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Impact of adjuvant external beam radiotherapy on survival in surgically resected gallbladder adenocarcinoma: A propensity score–matched Surveillance, Epidemiology, and End Results analysis

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Abstract

Background—We sought to define the utilization and effect of adjuvant external-beam radiotherapy (XRT) on patients having undergone curative-intent resection for gallbladder cancer (GBC).

Methods—Using the Surveillance, Epidemiology, and End Results (SEER) database, we identified 5,011 patients with GBC who underwent resection between 1988 and 2009. The impact of XRT on survival was analyzed by the use of propensity-score matching by comparing clinicopathologic factors between patients who received resection only versus resection plus XRT.

Results—Median age was 72 years, and most patients were female (73.4%); 66.2% patients had intermediate to poorly differentiated tumors, and 19.1% had lymph node metastasis. The majority (75.0%) had “localized” disease by Surveillance, Epidemiology, and End Results classification. A total of 899 patients (17.9%) received XRT whereas 4,112 patients did not. Factors associated with receipt of XRT were younger age (odds ratio [OR] 5.33), tumor extension beyond the serosa (OR 1.55), intermediate- to poorly differentiated tumors (OR 1.56), and lymph node metastasis (OR 2.59) (all $P < .05$). Median and 1-year survival were 15 months and 59.0%, respectively. On propensity-matched multivariate model, despite having more advanced tumors, XRT was independently associated with better long-term survival at 1 year (hazard ratio 0.45; $P < .001$), but not 5 years (hazard ratio 1.06; $P = .50$).

Conclusion—A total of 18% of patients with GBC received XRT after curative intent surgery. The use of adjuvant XRT was associated with a short-term survival benefit, but the benefit dissipated over time.

Despite being a relatively rare malignancy, gall-bladder cancer (GBC) is the fifth most common gastrointestinal malignancy and the most common biliary tract cancer.¹ Although many patients who present with GBC are diagnosed incidentally after a laparoscopic cholecystectomy, a subset of patients will present with more advanced, nonincidental disease.² Operative resection is the cornerstone of curative therapy for GBC. Resection may

involve radical cholecystectomy, partial hepatectomy, common bile duct resection, and regional lymph node dissection.^{2–5} Although patients with early-stage disease can have a long-term survival that approaches 80–100%, patients with more advanced disease can have a poor prognosis, with 5-year survival ranging from 20 to 40%.^{6–8} In addition to systemic disease, loco-regional recurrence can be a problem and lead to increased morbidity as well as tumor-related death.^{9–11} As such, radiation therapy (XRT) has been proposed—and to a varying degree is used currently—as adjuvant therapy for resected GBC. The role of adjuvant XRT for GBC, however, is not well established.

Although in several reports authors have suggested a possible benefit to adjuvant XRT, most previous studies were small ($n < 100$), nonrandomized, and included patients with a variety of different biliary tumors (GBC, extra- and intra-hepatic cholangiocarcinoma).^{11–17} In turn, extrapolation of these data to inform decisions around the efficacy of XRT for GBC is limited. Design and implementation of prospective trials to address XRT for GBC are challenging because of the rarity of the disease. Retrospective studies can also be problematic, given that patients who receive XRT are likely to have a very different clinicopathological profile compared with patients who do not receive XRT. In turn, retrospective comparisons of patient populations who did versus did not receive XRT can be confounded by indication, whereby receipt of XRT serves as a marker for more advanced disease.⁷

In such circumstances, it can be difficult to compare such disparate groups even with the use of multivariate analyses, which may not adequately account for major differences and lead to erroneous estimates of treatment effects.^{18,19} The objective of the current study was to define the use of XRT among patients with operatively resected GBC, as well as characterize which factors were associated with receipt of XRT. In addition, we sought to evaluate the treatment effect of XRT by using propensity score methods to control for any systematic differences in the background characteristics between patients who did and did not receive XRT.

METHODS

Data source

This retrospective cohort study was determined by an analysis of prospectively collected data from the Surveillance, Epidemiology, and End Results (SEER) database from 1988 to 2009. The SEER database provides extensive data on patient demographics, primary tumor site, tumor morphology and stage at diagnosis, first course of treatment, and follow-up vital status from population-based cancer registries covering approximately 28% of the U.S. population.¹⁹ For the present study, we considered patients with a pathologically confirmed diagnosis of GBC (International Classification of Diseases for Oncology, third edition)^{3,20} between January 1, 1988, and December 31, 2009. Fig 1 depicts a flowchart regarding patient selection for the study cohort. In brief, the cohort included all patients 20 years or older who had a histologic diagnosis of gallbladder adenocarcinoma who underwent surgery between 1988 and 2009. Patients with missing data on disease stage or radiation status were excluded; patients with cancer of the gallbladder other than adenocarcinoma were similarly excluded.

Data on clinicopathological characteristics, including patient age, sex, race, geographical region of residence, marital status, tumor grade, lymph node status, tumor extent, and extent of surgery, were obtained. Radical resection was defined in according to the SEER classification of surgery as partial or total removal of the primary site with a resection in continuity (partial or total removal) of other organs. Limited resection was defined as either partial or total operative removal of only the primary site. In addition, data on whether the

patient received external beam radiotherapy was collected. Vital status and time to death or censoring were determined by use of the SEER data.

Statistical analysis

Discrete variables were described as medians and interquartile range. Categorical variables were described as totals and frequencies. Univariate comparisons were assessed using the analysis of variance, Kruskal-Wallis test, or χ^2 test as appropriate. Univariate and multivariate logistic regression models were constructed to explore the association of covariates with adjuvant XRT. Variables with a univariate significance <0.20 were entered into the multivariate model in combination with important clinical variables and confounders. All reported P values were two tailed. Overall survival time was calculated from the date of the index procedure to the date of death as reported in the SEER database. Survival adjusted for censoring was calculated using the Kaplan-Meier method and medians compared using the log-rank test.

On the basis of tests for validity of proportional hazards assumption, receipt of XRT was entered as a time-varying covariate to the Cox Proportional Hazards model. Variables were entered into the Cox proportional hazards model if the log-rank P value for comparison using the Kaplan-Meier methods was $<.05$. Propensity score matching using the greedy matching algorithm was used to create comparable cohorts of patients for comparison of the effect of XRT on survival.²¹ A propensity score is calculated using a logistic regression model, with the treatment of interest (XRT) as the outcome measure. The propensity score represents the relationship between multiple characteristics and receipt of treatment.²² Matching on the propensity score can create covariate balance between the treatment and control group, thus reducing confounding due to indication.²³ All statistical analyses were performed using SAS 9.3 (SAS Inc, Cary, NC).

RESULTS

Patient and treatment details

Between 1988 and 2009, 5,011 patients underwent resection for gallbladder adenocarcinoma and met inclusion criteria. The demographic and clinical characteristics of these patients are presented in Table I. Median patient age was 72 years (interquartile range 62–80 years). Most patients were female ($n = 3,679$; 73.4%) and white ($n = 3,961$; 79.1%). A majority of patients ($n = 2,931$; 58.5%) resided in the Western United States. Most patients were diagnosed with gallbladder adenocarcinoma in the latter half of the study period: 1,565 (31.2%) patients between years 2000 and 2004 versus 1,739 patients in years 2005 and 2009. Most patients had intermediate- to poorly differentiated tumors on histology ($n = 3,317$; 66.2%); fewer had well-differentiated tumors ($n = 802$; 16.0%). A majority of patients did not have lymph node metastasis (N0 disease: $n = 3,190$, 63.7%), whereas a small subset had lymph node metastasis (N1 disease: $n = 959$, 19.1%) or had no nodal staging available (Nx disease: $n = 862$, 17.2%). The tumor did not extend beyond the serosal layer of the gallbladder in 3,758 (75.0%) patients; whereas a smaller proportion of patients had direct extension into liver ($n = 570$, 11.4%) or to organs other than liver ($n = 683$; 13.6%). With regard to operative treatment, most patients underwent radical resection ($n = 3,169$; 63.2%), whereas the rest had limited resection.

Survival after resection for GBC

A total of 3,505 (69.9%) patients died with a median survival of 17 months (95% confidence interval [95% CI] 16–18 months); 1-, 3-, and 5-year survival was 60.0%, 34.2%, and 26.4%, respectively. On univariate analysis, several factors were associated with survival. Specifically, older age, male sex, intermediate-to-poorly differentiated tumors, lymph node

metastasis, and extension beyond the serosa were all associated with a worse overall long-term survival (all $P < .05$). Nonclinical factors such as receipt of therapy in the Southern geographic region of the United States also were associated with a lower median survival (all $P < .05$). Interestingly, on nonpropensity matched analyses, XRT impacted short-term but not long-survival. As noted in Fig 2, A, the survival curves comparing patients with GBC who did and did not receive adjuvant XRT crossed at about 20 months. The 1-year survival of patients who underwent surgery plus XRT therapy was 68.2% versus 58.0% for patients who underwent surgery alone ($P = .03$). Long-term 5-year survival was, however, worse among patients who received adjuvant XRT versus patients who underwent surgery alone (20.2% vs 28.0%, respectively; $P = .04$).

Because the survival curves in the two groups crossed, on multivariate Cox proportion hazards analysis XRT was entered as a time-varying covariate. In this model, after we adjusted for other confounding variables, XRT remained independently associated with a short-term (ie, 1-year) survival benefit (hazard ratio [HR] 0.53, 95% CI 0.47–0.61; $P < .001$). In analyzing long-term outcomes, however, we found that receipt of XRT was associated with a worse 5-year survival (HR 1.23, 95% CI 1.09–1.39; $P < .001$). Other factors associated with worse long-term survival on multivariate analysis included younger patient age (< 49 years vs 80+ years: HR 0.34, 95% CI 0.29–0.39), male sex (HR 1.19, 95% CI 1.10–1.28), N1 disease (reference N0: N1 HR 1.48, 95% CI 1.35–1.61), and extension beyond the serosa (HR 2.64, 95% CI 2.31–2.82), all $P < .05$.

Factors associated with receipt of XRT

To better understand patterns of XRT use for GBC, we next sought to identify those factors associated with receipt of XRT. Among the 5,011 patients with GBC included in the study cohort, only a subset was treated with XRT ($n = 899$; 17.9%). On univariate analysis both nonclinical and clinical factors were associated with the likelihood that a patient received XRT (Table II). Perhaps not surprisingly, a number of adverse prognostic factors were associated with receipt of XRT on multivariate logistic regression analysis. Specifically, age was a determining factor, as younger patients were 5 times more likely to receive XRT (compared with 80+ years, < 49 years: OR 5.33, 95% CI 3.87–7.34; 50–59 years: OR 4.96, 95% CI 3.74–6.58; 60–69 years: OR 4.26, 95% CI 3.28–5.54; 70–79 years: 2.93, 95% CI 2.28–3.79; all $P < .001$). Other factors such as nodal status and histological grade were also independently associated with XRT administration. Among patients with either an intermediate- to poorly differentiated or undifferentiated tumor, use of XRT was much more common (reference well-differentiated: intermediate-poorly differentiated: OR 1.56, 95% CI 1.21–2.01; undifferentiated: OR 1.82, 95% CI 1.06–3.15; $P < .05$). Patients with N1 disease were also more than twice as likely to receive XRT compared with patients who had N0 disease (OR 2.59, 95% CI 2.17–3.11). In addition, patients with GBC that extended into the adjacent liver (OR 1.55, 95% CI 1.24–1.94) or to any other organ (OR 1.41, 95% CI 1.14–1.73) had a greater likelihood of receiving XRT than patients with disease localized to serosa. Of note, independent of clinical factors, XRT use was noted to decrease across the time periods examined (OR years 1988–1993 vs 2005–2009: 1.46, 95% CI 1.14–1.42).

Effect of XRT on survival in the propensity matched cohort

In view of the marked clinicopathological differences among patients who did versus did not receive XRT, propensity score methods were used to assess better the treatment effect of XRT. As described by our group¹⁸ and others,²⁴ standard model-based methods of analysis can potentially lead to inappropriate inferences when comparing two different treatment groups with multiple confounding covariates. Rather, propensity score methods can generate a probability that an individual patient might have received one therapy (eg, surgery alone) versus the other (eg, surgery plus adjuvant XRT).

As shown in Table II, using propensity matching, we identified a cohort of 1,788 patients with more similar baseline characteristics. Among the patients in the propensity matched cohort, 894 underwent operation alone and 894 had resection plus adjuvant XRT. Receipt of XRT was associated with a survival benefit; median overall survival was 11.0 months for patients treated with operation alone compared with 18.0 months for patients treated with resection plus adjuvant therapy (HR 0.45, 95% CI 0.39–0.53; $P < .001$; Fig 2, A).

We also reanalyzed data after excluding all patients who died within 90 days of surgery. On propensity score matched analysis of these 1,740 patients (870 XRT – 870 XRT + surgery) who survived >90 days after operation, multivariate adjusted Cox proportional hazards modeling of survival with XRT as a time-varying covariate revealed a persistent survival benefit in the short term (HR 0.66, 95% CI 0.56–0.78; $P < .001$) for those receiving XRT. In the propensity-adjusted model, patients with N1 disease and those with moderate-to-poorly differentiated tumors benefited the most from XRT therapy (Table III). In contrast, patients with N0 or well-differentiated GBC did not derive a comparable survival benefit from XRT (Figs 3 and 4).

DISCUSSION

A subset of patients with GBC will develop local recurrence even after radical resection. For this reason, regional treatment in the form of XRT is often considered after operation as adjuvant therapy. The National Cancer Center Network (NCCN) guidelines recommend XRT to be considered in the adjuvant setting for any patient with disease stage greater than T1N0.²⁵ The NCCN guidelines explicitly note, however, that this recommendation is determined by very limited clinical evidence. As such, the NCCN does not necessarily define XRT as standard therapy and even notes that whether adjuvant XRT provides a definitive benefit is controversial.²⁵ Although several studies in which investigators examined XRT for GBC have suggested a survival benefit, these studies were limited because of their small sample and, in some instances, the inclusion of groups of patients with disparate indications for XRT (eg, adjuvant and palliation).^{7,13,26,27} In two more recent studies, the authors used SEER data to examine XRT in the adjuvant setting for the treatment of GBC and found an advantage in certain populations.^{28,29} These studies were limited, however, because they did not adequately adjust for the disparate clinical and pathological characteristics among patients who did and did not receive XRT. Specifically, assessing the treatment effects of a specific therapy among patients with dramatically different baseline characteristics may be confounded even when using multivariate analyses.

The current study is important because we used propensity score matching methodology to control more fully for baseline differences in the two groups. In doing this, we were able to identify a comparable cohort of patients to assess the effect of XRT. We found that although XRT did have a survival benefit, the effect did not persist long-term. Furthermore, the benefit of XRT was most pronounced in those patients with more adverse prognostic features such as lymph node metastasis and moderately- to poorly-differentiated tumors.

Currently, there are only limited recommendations to consider the use of adjuvant XRT for GBC. Specific guidelines on radiation dosage, timing of radiation and modality are even more limited. Some data suggest that improved survival and local control can be achieved by the use of XRT, especially with doses of radiation 40 Gy.^{13,27,30,31} Kresl et al¹³ noted that local control was superior with radiation doses >54 Gy, with a trend toward long-term survival if adjuvant radiation was started within 2 months of resection. A more recent study investigated intraoperative XRT as a modality to treat GBC. Lindell et al³² reported on 20 patients, 10 of whom had a combination of intraoperative XRT and external beam XRT after resection. Although underpowered, the authors found combined intraoperative XRT/external

beam XRT was safe with a trend toward long-term survival. Other studies have suggested a role for adjuvant XRT with concurrent radio-sensitizing doses of chemotherapy. Several small studies have investigated outcomes of concurrent adjuvant chemoradiation with the use of 5-fluorouracil and have suggested a possible overall benefit of chemoradiation therapy.^{12,13}

In the current study, we found that only 18% of patients received adjuvant XRT after operation. As expected, receipt of XRT was not random but instead was related to specific clinical and pathological factors. Patients who underwent XRT had a number of more adverse characteristics compared with patients who underwent surgery alone. In particular, we found that factors including younger patient age, lymph node metastasis, moderately-poorly differentiated tumors and disease extending to the liver or other adjacent organs were all associated with a higher likelihood of receiving XRT. As such, we clearly demonstrated that patients receiving XRT were not comparable to patients who received surgery alone with regard to underlying tumor biology. It is not surprising therefore that on nonpropensity-matched analyses patients who received XRT had a worse 5-year overall survival. The use of propensity score matching in the current study was used to control for major, systematic differences in the baseline demographic and clinical characteristics between patients undergoing resection plus adjuvant XRT versus resection alone. In using propensity score analysis, we were able to better account for these differences. We identified matched cohorts that were more balanced with regard to clinicopathologic factors including age, N status, tumor differentiation, and extent of tumor thereby ensuring that any differences noted in outcome were attributable to XRT treatment rather than differences in baseline characteristics.

In the propensity matched cohort analysis receipt of XRT was associated with improved median survival and a 55% lower hazard of death within the first year. Wang et al²⁸ and Mojica et al²⁹ had previously reported a survival benefit of adjuvant XRT in patients with GBC. Mojica et al²⁹ had noted an improvement in median survival with adjuvant XRT from 11 months to 14 months. In the current study, we noted that receipt of XRT was associated with an improvement in median overall survival from 11.0 months for patients treated with surgery alone to 18.0 months for patients treated with surgery plus adjuvant therapy. Similar to previous work, we also noted that those patients who benefited the most from adjuvant XRT were those with more advanced staged disease, including lymph node metastasis or moderate-to-poorly differentiated tumors.²⁸ Unlike previous studies, we analyzed survival using propensity-matched cohorts and assessed the effect of XRT on both short- and long-term survival. Interestingly, although XRT was associated with a short-term survival benefit, the beneficial effect of XRT on survival appeared, to dissipate over time and was not associated with a long-term benefit at 5 years (Fig 2, B). The relative benefit of XRT on long-term survival has been a topic of much debate for other cancers including the rectum, breast, and pancreas.^{33–35} Our data are consistent with the general concept that XRT may impact short-term outcomes, but its role in improving long-term survival is less defined. Taken together, our data suggest that patients with N1 and moderately-poorly differentiated disease appeared to derive the most benefit from adjuvant XRT, especially with regard to short-term survival. Whether patients treated with adjuvant XRT for GBC derive a more long-term survival benefit remains to be further elucidated.

There are several limitations inherent in the current study. In using SEER we were limited by the factors within the database. As such, we were unable to account for certain details, including radiation dosage, fields of radiation, margin status, as well as details of chemotherapy. The phase 2 Southwest Oncology Group trial, studying the use of adjuvant chemoradiation in GBC and extrahepatic cholangiocarcinoma above the cystic duct, has recently closed.³⁶ In this study, patients with T2–T4 disease, N1 status, or R1 resection were

treated with adjuvant chemoradiation. The results of this trial will hopefully provide further insight into the potential role of adjuvant XRT for patients with advanced GBC and detail the role of chemotherapy both as a therapeutic modality and its role in radiosensitization among these patients. Because the current study was a nonrandomized retrospective analysis with many confounding variables, propensity score matching was used to balance the XRT and control cohorts. Although the use of propensity scoring matching allows for analytic analysis of all known factors, it is limited by unknown or unmeasured confounders. One important confounder that was not available in the SEER data was surgical margin status. Finally, SEER does not contain specific information on chemotherapy and therefore data on radio-sensitization with the use of chemotherapeutic agents could not be assessed.

In conclusion, we found that in a large national database sample of patients 65 years and older that only 18% of patients had receipt of adjuvant XRT. Adjuvant XRT was associated with improved short-term survival after resection for GBC despite more advanced tumors. The beneficial effect of XRT seemed to dissipate after 12 months because there was no difference in 5-year survival among patients who did versus did not receive adjuvant XRT.

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Fig 1.
Patient selection flowchart. ICD-O-3, *International Classification of Diseases for Oncology*, 3rd Edition.

Fig 2. Kaplan-Meier survival curves of overall survival comparing resection plus radiation to resection alone for GBC (A) before and (B) after propensity score matching.

Fig 3. Overall survival among patients with (A) N0 and (B) N1 disease in the propensity-matched cohort.

Fig 4. Overall survival among patients with (A) well-differentiated and (B) moderate-to-poorly differentiated disease in the propensity-matched cohort.

Table IDemographic and clinical characteristics of operatively treated patients with gallbladder cancer ($n = 5,011$)

Variable	Frequency
Age group, years	
49	392 (7.8)
50–59	654 (13.1)
60–69	1,057 (21.1)
70–79	1,515 (30.2)
80+	1,393 (27.8)
Male sex	1,332 (26.6)
Married	2,399 (47.9)
Race	
White	3,961 (79.1)
Black	438 (8.7)
Other	612 (12.2)
Year of diagnosis	
1988–1993	779 (15.6)
1994–1999	928 (18.5)
2000–2004	1565 (31.2)
2005–2009	1739 (34.7)
Tumor grade	
Well differentiated	802 (16.0)
Intermediate-to-poorly differentiated	3317 (66.2)
Undifferentiated	90 (1.8)
Unknown grade	802 (16.0)
Lymph node status	
N0	3190 (63.7)
N1	959 (19.1)
Nx	862 (17.2)
Tumor extent	
In situ/limited to serosa	3758 (75.0)
Extension to liver	570 (11.4)
Extension to any other or multiple organs	683 (13.6)
Region	
East	823 (16.4)
Midwest	736 (14.7)
South	521 (10.4)
West	2931 (58.5)
Surgery	
Limited	1842 (36.8)
Radical	3169 (63.2)

Table II

Comparison of patients in the XRT and non-XRT group before and after propensity score matching

Variable	Comparisons	Unmatched sample			Propensity score matched sample		
		NO XRT (n = 4,112)	XRT (n = 899)	P value	NO XRT (n = 894)	XRT (n = 894)	P value
Age group, years	49	286 (7.0)	106 (11.8)	<.001	95 (10.6)	103 (11.5)	.69
	50–59	479 (11.7)	175 (19.5)		164 (18.3)	173 (19.4)	
	60–69	805 (19.6)	252 (28.0)		245 (27.4)	252 (28.2)	
	70–79	1241 (30.2)	274 (30.5)		303 (33.9)	274 (30.7)	
	80+	1301 (31.6)	92 (10.2)		87 (9.7)	92 (10.3)	
Year of diagnosis	1988–1993	606 (14.7)	173 (19.2)	<.001	165 (18.5)	168 (18.8)	.92
	1994–1999	749 (18.2)	179 (19.9)		169 (18.9)	179 (20.0)	
	2000–2004	1321 (32.1)	244 (27.1)		253 (28.3)	244 (27.3)	
	2005–2009	1436 (34.9)	303 (33.7)		307 (34.3)	303 (33.9)	
	White	3270 (79.5)	691 (76.9)	.03	695 (77.7)	688 (80.0)	.83
Race	Black	339 (8.2)	99 (11.0)		90 (10.1)	98 (11.0)	
	Other races	503 (12.2)	109 (12.1)		109 (12.2)	108 (12.1)	
Sex	Males	1095 (26.6)	237 (26.4)	.87	238 (26.6)	236 (26.4)	.91
	Females	3017 (73.4)	662 (73.6)		656 (73.4)	658 (73.6)	
Grade	Well differentiated	698 (17.0)	104 (11.6)	<.001	90 (10.1)	104 (11.6)	.28
	Intermediate-poorly differentiated	2613 (63.5)	704 (78.3)		731 (81.8)	699 (78.2)	
	Undifferentiated	68 (1.7)	22 (2.5)		15 (1.7)	22 (2.5)	
	Unknown grade	733 (17.8)	69 (7.7)		58 (6.5)	69 (7.7)	
	N0	2761 (67.1)	429 (47.7)	<.001	425 (47.5)	429 (48.0)	.97
Lymph node status	N1	629 (15.3)	330 (36.7)		330 (36.9)	325 (36.3)	
	Nx	722 (17.6)	140 (15.6)		139 (15.6)	140 (15.7)	
Extension	In situ/limited to serosa	3190 (77.6)	568 (63.2)	<.001	579 (64.8)	568 (63.5)	.73
	To liver	417 (10.1)	153 (17.0)		154 (17.2)	152 (17.0)	
	To any other or multiple organs	505 (12.3)	178 (19.8)		161 (18.0)	174 (19.5)	
Region	East	678 (16.5)	145 (16.1)	.09	127 (14.2)	145 (16.2)	.70
	Midwest	580 (14.1)	156 (17.4)		156 (17.5)	154 (17.2)	
	South	434 (10.6)	87 (9.68)		88 (9.8)	87 (9.7)	
	West	2420 (58.9)	511 (56.8)		523 (58.5)	508 (56.8)	

Variable	Comparisons	Unmatched sample			Propensity score matched sample		
		NO XRT (n = 4,112)	XRT (n = 899)	P value	NO XRT (n = 894)	XRT (n = 894)	P value
Surgery	Limited	1511 (36.8)	331 (36.8)	.97	358 (40.4)	328 (36.7)	.14
	Radical	2601 (63.3)	568 (63.2)		536 (60.0)	566 (63.3)	

XRT, Radiation therapy.

Cox proportional hazard regression analysis of factors associated with survival after resection for gallbladder adenocarcinoma in the propensity score-matched cohort

Table III

Variable	Comparisons	Median survival, mo (95% CI)	P value	Survival analysis	
				Hazard ratio	P value
XRT	No	11 (10–13)	<.001	–	
	Yes	18 (17–20)			
XRT <12 m				0.45 (0.39–0.53)	<.001
XRT 12 m				1.06 (0.90–1.24)	.50
Age group, years	49	22 (17–27)	<.001	0.70 (0.42–1.17)	.17
	50–59	21 (17–23)		0.74 (0.47–1.15)	.18
	60–69	16 (14–17)		0.92 (0.63–1.36)	.69
	70–79	12 (11–14)		0.93 (0.70–1.24)	.63
	80+	11 (9–14)		Ref	
Year of diagnosis	1988–1993	13 (11–15)	.01	1.54 (1.24–1.91)	<.001
	1994–1999	14 (12–16)		1.40 (1.18–1.66)	<.001
	2000–2004	14 (13–16)		1.25 (1.07–1.45)	.01
	2005–2009	19 (16–22)		Ref	
Race	White	15 (14–16)	.36	–	
	Black	16 (13–18)		–	
	Other races	16 (13–20)		–	
Sex	Male	12 (11–14)	.01	Ref	
	Female	16 (15–17)		0.79 (0.70–0.89)	<.001
Tumor grade	Well differentiated	28 (20–34)	<.001	Ref	
	Intermediate to poorly differentiated	15 (12–18)		0.40 (0.29–0.59)	<.001
	Undifferentiated	7 (5–15)		0.71 (0.49–1.03)	.08
	Unknown grade	17 (14–21)		0.40 (0.25–0.65)	<.001
Lymph node status	N0	18 (17–20)		Ref	
	N1	15 (13–16)		1.79 (1.32–2.50)	<.001
	Nx	11 (9–12)		1.26 (1.08–1.47)	.01
Extension	In situ/limited to serosa	21 (19–23)	<.001	Ref	
	To liver	10 (8–12)		2.47 (2.05–2.97)	<.001

Variable	Comparisons	Median survival, mo (95% CI)	Survival analysis		
			P value	Hazard ratio	P value
Region	To any other/multiple organs	10 (8–11)		2.41 (2.04–2.85)	<.001
	East	16 (14–17)	.22	–	
	Midwest	15 (12–18)		–	
	South	14 (10–17)		–	
	West	16 (14–17)		–	
Surgery	Limited	13 (12–15)	.23	–	
	Radical	16 (15–18)		–	

XRT, Radiation therapy.