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Efficacy and Feasibility of Adjuvant Gemcitabine Plus Cisplatin Chemotherapy After Major Hepatectomy for Biliary Tract Cancer

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Abstract. *Background/Aim: The efficacy and feasibility of gemcitabine plus cisplatin (GC) chemotherapy in an adjuvant setting is unclear in patients with biliary tract cancer (BTC) undergoing major hepatectomy. Patients and Methods: Patients with BTC who underwent major hepatectomy between 2008 and 2018 were included. Patients who received adjuvant chemotherapy (AC) were then divided into two groups: a GC group and a gemcitabine (GEM) alone group. AC-related factors and patient outcomes were investigated. Results: Fifty (GC: 28, GEM: 22) patients received AC, and 33 patients did not. No difference in completion rate, relative dose intensity, or adverse events was seen between the two AC groups. Multivariate analysis revealed that AC with GC was an independent predictor of improved survival and reduction of early recurrence. Conclusion: AC with GC is tolerable and associated with better outcomes in patients with BTC who have undergone major hepatectomy.*

Although surgical resection is considered the only curative treatment that can provide a cure for patients with biliary tract cancer (BTC), the 5-year overall survival (OS) rate is still poor, ranging from 24.2% to 61.3% (1, 2). Although various randomized controlled trials (RCTs) of adjuvant chemotherapy (AC) for patients with BTC have been conducted to improve survival, the results of these RCTs did not show any survival benefit (3-6). Therefore, the development of more effective AC strategies to improve prognosis is urgently needed. The combination of gemcitabine plus cisplatin (GC) therapy is a widely known key regimen, and its efficacy has been confirmed by RCTs in patients with locally advanced or metastatic BTC (7, 8). Therefore, GC therapy may be a promising AC regimen for patients with BTC.

In patients with hilar BTC, including intrahepatic cholangiocarcinoma (ICC), perihilar cholangiocarcinoma (PHCC), and gallbladder cancer (GBC), a major hepatectomy is often required to achieve curative surgery (2, 9). However, a major hepatectomy for patients with hilar BTC is associated with higher mortalities and morbidities that can influence postoperative organ impairment and/or lead to a deterioration in the patient's condition (2, 9). Therefore, the feasibility of AC after a major hepatectomy may be relatively poor in patients with BTC.

Recently, a multicenter, randomized phase II study comparing adjuvant gemcitabine (GEM) and S-1 chemotherapy after major hepatectomy for BTC was conducted, and adjuvant S-1 therapy appeared to improve patient survival, compared to adjuvant GEM therapy; however, a relatively low completion rate, a low relative dose intensity (RDI), and a high incidence of adverse events were observed (10). Unfortunately, studies have been unsuccessful at demonstrating the efficacy and feasibility of GC therapy in an adjuvant setting in patients who have undergone a major hepatectomy for hilar BTC.

Therefore, the aim of the study was to investigate the efficacy and feasibility of AC with GC compared to AC with GEM or non-AC treatment after a major hepatectomy for hilar BTC.

Patients and Methods

Patients and study design. This was a single-center, retrospective study. The study subject were patients with histologically confirmed BTC, including ICC, PHCC, and GBC, who had received elective

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Key Words: Biliary tract cancer, adjuvant chemotherapy, gemcitabine plus cisplatin, major hepatectomy, early recurrence.

surgery consisting of a major hepatectomy at the Second Department of Surgery, Dokkyo Medical University Hospital, between January 2008 and December 2018. Patients with distant metastases or in-hospital deaths were excluded. Distant metastasis was evaluated using multidetector-row computed tomography and/or magnetic resonance imaging, and/or positron emission tomography. This study was approved by the ethical committee of Dokkyo Medical University (Ethical Committee review number R-26-10J).

Chemotherapy. AC was performed according to each patient's agreement and with his/her informed consent. The AC regimen used for each patient was either GC therapy or GEM monotherapy. The dosages of GC or GEM given as AC were based in the results of phase III studies examining GC *versus* GEM therapy (7, 8). GC was administered at a dose of 1,000 mg/m^2 plus 25 mg/m^2 on days 1 and 8, followed by a 1-week rest period (one cycle). This administration of GC was repeated every 3 weeks for up to eight cycles. GEM was administered at a dose of 1,000 mg/m^2 on days 1, 8, and 15, followed by a 1-week rest period (one cycle). This administration of GEM was repeated every 4 weeks for up to six cycles.

The AC dosages of GC and GEM were reduced from 100% to 80% or from 80% to 60% according to the degree of adverse events experienced or the patient's condition, based on the judgements of the physicians. AC was discontinued in cases with metastasis/recurrence, severe adverse events, a deterioration in the patient's condition, or at the patient's request. The starting dose of AC was determined by each physician based on the patient's condition prior to the initiation of AC.

Based on the results of previous studies, GEM monotherapy, S-1 monotherapy, GC therapy, or GEM plus S-1 therapy were performed as chemotherapy regimens in cases with recurrence (7, 8, 11, 12). Best-supportive care was chosen in cases with a deterioration in the patient's condition or at the patient's request. In the present patient cohort, none of the patients received neoadjuvant chemotherapy with or without radiation therapy prior to surgery.

The Common Terminology Criteria for Adverse Events, version 5.0, was used to evaluate treatment-related toxicities. Adverse events were graded based on each patient's medical chart. The RDIs for GC and GEM were calculated as the dose intensity achieved according to the standard schedule for each drug. Some patients received AC beyond the planned cycles. The adverse events and RDIs of these patients were examined only for the period lasting until the end of the planned cycles.

Surgery and pathological evaluation. Major hepatectomy was defined as the resection of more than three segments according to Couinaud's classification (13). The type of surgical procedure was classified using Brisbane 2000 terminology (14). A lymphadenectomy was not performed in patients with peripheral type ICC. Pathological reviews of resected specimens were performed by pathologists at our institution. The tumors were classified according to the 8th edition of the Union for International Cancer Control staging system for biliary tract cancer (15).

Patients visited the hospital once a month for the first 12 months after surgery and at 2- to 3-month intervals thereafter. Tumor marker levels, including carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9), were examined at each visit. Patients were monitored using contrast-enhanced computed tomography of the chest and abdomen at 3-month intervals for the first 12 months and at 4-month intervals thereafter. In the patients who did not receive AC (non-AC group), pre-AC data were measured at approximately 2 months after surgery. Early recurrence was defined as recurrence within 1 year after surgery.

Statistical analysis. SPSS version 26.0 (IBM Japan, Tokyo, Japan) was used for all the statistical analyses. Continuous data were expressed as the median with ranges and were compared using the Mann-Whitney *U*-test, while categorical data were compared using the chi-squared test or the Fisher exact test. Survival curves were generated using the Kaplan-Meier method and were compared using the log-rank test. Univariate and multivariate analyses were performed using the log-rank test, and the Cox proportional hazard model with forward stepwise selection was used to identify predictors of overall survival (OS). Univariate and multivariate analyses were also performed using the Chi-squared test or the Fisher's exact test, and a multiple logistic regression analysis with forward stepwise selection was used to identify predictors of recurrence within 1 year after surgery. The follow-up period was calculated as the interval between the date of surgery and the date of last follow-up or death. Differences at $p<0.05$ were considered statistically significant.

Results

A total of 91 patients who were scheduled for elective surgery consisting of a major hepatectomy were included. Eight (8.8%) patients were excluded from the study because they received AC regimens other than GC or GEM (n=7) or because of the discovery of carcinoma *in situ* in the pathological findings (n=1). As a result, 83 patients with or without AC were eligible for inclusion in the analysis. The primary disease was ICC in 22 patients (27%), PHCC in 48 patients (58%), and GBC in 13 patients (15%), respectively. Fifty patients (60.2%) received AC, and 33 patients (39.8%) did not receive AC. Patients who received AC were then divided into two groups: GC (n=28) or GEM (n=22). The major reasons for not receiving AC included patient refusal (n=19), early recurrence (n=7), and a deterioration in the patient's condition (n=7). The study cohort of 83 patients included 49 men (59%) and 34 women (41%) with a median age of 70 years (range=34-84 years). The median follow-up period was 27.8 months (range=1.7-132.5 months) for the entire study cohort.

Baseline patient characteristics. The baseline patient characteristics between patients with GC therapy (n=28) and those with GEM therapy (n=22) and between patients with GC therapy and those without AC (n=33) are shown in Table I. The median age was significantly higher in the non-AC group than in the GC group (p=0.001). The preoperative serum albumin level was significantly lower in the GEM group and the non-AC group than in the GC group (p=0.015 and p=0.003). However, no significant inter-group differences in the other variables were seen.

Table I. *Baseline patient characteristics*.

	GC (n=28)	GEM (n=22)	*p*-Value†	Non-AC (n=33)	*p*-Value‡
Age (years)	67 (44-78)	68 (34-79)	0.977	74 (52-84)	0.001
Male	17 (61%)	15 (68%)	0.585	17 (52%)	0.471
Body mass index (kg/m^2)	21.9 (15.7-27.1)	20.5 (15.4-32.1)	0.222	21.7 (13.9-28.5)	0.896
Total bilirubin (mg/dl)	0.7 (0.2-2.4)	0.9 (0.2-2.2)	0.631	0.7 (0.2-2.6)	0.637
Albumin (g/dl)	3.6 (2.5-4.4)	3.1 (2.3-4.2)	**0.015**	3.1 (2.2-4.3)	**0.003**
ICGR15 (%)	9.5 (4-35)	9.5 (3-29)	0.537	10 (2-69)	0.833
CEA (ng/ml)	2.4 (1-16.7)	3.6 (1-206)	0.180	2.9 (1-226)	0.235
CA 19-9 (U/ml)	39.5 (2-12,000)	44.5 (2-12,000)	0.792	43 (2-12,000)	0.954
Primary disease			0.680		0.820
ICC	8 (29%)	4 (18%)		10 (30%)	
PHCC	15 (54%)	14 (64%)		19 (58%)	
GBC	5 (17%)	4 (18%)		4 (12%)	

AC: Adjuvant chemotherapy; CA 19-9: carbohydrate antigen 19-9; GBC: gallbladder carcinoma; GC: gemcitabine plus cisplatin; CEA: carcinoembryonic antigen; GEM: gemcitabine; HPD: hepatopancreatoduodenectomy; ICC: intra-hepatic cholangiocarcinoma; ICG: indocyanine green retention rate; PHCC: perihilar cholangiocarcinoma. †GC *vs*. GEM; ‡GC *vs*. non-AC. Significant *p*-Values are shown in bold.

Surgical and pathological outcomes. Table II compares the surgical and pathological outcomes between patients with GC therapy and those with GEM therapy and between patients with GC therapy and those without AC. The median operation time was significantly shorter in the non-AC group than in the GC group (p=0.029). However, the differences between the other variables were not significant.

Pre-AC data, AC-related factors, and adverse events. The pre-AC data, AC-related factors, and adverse events associated with each AC regimen are shown in Table III. The proportion of patients who received the full starting dose was significantly higher in the GC group than in the GEM group (p<0.001). However, no significant differences in the RDI and course completion rates were seen between the GC group and the gemcitabine group (RDI: 78.8% and 80%, respectively, p=0.759; course completion rate: 43% and 54%, respectively, p=0.144). The proportion of patients with grade 3 or 4 adverse events tended to be higher in the GC group than in the GEM group (p=0.063). The median serum albumin level was significantly lower in the non-AC group than in the GC group (p=0.034). However, no significant intergroup differences in the other variables were observed.

Profiles of recurrence. Table IV shows the recurrence profiles. Nineteen (68%) of the 28 patients in the GC group, 17 (77%) of the 22 patients in the GEM group, and 19 (58%) of the 33 patients in the non-AC group developed a recurrence. The duration until recurrence (median) was 16.6 months in the GC group, 10.4 months in the GEM group, and 6.6 months in the non-AC group. The duration until recurrence was significantly shorter in the non-AC group than in the GC group (p=0.003). The proportion of early recurrence tended to be higher in the GEM group and the non-AC group than in the GC group (p=0.071 and p=0.082, respectively). The proportion of chemotherapy for the treatment of recurrence was significantly lower in the non-AC group than in the GC group (p=0.036). However, no significant differences in other variables were noted.

Predictors of overall survival. The results of the univariate and multivariate analyses of OS predictors are shown in Table V. Among 14 factors, 6 (preoperative serum albumin <3 g/dL, preoperative CEA >5 ng/ml, CEA >5 ng/ml before initiation of AC, GC regimen of AC, pN1, and a positive resection margin) were found to be significant in univariate analyses. A multivariate analysis revealed that a preoperative CEA level >5 ng/ml [hazard ratio (HR)=3.197; 95% confidence interval (CI)=1.590-6.427; p=0.001), a GC regimen for AC (HR=0.422; 95%CI=0.207-0.861; p=0.018), pN1 (HR=2.737; 95%CI=1.500-4.994; p=0.001), and a positive resection margin (HR=2.197; 95%CI=1.127-4.284; p=0.021) were independent predictors of OS.

Predictors of early recurrence. The results of univariate and multivariate analyses of early recurrence predictors are shown in Table VI. Among 14 factors, 5 (preoperative CEA >5 ng/ml, CEA >5 ng/ml and CA 19-9 >37 U/ml before initiation of AC, GC regimen of AC, and pN1) were found to be significant in univariate analyses. A multivariate analysis revealed that a CA 19-9 level >37 U/ml before the initiation of AC (odds ratio (OR)=3.889; 95%CI=1.214-12.457; p=0.022), a GC regimen for AC (OR=0.287; 95%CI=0.085-0.967; p=0.044), and pN1 (OR=4.694; 95%CI=1.544-14.273; p=0.005) were independent predictors for early recurrence.

Table II. *Surgical and pathological data*.

	GC (n=28)	GEM (n=22)	*p*-Value†	Non-AC (n=33)	*p*-Value‡
Type of surgery			0.236		0.227
Left hemihepatectomy	6 (21%)	9 (41%)		12 (36%)	
Right hemihepatectomy	19 (68%)	12 (55%)		20 (61%)	
Left medial sectionectomy+ right anterior sectorectomy	0	1 (4%)		1 (3%)	
Left trisectionectomy	2 (7%)	0		0	
Right posterior sectionectomy+segment 1	1 (4%)	0		0	
HPD	4 (14%)	5 (23%)	0.342	3 (9%)	0.406
Portal vein resection	2 (7%)	1 (4%)	0.591	1 (3%)	0.438
Resected liver weight (g)	589 (184-1,220)	490 (196-1,950)	0.392	545 (180-1,670)	0.377
Operation time (min)	536 (300-935)	531 (215-790)	0.434	464 (162-1,021)	**0.029**
Blood loss (ml)	644 (135-2,320)	695 (250-5,634)	0.984	621 (95-2,039)	0.845
Clavien-Dindo			0.642		0.309
Grade 0/1/2	16 (57%)	14 (64%)		23 (70%)	
Grade 3/4	12 (43%)	8 (36%)		10 (30%)	
Postoperative stay (days)	31 (14-65)	32 (14-62)	0.883	31 (9-119)	0.971
ICC		0.594		0.319	
T1	0	0		0	
T2	3 (10%)	1 (5%)		6 (18%)	
T3	5 (18%)	3 (13%)		4 (12%)	
T4	0	0		0	
PHCC			0.741		0.357
T1	1 (4%)	1 (5%)		0	
T2	14 (50%)	13 (59%)		18 (55%)	
T3	0	0		1 (3%)	
T4	0	0		0	
GBC			0.405		0.358
T1	0	0		0	
T2	0	0		1 (3%)	
T3	4 (14%)	2 (9%)		3 (9%)	
T4	1 (4%)	2 (9%)		0	
Lymphadenectomy			0.591		0.118
(-)*	2 (7%)	1 (5%)		7 (21%)	
(+)	26 (93%)	21 (95%)		26 (79%)	
ICC		0.583		0.583	
N0	5 (19%)	2 (10%)		2 (8%)	
N1	1 (4%)	1 (5%)		1 (4%)	
PHCC			0.876		0.205
N0	9 (35%)	8 (38%)		15 (58%)	
N1	6 (23%)	6 (29%)		4 (15%)	
GBC			0.556		0.405
N0	1 (4%)	0		2 (8%)	
N1	4 (15%)	4 (19%)		2 (8%)	
ICC		0.852		0.316	
Stage I	0	0		0	
II	2 (7%)	1 (5%)		6 (18%)	
III	5 (18%)	2 (9%)		3 (9%)	
IVA	1 (4%)	1 (5%)		1 (3%)	
PHCC			0.849		0.212
Stage I	1 (4%)	1 (5%)		0	
II	8 (29%)	6 (27%)		15 (45%)	
IIIA	0	0		0	
IIIB	6 (21%)	7 (32%)		4 (12%)	
IVA	0	0		0	
GBC			0.487		0.549
Stage I	0	0		0	

Table II. *Continued*

Table II. *Continued*

	GC (n=28)	GEM (n=22)	*p*-Value†	Non-AC (n=33)	*p*-Value‡
II	0	0		1 (3%)	
IIIA	1 (4%)	0		1 (3%)	
IIIB	3 (11%)	2 (9%)		2 (6%)	
IVA	1 (4%)	2 (9%)		0	
Resection margin			0.080		0.168
R0	19 (68%)	14 (64%)		25 (76%)	
R1	8 (29%)	2 (13%)		4 (12%)	
R2	1 (3%)	5 (23%)		4 (12%)	
Histology			0.146		0.058
Well	12 (43%)	6 (28%)		7 (21%)	
Moderately	12 (43%)	12 (57%)		17 (55%)	
Poorly	4 (14%)	1 (5%)		6 (19%)	
Others	0	2 (10%)		1 (3%)	

AC: Adjuvant chemotherapy; GBC: gallbladder carcinoma; GC: gemcitabine plus cisplatin; GEM: gemcitabine; HPD: hepatopancreatoduodenectomy; ICC: intra-hepatic cholangiocarcinoma; PHCC: perihilar cholangiocarcinoma. *Lymphadenectomy was not performed in peripheral type of ICC. †GC *vs*. GEM; ‡GC *vs*. non-AC. Significant *p*-Values are shown in bold.

Survival rates. Comparisons of the OS rates between patients with GC therapy (n=28) and those with GEM therapy (n=22) and between patients with GC therapy and those without AC (n=33) are shown in Figure 1. The OS rates for patients with GC therapy and those with GEM therapy were 58.5% and 22.7% at 5 years, respectively, with a median survival time (MST) of 32.1 and 29.1 months, respectively (Figure 1A). The OS rates for patients with GC therapy and those without AC were 58.5% and 31.5% at 5 years, respectively, with an MST of 32.1 and 24.2 months, respectively (Figure 1B). Significant differences between patients who received AC with GC and those who did not receive AC were observed (p=0.045). The OS rates tended to be higher for patients who received AC with GC than for those who received AC with GEM (p=0.099).

Discussion

To date, there is no significant evidence from RCTs to support the usefulness of AC in resected BTC patients (3-6). In addition, neoadjuvant therapy has not been established as part of a treatment strategy that contributes to a prolonged OS following surgery in patients with BTC (16). In this retrospective study, AC with GC was associated with improved survival and a decrease in early recurrence among patients with hilar BTC who underwent a major hepatectomy. This result provides an important clue to establishing a clinical treatment strategy for BTC, since studies in this field remain lacking. Possible reasons for this result include the maintenance of the RDI and course completion rate for GC therapy at median values of about 80% and 50%, respectively, which were similar to those for GEM monotherapy (Table III). As a result, AC with GC might enable the development of tumor recurrence to be controlled, contributing to an improved prognosis. The ABC-02 trial in the UK and the BT-22 trial in Japan were conducted to confirm the efficacy and safety of GC therapy, compared to GEM monotherapy, in patients with locally advanced or recurrent BTC, and these trials demonstrated an evident superiority of GC therapy to GEM monotherapy in terms of OS without the addition of substantial toxicity (7, 8). Therefore, GC therapy in an adjuvant setting may become an expected regimen that can offer a better outcome in selected cases. Although the adverse events of GC therapy were manageable in all patients, the incidence of adverse events with grades of 3 or 4 tended to be higher than that for patients receiving GEM monotherapy (Table III). A previous study evaluating the feasibility of adjuvant GC therapy for BTC reported that adverse events with grades of 3 or 4 included neutropenia (27%), leukopenia (14%), anemia (17%), and thrombocytopenia (7%) (17). With the exception of anemia, the incidence of these adverse events in the present study were relatively high, compared to those of the previous study (Table III). Mori *et al*. reported that patients with pancreatic ductal adenocarcinoma who developed grade 3 or 4 adverse events during AC had worse outcomes with a lower RDI and a lower AC completion rate (18). Accordingly, careful adjustment of the doses of AC and the management of adverse events are necessary to improve prognosis.

Because various surgical procedures, such as pancreaticoduodenectomy, major or minor hepatectomy, or hepatopancreatoduodenectomy, can be performed for patients with BTC (2, 9, 19), the background of subjects who receive AC can be relatively heterogeneous. In particular, a major

Table III. *Pre-adjuvant chemotherapy data, adjuvant chemotherapy-related factors and adverse events associated with each adjuvant chemotherapy regimen.*

	GC (n=28)	GEM (n=22)	*p*-Value†	Non-AC (n=33)	*p*-Value‡
Albumin (g/dl)	3.3 (1.4-4.3)	2.9 (1.8-4.1)	0.150	3 (1.7-3.9)	**0.034**
CEA (ng/ml)	2.3 (0.7-37.6)	2.9 (1-16.3)	0.204	2.9 (1.2-72.8)	0.079
CA 19-9 (U/ml)	13 (2-5,590)	10.5 (2-2,200)	0.977	13 (2-8,170)	0.947
Days after surgery until AC*	67 (38-159)	68 (23-545)	0.860		
Full starting dose	28 (100%)	13 (59%)	**<0.001**		
Course completion	12 (43%)	14 (54%)	0.144		
RDI (%)	78.8 (6.3-100)	80 (13.3-100)	0.759		
RDI					
≥80%	14 (50%)	14 (64%)	0.335		
<80%	14 (50%)	8 (36%)			
Adverse events					
Grades 0, 1, 2	8 (29%)	12 (55%)	0.063		
Grades 3, 4	20 (71%)	10 (45%)			
Types of adverse events (any grade/grade 3, 4)					
Neutropenia	22 (79%)/18 (64%)	13 (59%)/10 (45%)			
Leukocytopenia	21 (75%)/7 (25%)	13 (59%)/4 (18%)			
Thrombocytopenia	16 (57%)/3 (11%)	13 (59%)/0			
Anemia	14 (50%)/4 (14%)	9 (41%)/0			
Febrile neutropenia	4 (8%)/4 (8%)	0/0			
AST elevation	12 (43%)/0	6 (27%)/0			
ALT elevation	10 (36%)/0	5 (23%)/0			
Edema limbs	3 (11%)/0	2 (9%)/0			
Constipation	2 (7%)/0	1 (5%)/0			
Biliary tract infection	1 (4%)/0	1 (5%)/1 (5%)			
Oral mucositis	1 (4%)/0	1 (5%)/0			
Anorexia	2 (7%)/0	0/0			
Nausea	0/0	1 (5%)/1 (5%)			
Skin rash	1 (4%)/1 (4%)	0/0			
Alopecia	0/0	1 (5%)/0			
Hiccups	0/0	1 (5%)/0			
Peripheral neuropathy	1 (4%)/0	0/0			
Fatigue	0/0	1 (5%)/0			
Cough	1 (4%)/0	0/0			

AC: Adjuvant chemotherapy; CA 19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; GC: gemcitabine plus cisplatin; GEM: gemcitabine; RDI: relative dose intensity. *In the non-AC group, data measured approximately 2 months after surgery were utilized. †GC *vs*. GEM; ‡GC *vs*. non-AC. Significant *p*-Values are shown in bold.

Table IV. *Profiles of recurrence.*

	GC (n=28)	GEM (n=22)	*p*-Value†	Non-AC (n=33)	*p*-Value‡
Recurrence	19 (68%)	17 (77%)	0.462	19 (58%)	0.409
Early recurrence	6 (21%)	10 (45%)	0.071	14 (42%)	0.082
Duration until recurrence (months)	16.6 (3.6-44)	10.4 (1.5-58.7)	0.165	6.6 (1.2-24.2)	**0.003**
First recurrence sites			0.411		0.582
Intra-hepatic only	5 (26%)	8 (47%)		8 (42%)	
Extra-hepatic only	13 (68%)	8 (47%)		10 (53%)	
Both	1 (6%)	1 (6%)		1 (5%)	
Treatment for recurrence			0.434		**0.036**
Chemotherapy	16 (84%)	13 (76%)		10 (53%)	
Best supportive care	3 (16%)	4 (24%)		9 (47%)	

AC: Adjuvant chemotherapy; GC: gemcitabine plus cisplatin; GEM: gemcitabine. †GC *vs*. GEM; ‡GC *vs*. non-AC. Significant *p*-Values are shown in bold.

Table V. *Univariate and multivariate analyses for overall survival in the whole cohort (n=83).*

Variables	n	Univariate *p*-Value‡	Multivariate HR (95%CI)	*p*-Value§
Age >75 years	23	0.777		
Male	49	0.517		
BMI <20 kg/m^2	28	0.081		
Preoperative				
Albumin <3 g/dl	26	**0.015**	–	0.243
CEA >5 ng/ml	21	**0.001**	3.197 (1.590-6.427)	**0.001**
CA19-9 >37 U/ml	43	0.095		
Before initiation of AC*				
Albumin <3 g/dl	37	0.313		
CEA >5 ng/ml	14	**0.026**	–	0.891
CA 19-9 >37 U/ml	25	0.071		
AC (GC regimen)	28	**0.039**	0.422 (0.207-0.861)	**0.018**
pStage III, IV	41	0.197		
pN1†	29	**0.002**	2.737 (1.500-4.994)	**0.001**
Resection margin (+)	25	**0.021**	2.197 (1.127-4.284)	**0.021**
HPD	12	0.668		

AC: Adjuvant chemotherapy; BMI: body mass index; CA 19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; CI: confidence interval; GC: gemcitabine plus cisplatin; HPD: hepatopancreatoduodenectomy; HR: hazard ratio. *In the non-AC group, data that were measured at 2 months after surgery were utilized. †Lymphadenectomy was not performed in 10 intra-hepatic cholangiocarcinoma patients. ‡Log-rank test; §Cox proportional hazard model with forward stepwise selection. Significant *p*-Values are shown in bold.

Table VI. *Univariate and multivariate analyses for early recurrence in the whole cohort (n=83).*

Variables	n	Univariate *p*-Value‡	Multivariate HR (95%CI)	*p*-Value§
Age >75 years	23	0.873		
Male	49	0.741		
BMI <20 kg/m^2	28	0.164		
Preoperative				
Albumin <3 g/dl	26	0.430		
CEA >5 ng/ml	21	**0.020**	–	0.105
CA 19-9 >37 U/ml	43	0.114		
Before initiation of AC*				
Albumin <3 g/dl	37	0.227		
CEA >5 ng/ml	14	**0.018**	–	0.174
CA 19-9 >37 U/ml	25	**0.016**	3.889 (1.214–12.457)	**0.022**
AC (GC regimen)	28	**0.046**	0.287 (0.085–0.967)	**0.044**
pStage III, IV	41	0.056		
pN1†	29	**0.005**	4.694 (1.544–14.273)	**0.005**
Resection margin (+)	25	0.986		
HPD	12	0.223		

AC: Adjuvant chemotherapy; BMI: body mass index; CA 19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; CI: confidence interval; GC: gemcitabine plus cisplatin; HPD: hepatopancreatoduodenectomy; OR: odds ratio. *In the non-AC group, data that were measured at 2 months after surgery were utilized. †Lymphadenectomy was not performed in 10 intra-hepatic cholangiocarcinoma patients. ‡Chi-squared test or Fisher's exact test; §Multiple logistic regression analysis with forward stepwise selection. Significant *p*-Values are shown in bold.

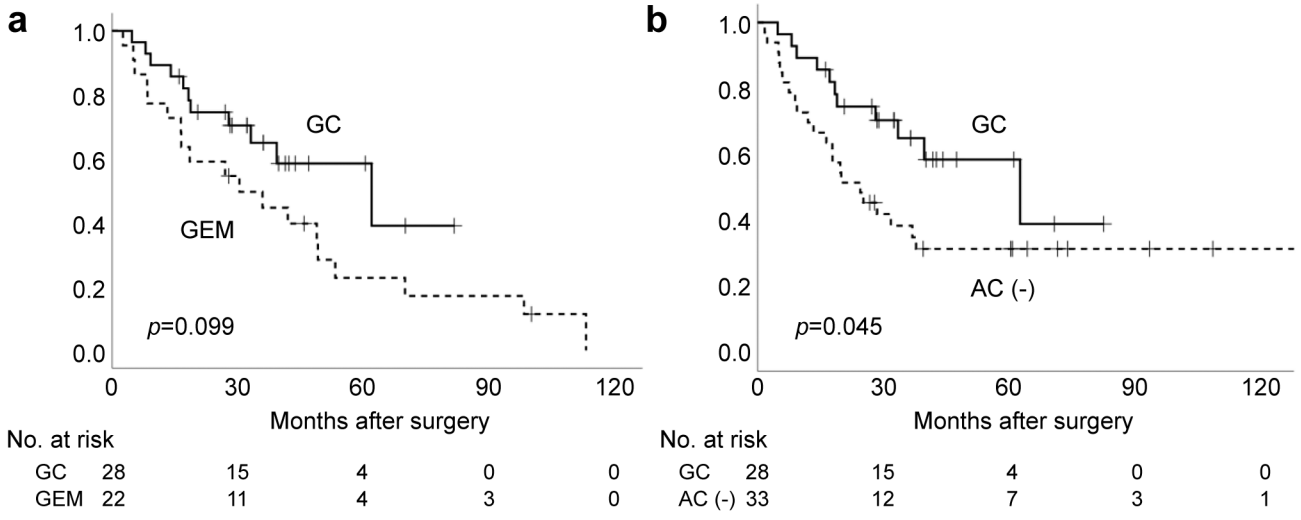

Figure 1. *Comparison of overall survival between (a) patients with gemcitabine plus cisplatin therapy (n=28) and those with gemcitabine monotherapy (n=22), and (b) patients with gemcitabine plus cisplatin therapy (n=28) and those without adjuvant chemotherapy (n=33).*

hepatectomy may influence postoperative hepatic impairment, which is associated with an increased risk of adverse events from chemotherapy (20, 21). Fujiwara *et al*. reported that a major hepatectomy did not affect the pharmacokinetics of gemcitabine or its main metabolite, 2',2'-difluorodeoxyuridine, although the standard regimen did cause a relatively high

hematological toxicity in BTC patients following a major hepatectomy (22). Kainuma *et al*. demonstrated that the standard dose of adjuvant GC therapy was tolerable within the expected levels of toxicities in patients with BTC who underwent a curative resection either with or without a major hepatectomy (17). In addition, the RDIs of GEM and cisplatin were 77% and 81%, respectively, which were similar to the results of the present study (78.8%).

Both the preoperative and pre-AC serum albumin levels were significantly lower and the patient age was significantly higher in the non-AC group than in the GC group (Table I and Table III). Similar differences were not observed between the GC group and the GEM group. Reduction in serum albumin levels can be linked to delays in the recovery of patient nutritional statuses because of inadequate oral food intake or systemic inflammatory responses after surgery (23, 24). These findings suggest that the physicians might have hesitated to administer AC to these patients, since the patients were not expected to be capable of tolerating the AC because of delays in the recovery of the patients' general conditions and/or advanced age. In contrast, patients who received AC with GC might have been expected to be capable of tolerating the full doses of AC agents prior to the actual initiation of AC; among these patients, the starting doses for the AC agents were 100%.

The duration until recurrence was significantly longer in the GC group than in the non-AC group (Table IV). Multivariate analysis revealed that AC with GC was one of the independent predictors of both the OS and early recurrence (Table V and Table VI). These results indicate that AC with GC would be beneficial to decrease the early recurrence after surgery and contribute to improved prognosis in patients with hilar BTC who underwent a major hepatectomy. In terms of the treatment of recurrence, most patients received chemotherapy in the GC group. In contrast, the best supportive care was chosen in a half of patients of the non-AC group (Table IV). These findings also indicate that the GC group might result in improved survival as compared with the non-AC group.

Taken together, these results suggest that the maintenance of chemotherapy as well as the patients' general conditions are two essential factors for achieving long-term survival.

The 5-year OS rate for the GC group tended to be higher than that for the GEM group (Figure 1A), even though the surgical and pathological outcomes, laboratory data (serum albumin and tumor markers) before the initiation of AC, and AC-related factors (days until AC, course completion rate, RDI, and adverse events) were not significantly different between the two groups. Accordingly, GC therapy might be preferable to GEM monotherapy as a promising regimen for adjuvant settings in patients who are expected to be capable of tolerating the full doses of AC agents prior to the actual initiation of AC. At present, a phase III trial (ACTICCA-1 study: adjuvant GC therapy *versus* observation alone) for BTC is being conducted (25). The results of this study will be available in the near future.

Our study had certain limitations. First, there may have been a selection bias in this series. Various factors, including pre-operative, intra-operative, and post-operative variables and the patients' age and general conditions, could have influenced the selection of AC. Second, this was a single-center, retrospective study that analyzed data for only a small number of Japanese patients with hilar BTC during an 11-year period. Within this study period, AC with GC was only introduced during the latter part of the study period. Third, decisions regarding the starting doses and the discontinuation of AC varied among the physicians. Therefore, further prospective studies with larger numbers of patients are required to reach definitive conclusions.

In conclusion, GC therapy in an adjuvant setting was feasible and beneficial for improving survival and decreasing early recurrence in patients with hilar BTC who had undergone a major hepatectomy.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Study concept and design: drafting of the manuscript: S.M.; data collection: S.M., Y.S., T.S., T.Y., K.P., T.M., T.S., and Y.I.; critical revision of the manuscript: T.A.; study supervision: K.K.

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