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Tumor location is a strong predictor of tumor progression and survival in T2 gallbladder cancer: an international multicenter study

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Abstract

Objective—To determine the prognostic impact of tumor location in gallbladder cancer.

Summary Background Data—Depth of tumor is a strong predictor of survival after curative resection of gallbladder cancer. However, the gallbladder has a unique anatomical relationship with the liver, and the clinical significance of tumor location remains unclear.

Methods—For 437 patients with gallbladder cancer resected at 4 international institutions, clinicopathologic characteristics and their association with survival were analyzed. Tumor location was defined as “hepatic side” or “peritoneal side”, and the prognostic significance of tumor location was evaluated.

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Results—Among the 252 patients with T2 disease, patients with tumors on the hepatic side (T2h, n=99) had higher rates of vascular invasion, neural invasion, and nodal metastasis than patients with tumors on the peritoneal side (T2p, n=153) (51% vs. 19%, 33% vs. 8%, and 40% vs. 17%, respectively, $P<0.01$ for all). After a median follow-up of 58.9 months, 3-year and 5-year survival rates were 52.1% and 42.6%, respectively, for T2h tumors and 73.7% and 64.7%, respectively, for T2p tumors ($P=0.0006$). No such differences were observed in T1 or T3 tumors. Multivariate analysis confirmed the independent association of hepatic-side location with survival in T2 tumors (hazard ratio, 2.7; 95% CI, 1.7 to 4.2; $P<0.001$). This subclassification of T2 tumors predicted recurrence in the liver (23% vs. 3%, $P=0.003$) and distant lymph nodes (16% vs. 3%, $P=0.019$) even after radical resection.

Conclusions—After curative resection of T2 gallbladder cancer, tumor location predicts the pattern of recurrence and survival.

INTRODUCTION

Gallbladder cancer is a relatively rare but highly aggressive malignancy affecting approximately 10,500 patients annually in the United States.[1] Surgical resection is the only effective treatment for gallbladder cancer because effective systemic therapy has not been established. Therefore, accurate prognostication is important to determine the curability and appropriate extent of surgery in this disease entity.

It is well known that the survival outcomes after curative resection of gallbladder cancer are strongly associated with the depth of tumor invasion through the gallbladder wall.

According to the largest series of patients with gallbladder cancer,[2] patients with T1 gallbladder cancer (tumor limited to the mucosal or lamina propria) had a 5-year survival rate of 85.9%, whereas patients with T3 and T4 tumors (tumor invading beyond the serosa) had dismal 5-year survival rates of 19.2% and 14.1%, respectively. Patients with T2 gallbladder cancer (tumor had reached the subserosal layer) had a moderate 5-year survival rate of 56.1%. Therefore, adequate surgical management for T2 gallbladder cancer has been of major clinical interest to surgeons.[3–7]

In surgical treatment of T2 gallbladder cancer, tumor biology plays a far greater role in outcome than does the extent of resection.[8, 9] Thus, the extent of resection and necessity of adjuvant therapy should be determined according to the likelihood of microscopic liver metastases or nodal involvement in individual patients. Because the gallbladder has a unique anatomical position, with half of its body being attached to the liver, the risk of tumor invasion and the mode of cancer spread might be influenced by whether the tumor is located on the hepatic side or the peritoneal side of the gallbladder. Nevertheless, the clinical significance of the position of the tumor has not yet been clarified, and the current edition of the American Joint Committee on Cancer staging system for gallbladder cancer[10] does not take into account the impact of tumor location. In this study, we sought to determine the impact of tumor location on disease progression and survival in patients undergoing resection of gallbladder cancer.

METHODS

Study Cohort and Clinicopathologic Variables

The Institutional Review Board of The University of Texas MD Anderson Cancer Center approved this study protocol. We identified 622 patients who underwent resection of gallbladder cancer between 1981 and 2011 at 4 major hepatobiliary centers: The University of Texas MD Anderson Cancer Center (Houston, TX, USA), Clinica Alemana Santiago (Santiago, Chile), Ospedale Mauriziano Umberto I (Turin, Italy), and University of Tokyo (Tokyo, Japan). To evaluate the prognostic factors for gallbladder cancer, we excluded patients with insufficient clinical and/or histopathologic data (n=134) and patients in whom potentially curative resection could not be achieved (n=43), and rare histopathologic subtypes other than adenocarcinoma (n=8). The remaining 437 patients who underwent macroscopically curative resection comprised the final cohort and were studied in detail.

Basic surgical approach and follow-up

Multidisciplinary clinical approaches including indication of preoperative or postoperative therapy varied among the institutions. However, basic surgical approaches were similar as follows. When gallbladder cancer was highly suspected in preoperative work-up, surgical resection was considered only when R0 resection was thought to be feasible. Simultaneous liver resection with wide surgical margin, regional lymphadenectomy, and additional resection of the surrounding organs were considered to achieve the R0 resection. The extent of liver resection or lymphadenectomy was determined based on the intraoperative findings and each institutional policy. For patients who were incidentally diagnosed with gallbladder cancer after simple cholecystectomy for other benign etiologies, additional resection (liver resection and/or regional lymphadenectomy) was considered based on the extent of tumor invasion, tumor grade, margin status, or risk of nodal involvement. In recent years, every institution has performed additional resection when tumor invasion reaches subserosal level (i.e. T2 stage).

Postoperatively, recurrence of tumor was monitored regularly by ultrasound and CT scan. Tumor markers such as carcinoembryonic antigen or CA19-9 were also measured to detect the recurrence of tumor which cannot be visualized in radiologic studies. When recurrence was observed, appropriate chemotherapy or radiation therapy was performed.

Histopathologic Evaluation and Definition of Tumor Location

Tumor stage was determined according to the seventh edition of the American Joint Committee on Cancer staging system.[10] All the specimens were reviewed by each institutional pathologists blinded to the clinical outcomes, and histopathologic findings were recorded, including depth of invasion, vascular invasion, neural invasion, nodal involvement, and presence of micrometastases at the adjacent liver parenchyma. The location of tumor was defined histopathologically according to the scheme presented in Figure 1. For T1 or T2 tumors (i.e., tumors that did not invade beyond the whole thickness of the gallbladder wall), tumors were classified as being located on the peritoneal side when tumor infiltrated only the free serosal side of the gallbladder and on the hepatic side when at least part of a tumor infiltrated the part of the gallbladder wall attached to the liver. For T3

or T4 tumors (i.e., tumors that invaded beyond the whole thickness of the gallbladder wall), tumors were classified as being located on the hepatic side when at least part of a tumor invaded directly into the liver parenchyma. All other tumors (without direct invasion into the liver parenchyma) were classified as being located on the peritoneal side regardless of the distribution of tumor within the gallbladder wall.

For patients who were incidentally diagnosed with gallbladder cancer after simple cholecystectomy, gross specimen was not always available for detailed mapping of cancer. For such cases, location of tumor was determined by the following protocol. When there was a part of liver tissue or exposed subserosal fibroadipose tissue (not outlined by serosa) at the deeper part of the tumor, the location of the tumor was classified as the “hepatic side”. Meanwhile, when none of these findings were observed and the tumor was clearly outlined by intact serosa microscopically, the location of tumor was classified as the “peritoneal side”.

Statistical Analysis

Statistical analysis was performed using IBM SPSS software (version 19.0, SPSS Inc, Chicago, IL, USA). Medians and ranges of continuous variables were compared using the Mann-Whitney *U* test. Categorical variables were compared using Pearson’s chi-squared test or Fisher’s exact test as appropriate. The overall survival was calculated on the basis of the time from surgery to death or last follow-up. Survival curves were generated using the Kaplan-Meier method and were compared by log-rank test. To identify prognostic factors after potentially curative resection, a multivariate regression analysis was performed with the Cox proportional hazards model using a backward-elimination procedure using all possible confounders. To prevent overfitting, only factors that showed statistically significant association with tumor recurrence with $P < 0.10$ were included in the final model.

RESULTS

Clinicopathologic Characteristics

One-hundred eighty (41%) patients were treated at Clinica Alemana Santiago, Chile, 111 (25%) at the University of Tokyo, Japan, 86 (20%) at Ospedale Mauriziano Umberto I, Turin, Italy, and 60 (14%) at MD Anderson Cancer Center, Houston, USA. When dividing the study period into 3 time periods based on the date of surgery, 61 (14%) patients were from 1981–1990, 172 (39%) patients were from 1991–2000, and 204 (47%) patients were from 2001–2012. Though the proportion of patients derived from each time periods varied among the four institutions ($p < 0.001$), the proportion was similar among the latter three institutions for T2 tumors ($p = 0.07$) which accounted for half of the population.

The median age of the 437 patients with gallbladder cancer was 63 years (range, 30–88 years); 134 (30%) were men. Details of surgical procedures and histopathologic findings are summarized in Table 1. Of the 437 patients, 311 (71%) patients underwent hepatic resection and lymphadenectomy at presentation ($n = 164$) or at re-resection after cholecystectomy ($n = 147$). Resection of additional organs was required in 43 (10%) patients.

With a median follow-up period of 58.9 months (range, 2–270 months), 199 (46%) patients died, 168 (38%) patients lost to follow-up at 48.6 months in median, and the remaining 70 (16%) patients survived at the time of analysis. The 3-year and 5-year survival rates of the entire cohort were estimated as 56.6% and 48.9%, respectively.

Tumor Location and Survival Rates

Among the 437 patients, the distribution of cancer was mapped in detail at the time of histopathologic diagnosis in 310 (71%) patients, while the location of tumor was inferred from the available slides in the remaining 127 (29%) patients following the protocol described above. As a result, 183 (42%) had hepatic-side tumors, and 254 (58%) had peritoneal-side tumors. The proportion of patients with hepatic-side tumors was 72% (33/46) among patients with T1 tumors, 39% (99/252) among those with T2 tumors, and 33% (43/131) among those with T3 tumors. All T4 tumors (n=8) were classified as hepatic-side tumors.

When long-term survival was compared between patients with hepatic-side and peritoneal-side tumors, a clear prognostic difference was observed in the T2 group: 3-year and 5-year survival rates were 52.1% and 42.6%, respectively, for hepatic-side tumors (T2h) and 73.7% and 64.7%, respectively, for peritoneal-side tumors (T2p) ($P=0.0006$) (Figure 2). T1 tumors were associated with a good prognosis regardless of location (5-year survival rate, 85% for hepatic-side tumors and 90% for peritoneal-side tumors and; $P=0.22$), and T3 tumors were associated with a poor prognosis regardless of location (5-year survival rate, 29% for hepatic-side tumors and 25% for peritoneal-side tumors and; $P=0.61$). These results were not influenced by whether or not gross findings were available for accurate cancer mapping at the time of histopathologic review.

T2 Tumor Location and Histopathologic Features

To investigate the histopathologic bases for the prognostic difference between T2h and T2p tumors, incidences of vascular invasion, neural invasion, nodal involvement, and liver metastases were compared between these tumor subgroups using evaluable histopathologic data. As presented in Figure 3, the rates of vascular invasion and neural invasion were significantly higher in T2h tumors than in T2p tumors. Similarly, the rates of nodal involvement and macroscopic liver metastasis observed in histopathologic specimens were higher in T2h tumors than in T2p tumors (40% vs. 17%, $P=0.002$, and 9% vs. 2%, $P=0.18$, respectively).

T2 Tumor Location and Histopathologic Evidence of Residual Cancer Cells after Simple Cholecystectomy

Among the 252 patients with T2 gallbladder cancer, 108 patients underwent radical resection of both liver and lymph nodes after simple cholecystectomy. Residual cancer cells were observed on the gallbladder bed at the time of additional resection in 18% (7/39) of patients with T2h tumors and 0% (0/69) in those with T2p tumors ($P=0.001$). In addition, micrometastatic foci was detected in the adjacent hepatic parenchyma in 33% (13/39) of the patients with T2h tumors and 6% (4/69) of the patients with T2p tumors at the time of re-resection ($P<0.001$). The incidence of metastasis in the resected lymph nodes was also

higher in patients with T2h tumors (11/39, 28%) than in those with T2p tumors (12/69, 17%) ($P=0.18$).

Prognostic Factors for Patients with T2 Gallbladder Cancer

To identify the prognostic factors for patients with T2 gallbladder cancer, multivariate analysis was performed. We chose 13 potential confounders: age, gender, institution, era (1981–1990 vs. 1991–2000 vs. 2001–2012), location of tumor (hepatic-side vs. peritoneal-side), nodal involvement (N1 vs. N0), postoperatively proven liver metastasis (M1 vs. M0), radical resection (i.e. liver resection + regional lymphadenectomy) (yes/no), bile duct resection (yes/no), margin status (R1 vs. R0), tumor grade (poorly differentiated vs. moderately differentiated vs. well differentiated), neoadjuvant therapy (yes/no), and adjuvant chemotherapy (yes/no).

Among these, hepatic-side location, moderate or poor tumor differentiation, and regional nodal involvement were selected as independent predictors for worse survival. Radical resection (i.e., liver resection plus regional lymphadenectomy) and more recent era were associated with improved survival. Positive margin status also showed tendency toward worse prognosis, though it was not statistically significant. Other factors were not selected as independent prognostic factors in the final model (Table 2).

Subclassification of T2 tumors by the tumor location effectively stratified patient prognosis (Figure 4A). This subclassification enabled further prognostic stratification of stage IB (T2N0M0) into T2pN0M0 and T2hN0M0, which were associated with 5-year survival rates of 66.0% and 52.4% respectively ($P=0.04$) (Figure 4B).

Surgical curability of T2p and T2h Tumors

Lastly, the curability of T2p and T2h tumors was assessed on the basis of the rates of recurrence in the liver or in distant lymph nodes (i.e., lymph nodes outside of the hepatoduodenal ligament) after radical procedures including liver resection and/or regional lymphadenectomy. The intrahepatic recurrence rate after liver resection was significantly higher for T2h tumors (15/66, 23%) than for T2p tumors (2/61, 3%) ($P=0.003$). Similarly, the distant nodal recurrence rate was significantly higher for T2h tumors (12/74, 16%) than for T2p tumors (2/67, 3%), even after regional lymphadenectomy ($P=0.019$). The incidence of local or peritoneal recurrence after additional radical resection secondary to simple cholecystectomy was also more frequent in patients with T2h tumors (7/39, 19%) than in those with T2p tumors (3/53, 6%) ($P<0.001$).

Figure 5 compares the survival curves of patients with T2 tumors stratified by tumor location and whether or not radical resection was performed. Among patients with T2p tumors, the 5-year survival rate was 75.5% among patients who underwent radical resection and 49.8% among patients who did not undergo radical resection ($P=0.006$). Similarly, among patients with T2h tumors, the patients who underwent radical resection had a better 5-year survival rate than the patients who did not undergo radical resection (48.2% vs. 28.9%; $P=0.19$). However, the overall prognosis of patients with T2h tumors remained inferior to that of patients with T2p tumors even after radical resection. Regarding the

efficacy of additional resection after simple cholecystectomy, the additional resection was apparently advantageous in patients with T2p tumors with significant improvement in survival outcomes compared to that after cholecystectomy only ($P=0.008$). Similar tendency was also observed in patients with T2h tumors, though the prognostic difference was not statistically significant (Figure 6).

When comparing the long term outcomes in patients with T2 tumors among the three time periods (1981–1990, 1991–2000, and 2001–2012), the 5-year survival rate had improved over time both in the patients with T2p tumors (47.1%, 60.5%, and 80.0%; $P=0.02$) and those with T2h tumors (0%, 35.8% and 51.1%; $P=0.0009$) with increased use of radical resection (44% in 1981–1990, 48% in 1991–2000, and 73% in 2001–2012; $P=0.0002$).

DISCUSSION

In this study, we analyzed the influence of tumor location on the long-term survival of patients with gallbladder cancer. Hepatic-side tumor location was strongly correlated with higher incidences of vascular invasion, nodal involvement, and hepatic metastasis in T2 gallbladder cancer, resulting in worse survival compared to the survival of patients with peritoneal-side tumor location. Our findings show that subclassification of T2 gallbladder cancer according to tumor location effectively stratifies patient prognosis after potentially curative resection of gallbladder cancer.

T2 gallbladder cancer is a good indication for surgery because hepatic resection and regional lymphadenectomy performed concomitantly with or after simple cholecystectomy have reportedly improved patient survival and possibly offer a chance of cure.[9, 11] As indicated in the multivariate analysis (Table 2), radical resection with curative intent was a favorable prognostic factor, and the overall survival rate was better in patients treated with liver resection and/or lymphadenectomy than in those treated without such radical procedures (Figure 5). Therefore, radical resection for T2 cancers should be the standard of care. After radical resections, the patients with peritoneal-side tumors (T2p) had a very high 5-year survival rate, 76%, while the patients with hepatic-side tumors (T2h) had a 5-year survival rate of less than 50%. These results suggest that T2p tumors could be managed with surgical resection alone. However, T2h tumors would require consideration of adjuvant therapy even after curative resection given their higher recurrence rate and poor prognosis.

The mode of spread of gallbladder cancer has been carefully examined in other studies.[12–14] As clearly confirmed in this study, T1 tumors are associated with a good prognosis with very low rates of vascular invasion and nodal and liver metastasis. However, when the tumor invades the subserosal layer, vascular invasion frequently occurs because the deeper subserosal layer contains dense and larger vessels.[15] Three types of spread of gallbladder cancer have been reported: lymph node metastasis through lymphatic invasion, tumor spread via lymphatic flow along the Glissonian pedicles, and hematogenous liver metastasis through the cystic veins.[12–14] Although it remains controversial whether the pericholecystic lymphatic vessels or the cystic veins play a major role in spread of gallbladder cancer, anatomic differences in the venous/lymphatic drainage route between the hepatic side and the peritoneal side of the gallbladder may explain the observed differences

in the rates of vascular invasion, nodal involvement, and liver metastases. Classical studies using staining methods have reported that the hepatic side of the gallbladder is drained by short cystic veins (2–20 in number) directly connecting with intrahepatic portal veins, while the peritoneal side is usually drained by 1 or 2 cystic veins terminating in the adjacent liver parenchyma or venous plexus at the hepatic hilum.[13, 16] As such, it is easy to speculate that the density of vascular structures and the length of the drainage route from the tumor to first-echelon lymph nodes or the liver affect the incidence of vascular invasion and metastasis.

Endo et al.[17] reported that microscopic liver metastases were frequently detected in patients with T2 gallbladder cancer on the hepatic side that had invaded the subserosa more than 3 mm. Similarly, the present study confirmed that residual cancer cells at the gallbladder bed and micrometastases in adjacent liver parenchyma were detected more frequently after simple cholecystectomy for hepatic-side tumors than after simple cholecystectomy for peritoneal-side tumors (18% vs. 0%, $P=0.001$ and 33% vs. 6%, $P<0.001$, respectively). These observations support the concept that hepatic-side tumors have a higher propensity for early metastasis, which would mean that the anatomic location of tumors in the gallbladder could be a predictor of microscopic tumor progression and surgical outcomes after potentially curative resection of T2 gallbladder cancer.

From a clinical standpoint, the current results are practically important. First, this study confirms that simple cholecystectomy is insufficient for T2 gallbladder cancer irrespective of tumor location. This result would support additional resection when T2 gallbladder cancer is incidentally diagnosed in the resection specimen after cholecystectomy. Second, when the tumor is located on the peritoneal side, radical resection offers a chance of cure and is associated with very high survival rates after potentially curative resection, whereas for patients with hepatic-side tumors, surgical resection alone cannot achieve satisfactory long-term outcomes. Therefore, patients with T2h tumors may be good candidates for adjuvant therapy after radical surgery.

The limitations of this study include its retrospective nature and selected population excluding 20% of initial cohort due to missing histopathologic specimens and old clinical data. However, gallbladder cancer is a relatively rare malignancy, and the present study is one of the largest series analyzing T2 gallbladder cancer. Importantly, the current data were from 4 high-volume centers in North America, South America, Europe, and Asia, and no prognostic impact of the factor “institution” was confirmed in the multivariate analysis. Additionally, in 127 (29%) patients who were incidentally diagnosed with gallbladder cancer after simple cholecystectomy, only limited number of microscopic slides were available for review and detailed mapping of tumor was difficult. However, the prognostic difference between T2h and T2p tumors was similar regardless of whether gross findings were available for accurate cancer mapping at the time of review. The proposed definitions of hepatic and peritoneal location offer a simple and reliable method to stratify patient survival in T2 gallbladder cancer that does not require any special techniques or biomarkers.

In conclusion, tumor location predicts survival after curative resection of T2 gallbladder cancer. This information can be used to individualize additional treatments and postoperative follow-up protocols.

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T1 or T2

Peritoneal side: Tumor infiltrating ONLY the free serosal side of the gallbladder.

Hepatic side: At least part of the tumor infiltrating the liver part of the gallbladder wall.

T3 or T4

Peritoneal side: Tumor not invading the liver parenchyma

Hepatic side: Tumor invading the liver parenchyma

Figure 1.

Definition of tumor location of gallbladder cancer.

Figure 2.
Prognostic influence of tumor location after resection of gallbladder cancer according to T stage.

Figure 3.

Histopathologic evidence of tumor invasion and incidence of nodal/liver metastases.

A. Histopathological evidence of vascular or neural invasion. B. Incidences of nodal involvement and liver metastases.

Vascular or neural invasion was assessed in 377 evaluable specimens excluding indeterminate cases due to the effect of adjuvant therapy or low quality of the specimens. The incidences of nodal involvement and macroscopic liver metastases were actual

incidences based on the histopathologic data only from the patients who underwent liver resection or lymphadenectomy for curative intent.

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Figure 4.

Survival after resection of gallbladder cancer

A. Comparison of survival according to T stage with subclassification of T2 tumors by tumor location.

B. Comparison of survival according to conventional TNM classification with subclassification of T2 tumors by tumor location.

N factor and M factor were clinically determined based on either histopathologic findings or radiographic evaluation.

	n	Survival Rates, %		
		1 year	3 years	5 years
T1	46	97.5	86.1	86.1
T2p, radical resection (+)	80	98.7	81.7	75.5
T2p, radical resection (-)	73	79.3	63.4	49.8
T2h, radical resection (+)	69	83.1	56.4	48.2
T2h, radical resection (-)	30	71.9	40.5	28.9
T3	131	65.7	34.1	26.3

Figure 5.

Prognostic impact of radical resection for T2 peritoneal-side tumors and T2 hepatic-side tumors.

Figure 6.
Efficacy of additional resection after simple cholecystectomy in T2 gallbladder cancer. A. T2 peritoneal-side tumors. B. T2 hepatic-side tumors.

Table 1**Patient, Tumor, and Treatment Characteristics***

Age, years, median (range)	63 (30–88)
Sex	
Male	134 (30)
Female	304 (70)
Surgical procedure	
Cholecystectomy only	126 (29)
Upfront extensive resection	164 (37)
Additional resection after cholecystectomy	147 (34)
Liver resection	279 (64)
Resection of the gallbladder bed	50 (11)
Segment 4b/5 resection	183 (42)
Extended hepatectomy	46 (11)
Bile duct resection	111 (25)
Regional lymphadenectomy	306 (70)
Additional organ resection	
Colon	19 (4)
Stomach/duodenum	4 (1)
Pancreas	20 (5)
Margin status	
R0	406 (93)
R1	31 (7)
Neoadjuvant therapy	22 (5)
Adjuvant therapy	79 (18)
T category	
T1	46 (11)
T2	252 (58)
T3	131 (30)
T4	8 (2)
N category ^a	
N0	316 (72)
N1	121 (28)
M category ^b	
M0	423 (97)
M1	14 (3)
Tumor location	
Hepatic side	183 (42)
Peritoneal side	254 (58)
Tumor grade	
Well differentiated	109 (24)
Moderately differentiated	164 (37)

Poorly differentiated	128 (29)
Indeterminate ^c	37 (10)
Microscopic vascular invasion	
Present	134 (30)
Absent	243 (55)
Indeterminate ^d	60 (15)
Microscopic neural invasion	
Present	89 (20)
Absent	288 (66)
Indeterminate ^d	60 (15)

* Values in table indicate number of patients (percentage) unless otherwise indicated.

^a Clinically classified as N0 (cN0) when cancer cells were not histopathologically proven (pN0, n=190) or when no radiographic evidence of lymphadenopathy was observed (pNx, n=126). N1 was also defined clinically (cN1) based on the histopathologic evidence of cancer in resected specimen (pN1, n=116) or radiographic evidence of lymphadenopathy (pNx, n=5).

^b All the metastases were liver metastases proven in the resected specimen.

^c Indeterminate subtypes including chemotherapy/radiotherapy effects.

^d Indeterminate due to chemotherapy/radiotherapy effects, tumor necrosis, or quality of specimen.

Table 2

Prognostic Factors for T2 Gallbladder Cancer

	<i>P</i> *	Coefficient [†]	Standard error	Wald chi-square	Hazard ratio	95% CI
Hepatic-side location						
Tumor differentiation						
Moderate vs. well	<0.001	0.978	0.238	16.9	2.66	1.67 to 4.24
Poor vs. well	<0.001	1.237	0.303	16.7	3.45	1.90 to 6.24
Radical resection (liver resection + lymphadenectomy)	0.004	1.009	0.346	8.5	2.74	1.39 to 5.41
Nodal involvement ^a	0.003	-0.717	0.245	8.6	0.49	0.30 to 0.79
Era	0.030	0.626	0.289	4.7	1.87	1.06 to 3.29
1991–2000 vs. 1981–1990	0.034	-0.636	0.300	4.5	0.53	0.29 to 0.95
2001–2012 vs. 1981–1990	<0.001	-1.341	0.319	17.7	0.26	0.14 to 0.49
Margin status (R1 vs. R0)	0.075	0.766	0.431	3.2	2.15	0.93 to 5.00

* Based on likelihood test adjusted for the other factors in the final model.

[†] Estimated coefficient for the variable and the associated standard error.

^a Clinical classification based on radiology and/or pathology.

Note. Multivariate Cox regression was applied with stepwise backward selection. Initially, all factors were included in the model. Then factors that showed no or limited statistically significant association ($P > 0.1$) with survival adjusted for the remaining factors in the model were deleted from the model in stepwise fashion. The 13 factors tested were as follows: age, gender, institution, era (1981–1990 vs. 1991–2000 vs. 2001–2012), location of tumor (hepatic side vs. peritoneal side), nodal involvement (N1 vs. N0), postoperatively proven liver metastasis (M1 vs. M0), radical resection (liver resection + regional lymphadenectomy) (yes/no), bile duct resection (yes/no), margin status (R1 vs. R0), tumor grade (poorly differentiated vs. moderately differentiated vs. well differentiated), neoadjuvant therapy (yes/no), and adjuvant chemotherapy (yes/no).