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Prediction of Conditional Probability of Survival After Surgery for Gastric Cancer: A Study Based on Eastern and Western Large Data Sets

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ABSTRACT

Background: The dynamic prognosis of patients who have undergone curative surgery for gastric cancer has yet to be reported. Our objective was to devise an accurate tool for predicting the conditional probability of survival for these patients.

Methods: We analyzed 11,551 gastric cancer patients from the Surveillance, Epidemiology, and End Results database. Two-thirds of the patients were selected randomly for the development set and one-third for the validation set. Two nomograms were constructed to predict the conditional probability of overall survival and the conditional probability of disease-specific survival, using conditional survival methods. We then applied these nomograms to the 4,001 patients in the database from Fujian Medical University Union Hospital, Fuzhou, China, one of the most active Chinese institutes.

Results: The 5-year conditional probability of overall survival of the patients was 41.6% immediately after resection and increased to 52.8%, 68.2%, and 80.4% at 1, 2, and 3 years after gastrectomy. The 5-year conditional probability of disease-specific survival "increased" from 48.9% at the time of gastrectomy to 59.8%, 74.7%, and 85.5% for patients surviving 1, 2, and 3 years, respectively. Sex; race; age; depth of tumor invasion; lymph node metastasis; and tumor size, site, and grade were associated with overall survival and disease-specific survival ($P < .05$). Within the Surveillance, Epidemiology, and End Results validation set, the accuracy of the conditional probability of overall survival nomogram was 0.77, 0.81, 0.82, and 0.82 at 1, 3, 5, and 10 years after gastrectomy, respectively. Within the other validation set from the Fujian Medical University Union Hospital ($n = 4,001$), the accuracy of the conditional probability of overall survival nomogram was 0.76, 0.79, 0.77, and 0.77 at 1, 3, 5, and 10 years, respectively. The accuracy of the conditional probability of disease-specific survival model was also favorable. The calibration curve demonstrated good agreement between the predicted and observed survival rates.

Conclusion: Based on the large Eastern and Western data sets, we developed and validated the first conditional nomogram for prediction of conditional probability of survival for patients with gastric cancer to allow consideration of the duration of survivorship.

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Gastric cancer is the fifth most frequently diagnosed cancer and the third leading cause of cancer-related death worldwide.[1] Estimations of the risk of death for patients with gastric cancer are usually based on American Joint Committee on Cancer (AJCC) staging or nomograms.[2,3] Most studies have only evaluated the risk of death, starting from the time of the gastric resection. However, various studies, including those of Wang et al.[4] and Kim et al.[5] have shown that the risk of death in patients with gastric cancer is not constant. This favorable feature of survivorship has been reported previously in prostate cancer, renal cell carcinoma, and glioblastoma.[6–8] The conditional probability of survival (CPS) represents the probability of surviving a certain number of years postdiagnosis based on the duration of time that the patient has already

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survived. Unlike the conventional static survival rate, CPS can provide a more accurate assessment of the dynamic changes in the risk of death as the patient lives longer after the gastrectomy. For cancer survivors, CPS estimates might allow patients to quantify the improvement in their prognosis over time. CPS estimates are equally necessary for clinicians, because they might then adjust the frequency and type of follow-up over time. Moreover, CPS estimates provide a reference for researchers who need to set deadlines for clinical research, resulting in optimal cost-effectiveness of follow-up programs for clinical trials. Therefore, predicting CPS has potentially important clinical value for patients, clinicians, and researchers.

A nomogram is a multivariate survival prediction model based on individual characteristics.[9] Recently, Kattan et al.[10] reported a nomogram that predicted disease-specific survival (DSS) for gastric cancer based on an American Cancer Center database. Han et al.[3] developed a Korean-derived nomogram to predict long-term survival after D2 gastrectomy for gastric cancer. Although these models showed high predictive accuracy with internal validation, they have not been applied widely to the general population.[11,12] Of importance, neither model can provide CPS predictions. CPS estimates might differ markedly from baseline survival probability predictions, particularly after several years of follow-up. Therefore, the aim of the current study was to devise the first accurate nomogram for predicting the CPS of patients at any time point after curative-intent gastrectomy. External validation was performed to evaluate the accuracy of the model, using a validation set derived from the most recent data of the Surveillance, Epidemiology, and End Results (SEER) database and a validation set from China as representative of the Asian population.

Materials and Methods

Population and covariates

To develop a prediction model with the potential for global application, data were obtained from the SEER database (Registration Number: 14088-Nov2015)[13] and from one of the most clinically active Chinese institutes for gastric cancer (Fujian Medical University Union Hospital [FJUH], Fuzhou, China).

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from all patients for being included in the study.

Because of changes in coding (specifically the AJCC staging) and the requirement for at least one year of follow-up, data were extracted from the SEER database 1988–2012. Additionally, all patients with gastric cancer treated 1995–2012 were selected from the FJUH database. All the cases were restaged according to the criteria described in the AJCC Staging Manual (7th edition).[2] The final SEER data set included 11,551 patients (Supplementary Fig. 1). Because the SEER data set had an internal database of sufficient size, the patients were divided randomly to use two-thirds in the SEER development set ($n = 7{,}700$) and one-third in the SEER validation set ($n = 3{,}851$), using the data-splitting method.[14]

Clinicopathologic data were collected routinely. Race was apportioned into three groups: white, black, and others (including Native American, Alaskan native, Asian, and Pacific Islander). Age was apportioned into four groups ($\leq$44, 45–59, 60–74, and $\geq$75 years) according to the international age standard survival classification categories.[15] The optimal cut-off points for tumor size (the greatest diameter) classified the patients into the following groups, using the "X-tile" program: <3 cm, 3–6 cm, >6 cm, linitis plastica, and size that cannot be assessed.[16] The tumor site was apportioned into four subsites as follows: middle and distal third (C16.2, C16.3, and C16.4), proximal third (C16.0 and C16.1), stomach, NOS (C16.5, C16.6, and C16.9), and overlapping (C16.8).[17] The tumors were categorized pathologically into low grade (well and moderately differentiated), high grade (poorly differentiated and undifferentiated), and Gx (grade cannot be evaluated). The histologic types were categorized into general types (8140–8389) and special types (8440–8499). The surgical procedures were divided into partial gastrectomy and total gastrectomy.

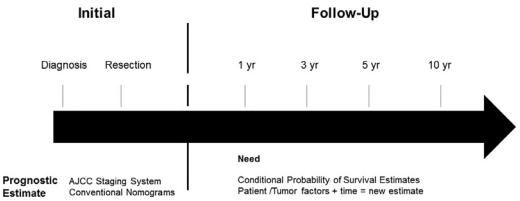

Fig. 1. The concept of conditional probability of survival. *AJCC*, American Joint Committee on Cancer.

The cause of death among the SEER cohorts was defined using the SEER cause-of-death codes.[13,18] All the patients in the FJUH validation set received a standard follow-up postoperatively, including visits every 3 months for 2 years, every 6 months from 3 to 5 years, and once per year thereafter. Most routine follow-up appointments included a physical examination, laboratory tests (including measurement of serum levels of CA19-9, CA72-4, and CEA), chest radiography, and abdominopelvic ultrasonography or computed tomography, as well as an annual upper endoscopic examination.[19–22] Patients were observed until death or the final follow-up date of December 2013, but patients were lost to follow-up at a rate of 8.6%. Deaths from gastric cancer were coded as disease-specific mortality.

Concept of conditional probability of survival The conditional probability of survival (CPS) is derived from the concept of conditional probability in biostatistics.[8,23] The CPS can be calculated from Kaplan-Meier survival data. The mathematical definition of CPS can be expressed as follows: CPS (y|x)=S(y)/S(x), (x<y), where CPS (y|x) is the survival probability y years after surgery (given that the patient has survived x years after surgery), S(y) is the survival probability y years after surgery, and S(x) is the survival probability x years after surgery.[24,25] In this study, the data for overall survival (OS) and gastric cancer-specific survival were used to calculate the conditional probability of overall survival (CPOS) and the conditional probability of disease-specific survival (CPDS), respectively. The variances in the conditional probabilities were estimated using the formula developed by Davis et al.[26] Initial prognostic estimates for patients were usually based on individual and tumor characteristics after resection. CPS estimates were recalculated by incorporating the patient and tumor characteristics, as well as survival time (Fig. 1).

Statistical analysis

The survival hazard curve was plotted using kernel density smoothing.[27] Within the development set, variables associated with OS and DSS were selected, using multivariate Cox regression models. Stepwise backward variable removal was applied to the multivariate model to identify the most accurate and parsimonious set of predictors.[28] Because a proportion of patients at risk of disease-specific mortality die because of other causes before they develop disease-specific mortality, competing-risks regression was used to test the significance of the DSS predictors after considering other-cause mortality.[29] The hazard ratios of these variables were used to develop two conditional nomograms for predicting the CPOS and CPDS, according to the duration of survival using a previously described methodology.[6,30]

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