Original Article

Prognostic models for stage I–III esophageal cancer: a comparison between existing calculators

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Background: Determining the best approach for esophageal cancer and predicting accurate prognosis are critical. Multiple studies evaluated characteristics associated with overall survival, and several prediction models have been developed. This study aimed to evaluate existing models and perform external validation of selected models.

Methods: A retrospective investigation of a multi-site institutional enterprise for patients with a diagnosis of esophageal cancer between 2013–2014 was performed. Selected survival prediction models included the Roswell Park Comprehensive Cancer Center (RPCCC) calculator, Oregon Health & Science University (OHSU) calculator, and two nomograms published by Shapiro *et al.* and Sun *et al.* One-year overall survival, level of agreement, and performance for each model were evaluated.

Results: A total of 104 patients were included and used to assess the prediction models. One-year overall survival was 0.76. Different calculators tended to rank patients similarly; however, they did not agree on predicted overall survival. The least disparity in correlation was observed between OHSU and Shapiro calculators. Shapiro's model achieved the highest performance [area under the curve (AUC) =0.63].

Conclusions: Selected models showed fair results in estimating individual overall survival, although none achieved a high performance. While these tools may support the decision-making process for esophageal cancer patients, their implementation in clinical practice requires improved refinement to optimize their clinical utility.

Keywords: Esophageal cancer; overall survival (OS); calculator; nomogram; neoadjuvant chemoradiation

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Introduction

Esophageal cancer (EC) is the sixth leading cause of cancer-related death and the eighth most common cancer worldwide (1). It is one of the most lethal tumors and is considered to have significantly poorer prognosis than other gastrointestinal neoplasms. In 2018, 17,290 new EC cases and 15,850 EC-related deaths were estimated in the United States (2).

Although the incidence of esophageal squamous cell carcinoma remains stable, the incidence of esophageal adenocarcinoma (EA) has increased dramatically in the

developed world in the last half century, positioning itself as the most dominant histological subtype of EC (3). There seem to be clear environmental influences, and predisposing factors (such as obesity, gastroesophageal reflux and Barrett's esophagus) also play an essential role in the natural history of EA (4-6).

Although the pathogenesis of EC is not fully defined, the underlying molecular changes are being investigated (7). Accordingly, there have been advances in the management of EC that have led to clinically relevant improvements in patient outcomes. Modern neoadjuvant chemoradiotherapy (CRT) followed by esophagectomy has surfaced as a promising approach, for stage II and III patients, to downstage and achieve pathological complete response (PCR), while improving overall survival (OS) (8-11). The most important randomized trial was performed by the Chemoradiation for Oesophageal Cancer Followed by Surgery Study (CROSS) group, which reported improved outcomes in terms of complete resection (R0) and median OS for patients with esophageal or esophagogastric-junction cancer with stages cT1N1 and cT2-3N0-1 after preoperative weekly administration of carboplatin, paclitaxel and concurrent radiotherapy compared with the surgery group alone (8). Currently, the CROSS trial represents the benchmark for the standard of care in patients with EC.

However, determining the most accurate therapeutic strategy for each patient remains challenging, and predicting survival represents a critical aspect for patients diagnosed with cancer. The presence of lymph node metastasis has been shown to be a significant prognosis factor for survival in EC patients (12,13). In addition to the stage of the disease, the response to therapy has also been reported to be strongly associated with survival rate (14-16). Nonetheless, these sole characteristics are not sufficient to estimate accurate prognosis for individual patients as multiple other patient-, tumor- and treatment-related factors are important predictors for OS (17,18).

To address this gap, several calculators and nomograms have been developed for patients diagnosed with EC (19-25). In order to increase accuracy, some of them have been designed for specific disease (metastatic or non-metastatic) or population (surgical vs non-surgical patients) settings. The following models, for instance, have been developed to assess individual OS for patients diagnosed with non-metastatic EC who undergo surgery after neoadjuvant CRT (nCRT): (I) Roswell Park Comprehensive Cancer Center (RPCCC) calculator (20); (II) Oregon Health & Science University (OHSU) calculator (19), and two nomograms published by (III) Shapiro *et al.* (22) and (IV) Sun *et al.* (23), respectively. Although the target population is similar, these models differ in the number and type of variables included to predict survival. Therefore, concordance among them can be often variable. The aims of this current study are to evaluate these chosen calculators and demonstrate their accuracy and performance in predicting OS for individual patients with stage Ib–III EC. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/jgo-20-337).

Methods

This retrospective analysis of a multi-site institutional experience was performed for patients with a diagnosis of clinical stage Ib–III EC. We selected calculators or nomograms that included EA and those that had surgery with or without neoadjuvant chemotherapy or radiation therapy as part of the multidisciplinary management of EA. Therefore, surgery and receipt of neoadjuvant therapy had to be included in the calculator or nomogram variables. We also excluded tools derived only from the treatment of squamous cell cancer as well as tools that did not explicitly include neoadjuvant chemotherapy, in order to provide more homogeneity and generalizability within the comparative analysis. The tools that met these criteria included the RPCCC and OHSU calculators and the nomograms developed by Shapiro *et al.* and Sun *et al.*

The selection of patients was limited to diagnoses made from January 2013 to December 2014 because patients from the National Cancer Data Base (NCDB) between 2006 and 2012 are included in the RPCCC calculator. Thus, we required an external cohort of patients outside the years used in the above-mentioned calculator due to Mayo Clinic's participation in the NCDB in order to perform an appropriate external validation. This aspect did not affect the other calculators since they were developed using either patients prior to 2011 or from different databases. Specifically, the OHSU calculator and the nomogram published by Sun were based on the Surveillance Epidemiology and End Results (SEER) and were comprised of patients from 1995 to 2007 and 2006 to 2012, respectively (19,23). The nomogram published by Shapiro was instead based on patients recruited in CROSS-I (2001–2004) and CROSS-II (2004–2009) trials, and patients treated at the Erasmus MC in Rotterdam or at the Academic Medical Centre in Amsterdam (post-CROSS, 2009–2013).

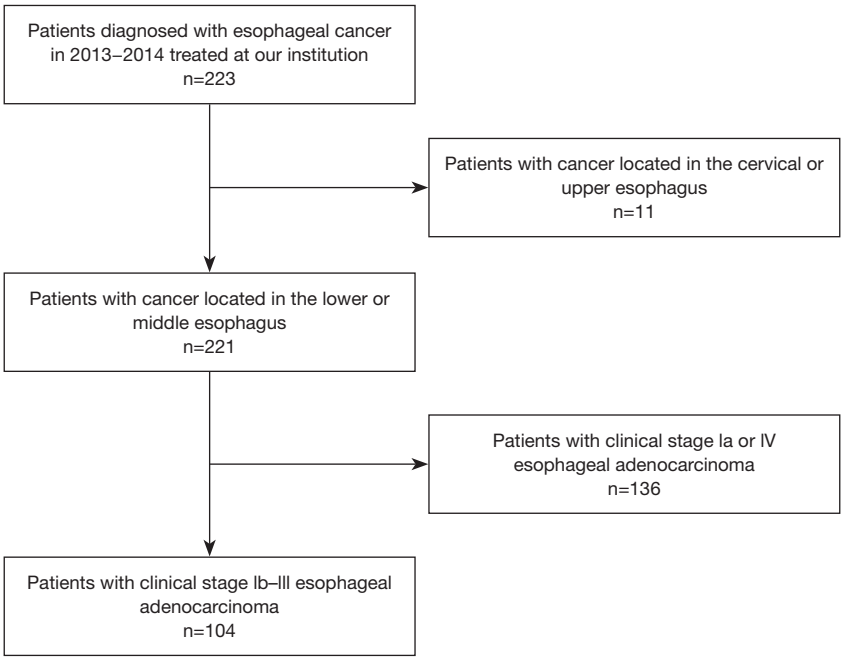


Figure 1 Inclusion and exclusion criteria used for patient selection for the comparison of the calculators.

Patients with clinical stage Ib–III adenocarcinoma of the middle and lower third of the esophagus who underwent surgery were included in the analysis. Patients with cancer located in the cervical and/or upper third of esophagus, carcinoma *in situ*, and more than one recorded malignancy were excluded from the study. *Figure 1* outlines our study's inclusion and exclusion criteria.

The following variables were collected: age at diagnosis, sex, marital status, Charlson-Deyo comorbidity score, histology, clinical and pathological T and N stages, tumor grade, number of harvested lymph nodes, chemotherapy, radiotherapy, and surgery status. *Table 1* summarizes the selected OS calculators' specific variables.

Statistical analysis

The subject characteristics were summarized using the mean, median, and standard deviation for continuous variables; and using frequencies and relative frequencies for categorical variables. Standard Kaplan-Meier methods were used to summarized OS; where estimates of median and 1-/3-year survival were achieved with 95% confidence intervals.

Each calculator's survival scores were summated using the mean, median, and standard deviation. A scatter plot matrix was used to visually examine the association between scores from different calculators, while the intra-class correlation coefficient (ICC) assessed their agreement. Each model's performance was assessed separately using the area under the 1-year receiver operating characteristic (ROC) curve (AUC) and calibration plot. No formal comparison was made across models. All analyses were conducted at a significance level of 0.05 in SAS v9.4 (Cary, NC, USA).

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was deemed exempt from the Mayo Clinic Florida Institutional Review Board (IRB), and informed consent was waived by our IRB as this retrospective study was deemed minimal risk to patients.

Results

Following the application of the selection criteria, a total of 104 patients were included. The overall patient, tumor, and treatment characteristics are listed in *Table 2*. The Kaplan-Meier curve in *Figure 2* shows OS for all comers and based on clinical stage. OS data were available for all 104 patients,

Table 1 Variables needed to calculate survival rates for each calculator

Variable	RPCCC	OHSU	Sun *et al.*	Shapiro *et al.*
Database	NCDB	SEER	SEER	Multisite
Age	•	•	•	
Sex		•	•	
Marital status			•	
Histology		•	•	
Pathological T stage		•		•
Pathological N stage		•		•
Clinical T stage	•		•	
Clinical N stage	•		•	•
Charlson-Deyo comorbidity score	•			
Grade	•		•	
N of lymph nodes harvested		•		
Radiotherapy			•	
Chemotherapy			•	
Surgery			•	
Outcomes	1-, 3-, 5-year OS: CRT + surgery; surgery alone	1-, 2-, 3-, 5-, 10-year OS: CRT + surgery; surgery alone Predicted median survival: CRT + surgery; surgery alone	1-, 3-year OS: any combination	1-, 5-year OS: CRT + surgery

RPCCC, Roswell Park Comprehensive Cancer Center; OHSU, Oregon Health State University; NCDB, National Cancer Data Base; SEER, Surveillance Epidemiology and End Results; OS, overall survival; CRT, chemoradiation therapy.

of which 56 experienced an event (morality). The median survival time was 37.5 months [95% confidence interval (CI): 26.3–52.2], and the 1-year OS was 0.76 (95% CI: 0.67–0.84). The median follow-up was 48.8 months.

Figure 3 shows the scatter plot matrix used to evaluate the agreement for each calculator. When examining how the survival scores performed individually, the scatter plot matrix indicates that patients were likely to be ranked similarly among the different calculators. That is, if a patient received the highest survival score using the Roswell Park calculator, then that patient tended to get one of the highest scores on the other three calculators, as indicated by the Spearman correlation coefficients. Interestingly, the calculators did not agree on predicted survival estimates, as indicated by the low ICC. The OHSU and Shapiro risk calculators appeared to have a reasonable level of agreement, but the other calculators had limited agreement. The highest level of agreement was observed between OHSU and Shapiro calculators (ICC 0.719), while the lowest occurred between OHSU and RPCCC calculators (ICC –0.055), which was due to the survival scores of RPCCC being the most optimistic.

The analysis of the performance of the calculators is reported in *Figure 4*. All the calculators performed similarly (AUC: min 0.5280–max 0.6313), with Shapiro calculator achieving the highest performance (AUC =0.6313). It is important to note that no formal statistical comparison of these 4 calculators was performed.

Discussion

The development of different models estimating OS has increased in the recent years, and their performance can provide useful information for the decision-making process and a more tailored approach to patient care (19,20,22-30). In this study, an external validation and comparison between selected

Table 2 Baseline characteristics used to compare survival calculators

Characteristics	Subcategory	Overall, n (%)
Overall	N	104 (100.0)
Age (years)	Mean/Std.	63.3/9.7
Sex	Male	93 (89.4)
	Female	11 (10.6)
Marital status	Married	87 (83.7)
	Single	17 (16.3)
Charlson-Deyo score	0	18 (17.3)
	1	35 (33.7)
	2	51 (49.0)
Clinical T	1	14 (13.5)
	2	23 (22.1)
	3	64 (61.5)
	4	3 (2.9)
Clinical N	0	37 (35.6)
	1	50 (48.1)
	2	14 (13.5)
	3	3 (2.9)
Pathological T	0	20 (19.2)
	1	28 (26.9)
	2	19 (18.3)
	3	36 (34.6)
	4	1 (1.0)
Pathological N	0	61(58.7)
	1	22 (21.2)
	2	16 (15.4)
	3	5 (4.8)
Grade	1	5 (4.9)
	2	37 (35.9)
	3	60 (58.3)
	4	1 (1.0)
Nodes examined	Mean/Std.	22.7/12.6
	Median/Min./Max.	20.0/3.0/84.0
Nodes positive	Mean/Std.	1.6/3.0
	Median/Min./Max.	0.0/0.0/17.0
Neoadjuvant CRT	No	5 (4.8)
	Yes	99 (95.2)

CRT, chemoradiation therapy.

existing calculators was performed with the intention of achieving an evaluation of their accuracy. Moreover, the comparison among calculators describes which oncologic specific factors were most reliable for creating an accurate model.

The Shapiro calculator achieved the best performance when examining the performance of the calculators in estimating 1-year survival rates (AUC =0.63). Herein, Shapiro *et al.* (22) used the pretreatment cN category and post-treatment ypN and ypT categories to develop their nomogram. In accordance to previous studies, the number of lymph nodes with metastasis has shown to be strongly associated with survival in patients with EA who receive preoperative chemoradiation (31,32). The OHSU risk calculator achieved a reasonable performance, being the second most accurate one (AUC =0.56). Interestingly, this nomogram also calculates the predicted survival benefit from CRT according to the ypTNM stage. Expectedly, both the OHSU and Shapiro calculators had the highest level of agreement (ICC =0.72). The Sun and RPCCC risk calculators, by contrast, showed a lower performance (AUC =0.53 and 0.52, respectively), even though these included a higher number of variables in their models.

It is challenging to explain the reasons underlying the non-optimal performances achieved by the calculators herein compared. It is possible that the variables selected in each calculator are not the most suitable and/or more are needed to provide accurate estimates of survival rate. Additionally, the diagnostic accuracy of clinical staging may have influenced the performance of those models that consider it as a prognostic factor. Furthermore, proposed nCRT agents and regimens differed among patients, as well as not every patient completed their neoadjuvant treatment. Thus, the low performance and agreement among calculators is possibly biased by these unaccounted differences. However, the development of clinical prediction tools has been applied to a myriad of other site-specific neoplasms, as in colorectal cancer, where calculators achieved good results in predicting 5-year OS, with RPCCC model being the one that achieving the best performance (AUC =0.91) (33).

Despite the difficulty for explanation of our results and uncertainty of how variables affect survival prediction, this study is important as it provides the first attempt at external validation for these nomograms. External validation is critical for these calculators as this is the avenue for improvement and expansion to a clinical tool that can be used across patient populations. The RPCCC achieved the

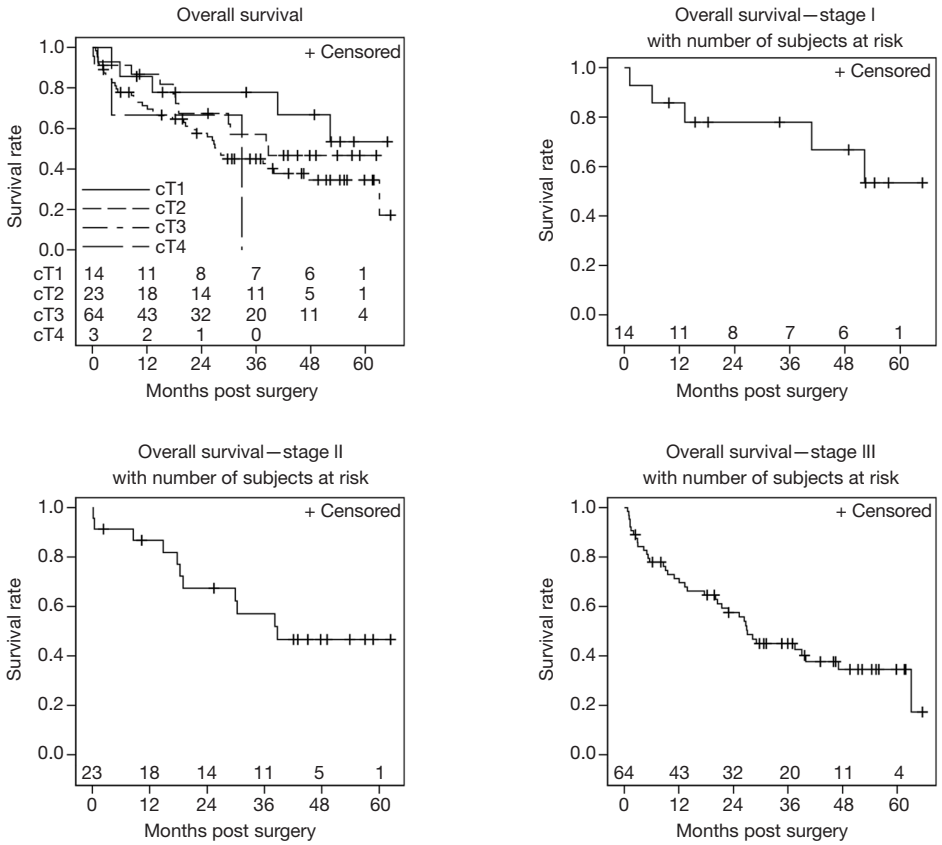
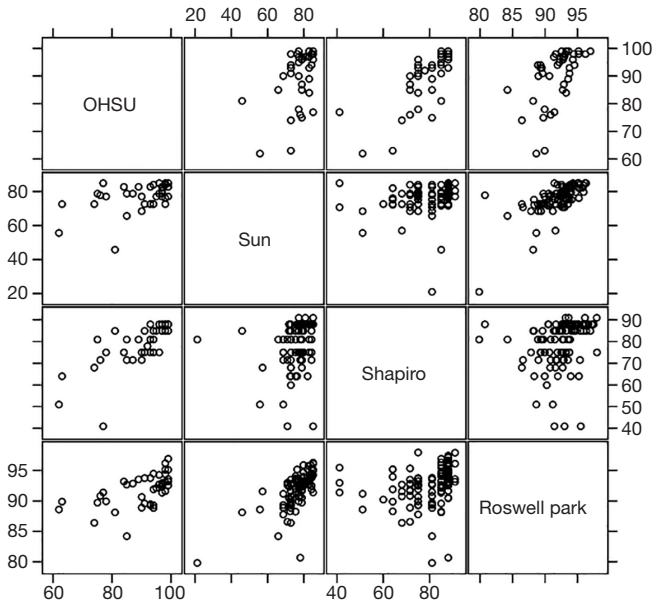


Figure 2 Kaplan-Meier curve showing 5-year OS for all-comers as well as by stage. cT, clinical T stage; OS, overall survival.

highest performance in a systematic review that evaluated nomograms with the Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies, the gold standard for nomogram comparison (34). Our study used a different, yet valid, comparison analysis. Our study shows the need for improvement of a superior calculator (RPCCC) due to the poor performance in our external validation of different statistical comparison to other nomograms. Future steps to improve the RPCCC nomogram should incorporate additional data and variables along with artificial intelligence (AI). AI is an emerging concept that may aid in diagnosis, prediction, treatment decision making and response (35). In terms of predicting outcomes, AI may be superior to a traditional TMN staging. By incorporating AI into a prediction nomogram, increased precision and accuracy can be achieved regardless the evaluation metric.

There are a number of limitations to our study. As with any retrospective study, this comparison may introduce bias in patient selection. An additional limitation to this study is that there are not clearly defined methods for the clinical diagnosis for T and N status. Commonly, clinical diagnosis is reported based on imaging [positron emission tomography (PET)-computed tomography (CT), magnetic resonance imaging (MRI), endoscopy] and biopsy, providing histological diagnosis. However, the specific preoperative diagnosis was not reported in our database. There was also a limited number of patients (n=104) in the available data which, subsequently, may alter the strength of the comparison. Nonetheless, our assessment of model performance was based on the AUC and calibration plots, which are unbiased and provide reasonable interval coverage even with just under 60 events. In this analysis, we did not compare all existing calculators that estimate survival rates for EC. For instance, the nomogram proposed by Xie *et al.* (25) for non-metastatic EC patients was not included because they selected patients who underwent only preoperative radiotherapy. Thus, it was not comparable to the population comprised in the calculators used. The prognostic models developed by Liu



Risk models	ICC	Spearman correlation coefficient
Overall (all models)	0.008	–
OHSU + Sun	0.352	0.37 (P=0.02)
OHSU + Shapiro	0.719	0.80 (P<0.01)
OHSU + Roswell Park	−0.055	0.61 (P<0.01)
Sun + Shapiro	0.220	0.41 (P<0.01)
Sun + Roswell Park	0.359	0.71 (P<0.01)
Shapiro + Roswell Park	0.101	0.40 (P<0.01)

Figure 3 Scatter plot matrix showing agreement between calculators. ICC, intra-class coefficient; OHSU, Oregon Health & Science University.

et al. and Tang *et al.* (21,24) included patients with M1 disease of EC. In the same way, the validated nomogram performed by Custodio *et al.* (36) was excluded because it focused on patients with unresectable locally advanced or metastatic adenocarcinoma of the distal esophagus, gastroesophageal junction, and stomach. Thus, these were all excluded from the comparison. Furthermore, predicting and comparing 1-year OS may provide limited applicability to clinical practice. Lastly, these equations and nomograms do not estimate OS instead of disease-free or disease-specific survival, which act as valid surrogates for OS (37) and provide more specific information about mortality rates directly related to cancer. However, the vast majority of recurrences in EA occur within 2 to 3 years of resection; therefore, in this study it would not be expected to differ significantly from the 1-year OS.

Despite these limitations, our analysis provides a valued juxtaposition among four EC survival nomogram models. We included patients from a multi-site Institution located in three different geographic regions in the United States, that provides important heterogeneity of the studied population, in addition to a robust statistical analysis. The Shapiro calculator estimated 1-year OS with superior performance, while the highest level of agreement was obtained by Shapiro and OHSU models, which share ypT and ypN stage as prognostic factors. The RPCCC model performed poorly in our external validation study despite superior performance in past studies. Subsequent steps will be taken to address our study's limitations and determine if higher performance can be achieved among these calculators.

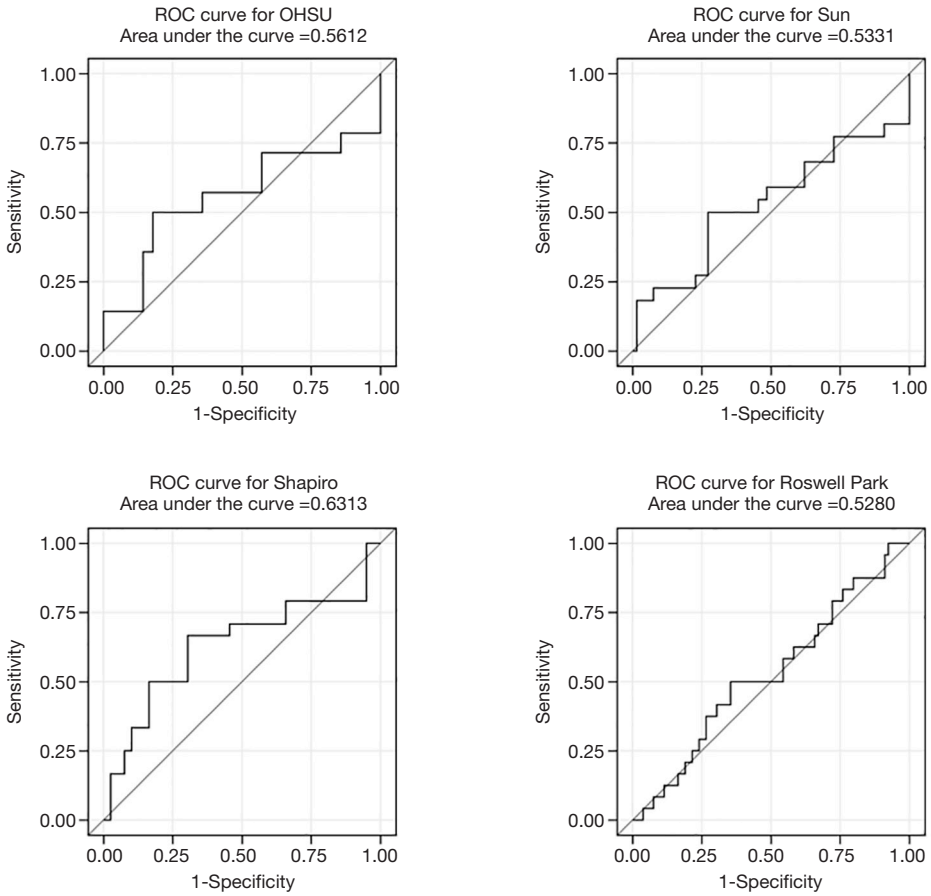


Figure 4 ROC curves showing calculators' performance. ROC, receiver operating characteristic.

Future plans include the addition of more patients prospectively, inclusion of AI, and increasing variables to include genetic/biologic variables that will likely be related to response to neoadjuvant chemotherapy and survival outcomes. In conclusion, although these tools may be used as a part of the decision-making process for EC patients, their value and implementation in clinical practice requires additional refinement to optimize their clinical utility.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://dx.doi.org/10.21037/jgo-20-337

Data Sharing Statement: Available at https://dx.doi.org/10.21037/jgo-20-337

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/jgo-20-337). Dr. RL reports grants from Mayo Clinic Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, during the conduct of the study. Dr. TDV reports grants from Mayo Clinic Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, during the conduct of the study. Dr. KA reports grants from Roswell Park Cancer Institute and National Cancer Institute, during the conduct of the study;

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Disclaimer: The American College of Surgeons Committee on Cancer provided the Participant User File from the National Cancer Data Base, but has not reviewed or validated the results or conclusions of our study.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was deemed exempt by the institutional review board of Mayo Clinic Florida, and individual consent for this retrospective analysis was waived as this retrospective study was deemed minimal risk to patients.

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