Asian Journal of Surgery 47 (2024) 3056–3062

Contents lists available at ScienceDirect

Asian Journal of Surgery

journal homepage: www.e-asianjournalsurgery.com

Original Article

Who would be the winner? A prognostic nomogram for predicting the benefit of postoperative radiotherapy ± chemotherapy in patients with locally advanced gastric cancer: TROD-02-01 study

Fatma Sert [a,*], Ilknur Bilkay Gorken [b], Serdar Ozkok [a], Didem Colpan Oksuz [c], Birsen Yucel [d], Esra Kaytan Saglam [e], Gamze Aksu [f], Eren Cetin [g], Meryem Aktan [h], Emine Canyilmaz [i], Nilgün Ozbek Okumus [j], Berna Yildirim [k], Serap Akyurek [l], Meltem Serin [m], Meral Kurt [n], Zumre Arican Alicikus [b], Eda Erdis [d], Deniz Yalman [a]

[a] *Ege University, Faculty of Medicine, Department of Radiation Oncology, Izmir, Turkey*
[b] *Dokuz Eylul University, Faculty of Medicine, Department of Radiation Oncology, Izmir, Turkey*
[c] *Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Radiation Oncology, Istanbul, Turkey*
[d] *Sivas Cumhuriyet University, Faculty of Medicine, Department of Radiation Oncology, Sivas, Turkey*
[e] *Biruni University, Department of Radiation Oncology, Istanbul, Turkey*
[f] *Akdeniz University, Faculty of Medicine, Department of Radiation Oncology, Antalya, Turkey*
[g] *Gazi University, Faculty of Medicine, Department of Radiation Oncology, Ankara, Turkey*
[h] *Necmettin Erbakan University, Faculty of Medicine, Department of Radiation Oncology, Konya, Turkey*
[i] *Karadeniz Technical University, Faculty of Medicine, Department of Radiation Oncology, Trabzon, Turkey*
[j] *On Dokuz Mayıs University, Faculty of Medicine, Department of Radiation Oncology, Samsun, Turkey*
[k] *University of Health Sciences, Prof Dr Cemil Tascioglu City Hospital, Department of Radiation Oncology, Istanbul, Turkey*
[l] *Ankara University, Faculty of Medicine, Department of Radiation Oncology, Ankara, Turkey*
[m] *Acıbadem Mehmet Ali Aydinlar University, Adana Hospital, Department of Radiation Oncology, Adana, Turkey*
[n] *Bursa Uludag University, Faculty of Medicine, Department of Radiation Oncology, Bursa, Turkey*

ARTICLE INFO

Article history:
Received 15 November 2023
Received in revised form
24 January 2024
Accepted 16 February 2024
Available online 4 March 2024

Keywords:
Gastric cancer
Nomogram
Radiotherapy

SUMMARY

Objectives: We aimed to develop a basic, easily applicable nomogram to improve the survival prediction of the patients with stage II/III gastric cancer (GC) and to select the best candidate for postoperative radiotherapy (RT).

Methods: In this multicentric trial, we retrospectively evaluated the data of 1597 patients with stage II/III GC after curative gastrectomy followed by postoperative RT ± chemotherapy (CT). Patients were divided into a training set (n = 1307) and an external validation set (n = 290). Nomograms were created based on independent predictors identified by Cox regression analysis in the training set. The consistency index (C-index) and the calibration curve were used to evaluate the discriminative ability and accuracy of the nomogram. A nomogram was created based on the predictive model and the identified prognostic factors to predict 5-year cancer-specific survival (CSS) and progression-free survival (PFS).

Results: The multivariate Cox model recognized lymph node (LN) involvement status, lymphatic dissection (LD) width, and metastatic LN ratio as covariates associated with CSS. Depth of invasion, LN involvement status, LD width, metastatic LN ratio, and lymphovascular invasion were the factors associated with PFS. Calibration of the nomogram predicted both CSS and PFS corresponding closely with the actual results. In our validation set, discrimination was good (C-index, 0.76), and the predicted survival was within a 10% margin of ideal nomogram.

Conclusions: In our relatively large cohort, we created and validated both CSS and PFS nomograms that could be useful for underdeveloped or developing countries rather than Korea and Japan, where the D2

* Corresponding author. Ege University, Faculty of Medicine, Department of Radiation Oncology, Kazım Dirik Mah, Universite Cad, No:1, Bornova, Izmir, Turkey.
E-mail addresses: fatma.sert@ege.edu.tr, gracilis81@gmail.com (F. Sert).

https://doi.org/10.1016/j.asjsur.2024.02.100

gastrectomy is routinely performed. This could serve as a true map for oncologists who must make decisions without an experienced surgeon and a multidisciplinary tumor board.

1. Introduction

Gastric cancer (GC) is the fourth most common malignant tumor in the world and the second leading cause of cancer-related deaths.[1] It has the greatest geographical distribution in East Asia and a relatively high incidence in Turkey as well.[2] Because there are no typical clinical symptoms or biochemical markers of local GC, the diagnosis rate of local disease is low, as a large proportion of patients with GC patients are diagnosed at the locally advanced or metastatic stage.[3] Curative oncologic surgery, supplemented by chemotherapy (CT) and radiotherapy (RT), remains the primary mode of treatment. Unfortunately, despite all oncological advances in treatment options, the overall survival (OS) rate remains unfavorable due to recurrence, metastasis, and other factors associated with poor outcomes.[4,5] Furthermore, recent randomized trials such as CRITICS[6] and ARTIST II[7] prompted us to ask what the optimal treatment strategy should be in locally advanced GC patients, as well as the role of postoperative RT for the D2 and R0 resected groups. Evidently, there is a need for corresponding risk stratification to obtain a better prediction of prognosis and to identify the best patient candidate for postoperative RT. This will also be a new trend in the field of oncological research as well as GC.

Until now, the TNM classification system of the American Joint Committee on Cancer's 8th edition has been the most commonly used staging system for GC. However, because the TNM classification system lacks clinicopathological factors and laboratory indicators, it is applicable to the general population rather than individual patients. Nomograms, a new method of quantifying cancer risk, show important prognostic factors and provide more accurate survival predictions. There are some well-established nomograms that can predict the survival rate of patients with GC patients. Han et al's 6-variable predictive model for patients with stage II/III GC demonstrated that its predictive value was significantly higher than that of the AJCC-TNM staging system.[8] However, its predictive power for both recurrence and the effect of postoperative RT was not assessed. Jiang et al presented a nomogram of the association of adjuvant chemotherapy with survival in patients with stage II/III GC, but its consistency index (C-index) was only 0.686.[9] There have also been GC prognostic models developed based on individual serum markers, but they lack external validation.[10] Furthermore, GC-related nomograms in previous studies had only limited research variables and did not attempt to select the best candidate for postoperative RT.

This study attempted to develop a basic, easily applicable nomogram to improve the survival prediction of patients with stage II/III GC patients and to select the best candidate for postoperative RT. This could help clinicians to identify high-risk patients and guide follow-up treatment.

2. Materials and methods

2.1. Patient selection

The clinical data of 1597 operated GC patients treated between January 2005 and December 2018 were collected from 13 institutions for this multi-institutional Turkish Radiation Oncology Group (TROD) study. The inclusion criteria were 1 stage II/III GC confirmed by histological pathology; 2 negative/microscopic positive surgical margin (R0/1); 3 adjuvant radiotherapy ± chemotherapy after curative gastrectomy; 4 complete clinic-pathological and follow-up data (all biomarkers were measured within 1 week before surgery); 5 no extra-intestinal nutrition, acute inflammation, or severe organ damage within 1 week before surgery; 7 no other malignant tumors, no cause of death other than GC. Exclusion criteria were 1 merging other systemic tumor/synchronous tumors; 2 lacking or incomplete clinical data; and 3 receiving neoadjuvant oxaliplatinum-based chemotherapy or preoperative radiotherapy. The tumor stage was reclassified according to the AJCC 8th TNM classification.

The study was performed in accordance with the Helsinki Declaration (as revised in 2013). The study was approved by the Ethics Committee of the Ege University Hospital (Approval No. 21-T12/33), and all patients provided informed consent.

This data set included patient demographics (age and sex), pathologic characteristics (location, size, gross type, histology, depth of invasion, number of examined and metastatic lymph nodes), adjuvant/neoadjuvant 5FU based/concomitant CT, postoperative RT, and follow-up data (follow-up duration and survival). The location of the tumor was classified as upper third, middle third, or lower third by the center of the lesion. Adenocarcinoma of the esophagogastric junction within the stomach was classified as upper-third gastric cancer. The size of the tumor was measured at the longest diameter. The histologic subtype was categorized as differentiated type (papillary adenocarcinoma, well-differentiated tubular adenocarcinoma, and moderately differentiated tubular adenocarcinoma) or undifferentiated type (poorly differentiated tubular adenocarcinoma, signet ring cell carcinoma, and mucinous adenocarcinoma). The depth of invasion was categorized as mucosa, submucosa, muscularis propria, subserosa, serosa, or adjacent organ invasion. The number of metastatic lymph nodes was classified using the node grouping of the eighth AJCC TNM classification. Adjuvant chemotherapy was categorized as received or not received. The duration of the follow-up was measured from the time of surgery to the last follow-up date, and information about the patient's survival status at the last follow-up was collected.

2.2. Nomogram construction

For nomogram construction and validation, we randomly assigned 80% of the patients to the training set (n = 1307) and 20% to the validation set (n = 290). The clinicopathologic characteristics of the training and validation sets were assessed. We used the collected TROD dataset as a training set to create a prognostic and predictive nomogram. The proportional hazards (PH) assumption and linearity assumption in continuous variables (size, examined lymph nodes) was investigated using restricted cubic splines[11,12]. Continuous variables were transformed to an appropriate form for fitting the PH and linearity assumptions. For categorical variables, a log−log survival plot was used to identify the PH assumption, and all variables were fitted to the PH assumption. Variables were selected by the forward stepwise selection method in the Cox PH regression model. A nomogram was created based on the predictive model and the identified prognostic factors to predict 5-year cancer-specific survival (CSS) and progression-free survival (PFS).

2.3. Nomogram validation

An independent set of TROD patient data was used to externally validate the prognostic performance of the nomogram. In brief, we used the concordance index (C-index) to assess the discriminative power of our nomogram, measuring the difference in predictive power between the observed and predicted results. Additionally, we plotted receiver operating characteristic (ROC) curves and calculated the area under the curve (AUC) to evaluate the accuracy of the 5-year survival prediction.

2.4. Statistical analysis

We used the chi-square test to compare variables between training and validation sets, then performed survival analysis using the Kaplan–Meier method and the log-rank test. Furthermore, we evaluated the effectiveness of our nomogram in predicting the prognosis of the patients by generating C index and AUC, and then compared the results to those from the TNM staging (8th AJCC). All statistical analyses were carried out at a 95% confidence level using packages implemented in R software version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria) (CI). Data followed by $P < 0.05$ were considered statistically significant.

3. Results

3.1. Clinicopathological characteristics of patients

The detailed clinicopathological characteristics of 1597 patients are provided in Table 1, including 1307 patients in the training cohort and 290 patients in the external validation cohort. Among the training cohort, the age at diagnosis was 20–91 years old, with a median age of 58. The majority of patients (1045, 80.0%) had good performance status with ≥80% Karnofsky performance score (KPS) level. There were 903 males (69.1%) and 404 females (30.9%). Tubular adenocarcinoma was the most common histopathological type (521, 39.9%). Poor differentiation (555, 42.5%) was the most common tumor grade.

The median tumor size was 4.0 cm (IQR, 3.0–8.0 cm). According to the AJCC 8th TNM classification, most of the tumors were pT3-4 (1112, 85.1%), lymph node metastasis was common (1092, 83.6%), and the majority were stage III (847, 64.8%). There was no significant difference between the groups, according to the Lauren classification. The number of the patients receiving LN dissection more than 16 were 1147 (%75,1) in our multi-centric relatively high numbered retrospective dataset. Overall, the baseline characteristics of the training and external validation cohorts were balanced.

The median follow-up time for all patients was 39 months (range, 2–250 months). In the training cohort 1-, 3-, 5-year CSS and PFS rates were 91.1%, 56.7%, 44.5%, and 83.8%, 58.5%, 54.2%, respectively. In the validation cohort 1-, 3-, 5-year CSS and PFS rates 82.9%, 56.1%, 44.2% and 82.2%, 62.2%, 54.4%, respectively.

3.2. Independent prognostic factors

We used the Cox proportional hazards regression models to analyze the independent prognostic factors for CSS and PFS. In univariate analysis, KPS, preoperative weight loss, tumor size, tumor differentiation, depth of invasion, lymph node involvement, Lauren classification, the extent of lymph node dissection, metastatic lymph node ratio, lymphovascular invasion, and perineural invasion were significant factors for CSS ($p \leq 0.05$) whereas lymph node involvement status ($p = 0.018$), the extent of lymph node dissection ($p = 0.005$) and metastatic lymph node ratio (0.001) were significant prognostic factors in multivariate analysis (Table 2). KPS, depth of invasion, lymph node involvement, the extent of lymph node dissection, metastatic lymph node ratio, lymphovascular invasion, and perineural invasion were significant prognostic factors for PFS in univariate analysis, whereas the depth of invasion ($p < 0.001$), lymph node involvement status ($p = 0.018$), the extent of lymph node dissection ($p < 0.001$), metastatic lymph node ratio ($p < 0.001$), and lymphovascular invasion ($p = 0.026$) were significant prognostic factors in multivariate analysis (Table 3). The hazard ratio (HR) and 95% confidence interval (CI) of the variables are also indicated in Tables 2 and 3.

Figs. 1 and 2 depict the nomogram for predicting 5-year CSS and PFS based on selected variables with hazard ratios. The nomogram might assign the probability of survival by adding up the scores identified on the points scale for each variable. The total score projected to the bottom scale indicates the probability of 5-year survival rates. Harrell's C-index was 0.74 (95% CI, 0.71 to 0.82).

4. Discussion

Individualized GC treatment, multi-disciplinary collaboration and supplementation approach that is expected to improve the efficacy of cancer treatment, is currently the focus of numerous medical research. In this study, we developed nomograms and corresponding practical maps to assess the CSS and PFS of patients with locally advanced GC who received postoperative RT ± CT.

Radiotherapy is central to the treatment of locally advanced gastric cancer. Seyedin et al[13] evaluated the treatment outcomes of 21,472 patients with stage I-IV GC in the SEER database. For patients with stage II, III, or IV, those treated with RT had the best outcome compared with other treatment modalities.[13] The study based on 21,447 patients with GC from the National Cancer Database showed that using RT in addition to CT was associated with a significant OS benefit.[14] Although the ARTIST trials did not yield positive results, INT0116 and CRITICS trials revealed that postoperative RT was effective for patients with specific treatment modalities and disease stages.[15–18]

In our current treatment results, RT was associated with superior therapeutic outcomes for patients with pN+, ≥25% metastatic LN ratio, and D1 dissection. Additionally, depth of invasion, pN+, D1 dissection, ≥25% metastatic LN ratio, and LVI were the prognostic factors for PFS. This brings up an important point. PFS should be recognized as an important endpoint in cancer trials. Almost all randomized phase III trials choose overall survival or CSS as an endpoint. As a result, they were unable to demonstrate any substantial benefit from postoperative RT in terms of these endpoints.

On the other hand, we should keep in mind that the side effects of both surgery and postoperative CT could harm the patient's general performance status, and as a result, overall survival may not reach the desired level due to the patient's compliance with postoperative RT. Similar issues were all discussed in the CRITICS[6] and ARTIST II[7] trials.

In comparison to a prior nomogram based on Han et al, we included Lauren classification and size in our nomogram. We included patients whose Lauren classification was known in our data collection because missing data would have lowered the statistical power of the trial. Furthermore, Lauren classification was not significantly associated with survival in the multivariate analysis in previous trials.[19] The ARTIST II trial, on the other hand, found that postoperative RT was the most beneficial for the intestinal type tumors. However, we already know that the intestinal type tumors have a higher survival rate than diffuse tumors. Unfortunately, we could not show any statistically significant effect of Lauren

Table 1
Baseline characteristics of patients in the training and validation cohorts.

Variables	No (%)		P
	Training Cohort (n = 1307)	Validation Cohort (n = 290)	
Age, years, median (IQR)	58 (20–91)	59 (29–82)	0.572
≤65			
>65			
Sex			0.237
Male	903 (69.1)	190 (65.5)	
Female	404 (30.9)	100 (34.5)	
KPS			0.068
80–100	1045 (80.0)	236 (51.4)	
50–70	64 (4.9)	9 (3.1)	
Unknown	198 (15.1)	45 (15.5)	
Preoperative weight loss			0.708
0–5%	292 (32.4)	45 (15.5)	
≥5%	777 (59.4)	161 (55.5)	
Unknown	238 (18.2)	84 (29.0)	
Tumor location			0.568
Upper 1/3	254 (19.4)	62 (21.4)	
Middle 1/3	458 (35.0)	97 (33.5)	
Lower 1/3	486 (37.2)	93 (32.0)	
Mixed	106 (8.4)	38 (13.1)	
Tumor differentiation			0.802
Well	119 (9.1)	25 (8.6)	
Intermediate	307 (23.5)	68 (23.4)	
Poor	555 (42.5)	134 (46.2)	
Undifferentiated	326 (24.9)	63 (21.7)	
Depth of invasion			0.290
T1-2	195 (14.9)	31 (11.7)	
T3-4	1112 (85.1)	259 (88.3)	
Lymph node status			0.441
N0	215 (16.4)	51 (17.6)	
N1-3	1092 (83.6)	239 (82.4)	
Histology			0.513
Tubular adenocarcinoma	521 (39.9)	124 (42.7)	
Mucinous adenocarcinoma	247 (18.9)	45 (15.5)	
Signet ring cell carcinoma	347 (26.5)	87 (30.0)	
Other	192 (14.7)	34 (11.8)	
Lauren classification			0.870
Intestinal	298 (22.8)	63 (21.7)	
Diffuse	177 (13.5)	31 (10.7)	
Unclassified	320 (24.5)	65 (22.4)	
Unknown	512 (39.2)	131 (45.2)	
Surgery			0.275
Total gastrectomy	761 (58.3)	178 (61.4)	
Partial gastrectomy	546 (41.7)	112 (38.6)	
Lymphatic dissection			0,245
D1	358 (29,9)	67 (25,2)	
D2	839 (70,1)	198 (74,8)	
LVI			0.265
(+)	860 (65.8)	199 (68.6)	
(–)	373 (28.5)	73 (25.2)	
Unknown	74 (5.7)	18 (6.2)	
PNI			0.198
(+)	801 (61.3)	182 (62.8)	
(–)	414 (31.7)	80 (27.5)	
Unknown	92 (7.0)	28 (9.7)	
Concomittan CT			0.445
(+)	1123 (85.9)	253 (87.2)	
(–)	184 (14.1)	37 (12.8)	
Postoperative CT			0.892
(+)	801 (61.3)	183 (63.1)	
(–)	506 (38.7)	107 (36.9)	
RT technique			0.803
3DCRT	681 (52.1)	157 (54.1)	
IMRT	626 (47.9)	133 (45.9)	
RT dose (Gy), median (IQR)	45 (45–54)	45 (45–54)	
Recurrence			0.783
(+)	516 (39.5)	113 (39.0)	
(–)	791 (60.5)	177 (61.0)	
Distant metastasis			0.672
(+)	445 (34.1)	118 (40.6)	
(–)	862 (65.9)	172 (59.4)	

Abbreviations: IQR: Interquartile range; KPS: Karnofsky Performance Score; LVI: Lymphovascular invasion; PNI: Perineural invasion; CT: Chemotherapy; RT: Radiotherapy: 3DCRT: 3 dimensional conformal radiotherapy; IMRT: Intensity modulated radiotherapy.

Table 2
Univariate and multivariate Cox regression analyses of prognostic factors for cancer-specific survival.

Variables	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	*p*	HR	95%	*p*
Age (≤65 vs > 65)	1.171	0.960–1.428	0.120			
Sex (Male vs Female)	1.003	0.832–1.208	0.977			
KPS (80–100 vs 50–70)	1.995	1.408–2.828	**<0.001**	1.539	0.886–2.674	0.126
Preoperative weight loss (0–5% vs ≥ 5%)	1.452	0.986–1.887	**0.050**	1.080	0.873–1.337	0.477
Tumor location						
Upper 1/3	1					
Middle 1/3	1.058	0.507–2.182	0.816			
Lower 1/3	0.925	0.387–1.752	0.658			
Mixed	1.205	0.625–2.368	0.589			
Tumor size (≥5 cm vs < 5 cm)	1.523	1.251–1.854	**<0.001**	0.863	0.593–1.254	0.439
Differentiation (Poor vs Well)	1.156	1.007–1.326	**0.039**	1.292	0.892–1.871	0.175
Depth of invasion (T1-2 vs T3-4)	2.422	1.759–3.335	**<0.001**	1.599	0.909–2.814	0.103
LN involvement status (N0 vs N1-3)	2.567	1.926–3.420	**<0.001**	2.467	1.164–5.227	**0.018**
Lauren classification (Intestinal vs Diffuse)	1.773	1.365–2.303	**<0.001**	0.837	0.668–1.050	0.125
LN dissection (D1 vs D2)	0.790	0.653–0.955	**0.015**	0.607	0.428–0.862	**0.005**
Dissected LN number (<16 vs ≥ 16)	0.946	0.778–1.151	0.580			
Metastatic LN ratio (<25% vs ≥ 25%)	2.512	2.086–3.026	**<0.001**	1.869	1.294–2.700	**0.001**
LVI (+ vs -)	1.545	1.262–1.890	**<0.001**	1.267	0.797–2.014	0.316
PNI (+ vs -)	1.333	1.101–1.614	**0.003**	1.323	0.856–2.046	0.208
Concomitant CT (+ vs -)	1.003	0.688–1.462	0.989			
Postoperative CT (+ vs -)	0.963	0.751–1.236	0.769			

Abbreviations: KPS: Karnofsky Performance Score; LN: Lymph node; LVI: Lymphovascular invasion; PNI: Perineural invasion; CT: Chemotherapy.

Table 3
Univariate and multivariate Cox regression analyses of prognostic factors for progression-free survival.

Variables	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	*p*	HR	95%	*p*
Age (≤65 vs > 65)	0.972	0.783–1.207	0.799			
Sex (Male vs Female)	1.120	0.921–1.362	0.255			
KPS (80–100 vs 50–70)	1.539	1.019–2.323	**0.040**	1.278	0.835–1.958	0.259
Preoperative weight loss (<5% vs ≥ 5%)	1.083	0.892–1.316	0.418			
Tumor location						
Upper 1/3	1					
Middle 1/3	0.875	0.565–1.211	0.742			
Lower 1/3	0.925	0.742–1.325	0.841			
Mixed	0.945	0.579–1.679	0.741			
Tumor size (≥5 cm vs < 5 cm)	1.121	0.920–1.364	0.257			
Differentiation (Poor vs Well)	0.882	0.727–1.070	0.204			
Depth of invasion (T1-2 vs T3-4)	2.714	1.873–3.932	**<0.001**	2.315	1.551–3.457	**<0.001**
LN involvement status (N0 vs N1-3)	2.801	2.038–3.849	**<0.001**	1.563	1.080–2.261	**0.018**
Lauren Classification (Intestinal vs Diffuse)	0.998	0.881–1.131	0.977			
LN Dissection (D1 vs D2)	0.745	0.617–0.898	**0.002**	0.678	0.552–0.832	**<0.001**
Dissected LN number (<16 vs ≥ 16)	0.972	0.787–1.200	0.793			
Metastatic LN ratio (<25% vs ≥ 25%)	2.115	1.744–2.565	**<0.001**	2.157	1.721–2.705	**<0.001**
LVI (+ vs -)	1.786	1.432–2.228	**<0.001**	1.349	1.036–1.757	**0.026**
PNI (+ vs -)	1.238	1.015–1.509	**0.035**	0.715	0.957–0.754	1.213
Concomitant CT (+ vs -)	1.016	0.688–1.500	0.937			
Postoperative CT (+ vs -)	1.010	0.783–1.303	0.927			

Abbreviations: KPS: Karnofsky Performance Score; LN: Lymph node; LVI: Lymphovascular invasion; PNI: Perineural invasion; CT: Chemotherapy.

classification over CSS and PFS in our multivariate analysis. We could only show a significant effect over CSS in univariate analysis and the significance was lost in the multivariate analysis.

Another distinction in our current study is that we assessed the metastatic LN ratio in D2 dissected patients. Previous nomograms did not thoroughly investigate this issue. In this regard, our trial-based nomogram is unique. We conducted the analyses after excluding D1 dissected patients because of their known poor prognostic effect. Neither Hans et al[8] nor the Western database[20] included this prognostic factor in their analyses. We found that a metastatic LN ratio of ≥25% had a negative prognostic value for D2 dissected ones.

In this study, we grouped the tumors as upper third, middle third, and lower third according to their location in the stomach. Although the 8th AJCC TNM classification accepts adenocarcinoma of the esophagogastric junction as esophageal cancer, Han et al demonstrated that adenocarcinoma of the esophagogastric junction within the stomach should be considered gastric cancer.[21] The proportion of upper-third stomach cancer in our trial was comparable to Han's nomogram (12.4% vs 19.7%, respectively). They found that upper-third-located gastric cancer contributed equally to the nomogram as a predictor of poor prognosis.[8] Unfortunately, we were unable to validate their findings in our relatively large cohort. We propose to use the AJCC TNM classification for both gastric and esophagogastric junction cancers unless new molecular or genetic factors are revealed in future trials.

The sixth edition of the AJCC staging for GC recommends that at least 16 LNs be examined for an accurate evaluation of the LN status.[22] Studies have reported that the evaluation of more than 15 LNs improves the prediction of prognosis in GC.[23,24] We grouped

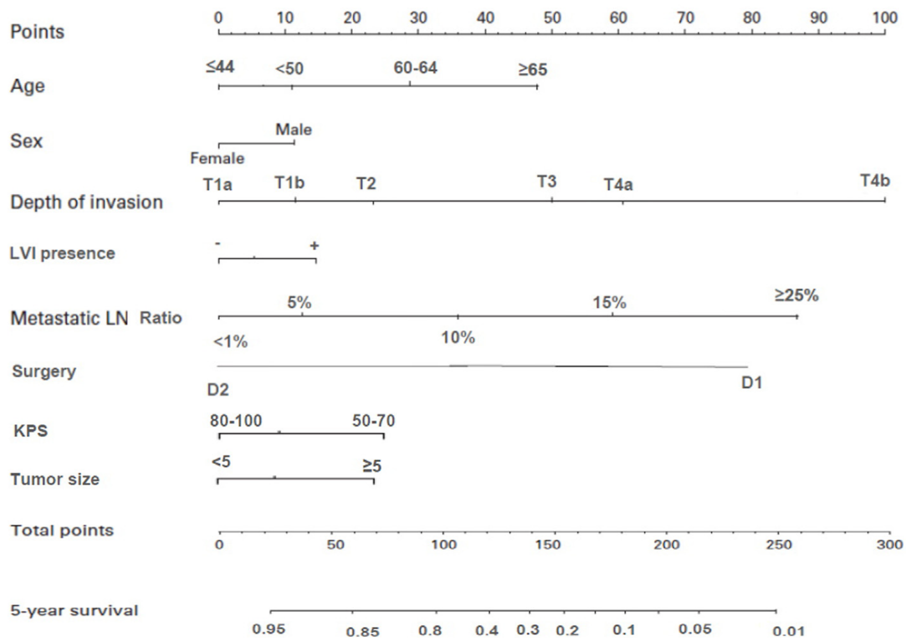

Fig. 1. The nomogram for predicting 5-year cause-specific survival based on selected variables with hazard ratios.

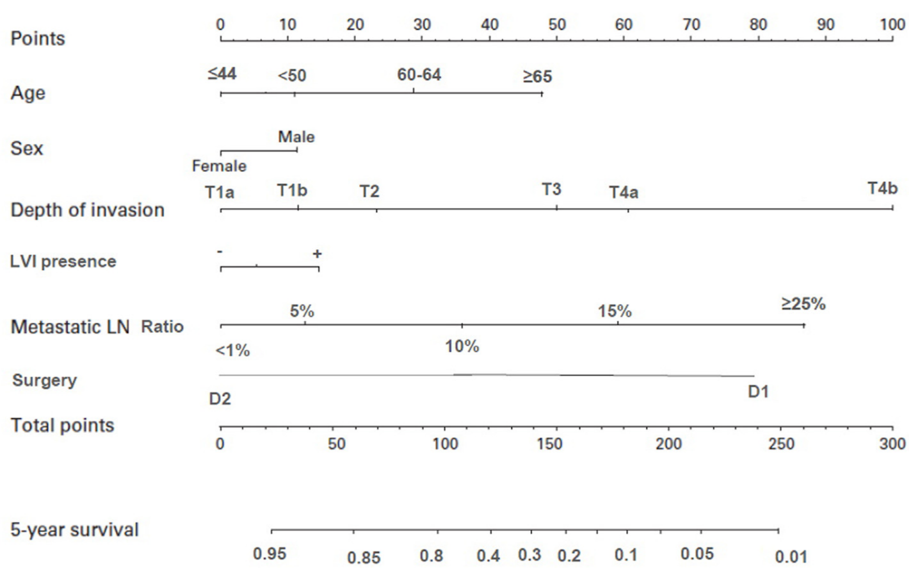

Fig. 2. The nomogram for predicting 5-year pregression-free survival based on selected variables with hazard ratios.

the patients based on the basis of the number of dissected LNs. This issue was not confirmed in our relatively large retrospective data set. We interpreted this result as dissected lymphatic regions were more important than the number of dissected LNs. On the other hand, a wide lymphatic dissection has some complications which are mainly associated with the experience of the surgeons. Gastric cancer surgery is performed in any part of Turkey even in low-volume centers. As a result, we often have to decide on the treatment for GC patients who have a D1 dissection. For the generalized use of our nomogram by other regions, which have not started to use both preoperative chemotherapy and D2 dissections standardly, it is important to improve postoperative treatment decisions and achieve better treatment outcomes. In this study, we included both D1 and D2 dissected ones. We found that not only PFS but also CSS were adversely affected by the extent of dissection. D2 dissection, which involves all stations and is performed by experienced surgeons, improves both CSS and PFS in patients with locally advanced GC.

Currently, adjuvant oral fluoropyrimidine (S-1) after gastrectomy with D2 dissection revealed a survival benefit in a large-scale randomized controlled trial.[25,26] Another phase III trial found that adjuvant capecitabine and oxaliplatin following D2 gastrectomy resulted in a 3-year disease-free survival benefit compared with gastrectomy alone (74% v 59%, respectively; $P < 00.001$).[27] In this study, we were unable to demonstrate any additional advantage in either the concurrent or postoperative period; therefore, CT was excluded in the nomogram. In our cohort, patients with stage II or III GC usually receive postoperative 5-FU based CT. Therefore, postoperative CT is accepted as having limited significance as a variable in the construction of this postoperative nomogram.

We acknowledge that this study had certain limitations. First, it was a retrospective study; therefore, future prospective studies must validate our nomograms. Second, the trial cohort was entirely Turkish, and we need to incorporate more information from diverse races to evaluate the models. Third, 25% of the included patients had <16 L N dissected. This could be accepted both limitation and strength of our trial. In low income countries, the oncologists were faced with this inadequate lymphatic dissected patients in daily practice similar with Turkey. So that our nomogram could be guide for them. In addition, we were unable to assess several potential predictors because they were not routinely reported, such as helicobacter pylori infection and EGFR mutations, etc. Finally, patient comorbidity was not depicted in the nomogram. We know that comorbidity may influence survival outcomes to some extent. We excluded comorbidity as a variable in our nomogram because of its wide range and subjective interpretation.

In conclusion, we developed and internally validated a nomogram that could effectively predict the CSS and PFS of locally advanced GC patients who underwent curative gastrectomy with postoperative RT $\pm$ CT. Our nomogram was developed in a relatively large cohort and would serve as a true map for oncologists who must make decisions without an experienced surgeon and a multidisciplinary tumor board. We believe that this nomogram could be useful for underdeveloped or developing countries rather than Korea and Japan, where the D2 gastrectomy is routinely performed. For the generalized use of this nomogram, validation by a Western cohort is required.

Funding

None.

Availability of data

Raw data were analyzed at Ege University. Derived data supporting the findings of this study are available from the corresponding author FS on request.

Ethics approval

The study was approved by the Ethics Committee of the Ege University Hospital (Approval No. 21-T12/33), and all patients provided informed consent.

Declaration of competing interest

All authors concluded that they have not any conflict of interest.

Acknowledgements

We would like to acknowledge and thank the Ege Faculty of Medicine, Department of Biostatistics and Medical Informatics who have graciously made their work available for the statistics and nomogram creations of this text.

References

1. Sitarz R, Skierucha M, Mielko J, Offerhaus GJA, Maciejewski R, Polkowski WP. Gastric cancer: epidemiology, prevention, classification, and treatment. *Cancer Manag Res*. 2018;10:239–248. https://doi.org/10.2147/CMAR.S149619.
2. Balakrishnan M, George R, Sharma A, Graham DY. Changing trends in stomach cancer throughout the world. *Curr Gastroenterol Rep*. 2017;19(8):36. https://doi.org/10.1007/s11894-017-0575-8.
3. Van Cutsem E, Sagaert X, Topal B, Haustermans K, Prenen H. Gastric cancer. *Lancet*. 2016;388(10060):2654–2664. https://doi.org/10.1016/S0140-6736(16)30354-3.
4. Gambardella V, Cervantes A. Precision medicine in the adjuvant treatment of gastric cancer. *Lancet Oncol*. 2018;19(5):583–584. https://doi.org/10.1016/S1470-2045(18)30131-1.
5. Kaytan Saglam E, Yucel S, Balik E, et al. Adjuvant chemoradiotherapy after D2 resection in gastric cancer: a single-center observational study. *J Cancer Res Clin Oncol*. 2015;141(2):361–367. https://doi.org/10.1007/s00432-014-1816-y.
6. Cats A, Jansen EPM, van Grieken NCT, et al. CRITICS investigators. Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial. *Lancet Oncol*. 2018 May;19(5):616–628. https://doi.org/10.1016/S1470-2045(18)30132-3.
7. Park SH, Lim DH, Sohn TSet al. ARTIST 2 investigators. A randomized phase III trial comparing adjuvant single-agent S1, S-1 with oxaliplatin, and postoperative chemoradiation with S-1 and oxaliplatin in patients with node-positive gastric cancer after D2 resection: the ARTIST 2 trial. *Ann Oncol*. 2021 Mar;32(3):368–374. https://doi.org/10.1016/j.annonc.2020.11.017.
8. Han DS, Suh YS, Kong SH, et al. Nomogram predicting long-term survival after d2 gastrectomy for gastric cancer. *J Clin Oncol*. 2012;30(31):3834–3840. https://doi.org/10.1200/JCO.2012.41.8343.
9. Jiang Y, Li T, Liang X, et al. Association of adjuvant chemotherapy with survival in patients with stage II or III gastric cancer. *JAMA Surg*. 2017;152(7):e171087. https://doi.org/10.1001/jamasurg.2017.1087.
10. Li L, Zeng Q, Xue N, et al. A nomogram based on aspartate aminotransferase/alanine aminotransferase (AST/ALT) ratio to predict prognosis after surgery in gastric cancer patients. *Cancer Control*. 2020;27(1):1073274820954458. https://doi.org/10.1177/1073274820954458.
11. Hess KR. Assessing time-by-covariate interactions in proportional hazards regression models using cubic spline functions. *Stat Med*. 1994;13:1045–1062.
12. Harrell Jr FE. *Regression Modeling Strategies with Application to Linear Models, Logistic Regression, and Survival Analysis*. New York, NY: Springer Verlag; 2001.
13. Seyedin S, Wang PC, Zhang Q, Lee P. Benefit of adjuvant Chemoradiotherapy for gastric adenocarcinoma: a SEER population analysis. *Gastrointest Cancer Res*. 2014;7(3–4):82–90.
14. Stump PK, Amini A, Jones BL, et al. *Adjuvant Radiotherapy Improves Overall Survival in Patients with Resected Gastric Adenocarcinoma: A National Cancer Data Base Analysis*. Cancer; 2017.
15. Park SH, Sohn TS, Lee J, et al. Phase III trial to compare adjuvant chemotherapy with Capecitabine and Cisplatin versus concurrent Chemoradiotherapy in gastric Cancer: final report of the adjuvant Chemoradiotherapy in stomach tumors trial, including survival and subset analyses. *J Clin Oncol*. 2015;33(28):3130–3136.
16. Cats A., Jansen E.P.M., van Grieken N.C.T., et al. Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial. Lancet Oncol. 2018.May:19(5):616-628
17. Lee J, Lim do H, Kim S, et al. Phase III trial comparing capecitabine plus cisplatin versus capecitabine plus cisplatin with concurrent capecitabine radiotherapy in completely resected gastric cancer with D2 lymph node dissection: the ARTIST trial. *J Clin Oncol*. 2012;30(3):268–273.
18. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med*. 2001;345(10):725–730.
19. Kattan MW, Karpeh MS, Mazumdar M, et al. Postoperative nomogram for disease-specific survival after an R0 resection for gastric carcinoma. *J Clin Oncol*. 2003;21:3647–3650.
20. Li N, Xiang X, Zhao D, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced gastric cancer: a multicenter propensity score-matched analysis. *BMC Cancer*. 2022 Feb 26;22(1):212. https://doi.org/10.1186/s12885-022-09297-7.
21. Suh YS, Han DS, Kong SH, et al. Should adenocarcinoma of the esophagogastric junction be classified as esophageal cancer? A comparative analysis according to the seventh AJCC TNM classification. *Ann Surg*. 2012;255:908–915.
22. American Joint committee on cancer: stomach. In: *AJCC Cancer Staging Manual*. ed 6. New York, NY: Springer Verlag; 2002.
23. Smith DD, Schwarz RR, Schwarz RE. Impact of total lymph node count on staging and survival after gastrectomy for gastric cancer: data from a large US-population database. *J Clin Oncol*. 2005;23:7114–7124.
24. Shen JY, Kim S, Cheong JH, et al. The impact of total retrieved lymph nodes on staging and survival of patients with pT3 gastric cancer. *Cancer*. 2007;110:745–751.
25. Sakuramoto S, Sasako M, Yamaguchi T, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med*. 2007;357:1810–1820.
26. Sasako M, Sakuramoto S, Katai H, et al. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. *J Clin Oncol*. 2011;29:4387–4393.
27. Bang YJ, Kim YW, Yang HK, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomized controlled trial. *Lancet*. 2012;379:315–321.