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Clinical parameters model for predicting pathologic complete response following preoperative chemoradiation in patients with esophageal cancer

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Background: Approximately 25% of patients with esophageal cancer (EC) who undergo preoperative chemoradiation, achieve a pathologic complete response (pathCR). We hypothesized that a model based on clinical parameters could predict pathCR with a high (≥60%) probability.

Patients and methods: We analyzed 322 patients with EC who underwent preoperative chemoradiation. All the patients had baseline and postchemoradiation positron emission tomography (PET) and pre- and postchemoradiation endoscopic biopsy. Logistic regression models were used for analysis, and cross-validation via the bootstrap method was carried out to test the model.

Results: The 70 (21.7%) patients who achieved a pathCR lived longer (median overall survival [OS], 79.76 months) than the 252 patients who did not achieve a pathCR (median OS, 39.73 months; OS, $P = 0.004$; disease-free survival, $P = 0.003$). In a logistic regression analysis, the following parameters contributed to the prediction model: postchemoradiation PET, postchemoradiation biopsy, sex, histologic tumor grade, and baseline $_{EUS}$T stage. The area under the receiver-operating characteristic curve was 0.72 (95% confidence interval [CI] 0.662–0.787); after the bootstrap validation with 200 repetitions, the bias-corrected AU-ROC was 0.70 (95% CI 0.643–0.728).

Conclusion: Our data suggest that the logistic regression model can predict pathCR with a high probability. This clinical model could complement others (biomarkers) to predict pathCR.

Key words: chemoradiation, esophageal cancer, esophageal preservation, nomogram, prediction of response

introduction

Esophageal cancer (EC) poses a significant health burden around the world [1, 2]. The incidence of adenocarcinoma has been rising dramatically in the West for decades [3–5]. EC is often diagnosed in its late stages, but ∼50% of patients have potentially curable disease. In patients who are physiologically fit for surgery and have a technically resectable EC, surgery alone results in a cure rate of <20% (stage II or III disease) [6]. Therefore, surgery is not favored as primary therapy for patients with clinical disease stage greater than cT1bN0. Combined modality therapeutic strategies have been implemented over the last 20 years to improve the cure rate. Preoperative chemoradiation [7] is favored over preoperative chemotherapy as a component of multimodality therapy [8–10] due to higher efficacy.

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Approximately 25% of patients with EC who undergo preoperative chemoradiation achieve a pathologic complete response (pathCR), defined as the absence of malignant cells in the resected specimen [11–15]. Many investigators have observed that a pathCR is associated with a longer overall survival (OS) duration [11–15]. Residual disease implies that the tumor is aggressive, chemoradiation resistant, and likely to have high metastatic potential [16]. Currently, no clinical parameters, including imaging studies, can be used to predict which patients will achieve a pathCR [17–21]. Similarly, biomarker studies have not established a validated signature that leads to the prediction of pathCR [22, 23]. Thus, because pathCR cannot be predicted, every patient who receives preoperative chemoradiation stands at a 25% probability of achieving a pathCR. However, the development of a model that predicts pathCR with a probability of ≥60% could allow for the investigation of novel treatment strategies.

Previous studies have shown that the rate of local recurrence after surgery is low in patients who achieve a pathCR [11, 16], but we cannot know the rate of local recurrence without

surgery in patients who achieve a pathCR because one cannot determine who has had a pathCR without examining the surgical specimen. The benefit of surgery in patients with EC who achieve a pathCR is unclear and is an important avenue for research. If pathCR could be predicted with high probability, then surgery could be used as a salvage procedure rather than as a planned procedure.

We hypothesized that if the relevant clinical parameters were selected (via univariate and multivariate analyses) in a large number of patients with EC (thus accounting for the inherent heterogeneity among these patients) and combined using the logistic regression method, a model to predict pathCR with a high probability (≥60%) could emerge. Such model could spur esophageal preservation strategies.

patients and methods

patients

We searched the prospectively maintained EC database in the Department of Thoracic and Cardiovascular Surgery at The University of Texas MD Anderson Cancer Center, to find consecutive patients who met all the required criteria to be included in the analysis.

All the patients who had a technically resectable tumor and were medically fit for surgery were eligible for this analysis. All the patients had chemoradiation followed by surgery, and their surgical specimens were scored for pathologic response using a validated process [24]. The patients were included only if they had all of the following additional information: baseline histologic confirmation, baseline histologic grade, results of upper gastrointestinal endoscopy with baseline clinical staging via endoscopic ultrasonography (EUS), baseline positron emission tomography (PET) results, postchemoradiation PET (done 5 or 6 weeks after the completion of chemoradiation) results, and postchemoradiation endoscopic biopsy results. Patient survival data were also collected. No other selection criteria were implemented. Staging was determined using the American Joint Committee on Cancer staging system [25]. The Institutional Review Board at MD Anderson approved this analysis.

therapy

Chemotherapy consisting of a fluoropyrimidine (i.v. or oral) and either a platinum compound or a taxane was given concurrently with a total radiation dose of 45–50.4 Gy, delivered in daily fractions of 1.8 Gy. The details of radiation therapy were similar to those published recently [26–28].

Approximately 5 or 6 weeks after the completion of chemoradiation, all the patients underwent esophagectomy and lymph node dissection with curative intent. Either transthoracic (Ivor-Lewis), transhiatal, total (three-field technique), or minimally invasive esophagectomy was performed at the discretion of the treating surgeon.

follow-up and survival

The patients were monitored periodically until at least 5 years after surgery or until death. Additional follow-up data were obtained from the MD Anderson tumor registry, hospital records, and the Social Security Death Index. Follow-up time was calculated from the date of surgery to the event (death, recurrence, or to the date of last contact).

statistical analysis

Data were collected prospectively using a standardized protocol. The death and event rates were calculated according to the Kaplan–Meier method, and the differences were assessed using the log-rank test. A univariate logistic regression model was utilized to examine the association between each clinicopathologic parameter and pathCR. Odds ratios with 95% confidence intervals (CIs) were used to quantify the strength of the association between parameters and pathCR. The preoperative parameters with a P value of ≤0.25 in the univariate analysis were entered into a multivariate logistic regression model. Using the Wald stepwise selection method with $P = 0.10$ as the entry and removal probability, we obtained the final model for the dataset.

All parameters that were statistically significant in the multivariate analysis were then used to construct a nomogram for predicting pathCR. A concordance index was obtained for the nomogram. Internal validation using the bootstrap method was then carried out to calculate a bias-corrected concordance index. All statistical analyses were carried out using the S-Plus 8.0 (rpart library; Tibco Software Inc., Palo Alto, CA) and SPSS 17.0 (SPSS Inc., Chicago, IL). Statistical significance was defined as $P < 0.05$.

results

patients

Supplementary Table S1, available at *Annals of Oncology* online shows relevant baseline patient and disease characteristics. As anticipated, most patients were men, and most patients had adenocarcinoma. The median tumor length as determined by baseline endoscopy was 5 cm. Of 322 specimens, 201 had poorly differentiated histology. The median baseline maximum standardized uptake value (SUV_{max}) of the primary tumor was 10.1 (range: 1–60).

Supplementary Table S2, available at *Annals of Oncology* online outlines patient and disease characteristics after therapy (postchemoradiation data). The median postchemoradiation SUV_{max} was 4 (0–44.1). Intriguingly, postchemoradiation biopsy revealed no cancer cells in almost 79% of patients but only 21.74% of patients had a pathCR.

OS and DFS

The median OS of the entire population was 48.033 months (95% CI 41.893–53.334 months). As of this writing, 26.1% of pathCR patients and 40.9% of non-pathCR patients have died. The median OS was 79.767 months (95% CI 56.402–77.528 months) in pathCR patients and 39.733 months (95% CI 41.893–53.334 months) in non-pathCR patients. This difference was statistically significant ($P = 0.004$; Supplementary Figure S1A, available at *Annals of Oncology* online).

The median DFS of the entire cohort was 42.10 months (95% CI 43.981–55.179 months). As of this writing, 32.8% of pathCR patients and 47.5% of non-pathCR patients have had recurrence and/or disease-specific death. The median DFS was 79.767 months (95% CI 53.273–75.142 months) in pathCR patients and 30.40 months (95% CI 38.263–49.979 months) in non-pathCR patients. This difference was statistically significant ($P = 0.003$; Supplementary Figure S1B, available at *Annals of Oncology* online).

univariate analysis

Variables were selected for inclusion in multivariate analysis on the basis of their significance in the univariate analysis (Supplementary Table S3, available at *Annals of Oncology* online); in addition, we selected other variables that have

prognostic relevance (e.g. tumor length [29], grade of differentiation [30], postchemoradiation SUV_{max} [31], and postchemoradiation endoscopic biopsy [32]). However, the inclusion of variables such as age, sex, and baseline T and N categories in the logistic regression analyses was generic. Our goal was to create a model that could be easily integrated in community practice and would be amenable to prospective validation.

Several parameters (e.g. age, tumor length, baseline, and postchemoradiation SUV_{max}) were tested as continuous variables in addition to their dichotomized values based on the median. Several variables [sex, histology, differentiation, baseline SUV, postchemoradiation SUV, primary tumor length, baseline T (but not N) category, and postchemoradiation biopsy results] were significantly associated with pathCR in the univariate analysis and were included in the multivariate analysis.

multivariate analysis

Table 1 shows the finalized multivariate analysis, in which five variables were associated with a higher chance of achieving pathCR (female sex, well or moderately differentiated histology, the absence of cancer cells on postchemoradiation biopsy specimens, lower postchemoradiation SUV_{max}, and baseline T category). It is not clear why the female gender was associated with pathCR, but the absence of cancer cells on postchemoradiation biopsy specimens and lower postchemoradiation SUV are consistent with a chemoradiation-sensitive EC. None of these variables can individually predict pathCR with a high (≥60%) probability; therefore, we constructed a nomogram by combining these significant variables.

nomogram

The nomogram (Figure 1) demonstrates that combining five variables can increase the probability of predicting pathCR to as high as 80% if a patient scores >160 points. Among the most influential factors for attaining the highest scores for predicting pathCR were lower postchemoradiation SUV_{max} and the absence of cancer cells on postchemoradiation biopsy specimens. Nine patients with resectable T4 disease skewed our data on the influence of baseline T category. Our results suggest that a patient with $_{EUS}$T4 disease at baseline would score more points than a patient with $_{EUS}$T1–3 disease at baseline, but this finding was likely due to the small number of patients with $_{EUS}$T4 disease. However, to avoid any selection bias, we elected not to remove patients with $_{EUS}$T4 disease from this analysis (all the patients who met the minimum eligibility requirements for this project were included from our entire database). Supplementary Table S4, available at *Annals of Oncology* online provides a three-patient scenario with total scores and predicted probability of pathCR.

The area under the receiver operating characteristic curve (AU-ROC) was 0.72 (95% CI 0.662–0.787), and after bootstrap validation with 200 repetitions, the bias-corrected AU-ROC was 0.70 (95% CI 0.643–0.728).

discussion

The outcomes of patients treated primarily with surgery and their OS curves for pathologic stage demonstrate that EC is a heterogeneous disease [6]. However, similar degree of heterogeneity is obvious even after multimodality therapy [27]. The aggressive tumor biology and resistance to therapy are most likely driven by genotypic alterations in the tumor DNA and its ability to adapt to injury (e.g. from chemoradiation) and evade apoptosis. In that respect, localized EC is an excellent model to study therapy resistance because most

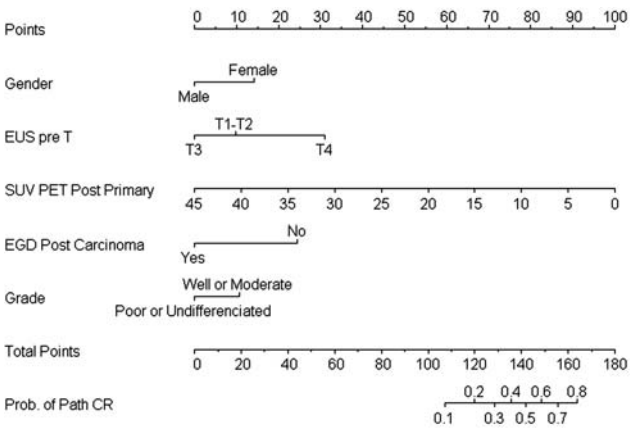

Figure 1 Nomogram for predicting pathCR based on clinical variables.

Table 1. Finalized multivariate logistic regression for outcome of pathCR

Variable	Subcategories	Frequency	*P*	Odds ratio	95% CI	
					Upper bound	Lower bound
Sex	Male (reference)	282	0.024	1.0		
	Female	40		2.438	1.122	5.297
Differentiation	Poorly differentiated (reference)	201	0.021	1.0		
	Well or moderately differentiated	121		1.966	1.107	3.491
Postchemoradiation biopsy results	Cancer (reference)	68	0.021	1.0		
	No cancer	254		4.647	1.706	12.658
Baseline T category	T3 (reference)	268	0.015	1.0		
	T1+2	45	0.107	1.844	0.877	3.878
	T4	9	0.011	7.035	1.575	31.419
Postchemoradiation SUV	Continuous	322	0.030	0.869	0.766	0.987

SUV, standardized unit value; pathCR, pathologic complete response; CI, confidence interval.

patients with localized EC receive preoperative chemoradiation, an examination of the surgical specimen shows the therapeutic effect (i.e. pathCR or non-pathCR), and this information is prognostic [11–15]. If we could predict the extreme categories of therapeutic effects such as pathCR or high degrees of resistance (defined by gross residual disease in the surgical specimen) [12, 24], then perhaps we could develop individualized treatment approaches according to these predictions. The tools that provide such information with high accuracy are desirable.

Could we preserve the esophagus of a patient who is expected to achieve a pathCR? Could we avoid chemoradiation-associated morbidity in a patient who has chemoradiation-resistant EC? Can we correctly identify a patient with EC who will benefit from chemoradiation and surgery? These questions cannot be answered until we develop models that can predict outcomes in patients with EC and those models are easily replicated. In this analysis, we focused on the prediction of pathCR. By combining variables that were independently associated with pathCR, we created a predictive model. We found that postchemoradiation SUV had the highest contribution in the nomogram followed by postchemoradiation biopsy results. If a patient with EC scores >160 points (before surgery), then the likelihood of achieving a pathCR is ≥60%. Clearly, this model must be replicated and validated before it can be further tested in the clinical decision-making process. As developed, this nomogram cannot be implemented in the clinic but will need considerable refinement and the development of complementary models. A focused investigation of predictive biomarkers could be of value. If a biomarker signature could be developed for the prediction of pathCR, it too could be integrated in this nomogram. However, the development of such a biomarker would be quite challenging and would require considerable effort.

We acknowledge the weaknesses in our analysis; they include its retrospective nature, the limited number of patients analyzed, and the need for replication and validation. However, our analysis was strengthened by the inclusion of variables that are practical and transportable to community oncology, its cross-validation, and its novel findings.

Our practical model for predicting pathCR in patients with EC is a preliminary step toward the development of an esophagus preservation strategy. The presented model needs to be replicated and then prospectively validated before it can be implemented in clinical practice. The integration of relevant biomarkers in this model may further improve its usefulness.

funding

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disclosure

The authors have declared no conflicts of interest.

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Survival analysis and prognostic nomogram for patients undergoing resection of extrahepatic cholangiocarcinoma

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Background: Tumor location of extrahepatic cholangiocarcinoma (CCA) might influence survival after resection.
Methods: A consecutive series of 175 patients who had undergone a potentially curative resection of extrahepatic CCA was analyzed. We calculated concordance indices of different constructed prognostic models for survival including TNM (tumour–node–metastasis) staging and developed a nomogram of the most sensitive model.
Results: Overall cancer-specific survival rates were 83%, 58%, and 26% at 1, 2, and 5 years, respectively. Cancer-specific survival according to location was 42% for proximal, 23% for mid, and 19% for distal CCA after 5 years. Tumor location was not an independent significant predictor ($P = 0.06$). A prognostic model using all potential prognostic variables predicted survival better compared with TNM staging (concordance index 0.65 versus 0.63). A reduced model containing only lymph node status, microscopically residual tumor status, and tumor differentiation grade, also outperformed TNM staging (concordance index 0.66).
Conclusions: Tumor location of extrahepatic CCA does not independently predict cancer-specific survival after resection. We developed a nomogram, based on a prognostic model with lymph node status, microscopically residual tumor status of resection margins, and tumor differentiation grade, that predicted survival better than TNM staging.
Key words: cancer-specific survival, extrahepatic cholangiocarcinoma, prognostic model, tumor location

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