

Original Article



External Validation of a Gastric Cancer Nomogram Derived from a Large-volume Center Using Dataset from a Medium-volume Center

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OPEN ACCESS

Received: Mar 29, 2017

Revised: Jul 6, 2017

Accepted: Jul 6, 2017

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ABSTRACT

Purpose: Recently, a nomogram predicting overall survival after gastric resection was developed and externally validated in Korea and Japan. However, this gastric cancer nomogram is derived from large-volume centers, and the applicability of the nomogram in smaller centers must be proven. The purpose of this study is to externally validate the gastric cancer nomogram using a dataset from a medium-volume center in Korea.

Materials and Methods: We retrospectively analyzed 610 patients who underwent radical gastrectomy for gastric cancer from August 1, 2005 to December 31, 2011. Age, sex, number of metastatic lymph nodes (LNs), number of examined LNs, depth of invasion, and location of the tumor were investigated as variables for validation of the nomogram. Both discrimination and calibration of the nomogram were evaluated.

Results: The discrimination was evaluated using Harrell's C-index. The Harrell's C-index was 0.83 and the discrimination of the gastric cancer nomogram was appropriate. Regarding calibration, the 95% confidence interval of predicted survival appeared to be on the ideal reference line except in the poorest survival group. However, we observed a tendency for actual survival to be constantly higher than predicted survival in this cohort.


Conclusions: Although the discrimination power was good, actual survival was slightly higher than that predicted by the nomogram. This phenomenon might be explained by elongated life span in the recent patient cohort due to advances in adjuvant chemotherapy and improved nutritional status. Future gastric cancer nomograms should consider elongated life span with the passage of time.

Keywords: Stomach neoplasms; Survival; Nomograms; Validation studies

INTRODUCTION

Gastric cancer is the fifth most common cancer in the world and the third most fatal [1]. Although the incidence of gastric cancer in Korea has decreased in recent years, it is still the second most common malignancy following thyroid cancer [2]. To predict gastric cancer patient survival, tumor, node, and metastasis (TNM) classification (based on the American

External Validation of a Gastric Cancer Nomogram

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Joint Committee on Cancer [AJCC] 7th edition) is used to evaluate invasion depth of the primary lesion, number of lymph node (LN) metastases, and the presence or absence of distant metastasis [3]. In addition, age, histological differentiation, location of the primary lesion, lymphatic invasion, tumor size, and the presence or absence of chemotherapy are known to influence prognosis of gastric cancer patients [4-6].

By including various prognostic factors, nomograms are useful for predicting individual survival. A nomogram predicting disease-specific survival after R0 resection for gastric cancer was first developed using Western databases [7]. Recently, a nomogram for predicting overall survival after D2 gastrectomy was developed at Seoul National University Hospital (SNUH), Korea, and was externally validated using the database of the Cancer Institute Ariake Hospital (CIAH), Japan [8]. The SNUH gastric cancer nomogram includes the following variables: age, sex, depth of invasion, location of the tumor, number of metastatic LNs, and number of examined LNs (Fig. 1). This nomogram could predict individualized overall survival more accurately than TNM classification. However, the hospitals studied were highly concentrated, large-volume centers, and thus the general applicability of the nomogram, particularly in smaller centers, was not established.

Therefore, this study used data from a medium-volume center in Korea to evaluate whether the gastric cancer nomogram can be applied to other cohorts.

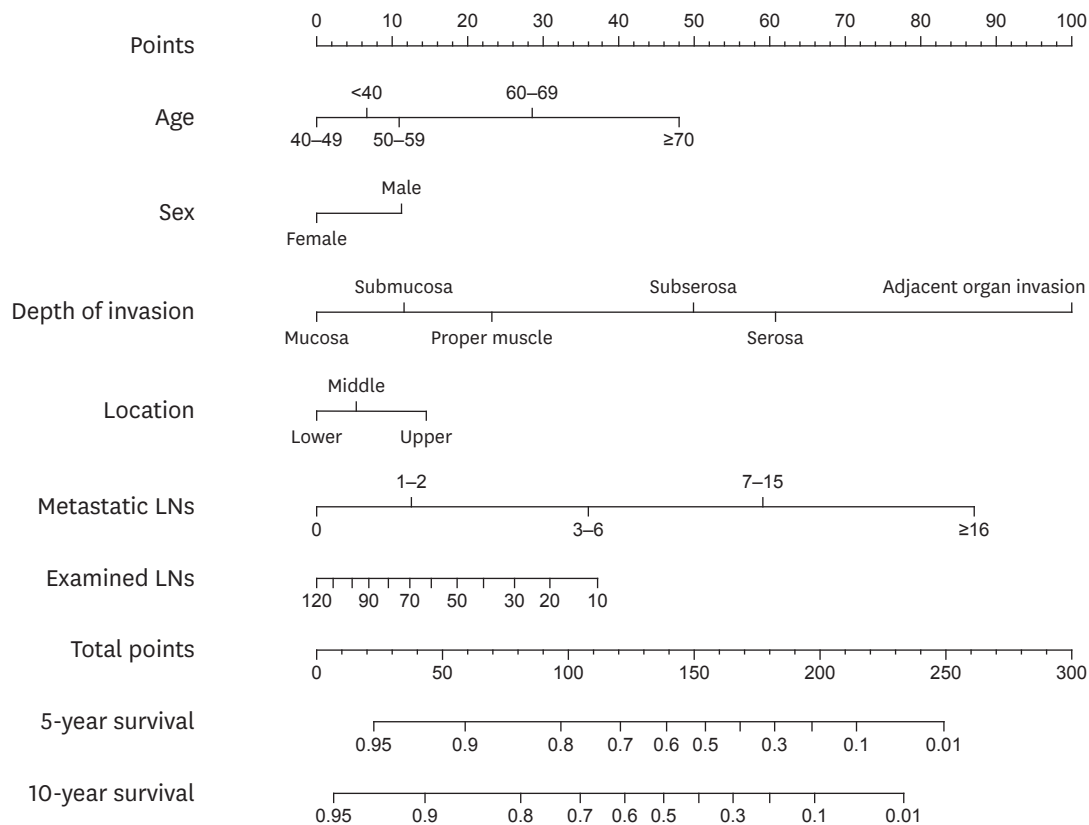


Fig. 1. SNUH gastric cancer nomogram. Figure is adapted from Han et al. [8]. SNUH = Seoul National University Hospital; LN = lymph node.

MATERIALS AND METHODS

Patients

This validation study was conducted retrospectively using electronic medical chart review. We collected data from patients who underwent gastric resection for gastric cancer at the Konkuk University Medical Center (KUMC), Korea from August 1, 2005 to December 31, 2011. Inclusion criteria were as follows: primary gastric cancer, D1+ or D2 lymphadenectomy in early gastric cancer, D2 lymphadenectomy in advanced gastric cancer, no associated malignancy, no preoperative chemotherapy, no distant metastasis, R0 resection (no residual macroscopic or microscopic tumor), more than 15 examined LNs, and without missing values. Finally, 610 patients fulfilled the inclusion criteria and were included in this study.

Age, sex, depth of invasion, location of the tumor, number of metastatic LNs, and number of examined LNs were investigated as variables for validation of the nomogram. Patient age was categorized into 5 groups (<40, 40s, 50s, 60s, and ≥ 70). The depth of invasion was categorized as mucosa, submucosa, proper muscle, subserosa, serosa, and adjacent organ invasion. The location of the tumor was categorized as upper, middle, or lower third, depending on where the center was located. The number of metastatic LNs was categorized according to the N stage of the 7th AJCC TNM classification.

Validation of the nomogram

External validation consisted of discrimination and calibration. Discrimination was evaluated using Harrell's C-index, which is appropriate for censored data [9,10]. The concordance index calculates the probability that for 2 randomly selected patients, when one patient has an event before the other, this patient has worse survival predicted by the nomogram. Generally, a C-index greater than 0.75 is considered to represent relatively good discrimination. Calibration was performed by comparing the means of predicted survival with actual survival. Comparison was conducted after grouping of the nomogram predicted survival data by decile. For each patient, the predicted 5-year survival was calculated using an equation integrated into the gastric cancer nomogram; actual 5-year survival was obtained using the Kaplan-Meier method. SAS version 9.2 (SAS Institute, Cary, NC, USA) and SPSS version 21 (SPSS Inc., Chicago, IL, USA) were used for all statistical analyses, and $P < 0.05$ was considered statistically significant.

This study was approved by the Institutional Review Board (IRB) of KUMC. The data were collected by electronic medical record review and the anonymity of the data was ensured. Identifying information of patients, including names, initials, addresses, admission dates, hospital numbers, or any other data that might identify patients were not included. The IRB approved the exemption of informed consent for this study.

RESULTS

The clinicopathologic characteristics of KUMC patients' data are listed in **Table 1**. There were 356 (58.4%) early gastric cancer patients, and 427 (70.0%) patients with no LN metastases. The most common location was the lower third of the stomach.

In the KUMC validation set, Harrell's C-index was 0.85 (95% confidence interval [CI]=0.61–0.98). **Fig. 2** demonstrates the consistency between 5-year overall survival

predicted by the nomogram and actual survival. Six hundred and ten patients were divided into 10 groups according to nomogram-predicted survival, the mean value was obtained

Table 1. Demographics and clinicopathological characteristics

Variables	No. of patients (n=610)
Sex	
Male	408 (66.9)
Female	202 (33.1)
Age	
<40	35 (5.7)
40-49	90 (14.8)
50-59	161 (26.4)
60-69	190 (31.1)
≥70	134 (22.0)
Depth of invasion	
Mucosa	212 (34.8)
Submucosa	144 (23.6)
Proper muscle	84 (13.8)
Subserosa	95 (15.8)
Serosa	70 (11.5)
Adjacent organ invasion	5 (0.8)
Metastatic LNs	
0	427 (70.0)
1-2	59 (9.7)
3-6	53 (8.7)
7-15	39 (6.4)
≥16	32 (5.2)
Examined LNs	43.9±18.0
Location	
Upper	83 (13.6)
Middle	237 (38.9)
Lower	290 (47.5)

Values are presented as number of patients (%).
LN = lymph node.

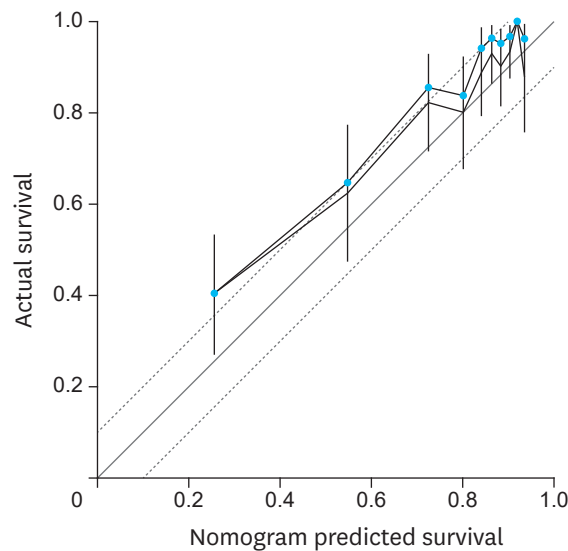


Fig. 2. Calibration of SNUH gastric cancer nomogram using KUMC patients' data. The x-axis represents 5-year survival predicted by the nomogram and the y-axis represents actual survival, calculated by the Kaplan-Meier method. The solid line is the baseline on which predicted survival and actual survival match. The dotted line represents the 10% margin of error.
SNUH = Seoul National University Hospital; KUMC = Konkuk University Medical Center.

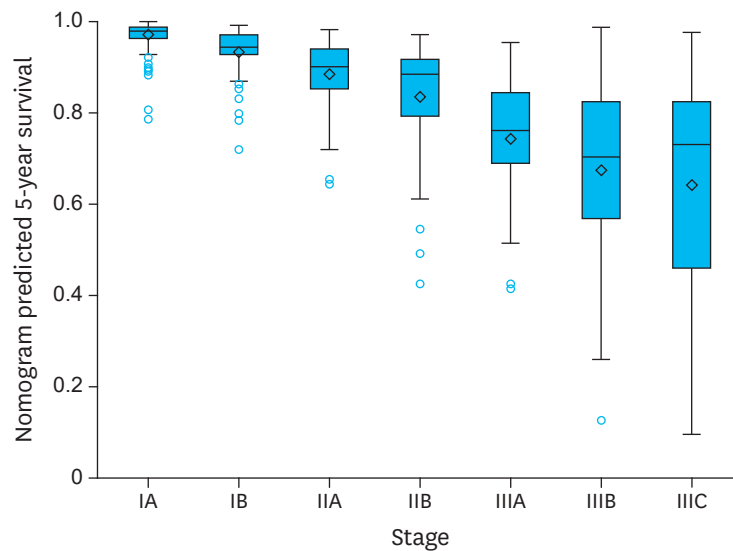


Fig. 3. The box plot shows the distribution of 5-year overall survival predicted by the nomogram in each group of TNM classification.
TNM = tumor, node, and metastasis.

(x-axis) and then compared with actual survival calculated using the Kaplan-Meier method (y-axis). The solid line is the ideal line upon which predicted survival and actual survival match; the dotted line represents a 10% margin of error. The 95% CIs lay on the ideal line except for the first group where the lowest survival rate was predicted. However, we observed a tendency for actual survival to be higher than predicted survival in the KUMC cohort.

Fig. 3 is a box plot representing the nomogram-predicted survival at each stage of TNM classification. The overall survival at each stage is presented as the mean of individualized survival of all patients within each TNM stage. The range of predicted survival was wider in higher TNM stages, because higher TNM stage was comprised of a diverse combination of nomogram variables. Unusually, we found higher median survival in stage IIIC patients than in stage IIIB patients. However, the mean survival of stage IIIC patients was lower than that of IIIB patients. This phenomenon might be caused by the small sample size and outliers in higher TNM stage.

DISCUSSION

Surgical resection plays an important part in the radical treatment of gastric cancer, and pathologic staging after surgery plays an important role in accurately predicting survival and guiding the direction of proper treatment after surgery. Standard TNM classification is used for predicting prognosis after surgery in gastric cancer, and is categorized based on depth of invasion, number of metastatic LNs, and the presence or absence of distant metastasis [3]. In addition to these factors, age, histological differentiation, location of the primary lesion, lymphatic invasion, size of the tumor, and ratio of metastatic LNs, among other variables, are known to influence the prognosis of gastric cancer [4-6,11]. Consequently, various distributions of predicted survival are shown even within the same TNM stage, as shown in **Fig. 2**. The advantage of the nomogram is that its prediction system can be made by using continuous risk scales, rather than using condensing sections of the risk spectra

in heterogeneous risk groups [12]. Therefore, unlike TNM classification that predicts the same survival within a specific disease stage, nomograms have the advantage of predicting individualized survival.

In order to predict disease-specific survival after radical surgery in gastric cancer, Peeters et al. [13] and Novotny et al. [14] developed a nomogram and carried out external validation using data from 2 European cohorts (C-indexes=0.770, 0.756). In East Asia, external validation was conducted in China (C-index=0.74) [15]. Thus, it was demonstrated that nomograms can predict survival more accurately than the TNM classification, and nomograms created in one organization can be applied to other organizations that use similar treatment strategies.

In the East, including Korea and Japan, the standard treatment of advanced gastric cancer is radical gastrectomy including D2 lymphadenectomy. In early gastric cancer, D1+ or D2 lymphadenectomy is performed. However, in the West, surgeons do not generally perform D2 lymphadenectomy due to the low prevalence of gastric cancer and higher morbidity rate of D2 gastrectomy. Until recently, the benefits of D2 lymphadenectomy could not be clearly defined using randomized clinical trials [16]. A Dutch trial was published in 2010 detailing 15-year follow-up results after gastric cancer surgery. They reported that recurrence rates and cancer-related deaths associated with gastric cancer were lower in the D2 lymphadenectomy group, and concluded that D2 lymphadenectomy is required to increase survival [17]. In the East, Han et al. [8] created a nomogram for predicting long-term survival after D2 gastrectomy which showed good discrimination and calibration. External validation was performed using patients' data from SNUH, Korea, and CIAH, Japan. The C-indexes were 0.78 and 0.79 in the SNUH and CIAH validation sets, respectively.

In Korea, the results of a national gastric cancer registration survey were reported in 2004 and the data of 11,293 patients were collected from 57 hospitals. For 10 years, the number of elderly gastric cancer patients aged 70 years or older increased, and cases of stage I gastric cancer increased from 38% to 56.7% [18]. The SNUH data was collected from 1986 to 2007, while the KUMC data was collected from 2005 to 2011. In this study, we found a tendency for actual survival of KUMC patients to be constantly higher than predicted survival, although the 95% CIs lay on the ideal line except in the first group where the poorest survival rate was predicted. Because the data from SNUH and KUMC were collected during different time periods, this phenomenon might be explained by elongated life span in the more recent patient cohort due to advances in adjuvant chemotherapy and improved nutritional status.

Looking at the number of surgeries per year, the national gastric cancer registration survey reported that the number of small-volume hospitals with less than 100 cases was 25, medium-volume hospitals with 100–500 cases was 26 and large-volume hospitals with more than 500 cases was 6 in Korea [18]. Because SNUH and CIAH are highly concentrated large-volume centers in Korea and Japan, the applicability of the SNUH gastric cancer nomogram to various size hospitals has yet to be demonstrated. This study used external validation data from a medium-volume center (KUMC) to evaluate whether it can be applied to hospitals of various sizes. Results showed that the discrimination was good (C-index=0.83).

The data from the KUMC are considered to be less affected by the average life expectancy of the patient or changes in treatment, according to medical technology development, because the collection period was relatively short (about 7 years). This study followed up for at least 3 years and the range could be considered acceptable in that most recurrences

occur within 2 years after surgery, and the survival rate after recurrence is low. Recurrent gastric cancer recurred in 59%–72% of patients within 2 years, and the median survival period after recurrence was about 6 months, and 70% died within a year [19,20].

In conclusion, although the discrimination power was good, the actual survival was constantly higher than nomogram-predicted survival in this cohort. This phenomenon might be explained by elongated life span in the more recent patient cohort due to advances in adjuvant chemotherapy and improved nutritional status. Future gastric cancer nomograms should consider the elongated life span with the passage of time.

ACKNOWLEDGMENTS

Statistical analysis was supported by the Medical Research Collaborating Center, Seoul National University Hospital, Seoul, Korea.

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