma.

Demographic and treatment characteristics	All patients n=431		Grade 1–2 n=263		Grade 3–4 n=168		p-value
	n	%	n	%	n	%	
Sex							0.767
Male	235	54.5%	145	55.1%	90	53.6%	
Female	196	45.5%	118	44.9%	78	46.4%	
Age							0.385
≤55 years	91	21.1%	61	23.2%	30	17.9%	
56–65 years	162	37.6%	101	38.4%	61	36.3%	
66–75 years	141	32.7%	81	30.8%	60	35.7%	
>75 years	37	8.6%	20	7.6%	17	10.1%	
Type of surgery							0.313
PD	358	83.1%	222	84.4%	136	81.0%	
SPE	53	12.3%	32	12.2%	21	12.5%	
TP	20	4.6%	9	3.4%	11	6.5%	
Adjuvant chemotherapy							0.408
Yes	287	66.6%	169	64.3%	118	70.2%	
No	98	22.7%	65	24.7%	33	19.6%	
Not available	46	10.7%	29	11.0%	17	10.1%	
Adjuvant radiotherapy							0.503
Yes	59	13.7%	32	12.2%	27	16.1%	
No	328	76.1%	203	77.2%	125	74.4%	
Not available	44	10.2%	28	10.6%	16	9.5%	

PD – pancreatoduodenectomy, SPE – splenopancreatectomy, TP – total pancreatectomy, n – number of patients, p – level of statistical significance.

Table 1b. Tumor characteristics of patients with pancreatic cancer. Clinical stages were determined using pathological TNM classification (7th edition of AJCC staging system).

Tumor characteristic	All patients n=431		Grade 1–2 n=263		Grade 3–4 n=168		p-value
	n	%	n	%	n	%	
Cancer staging (TNM classif.)							**0.029**
Stage 1A	26	6.0%	22	8.4%	4	2.4%	
Stage 1B	39	9.0%	25	9.5%	14	8.3%	
Stage 2A	106	24.6%	70	26.6%	36	21.4%	
Stage 2B	237	55.0%	136	51.7%	101	60.1%	
Stage 3	13	3.0%	5	1.9%	8	4.8%	
Stage 4	10	2.3%	5	1.9%	5	3.0%	
Tumor size (TNM – T)							0.080
1	35	8.1%	27	10.3%	8	4.8%	
2	78	18.1%	48	18.3%	30	17.9%	
3	305	70.8%	183	69.6%	122	72.6%	
4	13	3.0%	5	1.9%	8	4.8%	
Lymph nodes (TNM – N)							**0.016**
0	180	41.8%	122	46.4%	58	34.5%	
1	251	58.2%	141	53.6%	110	65.5%	
Distant metastasis (TNM – M)							0.521
0	421	97.7%	258	98.1%	163	97.0%	
1	10	2.3%	5	1.9%	5	3.0%	
Tumor grade							–
Grade 1	45	10.4%	45	17.1%	0	0%	
Grade 2	218	50.6%	218	82.9%	0	0%	
Grade 3	166	38.5%	0	0%	166	98.8%	
Grade 4	2	0.5%	0	0%	2	1.2%	

TNM – tumor nodes and metastatis classification, n – number of patients, p – level of statistical significance.

Regarding the factors affecting survival, univariate analysis proved lymph node status, tumor size, tumor stage and grade as statistically significant survival predictors (Table 2).

The searching for the correlation between the tumor grade and survival in different stages proved the higher grade as negative prognostic factor in all stages (Table 3).

In the most frequent stage II (n=343), the hazard ratio reached 3.09 (2.01; 4.77, CI 95%, p <0.001) for low differentiated (G3+G4) tumors. Better prognostic accuracy was observed when the tumor grade was added to the tumor stage. The multivariate Cox regression model showed the prognostic switch of patients with well-differentiated (G1+G2) tumors to the lower stage. On the contrary, low-differentiation (G3+G4) of the tumor worsened the prognosis, which became comparable to that in the higher stage. For instance, the median overall survival of the patient with stage IIB, G1 or G2 tumor was the same (19 months) as in the case of IIA, low-differentiated one. Taking into account these facts, TNMG classification was created (Table 4). Kaplan-Meier analysis verified statistically significant impact of new TNMG stages on survival (Figure 1).

Discussion

Prognosis of PDAC remains poor. Median overall survival in PDAC patients who undergo resection varies from 17 to 27 months in most series [10–13]. The patients' prognosis is based on TNM staging. Staging is also crucial for decision making in therapy. Current staging system used for PDAC does not reflect prognostic determinants other than the T, N, and M modalities [14]. Perhaps it is the reason of high survival variability within the particular stages. Therefore, several authors tried to incorporate other parameters to predict survival more precisely. The prognostic impact of tumor grade in PDAC was proved by several multivariate analyses [5–9]. In agreement with these series, our retrospective study also confirmed higher tumor grade as statistically significant negative prognostic factor with HR 2.52 (1.66; 3.82, CI 95%, p<0.001) for G3+G4 tumors. Regarding these facts, there is a question why the tumor grade has not been incorporated into the standard staging system yet as it was in soft tissue sarcomas [14]. Several studies on this topic have been already published. Wasif et al has tried to implement

Table 2. Univariate Cox regression model and median survival time after resection for pancreatic cancer.

Patient group	Overall survival after pancreatic resection for pancreatic cancer								
	Median survival time (months)			Univariate Cox regression model					
	estimate	95% CI – lower	95% CI – upper	regression coefficient	SE for reg. Coeff.	HR	95% CI for HR – lower	95% CI for HR – upper	p-value
All patients	18.0	16.1	19.9	–	–	–	–	–	–
Sex									
Male	18.0	15.9	20.1	–	–	1.00	–	–	–
Female	20.0	16.8	23.2	–0.036	0.111	0.96	0.78	1.20	0.747
Age									
≤55 years	16.0	13.1	18.9	–	–	1.00	–	–	–
56–65 years	19.0	15.8	22.2	–0.156	0.144	0.86	0.64	1.14	0.281
66–75 years	18.0	14.6	21.4	–0.191	0.149	0.83	0.62	1.11	0.201
>75 years	20.0	15.3	24.7	–0.260	0.229	0.77	0.49	1.21	0.256
Tumor size (TNM – T)									
1	25.0	17.3	32.7	–	–	1.00	–	–	–
2	20.0	14.0	26.0	0.314	0.246	1.37	0.85	2.22	0.201
3+4	17.0	15.0	19.0	0.680	0.215	1.97	1.29	3.01	**0.002**
Lymph nodes (TNM – N)									
0	22.0	18.8	25.2	–	–	1.00	–	–	–
1	15.0	13.7	16.3	0.532	0.115	1.70	1.36	2.13	**0.000**
Cancer staging (TNM classif.)									
Stage 1A	29.0	14.1	43.9	–	–	1.00	–	–	–
Stage 1B	22.0	10.9	33.1	0.097	0.324	1.10	0.58	2.08	0.764
Stage 2A	20.0	16.4	23.6	0.511	0.269	1.67	0.98	2.82	0.057
Stage 2B	16.0	14.4	17.6	0.833	0.255	2.30	1.40	3.79	**0.001**
Stage 3	16.0	11.0	21.0	1.001	0.390	2.72	1.27	5.84	**0.010**
Stage 4	9.0	0	18.3	1.042	0.400	2.84	1.30	6.20	**0.009**
Tumor grade									
Grade 1	28.0	19.5	36.5	–	–	1.00	–	–	–
Grade 2	20.0	17.5	22.5	0.593	0.208	1.81	1.20	2.72	**0.004**
Grade 3+4	14.0	12.2	15.8	0.924	0.212	2.52	1.66	3.82	**0.000**
Tumor grade									
Grade 1+2	22.0	19.5	24.5	–	–	1.00	–	–	–
Grade 3+4	14.0	12.2	15.8	0.436	0.112	1.55	1.24	1.93	**0.000**
Adjuvant chemotherapy									
Yes	17.0	14.8	19.2	–	–	1.00	–	–	–
No	21.0	16.1	25.9	–0.248	0.141	0.78	0.59	1.03	0.080
Adjuvant radiotherapy									
Yes	15.0	11.5	18.5	–	–	1.00	–	–	–
No	20.0	17.6	22.4	–0.314	0.163	0.73	0.53	1.01	0.054

TNM – tumor, nodes and metastatis classification, n – number of patients, p – level of statistical significance, CI – confidence interval, HR – hazard ratio.

the grade to the AJCC staging system creating new classification scheme, which offered more precise prognostic stratification of the patients [4]. These observation were supported by the study of Rochefort et al concluding in the group of 256 patients that grade is one of the strongest independent prognostic factors in PDAC and demonstrating improved prognostication using novel TNMG classification system [15].

Based on these results, we tried to independently verify these data in Czech pancreatic cancer population. Similarly to the previous studies [4, 15], median overall survival in every single stage was influenced by the tumor grade. Regarding tumor grade in the stage IIa patients, better differentiation (G1 or G2) brought median overall survival improvement up to 22 months (17.5; 26.5, CI 95%). On the other hand, in G3 and G4 tumors median survival decreased to 19 months (13.6; 24.4, CI 95%) which was the same as in stage IIb (that means lymph node positive) well-differentiated tumors.

Patient with high grade, localized, resectable, T3 tumor, without involvement of regional lymph nodes had similar prognosis as the one with low grade, T3 tumor with regional

Table 3. Multivariate Cox regression model for overall survival after resection of pancreatic cancer with interaction between tumor stage and grade.

Patient group	Multivariate Cox regression model					
	regression coefficient	SE for reg. Coeff.	HR	95% CI for HR – lower	95% CI for HR – upper	p–value
Sex						
Male	–	–	1.00	–	–	–
Female	–0.011	0.113	0,99	0.79	1.23	0.923
Age						
≤55 years	–	–	1.00	–	–	–
56–65 years	–0.188	0.147	0.83	0.62	1.10	0.201
>65 years	–0.300	0.144	0.74	0.56	0.98	**0.038**
Cancer staging and tumor grade						
Stage 1 + grade 1+2	–	–	1.00	–	–	–
Stage 1 + grade 3+4	0.802	0.342	2.23	1.14	4.36	**0.019**
Stage 2 + grade 1+2	0.761	0.214	2.14	1.41	3.25	**0.000**
Stage 2 + grade 3+4	1.129	0.221	3.09	2.01	4.77	**0.000**
Stage 3–4 + grade 1+2	1.089	0.378	2.97	1.41	6.24	**0.004**
Stage 3–4 + grade 3+4	1.259	0.364	3.52	1.73	7.18	**0.001**

n – number of patients, p – level of statistical significance, CI – confidence interval, HR – hazard ratio

Table 4. Restaging according to the TNMG classification based on multivariate Cox regression model.

	Median survival time (months)				
	n	estimate	95% CI – lower	95% CI – upper	p-value (log-rank)
TNM classification					**0.000**
Stage 1A	26	29.0	14.1	43.9	
Stage 1B	39	22.0	10.9	33.1	
Stage 2A	106	20.0	16.4	23.6	
Stage 2B	237	16.0	14.4	17.6	
Stage 3	13	16.0	11.0	21.0	
Stage 4	10	9.0	0	18.3	
TNM class. + tumor grade					**0.000**
Stage 1A + grade 1+2	22	42.0	10.5	73.5	
Stage 1A + grade 3+4	4	12.0	0	26.7	
Stage 1B + grade 1+2	25	38.0	19.9	56.1	
Stage 1B + grade 3+4	14	21.0	7.5	34.5	
Stage 2A + grade 1+2	70	22.0	17.5	26.5	
Stage 2A + grade 3+4	36	19.0	13.6	24.4	
Stage 2B + grade 1+2	136	19.0	15.4	22.6	
Stage 2B + grade 3+4	101	13.0	11.7	14.3	
Stage 3 + grade 1+2	5	15.0	4.3	25.7	
Stage 3 + grade 3+4	8	17.0	11.9	22.1	
Stage 4 + grade 1+2	5	15.0	8.6	21.4	
Stage 4 + grade 3+4	5	6.0	3.9	8.1	
TNMG classification					**0.000**
Stage IA	22	42.0	10.5	73.5	
Stage IB	29	29.0	12.6	45.4	
Stage IIA	84	22.0	18.5	25.5	
Stage IIB	172	19.0	15.4	22.6	
Stage III	106	13.0	11.6	14.4	
Stage IVA	13	17.0	12.8	21.2	
Stage IVB	5	6.0	3.9	8.1	

TNMG – tumor, nodes, metastatis and grade classification, n – number of patients, CI – confidence interval.

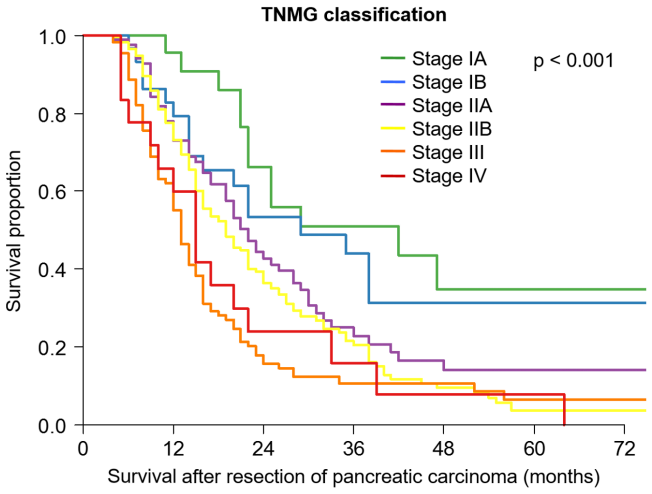

Figure 1. Kaplan-Meier survival curves according to the TNMG classification.

nodal involvement. Moreover, low tumor diferentiation (G3 or 4) in stage IIb disease caused prognostic shift of patients with resectable tumors to the prognostic group of non-resectable, T4 tumors with median survival of 13 months. Survival worsening between stages III (n=13) and IV (n=10) patients was not clearly proved, most probably due to small group. The results of the Wasif´s series seem to be more conclusive for these stages. Another attempt to use the grade as prognostic tool was done by Memorial Sloan Kettering Cancer Center (MSKCC). In this study, the authors incorporated additional factors (age, sex, portal vein infiltration, splenectomy, resection margin status, location of the tumor head-tail, tumor grade, posterior resection margin status, number of positive lymph nodes, number of negative lymph

nodes, back pain, T stage and weight loss) into the predictive model not included in the traditional TNM staging. This approach enabled to predict the probability with which a patient will survive pancreatic cancer for 1, 2, and 3 years from the time of the initial resection, assuming that there is not death from an alternate cause. The authors concluded that the calibration between observed and corrected was good, and variables not conventionally associated with standard staging systems improved the predictivity of the model [3]. Subsequently, the MSKCC nomogram was independently validated by the group at Massachusetts General Hospital on a cohort of 424 patients [16]. The advantage of tumor grade compared to some other parameters is the possibility of up-front surgery diagnosis using EUS guided cytology and histopathology. Especially, when 22G or 25G needles are applied [17]. Subsequently, the tumor grade could contribute to select an optimal therapeutic approach. Crippa in retrospective analysis of 502 PDAC patients proved greater benefit of adjuvant chemotherapy in G3 than in G1 and G2 tumors [18]. Regarding neoadjuvant CHT, several studies proved its benefit in borderline resectable PDAC [19]. Inclusion of the tumor grade into the decision-making process of neoadjuvant treatment could contribute to better selection and survival prognostication. Thereafter, low tumor cell differentiation could be an argument for neoadjuvant CHT not only in borderline resectable but also in resectable PDAC. On the other side, well differentiated tumors could be indicated for radical surgery even if arterial resection is necessary [20]. More studies verifying these theses are needed.

In conclusion, we can state that despite of the possible bias rising from retrospective character of the study, tumor grade was shown as an independent, statistically significant prognostic factor in patients undergoing resection for pancreatic ductal adenocarcinoma. Incorporation of the grade into the TNM classification enables more accurate prognosis prediction within particular clinical stages. That is why inclusion of the grade to the standard TNM classification should be discussed.

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