Original Article

Nomogram for Predicting the Benefit of Neoadjuvant Chemoradiotherapy for Patients With Esophageal Cancer

A SEER-Medicare Analysis

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BACKGROUND: The survival impact of neoadjuvant chemoradiotherapy (CRT) on esophageal cancer remains difficult to establish for specific patients. The aim of the current study was to create a Web-based prediction tool providing individualized survival projections based on tumor and treatment data. **METHODS:** Patients diagnosed with esophageal cancer between 1997 and 2005 were selected from the Surveillance, Epidemiology, and End Results (SEER)-Medicare database. The covariates analyzed were sex, T and N classification, histology, total number of lymph nodes examined, and treatment with esophagectomy or CRT followed by esophagectomy. After propensity score weighting, a log-logistic regression model for overall survival was selected based on the Akaike information criterion. **RESULTS:** A total of 824 patients with esophageal cancer who were treated with esophagectomy or trimodal therapy met the selection criteria. On multivariate analysis, age, sex, T and N classification, number of lymph nodes examined, treatment, and histology were found to be significantly associated with overall survival and were included in the regression analysis. Preoperative staging data and final surgical margin status were not available within the SEER-Medicare data set and therefore were not included. The model predicted that patients with T4 or lymph node disease benefitted from CRT. The internally validated concordance index was 0.72. **CONCLUSIONS:** The SEER-Medicare database of patients with esophageal cancer can be used to produce a survival prediction tool that: 1) serves as a counseling and decision aid to patients and 2) assists in risk modeling. Patients with T4 or lymph node disease appeared to benefit from CRT. This nomogram may underestimate the benefit of CRT due to its variable downstaging effect on pathologic stage. It is available at skynet.ohsu.edu/nomograms. ***Cancer*** **2013;000:000-000.** © *2013 American Cancer Society.*

KEYWORDS: nomogram, esophageal cancer, predictive tool, neoadjuvant, chemoradiotherapy.

INTRODUCTION

Esophageal cancer is a significant worldwide health problem, and its incidence in the United States and Western Europe is rapidly increasing.[1,2] Patients frequently present with advanced stage disease and compromised performance status, and have a poor prognosis even with aggressive interventions. In a recent prospective randomized trial, the addition of neoadjuvant chemoradiotherapy (CRT) to surgery has been found to improve 5-year survival probability from 34% for patients treated with isolated esophagectomy to 47% for patients treated with CRT followed by surgery for intermediate-staged cancers.[3]

However, response to neoadjuvant treatment can vary even among patients with similar clinical pretreatment disease stage (cTNM). The spectrum of heterogeneous responses ranges from no response at all to a pathologic complete response (pCR), with no invasive disease identified in the surgical specimen. If neoadjuvant treatment produces a pCR, outcomes are better: patients with a pCR can expect a 5-year survival rate of 48%, versus 18% for patients who do not respond.[4] However, selecting the therapeutic strategy for each patient continues to be challenging, as patients with early-stage disease may experience no benefit from CRT whereas those with lymph node (LN) involvement are more likely to receive benefit (Table 1). T1

Preoperatively, with only the cTNM stage available, the selection of the patients who will benefit from this aggressive treatment continues to be a challenge. Potentially, 3 categories of data allow for discriminating between which patients will obtain a benefit from CRT and which will solely be exposed to potential morbidity and mortality: clinical factors,

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TABLE 1. Demographic and Clinical Characteristics of Patients Included in the Analysis

Characteristic	Esophagectomy	Esophagectomy+ CRT	Total
Subjects (n = 824)	562 (68%)	262 (32%)	
Median age, y	72	70	71
Sex			
Female	150 (27%)	46 (18%)	196 (24%)
Male	412 (73%)	216 (82%)	628 (76%)
Histology			
Adeno	417 (74%)	200 (76%)	617 (75%)
SCCa	143 (26%)	62 (24%)	207 (25%)
T classification			
T1	233 (41%)	44 (17%)	277 (34%)
T2	112 (20%)	67 (26%)	189 (23%)
T3	162 (29%)	122 (47%)	284 (35%)
T4	28 (5%)	26 (10%)	54 (7%)
LN status			
N0	339 (60%)	152 (58%)	491 (60%)
N1	89 (16%)	57 (22%)	146 (18%)
N2	55 (10%)	39 (15%)	94 (11%)
N3	14 (3%)	10 (4%)	24 (3%)
Mean no. of LNs sampled	10.5	10.9	10.7
Median OS, mo	27	19	24

Abbreviations: Adeno, adenocarcinoma; CRT, chemoradiotherapy; LN, lymph node; OS, overall survival; SCCa, squamous cell carcinoma.

biomarkers, and functional imaging data. Although these last 2 are promising, to the best of our knowledge, no combination of available clinical data are currently reliable enough to indicate which patients are going to experience a notable survival benefit from receiving CRT followed by esophagectomy and which patients should be treated only with selected modalities. Thus, traditional clinical factors such as the available tumor stage and patient age and performance status are still used to select the best therapy for a particular patient.

Using the patient data available in the Surveillance, Epidemiology, and End Results (SEER)-Medicare database, the goal of the current study was to construct an interactive Web-based to tool to predict individual patient survival based on their individual pathologic, demographic, and treatment data and subsequently aid in medical decision-making, patient education, and, potentially, research protocol design.

MATERIALS AND METHODS

The SEER registry is the largest population-based database of oncology patients in the United States, as per their report covering approximately 26% of patients diagnosed with cancer in the nation.[5] The SEER-Medicare[6] database is linked via a deidentified numeric system to include Medicare claims data on catalogued SEER patients, thereby allowing for the inclusion of clinical information not contained in SEER, such as receipt of chemotherapy. The study cohort includes claims data from 1995 to 2007 linked to patients diagnosed between 1995 and 2005. Patients were selected using Site Recode = 11 for Esophageal Cancer (17325). Patients were included in our analysis if they were identified as having invasive, nonmetastatic disease on surgical pathology and underwent an attempted complete surgical resection of the primary tumor. The analysis was limited to patients aged > 65 years and who were receiving continuous Medicare part A and B coverage for at least 6 months after their diagnosis of esophageal cancer. Patients who received combined CRT before surgery were included in the analysis. Patients who received either isolated radiotherapy (RT) or chemotherapy were excluded. Using the SEER field for Extent of Disease (e10ex1) and LNs (e10 nd1), patients were grouped according to American Joint Committee on Cancer TNM staging (using the 7th edition) (SEER Patient Entitlement and Diagnosis Summary File). Patients with inadequate available data were excluded.

To determine which patients had received chemotherapy, linked Medicare carrier claims (National Claims History) and outpatient (Outpatient Standard Analytical File) files were used. Patients who had Healthcare Common Procedure Coding System claim codes 96400 to 96599, Q0083-85, or J8500-J9999 within 6 months of diagnosis were coded as having received chemotherapy. Patients who were coded as having received external beam RT before surgery were coded and as having received RT. Patients who received both of these treatments were included for analysis and were designated as having received neoadjuvant CRT.

Statistical Analysis

Data processing and modeling were performed using the R software package (r-project.org). Kaplan-Meier survival estimates were created using SPSS statistical software (version 20; IBM SPSS Inc, Armonk, NY). Covariates and interaction terms were selected a priori based on suspected clinically relevant oncologic data and the availability of data within our SEER-Medicare database. Included covariates were age, sex, histology, T classification, N classification, and the number of LN examined. Sex, histology, T classification, and N classification were assessed as discrete categorical variables. The total number of LNs harvested (total LN) and patient age were considered as continuous variables. Age was fitted to a smoothed restricted cubic spline function as per Herrell.[7] Interaction terms between treatment and T classification, N classification, and total LN were included. A propensity score

weighting method was used to balance observed covariates between treatment and observation groups.[8] Propensity scores reflect the probability that a patient will receive therapy based on observed covariates. By assigning propensity score weights to each variable and incorporating these weights into model construction, one can reduce the treatment bias inherent to retrospective nonrandomized regression analysis. Scores were calculated using the twang R library (cran.r-project.org/web/packages/twang/index.html), with CRT as the outcome of interest.

The primary endpoint of analysis was overall survival (OS). Multivariate regression survival analysis was performed using several different regression functions and their results were compared. Our method of model comparison has been reported previously.[9,10] We built both semiparametric models (Cox proportional hazards) and parametric models (Weibull, exponential, log logistic, and lognormal). All survival models were constructed using the rms R library by Harrell (cran.r-project.org/web/packages/rms).[7] Model performance was evaluated using the Akaike information criteria (AIC), a measure of goodness of fit, with the calculated value representing the amount of information lost in model creation.[11] Based on this AIC, we selected the log logistic regression survival function for definitive analysis. This survival model was internally validated using a bootstrap resampling. Discrimination was evaluated using the concordance index. The concordance index represents the percentage of all usable patient pairs in which the modeled prediction and the observed outcome are concordant.

The best performing survival prediction model, in our case the log logistic survival function, was then implemented into an online nomogram. Using this online interactive tool, a user can enter the analyzed multivariate parameters specific to a patient and obtain an estimate of the expected survival based on these factors and the treatment the patient received (CRT or isolated esophagectomy). The browser-based tool was programmed in JavaScript.

RESULTS

A total of 824 patients were included in the final analysis. Of these, 32% received CRT, with the remaining patients undergoing isolated esophagectomy (Table 1). Our demographic table demonstrates the stage of disease and demographic information for the study population both as a whole and stratified by treatment received. Patients who were treated with CRT tended to have a higher T classification (Table 1) and had generally equivalent rates of LN metastasis. One would expect that with a higher average T classification, the N classification would also be higher. The noted equivalence of rates of LN metastasis is likely due to some percentage of patients with LN disease being downstaged by their preoperative CRT. Given the higher average stage of disease and associated worse prognosis for patients undergoing trimodality therapy, it is not surprising that the unweighted beta coefficient for CRT has a strong negative prognostic effect (Table 2). However, when the interaction terms for CRT by T classification and N classification are considered, the beneficial effect of CRT on patients with these advanced disease stages, even within the setting of variable downstaging, is evident. Figure 1 represents a Kaplan-Meier OS curve comparing patients with LN disease who either received or did not receive CRT. A significant survival benefit was observed for patients with residual N1 disease who received CRT compared with those who did not ($P = .017$). The unadjusted median survival for all patients was 24 months. The median LN yield was 10.7 LNs.

Propensity score weighting was performed as described above, and the results of each variables' relative influence on treatment is shown in Table 2. After propensity weights were available, each model was evaluated for

TABLE 2. SEER-Medicare Predictive Log Logistic Multivariate Regression Model Parameters

Covariate	Beta Coefficient	*P*	OR	95% CI
Intercept	6.4560	.0096		
Age[a]	−0.0310	.4026	1.1	0.9-1.18
Age'	−0.3009	.0680	1.7	0.9-2.8
Age"	0.8060	.0218	0.3	0.01-0.8
Sex=female	0.3055	.0002	0.6	0.5-0.8
tstage=2	−0.3188	.0097	1.7	1.13-2.6
tstage=3	−0.8054	<.0001	3.9	2.6-5.7
tstage=4	−1.1091	<.0001	6.4	3.5-11.8
tx=CRT	−0.8059	<.0001	3.8	2.5-5.9
histology=squamous	−0.2701	.0003	1.6	1.23-2.0
nodes=1	−0.7019	<.0001	3.2	2.2-4.7
nodes=2	−0.9804	<.0001	5.2	3.3-8.1
nodes=3	−1.2394	<.0001	8.0	3.6-17.4
totalLN	0.0286	<.0001		
tstage=2* tx=CRT	0.5523	.0011		
tstage=3* tx=CRT	0.6674	<.0001		
tstage=4* tx=CRT	1.2559	<.0001		
tx=CRT* nodes=1	0.9149	<.0001		
tx=CRT* nodes=2	0.3996	.0262		
tx=CRT* nodes=3	0.4749	.1284		
tx=CRT* totalLN	−0.0167	.0243		
Log(scale)	−0.5176	<.0001		

Abbreviations: 95% CI, 95% confidence interval; CRT, chemoradiotherapy; nodes, number of lymph nodes; OR, odds ratio; SEER, Surveillance, Epidemiology, and End Results; totalLN, total lymph nodes examined; tstage, T classification; tx, treatment.
Age is modeled using a restricted cubic spine function with 4 knots requiring 3 independent coefficients: Age, Age', and Age".

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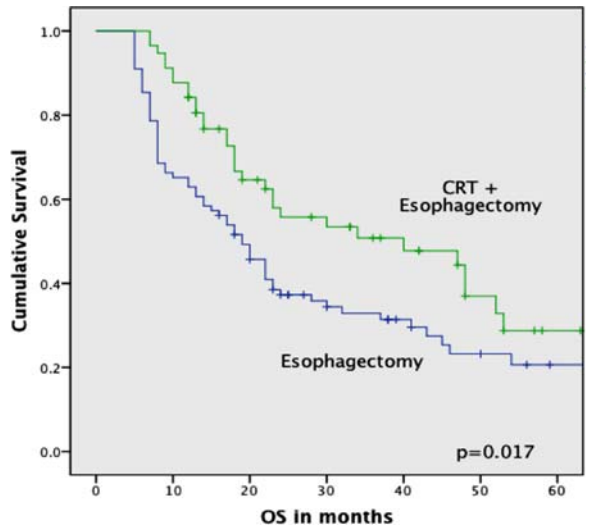

Figure 1. Kaplan-Meier overall survival (OS) curve is shown for patients with N1 disease. CRT indicates chemoradiotherapy.

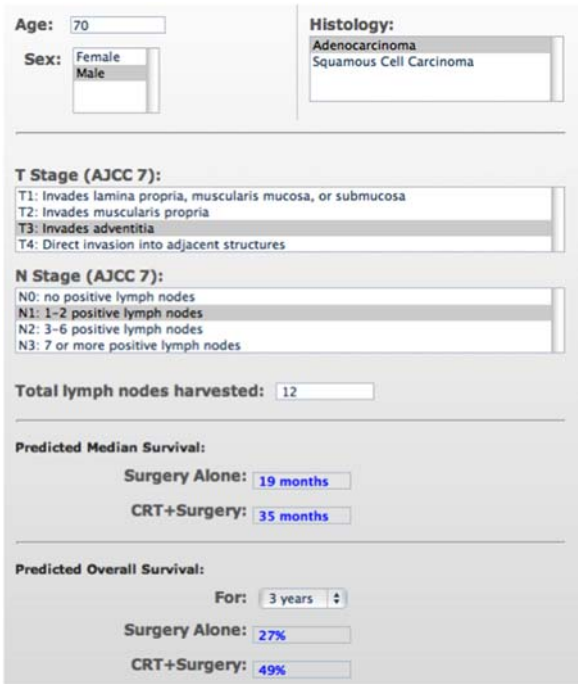

Figure 2. The log logistic model and the discussed beta coefficients were implemented as the online nomogram, which calculates the predicted survival benefit for chemoradiotherapy (CRT) according to the (y)pTNM stage. A representative example is shown. AJCC 7 indicates the 7th edition of the American Joint Committee on Cancer TNM staging system.

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its fidelity using the AIC, as described above. The log logistic model had the lowest AIC of 4135, indicating a better fit and least loss of information, in comparison with the other parametric and semiparametric regression models (Cox proportional hazards, 11,453; Weibull, 8230; exponential, 8255; and log normal, 8066). The survival function for the log logistic regression is calculated as $S(\text{time}) = 1/(1 + e^{((\ln(\text{time})-\text{Xbeta})/\text{Scale})})$. The scale value is represented in Table 2 as the log scale.

The log-logistic function had relatively good discrimination with a concordance index of 0.72. The complete list of beta coefficients is available in Table 2, along with the hazards ratio (HR) and relevant 95% confidence intervals for each independent variable (HRs for interaction terms are not reported). The interaction terms demonstrate how the effect of CRT varied across T classification, N classification, and incrementally for each LN assessed. The beta coefficients and odd ratios produced from the regression model are represented in Table 2. The log logistic model and the discussed beta coefficients were implemented as our online nomogram. This tool calculates the predicted survival benefit for CRT given the (y)pTNM stage. A representative example can be seen in Figure 2. This publically accessible Internet-based tool is available at skynet.ohsu.edu/nomograms, although its key findings are summarized in Table 2.

Table 3 summarizes the predicted outcomes for patients with selected pathologic disease stages based on our model (for a 70-year-old man with adenocarcinoma and 15 LNs examined). For patients with T1, T2, or T3 with N0 disease on final pathology, our model predicts no benefit for CRT when compared with patients with a comparable final pathologic stage who underwent isolated esophagectomy. For patients with T4 disease or patients with any LN disease, our model predicts a notable benefit for CRT, particularly for patients with N1 disease compared with those with N2 or N3 disease. For each LN harvested, this benefit decreases slightly, although this may be a surrogate for higher N stage. The largest benefit is predicted in patients with T3N1 and T4N1 disease. Table 3 demonstrates that for a patient with the above selected demographic and clinical data with ypT4N1 disease, our model predicts a 3-year survival rate of 20% for patients undergoing isolated esophagectomy versus 62% for patients treated with CRT followed by esophagectomy.

The predicted survival benefit from neoadjuvant CRT persisted for those patients with advanced disease present after treatment and for those with lower T classification disease with LN involvement. For example, after receipt of neoadjuvant CRT, the patient with ypT4N2 disease mentioned earlier would have a predicted 3-year OS rate of 29% versus 12% for patients treated without

TABLE 3. Estimated 3-year OS Benefit From CRT Stratified by Selected Pathologic Stage for a Man Aged 70 Years With Adenocarcinoma and 15 LNs Examined

Stage	Esophagectomy	CRT+Esophagectomy
T1N0	84%	No benefit
T2N0	73%	No benefit
T2N1	49%	66%
T3N0	58%	No benefit
T3N1	30%	51%
T4N0	45%	54%
T4N1	20%	61%

Abbreviations: CRT, chemoradiotherapy; LNs, lymph nodes; OS, overall survival.

CRT. A similar patient with ypT2N1 disease is predicted to have a 3-year OS rate of 64% with neoadjuvant CRT versus 45% with isolated esophagectomy.

DISCUSSION

Recent randomized and appropriately powered clinical data convincingly demonstrated the survival benefit of neoadjuvant CRT followed by esophagectomy compared with isolated esophagectomy for clinically determined patient populations with intermediate-stage esophageal cancer. Patients with advanced stage cancers, based on clinical staging, were not included in their analysis.[3] In addition, at least 30% of the patients treated achieved a limited response to treatment and derived significantly less survival benefit compared with patients with partial responses and CRs.[12] Many believe that the survival benefit observed among patients with advanced stage disease is not uniformly shared, being noted among those patients who achieve a pathologic response. In addition, survival benefit may be entirely absent for those patients with no observable downstaging.[13,14]

There is an evolving and progressive expectation among patients and medical providers for personalized medical care and treatment. Decision tools, incorporating clinical, molecular, and radiographic data to predict response to treatment paralleled by the likelihood of its toxicity, will be an integral part of personalized care. The production of clinical prediction tools, or nomograms, has greatly increased over the past several years. In addition to being applied to a myriad of site-specific neoplasms and treatment-specific survival, they are used for predicting perioperative morbidity, mortality, and dichotomous selected outcomes. For example, in patients with esophageal cancer alone, there are institutional- and database-derived predictive tools available for perioperative morbidity and mortality, OS after isolated esophagectomy, pathologic LN involvement based on clinical data, and OS after definitive CRT, also known as bimodal therapy.[7,15-18] To the best of our knowledge, there has been no report to date that includes production of a tool predicting outcomes after trimodality therapy or comparing trimodality therapy with esophagectomy and we believe ours is the first.

Analysis of our demographic data, available in Table 1, demonstrates similar stage distribution and survival outcomes in comparison with established large-volume databases.[19] The distribution of TNM staging is similar to the largest compiled database of patients with resected esophageal cancer, with a relative paucity of T2 patients. The same database found 57% of their patients to be free of LN metastasis, which is similar to our cumulative value of 60%. Patients who were treated with CRT tended to have a higher T classification (Table 1), and had generally equivalent rates of LN metastasis. One might expect that with a higher average T classification, the N classification would also be higher. The noted equivalence of rates of LN metastasis could be due to some percentage of patients with LN disease being downstaged by their preoperative CRT. The patients treated with CRT and isolated esophagectomy were found to have similar mean LN yields (10.5 LNs and 10.9 LNs, respectively).

Standard pathologic TNM staging from the surgical specimen after neoadjuvant CRT (ypTNM) continues to be more prognostic of survival than restaging or preoperative data, despite a variable downstaging effect.[20] A neoadjuvant treatment strategy makes estimating the survival benefit of CRT based on surgical stage challenging due to pathologic downstaging in approximately 70% of patients.[12] Meanwhile, currently available techniques for clinical TNM staging, especially restaging, are unreliable.[7,21]

However, the survival benefit of CRT is likely not distributed evenly across all patients. Those patients who achieve a pCR, with no residual tumor identifiable in the surgical specimen, or even those with a partial response after neoadjuvant CRT, have a better prognosis than those that have no appreciable or minimal response to CRT.[13,14] Identification of a molecular or histologic marker that is that predicts pCR following CRT would provide useful adjunctive clinical information, although others have attempted to predict clinical surrogates for benefit from CRT.[22] It is worth noting that based on our model, even patients with a heavy residual disease burden demonstrated on pathology after CRT received a survival benefit from their trimodality treatment when compared with patients with comparable pathologic stage

undergoing isolated esophagectomy. We predict that a typical patient with ypT4N3 disease received an estimated 9-month median survival benefit from their CRT, irrespective of their clinical stage of disease.

However, evaluation of the applicable and clinical significance of the survival data from the current study and subsequent model reveals several limitations inherent to the SEER-Medicare database. Primarily, there are no clinical staging data within the database that are appropriate for analysis. Therefore, all staging is based on final pathology. Subsequently, a patient's response to CRT cannot be assessed. Other limitations intrinsic to the SEER-Medicare database that are relevant to esophageal cancer include the lack of information regarding surgical margins, disease recurrence, or chemotherapy agent. There are data available regarding the "largest recorded size of the tumor." However, this data point was variably recorded and was not available for a significant number of patients in the current study. In addition, because the analysis uses the Medicare data set, it would not be appropriate to apply the predictive tool to patients aged < 65 years. Although a similar predictive tool that includes institutional prospectively collected clinical data and specific chemotherapeutic regimens would be ideal, and will likely ultimately be possible, several obstacles currently exist to its production and implementation.

Institutional data may not be widely applicable. Several nomograms that have attempted to estimate perioperative morbidity and mortality have resulted in relatively low predictive power when compared across institutions.[17,18] Although the issue of generalizability is perennial, it is particularly troublesome for a disease as complex as esophageal cancer. Similarly, with regard to the incorporation of clinical data, specifically endoscopic ultrasound and positron emission tomography, institutional protocols and interpretation vary greatly. A recent review has detailed the difficulties in comparing positron emission tomography standardized uptake value changes for esophageal cancer across studies and institutions.[23] Although endoscopic ultrasound is widely used for clinical staging, its value in predictive tools similar to ours may be limited due to its low predictive power of LN involvement and interoperator variability.[15,24] Finally, pathologic stage has been validated as a powerful predictor of outcome after receipt of CRT and esophagectomy.[20]

Because of the technical limitations of our data set, a direct comparison of patients who received CRT with those who did not in our population presents a challenge. However, one can say that even patients with significant residual disease after CRT obtained a significant survival benefit from their receipt of CRT in comparison with similarly staged patients who underwent surgery. Certainly, patients with LN metastases on clinical staging or those with a high suspicion of LN metastases should be strongly considered for CRT before surgery.

Because it is based on pathologic stage, this analytic tool is most applicable in the postoperative setting, when the ypTNM stage is available for postoperative counseling, comparison, and treatment planning. In addition, such risk modeling is helpful in the design of research protocols for the identification of homogenous high-risk groups. One would expect the model to underestimate the benefit of neoadjuvant therapy due to its expected downstaging effect on ypTNM staging compared with cTNM staging. The ultimate goal of a predictive decision aid for designing an individualized treatment course would include early identification, or even prediction, of responders and nonresponders, thereby leading to avoidance of ineffective and dangerous applications of both CRT and surgery. The development of a widely applicable and highly discriminatory decision aid that identifies those patients who will benefit from CRT with a low likelihood of toxicity will likely include traditional TNM staging, functional radiologic assays, performance status of the patient, and, potentially, a compiled genetic signature.

Although the predictive tool described in the current study does suffer from retrospective and pathologic staging limitations, it provides a statistical, usable, and patient-friendly blue print for predicting survival based on treatment and patient-specific clinical variables. Our online tool is currently available for use and can be found at skynet.ohsu.edu/nomograms.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

REFERENCES

1. Holmes RS, Vaughan TL. Epidemiology and pathogenesis of esophageal cancer. *Semin Radiat Oncol*. 2007;17:2-9.
2. Siegel R, DeSantis C, Virgo K, et al. Cancer treatment and survivorship statistics, 2012. *CA Cancer J Clin*. 2012;62:220-241.
3. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med*. 2012;366:2074-2084.
4. Berger AC, Farma J, Scott WJ, et al. Complete response to neoadjuvant chemoradiotherapy in esophageal carcinoma is associated with significantly improved survival. *J Clin Oncol*. 2005;23:4330-4337.
5. National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database: Incidence-SEER 17 Regs Public Use, Nov 2005 Sub (1973-2003 varying). Bethesda, MD: National Cancer Institute, Division of Cancer Control and

Population Sciences, Surveillance Research Program, Cancer Statistics Branch; 2006.
6. National Cancer Institute. Surveillance Epidemiology, and End Results (SEER)-Medicare. SEER-Medicare Linked Database. healthservices.cancer.gov/seermedicare. Accessed March 12, 2012.
7. Harrell FE. Regression Modeling Strategies. New York, NY: Springer-Verlag; 2010.
8. Austin PC. The relative ability of different propensity score methods to balance measured covariates between treated and untreated subjects in observational studies. *Med Decis Making*. 2009;29:661-677.
9. van Vliet EP, Heijenbrok-Kal MH, Hunink MG, et al. Staging investigations for oesophageal cancer: a meta-analysis. *Br J Cancer*. 2008;98:547-557.
10. Wang SJ, Lemieux A, Kalpathy-Cramer J, et al. Nomogram for predicting the benefit of adjuvant chemoradiotherapy for resected gallbladder cancer. *J Clin Oncol*. 2011;29:4627-4632.
11. Akaike H. A new look at the statistical model identification. *IEEE Trans Autom Control* 1974;19:716-723.
12. Swisher SG, Hofstetter W, Wu TT, et al. Proposed revision of the esophageal cancer staging system to accommodate pathologic response (pP) following preoperative chemoradiation (CRT). *Ann Surg*. 2005;241:810-817; discussion 817-820.
13. Donahue JM, Nichols FC, Li Z, et al. Complete pathologic response after neoadjuvant chemoradiotherapy for esophageal cancer is associated with enhanced survival. *Ann Thorac Surg*. 2009;87:392-398.
14. Brucher BL, Becker K, Lordick F, et al. The clinical impact of histopathologic response assessment by residual tumor cell quantification in esophageal squamous cell carcinomas. *Cancer*. 2006;106:2119-2126.
15. Gaur P, Sepesi B, Hofstetter WL, et al. A clinical nomogram predicting pathologic lymph node involvement in esophageal cancer patients. *Ann Surg*. 2010;252:611-617.
16. Suzuki A, Xiao L, Hayashi Y, et al. Nomograms for prognostication of outcome in patients with esophageal and gastroesophageal carcinoma undergoing definitive chemoradiotherapy. *Oncology*. 2012;82:108-113.
17. Streyerberg EW, Neville BA, Koppert LB, et al. Surgical mortality in patients with esophageal cancer: development and validation of a simple risk score. *J Clin Oncol*. 2008;24:4277-4283.
18. Grotenhuis BA, van Hagen P, Reitsma JB, et al. Validation of a nomogram predicting complications after esophagectomy for cancer. *Ann Thorac Surg*. 2010;90:920-925.
19. Rice TW, Rusch VW, Apperson-Hansen C, et al. Worldwide esophageal cancer collaboration. *Dis Esophagus*. 2009;22:1-8.
20. Chirieac LR, Swisher SG, Ajani JA, et al. Posttherapy pathologic stage predicts survival in patients with esophageal carcinoma receiving preoperative chemoradiation. *Cancer*. 2005;103:1347-1355.
21. Kalha I, Kaw M, Fukami N, et al. The accuracy of endoscopic ultrasound for restaging esophageal carcinoma after chemoradiation therapy. *Cancer*. 2004;101:940-947.
22. Ajani JA, Correa AM, Hofstetter WL, et al. Clinical parameters model for predicting pathologic complete response following preoperative chemoradiation in patients with esophageal cancer. *Ann Oncol*. 2012;23:2638-2642.
23. Omloo JM, van Heijl M, Hoekstra OS, et al. FDG-PET parameters as prognostic factor in esophageal cancer patients: a review. *Ann Surg Oncol*. 2011;18:3338-3352.
24. Fockens P, Van den Brande JH, van Dullemen HM, van Lanschot JJ, Tytgat GN. Endosonographic T-staging of esophageal carcinoma: a learning curve. *Gastrointest Endosc*. 1996;44:58-62.

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A user-friendly Web-based survival prediction tool for patients with esophageal cancer was developed and implemented. This tool is of potential use for patients and practitioners and provides personalized outcome estimates.