

Adjuvant Therapy in Patients with Gallbladder Carcinoma

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ABSTRACT

AIM: This study aimed to investigate the effects of adjuvant therapy and chemotherapeutic agents on survival of patients with gallbladder carcinoma. Factors that may affect survival were examined.

METHOD: The files of 74 patients who had been followed between 2004 and 2013 were retrospectively reviewed. Only stage I-III gallbladder carcinoma patients were included in the study.

RESULTS: The median age was 65 (36-82) years and 55 (74.4%) of the patients were female. Stage I was determined in 12 (16.2%) patients, whereas Stage II and III were determined in 62 (83.8%) patients. All of the patients had undergone surgical intervention. Positive surgical margin was present in 21 (28.4%) patients and 14 (58.4%) of these patients were re-operated. Thirty-nine (52.7%) patients received chemotherapy. The combination of cisplatin-fluorouracil was the most commonly used chemotherapy regimen, received by 15 (38.5%) patients. Radiotherapy alone was performed in none of the patients, while 8 (10.8%) patients received chemoradiotherapy. Whereas DFS was 21±1.7 (17.2-24.9 95% CI) in the adjuvant therapy arm, OS was found to be 24±2.05 (19.9-28.9 95% CI). DFS was 23±6.7 (9.7-36.3 95% CI) and OS was 28±2.8 (22.5-33.5 95% CI) in the patients that did not receive adjuvant

therapy. The differences in both DFS ($p=0.246$) and OS were not statistically significant ($p=0.534$). The effectiveness of adjuvant therapy on DFS and OS in the subgroups (surgical margin positivity, stage II patients, older than 65 years old) was statistically significant.

CONCLUSION: There is no standard adjuvant therapy for gallbladder carcinoma. The present study demonstrated the favorable effect of adjuvant therapy, particularly for selected patients. Prospective studies in large patient groups are needed to clarify the benefits of adjuvant therapy.

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Key words: Carcinoma; Gallbladder; Adjuvant treatment; Survival

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INTRODUCTION

Gallbladder cancer (GBC) is the 5th most common cancer of the gastrointestinal system^[1]. It is 2-6 times more prevalent in females^[2]. Gallstones (GS) enhance the risk of cancer by leading to chronic inflammation^[3] and 80-90% of cancer patients have GS^[4,5]. The incidence of cancer in the individuals with GS is 0.5-3%^[6]. The disease has quite a poor prognosis. The five-year survival rate is 5-10% and median survival is approximately 3-6 months^[6,7-9]. Surgery is the only curative therapeutic method in early-stage disease. There are studies reporting that the postoperative 5-year survival rate reaches to 90%^[10,11]. However, curative surgery is very rare since 80% of GBC are detected at an advanced stage^[12,13]. The disease is usually diagnosed at an advanced stage since there is no specific symptom or sign for GBC, since these symptoms may be seen also in benign diseases such as cholecystitis and cholelithiasis,

and lymphogenous and hematogenous spread is rapid. Surgical excision is the standard method for early-stage disease but there is as yet no consensus on adjuvant therapy^[14-16]. Postoperative radiotherapy and chemotherapy are recommended because of a postoperative local relapse rate of 50%, even after R0 resection^[17-20]. Chemotherapeutics used in adjuvant chemotherapy as single therapy or in combination include 5-Fluorouracil (5-FU), mitomycin, adriamycin, cisplatin and gemcitabine^[15,21].

METHODS

Medical records of patients followed at two different oncology centers were reviewed. Files including the diagnosis of gallbladder cancer made between February 2004 and July 2013 were examined. Cases with bile duct carcinoma, cholangiocellular carcinoma, carcinoma of the ampulla of Vater, and stage IV gallbladder carcinoma were excluded.

Disease free survival (DFS) was determined as the time up to local recurrence, metastasis, death without evidence of disease or last control since surgery. Overall survival (OS) was determined as the time up to death or last control. Both of these were calculated as the mean in months. Statistical analyses were performed with Statistical Package for the Social Sciences (SPSS 20.0) software. Survival analyses were done according to the Kaplan- Meier method, and Fisher's exact test and chi-square test were used to evaluate nominal variables and numeric data.

RESULTS

Clinical and pathological characteristics of patients are summarized in table 1. The median age at diagnosis was 65 (36-82) years and 55 (74.4%) of the patients were female. GS and/or cholecystitis were present in 47 (63.5%) patients. Stage I disease was detected in only 12 (16.2%) patients, while the number of patients with stage II and III disease was 62 (83.8%). A significant relation was determined between poor differentiation and patient age over 65 years ($p=0.004$), as well as female gender ($p=0.007$). Stage III disease was more prevalent in female patients ($p=0.001$), in calculous cholecystitis ($p=0.04$), and in patients who received chemotherapy ($p=0.001$).

All of the patients had undergone surgery. Positive surgical margin was detected in 21 (28.4%) patients, of whom only 14 (58.4%) had undergone re-operation. The number of patients who underwent surgery for prediagnosis of cholecystitis with gallstones was 26 (35.2%).

Chemotherapy was used in only 39 (52.7%) patients. None of the patients with stage I disease received chemotherapy. The combination of cisplatin- fluorouracil was the most common chemotherapy regimen, used in 15 (38.5%) patients, the second most common chemotherapy regimen was the combination of mitomycin-5-Fluorouracil, used in 8 (20.5%) patients. 5-FU/ calcium folinate, gemcitabine/cisplatin, single-agent gemcitabine, and capecitabine/oxaliplatin were the other chemotherapeutic agents used. Chemotherapeutic agents and their doses are summarized in table 2. None of the patients received radiotherapy alone, whereas 6 (8.1%) patients received chemoradiotherapy, all of whom had a positive surgical margin and had not undergone re-operation. Total radiotherapy dose performed varied between 45 and 60 Gy in 25 fractions. In the group receiving adjuvant therapy, DFS was 21 ± 1.7 (17.2-24.9 95% CI) and OS was found to be 24 ± 2.05 (19.9-28.9 95% CI). On the other hand, DFS was 23 ± 6.7 (9.7-36.3 95% CI) and OS was 28 ± 2.8 (22.5-33.5 95% CI) in the group receiving no adjuvant therapy. Adjuvant therapy and survival curves are presented in figure

Table 1 Patient Characteristics.

Median age (min-max)	65 (36-82)
Gender	19(25.6%)
Male	55(74.4%)
Female	
Age	41(55.4%)
<65	33(44.6%)
>65	
Histological type	
Adenocarcinoma	70(94.4%)
Adenosquamous carcinoma	3(4%)
Adenoacanthoma	1(1.6%)
Cholecystitis with gallstones	
Yes	47(63.5%)
No	27(36.5%)
Surgical procedure	
C	38(51.4%)
C, LWR	21(28.4%)
C, LWR, LND	15(20.2%)
Histological differentiation	
Good	21(38.4%)
Moderate	33(44.6%)
Poor	20(27%)
Lymphovascular Invasion	
Yes	30(40.5%)
No	44(59.5%)
Perineural Invasion	
Yes	41(55.4%)
No	33(44.6%)
Stage	
I	11(14.9%)
II	31(41.9%)
III	32(43.2%)
Adjuvant Chemotherapy	
Yes	39(57.2%)
No	35(42.8%)
Chemoradiotherapy	6(8.1%)

C: Cholecystectomy; LWR: Liver wedge resection; LND: Lymph node dissection.

Table 2 Chemotherapy regimens used in adjuvant setting.

Chemotherapy regimens	Number of patients	Explanation
Cisplatin/ Fluorouracil	15	Cisplatin 50 mg/m ² , day 1; Folinic acid 200 mg/m ² day 1; and 5-FU 400 mg/m ² day 1 bolus and 1600 mg/m ² for 48 h continuous infusion, every 15 days
Mitomycin/ 5-FU	8	Mitomycin C 6 mg/m ² , day 1; 5-FU 600 mg/m ² /day 5 days continuous infusion, every 21 days
Gemcitabine/ cisplatin	7	Gemcitabine 1,200 mg/m ² day 1 and 8; Cisplatin 75 mg/m ² day 1, every 21 days
FUFA	2	Folinic acid 200 mg/m ² day 1; and 5-FU 400 mg/m ² day 1 bolus and 1,600 mg/m ² for 48h continuous infusion, every 15 days
Gemcitabine	2	Gemcitabine 1,200 mg/m ² days 1 and 8, every 21 days
Capecitabine/ Oxaliplatin	2	Oxaliplatin 130mg/m ² IV over 2 hours day1 Capecitabine 850-1,000 mg/m ² twice daily PO for 14 days repeat every 3 weeks

1 and figure 2. The effectiveness of adjuvant therapy on DFS and OS in the subgroups is summarized in table 3. 5-FU-based chemotherapy regimens had a favorable effect on both DFS ($p=0.001$) and OS ($p=0.001$) as compared to the other chemotherapy regimens.

The number of patients who developed progression, and the time to progression in the group receiving adjuvant therapy were 35 (89.7%) and a median of 21 (8-60) months, respectively. Liver was the most common site of metastasis. The number of patients who received chemotherapy in the metastatic phase was 30 (65.2%). Gemcitabine was the most frequently used first-line chemotherapeutic regimen,

performed in 13 (43.3%) patients.

The median follow-up period was 24 (2-70) months. DFS was 22±1.4 (19.4-24.6 95% CI) and OS was 26±1.9 (22.2-29.8 95% CI). DFS rates for 2 and 3 years were 37% and 17%, whereas OS rates were found to be 60% and 30%, respectively. Parameters that might have an effect on DFS and OS are summarized in table 4.

DISCUSSION

Gallbladder carcinoma is an uncommon but fatal cancer. Although cancer-related symptoms are not cancer-specific, they are similar to the symptoms seen in cholecystitis and cholelithiasis. On radiological examination, neither ultrasound nor tomography findings are specific to cancer and may be seen in other inflammatory diseases of the gallbladder^[22-24]. Therefore, the disease is usually at an advanced stage when diagnosed.

Table 3 The efficacy of adjuvant treatment on OS and DFS in selected subgroups.

Subgroups	n(%)		P value	
	Adjuvant treatment	No treatment	Adjuvant treatment OS	DFS
Surgical margin positivity				
Yes	17 (23)	4 (5.5)	0.028	<0.001
No	22 (29.8)	31 (41.7)	0.721	0.045
Stage				
II	19 (25.7)	14 (18.9)	0.046	0.123
III	24 (32.4)	8 (10.8)	0.368	0.941
Age				
<65	20 (27)	21 (28.4)	0.001 ¹	0.003 ¹
>65	19 (25.7)	14 (18.9)	0.001	0.012
Cholelithiasis				
Yes	29 (39.2)	18 (24.3)	0.526	0.932
No	10 (13.5)	17 (23)	0.169	0.301

OS: overall survival, DFS: disease free survival; ¹p-value is significant for the no treatment group.

Table 4 P Value of Prognostic Factors.

Factor	Disease-free survival p value	Overall survival p value
Gender	0.902	0.315
Age	0.85	0.929
Cholecystitis with gallstones	0.003	0.023
Differentiation	0.05	0.22
LVI	0.048	0.409
Perineural invasion	0.043	0.201
Stage	0.001	0.032
Adjuvant therapy	0.246	0.534
Adjuvant chemotherapy	0.323	0.106
Adjuvant chemoradiotherapy	0.672	0.122

LVI: lymphovascular invasion.

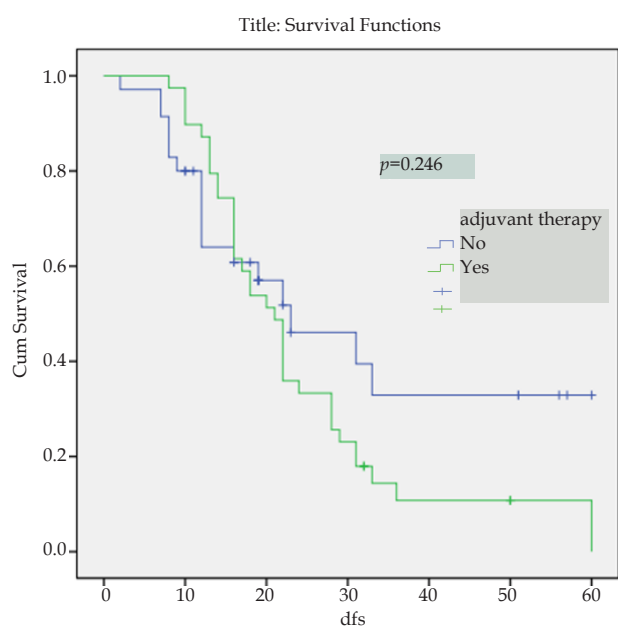


Figure 1 Disease free survival of both groups.

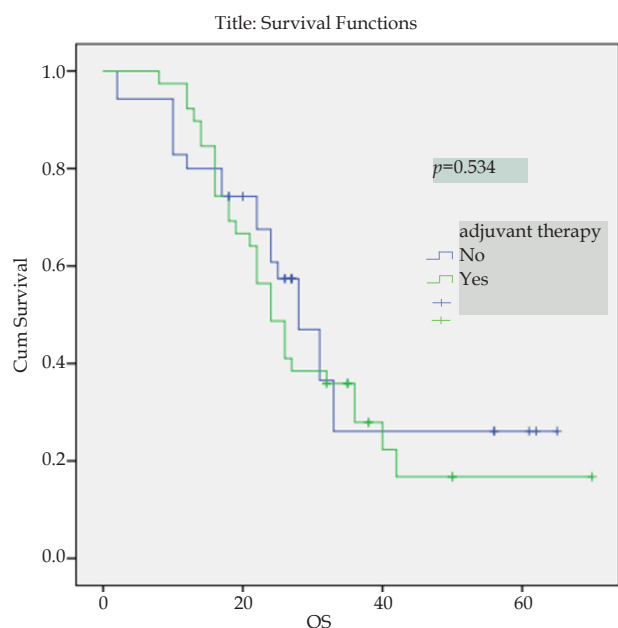


Figure 2 Overall survival of both groups.

Surgery is a therapeutic option with a chance of cure in early-stage patients. There is no consensus on the surgical method necessary to be performed^[12,25,26]. Cholecystectomy is deemed adequate for Tis and T1a tumors. Radical cholecystectomy (cholecystectomy, liver resection and lymph node dissection) is recommended for advanced-stage tumors^[27]. However, relapses are quite prevalent in patients particularly with T3 and lymph node involvement even after R0 resection, in which the tumor is removed as a whole. There are studies that report postoperative 5-year survival rates to be low as 5-11.8%^[6,8], as well as studies that report 5-year survival rate to be 50.7%^[12]. In the present study, 3-year DFS and OS rates in the patients that had undergone surgery alone without adjuvant therapy were 33% and 25.3%, respectively. Todoroki *et al* defended the viewpoint that radical cholecystectomy can be performed even in stage-IV disease^[28].

Poor prognosis after surgery alone has brought forward chemotherapy and/or radiotherapy as adjuvant settings. Today, there is as yet no standard practice for adjuvant therapy. Jarnagin *et al* conducted a study in 97 patients that had undergone radical cholecystectomy and found the incidence of distant metastasis to be 85% and local relapse to be 15%^[14]. Incidence of distant metastasis has brought adjuvant chemotherapy as a systemic treatment. The most comprehensive randomized study for adjuvant chemotherapy was done by Takada *et al*^[16]. This study comprised other cancers of the pancreaticobiliary system. In this study, in which the number of cases with gallbladder cancer was 118 and a combination of mitomycin C/fluorouracil was used as the adjuvant chemotherapy, the 5-year survival rate was 26% in the group receiving chemotherapy and 14.4% in the group that underwent surgery alone. These results are statistically significant as well ($p=0.036$). In subgroup analyses, it was reported that chemotherapy was beneficial also in the group that did

not undergo curative surgery.

Adjuvant chemoradiotherapy has become a current issue for preventing local relapses, particularly in cases that have a positive surgical margin. Information on the efficacy of radiotherapy has been obtained from retrospective studies. Although there are studies that demonstrate survival benefits of radiotherapy alone or in combination with adjuvant therapies, particularly when used at a dose >40Gy with fluoropyrimidine^[29-32], there are also studies demonstrating that it does not provide a survival advantage^[33]. Wang *et al* investigated the efficacy of adjuvant radiotherapy alone and chemoradiotherapy in two different studies and similarly reported that >T2 node-positive patients benefited from adjuvant therapies^[34,35].

Horgan *et al* carried out a meta-analysis and compared the group that underwent surgery alone with the group receiving any adjuvant therapy after surgery, but failed to find a significant difference in terms of survival^[36]. However, subgroup analyses revealed that node-positive and surgical margin-positive cases benefited from adjuvant therapy. Nevertheless, this analysis also failed to make a clear definition as to which therapeutic modality (chemotherapy or chemoradiotherapy) is the most effective in high-risk patients and whether adjuvant therapy is necessary in low-risk patients.

The efficacy of neoadjuvant therapies on locally advanced disease that cannot be resected has been investigated, but none of these studies reported a statistically significant survival advantage^[37-39].

There is no standard adjuvant therapy because of the limited number of studies defining the role of adjuvant therapy in gallbladder carcinomas. Despite inadequate evidence, adjuvant therapy is recommended in patients with \geq T2, positive surgical margin and positive node since these are strong prognostic factors^[40].

In the present study, none of the treatment modalities had a significant benefit on survival. This unfavorable effect can be explained by poorer risk factors in the patients that received adjuvant therapy. However, longer DFS and OS were obtained in the group receiving adjuvant treatment. Comparing 5-FU-based chemotherapeutic regimens with other agents, its favorable effect on both DFS ($p=0.001$) and OS ($p=0.001$) is also consistent with the literature.

The fact that the majority of the studies in the literature comprise hepatobiliary cancers whereas the present study comprises only gallbladder cancers makes this unfavorable effect notable. Prospective randomized studies are required to eliminate conflicting results on adjuvant therapy for gallbladder cancers.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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