Novel Calculator to Estimate Overall Survival Benefit from Neoadjuvant Chemoradiation in Patients with Esophageal Adenocarcinoma

Emmanuel Gabriel, MD, PhD, Kristopher Attwood, PhD, Rupen Shah, MD, Steven Nurkin, MD, FACS, Steven Hochwald, MD, FACS, Moshim Kukar, MD

BACKGROUND: Our group reported that patients with clinically node-negative esophageal adenocarcinoma do not derive overall survival (OS) benefit from neoadjuvant chemoradiation (nCRT) compared with clinically node-positive patients. The aim of this study was to develop a calculator that could more easily identify which patients derive OS benefit from nCRT.

STUDY DESIGN: Using the National Cancer Data Base (2006 to 2012), patients with clinical status T1b to T4a, N−/+, M0 adenocarcinoma of the esophagus who underwent resection were selected. Of this cohort, 80% were randomly selected to develop and test the prediction model using Cox regression. The remaining 20% were used to internally validate the model, and performance was evaluated using receiver operating characteristic curves and area under the curves.

RESULTS: A total of 8,974 patients met study criteria. Using the model testing cohort (7,179 patients), variables that were independently associated with OS in multivariable analysis were included in the model. These variables included Charlson-Deyo comorbidity score, tumor grade, clinical T and N status, and nCRT before surgery. Factors associated with increased risk of death were higher grade and higher T or N status. Receipt of nCRT was associated with improved OS. After validation, model performance showed an area under the curve of 0.630 and 0.682 for 1-year and 3-year OS, respectively.

CONCLUSIONS: A novel OS calculator was developed for esophageal adenocarcinoma that reasonably predicts which patients are expected to derive OS benefit from nCRT. This tool can be helpful in determining OS benefit from nCRT to assist with treatment decision making. (J Am Coll Surg 2017;224:884−894. © 2017 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

Neoadjuvant chemoradiation (nCRT) for esophageal adenocarcinoma is established practice for patients with locally advanced and/or node positive tumors.[1] There have been several randomized controlled trials that support neoadjuvant therapy for esophageal adenocarcinoma before surgical resection.[2-5] The largest of these was conducted by the Chemoradiation for Oesophageal Cancer Followed by Surgery Study (CROSS) group, which showed improved long-term oncologic benefits for patients treated with preoperative weekly paclitaxel and carboplatin with radiation compared with patients treated with surgery alone.[3] Conversely, the French randomized trial FFCD 9901 showed that for patients with early stage I/II esophageal cancers, the addition of nCRT (cisplatin plus fluorouracil) did not improve overall survival (OS) and actually increased postoperative mortality.[6,7] Our group has recently published new results comparing the benefit of nCRT in patients who were node positive compared with those who were node negative, which raised questions as to the survival benefit of nCRT in node-negative patients.[8]

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From the Departments of Surgical Oncology (Gabriel, Shah, Nurkin, Hochwald, Kukar) and Biostatistics (Attwood), Roswell Park Cancer Institute, Buffalo, NY.

Correspondence address: Moshim Kukar, MD, Department of Surgical Oncology, Roswell Park Cancer Institute, Elm & Carlton St, Buffalo, NY 14263. email: moshim.kukar@roswellpark.org

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Abbreviations and Acronyms

AUC = area under the curve
CD = Charlson-Deyo
NCDB = National Cancer Data Base
nCRT = neoadjuvant chemoradiation
OS = overall survival
ROS = receiver operating characteristic

In translating the clinical relevance of such studies to everyday practice, some groups have developed models and nomograms to predict the individualized outcomes for patients with esophageal cancer.[9-11] The National Cancer Data Base (NCDB) is a large database jointly maintained by the American College of Surgeons Commission on Cancer and the American Cancer Society. This database captures up to 70% of the nation's cancer cases through its participating hospitals.[12] The NCDB has not been used in OS calculators for esophageal cancer. Analyzing the NCDB in a manner similar to our earlier study,[8] which used the NCDB OS data up to 2006, the purpose of this current study was to create a user-friendly calculator for patients with esophageal adenocarcinoma to predict which patient populations would benefit from nCRT in terms of OS. At the time of this study, the NCDB provided data up to 2012, allowing for a more contemporary analysis and update of our earlier work now incorporated into a survival calculator.

METHODS

Patients

We queried the American College of Surgeons NCDB (2006 to 2012) for all patients with adenocarcinoma of the middle and lower esophagus who were clinical stage T1b, N1 to N3, M0, or T2 to T4a, N−/+, M0 and had undergone surgery. At the time of this study, the most recent NCDB Participant User File included patients with vital status from 2006 to 2012. This study was deemed exempt by the IRB. The following ICD-O-3 codes were used to identify patients with adenocarcinoma: 8140 to 8148, 8200 to 8239, 8260 to 8263, 8480 to 8496, 8500 to 8503, and 8560 to 8573.

Patients who met inclusion and exclusion criteria as described previously were included in our analysis.[8] Figure 1 summarizes the inclusion and exclusion criteria used in this study. Patient factors initially studied in this calculator and reported in the NCDB included age, sex, and Charlson-Deyo (CD) comorbidity score as a measure of comorbid conditions. Clinical variables used in this calculator include grade, clinical T status, and clinical N status. The NCDB also recorded data on the administration of neoadjuvant therapy (both chemotherapy and radiation), although the specific chemotherapy regimens were not available as part of the database.

Statistical analysis for creating overall survival calculator

In developing the OS calculator, the patients were randomly divided into testing (n_t) and validation (n_v) cohorts using an 80/20 allocation. Descriptive statistics were reported using the mean, median, and SD for continuous variables; and using frequencies and relative frequencies for categorical variables. Cohorts were compared using Mann-Whitney U and chi-square tests for continuous and categorical variables, respectively. Kaplan-Meier methods were used to summarize OS, from which estimates of median and 1- and 3-year survival rates were obtained with 95% CI.

The following analyses were conducted using the n_t cohort. Because the purpose of the calculator was to estimate OS benefit from nCRT, only preoperative data were used to develop the model. Univariate associations between OS and patient variables were examined using a Cox regression model. The models were fit using Firth's penalized function, and hazard ratios with 95% CIs were obtained from model estimates.[13,14] A prediction model was then developed using a multivariable Cox regression model, where the model form was developed in 2 steps. First, the main effects were chosen using a bootstrap backwards selection method (α-exit = 0.1) with all variables that were significant on univariate analysis used as candidates. Second, all 2-way interactions between the selected main effects and neoadjuvant chemoradiation status were considered, and significant interactions were selected using the bootstrap backwards selection method. The final model included the selected main effects and 2-way interactions, and model estimates were obtained using standard bootstrap techniques.

The estimated baseline 1- and 3-year OS rates were obtained from the final Cox regression model using the BASELINE function available in SAS, version 9.4 software's PHREG procedure (SAS Institute), and correspond to the estimated 1- and 3-year OS rate for individuals with reference-level covariate values. The final model's parameter estimates and the corresponding baseline 1- and 3-year OS estimates were then used to generate 1- and 3-year OS prediction models. The models were recalibrated using standard bootstrap cross-validation methods. Model performance was assessed using time-dependent receiver operating characteristic (ROC) curves,[15] the corresponding area under the ROC curve (AUC), and calibration plots.