

# Prognostic Factors of Patients with Advanced Gallbladder Carcinoma Following Aggressive Surgical Resection

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## Abstract

**Background** The prognosis for patients with advanced gallbladder carcinoma is dismal despite aggressive surgical resection. The aim of this study is to determine useful prognostic factors for patients with gallbladder carcinoma following aggressive surgical resection.

**Methods** Medical records of 62 patients with gallbladder carcinoma who underwent surgical resection were retrospectively reviewed. Univariate and multivariate models were used to analyze the effect of clinicopathological factors on long-term survival.

**Results** According to the UICC staging system, ten (16%), 11 (18%), eight (13%), 16 (25%), nine (15%), and eight patients (13%) were diagnosed with stages I, II, IIIA, IIIB, IVA, and IVB disease, respectively. Partial hepatectomy and pancreatoduodenectomy were performed for 43 (69%) and 11 (18%) patients, respectively. Overall survival rates of all 62 and 41 patients with UICC stages III and IV disease were 71% and 56% at 1 year, 48% and 23% at 3 years, and 48% and 23% at 5 years, respectively (median survival time, 15.8 and 12.7 months, respectively). Multivariate analysis revealed that independent prognostic factors included tumor differentiation ( $p=0.006$ ), hepatic invasion ( $p=0.002$ ), lymph node metastasis ( $p=0.009$ ), and surgical margin status ( $p=0.002$ ) for all patients, and adjuvant chemotherapy ( $p=0.005$ ), tumor differentiation ( $p=0.008$ ), hepatic invasion ( $p=0.001$ ), and surgical margin status ( $p=0.022$ ) for patients with UICC stages III and IV disease.

**Conclusions** R0 resection and adjuvant chemotherapy are significant prognostic factors in advanced gallbladder carcinoma and should be performed to improve survival.

**Keywords** Gallbladder carcinoma · Prognostic factor · R0 resection · Adjuvant chemotherapy

## Introduction

Gallbladder carcinoma is a relatively uncommon malignancy with an estimated 9,760 new cases of gallbladder or bile

duct carcinoma diagnosed per year in the USA.<sup>1</sup> Higher incidence rates have been reported in Chile, Peru, Korea, and Japan while the USA and Europe have lower incidence rates.<sup>2,3</sup> However, according to the reports from these countries, the prognosis of this disease is often unfavorable, with reported 5-year survival rates at less than 15%, including unresectable and resected cases.<sup>4,5</sup> It was common to find invasion into the surrounding organs, including the duodenum, pancreas, and colon, and metastasis to lymph nodes, peritoneum, and liver at the time of diagnosis. Therefore, despite the fact that complete surgical resection is the only potentially curative treatment option, only a small proportion of patients are candidates for resection.<sup>6–8</sup> In order to improve survival of patients with this disease, aggressive surgical procedures including major hepatectomy,

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pancreatoduodenectomy,<sup>9–13</sup> and extended lymphadenectomy, as well as adjuvant therapeutic modalities including chemotherapy and radiotherapy,<sup>14–22</sup> have been advocated by several investigators. However, despite the use of aggressive surgery and adjuvant therapy, the 5-year survival following surgical resection remains low, especially in advanced gallbladder carcinoma.<sup>7,9,10,14,15,23–35</sup> Therefore, evaluation of prognostic factors and establishment of new therapeutic strategies are necessary to improve long-term survival of patients with gallbladder carcinoma.

Several investigators have described prognostic factors of patients with gallbladder carcinoma following surgical resection.<sup>7,10,15,19–35</sup> However, these reports are based on patients with many stages of gallbladder carcinoma. The aim of this study is to utilize univariate and multivariate survival analysis to determine useful prognostic factors for patients with advanced gallbladder carcinoma who have undergone aggressive surgical resection in a single institution.

## Patients and Methods

### Study Design

Medical records of 62 patients with gallbladder carcinoma treated at the Department of Surgery, Hiroshima University Hospital between January 1990 and December 2010 were retrospectively reviewed. All patients underwent tumor resection with curative intent and had a confirmed pathological diagnosis. Factors analyzed included patient demographics, perioperative factors, tumor characteristics, and patient survival. Univariate and multivariate survival analysis was performed on 11 factors (gender, age, hepatic resection, use of adjuvant chemotherapy, tumor differentiation, hepatic invasion, choledochal invasion, lymph node metastasis, surgical margin status, the International Union Against Cancer (UICC)<sup>36</sup> pT factor, and UICC stage) to determine useful prognostic factors of patients with gallbladder carcinoma following surgical resection. Written informed consent was obtained from all patients for surgical treatment and pathological examinations according to the institutional guidelines.

### Preoperative Workup and Surgical Procedures

Preoperative workup included ultrasonography, computed tomography, endoscopic ultrasonography, endoscopic retrograde cholangiography, and percutaneous transhepatic cholangiography to evaluate the local or distant extension of the tumors. If jaundice (serum bilirubin level more than 3 mg/mL) was identified preoperatively, percutaneous transhepatic biliary drainage (PTBD) or endoscopic retro-

grade biliary drainage (ERBD) was performed to reduce the cholestatic liver damage. Radical surgery was performed when serum bilirubin level decreased to 3 mg/dL. Preoperative percutaneous transhepatic portal embolization (PTPE) was performed on the liver segment to be resected to induce compensatory hypertrophy of the future remnant liver. This was done if the estimated liver resection volume exceeded 60% of the whole liver as calculated by computed tomography. Two or three weeks after PTPE, the future remnant liver volume was reevaluated by computed tomography. Hepatic resection was performed if the future remnant liver volume exceeded 40% of the whole liver.

All surgical resections included cholecystectomy with or without resection of liver or extrahepatic bile duct. If the tumor invaded the pancreatic head, duodenum, or colon, then, pancreatoduodenectomy or partial resection of the duodenum or colon was also performed. All patients underwent dissection of the regional lymph nodes, which included the nodes along the common hepatic artery, nodes in the hepatoduodenal ligament, and posterior pancreaticoduodenal nodes. Intraoperative pathological assessment of the proximal or distal bile duct transection lines was performed with frozen tissue sections. If the bile duct transection line was positive for malignant cells, further resection of the bile duct was performed to the maximum extent possible. Biliary continuity was restored by a Roux-en-Y biliary-enteric anastomosis when extrahepatic bile duct was resected.

### Pathological Investigations

Following tumor resection, permanent sections with hematoxylin and eosin staining were prepared. All specimens were examined pathologically, and each tumor was classified as well-differentiated, moderately differentiated, or poorly differentiated adenocarcinoma according to the predominant pathological grading of differentiation. Hepatic invasion, choledochal invasion, and lymph node metastasis were all examined pathologically. Surgical margins were considered positive if infiltrating adenocarcinoma was present at the hepatic transection line, the proximal or distal bile duct transection line, or dissected periductal soft tissue margins. The final stage of gallbladder carcinoma was determined pathologically according to the TNM classification system of malignant tumors published by the UICC, 7th edition.<sup>36</sup>

### Postoperative Adjuvant Chemotherapy

Postoperative adjuvant chemotherapy was administered to patients with UICC stages III and IV disease, beginning in 2002. The regimen of adjuvant chemotherapy has been

described previously.<sup>16,37–39</sup> In summary, patients were treated with ten cycles of gemcitabine plus S-1 every 2 weeks. Each chemotherapy cycle consisted of intravenous gemcitabine at a dose of 700 mg/m<sup>2</sup> on day 1 and orally administered S-1 at a dose of 50 mg/m<sup>2</sup> for seven consecutive days, followed by a 1-week break from chemotherapy. Neither external beam radiation nor intraoperative irradiation was administered to any patients during the study period.

**Survival**

Patients were followed up regularly in outpatient clinics at 3-month intervals by undergoing a blood test, ultrasonography, and computed tomography for up to 5 years after surgery. Information after 5 years was collected by telephone or personal interview. For patients who died, survival time after surgery and the cause of death were recorded. For surviving patients, postoperative survival time and status of recurrence were recorded. The median follow-up time after operation was 157 months (range, 2–255 months).

**Statistical Analysis**

Survival curves were constructed using the Kaplan–Meier method, and differences in survival curves were compared by univariate log-rank (Mantel–Cox) test. Factors found to be  $p < 0.05$  on univariate analysis were subjected to multivariate analysis using a Cox proportional hazards model.  $p < 0.05$  was considered statistically significant. Statistical analysis was performed with the

Macintosh version of StatView (version 5.0; SAS Institute, Cary, NC).

**Results**

**Patient Demographics and Operative Procedures Performed**

The 60 eligible patients included 32 men and 30 women (median age, 69 years; range, 33–92 years), and 31 patients (50%) were more than 70 years old. Preoperative jaundice was identified in 16 patients (26%). For reduction of serum bilirubin levels or preoperative workup, PTBD and ERBD were performed for 15 and one patients, respectively. Percutaneous transhepatic portal embolization was performed in two patients who underwent right hemihepatectomy. Depending on the local extension of the tumor, a wide variety of surgical procedures were performed. Partial hepatectomy and pancreatoduodenectomy were performed for 43 (69%) and 11 (18%) patients, respectively. In addition to surgical procedures listed in Table 1, four patients each underwent partial resection of the duodenum or colon. Surgical procedures performed for patients with UICC stages III and IV disease are also listed in Table 1. There were no perioperative deaths within 30 days of operation.

**Tumor Characteristics**

Pathologically, tumors were identified as well-differentiated adenocarcinoma in 25 patients (40%), moderately differentiated adenocarcinoma in 16 patients (26%), and poorly differentiated adenocarcinoma in 21 patients (34%). Hepat-

**Table 1** Operative procedures of patients with gallbladder carcinoma

	No. of patients	
	All patients (n=62)	Patients with UICC stages III and IV disease (n=41)
Right trisectionectomy+CHx+BDR	1	1
Right hepatectomy+CHx+BDR	5	5
Right hepatectomy+CHx+PD	1	1
Right hepatectomy+CHx+PPPD	1	1
(S4a+S5) hepatectomy	1	
(S4a+S5) hepatectomy+BDR	3	3
(S4a+S5) hepatectomy+PD	2	2
(S4a+S5) hepatectomy+PPPD	1	1
Gallbladder bed resection	7	3
Gallbladder bed resection+BDR	13	7
Gallbladder bed resection+PPPD	5	4
Gallbladder bed resection+PD	1	1
Cholecystectomy+BDR	3	3
Cholecystectomy	18	9

In addition to surgical procedures above, each four patients underwent partial resection of the duodenum or colon  
 CHx caudate lobectomy,  
 BDR bile duct resection, PPPD pylorus-preserving pancreatoduodenectomy, PD conventional pancreatoduodenectomy

ic invasion and choledochal invasion were identified in 21 (34%) and 15 patients (24%), respectively. There were 30 tumors (48%) with lymph node metastasis and 32 (52%) without lymph node metastasis. Forty-nine patients (79%) had negative surgical margins. According to the UICC staging system, eight (13%), three (5%), 21 (34%), 21 (34%), and nine patients (15%) had pT1a, pT1b, pT2, pT3, and pT4 tumors, respectively, and ten (16%), 11 (18%), eight (13%), 16 (25%), nine (15%), and eight patients (13%) were diagnosed with stages I, II, IIIA, IIIB, IVA, and IVB disease, respectively.

### Survival

Actuarial overall survival rates for the 62 patients were 71% at 1 year, 48% at 3 years, and 48% at 5 years (median survival, 15.8 months; range, 2–243 months). Actuarial overall survival rates for 21 patients with UICC stages I and II disease were 100% at 1 year, 94% at 3 years, and 94% at 5 years while actuarial overall survival rates for 41 patients with UICC stages III and IV disease were 56% at 1 year, 23% at 3 years, and 23% at 5 years (median survival, 12.7 months; range, 2–244 months; Fig. 1). Tumor recurrence occurred in 30 patients. The sites and nature of recurrence in these patients included peritoneal dissemination ( $n=17$ ), liver metastases ( $n=6$ ), and local disease ( $n=7$ ). Twenty-nine patients died of recurrent disease. One patient with peritoneal recurrence was still alive at the time of this writing.

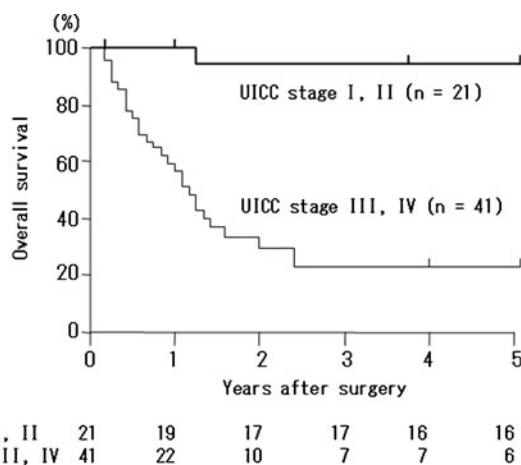
Eleven clinicopathological factors were investigated in all patients to determine their prognostic significance. The results of the log-rank test are shown in Table 2. Gender, age, hepatic resection, and adjuvant chemotherapy did not influence postoperative survival by univariate survival analysis. In contrast, univariate analysis revealed that tumor

differentiation ( $p<0.001$ ), hepatic invasion ( $p<0.001$ ), choledochal invasion ( $p=0.002$ ), lymph node metastasis ( $p<0.001$ ), surgical margin status ( $p<0.001$ ), UICC pT factor ( $p<0.001$ ), and UICC stage ( $p<0.001$ ) were significantly associated with survival. These factors were entered into multivariate analysis with a Cox proportional hazards model, and tumor differentiation ( $p=0.006$ ), hepatic invasion ( $p=0.002$ ), lymph node metastasis ( $p=0.009$ ), and surgical margin status ( $p=0.002$ ) remained independently associated with survival (Table 2). Table 3 indicates prognostic factors of 41 patients with UICC stages III and IV disease. Tumor differentiation ( $p=0.015$ ; Fig. 2a), hepatic invasion ( $p=0.036$ ; Fig. 2b), lymph node status ( $p=0.016$ ), surgical margin status ( $p=0.012$ ; Fig. 3a), and adjuvant chemotherapy ( $p=0.005$ ; Fig. 3b) were found to be significant survival prognostic factors. These five factors were entered into a Cox proportional hazards model. Multivariate analysis showed that adjuvant chemotherapy ( $p=0.005$ ), tumor differentiation ( $p=0.008$ ), hepatic invasion ( $p=0.001$ ), and surgical margin status ( $p=0.022$ ) were independent prognostic factors of patients with UICC stages III and IV disease. Lymph node status did not reach significance by multivariate analysis ( $p=0.076$ ).

There were six 5-year survivors with UICC stages III and IV disease. Of the six patients, five patients underwent hepatic resection or pancreatoduodenectomy. Nodal involvement and hepatic invasion were found in two and three patients, respectively. All six patients underwent R0 resection and three patients received adjuvant chemotherapy.

### Discussion

Survival after surgical resection for patients with gallbladder carcinoma depends heavily on stage of disease. According to previous reports, 5-year survival rates of patients with resected gallbladder carcinoma are 33–63%<sup>26,28,32,34,35</sup> for patients at all disease stages and 9–20%<sup>9,10,25</sup> for patients with UICC stages III and IV disease (Table 4). In the current study, 5-year survival rates for all patients and patients with UICC stages III and IV disease were 48% and 23%, respectively. These results are comparable to previous reports. Most patients with UICC stages I and II disease, who have mucosal carcinoma or subserosal carcinoma without nodal involvement, have survived for more than 5 year without recurrence if complete tumor resection is performed. However, the prognosis is extremely poor once the tumor invades the surrounding organs including liver, common bile duct, duodenum and colon or metastasizes to regional lymph nodes. It is mandatory to evaluate prognostic factors and to establish optimal therapeutic strategies especially for patients with UICC stages III and IV gallbladder carcinoma.



**Fig. 1** Comparison of postoperative survival in patients with gallbladder carcinoma who underwent surgical resection, stratified by UICC stage ( $p<0.001$ )

**Table 2** Univariate and multivariate survival analysis of prognostic factors for patients with gallbladder carcinoma ( $n=62$ )

Factors	Univariate analysis			Multivariate analysis	
	No. of patients	5-year survival rate (%)	<i>p</i> Value	Hazard ratio (95% CI)	<i>p</i> Value
Gender					
Male	32	51	0.547		
Female	30	45			
Age (years)					
<70	31	49	0.928		
≥70	31	48			
Hepatic resection					
Yes	43	40	0.133		
No	19	67			
Adjuvant chemotherapy					
Yes	11	48	0.579		
No	51	47			
Tumor differentiation					
Well	25	83	<0.001	4.50 (1.53–13.3)	0.006
Moderate, poor	37	23			
Hepatic invasion					
Yes	21	12	<0.001	6.08 (1.93–19.1)	0.002
No	41	69			
Choledochal invasion					
Yes	15	13	0.002	2.87 (0.98–8.43)	0.055
No	47	62			
Lymph node metastasis					
Yes	30	13	<0.001	4.14 (1.42–12.0)	0.009
No	32	82			
Surgical margin					
Positive	13	0	<0.001	3.86 (1.63–9.14)	0.002
Negative	49	61			
UICC pT factor					
pT1 and 2	32	78	<0.001		
pT3 and 4	30	17			
UICC stage					
I and II	21	94	<0.001		
III and IV	41	23			

CI confidence interval, UICC International Union Against Cancer

Many investigators have used multivariate analysis to determine useful prognostic factors for gallbladder carcinoma after surgical resection (Table 4).<sup>7,10,15,23–25,27–34</sup> According to these reports, potentially significant factors include nodal involvement,<sup>15,23,24,29–34</sup> hepatic invasion,<sup>23,31</sup> choledochal invasion,<sup>23,31</sup> pathological grading of differentiation,<sup>24,32</sup> perineural invasion,<sup>24,33</sup> and pathologically curative resection.<sup>7,24,25,27,29</sup> In the current study, multivariate analysis revealed that adjuvant chemotherapy, tumor differentiation, hepatic invasion, and surgical margin status were independent prognostic factors for patients with UICC stages III and IV disease. To our knowledge, there

have been no multivariate analysis reports of survival benefits of adjuvant chemotherapy on patients with advanced gallbladder carcinoma (Table 4). We believe the new adjuvant chemotherapy regimen of gemcitabine plus S-1 may contribute to long-term survival of patients with UICC stages III and IV disease.

There have been a few studies on adjuvant therapy for patients with gallbladder carcinoma in the previous literature. With regard to adjuvant chemoradiotherapy, Cho et al. reported a retrospective study in which radiotherapy with concurrent 5-fluorouracil (5-Fu) improved overall survival for patients with gallbladder carcinoma, especially for

**Table 3** Univariate and multivariate survival analysis of prognostic factors for UICC stages III or IV patients with gallbladder carcinoma ( $n=41$ )

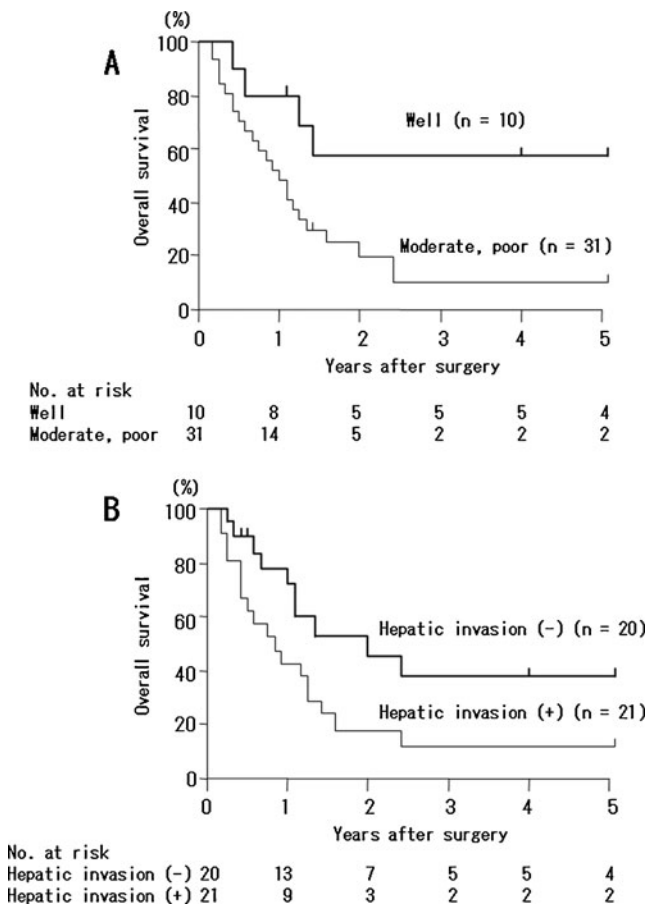
Factors	Univariate analysis			Multivariate analysis	
	No. of patients	5-year survival rate (%)	<i>p</i> Value	Hazard ratio (95% CI)	<i>p</i> Value
Gender					
Male	21	29	0.382		
Female	20	18			
Age (years)					
<70	19	21	0.770		
≥70	22	27			
Hepatic resection					
Yes	32	20	0.740		
No	9	40			
Adjuvant chemotherapy					
Yes	10	48	0.036	5.72 (1.71–19.1)	0.005
No	31	16			
Tumor differentiation					
Well	10	57	0.015	4.61 (1.50–14.1)	0.008
Moderate, poor	31	10			
Hepatic invasion					
Yes	21	11	0.036	4.72 (1.86–12.0)	0.001
No	20	38			
Choledochal invasion					
Yes	15	13	0.479		
No	26	33			
Lymph node metastasis					
Yes	30	13	0.016	2.86 (0.90–9.14)	0.076
No	11	56			
Surgical margin					
Positive	13	0	0.012	2.55 (1.15–5.69)	0.022
Negative	28	36			
UICC pT factor					
pT1 and 2	11	45	0.195		
pT3 and 4	30	17			

CI Confidence interval, UICC International Union Against Cancer

node-positive patients.<sup>14</sup> In addition, other investigators reported survival benefits from adjuvant chemoradiotherapy for patients with gallbladder carcinoma.<sup>16–18</sup> However, these analyses were based on a small number of patients, and no beneficial effects of chemoradiotherapy have been reported by other investigators.<sup>15</sup> Survival benefits of chemoradiotherapy on patients with resected gallbladder carcinoma are controversial. Furthermore, Jarnagin et al. reviewed 97 patients with resected gallbladder carcinoma and reported that initial recurrence involving a distant site occurred in 85% of patients. They concluded that an adjuvant therapeutic strategy targeting locoregional disease, such as radiotherapy, is unlikely to have a significant impact on the overall survival of gallbladder carcinoma.<sup>40</sup> In the current study, distant recurrence including peritoneal

dissemination or liver metastasis occurred in 77% of patients. Based on these results, we believe that systemic chemotherapy, but not radiotherapy, is the preferred strategy for adjuvant therapy of gallbladder carcinoma.

Reports concerning adjuvant chemotherapy for gallbladder carcinoma are scarce. To our knowledge, there has been only one randomized controlled study of survival effects of adjuvant chemotherapy for patients with gallbladder carcinoma. Takada et al. compared therapy with mitomycin C and 5-Fu to surgery alone after radical resection of gallbladder carcinoma; they reported that the 5-year survival rate was significantly better in the chemotherapy group (26%) compared with the surgery alone group (14%).<sup>21</sup> In addition, Kayahara et al. reported survival benefits of adjuvant chemotherapy for patients with

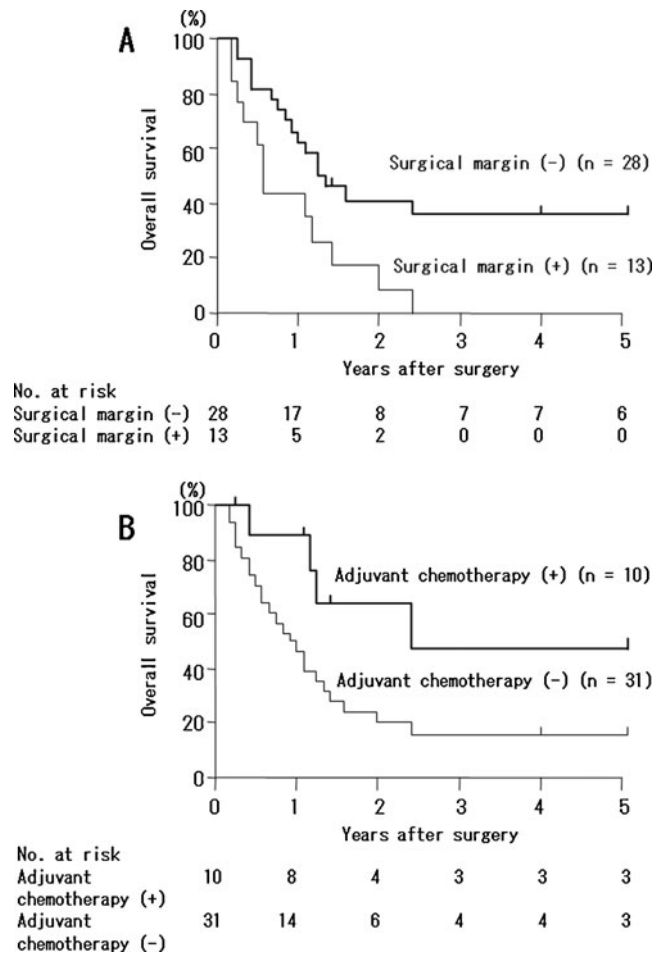


**Fig. 2** Comparison of postoperative survival in UICC stages III and IV patients with gallbladder carcinoma who underwent surgical resection. **a** Stratified by tumor differentiation ( $p=0.015$ ). **b** Stratified by the presence or absence of hepatic invasion ( $p=0.036$ )

advanced gallbladder carcinoma based on data from the Japanese Biliary Tract Cancer Registry.<sup>28</sup> Recently, new anticancer drugs including gemcitabine,<sup>41–43</sup> cisplatin,<sup>42</sup> and S-1<sup>43,44</sup> have been reported to have favorable anticancer effects on patients with unresectable biliary tract carcinoma. We have already reported that adjuvant gemcitabine plus S-1 chemotherapy improves survival significantly after surgery for biliary carcinoma.<sup>19</sup> In the current study, patients with UICC stages III and IV disease, who underwent resection after 2002, received adjuvant gemcitabine plus S-1 chemotherapy. As a result, three patients have survived for more than 5 years and adjuvant chemotherapy was an independent prognostic factor among patients with UICC stages III and IV disease. These results suggest that adjuvant gemcitabine plus S-1 chemotherapy may improve survival of patients with advanced gallbladder carcinoma.

Previous reports showed that curative (R0) resection was performed in 66–100% of patients with gallbladder carcinoma undergoing surgical resection (Table 4).<sup>7,10,14,15,23–27,29</sup> In the current study, the rate of patients resected with negative

margin was 79% for all patients and 68% for patients with UICC stages III and IV disease, and surgical margin status was also identified as an independent prognostic factor. All patients with positive surgical margins died of recurrent disease within 3 years and six 5-year survivors with UICC stages III and IV disease had negative surgical margins. Kai et al. reported that in an analysis of 39 patients with advanced gallbladder carcinoma, survival of patients with negative surgical margins was significantly better than that of patients with positive surgical margins and concluded that long-term survival can be expected by an operation with tumor-free surgical margins even in patients with advanced gallbladder carcinoma.<sup>29</sup> Other investigators also have presented that pathologically curative resection (R0 resection) can improve patient survival.<sup>24,25,27</sup> Surgeons should carefully pursue R0 resection whenever possible, even in advanced gallbladder carcinoma, by performing extended surgical resection including hepatectomy or pancreatoduodenectomy.



**Fig. 3** Comparison of postoperative survival in UICC stages III and IV patients with gallbladder carcinoma who underwent surgical resection. **a** Stratified by the presence or absence of positive surgical margins ( $p=0.012$ ). **b** Stratified by use of adjuvant chemotherapy ( $p=0.036$ )

**Table 4** Recent reports on resectional treatment of gallbladder carcinoma

Author	Year	No. of patients	UICC stage	Mortality (%)	R0 resection (%)	Nodal involvement (%)	Median survival (months)	5-year survival rate (%)	Prognostic factors by multivariate analysis
Present study	2010	62	I–IV	0	79	48	16	48	Hinf, R, N, and G
		41	III and IV	0	68	73	13	23	Hinf, R, G, and AC
Kim <sup>15</sup>	2010	166	I–IV	–	100	39	–	–	N
Cho <sup>14</sup>	2010	68	II–III	–	91	59	–	59	–
Miura <sup>23</sup>	2010	149	II–IV	7	47	55	–	35	Hinf, N, and Binf
Choi <sup>24</sup>	2010	83	II and III (pT2)	1	77	22	33	29	R, N, G, PN, and VI
Wakai <sup>25</sup>	2010	42	III and IV	–	79	71	11	20	R and MHS
Miyakawa <sup>26</sup>	2009	1094	I–IV	1	69	39	–	42	–
Shibata <sup>27</sup>	2009	72	I–III	–	75	33	–	–	pT, LI, and R
Kayahara <sup>28</sup>	2008	3023	I–IV	–	–	–	–	40	Age, sex, stage, and OP
Kai <sup>29</sup>	2007	90	I–IV	0	80	46	–	–	PV, N, and R
Yokomizo <sup>30</sup>	2007	94	II and III (pT2)	–	–	30	–	80	N
Shimizu <sup>10</sup>	2007	79	III and IV	11	66	65	–	9	None
Yagi <sup>31</sup>	2006	50	II–IV	0	–	46	–	–	Hinf, N, and Binf
Kokudo <sup>32</sup>	2003	152	I–IV	–	–	38	–	63	N, G, and pT
Kondo <sup>9</sup>	2002	29	IV	21	–	–	12	17	–
Yamaguchi <sup>33</sup>	2002	68	I–IV	10	–	44	–	–	N and PN
Puhalla <sup>7</sup>	2002	60	I–IV	11	75	32	–	–	R
Fong <sup>34</sup>	2000	100	I–IV	10	–	36	26	38	N and pT
Shimada <sup>35</sup>	1997	41	I–IV	2	–	63	–	33	–

UICC International Union Against Cancer, Hinf hepatic invasion, R pathologically curative resection, N nodal involvement, Binf choledochal invasion, G pathological grading of differentiation, AC adjuvant chemotherapy, PN perineural invasion, VI vascular invasion, MHS mode of hepatic spread, pT UICC pT factor, OP operative procedures, PV portal vein invasion

Hepatic invasion occurred in 51% of patients with UICC stages III and IV disease and it was also an independent prognostic factor in this series. Prognostic impact of hepatic invasion has been reported by other investigators.<sup>23,31</sup> In order to resect invaded areas of liver or prevent hepatic recurrence, several surgeons have advocated gallbladder bed resection or S4a+S5 hepatectomy. However, the optimal procedure for gallbladder carcinoma with hepatic invasion is inconclusive. Araidá et al. analyzed 485 cases of pT2 and pT3 stage gallbladder carcinoma treated at 112 institutions belonging to the Japanese Society of Biliary Surgery, and found no significant differences in survival rates or hepatic recurrence rates between patients undergoing gallbladder bed resection and patients undergoing S4a+S5 hepatectomy, and ultimately concluded that gallbladder bed resection is more preferable for surgical hepatic procedure.<sup>45</sup> In the current study, three of six 5-year survivors with UICC stages III and IV disease underwent gallbladder bed resection.

The frequency of nodal involvement has been reported to range from 33–71% in patients with gallbladder carcinoma who underwent surgical resection,<sup>7,14,15,23–27,29–35</sup> although

it depended on disease stage. In this series, nodal involvement developed in 48% of all patients and 73% of patients with UICC stages III and IV disease. The rate of nodal involvement in patients with advanced gallbladder carcinoma was somewhat high compared with that of previous reports. Many authors have described a significant correlation between nodal involvement and patient survival.<sup>15,23,24,29–34</sup> In the present study, multivariate analysis revealed that statistical significance in lymph node status was not obtained among patients with UICC stages III and IV disease although patients with nodal involvement had significantly worse survival by univariate analysis. Five-year survival rate in patients with nodal involvement was 13%, and two patients with nodal involvement have been alive for more than 5 years. Dissection of regional lymph nodes, which is routinely performed in our institution, may contribute to improved survival of patients with nodal involvement.

In conclusion, adjuvant chemotherapy, tumor differentiation, hepatic invasion, and surgical margin status are independent prognostic factors in patients with UICC stages III and IV gallbladder carcinoma following surgical



resection. Curative resection and adjuvant chemotherapy are recommended for long-term survival of patients with advanced gallbladder carcinoma. However, the limitations of this study are its retrospective design and the small number of patients studied. Further studies on larger numbers of patients, including prospective studies, are required to confirm the results of this study.

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