The American Journal of Surgery 221 (2021) 642–648

Contents lists available at ScienceDirect

The American Journal of Surgery

journal homepage: www.americanjournalofsurgery.com

Original Research Article

Postsurgical radiotherapy in stage IIIB gallbladder cancer patients with one to three lymph nodes metastases: A propensity score matching analysis

Yu-Long Cai, Yi-Xin Lin, Xian-Ze Xiong, Hui Ye, Fu-Yu Li, Nan-Sheng Cheng*

Department of Biliary Surgery, West China Hospital, Sichuan University, Chengdu, 610041, Sichuan Province, China

ARTICLE INFO

Article history:
Received 26 June 2020
Received in revised form
30 July 2020
Accepted 8 August 2020

Keywords:
Gallbladder cancer
Radiotherapy
AJCC
SEER

ABSTRACT

Background: The effect of postsurgical radiotherapy (PSRT) among T1-3 gallbladder cancer (GBC) patients with one to three lymph node metastases remains controversial. The aim of this study was to assess the impact of PSRT on gallbladder cancer-specific survival (GBCSS) in patients with stage IIIB.
Methods: The data of GBC patients were obtained from the American Surveillance, Epidemiology, and End Results (SEER) Data resources between 2004 and 2015. Then, a 1:1 propensity score matching (PSM) method was performed. GBCSS was compared among all patients. Subgroup analysis was conducted to identify patients who would benefit from PSRT.
Results: 726 AJCC (8th edition) stage IIIB GBC patients were included. PSRT failed to improve GBCSS ($p = 0.168$). Male sex, tumor size $\geq$ 4 cm and absence of chemotherapy were independent negative prognostic factors. No significant survival benefit from PSRT was found in any subgroup.
Conclusions: PSRT provides no survival benefit for IIIB GBC.

Introduction

Gallbladder cancer (GBC) is the sixth most common gastrointestinal malignancy and the most common of all biliary tract cancers.[1] Currently, the only curative treatment for patients with GBC is complete resection with negative margins.[2] However, only patients with American Joint Committee on Cancer (AJCC) stage I and some stage II GBC are associated with a satisfactory postoperative 5-year survival rate. Most patients are diagnosed at advanced stages, and stage III or higher GBC patients rarely experience long-term survival.[3,4] The poor prognosis after surgery is mainly attributed to the high rate of locoregional recurrence and/or distant metastasis.[5,6]

The 8th edition of the AJCC staging guidelines are the most commonly used clinical staging system at present.[7] The definition of the N category in the previous edition was based on the anatomic location of lymph nodes, but this has been changed to the number of metastatic lymph nodes in the 8th edition. Nodal categories are defined as N1 (1–3 metastatic lymph nodes) and N2 (≥4 metastatic lymph nodes).[8] When the patient presents with stage T1-T3N1M0, the TNM stage is classified as stage IIIB. According to current studies, the overall 5-year survival rate of patients with stage IIIB GBC is only approximately 20%.[9–11]

To date, the role of adjuvant radiotherapy has been unclear. The National Comprehensive Cancer Network (NCCN) guidelines recommend that adjuvant chemotherapy or chemoradiation is preferred for postsurgical GBC patients with positive regional nodes.[12] However, the usefulness of adjuvant radiotherapy alone is not mentioned. The Japanese guidelines for biliary tract cancers state that although adjuvant radiotherapy is useful based on some studies, the evidence is weak and thus does not support a recommendation of postsurgical radiotherapy.[13] Samuel et al. constructed a prediction model, which showed that adjuvant radiotherapy provides a survival benefit in node-positive cases, especially in ≥ T2 GBC patients.[14] A recent study from Korea reported that postoperative radiotherapy might be an effective treatment in terms of locoregional control in patients with GBC, but this treatment did not show an overall-survival benefit.[15] Thus, the paucity of quality data to date cannot guide hepatobiliary surgeons or oncologists in the choice of radiotherapy with or without chemotherapy for GBC patients with positive lymph nodes.

Whether postsurgical radiotherapy (PSRT) can improve the

* Corresponding author. Department of Biliary Surgery, West China Hospital, Sichuan University, No. 37 Guo Xue Xiang, Chengdu, 610041, Sichuan Province, China.
E-mail address: nanshengcheng2012@163.com (N.-S. Cheng).

https://doi.org/10.1016/j.amjsurg.2020.08.007
0002-9610/

prognosis of T1-3 gallbladder cancer patients with one to three lymph node metastases remains controversial. The aim of this study was to assess the impact of PSRT on cancer-specific survival in stage IIIB GBC patients and to explore possible predictors for positive survival outcomes with PSRT.

Methods

Patients and selection criteria

The data of GBC patients were obtained from the American Surveillance, Epidemiology, and End Results (SEER) 18 Registry Research Data resources between 2004 and 2015. The SEER database contains information on patient demographics, tumor characteristics, treatment, and follow-up for vital status. In this study, SEER*stat software (version 8.3.6) was used to identify eligible patients. The SEER database is freely available with patient anonymization; thus, the approval from the ethics committee was not required.

The inclusion criteria for selection data in this study were as follows: 1) tumor stage T1-T3, one to three lymph node metastases and no distance metastasis at diagnosis (AJCC 8th edition stage IIIB, T1-3N1M0); 2) age >18 years old; 3) diagnosis was confirmed by positive histology; 4) only one primary tumor; and 5) surgical treatment. The exclusion criteria were as follows: 1) missing or incomplete patient data, such as age at diagnosis, radiotherapy record, chemotherapy record, grade, tumor stage, survival status and time; 2) radiotherapy other than PSRT; and 3) death due to causes other than GBC.

The demographics, clinicopathological variables such as marital status at diagnosis, age at diagnosis, race sex, and the tumor characteristics such as differentiation grade, histological type, AJCC stage, tumor size, number of positive regional lymph nodes, chemotherapy record, radiotherapy record, follow-up, and vital status were collected. The SEER coding system classifies GBC into 4 grades: grade I, well differentiated; grade II, moderately differentiated; grade III, poorly differentiated; and grade IV, undifferentiated/anaplastic. Because most GBC histological types are adenocarcinoma, the histological subtypes are classified as “adenocarcinoma” and “others”.

Statistical analysis

Categorical data are presented as counts and percentages. Pearson’s chi-square test was used to compare the clinicopathological variables between the postsurgical radiotherapy (PSRT) group and no-postsurgical radiotherapy (no-PSRT) group. To balance the baseline characteristics of these two groups, a 1:1 propensity score matching (PSM) method was performed. The Kaplan-Meier method with the log-rank test was used to compare GBCSS

Table 1
The clinicopathological characteristics of postsurgical GBC patients before PSM and after PSM.

Variables	Before PSM		*P* value	After PSM		*P* value
	PSRT $N = 272$	No-PSRT $N = 454$		PSRT $N = 272$	No-PSRT $N = 272$	
Age (years)						
<70	190 (69.9)	217 (47.8)	<0.001	190 (69.9)	179 (65.8)	0.313
≥70	82 (30.1)	237 (52.2)		82 (30.1)	83 (34.2)	
Race						
White	201 (73.9)	355 (78.2)	0.304	201 (73.9)	208 (76.5)	0.331
Black	38 (14.0)	47 (10.4)		38 (14.0)	27 (9.9)	
Others[a]	33 (12.1)	52 (11.5)		33 (12.1)	37 (13.6)	
Sex						
Male	80 (29.4)	136 (30.0)	0.887	80 (29.4)	72 (26.5)	0.445
Female	192 (70.6)	318 (70.0)		192 (70.6)	200 (73.5)	
Marital status						
Married	178 (65.4)	224 (49.3)	<0.001	178 (65.4)	174 (64.0)	0.720
Unmarried[b]	94 (34.6)	230 (50.7)		94 (34.6)	98 (36.0)	
Grade						
I	27 (9.9)	47 (10.4)	0.518	27 (9.9)	33 (12.1)	0.321
II	118 (43.4)	175 (38.5)		118 (43.4)	102 (37.5)	
III	108 (39.7)	204 (44.9)		108 (39.7)	123 (45.2)	
IV	19 (7.0)	28 (6.2)		19 (7.0)	14 (5.1)	
Histology						
Adenocarcinoma	242 (89.0)	397 (87.4)	0.540	242 (89.0)	242 (89.0)	1.000
Others[c]	30 (11.0)	57 (12.6)		30 (11.0)	30 (11.0)	
AJCC T stage						
T1	14 (5.1)	21 (4.6)	0.949	14 (5.1)	9 (3.3)	0.542
T2	130 (47.8)	217 (47.8)		130 (47.8)	136 (50.0)	
T3	128 (47.1)	216 (47.6)		128 (47.1)	127 (46.7)	
No. of LNs positive						
1	178 (65.4)	346 (76.2)	0.007	178 (65.4)	182 (66.9)	0.929
2	65 (23.9)	76 (16.7)		65 (23.9)	63 (23.2)	
3	29 (10.7)	32 (7.0)		29 (10.7)	27 (9.9)	
Tumor size						
<4	127 (46.7)	200 (44.1)	0.489	127 (46.7)	129 (47.4)	0.864
≥4	145 (53.3)	254 (55.9)		145 (53.3)	143 (52.6)	
Chemotherapy						
Yes	239 (87.9)	161 (35.5)	<0.001	239 (87.9)	161 (59.2)	<0.001
No	33 (12.1)	293 (64.5)		33 (12.1)	111 (40.8)	

Data expressed as a number (%).
GBC, Gallbladder Cancer; PSM, propensity score matching; PSRT, Postsrugical Radiotherapy; LNs, Lymph Nodes.
[a] Includes: American Indian/native Alaskan and Asian/Pacific Islander.
[b] Includes: divorced, separated, single, domestic partner and widowed.
[c] Includes: epithelial neoplasms, cystic, mucinous and serous neoplasms, squamous cell neoplasms.

between the PSRT group and the no-PSRT group in all patients and the subgroup with one to three positive lymph nodes. The hazard ratios (HRs) with 95% confidence intervals (CIs) for gallbladder cancer-specific survival (GBCSS) of patients in the PSRT group were compared with those of in the no-PSRT group via univariate and multivariate Cox regression models. Parameters with a statistical significance in the univariate analysis were included in the multivariate Cox model. A Cox proportional hazard model was used in the subgroup analysis to identify patients who would potentially benefit from radiotherapy. The forest plot was created by GraphPad Prism 8. A *P* value of less than 0.05 was considered significant. The above statistical analyses were calculated by SPSS software (version 24.0) and R software (version 3.2.2).

Results

Study population and patient characteristics

A total of 13,361 patients with GBC were found within the SEER database during the period from 2004 to 2015. According to the inclusion and exclusion criteria, 726 patients with historically confirmed AJCC (8th edition) stage IIIB GBC were identified and included in the final analysis. Of these eligible patients, 272 patients were received radiotherapy after surgery.

The demographics and clinicopathological characteristics are summarized in Table 1. Before propensity score matching (PSM), age, marital status, number of positive lymph nodes and

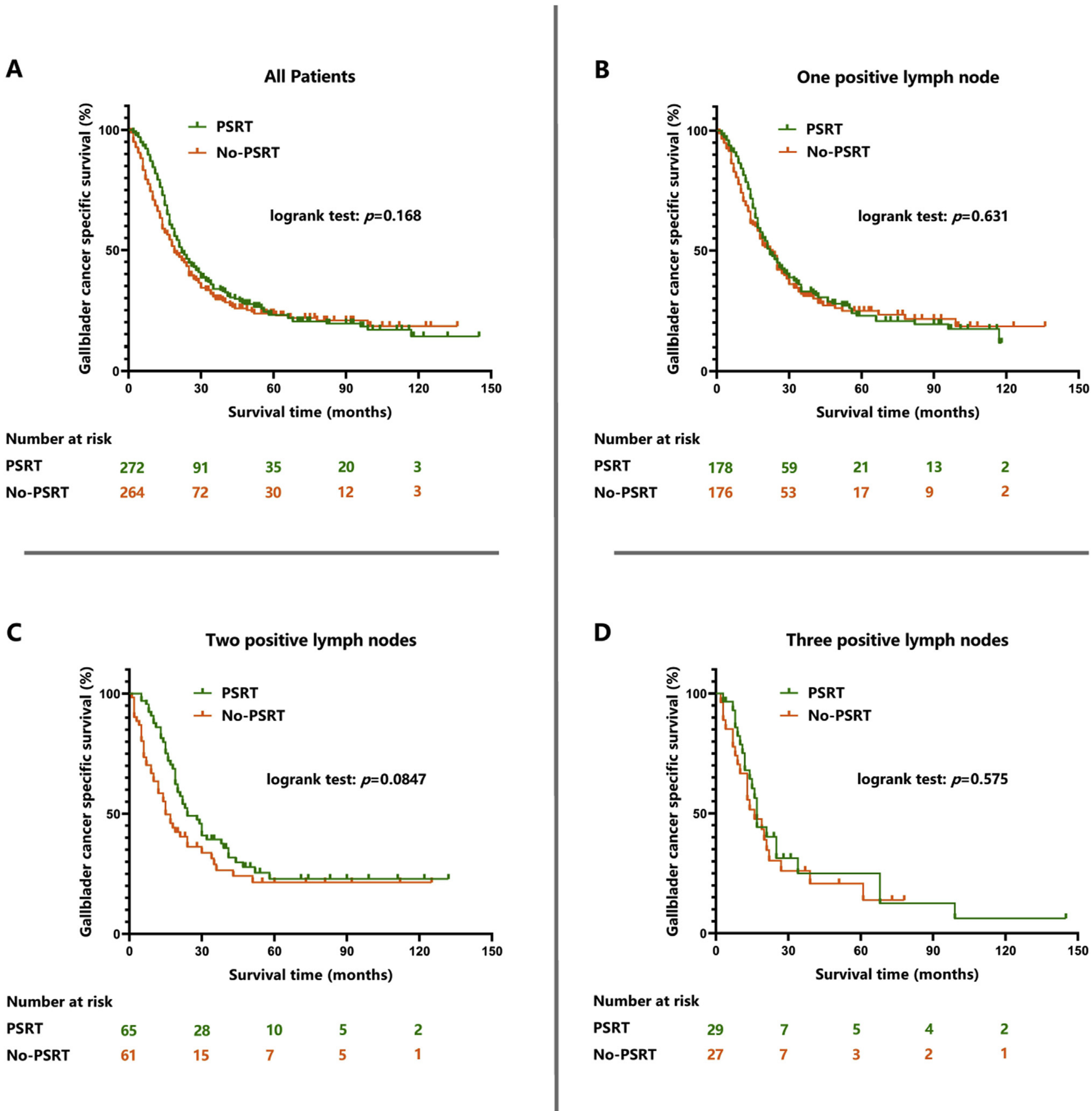

Fig. 1. Survival curves of stage IIIB gallbladder patients with and without PSRT. (A) All stage IIIB patients; (B) Stage IIIB patients with one positive lymph node; (C) Stage IIIB patients with two positive lymph nodes; (D) Stage IIIB patients with three positive lymph nodes.

Table 2
Univariate and multivariate analysis for GBCSS in patients with one to three LNs positive.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (years)				
<70	Reference			
≥70	1.141 (0.921–1.414)	0.227		
Sex				
Male	Reference		Reference	
Female	0.776 (0.621–0.969)	0.025	0.766 (0.613–0.957)	0.019
Race				
White	Reference			
Black	0.900 (0.653–1.239)	0.518		
Others[a]	0.999 (0.725–1.376)	0.996		
Marital status				
Married	Reference			
Unmarried[b]	0.989 (0.801–1.221)	0.918		
Grade				
I	Reference			
II	1.023 (0.716–1.461)	0.900		
III	1.282 (0.901–1.822)	0.167		
IV	1.001 (0.596–1.680)	0.998		
Histology				
Adenocarcinoma	Reference			
Others[c]	1.147 (0.837–1.570)	0.394		
AJCC T stage				
T1	Reference			
T2	0.764 (0.456–1.281)	0.308		
T3	1.621 (0.975–2.695)	0.063		
N1				
No. of LNs positive				
1	Reference			
2	1.000 (0.785–1.273)	1.000		
3	1.269 (0.918–1.755)	0.150		
Tumor size				
<4	Reference			
≥4	1.246 (1.018–1.526)	0.033	1.245 (1.016–1.524)	0.034
Chemotherapy				
No	Reference		Reference	
Yes	0.772 (0.615–0.968)	0.025	0.753 (0.600–0.945)	0.014
Radiotherapy				
No	Reference			
Yes	0.852 (0.697–1.042)	0.120		

GBCSS, Gallbladder Cancer-Specific Survival; LNs, Lymph Nodes.

chemotherapy status showed significant differences between the PSRT and no-PSRT groups. After using PSM to balance the baseline features of these two groups, each group consisted of 272 patients. Between the propensity score matched cohorts, only chemotherapy showed a statistically significant difference, while the other characteristics were all balanced.

Cancer-specific survival in a 1:1 PSM sample

Among the PSM samples, the median survival was 22 and 19 months in the PSRT and no-PSRT groups, respectively. There were 195 (71.7%) gallbladder cancer-specific death events observed in the PSRT group and 181 (66.5%) in the no-PSRT group. The 5-year cancer-specific survival rates were comparable between the two groups (PSRT 22.0% vs. no-PSRT 23.6%). Kaplan-Meier analysis showed that postsurgical radiotherapy failed to improve GBCSS (the log-rank test, $p = 0.168$) (Fig. 1A). In addition, to determine whether the difference in the number of positive lymph nodes affected the prognosis of patients who received radiotherapy after surgery, PSM cohort patients were divided into three subgroups based on the number of positive lymph nodes. In the subgroup with one positive lymph node, the 5-year cancer-specific survival rate was 22.8% in the PSRT group and 24.8% in the no-PSRT group. There was no significant difference in GBCSS between the two groups (PSRT vs. no-PSRT, 22 vs. 22 months, $p = 0.631$) (Fig. 1B). In the subgroup with two positive lymph nodes, the 5-year cancer-specific survival rate was 22.9% in the PSRT group and 21.4% in the no-PSRT group. Although the median survival duration was longer in the PSRT group, the difference in GBCSS is not statistically significant (PSRT vs. no-PSRT, 24 vs. 15 months, $p = 0.084$) (Fig. 1C). In the subgroup with three positive lymph nodes, the 5-year cancer-specific survival rate was 12.5% in the PSRT group and 13.9% in the no-PSRT group. Postsurgical radiotherapy did not improve the GBCSS (PSRT vs. no-PSRT, 17 vs. 16 months, $p = 0.575$) (Fig. 1D).

Risk factors for cancer-specific survival

To identify risk factors for GBCSS among stage IIIB GBC patients, univariate and multivariate Cox regression analyses were performed. The results are presented in Table 2. In the univariate analysis, sex, tumor size and chemotherapy were significantly associated with GBCSS. These three factors were included in the multivariate Cox regression model. The results of the multivariate analysis were consistent with the univariate analysis. Tumor size ≥4 cm was a negative prognostic factor for GBCSS, while female sex and chemotherapy were positive factors for GBCSS. Radiotherapy alone after surgery does not help stage IIIB patients to achieve a better prognosis (HR = 0.852, 95% CI = 0.697–1.042, $p = 0.120$).

Table 3
Subgroup analyses of radiotherapy effect on GBCSS in patients with different features.

Variables	PSRT group death/patients	No-PSRT group death/patients	HR (95% CI)	*P* value
Age (years)				
<70	134/190	121/179	0.826 (0.646–1.056)	0.127
≥70	61/82	64/93	0.921 (0.649–1.309)	0.647
Sex				
Male	59/80	52/72	0.821 (0.564–1.195)	0.302
Female	136/192	133/200	0.845 (0.665–1.074)	0.169
Race				
White	149/201	145/208	0.889 (0.707–1.118)	0.315
Black	24/38	19/27	0.576 (0.313–1.058)	0.075
Others[a]	22/33	21/37	0.988 (0.542–1.800)	0.969
Marital status				
Married	126/178	120/174	0.842 (0.656–1.082)	0.179
Unmarried[b]	69/94	65/98	0.852 (0.607–1.198)	0.358
Grade				
I	20/27	18/33	1.222 (0.645–2.314)	0.538
II	81/118	68/102	0.810 (0.586–1.119)	0.202
III	82/108	88/123	0.850 (0.629–1.150)	0.292
IV	12/19	11/14	1.527 (0.668–3.491)	0.316
Histology				
Adenocarcinoma	175/242	161/242	0.872 (0.704–1.081)	0.211
Others[c]	20/30	24/30	0.719 (0.396–1.304)	0.277
AJCC T stage				
T1	9/14	7/9	0.519 (0.179–1.508)	0.228
T2	79/130	72/136	1.058 (0.768–1.456)	0.731
T3	107/128	106/127	0.802 (0.613–1.050)	0.108
No. of LNs positive				
1	127/178	120/182	0.919 (0.716–1.180)	0.510
2	46/65	44/63	0.685 (0.452–1.037)	0.074
3	22/29	21/27	0.844 (0.460–1.548)	0.583
Tumor size				
<4	86/127	82/129	0.863 (0.637–1.168)	0.339
≥4	109/145	103/143	0.840 (0.642–1.101)	0.206
Chemotherapy				
No	28/33	75/111	1.025 (0.664–1.583)	0.911
Yes	167/239	110/161	0.867 (0.681–1.103)	0.244

GBCSS, Gallbladder Cancer-Specific Survival; PSRT, Postsurgical Radiotherapy.
LNs, Lymph Nodes.

Subgroup analysis

In addition, a Cox proportional hazard model was created in the subgroup analysis to identify the relationship between postsurgical radiotherapy and GBCSS of stage IIIB patients. The results are summarized in Table 3 and Fig. 2. No significant survival benefit from postsurgical radiotherapy was found in any subgroup.

Discussion

The number of positive lymph nodes is an established prognostic factor in patients with several gastrointestinal malignancies, such as colorectal carcinoma, gastric carcinoma and gallbladder carcinoma.[8,16,17] The updated definition of the N category in the 8th edition AJCC staging system has further confirmed the importance of this factor in patients with GBC. The number of node metastases reflects the tumor burden. Therefore, greater lymph node positivity is associated with a higher incidence of locoregional spread and recurrence in patients with GBC making postoperative radiotherapy an attractive therapeutic option.[9,18]

In the present study, we investigated the value of PSRT for stage IIIB GBC patients using data from the SEER database. After using the PSM method, we found that 87.9% of patients in the PSRT groups underwent chemotherapy, which was significantly higher proportion than that in the no-PSRT group (59.2%). In our view, the reason for this difference is that most medical institutions use chemoradiotherapy, while few institutions use radiotherapy alone.

Gold et al. performed a retrospective study of GBC patients who underwent R0 resection. They included patients with T1-3N0-1M0 disease and reported the median overall survival (OS) was no different in patients treated with surgery and adjuvant chemoradiotherapy vs. in those treated with surgery alone.[19] Similarly, Itoh et al. used the Cox regression method to compare the 5-year survival rate between the resection and radiotherapy and resection alone for patients with GBC.[20] Again, the results revealed no significant difference.

In our current study, only stage IIIB GBC patients (T1-3N1M0) were included. Consistent with the aforementioned prior research, postsurgical radiotherapy did not improve the GBCSS in all stage IIIB patients.

Moreover, in subgroup analysis, our results found that patients with a higher number of positive lymph nodes had a worse cancer-specific survival, but the overall cancer-specific survival consistently remained comparable between the PSRT and no-PSRT subgroups. These findings are consistent with a previous study. Hyder et al. reported significantly improved 1-year survival rates with the use of adjuvant radiotherapy, and the survival benefit was more pronounced for N1 disease. However, the benefit was not significant at 5 years.[21] We believe that the short-term survival benefit from radiotherapy is due to temporarily controlling locoregional recurrence.[15] However, Jarnagin et al. reported that GBC recurrences involved a distant site, either alone or concomitant with locoregional disease recurrence. Thus, it would be difficult to advocate the routine use of adjuvant radiotherapy for patients with GBC, given the fraction of patients who experience disease recurrence at locoregional sites alone. There would appear to be no potential benefit, with respect to survival, for the majority of patients who develop disease recurrence at distant sites.[5] Our results,

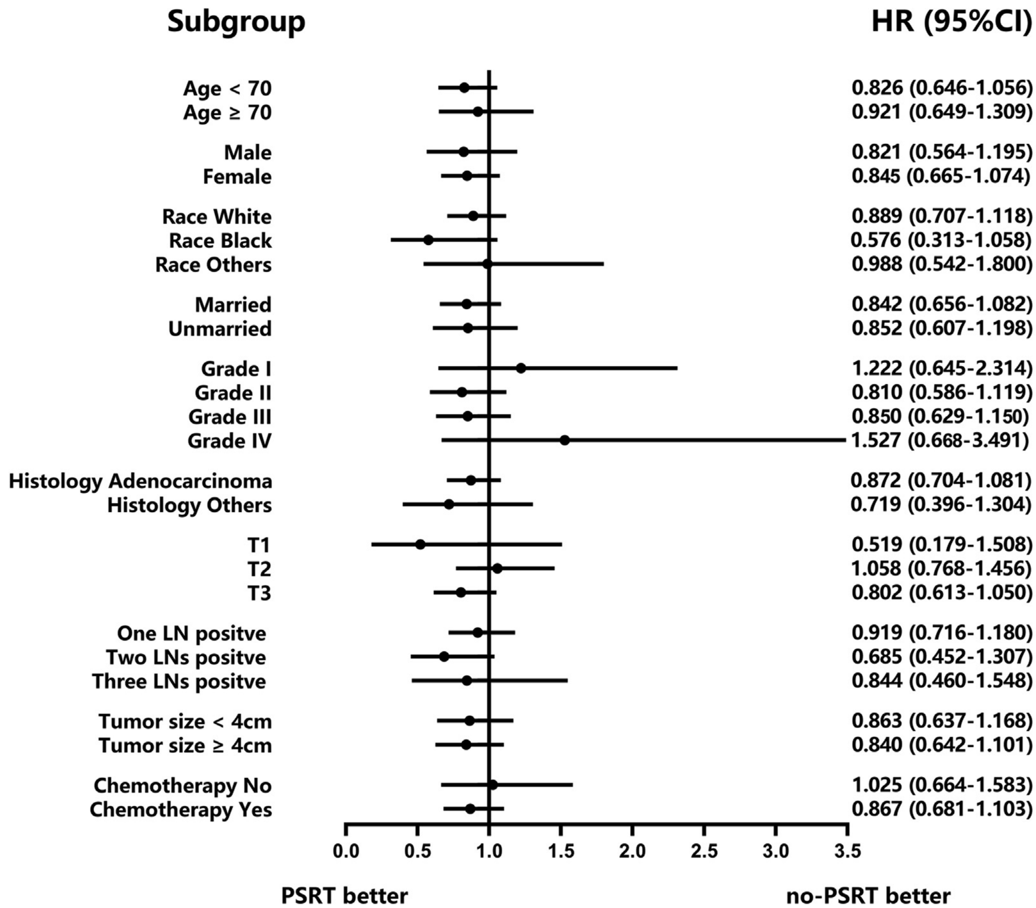

Fig. 2. The forest plot of HRs comparing GBCSS between the PSRT group and no-PSRT group according to different variables.

which reveal that postsurgical radiotherapy does not improve the overall GBCSS in stage IIIB patients, support this opinion.

Through univariate and multivariate Cox regression analysis, we found that male sex, tumor size ≥4 cm, and no-chemotherapy were independent negative prognostic factors for stage IIIB GBC patients. In addition, among the 454 patients with no-PSRT, 293 patients received the postsurgical chemotherapy and 161 patients did not receive postsurgical chemotherapy. We compared the GBCSS between these two groups. The postsurgical chemotherapy alone has significantly improved the survival (Log rank test, $p < 0.0001$). These results are consistent with the study of Woods et al. A nomogram in that study predicted the prognosis of non-metastatic GBC patients after surgery. That study also revealed that male sex, larger tumor size, and a lack of chemotherapy predicted a lower cancer-specific survival rate.[22] However, in both the study form *Woods* and our current study, radiotherapy was not associated with better survival. A recent expert consensus from the American Hepato-Pancreato-Biliary Association states that following R0 resection of T2-4 disease in patients with N1 GBC, patients should be considered for adjuvant systemic chemotherapy and/or chemoradiotherapy.[23] The outcomes of the present study continue to support this suggestion for postsurgical stage IIIB (AJCC 8th edition) GBC patients.

To explore the predictors for choosing of PSRT, subgroup analysis was performed according to different variables. Unfortunately, PSRT failed to improve gallbladder cancer-specific survival in any subgroup of patients. A meta-analysis published by Horgan et al. showed that radiation therapy is less effective than chemotherapy plus radiation therapy.[24] Moreover, the South West Oncology Group (SWOG) conducted a phase II intergroup trial of adjuvant capecitabine and gemcitabine followed by radiotherapy and concurrent capecitabine in patients with GBC. SWOG S0809 reported that for all patients, the 2-year survival rate was 65% (95% CI, 53%–74%) and that of R0 and R1 patients was 67% and 60%, respectively.[25] A recent clinical practice guideline also recommended that patients with gallbladder cancer who achieved R1 resection may undergo chemotherapy plus radiation.[26] However, in our study, the outcomes shown in Table 3 and Fig. 2 (last line) revealed that there was no significant difference between the subgroups of patients who received postsurgical chemoradiotherapy and patients who received postsurgical chemotherapy alone (239 patients vs. 161 patients, $p = 0.244$). On the other hand, radiation enteritis is a common side effect after radiotherapy for abdominal malignancies and can sometimes lead to a reduction in patient quality of life as well as death.[27] Thus, although some studies have reached conclusions about the effects of chemotherapy plus radiation therapy in patients with GBC, our data show that chemoradiation is not superior to chemotherapy alone for patients with stage IIIB GBC. Randomized studies are needed to examine the role of chemotherapy plus radiation therapy.

There are several limitations in our study. First, the SEER database does not include the status of surgical margins. A positive surgical margin or R1 resection is an important factor that affects the prognosis. Additionally, a positive surgical margin could potentially be an indication for using postsurgical radiotherapy. We recommend that future studies can be considered only include GBC patients with positive margins, in order to evaluate the role of PSRT. Second, our study is a retrospective study. Although a PSM method was used to reduce the confounding factors, selection bias could not be avoided. Third, the radiation dosage as well as chemotherapy regimens were varied. The SEER database was not able to provide the details of systematic adjuvant therapy for each patient.

Conclusion

For stage IIIB GBC patients with one to three lymph nodes metastases, postsurgical radiotherapy does not improve the overall GBCSS. Moreover, the chemoradiation is not superior to chemotherapy alone. Postsurgical radiotherapy alone is not recommended for stage IIIB GBC patients. A multicenter phase III trial is needed to clarify the role of radiotherapy in the adjuvant treatment of patients with stage IIIB GBC.

Source of funding

This research was supported by the Sichuan Science and Technology Program (No.2020YFS0098).

Declaration of competing interest

We, all the authors listed above, attest that we have no conflicts of interests to disclose.

Acknowledgements

We would like to acknowledge the support of the Department of Biliary Surgery, West China Hospital, Sichuan University, China.

References

1. Levy AD, Murakata LA, Rohrmann Jr CA. Gallbladder carcinoma: radiologic-pathologic correlation. *Radiographics*. 2001 Mar-Apr;21(2):295–314. questionnaire, 549-55. PubMed PMID: 11259693. Epub 2001/03/22.
2. Dixon E, Vollmer Jr CM, Sahajpal A, et al. An aggressive surgical approach leads to improved survival in patients with gallbladder cancer: a 12-year study at a North American Center. *Ann Surg*. 2005 Mar;241(3):385–394. PubMed PMID: 15729060. Pubmed Central PMCID: PMC1356976. Epub 2005/02/25.
3. Henson DE, Albores-Saavedra J, Corle D. Carcinoma of the gallbladder. Histologic types, stage of disease, grade, and survival rates. *Cancer*. 1992 Sep 15;70(6):1493–1497. PubMed PMID: 1516000. Epub 1992/09/15.
4. Duffy A, Capanu M, Abou-Alfa GK, et al. Gallbladder cancer (GBC): 10-year experience at memorial sloan-kettering cancer centre (MSKCC). *J Surg Oncol*. 2008 Dec 1;98(7):485–489. PubMed PMID: 18802958. Epub 2008/09/20.
5. Jarnagin WR, Ruo L, Little SA, et al. Patterns of initial disease recurrence after resection of gallbladder carcinoma and hilar cholangiocarcinoma: implications for adjuvant therapeutic strategies. *Cancer*. 2003 Oct 15;98(8):1689–1700. PubMed PMID: 14534886. Epub 2003/10/10.
6. Kopelson G, Galdabini J, Warshaw AL, Gunderson LL. Patterns of failure after curative surgery for extra-hepatic biliary tract carcinoma: implications for adjuvant therapy. *Int J Radiat Oncol Biol Phys*. 1981 Mar;7(3):413–417. PubMed PMID: 7275721. Epub 1981/03/01.
7. Amin MB, Greene FL, Edge SB, et al. The Eighth Edition AJCC Cancer Staging Manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA A Cancer J Clin*. 2017 Mar;67(2): 93–99. PubMed PMID: 28094848. Epub 2017/01/18.
8. Sakata J, Shirai Y, Wakai T, et al. Number of positive lymph nodes independently determines the prognosis after resection in patients with gallbladder carcinoma. *Ann Surg Oncol*. 2010 Jul;17(7):1831–1840. PubMed PMID: 20077022. Epub 2010/01/16.
9. Lim H, Seo DW, Park DH, et al. Prognostic factors in patients with gallbladder cancer after surgical resection: analysis of 279 operated patients. *J Clin Gastroenterol*. 2013 May-Jun;47(5):443–448. PubMed PMID: 23188077. Epub 2012/11/29.
10. Hwang KY, Yoon YI, Hwang S, et al. Survival analysis following resection of AJCC stage III gallbladder carcinoma based on different combinations of T and N stages. *Korean J Hepatobiliary Pancreat Surg*. 2015 Feb;19(1):11–16. PubMed PMID: 26155271. Pubmed Central PMCID: PMC4494090. Epub 2015/07/15.
11. Sung YN, Song M, Lee JH, et al. Validation of the 8th edition of the American Joint committee on cancer staging system for gallbladder cancer and implications for the follow-up of patients without node dissection. *Cancer Res Treat*. 2020 Apr;52(2):455–468. PubMed PMID: 31623417. Pubmed Central PMCID: PMC7176947. Epub 2019/10/19.
12. Benson AB, D'Angelica MI, Abbott DE, et al. Guidelines insights: hepatobiliary cancers, version 2.2019. *J Natl Compr Canc Netw*. 2019 Apr 1;17(4):302–310. PubMed PMID: 30959462. Epub 2019/04/09.
13. Miyazaki M, Yoshitomi H, Miyakawa S, et al. Clinical practice guidelines for the management of biliary tract cancers 2015: the 2nd English edition. *J Hepatobiliary Pancreat Sci*. 2015 Apr;22(4):249–273. PubMed PMID: 25787274. Epub 2015/03/20.
14. Wang SJ, Fuller CD, Kim JS, et al. Prediction model for estimating the survival benefit of adjuvant radiotherapy for gallbladder cancer. *J Clin Oncol*. 2008 May 1;26(13):2112–2117. PubMed PMID: 18378567. Epub 2008/04/02.
15. Jeong Y, Park JH, Lee YJ, et al. Postoperative radiotherapy for gallbladder cancer. *Anticancer Res*. 2014 Oct;34(10):5621–5629. PubMed PMID: 25275065. Epub 2014/10/03.
16. Cohen AM, Tremiterra S, Candela F, et al. Prognosis of node-positive colon cancer. *Cancer*. 1991 Apr 1;67(7):1859–1861. PubMed PMID: 2004298. Epub 1991/04/01.
17. Kodera Y, Yamamura Y, Shimizu Y, et al. The number of metastatic lymph nodes: a promising prognostic determinant for gastric carcinoma in the latest edition of the TNM classification. *J Am Coll Surg*. 1998 Dec;187(6):597–603. PubMed PMID: 9849732. Epub 1998/12/16.
18. Ribelles N, Perez-Villa L, Jerez JM, et al. Pattern of recurrence of early breast cancer is different according to intrinsic subtype and proliferation index. *Breast Cancer Res*. 2013;15(5):R98. PubMed PMID: 24148581. Pubmed Central PMCID: PMC3978680. Epub 2013/10/24.
19. Gold DG, Miller RC, Haddock MG, et al. Adjuvant therapy for gallbladder carcinoma: the mayo clinic experience. *Int J Radiat Oncol Biol Phys*. 2009 Sep 1;75(1):150–155. PubMed PMID: 19297105. Epub 2009/03/20.
20. Itoh H, Nishijima K, Kurosaka Y, et al. Magnitude of combination therapy of radical resection and external beam radiotherapy for patients with carcinomas of the extrahepatic bile duct and gallbladder. *Dig Dis Sci*. 2005 Dec;50(12): 2231–2242. PubMed PMID: 16416167. Epub 2006/01/18.
21. Hyder O, Dodson RM, Sachs T, et al. Impact of adjuvant external beam radiotherapy on survival in surgically resected gallbladder adenocarcinoma: a propensity score-matched Surveillance, Epidemiology, and End Results analysis. *Surgery*. 2014 Jan;155(1):85–93. PubMed PMID: 23876364. Pubmed Central PMCID: PMC3979596. Epub 2013/07/24.
22. Zhang W, Hong HJ, Chen YL. Establishment of a gallbladder cancer-specific survival model to predict prognosis in non-metastatic gallbladder cancer patients after surgical resection. *Dig Dis Sci*. 2018 Sep;63(9):2251–2258. PubMed PMID: 29736837. Epub 2018/05/08.
23. Aloia TA, Jarufe N, Javle M, et al. Gallbladder cancer: expert consensus statement. *HPB (Oxford)*. 2015 Aug;17(8):681–690. PubMed PMID: 26172135. Pubmed Central PMCID: PMC4527853. Epub 2015/07/15.
24. Horgan AM, Amir E, Walter T, Knox JJ. Adjuvant therapy in the treatment of biliary tract cancer: a systematic review and meta-analysis. *J Clin Oncol*. 2012 Jun 1;30(16):1934–1940. PubMed PMID: 22529261. Epub 2012/04/25.
25. Ben-Josef E, Guthrie KA, El-Khoueiry AB, et al. Swog S0809: a phase II intergroup trial of adjuvant capecitabine and gemcitabine followed by radiotherapy and concurrent capecitabine in extrahepatic cholangiocarcinoma and gallbladder carcinoma. *J Clin Oncol*. 2015 Aug 20;33(24):2617–2622. PubMed PMID: 25964250. Pubmed Central PMCID: PMC4534524. Epub 2015/05/13.
26. Shroff RT, Kennedy EB, Bachini M, et al. Adjuvant therapy for resected biliary tract cancer: ASCO clinical practice guideline. *J Clin Oncol*. 2019 Apr 20;37(12): 1015–1027. PubMed PMID: 30856044. Epub 2019/03/12.
27. Musa AE, Shabeeb D, Alhilfi HSQ. Protective effect of melatonin against radiotherapy-induced small intestinal oxidative stress: biochemical evaluation. *Medicina (Kaunas)*. 2019 Jun 25;55(6). PubMed PMID: 31242652. Pubmed Central PMCID: PMC6631393. Epub 2019/06/28.