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Original Article

Evaluation and Comparison of Predictive Value of Tumor Regression Grades According to Mandard and Becker in Locally Advanced Gastric Adenocarcinoma

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Purpose Tumor regression grade (TRG) has been widely used in gastrointestinal carcinoma to assess pathological responses to neoadjuvant chemotherapy (NCT). There are various standards without a consensus, and it is still unclear which kind of system has better predictive value. This study aims to investigate and compare the predictive ability of the Mandard and Becker TRGs in patients with locally advanced gastric cancer.

Materials and Methods A total of 290 patients with locally advanced gastric adenocarcinoma who underwent NCT and curative surgery were studied. Survival analysis for overall survival (OS) and disease-free survival (DFS) were based on the Kaplan-Meier method and Cox proportional hazards method. Predictive values of TRGs and models were assessed by time-dependent receiver operating characteristic (ROC) curve, the area under the ROC curve (AUC), nomogram, and calibration curve.

Results In multivariable analysis, the Mandard TRG was associated with OS (hazard ratio [HR], 1.806; p=0.026) and DFS (HR, 1.792; p=0.017). The Becker TRG was also related to OS (HR, 1.880; p=0.014) and DFS (HR, 1.919; p=0.006). The Mandard and Becker TRG AUCs for 5-year survival were 0.72 and 0.71, respectively. The whole models showed an increased predictive value, with AUCs of 0.85 and 0.86, respectively. There was no significant difference between the two TRGs and two models.

Conclusion TRG was an independent predictor for survival, and there was no significant difference between these two systems.

Key words Stomach neoplasms, Tumor regression grade, Neoadjuvant chemotherapy, Pathological assessment, Prognosis

Introduction

Neoadjuvant chemotherapy (NCT) followed by surgery has become the primary treatment for locally advanced gastric cancer (GC), because of its potential benefits, including reducing tumor volume [1], downstaging of the primary tumor [2], eliminating metastases or micrometastases [3], increasing the rate of complete surgical resection [4], and improving survival [1].

The evaluation of the effectiveness of NCT is becoming increasingly important. Pathologically, TNM stage is a widely accepted standard to assess efficacy, but it sometimes loses its significance as a prognostic predictor in multivariable analysis [5,6]. This might be because this standard only focuses on the location of residual tumor and does not consider the amount of residual tumor.

Tumor regression grade (TRG) is a system to assess the quantity of residual tumor, which could provide extra information to evaluate the curative effects and prognosis [1,4]. Nevertheless, there are various systems without a consensus [7-10]. These systems can be divided into two main classifications based on different definitions: the relative amount of residual tumor and fibrosis [7,8], and the proportion of residual tumor in the tumor bed [9,10]. TRGs according to Mandard et al. [7] and Becker et al. [9] are commonly used in these two categories, respectively.

Many studies have proved that both of these two kinds of systems can evaluate the effect of therapy and assess the prognosis [2-4,11]. However, it is still unknown whether there are differences between these two categories in predicting survival. Moreover, whether studies based on different TRGs could be compared with each other is also unclear.

This study aims to assess the prognostic value of TRG in primary GC and to compare the capability of predicting the prognosis between the Mandard and Becker TRGs.

Materials and Methods

1. Patients

All patients with locally advanced gastric adenocarcinoma who received NCT between January 2010 and June 2016 at

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our institute were identified from our electronic database. The inclusion criteria were as follows: (1) pathologically confirmed gastric adenocarcinoma; (2) locally advanced gastric carcinoma (8th American Joint Committee on Cancer [AJCC] clinical stage: cT2N1M0-T4N3M0, II-III); (3) underwent NCT with or without postoperative therapy; (4) received curative gastrectomy surgery; and (5) aged from 20 to 80 years old. Exclusion criteria included the following: (1) underwent preoperative radiotherapy; (2) suffering from gastric remnant cancer or other malignant tumors; or (3) incomplete information on staging or therapy. Among 3,196 patients, 290 met the inclusion criteria of our study.

2. Pathological response assessment

All the slides or blocks indicating surgical specimens were retrieved from the biospecimen library of our hospital and were separately reviewed by two experienced gastrointestinal pathologists (Y.Z. and D.L.). The gross examination protocol was according to the study of Langer and Becker [12]. TNM stage was reevaluated according to the eighth edition of the AJCC cancer staging guideline. Histological regression grade of the primary tumor was assessed according to the Mandard system: TRG 1 (complete fibrosis with no evidence of residual tumor, i.e., complete regression), TRG 2 (fibrosis with scattered tumor cells), TRG 3 (fibrosis and residual tumor with a dominance of fibrosis), TRG 4 (fibrosis and residual tumor with a dominance of tumor), and TRG 5 (extensive residual tumor without evidence of regression) and to the Becker system: TRG 1a (complete tumor regression), TRG 1b (< 10% of vital tumor tissue), TRG 2 (10%-50% residual tumor in tumor bed), and TRG 3 (> 50% viable tumor remaining). When disagreement appeared between pathologists, an agreement would be reached by joint rereview and discussion through a multihead microscope. Other extracted histopathologic characteristics were reconfirmed during the evaluation process.

3. Statistical methods

Survival curves for overall survival (OS) and disease-free survival (DFS) were obtained using the Kaplan-Meier method, and the log-rank test was used to compare differences. The predictive values of both grading systems were assessed by time-dependent receiver operating characteristic (ROC) curves and the area under the ROC curve (AUC). Cox regression analysis was used to assess the prognostic risk of clinicopathological characteristics on OS and DFS. The forward selection method was used to determine the factors to be included in the multivariable analysis, and the factors with p-value < 0.05 were considered significant. Nomograms were built based on the Cox proportional hazards model, and the predictive accuracy was measured by the concordance index (c-index). Calibration curves were plotted to evaluate the consistency between predicted survival probability and actual survival proportion. All patients were followed up every 3 months during the first 2 years, every 6 months for the following 3 years and annually thereafter. OS was the time from initial treatment to death from any cause or last date of follow-up, while DFS was calculated from the surgery to the date of recurrence or date of previous follow-up. Data were proceeded by SPSS ver. 25.0 (IBM Corp., Armonk, NY) and R 3.6.1 software (R Foundation for Statistical Computing, Vienna, Austria).

Results

1. Patient and clinical characteristics

The baseline characteristics of 290 patients were listed according to the Mandard TRG (Table 1) and Becker TRG (S1 Table), respectively.

Most patients were male (74.1%), and median age at diagnosis was 59 years (range, 25 to 77 years). More than half of the tumors were located in the lower third of the stomach (59.3%). Most patients (73.8%) received preoperative therapy with SOX, and a few underwent FOLFOX (19.0%) and XELOX (7.2%). All patients experienced 2-4 cycles of neoadjuvant therapy, with a median of 2 cycles. The median operation interval, the time between completion of preoperative treatment and surgery, was 31 days, with an interquartile range of 28 to 36 days. Primary operation methods were distal gastrectomy (52.8%) and total gastrectomy (46.6%). Only two patients received proximal gastrectomy. D2 (77.9%) or D2+ (22.1%) lymphadenectomy was performed in all cases. The average number of lymph nodes removed was 28, with an interquartile range from 19 to 33. One hundred patients had no lymph node metastasis. One hundred ninety patients had at least one lymph node metastasis, with the average number of positive nodes being 7.

2. Pathological assessment

In total, 1,306 slices indicating surgical specimens were reviewed. The median number was 4, with an interquartile range from 3 to 5. After reevaluation, most patients (77.3%) had ypT3-4 cancer and lymph node involvement (65.5%). For tumor regression grade, the number of patients in every group was 9, 84, 90, 85, and 22 for the Mandard TRG 1, 2, 3, 4, and 5, respectively, and 9, 88, 81, and 112 for Becker 1a, 1b, 2, and 3, respectively. The examples of TRGs are shown in Fig. 1. These two grading systems showed a highly significant correlation ($p < 0.001$), although there were some discrepancies among Mandard TRG 2-4 and Becker 1b-2 (S2 Table). Some disputable cases are shown in S3 Fig. Pathologi-

Table 1. Clinicopathological characteristics according to Mandard TRG

Variable	TRG 1-2 (n=83)	TRG 3 (n=90)	TRG 4-5 (n=107)	p-value	Total
Sex					
Male	69 (23.8)	63 (21.7)	83 (28.6)	0.482	215 (74.1)
Female	24 (8.3)	27 (9.3)	24 (8.3)		75 (25.9)
Age (yr)					
< 65	72 (24.8)	71 (24.5)	78 (26.9)	0.583	221 (76.2)
≥ 65	21 (7.2)	19 (6.6)	29 (10.0)		69 (23.8)
Tumor location					
Lower third	53 (18.3)	56 (19.3)	63 (36.6)	0.171	172 (59.3)
Middle third	25 (8.6)	14 (4.8)	15 (5.2)		54 (18.6)
UGEJ	11 (3.8)	11 (3.8)	18 (6.2)		40 (13.8)
Diffuse	4 (1.4)	9 (3.1)	11 (3.8)		24 (8.3)
Tumor size (cm)					
< 5	56 (19.3)	31 (10.7)	28 (9.7)	< 0.001	115 (39.7)
≥ 5	37 (12.8)	59 (20.3)	79 (27.2)		175 (60.3)
ypT					
0	9 (3.1)	0	0	< 0.001	9 (3.1)
1-2	49 (16.9)	4 (1.4)	4 (1.4)		57 (19.6)
3-4	35 (12.1)	86 (29.7)	103 (35.5)		224 (77.3)
ypN					
0	56 (19.3)	27 (9.3)	17 (5.9)	< 0.001	100 (34.5)
1	19 (6.6)	19 (6.6)	11 (3.8)		49 (16.9)
2	16 (5.5)	24 (8.3)	39 (13.4)		79 (27.2)
3	2 (0.7)	20 (6.9)	40 (13.8)		62 (21.4)
ypTNM					
I	48 (16.6)	3 (1.0)	1 (0.3)	< 0.001	52 (17.9)
II	27 (9.3)	27 (9.3)	17 (5.9)		71 (24.5)
III	18 (6.2)	60 (20.7)	89 (30.7)		167 (57.6)
Histological type					
Adenocarcinoma	72 (24.8)	55 (19.0)	59 (20.3)	0.004	186 (64.1)
Poorly cohesive carcinoma	21 (7.2)	35 (12.1)	48 (16.6)		104 (35.9)
Lauren classification					
Intestinal	58 (20.0)	42 (14.5)	43 (14.8)	0.006	143 (49.3)
Diffuse or mixed	35 (12.1)	48 (16.6)	64 (22.1)		147 (50.7)
Grade of differentiation					
Well	44 (15.2)	12 (4.1)	14 (4.8)	< 0.001	70 (25.2)
Moderate or poor	49 (16.9)	78 (26.9)	93 (32.1)		220 (74.8)
Vascular or lymphatic invasion					
No	82 (28.3)	66 (22.8)	70 (24.1)	< 0.001	218 (75.2)
Yes	11 (3.8)	24 (8.3)	37 (12.8)		72 (24.8)
Nervous invasion					
No	86 (29.7)	54 (18.6)	82 (28.3)	< 0.001	222 (76.6)
Yes	7 (2.4)	36 (12.4)	25 (8.6)		68 (23.4)
Adjuvant treatment					
No	11 (3.8)	8 (2.8)	12 (4.1)	0.793	31 (10.7)
Yes	82 (28.3)	82 (28.3)	95 (32.8)		259 (89.3)

Values are presented as number (%). TRG, tumor regression grade; UGEJ, upper third and gastroesophageal junction.

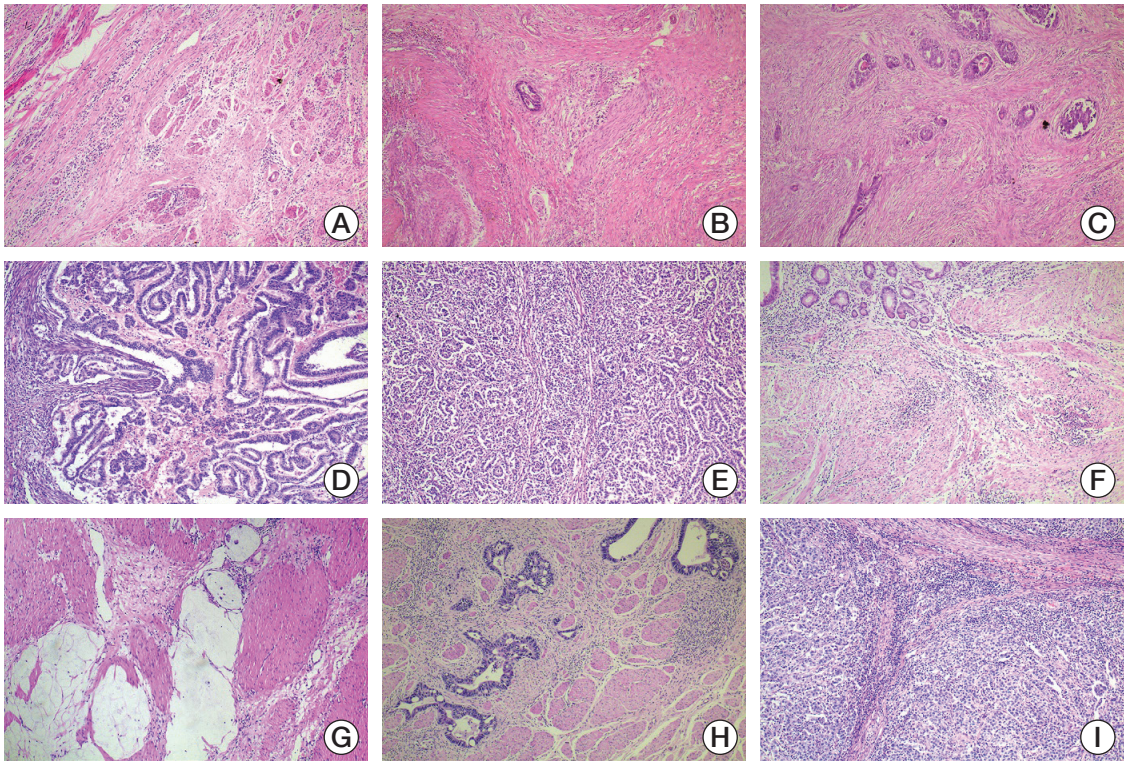

Fig. 1. (A-E) Examples of Mandard tumor regression grade (TRG) (×40). (A) TRG 1, complete tumor regression. (B) TRG 2, rare residual tumor. (C) TRG 3, more residual tumor but less than fibrosis. (D) TRG 4, residual tumor with signs of regression. (E) TRG 5, residual tumor without regression. (F-I) Examples of Becker TRG (×40). (F) TRG 1a, complete tumor regression. (G) TRG 1b, < 10% residual tumor. (H) TRG 2, 10%-50% residual tumor. (I) TRG 3, > 50% residual tumor.

Table 2. Univariate analysis of TRG

	No. (%) (n=290)	Overall survival			Disease-free survival		
		5-Year survival (%)	95% CI	p-value	5-Year survival (%)	95% CI	p-value
Mandard TRG							
TRG 1-2	93 (32.1)	76.6	67.0-86.2	< 0.001	70.7	60.9-80.5	< 0.001
TRG 3	90 (31.0)	43.7	32.3-55.1		39.2	28.1-50.4	
TRG 4	85 (29.3)	32.0	19.7-44.2		26.8	15.3-38.3	
TRG 5	22 (7.6)	15.2	0.0-39.5		19.1	2.3-35.9	
Pathologic response							
Responders (TRG 1-2)	93 (32.1)	76.6	67.0-86.2	< 0.001	70.7	60.9-80.5	< 0.001
Non-responders (TRG 3-5)	197 (67.9)	36.1	28.1-44.2		31.2	23.6-38.9	
Becker TRG							
TRG 1a-1b	97 (33.4)	76.6	67.3-85.9	< 0.001	71.0	61.5-80.5	< 0.001
TRG 2	81 (27.9)	42.0	29.8-54.3		36.9	24.9-48.9	
TRG 3	112 (38.6)	30.1	19.4-40.8		25.4	15.8-35.1	
Pathologic response							
Responders (TRG 1a-1b)	97 (33.4)	76.6	67.3-85.9	< 0.001	71.0	61.5-80.5	< 0.001
Non-responders (TRG 2-3)	193 (66.6)	35.1	26.9-43.2		30.2	22.5-37.8	

CI, confidence interval; TRG, tumor regression grade.

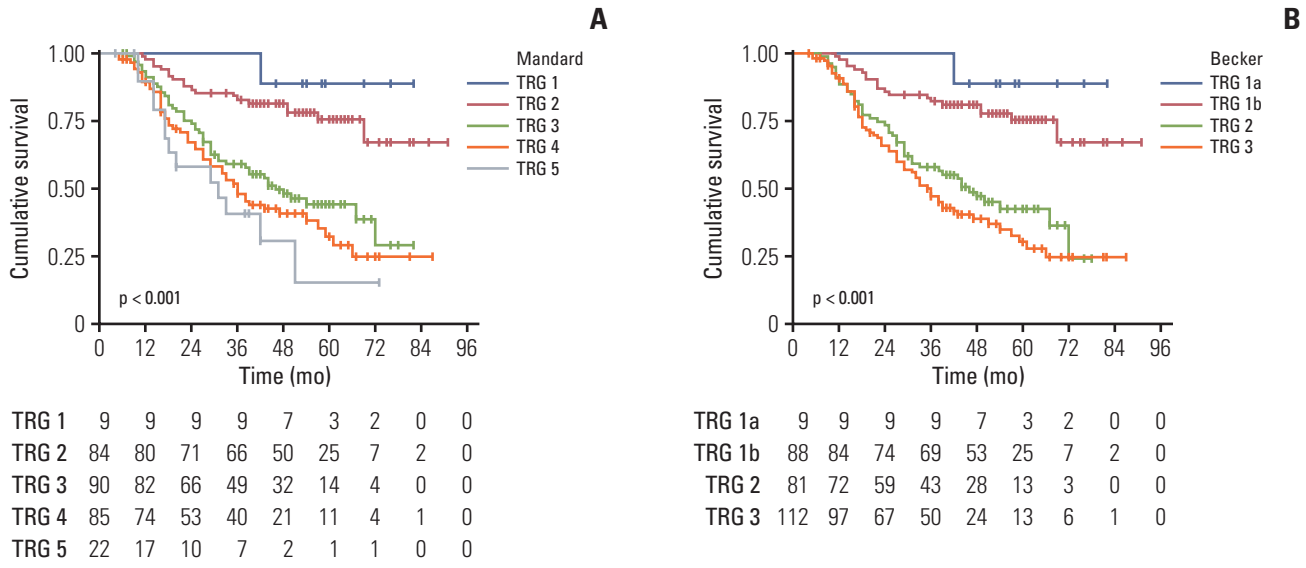

Fig. 2. Kaplan-Meier curves for overall survival of Mandard tumor regression grade (TRG) (A) and Becker TRG (B). When grouped into responders and non-responders, Mandard TRG 3-5 (hazard ratio [HR], 3.822; 95% confidence interval [CI], 2.371 to 6.162; p < 0.001) and Becker TRG 2-3 (HR, 3.876; 95% CI, 2.427 to 6.192; p < 0.001) owned worse prognosis.

Table 3. Multivariate analysis of prognostic factors

Variable	Overall survival		Disease-free survival	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Mandard TRG				
Age (≥ 65 yr)	1.745 (1.186-2.567)	0.005	1.492 (1.033-2.155)	0.033
Tumor size (≥ 5 cm)	1.888 (1.226-2.907)	0.004	1.645 (1.105-2.448)	0.014
ypN		< 0.001		< 0.001
0	1		1	
1	4.872 (2.456-9.665)	< 0.001	3.093 (1.714-5.583)	< 0.001
2	4.657 (2.495-8.692)	< 0.001	3.245 (1.918-5.491)	< 0.001
3	7.122 (3.673-13.810)	< 0.001	4.811 (2.718-8.518)	< 0.001
Lauren classification (diffuse or mixed)	1.676 (1.155-2.433)	0.007	1.622 (1.142-2.305)	0.007
Vascular or lymphatic invasion	1.506 (1.034-2.194)	0.033	1.318 (0.915-1.899)	0.138
Adjuvant treatment	2.287 (1.355-3.858)	0.002	2.247 (1.369-3.686)	0.001
TRG 3-5	1.806 (1.075-3.305)	0.026	1.792 (1.112-2.888)	0.017
Becker TRG				
Age (≥ 65 yr)	1.716 (1.166-2.526)	0.006	1.467 (1.016-2.119)	0.041
Tumor size (≥ 5 cm)	1.907 (1.241-2.930)	0.003	1.662 (1.119-2.468)	0.012
ypN		< 0.001		< 0.001
0	1		1	
1	4.908 (2.475-9.735)	< 0.001	3.120 (1.729-5.630)	< 0.001
2	4.590 (2.459-8.569)	< 0.001	3.184 (1.882-5.387)	< 0.001
3	7.145 (3.695-13.816)	< 0.001	4.829 (2.742-8.506)	< 0.001
Lauren classification (diffuse or mixed)	1.632 (1.123-2.371)	0.010	1.662 (1.119-2.468)	0.012
Vascular or lymphatic invasion	1.485 (1.018-2.165)	0.040	1.291 (0.895-1.861)	0.172
Adjuvant treatment	2.272 (1.348-3.831)	0.002	2.244 (1.370-3.678)	0.001
TRG 2-3	1.880 (1.136-3.112)	0.014	1.919 (1.207-3.051)	0.006

CI, confidence interval; HR, hazard ratio; TRG, tumor regression grade.

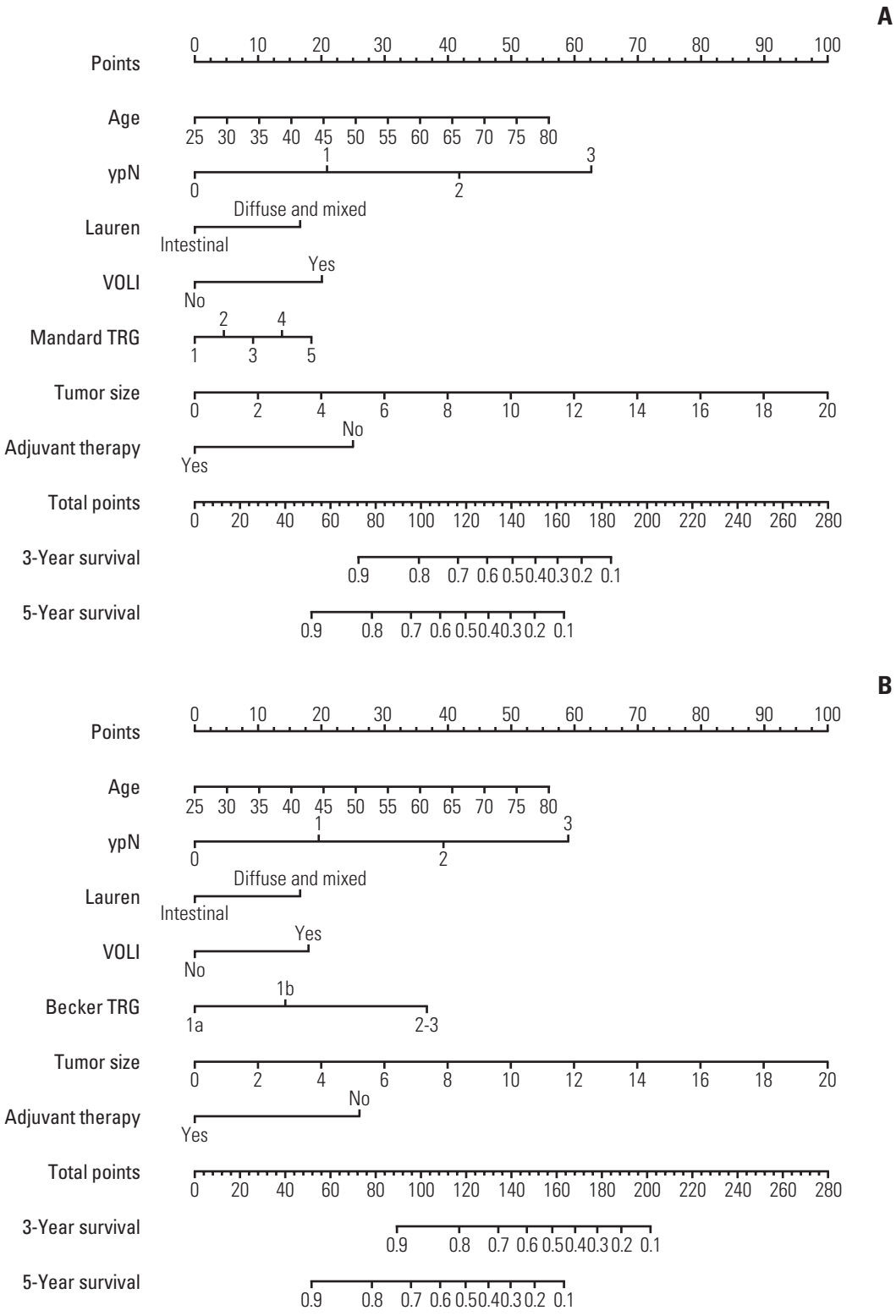

Fig. 3. Nomograms of Mandard tumor regression grade (TRG) model (A) and Becker TRG model (B). VOLI, vascular or lymphatic invasion.

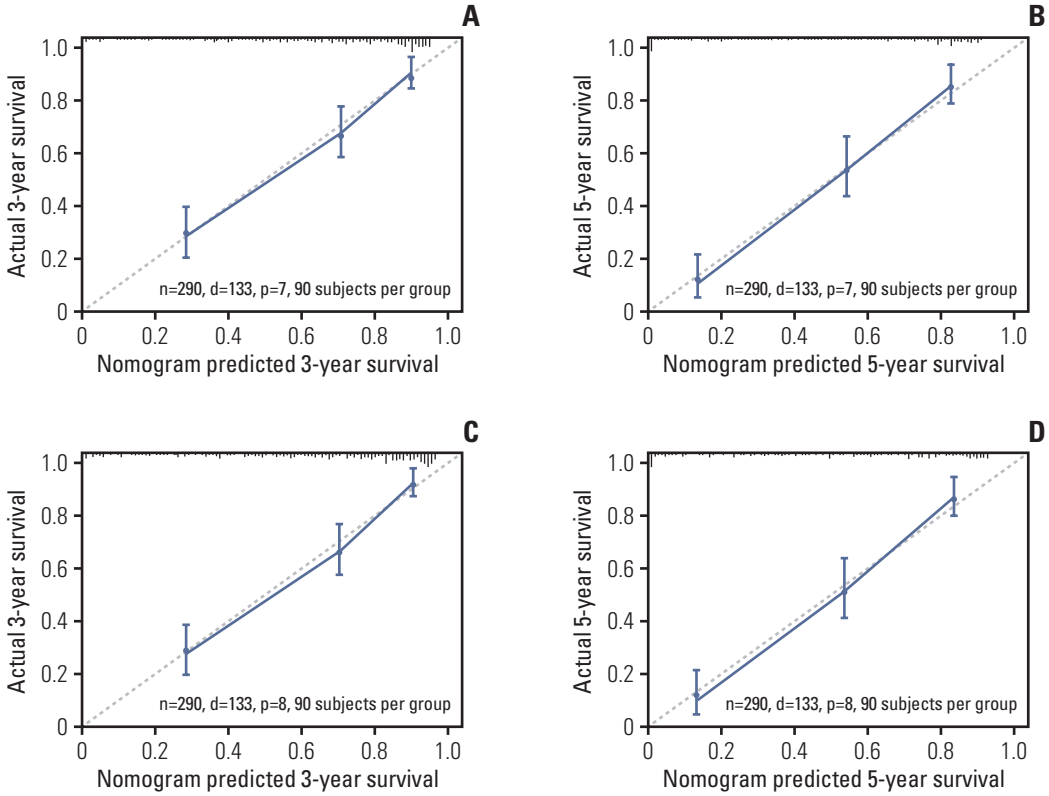

Fig. 4. Calibration curves of Mandard tumor regression grade (TRG) model for 3-year survival (A) and 5-year survival (B). Calibration curves of Becker TRG model for 3-year survival (C) and 5-year survival (D).

cal factors including tumor size, ypT, ypN, ypTNM, histological type, Lauren classification, grade of differentiation, vascular or lymphatic invasion (VOLI), and nervous invasion were associated with TRG (Table 1, S1 Table).

3. Survival analysis of TRG

In survival analysis, for the Mandard TRG, there was no significant difference between patients with TRG 1 and 2 in OS (p=0.342) and DFS (p=0.234). In patients with TRG 3, 4, and 5, a significant difference was found in DFS (p=0.019), while not in OS (p=0.170). Similarly, for the Becker TRG, between patients with TRG 1a and 1b, significance was found in DFS (p=0.031) but not in OS (p=0.084), and there was no significant between patients with TRG 2 and 3 in OS (p=0.190) and DFS (p=0.083). Therefore, the patients were divided into two groups. Mandard TRG 1-2 and Becker TRG 1a-1b were defined as responders, and Manrard TRG 3-5 and Becker TRG 2-3 were defined as non-responders.

For the Mandard TRG, 93 patients were in the TRG 1-2 group, with the median OS and DFS being 53 and 51 months, respectively. One hundred ninety-seven patients were in the TRG 3-5 group, with the median OS and DFS being 35 and 24 months, respectively. The 5-year survival rate of responders was significantly higher than that of non-responders in OS ($p < 0.001$) and DFS ($p < 0.001$) (Table 2).

For the Becker TRG, 97 patients were in the TRG 1 group, with the median OS and DFS being 53 and 51 months, respectively. One hundred ninety-three patients were in the TRG 2-3 category, with the median OS and DFS being 33 and 24 months, respectively. The 5-year survival rate of responders was significantly higher than that of non-responders in OS ($p < 0.001$) and DFS ($p < 0.001$) (Table 2).

The survival curves of both tumor regression systems are shown in Fig. 2. These two curves showed similar trends, and both systems were associated with prognosis ($p < 0.001$).

In multivariate analysis, seven clinicopathologic factors were associated with prognosis. Among them, both tumor regression systems were related to survival ($p < 0.05$). It was noteworthy that lymph node metastasis owned the largest hazard ratio (HR) (Table 3).

The nomograms showed that both TRGs could be used as predictors of prognosis, although age, ypN, and tumor size contributed more to the outcome. It was noteworthy that the contribution of the Mandard TRG was similar to that of Lau-

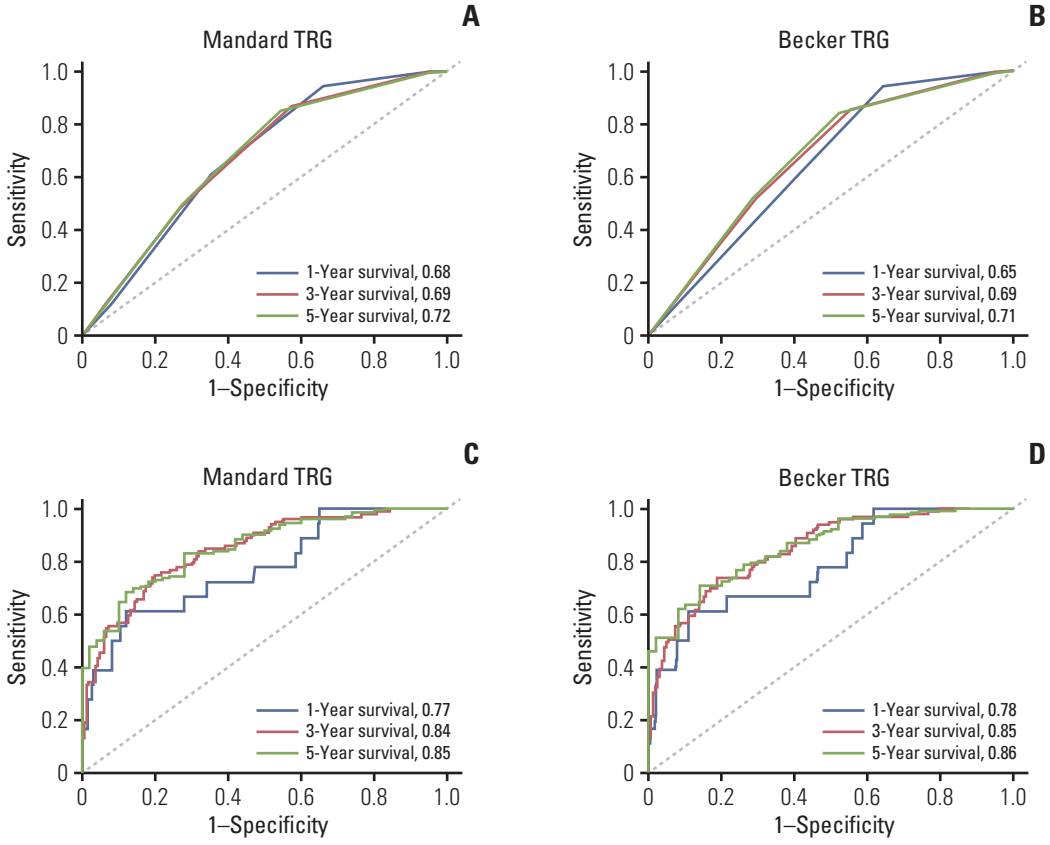

Fig. 5. Time-dependent receiver operating characteristic (ROC) curves of Mandard tumor regression grade (TRG) (A) and Becker TRG (B), and the areas under the ROC curve (AUC) for 1-, 3-, and 5-year survival. The p-values of the comparation between two systems were 0.513, 0.943, and 0.636 for 1, 3, and 5 years. Time-dependent ROC curves and AUC of Mandard TRG model (C) and Becker TRG model (D). The p-values of the comparation between two models were 0.584, 0.767, and 0.780 for 1, 3, and 5 years.

ren, VOLI, and adjuvant therapy, while the Becker TRG was higher than the three factors (Fig. 3).

4. Comparison of two TRG

In multivariate analysis, the Mandard TRG and Becker TRG were included, respectively (Table 3). Mandard TRG 3-5 was correlated with worse OS (HR, 1.806; p=0.026) and DFS (HR, 1.792; p=0.017). Becker TRG 2-3 had similar hazard ratios in OS (HR, 1.880; p=0.014) and DFS (HR, 1.919; p=0.006).

In the nomogram, Becker TRG 2 and 3 were classified into one group because they were too close to distinguish. The points of the Mandard TRG were 0, 4.61, 9.21, 13.82, and 18.42 respectively, and the points of the Becker TRG were 0, 14.43, and 36.76, respectively. The Becker TRG showed a higher point total than that of the Mandard TRG. When the Mandard TRG was divided into two groups, its point total increased to 22, which was still lower than that of the Becker TRG. The c-index for the nomogram of the Becker TRG to predict OS (0.774; 95% confidence interval [CI], 0.735 to 0.813) was higher than that of the Mandard TRG (0.768; 95% CI, 0.728 to 0.808), but this difference was statistically insignificant (p=0.233). The calibration plots of both models presented a good agreement between the nomogram prediction and actual observation for 3- and 5-year OS (Fig. 4).

The time-dependent ROC curves are shown in Fig. 5. For TRG alone (Fig. 5A and B), the ability of the Mandard TRG to predict 5-year survival was higher than that to predict 1- and 3-year survival (0.72 vs. 0.68 and 0.69) (Fig. 5A). For the Becker TRG, the curves showed a similar outcome (0.71 vs. 0.65 and 0.69) (Fig. 5B). When comparing the two grading systems, the AUC of the Mandard TRG was higher than that of the Becker TRG for 1-year survival (0.68 vs. 0.65). However, the difference was statistically insignificant (p=0.513). For 3-year survival, the abilities to predict the prognosis of both systems were the same (0.69 vs. 0.69, p=0.943). For 5-year survival, both systems owned an acceptable prognostic value (0.72 vs. 0.71, p=0.636).

For the whole model (Fig. 5C and D), the Mandard TRG model owned a good ability to predict 1-, 3- and 5-year survival (all AUC > 0.7). Its ability to predict 5- and 3-year survival was higher than that to predict the 1-year survival (0.85 vs. 0.84 and 0.77) (Fig. 5A). Similarly, the Becker TRG model also had a good ability to evaluate 1-, 3- and 5-year survival (all AUC > 0.7), and its ability to predict 5- and 3-year survival was higher than that to predict 1-year survival (0.86 vs. 0.85 and 0.78) (Fig. 5B). When comparing the two grading systems, the AUC of the Mandard TRG model was lower than that of the Becker TRG model, but the differences were not significant, with the results being 0.77 vs. 0.78 (p=0.583), 0.84 vs. 0.85 (p=0.767), and 0.85 vs. 0.86 (p=0.780) for 1-year, 3-year, and 5-year survival, respectively. Both models had a good predictive value in evaluating long-term survival.

Discussion

In our study, we explored the relationships between TRG and other clinicopathologic characteristics. The results indicated that nine of them were associated with TRG. Among them, it was unexpected that ypT and ypTNM were not included in the multivariable analysis when using the forward selection method. When these factors were included on purpose, TRG would lose its significance. This result might suggest that there was a strong collinearity between TRG and these factors, and this relationship might be a contributor to the loss of the predictive significance of the TRG and TNM system. Other studies have found different outcomes on this point. In the studies of Rullier et al. [13] and Wang et al. [14], ypT and the Mandard TRG were both prognostic factors in univariable analysis, but in multivariable analysis, they lost their significance. Nevertheless, Donohoe et al. [15] suggested both factors were independent prognostic factors. In addition, in the studies of Karagkounis et al. [16] and Becker et al. [6], TRG rather than ypT was an independent prognostic factor. On the other hand, Schmidt et al. [17] supported ypT rather than TRG was an independent prognostic factor.

In univariate analysis, the Mandard and Becker TRGs were both related to OS and DFS, and these connections became more obvious when they were divided into responders and non-responders. In this respect, researches suggested different boundaries. For the Mandard TRG, some studies supported that TRG 1-2 should be classified into responders, which was in accordance with our study [7,18,19], while some others believed that TRG 1-3 was better in distinguishing the prognosis [20-22]. For the Becker TRG, there were studies supporting the same consequence as ours [1,23-25], while others suggested TRG 1-2 owned a better prognosis than TRG 3 [9,10,26,27]. This discrepancy might partly derive from the differences in subjective evaluations of the pathologists. Hence, more studies are needed to determine the boundary.

When comparing these two grading systems, they showed a similar trend in the survival curves, and this trend became even more apparent when patients were divided into two groups. This might suggest that Mandard TRG 1-2 vs. 3-5 had similar predictive value with Becker TRG 1a-1b vs. 2-3. In this aspect, the survival curves of another study showed a similar trend, despite the difference that the TRGs in their study were divided into three groups [28].

Then, we explored the predictive capabilities of these two systems using the time-dependent ROC curves. Although the Mandard TRG could predict 1-year survival more accurately than the Becker TRG, the difference was not significant. When assessing longer survival, the abilities of these two systems were at the same level. In addition, both systems had a good predictive value (AUC > 0.7) when evaluating five-year survival, which meant TRG could be used as a prognostic factor in locally advanced GC. Although many studies supported TRG could be a survival-related factor, few of them showed a time-dependent ROC curve [29,30].

In multivariable analysis, the hazard ratios of Mandard TRG 3-5 were close to those of Becker TRG 2-3 in both OS and DFS, which added evidence that the abilities of both systems to predict survival were comparable. In addition, in our study, the lymph node metastasis owned the greatest hazard ratio, which was in line with many other studies [4,6,19].

In the nomogram, we found that both grading systems could be used as a survival predictor. Unexpectedly, the Becker TRG had a higher score than the Mandard TRG. This might be because the Becker TRG had fewer tiers than the Mandard TRG.

In the ROC curves of models, both models owned a good predictive value, and there was no significant difference between these two models. This might suggest that these two grading systems had similar functions in evaluating the prognosis when combined with other clinicopathologic factors.

There are some limitations to the present study. This study is retrospective and conducted at a single institution, which means a potential selection bias might exist. The sample size is relatively small, which leads to a limited number of patients in each group and might contribute to the similar trend of the survival curves. The follow-up time of some patients is not long enough, which might weaken the significance of clinicopathologic factors and enlarge the range of the confidence interval. The evaluation mainly depends on the experience of pathologists, so observer bias may exist. However, our study concentrated on a specific group of patients and confirmed the value of TRG in patients with

locally advanced GC. Additionally, we used several different methods to compare the predictive value of two kinds of TRGs and found that there was no significant difference between these two systems. This result suggested that both systems could be used as independent predictive factors and that it is possible for these criteria to reach a consensus.

In conclusion, TRG is a promising system to evaluate the efficacy of neoadjuvant therapy and long-term survival in patients with advanced GC. There is no significant difference in predictive value between the two kinds of systems, which means that it is possible to unify these systems.

Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (https://www.e-crt.org).

Ethical Statement

The study was approved by the Institutional Review Board (IRB) of Liaoning Cancer Hospital and Institute (Cancer Hospital of China Medical University). Due to the retrospective nature of this study, informed consent was waived by IRB.

Author Contributions

Conceived and designed the analysis: Zhang J, Tong Y.
Collected the data: Tong Y, Shan Z.
Contributed data or analysis tools: Zhu Y, Liu D.
Performed the analysis: Tong Y.
Wrote the paper: Tong Y.
Reviewed and revised the manuscript: Zhang J, Zhao Y.

Conflicts of Interest

Conflicts of interest relevant to this article was not reported.

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