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Original Research

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

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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

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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