Nomogram for Predicting the Benefit of Adjuvant Chemoradiotherapy for Resected Gallbladder Cancer

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A B S T R A C T

Purpose

Although adjuvant chemoradiotherapy for resected gallbladder cancer may improve survival for some patients, identifying which patients will benefit remains challenging because of the rarity of this disease. The specific aim of this study was to create a decision aid to help make individualized estimates of the potential survival benefit of adjuvant chemoradiotherapy for patients with resected gallbladder cancer.

Methods

Patients with resected gallbladder cancer were selected from the Surveillance, Epidemiology, and End Results (SEER)–Medicare database who were diagnosed between 1995 and 2005. Covariates included age, race, sex, stage, and receipt of adjuvant chemotherapy or chemoradiotherapy (CRT). Propensity score weighting was used to balance covariates between treated and untreated groups. Several types of multivariate survival regression models were constructed and compared, including Cox proportional hazards, Weibull, exponential, log-logistic, and lognormal models. Model performance was compared using the Akaike information criterion. The primary end point was overall survival with or without adjuvant chemotherapy or CRT.

Results

A total of 1,137 patients met the inclusion criteria for the study. The lognormal survival model showed the best performance. A Web browser–based nomogram was built from this model to make individualized estimates of survival. The model predicts that certain subsets of patients with at least T2 or N1 disease will gain a survival benefit from adjuvant CRT, and the magnitude of benefit for an individual patient can vary.

Conclusion

A nomogram built from a parametric survival model from the SEER-Medicare database can be used as a decision aid to predict which gallbladder patients may benefit from adjuvant CRT.

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INTRODUCTION

Gallbladder cancer is the most common biliary tract neoplasm, with an annual incidence of almost 10,000 and annual mortality of 3,300.¹⁻³ Surgery remains the only definitively curative therapy.⁴ However, even after complete resection, locoregional recurrence rates are high. Consequently, there is considerable interest in exploring the potential benefit of adjuvant chemotherapy or chemoradiotherapy (CRT).⁵ Because of the rarity of this disease, most published gallbladder studies are small, single-institution series, some of which seem to indicate potential benefit from adjuvant chemotherapy or CRT.⁶⁻¹¹ Given the low incidence of biliary tract carcinomas, few attempts have been made to conduct large-scale prospective clinical

trials.¹² As a result, clinicians have little evidence to rely on when attempting to determine whether adjuvant therapy will be beneficial for a patient. It is likely that only certain subsets of high-risk patients gain benefit from adjuvant therapy, but determining which patients will benefit remains a challenge. In this setting, prediction models may provide insight into these important clinical questions.

The overall goals of this project were to construct a decision aid that can be used to predict which patients will obtain a survival benefit from adjuvant chemotherapy or CRT and estimate the magnitude of the benefit. The purpose was to provide additional information to clinicians and patients to aid in the decision-making process regarding adjuvant therapy.

We previously published a survival model¹³ built from the Surveillance, Epidemiology, and End Results (SEER) database¹⁴ that makes individualized predictions of the benefit of adjuvant radiotherapy for patients with gallbladder cancer. We undertook the current study to enhance this model by adding the effects of adjuvant chemotherapy using the SEER-Medicare linked database¹⁵ and construct an improved nomogram that utilizes alternative survival modeling techniques to predict the survival benefit of adjuvant chemotherapy and CRT.

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.¹⁴ The SEER-Medicare linked database¹⁵ is augmented with Medicare claims data, which can be used to obtain additional clinical information not contained in SEER, such as chemotherapy information.

The study cohort was created from the most recent 10 years of available data in the SEER-Medicare 2008 release,¹⁵ which includes claims from 1995 to 2007 linked to patients with cancer diagnosed from 1995 to 2005. Initial patients were selected using Site Recode = 31 for gallbladder cancer (4,459 patients). Patients were included in this study if they had nonmetastatic invasive disease and had undergone complete surgical resection of the primary site, with or without regional lymph node dissection (2,443 patients). The analysis was limited to patients older than 65 years of age with complete data records who had equal and continuous Medicare Parts A and B coverage during the first 6 months after diagnosis (1,487 patients). To account for postoperative mortality, 266 patients who survived fewer than 2 months after surgery were excluded. Eighty-four patients who received adjuvant radiotherapy alone were also excluded. Using the SEER Extent of Disease 10 fields for extent (*e10ex1*) and nodes (*e10nd1*), we grouped patients according to American Joint Committee on Cancer TNM staging (seventh edition).

Patients who received adjuvant external beam radiotherapy within the first 6 months of diagnosis (Patient Entitlement and Diagnosis Summary File *rad1* codes 1, 4, 5, or 6) were coded as having received adjuvant radiotherapy. 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 claims codes 96,400 to 96,599, Q0083-Q0085, or J8500-J9999 within 6 months of diagnosis were coded as having received adjuvant chemotherapy. Patients were considered to have received adjuvant chemoradiotherapy if they had received both radiotherapy and chemotherapy within 6 months after diagnosis.

Statistical Analysis

All statistical analyses were performed using the R software package (<http://www.r-project.org>). Covariates were selected based on our prior gallbladder nomogram work,¹³ known clinically prognostic factors, and availability in the SEER-Medicare database. Included covariates were age, sex, race, American Joint Committee on Cancer seventh edition TNM stage, and receipt of adjuvant chemotherapy or CRT. All covariates were treated as discrete and converted to binary variables, except for age, which was modeled as a continuous variable and fitted to a smoothed restricted cubic spline function as per Harrell.¹⁶ As per SEER-Medicare data use guidelines, stage groupings with fewer than 11 patients were grouped with the closest neighboring group. Interaction terms between treatment variables and stage were investigated to assess their influence on the benefit of adjuvant chemotherapy and CRT. We used a model-building approach promoted by Harrell,¹⁶ in which all covariates are included in the final model, with no stepwise variable selection performed.

We used a propensity score weighting method to balance observed covariates between treatment and observation groups.¹⁷ Propensity scores reflect the probability that a patient will receive therapy based on observed covariates.¹⁷ By assigning propensity score weights to each patient and incorporating these weights into model construction, we can reduce treatment bias inherent in retrospective nonrandomized regression analyses. Propensity scores were calculated using the *twang* R library (<http://cran.r-project.org/web/packages/twang/index.html>), with adjuvant CRT as the outcome of interest.

The primary end point in this study was overall survival. Multivariate regression survival analysis was performed using several survival modeling methods and results were compared. Details of our comparison of different survival modeling methods have been described previously.^{18,19} We built semiparametric models (Cox proportional hazards [CPH]) and accelerated failure time parametric models (Weibull, exponential, log logistic, and lognormal [LN]). All survival models were constructed using the *rms* R library by Harrell¹⁶ (<http://cran.r-project.org/web/packages/rms>). Model performance was compared using the Akaike information criterion (AIC), a measure of goodness of fit for statistical models, and the model with the best (lowest) AIC was selected.²⁰ To determine if the functional form of the chosen model had an appropriate fit for this data set, we plotted the quantile function (inverse of cumulative distribution function) of the selected model and evaluated the straight-line fit. Survival models were also internally validated (using bootstrapping to correct for optimistic bias) by measuring both discrimination and calibration. Discrimination was evaluated using the concordance index (C-index). The C-index measures the probability that given a pair of randomly selected patients, the model correctly predicts which patient will experience failure first. Calibration, which compares predicted with actual survival, was evaluated with a calibration curve.¹⁶

The best-performing survival prediction model was then implemented into an online nomogram, into which a user can enter parameters for a specific patient and obtain an estimate of the expected survival benefit from adjuvant chemotherapy or CRT. The browser-based software tool was programmed in JavaScript.

RESULTS

A total of 1,137 patients were included in the study. Of these, 126 patients (11%) received adjuvant chemotherapy, and an additional 126 patients (11%) received adjuvant CRT. Table 1 shows a compar-

Table 1. Patient Demographics and Clinical Characteristics Before and After PS Weighting Applied to Balance Covariates Between Untreated and Treated Groups (N = 1,137)

Characteristic	Original			PS Weighted		
	No CRT	CRT	P	No CRT	CRT	P
Mean age, years	78	73	< .001	73	73	.866
Female sex, %	73	71	.674	71	71	.877
Race, %			.149			.944
White	82	87		88	87	
African American	8	9		8	9	
Asian/Pacific Islander	10	5		4	5	
T stage, %			< .001			.972
T1	30	13		12	13	
T2	29	32		33	32	
T3	35	48		49	48	
T4	6	7		6	7	
N stage, %			< .001			.989
N0	63	50		50	50	
N+	17	41		41	41	

Abbreviations: CRT, chemoradiotherapy; PS, propensity score.

Fig 1. Kaplan-Meier overall survival plot for all patients with gallbladder disease grouped by T stage.

ison of baseline characteristics between the treated and untreated groups. Treated patients tended to be younger and have higher T- and N-stages. After propensity score weighting, all covariates were balanced and no longer had statistically significant differences.

A Kaplan-Meier overall survival plot for all patients by T-stage is shown in Figure 1. Unadjusted median overall survival for all patients was 16 months. In comparing the performance of survival models, the LN model had the lowest AIC of 9,263, indicating a better overall fit than the other models (CPH, 19,986; Weibull, 9,540; exponential, 9,538; log logistic, 9,304). For an LN model, the appropriate quantile function plot is $\Phi^{-1}[1 - \hat{S}(t)]$ versus $\ln(t)$, where Φ^{-1} is the inverse of the standard normal cumulative distribution function, $\hat{S}(t)$ is the Kaplan-Meier estimate of the survival function, and $\ln(t)$ is the natural logarithm of time. A plot of this quantile function approximated a straight line, indicating a reasonable fit for these data. The LN model had good discrimination, with a C-index of 0.67. The calibration curve also showed good agreement between predicted and observed outcomes for the LN model.

The beta coefficients for the LN model are listed in Table 2. Interaction terms indicate how the influence of adjuvant chemotherapy or CRT varies by T and N stages. The LN model was implemented as an online survival prediction nomogram (Fig 2) that calculates the expected survival benefit from adjuvant chemotherapy and adjuvant CRT. This browser-based software tool is available at <http://skynet.ohsu.edu/nomograms>.

Table 3 summarizes the key findings from the nomogram. For patients with T1 disease, the model estimates no survival benefit from the addition of adjuvant therapy, regardless of nodal status and other factors. For patients with T2 or greater disease, the model predicts that most patients will derive at least a small benefit from adjuvant CRT, regardless of nodal status. For example, a white man age 75 years with T2N0 disease would be predicted to see an improvement in 3-year survival from 42% to 51% with adjuvant CRT. For patients with node-positive disease, the model predicts a small survival benefit from adjuvant chemotherapy and a larger benefit from CRT. For example, for a white woman age 65 years with T3N1 disease, the model predicts that 3-year overall survival would increase from 11% with surgery

Table 2. Gamel Boag Lognormal Multivariate Regression Model Parameters

Covariate	Beta Coefficient	P
Intercept	1.6462	.177
Age†	0.0323	.065
Age'	-0.1829	.001
Age''	0.4952	.004
Male sex	-0.1490	.013
Race		
African American	-0.3721	< .001
Asian/Pacific Islander	-0.3503	< .001
T stage		
T2	-0.3442	< .001
T3	-1.1097	< .001
T4	-1.8108	< .001
N stage		
N1	-0.5814	< .001
NA	-0.2965	.002
Chemotherapy	-0.5341	.036
Chemoradiotherapy	-0.5522	< .001
T2 * chemotherapy	0.2600	.421
T3 * chemotherapy	0.4973	.089
T4 * chemotherapy	0.7656	.069
T2 * chemoradiotherapy	0.7886	< .001
T3 * chemoradiotherapy	0.8919	< .001
T4 * chemoradiotherapy	1.2876	< .001
N1 * chemotherapy	0.4993	.034
NA * chemotherapy	0.0269	.926
N1 * chemoradiotherapy	0.8060	< .001
NA * chemoradiotherapy	0.4845	.002
Log(sigma)	0.1157	< .001

Abbreviation: NA, not available.

†Age modeled using restricted cubic spline function with four knots, requiring three independent coefficients: age, age', and age''.

alone to 21% with adjuvant chemotherapy and 42% with adjuvant CRT (Fig 3).

DISCUSSION

Clinical prediction calculators and nomograms are becoming increasingly popular decision aids for use in predicting cancer risk, prevention, and therapeutic outcomes.²¹ There are a number of important cancer risk prediction models being used today for prostate,²²⁻²⁶ breast,²⁷⁻³¹ pancreatic,³² and other cancers.³³ Clinical prediction tools are useful for individualizing therapeutic recommendations for a specific patient. Although prediction models can never substitute for evidence from prospective randomized clinical trials, these tools are useful adjuncts to clinical decision making in situations in which clinical trial data are not available, and optimal therapeutic management remains controversial.

In keeping with our findings, recent series have also suggested a survival benefit from adjuvant chemoradiotherapy, with encouraging 5-year survival rates over 30%,⁸⁻¹¹ compared with historical reports of 10% to 30% after resection alone.³⁴⁻³⁶ Duke University reported its experience in 22 patients with resected gallbladder carcinoma treated with adjuvant therapy.⁸ Despite the locally advanced nature of patients' disease (86% of patients were T3/4 and/or node positive), 5-year survival was 37%. Median survival was 22.8 months, compared

Gallbladder Cancer Survival Prediction Model
<http://skynet.ohsu.edu/nomograms/>
Gallbladder Cancer Adjuvant Therapy

Instructions: Enter details below for a patient who has had surgery for gallbladder cancer, and the calculator will estimate benefit from post-operative chemotherapy or chemoradiotherapy.

Age: 70	Sex: Male	Race: White
T Stage (AJCC 7th):	T1: localized (lamina propria or muscular layer) T2: perimuscular connective tissue T3: serosa, liver, or 1 of (EHBD, duodenum, pancreas, stomach, colon) T4: >1 of (EHBD, duodenum, pancreas, stomach, colon) or PV or HA	
N Stage (AJCC 7th):	N0: no positive lymph nodes N1: cystic duct, CBD, hepatic artery, or portal vein LNs N2: para-aortic, pericaval, SMA, or celiac artery LNs unknown	
Predicted Median Survival:	Surgery Alone: 9 months	Surgery + Chemo: 14 months
Predicted 3-year Overall Survival:	Surgery Alone: 11%	Surgery + Chemo: 21%
	Surgery + ChemoRT: 28 months	Surgery + ChemoRT: 42%

Fig 2. Online prediction calculator estimating benefit of adjuvant chemotherapy or chemoradiotherapy for individual patient; Web-based tool available at <http://skynet.ohsu.edu/nomograms>. CBD, common bile duct; EHBD, extrahepatic bile duct; HA, hepatic artery; LN, lymph node; PV, portal vein; RT, radiotherapy; SMA, superior mesenteric artery.

with 16 months in our study, which may be explained by the higher proportion of patients undergoing radical resection and lymphadenectomy in that series. Baeza et al⁹ reported their experience of treating 49 patients with resected gallbladder cancer with chemoradiotherapy. In this series, all patients underwent lymphadenectomy in addition to cholecystectomy, with a resultant 5-year overall survival of 52%. The Mayo Clinic¹⁰ published its experience of R0 resected gallbladder carcinomas treated with adjuvant chemoradiotherapy. As in our study, adjuvant chemoradiotherapy in this series significantly improved overall survival (hazard ratio for death, 0.30; 95% CI, 0.113 to 0.69; $P = .004$). Also, in a recently published Korean study¹¹ of a series of 100 patients, those with node-positive T2 or T3 disease experienced a survival benefit from adjuvant chemoradiotherapy.

In comparing adjuvant chemotherapy alone versus adjuvant CRT, our model found that CRT outperformed chemotherapy alone for virtually all patient subsets. This finding is consistent with what others have found for hepatobiliary cancers from SEER-Medicare. In fact, Davila et al³⁷ found that SEER-Medicare patients with pancreatic cancer who received adjuvant chemotherapy had worse outcomes than those who received surgery alone. However, it is important to note that the majority of patients in these SEER-Medicare studies received fluorouracil alone in an era before gemcitabine was widely used. The outcomes predicted by our survival model are consistent with current National Comprehensive Cancer Network 2011 guidelines (<http://www.nccn.org>) for gallbladder cancer, which state that one should consider a fluoropyrimidine-based adjuvant

chemotherapy or CRT regimen for all patients, except those with T1b or N0 disease.

When using observational data to model treatment effects, there will always be inherent selection bias between treated and untreated groups, because patient selection for treatment can be influenced by patient or tumor characteristics. Propensity score methods can be used to reduce the impact of this treatment selection bias.^{17,38-41} The propensity score is defined as the probability of receiving treatment conditional on the patient's observed baseline covariates.^{38,39} There are several methods in which propensity scores have been incorporated into statistical modeling, including stratification, matching, covariate adjustment, and inverse probability of treatment weighting. Austin¹⁷ compared these four methods and found that matching and inverse treatment weighting performed better than the other two methods. We chose to implement the inverse treatment weighting approach, because this method yields a final survival model, the parameters of which can be readily incorporated into an interactive Web tool.

Table 3. Summary of Nomogram Predictions

Stage	Adjuvant Chemotherapy	Adjuvant CRT
T1N0	0	0
T2N0	0	+
T3N0	0	+
T4N0	+	+++
T1N+	+	+++
T2N+	+	+++
T3N+	+	+++
T4N+	+	+++

Abbreviations: 0, no benefit; +, small benefit; +++, large benefit; CRT, chemoradiotherapy.

Fig 3. Example survival plot: comparison of Kaplan-Meier (KM) survival curve versus predicted lognormal (LN) survival for white woman age 65 years with stage T3N1 gallbladder cancer after surgery alone (S) or surgery plus chemoradiotherapy (CRT).

We used the AIC to compare the relative performance of the models. The AIC is a measure of the goodness of fit of regression models that is based on the concept of entropy.²⁰ It can be viewed as the amount of information lost when a model is used to describe a set of observations. The AIC includes a penalty for number of model parameters and thus represents the tradeoff between bias and variance. Lower AIC values indicate a better model fit, and in our analysis, the LN model had the lowest AIC.

The LN survival is an accelerated failure time parametric survival model that has a long history of usage in cancer survival.⁴² Although not as popular as the semiparametric CPH model, in many settings in which the proportionality assumption does not hold, the LN model has been shown to be a more appropriate survival model in, for example, breast⁴²⁻⁴⁵ and lung cancers.⁴⁶ Gamel et al⁴⁷ developed an extension to the original Boag model that allows prognostic covariates to be incorporated into the LN model. In this LN survival model, the log of survival time has a normal distribution and is a linear function of covariates. In this setting, the hazard function is not constant over time but instead rises quickly to a peak and then declines over time. We have previously demonstrated that this LN model performs well in modeling extrahepatic cholangiocarcinoma,⁴⁸ and the current study indicates that an LN model also demonstrates a good fit for gallbladder cancer.

Our current findings are consistent with the overall conclusions from our original SEER-based gallbladder nomogram¹³ (ie, most patients with T2 or N+ gallbladder cancer or greater would be predicted to benefit from adjuvant therapy). Chemotherapy was not included in the original model, because this information is not available in SEER, but our current SEER-Medicare analysis confirms that the majority of these patients also received chemotherapy. Differences between the two nomograms in the actual predicted survival estimates are mainly the result of the incorporation of more recent data and use of improved survival modeling methods.

There are several limitations to this study. This study was performed using SEER-Medicare data and was limited to predictive factors available in this database. SEER does not include information on margins or performance status, so these prognostic factors could not be included. Patients who received both radiotherapy and chemotherapy within a 6-month time window were assumed to have received concurrent adjuvant CRT. We also examined a shorter 4-month time window and found similar results. Because SEER does not capture cancer recurrence, this approach may have also inadvertently captured patients who received therapy for an early recurrence within 6 months and those who received sequential and not concurrent therapy, and it would have missed adjuvant therapy administered after 6 months.

Perioperative mortality can bias the apparent effect of adjuvant therapy in nonrandomized observational studies. To partially compensate for this bias, we excluded all patients who died within 2 months of surgery. However, it is important to note that this type of exclusion may have subjected the results to a different type of bias resulting from conditional survival,⁴⁹ in which all patients' prognoses improve when they are presumed to have already survived a period of time since treatment.

To capture the largest relevant data set, we included all patients who underwent at least a total cholecystectomy. In looking at extent of resection, several studies have established that gallbladder cancer survival outcomes are improved with radical resection and

lymphadenectomy.⁵⁰⁻⁵⁴ In fact, some series have demonstrated that patients who incidentally discover T2 gallbladder cancer after simple cholecystectomy have better outcomes if they undergo re-resection with radical surgery and lymphadenectomy.⁵⁵ Unfortunately, the number of SEER-Medicare patients coded as having undergone these extended procedures is low (6% to 7%), which precluded our ability to incorporate these variables in our final nomogram. However, our preliminary analysis indicated that these patients generally had better survival outcomes compared with those who did not, even after adjuvant CRT, suggesting that patients with gallbladder disease should have these extended procedures performed whenever possible. Interestingly, our preliminary analysis suggests that patients who underwent extended lymphadenectomy did not derive as large a benefit from adjuvant chemotherapy or CRT. In the future, when more of these patient cases have accumulated in SEER-Medicare, we plan to incorporate radical resection and lymphadenectomy as additional covariates in the next version of our nomogram.

In some cases, the model predicted only a small-percentage improvement from the addition of adjuvant therapy, such as in certain cases of node-negative disease. We did not specify a specific threshold at which adjuvant therapy should be recommended. We believe that the final decision of whether adjuvant therapy should be administered is a decision that should be made after thoughtful discussion between clinician and patient, taking into account multiple factors, many of which cannot be accounted for in a prediction model. Quality of life and specific patient preferences are also important considerations in treatment decision making.

Recently, there has been a movement toward personalized medicine, in which specific information about an individual patient is used to optimize the patient's care. We believe that these types of predictive models will become increasingly important in the future, as we attempt to improve outcomes by individualizing therapeutic recommendations.

In summary, we have built an interactive survival prediction model that can make an individualized estimate of the net survival benefit of adjuvant therapy for patients with gallbladder cancer. This tool can assist clinicians and patients in quantifying the potential benefit of adjuvant chemotherapy or CRT after surgical resection of gallbladder cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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