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Original Research

Nomogram for 5-year relapse-free survival of a patient with advanced gastric cancer after surgery

Yusuke Muneoka [a, b, *], Kohei Akazawa [b], Takashi Ishikawa [a, b], Hiroshi Ichikawa [a], Atsushi Nashimoto [c], Hiroshi Yabusaki [d], Norio Tanaka [e], Shin-ichi Kosugi [f], Toshifumi Wakai [a]

[a] Division of Digestive and General Surgery, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan
[b] Department of Medical Informatics, Niigata University Medical and Dental Hospital, Niigata, Japan
[c] Department of Surgery, Nanbugo General Hospital, Niigata, Japan
[d] Department of Surgery, Niigata Cancer Center Hospital, Niigata, Japan
[e] Department of Surgery, Shibata Prefectural Hospital, Niigata, Japan
[f] Department of Digestive and General Surgery, Uonuma Institute of Community Medicine, Niigata University Medical and Dental Hospital, Niigata, Japan

HIGHLIGHTS

- We developed a nomogram to predict 5-year RFS for stage II/III gastric cancer.
- Predictive accuracy of the nomogram was superior to that of the TNM classification.
- This tool will be useful for selecting good candidates for adjuvant therapy.

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ABSTRACT

Background: Prognoses vary substantially among patients with advanced gastric cancer following curative surgery. The aim of the current study was to develop and verify the validity of a novel nomogram that predicts the probability of 5-year relapse-free survival (RFS) in patients who underwent curative resection for stage II/III gastric cancer.

Materials and methods: A nomogram to predict 5-year RFS following surgical resection of gastric cancer was constructed based on the data of patients who underwent surgery for primary gastric carcinoma at three institutions in Japan in January 2001–December 2006. Multivariate analysis using a Cox proportional hazards regression model was performed, and the nomogram's predictive accuracy (discrimination) and the agreement between observed outcomes and predictions (calibration) were evaluated by internal validation.

Results: Multivariate analyses revealed that age at operation, depth of tumor, tumor location, lymph node classification, and presence of combined resection were significant prognostic factors for RFS. In the internal validation, discrimination of the developed nomogram for 5-year RFS was superior to that of the American Joint Committee on Cancer TNM classification (concordance indices of 0.80 versus 0.67; $P < 0.001$). Moreover, calibration appeared to be accurate. Based on these results, we have created free software to more easily predict 5-year RFS.

Conclusion: We developed and validated a nomogram to predict 5-year RFS after curative surgery for stage II/III gastric cancer. This tool will be useful for the assessing a patient's individual recurrence risk when considering additional therapy in clinical practice.

1. Introduction

Gastric cancer is the fifth most common cancer worldwide and was the third most frequent cancer-related cause of death in 2012

* Corresponding author. Department of Medical Informatics, Niigata University Medical and Dental Hospital, 1-757 Asahimachi-dori, Niigata 951-8510, Japan.
E-mail address: yusukem1986@med.niigata-u.ac.jp (Y. Muneoka).

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(723,000 deaths, 8.8% of all cancer deaths) [1]. The prognosis of gastric cancer varies considerably depending on different tumor and patient characteristics.

The American Joint Committee on Cancer (AJCC) defined a staging system that classifies gastric cancer by the depth of tumor invasion (T), number of metastatic lymph nodes (N), and presence or absence of distant metastases (M) [2]. This staging system has been widely used to stratify patients into risk groups and predict their prognosis. However, different prognoses were frequently observed among patients at the same stage. These differences may be due to other prognostic factors such as age, sex, tumor size, or histological type [3–6]. In particular, outcomes of patients who have undergone curative surgery for advanced gastric cancer and been diagnosed with pathological stage II or III disease are heterogeneous. This differs from stage I disease, which rarely develops recurrence and has an excellent prognosis, and stage IV disease, which is unresectable and has a considerably poor prognosis. Aoyama et al. [3] reported that the 5-year survival rate of stage II or III disease with a macroscopic tumor diameter of <70 and ≥70 mm was 64.9% and 33.1%, respectively. Thus, heterogeneity of the recurrence risk within stage II and III gastric cancer surely exists, but we cannot yet accurately predict these patients' individual recurrence risk. Accurate prediction of the recurrence risk may be helpful for individualized treatment decisions and postoperative counseling.

Statistical prediction models have been developed for most cancer types. One such predictive tool is the nomogram, which attempts to combine all proven prognostic factors and quantify risk as precisely as possible using a simple graphical representation [7–9]. Previous comparisons using risk-grouping approaches for prostate cancer and soft tissue sarcoma suggest that a high-quality nomogram will improve predictive accuracy relative to the formation of risk groups [10,11]. A few effective nomograms that predict the survival or recurrence of gastric cancer have been developed [3,12,13]. However, most nomograms for gastric cancer were developed based on data from wide patient populations that included both early cancer and unresectable advanced cancer. Few reports have described predictive tools that select only patients with stage II and III gastric cancer.

The aim of the current study was to develop a novel nomogram with which to accurately predict the individual risk of recurrence and mortality of patients who have undergone curative resection for stage II or III gastric cancer, and who never received any adjuvant chemotherapy. Analyzing these patients' recurrence risk will allow us to identify pure oncological prognostic factors affecting cancer recurrence. We expected this nomogram could be helpful in selecting good candidates for adjuvant therapy.

2. Material and methods

2.1. Patients

From January 2001 to December 2006, 789 patients underwent curative gastrectomy for stage II or III gastric cancer at three institutions in Japan (Niigata University Medical and Dental Hospital, Niigata Cancer Center Hospital, and Niigata Shibata Prefectural Hospital). Among these patients, we excluded those who met any of the following criteria: T1 and T3 (SS)N0 disease, simultaneous or metachronous cancer(s), carcinoma in the remnant stomach, or receiving preoperative or postoperative adjuvant chemotherapy. In this study, we aimed for accurate prediction of the cancer recurrence risk which is not influenced by adjuvant chemotherapy. Therefore, we excluded patients receiving preoperative or postoperative adjuvant chemotherapy. Now in Japan, S-1 postoperative adjuvant chemotherapy became the standard treatment for patients with stage II and III gastric cancer based on Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) [14]. However, the patients classified as stage II due to T1/N2-N3 status and T3N0 status, who had been regarded as relatively good prognosis group, were ineligible for the ACTS-GC. Accordingly, we also excluded T1 and T3N0 disease from this study. Finally, 207 patients were enrolled in this study. The institutional review board at each participating institution approved this study.

2.2. Clinicopathological factors

The definition and documentation of factors were described according to the Japanese Classification of Gastric Carcinoma, 3rd English edition [15]. The Japanese Classification of Gastric Carcinoma stage grouping in this edition is the same as the 7th AJCC TNM stage classification. The clinicopathological factors that we used to predict the probability of 5-year RFS are shown in Table 1. The macroscopic types were divided according to the Bormann classification. The location of the tumor was categorized as upper third, middle third, or lower third by the center of the lesion. The histological subtype was categorized as differentiated or undifferentiated. The differentiated type included papillary adenocarcinoma (pap), well-differentiated tubular adenocarcinoma (tub1), and moderately differentiated tubular adenocarcinoma (tub2). The undifferentiated type included poorly differentiated adenocarcinoma (por), signet-ring cell carcinoma (sig), mucinous adenocarcinoma (muc), and other special types such as hepatoid carcinoma and endocrine carcinoma. The extent of lymph node dissection was determined according to the Japanese treatment guidelines [16]. Combined resection was defined as resection of adjacent organs that had been directly invaded by the primary tumor or metastatic lesion; therefore splenectomy for complete clearance of No. 10 lymph nodes and cholecystectomy for gallbladder stones were excluded.

2.3. Follow-up

After surgery, the patients were followed up regularly with physical examinations and laboratory tests (including evaluation of the tumor markers carcinoembryonic antigen and carbohydrate antigen 19-9) every 3 months as well as computed tomography once or twice per year until 5 years after surgery. Disease status at the last follow-up was based on a retrospective review of the medical records and the registration data at each of the three institutions. The follow-up period was calculated from the date of surgery to that of the last follow-up. RFS was defined as the time of surgery to the time of recurrence or death of any cause.

2.4. Statistical analysis

As descriptive statistics, mean ± standard deviation or median (range) was used for continuous variables, and frequency and proportion were used for discrete variables. Binary variables were generated regarding the following variables. The depth of the tumor invasion (T) was categorized as T2, T3, and T4. The lymph node classification (N) was categorized as N0/1, N2, and N3. The extent of lymph node dissection was classified as <D2 and ≥D2. The tumor size was classified as <5 and ≥5 cm.

RFS among the groups as stratified by a single factor was estimated by the Kaplan–Meier method, and significant differences were assessed by a log-rank test. A Cox proportional hazards regression analysis (Cox analysis) was used to select the significant and independent prognostic factors significantly affecting RFS with forward stepwise regression.

Based on the predictive model with the identified prognostic

Table 1
Patient and tumor characteristics in stage II/III gastric cancer.

Characteristics	Distribution
Age (years)	
Median (range)	69 (22–95)
Sex	
Male	137
Female	70
Depth of tumor invasion	
T2	55
T3	77
T4	75
Macroscopic type	
Type 0	26
Type 1	12
Type 2	83
Type 3	71
Type 4	15
Tumor size (cm)	
Median (range)	5.3 (1.8–17.8)
Tumor location	
U	60
M	73
L	71
Histological type	
Differentiated	112
(pap/tub1/tub2)	(4/27/81)
Undifferentiated	95
(por1/por2/sig/muc/others)	(27/47/13/4/4)
Lymphatic invasion	
Negative	7
Positive	200
Venous invasion	
Negative	42
Positive	165
Extent of gastric resection	
DG	121
TG	84
PG	2
Extent of lymph node dissection	
D1	57
D2	143
D2+	7
Number of metastatic lymph nodes	
Median (range)	3 (0–35)
Number of examined lymph nodes	
Median (range)	38 (10–102)
Combined resection	
Absent	184
Present	23
Stage (TNM 7th Ed.)	
II (IIA/IIB)	98 (35/63)
III (IIIA/IIIB/IIIC)	109 (52/25/32)
Recurrence	
Absent	153
Present	54

Data are presented as number of patients unless otherwise indicated.
por1: poorly differentiated adenocarcinoma, solid type, por2: poorly differentiated adenocarcinoma, nonsolid type, DG: distal gastrectomy, TG: total gastrectomy, PG: proximal gastrectomy.

factors, a nomogram was constructed to predict 5-year RFS. The accuracy of the nomogram was measured by Harrell's concordance index (c-index) [17] and assessed by comparing the nomogram-predicted versus observed Kaplan–Meier estimates of RFS probability. Bootstraps with 1000 resamples were used for discrimination and calibration. Student's *t*-test was performed to compare the distribution of the c-index of our nomogram with that based on the AJCC TNM classification. All analyses were performed using SPSS ver. 22 (IBM Corp., Armonk, NY) and R ver. 3.2.1 software. In all statistical analyses, *P*-values of less than 0.05 were considered to indicate statistical significance.

3. Results

3.1. Baseline characteristics

Descriptive statistics for this cohort appear in Table 1. The median age was 69 years (range, 22–95 years), and the study population comprised 137 (66%) male and 70 (34%) female patients, respectively. The median follow-up period after gastrectomy was 74.7 months (range, 2–162 months).

Recurrence of gastric cancer during the follow-up was detected in 54 (26.1%) of 207 patients included in the study group; 26 patients (12.6%) had hematogenous metastases, 21 (10.1%) had peritoneal metastases, and 21 (10.1%) had lymph node metastases (some patients had a relapse at more than one site).

3.2. Survival analysis according to each characteristic

The RFS curves are shown in Fig. 1. The 5-year overall survival and RFS rates of the 207 patients were 68.0% and 66.1%, respectively. Table 2 shows the estimated 5-year RFS rate and the results of the log-rank test for each clinical factor. The univariate analysis revealed that age at operation, depth of invasion, tumor size, main tumor location, extent of gastric resection, number of metastasized lymph nodes, and the presence of combined resection were significant prognostic factors. In particular, the depth of invasion, number of positive lymph nodes, and presence of combined resection showed a ≥30% difference in the 5-year RFS rate between each group.

3.3. Multivariate analysis

Cox analysis was performed with forward stepwise regression, in which all variables were used as candidates of prognostic variables. Cox analysis revealed that age at operation, depth of invasion, main tumor location, number of metastasized lymph nodes, and the presence of combined resection were independent and significant prognostic factors affecting RFS (Table 3).

3.4. Nomogram and evaluation of validation

A prognostic nomogram was constructed according to Harrell

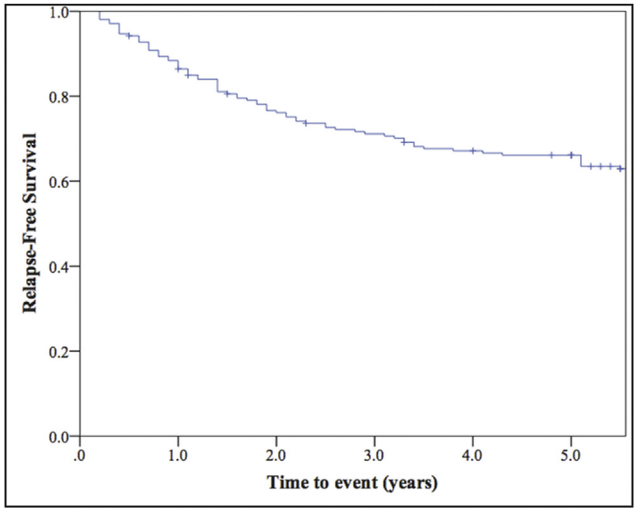

Fig. 1. Kaplan–Meier estimates of relapse-free survival (RFS) for all patients. The probability of 5-year RFS was 66.1%.

Table 2
Five-year relapse-free survival rates according to the clinicopathological characteristics of patients with stage II/III gastric cancer.

Characteristics	*n*	5-year RFS (%)	*P*
Age (years)			<0.001
<70	107	77.2	
≥70	100	54.4	
Sex			0.705
Male	137	67.4	
Female	70	63.6	
Depth of tumor invasion			<0.001
T2	55	90.8	
T3	77	65.6	
T4	75	49.2	
Macroscopic type			0.159
Type 0	26	88.5	
Type 1	12	66.7	
Type 2	83	63.2	
Type 3	71	64.3	
Type 4	15	50.6	
Tumor size (cm)			0.002
<5	86	78.7	
≥5	121	57.2	
Tumor location			0.001
Upper third	63	49.2	
Middle third	73	73.7	
Lower third	71	73.7	
Histological type			0.984
Differentiated	112	68.4	
Undifferentiated	95	63.6	
Lymphatic invasion			0.440
Negative	7	71.4	
Positive	200	65.9	
Venous invasion			0.752
Negative	42	62.6	
Positive	165	67.0	
Extent of gastric resection[a]			<0.001
DG	121	78.0	
TG	84	48.4	
Extent of lymph node dissection			0.745
D1	57	64.5	
D2	143	67.3	
D2+	7	57.1	
Number of metastatic lymph node			<0.001
<3	101	76.7	
3–6	60	68.0	
≥7	46	40.6	
Number of examined lymph node			0.195
<16	10	40.0	
≥16	197	67.5	
Combined resection			<0.001
Absent	184	72.4	
Present	23	14.3	
Stage			<0.001
II	98	82.3	
III	109	51.9	

RFS: relapse-free survival, DG: distal gastrectomy, TG: total gastrectomy.
[a] We excluded the patients who underwent proximal gastrectomy from the univariate analysis because of the small number of such patients (n = 2).

Table 3
Summarized variables associated with relapse-free survival according to Cox proportional hazards regression analysis.

Factor	Category	β	HR	95% CI
Age (years)				
	<70	0.00		
	≥70	1.27	3.57	2.21–5.78
Depth of tumor invasion				
	T2	0.00		
	T3	0.80	2.22	1.05–4.73
	T4	1.11	3.03	1.41–6.51
Tumor location				
	L	0.00		
	M	0.25	1.28	0.71–2.31
	U	1.06	2.87	1.66–4.99
Combined resection				
	Absent	0.00		
	Present	1.54	4.68	2.70–8.12
Number of metastatic lymph nodes				
	<3	0.00		
	3–6	0.59	1.80	1.03–3.14
	≥7	0.82	2.28	1.35–3.84

β: parameter estimate, HR: hazard ratio, 95% CI: 95% confidence interval.

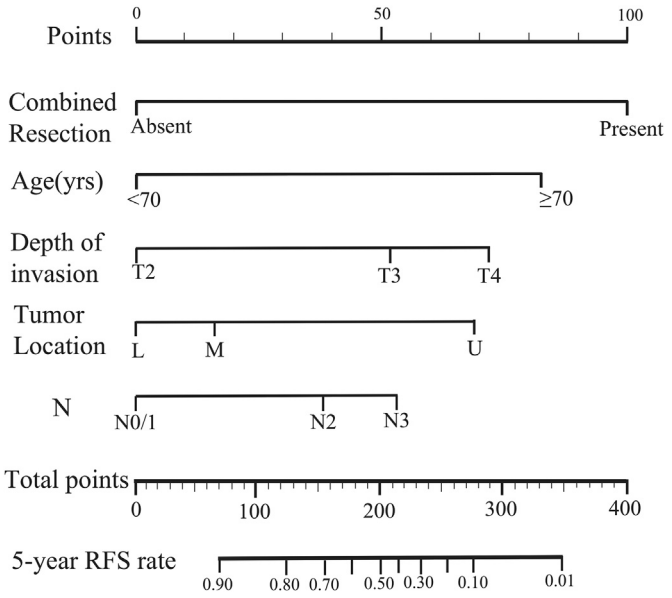

Fig. 2. Nomogram predicting the probability of 5-year relapse-free survival (RFS) of patients with postoperative advanced gastric cancer.

et al. [17] and based on the estimated regression coefficients in our Cox analysis (Fig. 2). Fig. 3 shows the 5-year RFS predicted by the nomogram in each AJCC-TNM stage. A wide range of predicted survival rates were identified in each stage. Heterogeneity was present in several of the stage groups, particularly groups IIB and IIIA. The mean ± standard deviation of the c-index of the nomogram predicting the 5-year RFS rate was estimated using 1000 data sets created by the bootstrap method (0.80 ± 0.07). The estimated c-index was found to be significantly better than that of the AJCC TNM classification (0.67 ± 0.07, $P < 0.001$). Fig. 4 illustrates the calibration of the nomogram. The calibration appeared to be accurate for prediction of the 5-year RFS. Furthermore, Web software was created to predict the probability of 5-year RFS by entering the values of age at operation, depth of invasion, main tumor location, lymph node classification, and presence of combined resection (http://www.med.niigata-u.ac.jp/su1/patient/clinical_trial/Stage23GC.html).

4. Discussion

In this study, we constructed a nomogram that accurately predicts an individual's RFS following curative gastrectomy according to five clinically available variables: age at operation, depth of invasion, main tumor location, lymph node classification, and presence of combined resection. This study is significant because a cohort of limited patients who underwent curative gastrectomy for stage II or III gastric cancer was used to develop the nomogram. This nomogram was more accurately predictive than the seventh AJCC stage grouping, with a c-index of 0.80 and good calibration. To simplify the complexity of drawing lines and adding points on the

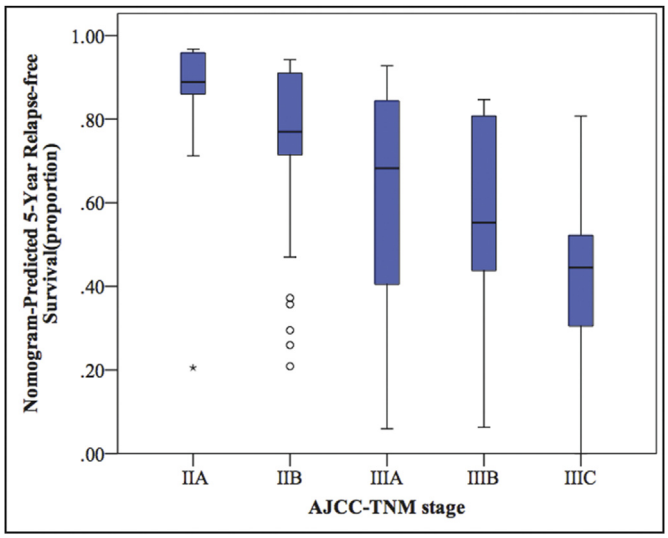

Fig. 3. Box plot representing the distribution of nomogram-predicted 5-year relapse-free survival according to the 7th edition of the American Joint Committee on Cancer TNM classification. A wide range of predicted survival rates can be identified in each TNM stage.

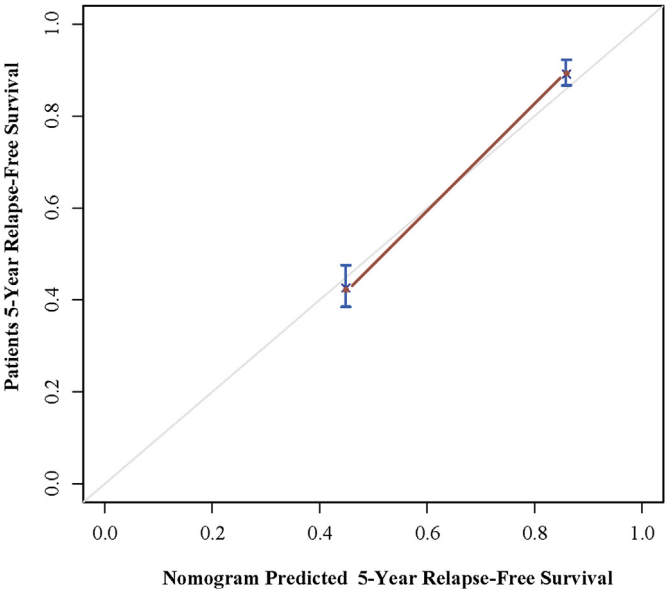

Fig. 4. Calibration plot comparing predicted and actual relapse-free survival probabilities at 5-year follow-up.

nomogram, we also constructed free Web software.

Kim et al. [18] from the US recently developed a postoperative nomogram to predict disease-free survival of patients with gastric cancer after curative surgery. The variables used in their nomogram included age, tumor site, depth of invasion, and lymph node ratio (LNR), which were mostly the same as in our nomogram. The LNR is the ratio of the number of metastasized lymph nodes to the number of examined lymph nodes. Kong et al. [19] reported that the LNR was superior in assessing prognosis compared with the simple lymph node status alone in a study of a large cohort of patients with gastric cancer who underwent gastrectomy in Korea. In the current study, we evaluated a model that included the LNR, but the value of the −2log-likelihood of the model was 753.1, which was lower than 755.3 that in a model using the simple number of metastasized lymph nodes. Therefore, we adopted the latter model. The presence of combined resection of adjacent organs, which was not used in previous nomograms, was selected as an independent prognostic factor and entered into our nomogram. In several studies, the prognosis of patients who underwent radical gastrectomy with combined resection of other organs was poor [20,21]. The Japanese treatment guidelines recommend combined resection, which is performed to obtain curative resection for tumors in which the primary or metastatic lesion directly invades adjacent organs. However, histological cancerous invasion is not always present on pathological examination, even if surgeons determine that combined resection is needed because the laparotomy findings suggest macroscopic invasion to adjacent structures. Actually, only three patients in our study had tumors with histological cancerous invasion. Nevertheless, the hazard ratio of combined resection for recurrence was 4.68 (95% confidence interval, 2.70–8.12). Thus, the degree of the contribution of combined resection (which is performed at the surgeon's discretion based on the laparotomy findings) to the risk of recurrence is high, and this factor was therefore used in our nomogram.

The c-index of our nomogram was 0.80, which was similar to those reported in previous studies (0.70–0.80 in different patient populations). The median predicted 5-year RFS by our nomogram was similar to the actual survival rate calculated from the Kaplan–Meier test. In the internal validation, discrimination of the developed nomogram was superior to that of the AJCC TNM classification (concordance indices of 0.80 versus 0.67, respectively; $P < 0.001$). Therefore, the Web software created based on our nomogram can predict the individualized recurrence risk more accurately and provide additional prognostic information based on the TNM classification.

Based on the ACTS-GC, patients in this study with stage II or III disease have been recommended to undergo 1-year postoperative treatment with S-1 [14,22]. However, heterogeneity of individual recurrence and mortality risk within stage II and III gastric cancer has been reported [12,18,23]. In the current study, six patients (6.1%) were diagnosed with pathological stage II disease and had a predicted 5-year RFS rate of <50% according to our nomogram. Accurate identification of and more aggressive postoperative treatment for patients with a poor predicted prognosis may help to improve their prognosis. Conversely, 33 patients (30.3%) were diagnosed with pathological stage III disease and had a predicted 5-year RFS rate of >80% according to our nomogram. These patients may obtain adequate benefit from S-1 monotherapy. However, adjuvant chemotherapy often causes adverse events such as anorexia, nausea, and diarrhea. The ACTS-GC reported that treatment was continued for 12 months in only 65.8% of patients and that the most common cause of withdrawal was the occurrence of adverse events [14]. Adjuvant chemotherapy for patients who have undergone gastrectomy is not easy and may decrease the quality of life. Moreover, in recent years, the percentage of older patients with gastric cancer or those with gastric cancer plus comorbidities has increased remarkably [24]. Older patients with cancer often have comorbidities and age-related physiological problems that can lead to greater drug toxicity compared with younger patients [25]. From this viewpoint, a predictive tool that accurately predicts the recurrence risk of advanced gastric cancer is expected to be developed and will be helpful in selecting good candidates for adjuvant therapy. Our nomogram may be a useful tool with which to select patients who are unlikely to benefit from adjuvant chemotherapy. For example, we may be able to omit adjuvant chemotherapy in elderly or comorbid patients if the predicted 5-year RFS according this nomogram is >90%.

The current study had several limitations. First, the number of patients was 207, which is less than that in previous studies of

nomograms for gastric cancer. This is why we selected patients during a short time period (2001–2006), when adjuvant chemotherapy was not common, to reduce the bias that arises from variation in survival outcomes. Although preoperative or postoperative chemotherapy are increasingly used, we needed to analyze chemo-naive patients to accurately predict the individual risk of recurrence and mortality based on the oncological prognostic factors which were not influenced by chemotherapy. In addition to this, we limited to stage II or III patients and excluded T1 and T3N0 cases to accommodate ACTS-GC trial. Accordingly, we can make it easy to use our nomogram as a tool for selecting good candidates for adjuvant therapy. Furthermore, we excluded patients with other malignancies to minimalize the impact of comorbidity on survival. Second, collaboration with multiple institutions limited the ability to easily standardize the diagnostic and treatment criteria, which may have led to selection bias. Finally, while the nomogram was internally validated using bootstrapped calibration, future studies are needed to externally validate the proposed nomogram.

5. Conclusions

We developed and validated a nomogram to predict 5-year RFS after curative surgery for stage II or III gastric cancer based on a multicenter database. This nomogram would be useful for assessing a patient's individual risk of recurrence and mortality when considering additional therapy in clinical practice.

Ethical Approval

The institutional review board at Niigata University Graduate School of Medical and Dental Sciences approved this study. Judgment's number was 2031.

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Author contribution

Study design: Yusuke Muneoka, Kohei Akazawa, and Toshifumi Wakai.

Data analysis: Yusuke Muneoka and Kohei Akazawa.

Data collection: Yusuke Muneoka, Atsushi Nashimoto, Hiroshi Yabusaki, and Norio Tanaka.

Drafting the manuscript: Yusuke Muneoka, Takashi Ishikawa, and Hiroshi Ichikawa.

Revising the manuscript, final approval of the version to be published: All authors.

Conflicts of interest

The author have no financial conflicts of interest.

Trial registry number

This research was not an RCT.

Guarantor

Kohei Akazawa is the guarantor of this study.

Research Registration Unique Identifying Number (UIN)

UIN of this study was researchregistry1468.

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