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Prediction Model for Estimating the Survival Benefit of Adjuvant Radiotherapy for Gallbladder Cancer

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ABSTRACT

Purpose
The benefit of adjuvant radiotherapy (RT) for gallbladder cancer remains controversial because most published data are from small, single-institution studies. The purpose of this study was to construct a survival prediction model to enable individualized predictions of the net survival benefit of adjuvant RT for gallbladder cancer patients based on specific tumor and patient characteristics.

Methods
A multivariate Cox proportional hazards model was constructed using data from 4,180 patients with resected gallbladder cancer diagnosed from 1988 to 2003 from the Surveillance, Epidemiology, and End Results database. Patient and tumor characteristics were included as covariates and assessed for association with overall survival (OS) with and without adjuvant RT. The model was internally validated for discrimination and calibration using bootstrap resampling.

Results
On multivariate regression analysis, the model showed that age, sex, papillary histology, stage, and adjuvant RT were significant predictors of OS. The survival prediction model demonstrated good calibration and discrimination, with a bootstrap-corrected concordance index of 0.71. The model predicts that adjuvant RT provides a survival benefit in node-positive or ≥ T2 disease. A nomogram and a browser-based software tool were built from the model that can calculate individualized estimates of predicted net survival gain attributable to adjuvant RT, given specific input parameters.

Conclusion
In the absence of large, prospective, randomized, clinical trial data, a regression model can be used to make individualized predictions of the expected survival improvement from the addition of adjuvant RT after gallbladder cancer resection.

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INTRODUCTION

Biliary tract cancers are relatively rare in the United States but carry a poor prognosis.[1] Gallbladder cancer is the most common biliary tract neoplasm, with an annual incidence of approximately 5,000 cases per year and an annual mortality of 2,800 deaths per year.[2] Surgery remains the only definitively curative therapy for resectable gallbladder cancer.[3] Even after complete resection, however, locoregional recurrence rates are high. Consequently, there is considerable interest in exploring the potential benefit of adjuvant chemotherapy and/or radiotherapy (RT). Because of the rarity of gallbladder cancer, the actual benefit of adjuvant therapy has not been well established.[4] Only small gallbladder studies are reported in the literature, some of which seem to indicate a potential benefit from adjuvant chemotherapy and/or RT.[5-7] Because of the rarity of gallbladder cancer, it may prove to be difficult to accrue sufficient numbers of patients for a large-scale prospective randomized clinical trial. As a result, clinicians currently have little evidence to rely on when attempting to determine whether adjuvant RT will be beneficial to their patients.

The specific aim of this study was to construct a survival prediction model to estimate the potential survival benefit of adjuvant RT after resection of gallbladder cancer. To this end, we constructed a Cox proportional hazards multivariate regression model based on the Surveillance, Epidemiology, and End Results (SEER) database,[8] the largest epidemiologic cancer registry in the United States. The goal was to construct a decision aid that can estimate the potential benefit of adjuvant RT for an individual gallbladder cancer patient.

METHODS

Study Population

The SEER database of the National Cancer Institute is the largest population-based cancer registry in the United States, covering approximately 26% of the US population. The SEER program registries collect data on patient demographics, primary tumor site, tumor morphology, cancer stage, and first course of treatment for all patients diagnosed with cancer in 17 defined geographic regions across the United States. For this analysis, the April 2006 release of the SEER 17 database was used for case extraction. The study cohort consisted of all SEER patients with resected gallbladder cancer diagnosed between 1988 and 2003. Initial patient selection was based on the SEER Site Recode "gallbladder" (equivalent to International Classification of Diseases for Oncology, third edition site code C239). Patients were included if they received surgical interventions with curative intent, namely, at least a simple cholecystectomy or any more extensive surgery. To this end, for patients diagnosed up through 1997, patients were included with "Site specific surgery (1983-1997)" field codes of 40 to 60 or 90. For patients diagnosed in 1998 or later, patients with "RX Summ–Surg Prim Site (1998+)" field codes between 30 and 90 were included.

Statistical Analysis

The primary end point of interest in this study was overall survival (OS), which was plotted using the life-table method and measured from the time of diagnosis. Multivariate regression analysis was performed using Cox proportional hazards modeling, and this model formed the basis for the survival prediction model. Covariates included in the prediction model were selected based on known clinically prognostic factors and availability in the SEER database. Included covariates were age, sex, race (white, black, or Asian/Pacific Islander), American Joint Committee on Cancer sixth edition TNM stage, papillary histology (yes or no), and adjuvant RT (yes or no). Discrete variables were converted to binary variables, and continuous variables were fitted to smoothed functions as per Harrell.[9] Interaction terms between RT and stage were also included to reflect the possible effects of stage on the benefit of adjuvant RT. Covariates that did not reach statistical significance were not excluded from the survival prediction model because it has been shown that inclusion of such variables can still improve the accuracy of a predictive model.[9] The prediction model was implemented into a nomogram to enable use on plain paper and also implemented as an Internet browser-based software application.

The survival prediction model was internally validated by measuring both discrimination and calibration. Discrimination was evaluated using the concordance index (C-index), which is similar in concept to the area under a receiver operating characteristic curve. The C-index measures the probability that, given a pair of randomly selected patients, the model correctly predicts which patient will experience an event first. The C-index of the model can range between 0.5, which represents random chance, and 1.0, which represents a perfectly discriminating model. The second validation measure evaluated was calibration, which compares the predicted survival with actual survival. This was evaluated with a calibration curve, where patients are grouped by predicted survival and then plotted as actual versus predicted survival. Both discrimination and calibration were evaluated on the original study cohort using bootstrapping with 200 resamples.[9]

All statistical analyses were performed using a software package called R (http://www.r-project.org/), with an optional module installed, called Design.[9] The Internet browser-based software tool was programmed in JavaScript.

RESULTS

A total of 4,180 patients met the inclusion criteria and were included in the study. The patient and tumor characteristics are listed in Table 1. Overall, 73% of the study population was female, and 80% was white. Papillary histology was found in 6% of patients. Forty percent of patients had T1 or T2 disease. Twenty-two percent had known node-positive disease. Actuarial OS plot for all patients is shown in Figure 1A. The median OS time for all patients was 10 months (95% CI, 9 to 11 months). The 1-year, 2-year, 3-year, and 5-year OS rates for the entire patient cohort were 46%, 30%, 23%, and 17%, respectively.

A total of 760 patients (18%) in this series received adjuvant RT after surgical resection. Patients with more locally advanced disease (T2 or greater, but not M1) and patients with node-positive disease were more likely to have received adjuvant RT (Table 1). The actuarial OS grouped by receipt of adjuvant RT is shown in Figure 1B. The

Table 1. Patient and Tumor Characteristics

Characteristic	No RT (n = 3,420)		RT (n = 760)		All (N = 4,180)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Age, years						
Median	73		67		72	
Range	18-102		23-90		18-102	
Female	2,555	75	551	75	3,106	73
Race						
White	2,812	82	611	80	3,423	80
African-American	265	8	62	8	327	8
Asian/Pacific Islander	343	10	87	11	430	10
Papillary histology	214	6	47	6	267	6
Stage						
T1	853	25	107	14	960	22
T2	568	17	177	23	745	17
T3	995	29	313	41	1,308	31
T4	218	6	68	9	286	7
M1	786	23	95	13	881	21
N0	1,580	46	313	41	1,893	44
N1	665	19	258	34	923	22

Abbreviation: RT, radiotherapy.

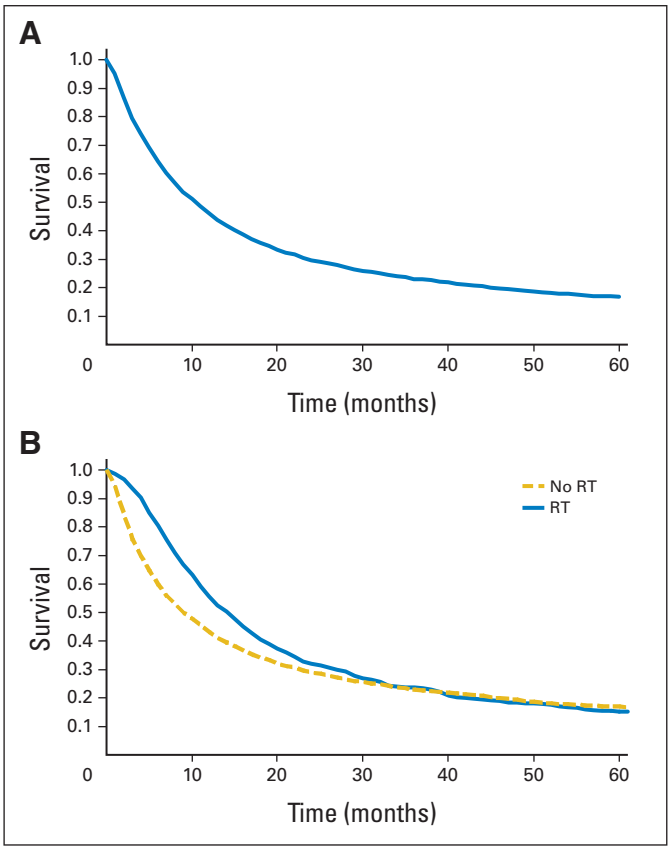

Fig 1. (A) Actuarial overall survival (OS) plot for all patients in study. Median OS time was 10 months. (B) Actuarial OS grouped by adjuvant radiotherapy (RT). The median OS time for patients who received RT was 15 months compared with 8 months for patients who did not receive RT (log-rank $P < .0001$).

Table 2. Cox Proportional Hazards Multivariate Regression Analysis Results

Covariate	β Coefficient	Hazard Ratio	95% CI	P
Age	0.0176	—*	—	.003
Age′	−0.0079	—*	—	.519
Age″	0.1647	—*	—	.032
Male	0.1204	1.13	1.02 to 1.25	.019
Race				
Asian or Pacific Islander	−0.1863	0.83	0.71 to 0.97	.014
Black	0.1014	1.11	0.94 to 1.31	.223
Papillary histology	−0.5799	0.56	0.45 to 0.69	< .001
T stage				
T2	0.2684	1.31	1.11 to 1.54	.001
T3	0.7918	2.21	1.91 to 2.55	< .001
T4	1.5367	4.65	3.75 to 5.76	< .001
Distant metastases, M1	1.6198	5.05	4.26 to 5.99	< .001
Node positive, N1	0.4013	1.49	1.33 to 1.68	< .001
Received RT	0.3755	1.46	1.07 to 1.98	.014
Interaction terms				
T2 × RT	−0.4414	0.64	0.44 to 0.95	.023
T3 × RT	−0.5196	0.59	0.42 to 0.84	.002
T4 × RT	−1.0081	0.36	0.23 to 0.58	< .001
M1 × RT	−0.6691	0.51	0.33 to 0.79	.002
N1 × RT	−0.308	0.73	0.58 to 0.93	.008

Abbreviation: RT, radiotherapy.
*Age was modeled using a restricted cubic spline function with three independent β coefficients, annotated as Age, Age′, and Age″, which yields an effective hazard ratio that varies continuously with age.

unadjusted median OS time for patients who received RT was 15 months (95% CI, 13 to 16 months) compared with 8 months (95% CI, 8 to 9 months) for patients who did not receive RT (log-rank $P < .0001$).

Results of the multivariate regression model are listed in Table 2. Statistically significant covariates were age, sex, Asian or Pacific Islander race, papillary histology, TNM stage, and receipt of adjuvant RT. As can be seen from the hazard ratios of the RT interaction terms, the influence of adjuvant RT on survival varies by stage. Nomograms were constructed from the β coefficients from this model. To estimate the net survival benefit from adjuvant RT, the two nomograms are used together (Figs 2A and 2B). The first nomogram (Fig 2A) estimates the predicted survival without adjuvant RT, and the second nomogram (Fig 2B) estimates survival with adjuvant RT. The difference between the two estimates is the expected net survival benefit from the addition of adjuvant RT. To use the nomogram, first draw a vertical line up to the top Points row to assign points for each variable. Then, add up the total points and drop a vertical line from the Total Points row to obtain the 12-month OS, 24-month OS, and median OS (in months). A software application was also implemented (Fig 3) that can calculate the estimated net survival benefit from the addition of adjuvant RT after the user enters the requested patient and tumor characteristics. This browser-based software tool is available for use at the Oregon Health and Science University Web site (http://www.ohsu.edu/radmedicine/predict.cfm).

Model performance was internally validated for discrimination and calibration. Discrimination, as measured by the bootstrap-corrected C-index, was 0.71. The calibration curve (Fig 4) showed good agreement between predicted and observed outcomes.

For patients with T1 disease, the survival model estimates no survival benefit from the addition of postoperative RT, regardless of nodal status or other factors. In comparison, the model predicts that patients with higher stage (T2 or greater), node-positive disease will derive the greatest net benefit from adjuvant RT. This can be seen from the hazard ratios of the RT interaction terms in Table 2. For example, for a hypothetical 70-year-old white female with T3N1 nonpapillary gallbladder carcinoma, the model predicts that the 2-year OS rate would increase from 17% to 33% with the addition of adjuvant RT, with the median survival time improving from 9 months to 14 months (Fig 2). Patients with node-negative disease may derive some benefit from adjuvant RT; however, this improvement is variable and may not be statistically or clinically significant. For example, for a 50-year-old white female with a T3N0 nonpapillary tumor, the model predicts that the 2-year OS rate may increase from 42% to 47% with the addition of adjuvant RT, but this benefit is not statistically significant at the $P = .05$ level. Patients with papillary histology had the most favorable outcomes overall, and the nomogram suggests potential for even further benefit from adding adjuvant RT; for example, for a 70-year-old white female with T3N1 papillary carcinoma, 2-year OS rate was predicted to increase from 38% to 54% with the addition of adjuvant RT.

DISCUSSION

In the absence of large, prospective, randomized controlled clinical trials, controversy continues over the role of adjuvant RT for resected

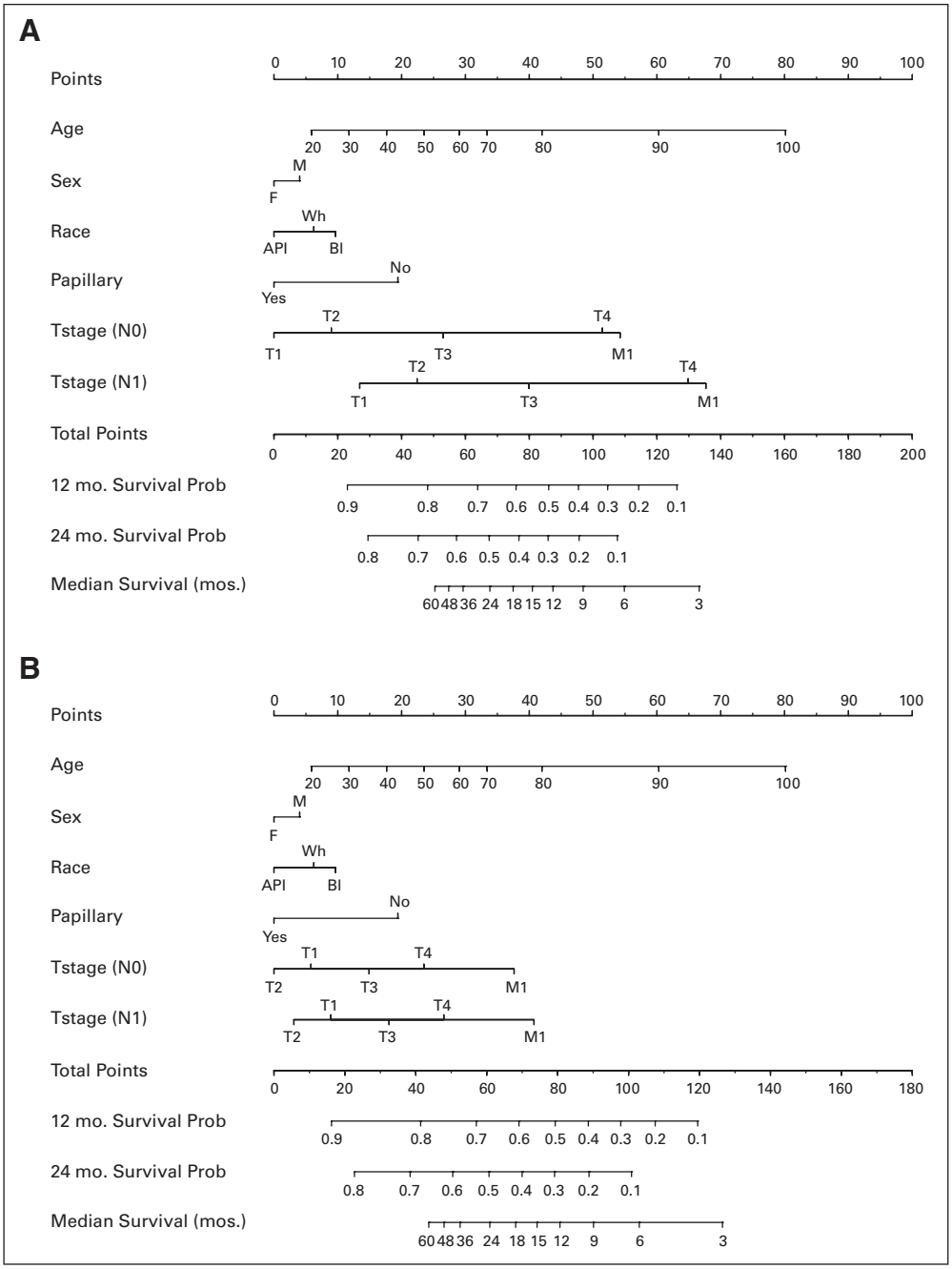

Fig 2. (A and B) Nomograms for comparing the expected survival with and without adjuvant radiotherapy (RT). For an individual patient, first use nomogram A to calculate the expected survival without adjuvant RT, and then use nomogram B to calculate the expected survival with adjuvant RT. The difference between the two estimates is the expected net survival gain from adjuvant RT. M, male; F, female; API, Asian or Pacific Islander; Wh, white; Bl, black; Prob, probability; mo., month.

gallbladder cancer. Several small retrospective studies on gallbladder cancer have been published; however, most are small single-institution studies.[5-7] Because most of these retrospective series on gallbladder cancer are small, many current recommendations regarding adjuvant treatment of gallbladder cancer are extrapolations from studies of pancreatic and/or biliary tract carcinomas. There is evidence, however, that the patterns of failure for gallbladder cancer are even different when compared with cholangiocarcinoma. Jarnagin et al[10] observed that gallbladder carcinoma has a higher incidence of distant metastases as a first site of failure compared with hilar cholangiocarcinoma. This finding, again, raised the question of whether an adjuvant locoregional therapy such as RT would actually improve OS. However, our SEER-derived model suggests that adjuvant RT can improve survival for specific subcohorts of patients, even after adjusting for other factors in multivariate analysis.

The outcomes predicted by our survival model are consistent with current National Comprehensive Cancer Network 2007 guidelines, which state that, although there is limited clinical trial data to support a standard regimen, all patients with stage higher than T1N0 should be considered for adjuvant therapy.

There are several limitations to this study. This study was performed using SEER data and, therefore, was limited to predictive factors available in this database. Adjuvant therapy for gallbladder cancer is often recommended in the form of chemoradiotherapy;

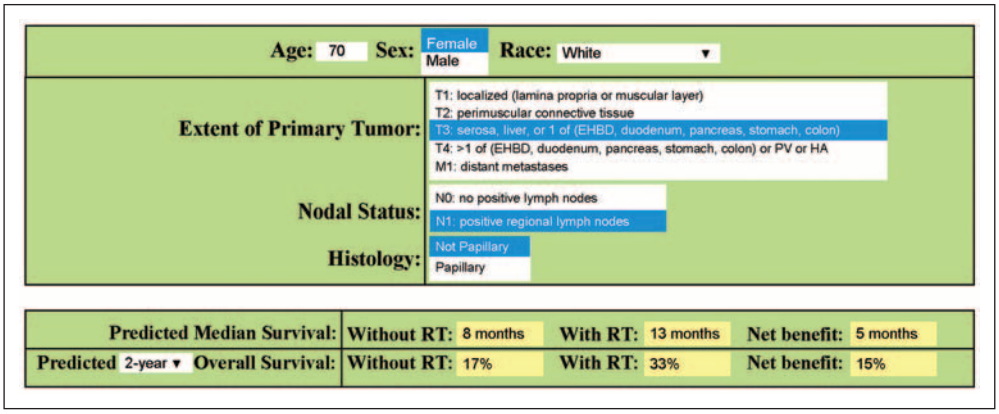

Fig 3. Browser-based software application that can be used to help make clinical decisions regarding the potential benefit of adjuvant radiotherapy (RT) for an individual patient. The system will calculate an individualized estimate of survival probability both with and without RT and then estimate the net survival benefit from the addition of adjuvant RT. This browser-based tool can be accessed at http://www.ohsu.edu/radmedicine/predict.cfm. EHBD, extrahepatic bile duct; PV, portal vein; HA, hepatic artery.

however, chemotherapy details are not available in SEER, which precluded inclusion of chemotherapy in our predictive model. SEER also does not have information regarding performance status, which is an important consideration when considering adjuvant therapies. SEER does not contain information on disease recurrence, so OS was used as our primary outcome measure.

In some cases, the model predicts that the addition of RT would result in either no added benefit or a small percentage of improvement, such as for node-negative disease. However, we did not specify a specific threshold at which adjuvant RT should be recommended; we believe that the final decision of whether adjuvant RT should be administered remains a decision that should be made after careful discussion between the clinician and patient, accounting for multiple factors, many of which cannot be accounted for in a prediction model. Although net potential survival benefit as predicted by this model is an important element of this discussion, it should not be the sole basis for decision making. Quality of life and specific patient preferences are also important considerations in treatment decision making.

Despite its limitations, as a population-based database, SEER still provides us with the largest series of gallbladder cancer patients available, which makes it a valuable resource for building predictive models for rare tumors when large numbers of patients are required. Consequently, no other currently available population-based registry can afford the statistical power of SEER for model building for gallbladder carcinoma. Although some have raised concerns about the heterogeneity of the SEER patient population and the actual treatments delivered, we believe this diversity may actually yield more realistic survival estimates that are reflective of cancer survival in actual practice across the country.

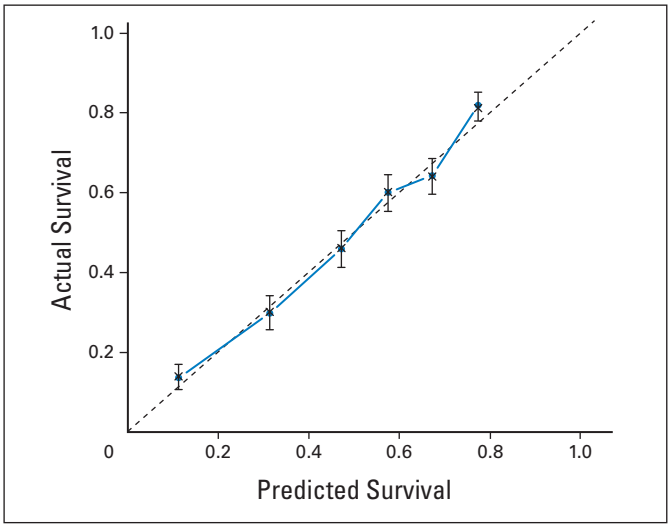

Fig 4. Calibration curve demonstrating how survival predictions from the model compare to the actual observed survival.

Recently, there has been growing interest in the development of cancer prediction models.[11] There are a number of important cancer risk prediction models being used today for prostate,[12-22] breast,[23-35] and pancreas cancer[36] and other cancer sites. Although prediction models can never substitute for evidence from large prospective randomized clinical trials, these tools are particularly useful to aid in clinical decision making in cases of rare tumors where no clinical trial data are available. Such models are certainly preferable to relying on any individual clinician's limited personal experience, and they may be more accurate than relying on extrapolation from other cancer sites. Customized survival predictions are also more relevant to individual patients compared with recommendations based on coarse groupings of large numbers of heterogeneous patients. Estimating survival probability solely based on stage is not always accurate because our model aptly illustrates how prognosis changes markedly with variation in other factors as well, such as patient age and histology. As more specific patient and tumor information becomes routinely collected in the future, such as genetic information and molecular tumor markers, use of these types of predictive models will become increasingly important.

Future efforts will seek to test our model performance in external validation using other patient databases. We will also explore the possibility of including additional prognostic variables using the SEER-Medicare linked database[37] to further improve the performance of the model. Other regression modeling techniques will also be explored to determine whether predictive accuracy can be further improved.[38,39]

In summary, we present a survival prediction model that can make an individualized estimate of the net survival benefit of adding adjuvant RT for gallbladder cancer patients. Our model predicts that patients with node-positive disease with stage T2 or higher will derive the greatest benefit from adjuvant RT. In the absence of prospective clinical trials, this tool can assist clinicians and patients in quantifying the benefit of adjuvant RT after surgical resection of gallbladder cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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