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A Novel Calculator for Esophageal Adenocarcinoma Accurately Predicts Overall Survival Benefit from Neoadjuvant Chemoradiation

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Abstract

Introduction—Our group recently published that patients with clinically node negative (cN–) esophageal adenocarcinoma do not derive an overall survival (OS) benefit from neoadjuvant chemoradiation (nCRT) compared to clinically node positive (cN+) patients. The aim of this study was to develop a calculator which could more precisely identify which patients derive OS benefit from nCRT.

Methods—Using the National Cancer Data Base (NCDB) from 2006–2012, patients with clinical stage T1b, N1–N3 or T2–T4a, N–/+, M0 adenocarcinoma of the middle or lower esophagus who underwent surgical resection were selected. The primary endpoint was overall survival (OS). Of this cohort, 80% was used to create the prediction model using Cox regression. The remaining 20% of the cohort was used to internally validate the model, the performance of which is measured using receiver operating characteristic (ROC) curve and the associated area under the curve (AUC).

Results—A total of 8,974 patients were used to generate the model. This incorporated patient age, Charlson-Deyo comorbidity score, tumor grade, clinical T and N stage, and nCRT prior to surgery. Each of these variables was independently associated with OS on multivariable analysis. Factors associated with an increased risk of death included advanced age, higher grade, and higher T or N stage. Receipt of nCRT was associated with improved survival. Model performance showed an AUC of 0.644 and 0.689 for 1-year and 3-year OS, respectively.

Conclusions—A novel OS calculator incorporating patient and treatment factors was developed for esophageal adenocarcinoma, which accurately predicts which patient subsets are expected to derive OS benefit from nCRT. This tool can be very helpful in generating real-time estimates of

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OS benefit from nCRT in an individualized manner in order to assist with patient care decision making.

Keywords

esophageal cancer; survival calculator; National Cancer Data Base

Introduction

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 which support neoadjuvant therapy for esophageal adenocarcinoma prior to 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 pre-operative weekly paclitaxel and carboplatin with radiation compared to 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 survival yet actually increased post-operative mortality.⁶ In the current era of suboptimal imaging for patients with esophageal cancer and in the setting of both the CROSS and FFCD 9901 trials, it is often difficult to predict which patients will derive survival benefit from nCRT.⁷ Our group has recently published new results comparing the benefit of nCRT in patients who were node positive with those who were node negative, which raised questions as to the benefit of nCRT in node negative patients.⁸

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 Commission on Cancer (CoC) of the American College of Surgeons (ACS) and the American Cancer Society. This database captures up to 70% of nation's cancer cases through its participating hospitals.¹² The NCDB has not been utilized in OS calculators for esophageal cancer. Thus, analyzing the NCDB in a similar manner to our prior study,⁸ the purpose of this current study was to create a user-friendly calculator for patients with esophageal adenocarcinoma in order to predict which patient populations would benefit from nCRT in terms of OS.

Methods

Patients

We queried the American College of Surgeons National Cancer Data Base (ACS-NCDB) 2006–2012 for all patients with adenocarcinoma of the middle and lower esophagus who were clinical stage T1b, N1–N3, M0 or T2–T4a, N–/+, M0 who had undergone surgery. At the time of this study, the most recent NCDB participant user file (PUF) included patients with vital status from 2006–2012. This study was deemed exempt from the institutional review board (IRB). The following International Classification of Diseases for Oncology,

Third Edition (ICD-O-3) codes were used to identify patients with adenocarcinoma: 8140-8148, 8200-8239, 8260-8263, 8480-8496, 8500-8503, and 8560-8573.

Patients were identified using sequential inclusion criteria similar to our previous publication.⁸ Figure 1 summarizes the sequential inclusion criteria used in this study. Patient factors reported in the NCDB that were used in this calculator include age and Charlson-Deyo comorbidity score (CD) as a measure of comorbid conditions. Clinical variables used in this calculator include grade, clinical T stage and clinical N stage. The NCDB also records data on the administration of neoadjuvant therapy (both chemotherapy and radiation), although the specific chemotherapy regimens are not available as part of the data base.

Statistical analysis for creating OS calculator

In developing the OS calculator, the patients were randomly divided into testing (n_t) and validation (n_v) cohorts using a 80/20 allocation. Descriptive statistics were reported using the mean, median and standard deviation 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 (KM) methods were used to summarize OS, from which estimates of median and 1- and 3-year survival were obtained with 95% confidence intervals.

The following analyses were conducted using the n_t cohort. Because the purpose of the calculator was to estimate OS benefit from nCRT, only pre-operative data was used to develop the model. Univariable associations between OS and patient variables were examined using a Cox regression model. A multivariable Cox regression model was obtained using a bootstrap backwards selection method (α exit = 0.1). The models were fit using Firth's penalized function and hazard ratios (HRs), with 95% confidence intervals, were obtained from model estimates.^{13,14} The baseline 1- and 3-year OS rate was obtained from the fitted Cox regression model using the BASELINE function available in SAS v9.4 software's PHREG procedure, and corresponds to the estimated 1- and 3-year OS rate for individuals with baseline covariate values. The multivariable model's parameter estimates and estimated baseline 1- and 3-year OS rate were used to generate prediction models. The models were recalibrated using standard bootstrap cross-validation methods. Model performance was assessed using time-dependent receiver operating characteristic (ROC) curves, the corresponding area under the ROC curve (AUC), and calibration plots.

The 1- and 3-year OS prediction models were then applied to the n_v cohort, with model performance assessed using ROC curves with corresponding AUC and calibration plots. The calibration plots for 1- and 3-year OS show the predicted survival rates on the horizontal axis versus the observed survival rates on the vertical axis. These calibration plots identify when the prediction models over, under or accurately predicted the OS rates.

All analyses were conducted using SAS v9.4 (Cary, NC), at a significance (p-value) level of 0.05.

Results

Data extraction yielded 8,974 patients. From this cohort, 7,179 patients (80.0%) and 1,795 patients (20.0%) were randomly allocated to n_t and n_v cohorts, respectively. Patient and tumor variables are shown in Table 1. The comparison of n_t and n_v cohorts showed no statistically meaningful differences. The overall patient and tumor characteristics are shown in the second column from the right in Table 1.

Figure 2 shows the Kaplan-Meier curves for OS. Median follow-up was 49.0 months (0.0 – 104.5). OS analysis demonstrated a 1- and 3-year OS of 0.83 (0.82–0.84) and 0.54 (0.53–0.55), respectively. Survival results for the n_t and n_v cohorts were similar to the group as a whole.

Table 2 shows the multivariable analysis of the selected factors with OS. Each of these variables was independently associated with OS to significant levels. Gender was not included as it was not statistically significant on multivariable analysis.

The mathematical models generated from n_t for predicted probability ‘P’ of 1- and 3-year OS are expressed as follows: $P(1\text{-year survival}) = 0.989 \times e^{I_p}$ and $P(3\text{-year survival}) = 0.964 \times e^{I_p}$, where I_p equals:

$$\begin{aligned} I_p = & 0.986 \times [(0.026 \times \text{Age} \\ & + 0.125 \times (\text{CD}=1) + 0.250 \times (\text{CD}=2) \\ & + 0.172 \times (\text{Grade}=\text{Moderately differentiated}) + 0.667 \times (\text{Grade}=\text{Poorly differentiated or undifferentiated}) \\ & + 0.311 \times (\text{N stage}=\text{positive, or } 1/2/3) \\ & + 0.715 \times (\text{T stage}=2) + 1.125 \times (\text{T stage}=3) + 2.578 \times (\text{T stage}=4) \\ & + [(\text{Neoadjuvant chemoradiation}) \times [1.490 - (0.010 \times \text{Age}) \\ & - 0.085 \times (\text{Grade}=\text{Moderately differentiated}) - 0.354 \times (\text{Grade}=\text{Poorly differentiated or undifferentiated}) \\ & - 0.137 \times (\text{N stage}=\text{positive, or } 1/2/3) \\ & - 0.665 \times (\text{T stage}=2) - 0.888 \times (\text{T stage}=3) - 2.185 \times (\text{T stage}=4)]]. \end{aligned}$$

This base components 0.989 and 0.964 reflect the estimated baseline 1- and 3-year OS, respectively, observed in the prediction models. For continuous variables (which only includes age), the age in years of the patient is entered. For all other variables, a “0” or “1” is entered if the variable is not true or is true, respectively, as it pertains to an individual patient.

The calibration plots and ROC curves for the 1- and 3-year OS prediction models are shown in Figure 3. The performance of the 3-year OS model was slightly higher than the 1-year OS model, as indicated by the AUC (1-year OS AUC = 0.655 and 3-year OS AUC = 0.669).

The recalibrated model constructed by utilizing n_v showed a small drop in performance for the 1-year OS but an improved 3-year OS performance with AUC = 0.644 and 0.689, respectively (Figure 4).

Discussion

For patients with esophageal cancer, assessment of the benefit derived from nCRT can provide useful information and aid in the care of these patients. The challenge lies within the ability to determine which subset of patients will derive this benefit as the spectrum of outcomes from nCRT spans from pathologic complete response (pCR) to persistent or even progressive disease. Up to 70% of patients will be downstaged as a result of nCRT.¹⁵ For patients who achieve pCR with nCRT, the benefit to OS is significant, with studies reporting 5-year OS that is 20–30% higher than in patients who do not experience pCR.^{16, 17} Imaging after nCRT, commonly in the form of a 18F-Fluorodeoxyglucose Positron Emission Tomography (PET-CT), can be helpful in estimating response to nCRT but does not have high accuracy in predicting residual disease or pCR.^{18–20} Therefore, the standard of care for patient achieving pCR remains surgical resection. Tools which could accurately predict which patients derive the most benefit from nCRT would therefore have much needed utility in the treatment of esophageal cancer.

In this study, we have developed a new calculator used to predict 1- and 3-year OS in patients treated for esophageal cancer. The mathematical prediction equation incorporates an important list of pre-treatment tumor variables and whether the patient receives nCRT, all of which have been shown to impact OS in esophageal cancer. The majority of these factors are expressed as discrete variables within the equation. Using grade, for example, a tumor that is poorly or undifferentiated would receive a value of 1 (or “yes”) in the corresponding sections of the equation, whereas a tumor that is well or moderately differentiated would receive a value of 0 (or “no”). The coefficient preceding each variable reflects the weight of that specific variable on the OS prediction. The “Ip” component of the mathematical equation is an exponent for the base constant 0.989 and 0.964 for the 1- and 3-year models, respectively. Variables that are additive to Ip subsequently lessen the OS. Conversely, variables that are subtractive to Ip result in elimination of the variable (through a value of 0) or decrease Ip, which subsequently increases the OS. The role of nCRT in latter part the equation is dependent on the other patient and tumor variables. Therefore, nCRT does not have a simple linear association with the predicted OS, but rather its effect on the equation will vary depending on the other individualized patient and tumor characteristics (namely age, grade, T stage and N stage). Herein lies the novel utility and applicability of our prediction models in order to more precisely identify which patients with derive OS benefit from nCRT.

In general, patients who tended to benefit from nCRT included: (1) those with both higher clinical T and N stage at any age or grade, (2) older patients with clinical T stage 3/4, and (3) patients with clinical T stage 3/4 tumors that are also higher grade. As an example of the utility of this model, two patients with hypothetical clinical and tumor characteristics are used. Patient 1 is 50 years old with a CD score =1 and a T2 N0 moderately differentiated tumor. Patient 2 is 70 years old with a CD score = 1 and a T3 N+ poorly differentiated tumor. The predicted 3-year OS rates for patient 1 with and without nCRT are predicted to be 63.5% and 69.9%, respectively. In this case, the addition of nCRT is predicted to have an absolute detriment of 6.4%. In contrast, the predicted 3-year OS rates for patient 2 with and without nCRT are 33.0% and 13.8%, respectively. As expected, the OS for patient 2 is

predicted to be lower than patient 1, inherent to the older age and less favorable tumor characteristics of patient 2. However, in the case of patient 2, the addition of nCRT is predicted to have an absolute benefit of 19.2%. Therefore, it is logical to offer nCRT to patient 2, but this is not necessarily the case for patient 1. In fact, our calculator predicts that patient 1 actually has poorer OS with nCRT followed by surgery as compared to surgery alone. This finding may be consistent with the results of the FFCO 9901 trial, which showed a detriment to early stage patients with esophageal cancer who received nCRT.⁵

The use of calculators or nomograms to estimate outcomes are becoming increasingly common and applied to real-time clinical situations to aid in treatment decision making and provide patients with realistic expectations of survival. One calculator derived from a dual institutional database included 273 patients with esophageal adenocarcinoma to develop a nomogram that predicts pathologic lymph node involvement.⁹ Other calculators have been derived using large patient samples from the SEER Data Base. The most relevant example is an on-line calculator derived from 824 patients with esophageal cancer, of which 471 (74%), had adenocarcinoma and the remaining 26% has squamous cell carcinoma (SCC).¹⁰ This nomogram incorporates age, gender, histology (adenocarcinoma versus SCC), pathologic T and N stage (as opposed to clinical staging), number of lymph nodes harvested and CRT. Unlike our calculator which uses the NCDB, this nomogram limited its analysis to patients > 65 who had Medicare part A and B and defined neoadjuvant chemotherapy within 6 months of diagnosis as opposed to receipt of chemotherapy prior to surgery.¹⁰ In contrast, radiation therapy was clearly defined as occurring prior to surgery. Despite these acknowledged limitations, internal validation of the nomogram showed high performance, with the most significant benefit of their defined nCRT being derived for patients with nodal (pN1) disease. Among patients with pathologic node negative disease (pN0), the only subset of patients which derived benefit from nCRT were patients with T4N0 disease, whereby patients who received nCRT and surgery had a 3-year OS of 54% compared to 45% in patients who had surgery alone. These results are overall consistent with our prior study,⁷ as well as the populations shown to have benefit by our developed calculator.

Contrary to other databases, the items included in the NCDB include pre-treatment patient tumor factors, including clinical T and N stage. This reflects a higher level of practicality of our calculator in estimating the benefit of nCRT, namely that this prediction should be performed prior to any treatment to assess which individual patient would derive benefit from nCRT. Using a model that estimates the benefit of OS for nCRT after this and surgical resection have already been performed does provide useful information in terms of individualized patient mortality, but is less relevant to the goal of identifying which patient will derive an OS benefit prior to initiating therapy. Consequently, models based on pathologic staging are unable to identify the patients who are not expected to benefit from and thus may be spared nCRT.

Another important benefit of the NCDB is that it provides a sufficient amount of patient data, which allows for a robust statistical analysis. This calculator includes over ten-fold the number of patients with esophageal adenocarcinoma than the next largest database. The NCDB also includes information of histologic grade, which has been shown to affect the behavior and outcomes of esophageal cancer, including response to nCRT,²⁰ which is highly

relevant to the purpose of this study. There are no age or insurance constraints among the population used in our model, which may minimize different selection biases that can affect OS. Therefore, we believe that our calculator is consistent with other existing calculators and is a progressive step in the general development of risk and outcome calculators available for surgical patients. Indeed, one of our future directions includes validating our innovative calculator prospectively and assessing the ease of its use in our colorectal clinics. We also plan to compare our calculator with the few existing calculators discussed above. As updated and more contemporary data is released from the NCDB, we plan on refining our prediction models.

We acknowledge that there are shortcomings to our prediction model, reflective of large databases that are often less granular, specifically in terms of the specific types of nCRT received. Similar to the SEER database, the nCRT regimens that these patients received are not defined. Since some of these patients were included in the NCDB prior to the results of the CROSS and FFCD 9901 trials, the nCRT regimens were likely not standardized across the different participating institutions. As more recent information is released by the NCDB, a refinement of our model will be performed which would likely include a higher proportion of patients who received the CROSS nCRT regimen among the NCDB participating institutions. Another important limitation is that methods for the clinical diagnosis for T and N stage are not clearly defined. Clinical diagnosis is reported based on imaging, biopsy providing histologic diagnosis or some combination thereof. However, the precise imaging used to make the diagnosis (PET-CT, MRI or endoscopy) is not reported. The role of adjuvant chemotherapy, which is still controversial, is also not incorporated into this calculator.

Despite these limitations, we developed an individualized OS calculator for esophageal adenocarcinoma that shows strong performance in predicting subsets of patients who would benefit from nCRT followed by esophagectomy. The practicality and applicability of our calculator is highlighted earlier with a straightforward example, commonly seen in our practice. Utilizing important pretreatment factors known to affect outcomes, this calculator can serve as a highly useful tool in estimating post-treatment OS and assisting in the decision-making process to receive nCRT in the patient with esophageal adenocarcinoma.

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Figure 1.

Flowchart showing sequential inclusion criteria used to select patients incorporated into the esophageal survival calculator.

Figure 2.

Overall survival (OS) used to create calculator. No difference between the model building (n_t) and validation (n_v) cohorts was observed, with similar median OS of the model cohort (42.6 months) compared to the validation cohort (46.2 months).

Figure 3.

Calibration plots (A) and receiver operating characteristic (ROC) curves (B) for the building prediction model using the n_t cohort for 1- and 3-year OS. For the calibration plot, the proximity of the dotted line to the solid line indicates performance of the model, whereby the closer the two lines are, the higher the accuracy of the predicted OS to the observed or actual OS. Bars indicate 95% confidence intervals about a given data point. For the ROC curve, the closer the value of the area under the curve (AUC) is to 1.0, the higher the performance of the model.

Figure 4. Calibration plots (A) and ROC curves (B) for the prediction model following validation with the n_v cohort. The area under the curve (AUC) shows similar performance to the building prediction model, with a value of 0.644 for 1-year OS and 0.689 for 3-year OS.

Table 1

Characteristics of patients used to construct the esophageal overall survival (OS) calculator. Patients were identified from the NCDB who were diagnosed between 2006 and 2012. From the entire cohort, 80% were randomly assigned to model development derived from the n_1 cohort (designated Building cohort) and 20% to the Validation cohort (n_v).

		Building cohort (n_b)	Validation cohort (n_v)	Overall	P-value
Overall	N	7,179 (80.0)	1,795 (20.0)	8,974 (100%)	
Age (years)	Mean $\pm$ Standard deviation	63.0 $\pm$ 9.8	63.1 $\pm$ 9.7	63.0 $\pm$ 9.8	0.49
Gender	Male	6,331 (88.2%)	1,600 (89.1%)	7,931 (88.4%)	0.26
	Female	848 (11.8%)	195 (10.9%)	1,043 (11.6%)	
CD *	0	5,217 (72.7%)	1,320 (73.5%)	6,537 (72.8%)	0.46
	1	1,553 (21.6%)	386 (21.5%)	1,939 (21.6%)	
	2	409 (5.7%)	89 (5.0%)	498 (5.5%)	
Grade	Well differentiated	502 (8.2%)	136 (8.8%)	638 (8.3%)	0.73
	Moderately differentiated	2,627 (42.9%)	661 (42.8%)	3,288 (42.8%)	
	Poorly differentiated	3,000 (48.9%)	748 (48.4%)	3,748 (48.8%)	
	Undifferentiated	1,702 (23.7%)	432 (24.1%)	2,134 (23.8%)	0.94
Clinical T stage	1	1,528 (21.3%)	370 (20.6%)	1,898 (21.1%)	
	2	3,791 (52.8%)	954 (53.1%)	4,745 (52.9%)	
	3	158 (2.2%)	39 (2.2%)	197 (2.2%)	
	4	3,700 (51.5%)	939 (52.3%)	4,639 (51.7%)	0.82
Clinical N stage	0	3,128 (43.6%)	777 (43.3%)	3,905 (43.5%)	
	1	299 (4.2%)	68 (3.8%)	367 (4.1%)	
	2	52 (0.7%)	11 (0.6%)	63 (0.7%)	
	3	2,213 (30.8%)	573 (31.9%)	2,786 (31.0%)	
Treatment	None	4,966 (69.2%)	1,222 (68.1%)	6,188 (69.0%)	0.37
	Neoadjuvant Chemoradiation	2,213 (30.8%)	573 (31.9%)	2,786 (31.0%)	

* Charlson-Deyo comorbidity score is an estimate of comorbid conditions based on ICD-9 diagnosis codes. A score of 0 indicates no comorbidities. Point values are assigned to comorbid conditions based on severity. The NCDB truncates possible scores to 0, 1 and 2 due to the small proportion of cases exceeding a score of 2.

Table 2

Multivariable analysis of variables to identify factors independently associated with OS. Each of these variables was incorporated into the prediction model in order to estimate 1- and 3-year OS.

Variable		Hazard Ratio	P-value
Age	1 Year increase	1.02 (1.02, 1.02)	<.001
CD	2 vs 0	1.12 (1.03, 1.23)	<.001
	1 vs 0	1.27 (1.09, 1.49)	
Grade	Poorly/undifferentiated vs well differentiated	1.19 (1.00, 1.42)	<.001
	Moderately differentiated vs well differentiated	1.62 (1.36, 1.93)	
Clinical T stage	4 vs 1	1.88 (1.64, 2.15)	<.001
	3 vs 1	2.32 (2.01, 2.67)	
	2 vs 1	2.84 (2.16, 3.73)	
Clinical N stage	3 vs 0	1.23 (1.14, 1.33)	<.001
	2 vs 0	1.50 (1.26, 1.79)	
	1 vs 0	2.51 (1.73, 3.63)	
Treatment	Neoadjuvant Chemoradiation vs None	0.86 (0.76, 0.96)	0.008