Adjuvant Chemotherapy with Gemcitabine for Resected Biliary Tract Cancer : A Single-Arm Phase 2 Study

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Objective : This phase 2, single-arm trial aimed to evaluate the efficacy and safety of gemcitabine in the adjuvant setting for patients with biliary tract carcinoma (BTC).

Method : Patients undergoing surgery subsequently received 6 cycles of adjuvant gemcitabine (1000 mg/m^2) intravenously over 30 minutes on days 1, 8, and 15 every 4 weeks. The primary end point was a two-year disease-free survival (DFS) rate and secondary end points were a two-year overall survival (OS) rate, tolerability, and the frequency of grade 3 or 4 toxicity.

Results : A total of 55 patients were enrolled. Primary tumor sites were intrahepatic bile duct in 14, extrahepatic bile duct in 34, gallbladder in 3, and ampulla of Vater in 4. During median follow-up of 40 months, 34 patients developed disease recurrence. Two-year DFS and OS rates were 47.7 % and 78.2 %, and median DFS and OS were 23 months and 46 months, respectively. The long-term outcomes in patients with extrahepatic bile duct carcinoma were similar compared with a historical cohort who underwent surgery alone. The completion rate and total dose intensity were 61.8 % and 70.3 %, respectively. Twenty-six patients (47.3 %) had grade 3 or 4 toxicity, none of which culminated in a fatal event.

Conclusion : The present study failed to show significant benefits of gemcitabine in the adjuvant setting for patients with resected BTC, although the regimen was well tolerated. *Shinshu Med J 65 : 99—111, 2017*

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Key words : biliary tract cancer, adjuvant chemotherapy, gemcitabine

I Introduction

Complete surgical resection is the only modality that offers a chance for long-term survival for biliary tract carcinoma (BTC). However, long-term outcomes of patients treated with surgery alone remain unsatisfactory, with a reported 5-year survival rate of 28-48 % for intrahepatic cholangiocarcinoma (ICC)[1)-3)], 24-50 % for extrahepatic bile duct carcinoma (EBC)[4)-8)], 7-53 % for gallbladder carcinoma (GBC)[9)-11)], and 50-68 % for carcinoma of the ampulla of Vater (CAV)[12)-14)]. The main reason for this is the high rate of cancer recurrence, which occurs even after curative resection[15)-17)], and once the disease recurs, the prognosis is extremely poor. To this end, adjuvant radiation therapy or chemotherapy, or both, have been explored as a means of reducing the rate of disease relapse[16)18)-21)].

So far, data supporting adjuvant chemotherapy for BTC are sparse. There was one phase III trial, evaluating the efficacy of the adjuvant chemotherapy using 5-FU and mitomycin C on long-term outcomes for patients with pancreatobiliary malignancies. This study showed that the adjuvant chemotherapy

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significantly prolonged the 5-year survival rate in patients with stage II or greater gallbladder cancer, whereas no significant difference was observed between patients with and without the adjuvant therapy in pancreatic cancer, bile duct cancer, and CAV.

Gemcitabine is a key drug of chemotherapy for pancreatic carcinoma. Previous study showed that administration of gemcitabine in an adjuvant setting significantly delayed the development of recurrent disease compared with surgery alone[22]. However, there have been few published prospective studies of adjuvant gemcitabine chemotherapy for resected BTC. We therefore conducted a phase 2, single-arm trial aimed at evaluating the efficacy and safety of gemcitabine in the adjuvant setting for patients with BTC.

Ⅱ Method

A Patient selection

Patients with histologically verified BTC were eligible if they had undergone macroscopically curative resection and no prior chemotherapy and/or radiotherapy. Additional eligibility requirements included : 20 years ≤ age < 80 years ; Eastern Cooperative Oncology Group performance status of 0–2 ; adequate bone marrow function (leucocyte count ≥ 4,000/mm^3, neutrophil count ≥ 2,000/mm^3, hemoglobin ≥ 10 g/dl, and platelet count ≥ 100,000/mm^3), adequate liver function (serum albumin ≥ 3.0 g/dl, total bilirubin ≤ 2 times the upper limit of normal (ULN) and aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≤ 3 times ULN) ; adequate renal function (creatinine ≤ 1.0 mg/dL) ; and life expectancy ≥ 3 months. All patients provided written informed consent. Exclusion criteria included contracting active infection, synchronous cancer, pregnancy or lactation, a history of severe drug allergy and other severe comorbid diseases. The protocol was approved by the institutional review board at Shinshu University. All procedures were performed in accordance with the 1964 Declaration of Helsinki. Clinical trials identification number was UMIN000014018.

B Adjuvant chemotherapy with gemcitabine

Patients received adjuvant chemotherapy with 6 cycles of gemcitabine every 4 weeks, primarily within 8 weeks following surgery. Each chemotherapy cycle consisted of 3 weekly infusions of gemcitabine 1,000 mg/m^2 given by intravenous infusion during a 30-minute period, followed by a 1-week rest. No premedication was administered in each gemcitabine treatment. The treatment regimen was terminated in the case of disease progression, intolerable adverse events or patient refusal.

C Toxicity and dose modification

The toxicities were graded according to the Common Terminology Criteria for Adverse Events version 3.0[23]. Gemcitabine doses should be interrupted in cases of grade 2 or higher events and treatment should be delayed until complete recovery or until the adverse event improves to grade 0 or 1. Gemcitabine was decreased by 20 % in subsequent cycles at the first occurrence of a grade 4 toxicity, and it was reduced by 40 % at the second occurrence of a given grade 4 toxicity. Treatment with gemcitabine was permanently stopped if, despite dose reduction, a grade 4 toxicity occurred for the third time.

D Study end points

The primary end point was a two-year disease-free survival (DFS) rate and secondary end points were a two-year overall survival (OS) rate, tolerability, and the frequency of grade 3 or 4 toxicity. Tolerability was further analyzed after the stratification of the patients according to whether they had undergone a major hepatectomy, defined as the resection of three or more Couinaud's segments[24].

E Statistical analyses

The trial was designed to have 80 % power to detect an increase in two-year DFS rate from 40 % in the historical cohort with surgery alone at our institution to 60 % in patients receiving adjuvant gemcitabine chemotherapy. A total of 48 patients would be required with a two-sided significance level of 5 %. To allow for dropouts and to ensure that we had sufficient evidence to meet the trial objectives, we aimed to recruit 55 patients. All analyses were performed on an intention-to-treat basis. Data were expressed as medians with range. The significance of differences between the groups was assessed by the

chi-square test, Fischer's exact test, unpaired Student's t-test, Welch's t-test, Mann-Whitney U test, log-rank test and Cox's proportional hazard model as appropriate. A p value less than .05 was used to indicate a significant difference. All statistical analyses were made using the JMP software version 10.0 (SAS Institute, Cary, North Carolina, USA).

Ⅲ Results

A Patient characteristics

Between April 2006 and February 2010, a total of 55 patients were enrolled in the present study with the diagnosis of intrahepatic cholangiocarcinoma (ICC) in 14, extrahepatic bile duct carcinoma (EBC) in 34, gallbladder carcinoma (GBC) in 3, and carcinoma of the ampulla of Vater (CAV) in 4. The background characteristics are summarized in **Table 1**. The median age was 67 (34-78) years. A median preoperative CEA and CA19-9 values were 2.4 ng/mL and 44.3 U/ml, respectively. The most frequently performed surgical procedure was hepatectomy with bile duct resection (26 patients ; 47.3 %), followed by pancreaticoduodenectomy (15 patients ; 27.2 %). In pathologic staging based on 7th edition American Joint Committee on Cancer (AJCC) classification, almost three fourths were categorized as having T2 (n = 21, 38.2 %) or T3 (n = 17, 30.9 %) primary tumors. Lymph node involvement was observed in 24 patients (43.6 %). An R0 resection was achieved in 41 patients (74.5 %).

B Treatment administration

Thirty-four patients (61.8 %) received the full 6 cycles of adjuvant chemotherapy. The reasons for withdrawal from treatment included tumor recurrence (8 patients ; 38.1 %), adverse events (8 patients ; 38.1 %), and patient preference (5 patients ; 23.8 %). The median relative dose intensity (RDI) was 70.3 % (range, 9.9-100 %). The completion rate and the RDI tended to be lower among patients who had undergone a major hepatectomy, compared with those who had not ($p = 0.199$ and 0.103, respectively) (**Table 2**).

C Adverse events

The incidence of adverse events is shown in **Table 3**. The grade 3 or 4 toxicities included leucopenia (23.6 %), neutropenia (45.5 %), thrombocytopenia (1.8 %), and fatigue (1.8 %). There were no treatment-related deaths.

D Long-term outcomes

During a median follow-up period of 40 months, a total of 34 patients (61.8 %) developed tumor recurrence with median time to recurrence of 11.5 months (range, 1.8-55.8 months). Liver was the most common recurrence site (47.0 %) (**Table 1**). The 2-year DFS rate and OS rate was 47.7 % and 78.2 % (**Fig. 1A, B**), and median DFS and OS were 23 months and 46 months, respectively.

We analyzed the effectiveness of adjuvant chemotherapy for patients with EBC in comparison with the historical cohort of surgery alone (n = 187), because of the relatively smaller number of patients with ICC, GBC and CAV. No significant difference was observed in clinicopathological data between patients with and without adjuvant chemotherapy except for preoperative carcinoembryonic antigen (CEA) (**Table 4**). There was no statistically significant difference in DFS (two-year DFS rate of 42.5 % vs. 49.8 %, $p = 0.495$) and OS (two-year OS rate of 76.5 % vs. 64.4 %, $p = 0.568$) between patients with and without adjuvant chemotherapy (**Fig. 2A, B**). No significant survival advantage was observed in EBC patients receiving adjuvant chemotherapy when the patients were stratified according to the presence or absence of lymph node involvement or curability (**Fig. 3A-D**).

Ⅳ Discussion

This study tested the null hypothesis that adjuvant gemcitabine chemotherapy increases two-year DFS rate from 40 % to 60 %. However, we failed to show a significant survival benefit of adjuvant chemotherapy. In a subgroup analysis, no significant difference was observed in DFS and OS between EBC patients with and without adjuvant chemotherapy. Although a recent meta-analysis showed a survival benefit of adjuvant therapy for patients with lymph node involvement or those undergoing R1 resection[25], adjuvant chemotherapy did not prolong the survival of such high-risk patients in the present

Table 1 Background characteristics and perioperative data of the patients who received adjuvant chemotherapy (n = 55)[a]

Characteristic	
Age (years)[b]	67 (34–78)
Gender	
Male	36 (65.5)
Female	19 (34.5)
Tumor location	
Intrahepatic cholangiocarcinoma	14 (25.4)
Extrahepatic bile duct carcinoma	34 (61.8)
Gallbladder carcinoma	3 (5.5)
Carcinoma of the ampulla of Vater	4 (7.3)
CEA (ng/mL)[b]	2.4 (0.9–16.8)
CA19–9 (U/mL)[b]	44.3 (0.6–14155.0)
Operative procedure	
Hepatectomy with bile duct resection	26 (47.3)
Hepatectomy with PD	3 (5.5)
Hepatectomy	8 (14.5)
PD	15 (27.2)
Bile duct resection	3 (5.5)
AJCC grading	
T	
T1	8 (14.5)
T2	21 (38.2)
T3	17 (30.9)
T4	9 (16.4)
N	
N0	31 (56.4)
N1	24 (43.6)
Stage	
Stage Ⅰ	12 (21.8)
Stage Ⅱ	23 (41.8)
Stage Ⅲ	11 (20.0)
Stage Ⅳ	9 (16.4)
G	
G1	35 (63.6)
G2	8 (14.6)
G3	11 (20.0)
G4	1 (1.8)
R	
R0	41 (74.5)
R1	14 (25.5)
Postoperative course	
Recurrence	34 (61.8)
Time–to–recurrence (months)[b]	11.5 (1.8–55.8)
Disease recurrence sites	
Liver	16 (47.0)
Lymph node	7 (20.6)
Locoregional	4 (11.8)
Other sites	7 (20.6)
Last follow–up	
Alive	22 (40.0)
Dead	33 (60.0)
Cause of death	
From disease	31 (93.9)
From other causes	2 (6.1)

[a]Values in parentheses are percentages unless indicated otherwise.
[b]Values in parentheses are ranges.
CEA, carcinoembryonic antigen ; CA19–9, carbohydrate antigen 19–9 ; PD, pancreaticoduodenectomy ; AJCC, American Joint Committee on Cancer.

Table 2 Tolerability of adjuvant chemotherapy stratified according to whether a major hepatectomy had been performeda

	Major hepatectomy[b] (n = 28)	Other operative procedures (n = 27)	*P* value
Completion rate (%)	57.1	77.8	0.103
Relative dose intensity (%)	65.2 (9.9–100.0)	92.1 (10.7–100.0)	0.054

[a]Values in parentheses are ranges.
[b]Major hepatectomy was defined as removal of three or more Couinaud segments[24].

Table 3 Adverse events as evaluated according to the Common Terminology Criteria for Adverse Events (version 3.0)

Adverse event	Any grade (%)	Grade 3 or 4 (%)
Hematological		
Leucopenia	43 (78.2)	13 (23.6)
Neutropenia	42 (76.4)	25 (45.5)
Anemia	24 (43.6)	0 (0.0)
Thrombocytopenia	25 (45.5)	1 (1.8)
Non-hematological		
Liver dysfunction	6 (10.9)	0 (0.0)
Fatigue	5 (9.1)	1 (1.8)
Anorexia	13 (23.6)	0 (0.0)
Nausea	7 (12.7)	0 (0.0)
Rash	6 (10.9)	0 (0.0)

study. Previous studies on postoperative adjuvant treatment of BTC are summarized in **Table 5**[15)16)18)-20)26)-36)]. Although some studies have suggested hopeful effects of adjuvant treatment, others could not reveal that adjuvant treatments contribute to delaying the development of recurrence and prolonged survival. In particular, 2 RCTs failed to demonstrate significant benefit for adjuvant chemotherapy in patients with curatively resected BTC[15)36)]. Thus, at present, the evidences seems to be insufficient support this treatment strategy, in spite of its worldwide adoption in many major institutions[37)].

Previous study demonstrated that the incidence of serious adverse events was significantly lower in patients treated with adjuvant gemcitabine alone than that in patients treated with fluorouracil plus leucovorin (30 % vs. 49 %, $p < 0.01$) for resected periampullary carcinoma[36)]. In the present study, adjuvant gemcitabine could be safely administered to patients with resected BTC. Although 47.3 % of patients experienced grade 3 or 4 neutropenia during the treatment, most of these toxicities were transient, and no fatal event occurred. Furthermore, the occurrence rate was comparable to that of the previously reported phase 3 trial of adjuvant gemcitabine for resected pancreatic carcinoma in Japan, JSAP-02 (70.0 %)[38)].

Considering that gemcitabine is rapidly deaminated to its inactive metabolite, 2, 2-difluorodeoxyuridine, by cytidine deaminase, which abounds in the liver[39)40)], the removal of a large amount of liver parenchyma might enhance the toxicity of gemcitabine, making the continuation of chemotherapy difficult. Indeed, two recent phase I studies examining adjuvant gemcitabine monotherapy in patients with BTC undergoing a major hepatectomy revealed that the recommended dose of gemcitabine was much lower than the regular dose for unresectable and recurrent BTC[21)41)]. In line with these findings, the present study showed that the completion rate and the RDI tended to be lower among patients who had undergone a major hepatectomy, compared with those who had not.

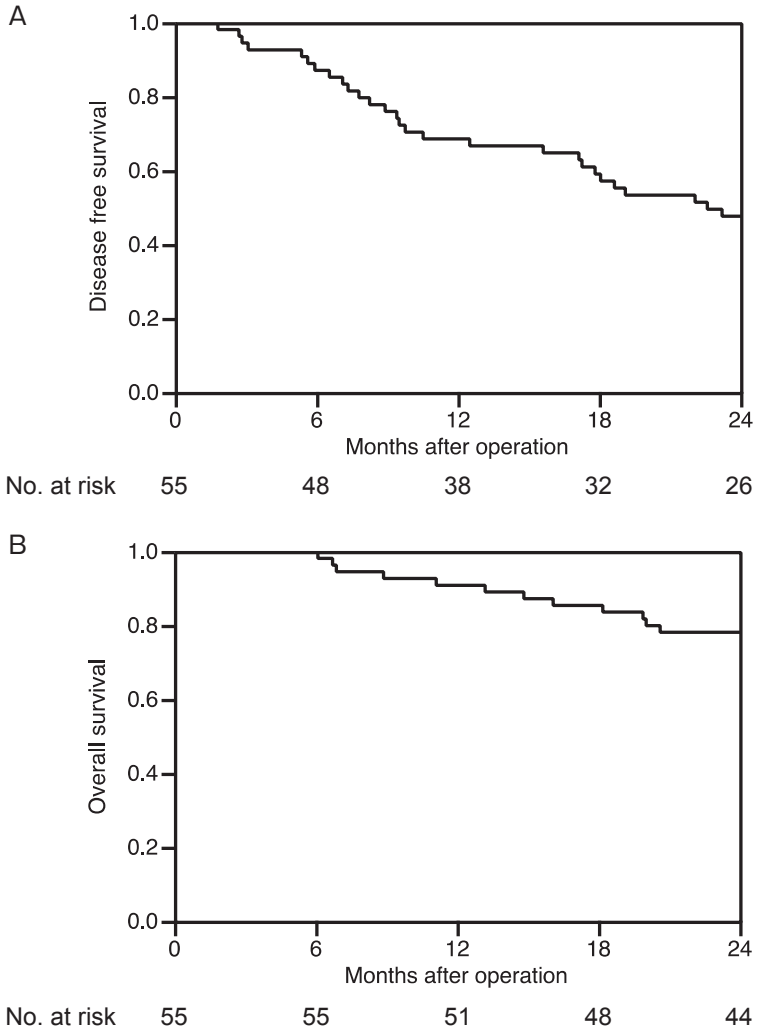

Fig. 1 The disease-free survival (DFS) (A) and overall survival (OS) (B) curves for patients receiving adjuvant chemotherapy using gemcitabine. The 2-year DFS and OS rates were 47.7 % and 78.2 %, respectively.

Table 4 Clinicopathological data of patients with extrahepatic biliary carcinoma stratified according to whether adjuvant chemotherapy was performed[a]

Characteristic	Adjuvant chemotherapy (n = 34)	Surgery alone (n = 187)	*P* value
Age (years)	67 (34-78)	69 (39-84)	0.302
Gender (male/female)	29/5	135/52	0.108
AJCC grading			
T (T1/T2/T3/T4)	5/16/12/1	29/91/49/18	0.497
N (N0/N1)	20/14	106/81	0.817
Stage (I/II/III/IV)	9/15/9/1	43/76/50/18	0.631
G (G1/G2/G3/G4)	20/7/7/0	103/57/26/1	0.555
R (R0/R1)	26/8	161/26	0.152

[a]Values in parentheses are ranges.
AJCC, American Joint Committee on Cancer.

An analysis of initial recurrence site in the present study showed that distant metastasis occurred more frequently than local recurrence, and the most prevalent site of distant metastasis was the liver. Our results are in line with the previous studies of hilar cholangiocarcionoma[42], distal cholangiocarcinoma[32)43)], and carcinoma of the ampulla of Vater[14)44)45)]. Considering these results, although it remains con-

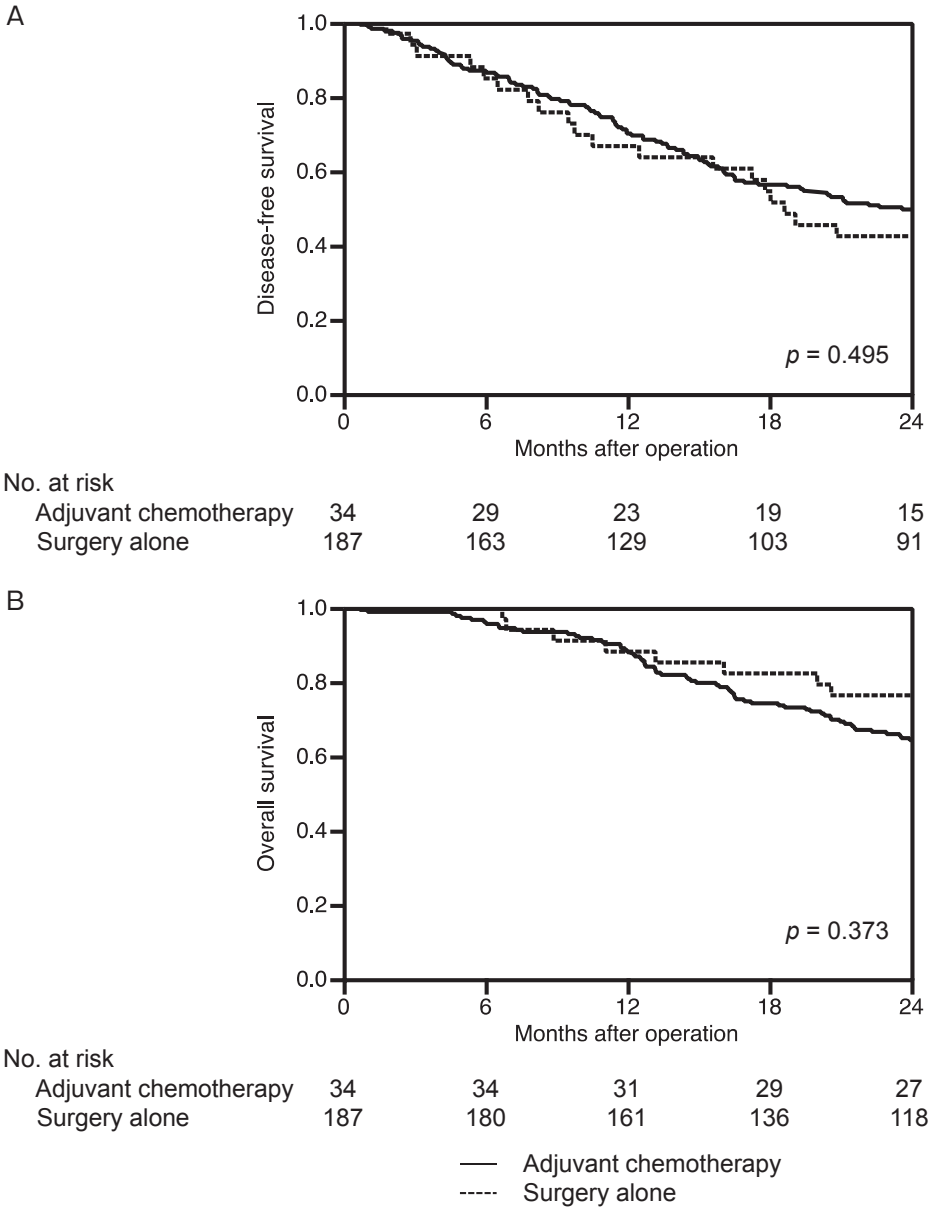

Fig. 2 Comparison of DFS and OS between extrahepatic bile duct carcinoma patients with and without adjuvant chemotherapy. There was no statistically significant difference in 2-year DFS and OS rates between two groups (42.5 % vs. 49.8 %, $p = 0.495$, and 76.5 % vs. 64.4 %, $p = 0.568$, respectively).

troversial whether systemic chemotherapy or radiotherapy is suitable for adjuvant treatment for resected BTC, systemic therapy could play a role as an adjuvant treatment modality. Indeed, a meta-analysis demonstrated that patients receiving chemotherapy or chemoradiotherapy showed better long-term outcomes than those undergoing radiotherapy alone[25].

Although gemcitabine monotherapy was used for advanced BTC as the community standard in the 2000s[46)-48)], the first-line chemotherapeutic regimen for advanced BTC is, at present, considered to be gemcitabine-based combined therapy[49)50)] because of its superior anti-tumor effect[51]. In the adjuvant setting, there was no previous study in the English literature except for a report from Murakami et al. They retrospectively studied the effect of gemcitabine plus S-1 chemotherapy for resected BTC, and showed that the combined regimen contributed to improved long-term outcomes in patients with International Union Against Cancer stage II BTC[19]. Further studies are needed to develop the effective regimen of adjuvant chemotherapy for resected BTC.

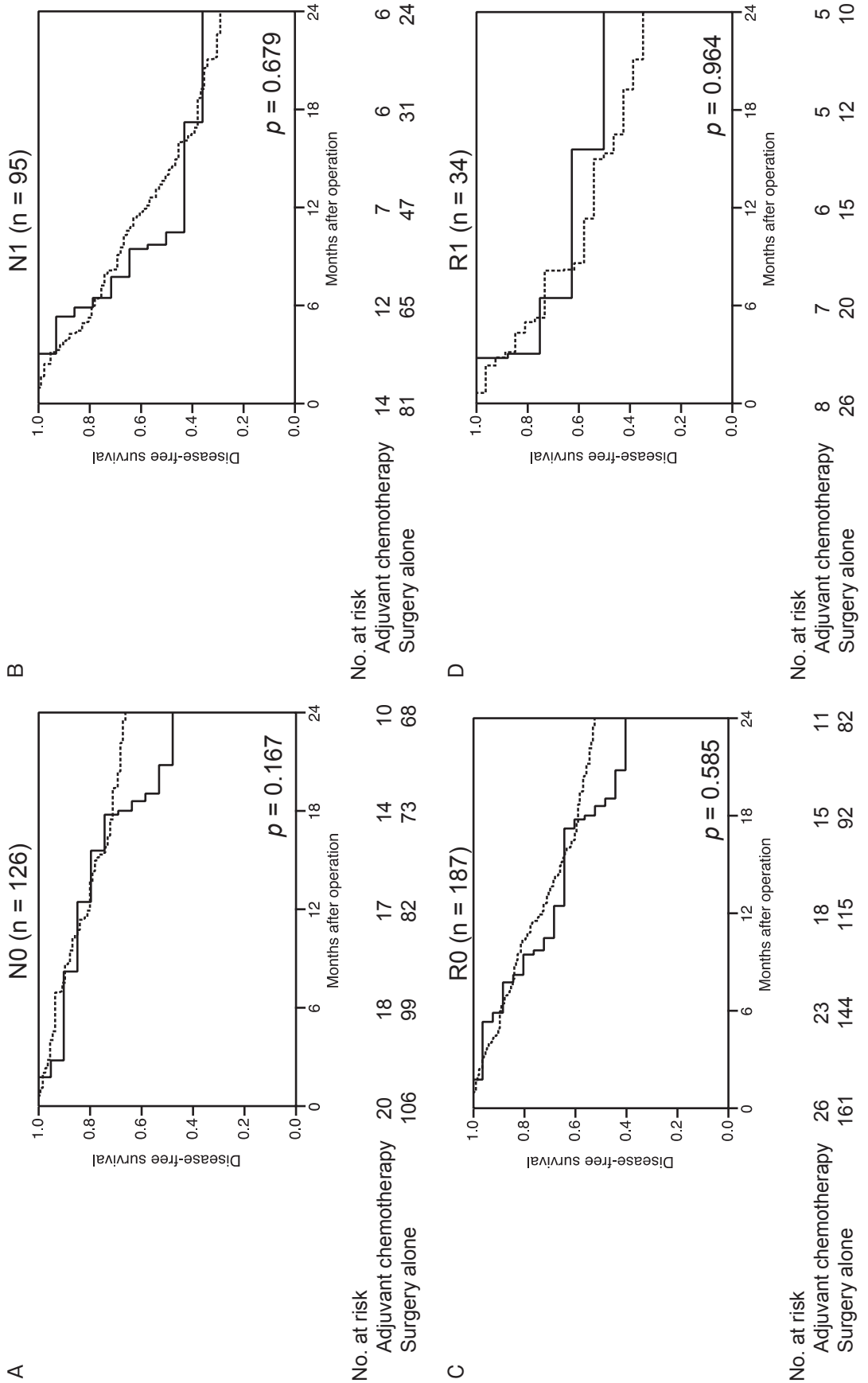

Fig. 3 Effects of adjuvant chemotherapy in patients with extrahepatic bile duct carcinoma stratified according to their N or R categories. No significant prolongation of the DFS was observed among patients receiving adjuvant chemotherapy in all the subgroups. A) N0 (n = 126) ; B) N1 (n = 95) ; C) R0 (n = 187) ; D) R1 (n = 34).

Table 5 Literature review of long-term outcomes of patients with resected biliary tract cancer who received adjuvant therapy (published after 2000)

Author	Year	Tumor location	No. of patients		Adjuvant therapy		5-year DFS rate (%)			5-year OS rate (%)		
			Adjuvant therapy	Surgery alone	CT	RT	Adjuvant therapy	Surgery alone	*P* value	Adjuvant therapy	Surgery alone	*P* value
Todoroki[26)a]	2000	EBC	28	19	NA	ERBT	NR	NA	NA	34	13	0.014
Kresl[27)a]	2002	GBC	21	NA	5FU	ERBT	NR	NR	NR	33	NA	NA
Kim[18)a]	2002	EBC	84	NA	5FU	ERBT	26	NA	NA	31	NA	NA
Nakeeb[28)a]	2002	ICC, EBC, GBC	42	NA	5FU or GEM	ERBT	NR	NA	NA	13	NA	NA
Takada[15)b]	2002	EBC	58	60	5FU + MMC	NA	21	15	0.889	27	24	NS
		GBC	69	43	5FU + MMC	NA	20	12	0.021	26	14	0.037
		CAV	24	24	5FU + MMC	NA	25	21	0.900	28	34	NS
Gerhards[29)a]	2003	EBC	71	20	NA	ERBT ± ILRT	NR	NA	NA	NR	NR	< 0.050
Sikora[30)a]	2005	CAV	49	55	5FU	ERBT	NR	NR	NR	28	38	0.330
Czito[16)a]	2005	GBC	22	NA	NA	ERBT	33	NA	NA	37	NA	NA
Sagawa[31)a]	2005	EBC	39	30	NA	ERBT ± ILRT	NR	NR	NR	24	NR	0.554
Hughes[32)a]	2007	EBC	34	30	5FU	ERBT	NR	NR	NR	35	27	< 0.040
Krishnan[33)a]	2008	CAV	55	41	5FU or Cap	ERBT	NR	NR	NR	60	69	0.530
Borghero3[4)a]	2008	EBC	42	23	5FU or Cap	ERBT	NR	NR	NR	36	42	0.590
Nelson[20)a]	2009	EBC	45	NA	5FU	ERBT	37	NA	NA	33	NA	NA
Gold[35)a]	2009	GBC (AJCC stage Ⅰ or Ⅱ)	25	48	5FU	ERBT	NR	NA	NA	NR	NR	0.560
Murakami[19)c]	2009	EBC, GBC, CAV (UICC stage Ⅱ)	50	53	GEM + S－1	NA	60	NR	NR	57	24	< 0.001
Neoptolemos[36)b]	2012	EBC, CAV	141	144	GEM	NA	NR	NR	NR	NR	NR	0.230
			143	144	5FU + FA	NA	NR	NR	NR	NR	NR	0.740
Present Study[c]	2015	ICC, EBC, GBC, CAV	55	NA	GEM	NA	33	NA	NA	37	NA	NA

[a]A retrospective study
[b]A prospective randomized controlled trial
[c]A prospective study compared to historical control
DFS, disease-free survival ; OS, overall survival ; CT, chemotherapy ; RT, radiation therapy ; EBC, extrahepatic bile duct carcinoma ; NA, not applicable ; ERBT, external-beam radiation therapy ; NR, details not reported ; GBC, gallbladder carcinoma ; ICC, intrahepatic cholangiocarcinoma ; 5FU, 5-fluorouracil ; GEM, gemcitabine ; MMC, mitomicin C ; NS, not significant ; CAV, carcinoma of the ampulla of Vater ; ILRT, intraluminal radiation therapy ; Cap, capecitabine ; AJCC, American Joint Committee on Cancer ; UICC, International Union Against Cancer ; FA, folinic acid.

There were several limitations in this study. The study design was single-arm. The most important limitation of the present study was the heterogeneity of the study population, consisting of all types of BTC including ICC, EBC, GBC, and CAV. Some researchers have reported that the biological behavior might be different among the tumor types based on the results of sensitivity to non-surgical treatments [36)52)-54)] or survival profile after surgery[36)55)56)]. Therefore, a stratified analysis according to tumor type may reveal the true impact of adjuvant treatment in each tumor type of BTC. Despite these limitations, however, we believe that our results are of interest, because there have been so few reports in the English literature of a phase 2 trial of adjuvant gemcitabine monotherapy for resected BTC.

In conclusion, the present study failed to show significant benefits of gemcitabine in the adjuvant setting for patients with resected BTC, although the regimen was well tolerated. Further investigation of adjuvant treatments might be needed to improve long-term outcomes in BTC patients.

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