ANTICANCER RESEARCH *39*: 2155-2161 (2019)
doi:10.21873/anticanres.13329

The Efficacy and Limitations of Postoperative Adjuvant Chemotherapy in Patients With Extrahepatic Cholangiocarcinoma

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Abstract. *Background/Aim: The impact of adjuvant chemotherapy (AC) for extrahepatic cholangiocarcinoma (ECC) remains unclear. This study evaluated the efficacy and limitations of AC. Patients and Methods: Between 2006 and 2016, 106 patients with stage II-IV ECC who underwent curative resection with biliary tract reconstruction were retrospectively analyzed. Patients were divided into two groups: Those who received AC (n=57) and those who did not (n=49). Results: Fewer grade 3-4 complications were observed in the AC group compared to the non-AC group (38.6 vs. 61.2%, p=0.03). In the non-AC group, complications were the most frequent reason for omitting AC (n=21, including 13 with biliary fistula). In the AC group, the therapy completion rate was 56.1% and the main reason for discontinuation was adverse events (n=12, including six with cholangitis). AC was not associated with survival benefits (median survival: 50.4 vs. 37.3 months, p=0.916). Conclusion: AC for ECC might be inadequate as a standard strategy due to the low implementation and completion rates because complications often hamper administration.*

While uncommon, cancer of the biliary tract (BTC) is often highly aggressive and its incidence is increasing world-wide. BTC includes intrahepatic cholangiocarcinoma (ICC), extrahepatic cholangiocarcinoma (ECC), gallbladder cancer and carcinoma of the ampulla of Vater. Surgical resection is the only curative treatment, although the recurrence rate following surgery is high (50-60%) (1-3). The 5-year survival rate for BTC is around 30% (4). The poor prognosis for BTC highlights the need for alternative treatment strategies (5-7).

Retrospective studies demonstrate that adjuvant therapy may be beneficial, particularly in high-risk patients with BTC [*e.g.* in those with node-positive (N+) disease or patients with an R1 resection margin] (8). In a recent phase III randomized clinical trial (BILCAP), adjuvant capecitabine chemotherapy was associated with improved overall survival (OS) compared to patients who underwent observation alone (but non-significant difference for intent-to-treat analysis) (9). Based on these findings, some propose that surgery plus adjuvant chemotherapy for BTC should be considered a standard approach.

We previously reported the efficacy of adjuvant chemotherapy (AC) in selected patients with BTC (10) and ICC (11). However, using subgroup analysis, we did not find AC to be beneficial for patients with ECC [hazard ratio (HR)=0.91, 95% CI=0.38-2.19, p=0.84] (10). As a result, the efficacy of AC in patients with ECC remains controversial. Moreover, ECC requires complex surgeries (*e.g.* pancreaticoduodenectomy or extended hepatectomy) with biliary tract reconstruction and is often accompanied by complications. This often results in a lower completion rate of AC in patients with ECC than in those with other malignancies. Therefore, comprehensive analysis of all patients undergoing AC is important to allow for intent-to-treat analysis. In this study, we review our experiences from an ECC patient cohort, evaluate the prognostic impact of AC, and evaluate the potential therapeutic efficacy.

Patients and Methods

Study design. This study was a retrospective observational study in a single institution. The study protocol was approved by the Ethics Committee of the Graduate School of Medicine at Kyoto University Graduate School (approval code: R1318). Written informed consent was obtained from all study participants.

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Key Words: Extrahepatic cholangiocarcinoma, adjuvant chemotherapy, postoperative complication.

Selection criteria. Between January 2006 and June 2016, 132 patients underwent curative-intent surgery for ECC with biliary tract reconstruction at Kyoto University Hospital. The follow-up data relating to these patients was updated in December 2018. The exclusion criteria included postoperative death and stage I disease (Japanese classification, fifth edition) (12). Since 2006, we have routinely administered AC for patients with stage II-IV ECC, since outcomes remain unsatisfactory.

AC regimen. The AC agents gemcitabine hydrochloride and tegafur-gimeracil-oteracil-potassium (S-1; Taiho Pharmaceutical) were authorized for use in Japanese patients with BTC in 2006 and 2007, respectively. Patients were assigned to one of two treatment regimens, receiving either gemcitabine or S-1. Gemcitabine was administered intravenously at a dose of 800-1000 mg/m^2 on either: days 1, 8, and 15 during a 4-week cycle; or once biweekly. S-1 was administered orally at a dose of 80 mg/m^2/day for either: 4 weeks followed by 2 weeks of rest (a 6-week cycle); or for 2 weeks, followed by a week of rest (a 3-week cycle). In both cases, treatment cycles were repeated until patients had received AC for 24 weeks.

Study variables. The clinical characteristics obtained from each patient included age, gender, evidence of tumor markers, tumor differentiation, T factor, N factor, stage (based on the International Union Against Cancer classification, sixth edition) (13), operative procedures (hepatectomy, pancreaticoduodenectomy, or both), postoperative complications (Clavien–Dindo classification version 2.0) (14), operative time, details of blood transfusion, and postoperative hospital stay (in days).

Outcomes. Patients were classified into those who received AC (AC group) and those who did not (non-AC group). Our primary outcome was OS, which was defined as the period of time from surgery to all-cause mortality. Data for OS were censored at either the date of the final confirmation of survival for surviving patients, or for patients lost to follow-up, at the date of the most recent confirmation of survival, and at the date of death for patients who died.

The secondary endpoints in this study were relapse-free survival (RFS), adverse events, completion rate of AC, reasons for not assigning patients to AC, and discontinuation in the AC group. RFS was the time from surgery to the date of relapse or death from any cause. We calculated toxicity grades of adverse events using the Common Terminology Criteria for Adverse Events (version 4.0) (15). The reasons for omission and discontinuation of AC were identified by analysis of medical records. Patients in the AC group underwent laboratory tests and assessment of clinical symptoms during every AC cycle of the treatment period and then every 3 months during follow-up. Patients in both groups underwent computed tomography with/without ultrasonography at 3-month intervals after surgery, unless there was a confirmed relapse. The tumor markers, carcinoembryonic antigen and cancer antigen 19-9 (CA19-9), were also measured every 3 months unless there was confirmed relapse.

Statistical analyses. Continuous variables are expressed as the median (with range) and compared using the Mann–Whitney *U*-test. Categorical variables were compared using Fisher's exact test. OS and RFS were calculated by the Kaplan–Meier method and compared between each group using the generalized Wilcoxon method. Prognostic factors for survival were identified using a multivariate Cox proportional hazard model with stepwise selection; variables that were identified as significant in univariate analysis of this study, as well as those generally reported as high-risk factors (*i.e.* lymph node metastasis, tumor stage, tumor grade, surgical margin), were placed in a multivariate model. All tests were two-tailed, and differences were considered significant at a p-value of less than 0.05. Statistical analysis was performed using JMP version 13.2 software (SAS Institute, Inc., Cary, NC, USA).

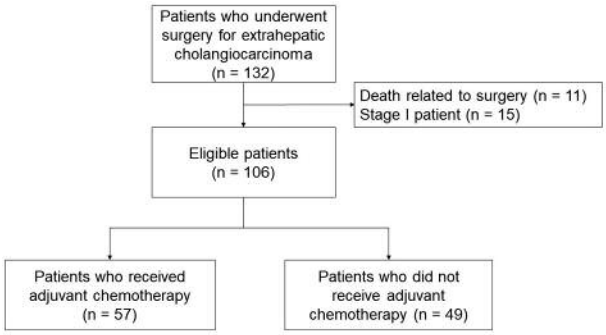

Figure 1. *Study flow diagram*.

Results

Patient demographics. Figure 1 indicates the patient inclusion flow diagram for this study. A total of 132 patients who were diagnosed with ECC and underwent surgical resection with bile tract reconstruction were initially eligible for this study. Patients became ineligible based on the exclusion criteria of postoperative death (n=11) or stage I diagnosis (n=15). After application of the exclusion criteria, 106 patients were included in the study. The median follow-up time was 31.9 months (range=1.0-131.2 months), whereas the median survival time (MST) and 5-year OS rate were 37.3 months and 42.3%, respectively.

Relationship between patient characteristics and AC administration. Of 106 patients, 57 (53.7%) received AC; of those patients, 46 patients received gemcitabine and 11 patients received S-1. The remaining 49 patients (46.3%) did not receive any AC. The clinical characteristics of the study patients are shown in Table I. There were significant differences in the AC *vs*. the non-AC group in terms of the number of patients ≥65 years of age (n=27 *vs*. 35, p=0.017), CA19-9 level ≥37 U/ml (n=41 *vs*. 25, p=0.029), lymph node metastasis (n=32 *vs*. 16, p=0.033), postoperative complications (n=22 *vs*. 30, p=0.031), and requiring blood transfusion (n=13 *vs*. 22, p=0.011).

A prolonged hospital stay (>10 weeks) due to complications was the most frequent reason (n=15) for

Table I. *Patient and clinicopathological characteristics*.

Variable	AC (n=57)	Non-AC (n=49)	*p*-Value*
Age ≥65 Years, n (%)	27 (47.4%)	35 (71.4%)	0.017
Gender: M:F, n (%)	35:22	29:20	0.844
CEA ≥5 ng/ml, n (%)	8 (14.0%)	4 (8.2%)	0.376
CA19-9 ≥37 U/ml, n (%)	41 (71.9%)	25 (51.0%)	0.029
T-Stage ≥3, n (%)	38 (66.6%)	24 (48.9%)	0.077
N0, n (%)	23 (40.3%)	31 (63.2%)	0.033
N1, n (%)	32 (56.1%)	16 (32.6%)	
NX, n (%)	2 (3.5%)	2 (4.0%)	
Poorly differentiated, n (%)	11 (19.3%)	6 (12.2%)	0.428
Positive surgical margin, n (%)	22 (38.6%)	14 (28.5%)	0.309
Stage, n (%)§			
Ib	7 (12.2%)	15 (30.6%)	0.250
IIa/b	12/20 (21.0/35.0%)	9/10 (18.3%)	
III	13 (22.8%)	11 (22.4%)	
IV	3 (5.2%)	2 (4.1%)	
Hepatectomy, n (%)	23 (40.3%)	23 (46.9%)	0.222
Pancreaticoduodenectomy, n (%)	28 (49.1%)	18 (36.7%)	
Hepato-pancreaticoduodenectomy, n (%)	6 (10.5%)	5 (10.2%)	
Complication, grade ≥3‡	22 (38.6%)	30 (61.2%)	0.031
Blood loss (ml)†	1075 (80-14500)	1212 (207-4420)	0.809
Operative time (min)†	596 (384-1274)	593 (395-1156)	0.671
Blood transfusion required, n (%)	13 (22.8%)	22 (47.8%)	0.011
Postoperative hospital day ≥70 days, n (%)	8 (14.0%)	18 (36.7%)	0.006

AC: Adjuvant chemotherapy; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9. †Median (range). §According to the International Union Against Cancer Classification, sixth edition (13). ‡According to Clavien–Dindo classification version 2.0 (14). *Continuous variables were compared using Mann–Whitney *U*-test and categorical variables were compared using Fisher's exact test.

omitting chemotherapy for patients in the non-AC group, followed by patient refusal (n=11), postoperative sequelae (n=8), old age (n=7), acute recurrence (n=6), and other/unknown (n=2). The most common grade 3 or more complications (in ≥5%) observed in the non-AC group were biliary fistula (n=13), pancreatic fistula (n=7), pleural effusion (n=5), postoperative bleeding (n=5), abdominal abscess (n=4), ascites (n=4), and cholangitis (n=3). In the AC group, the most common grade 3 or more complications were pancreatic fistula (n=10), biliary fistula (n=4), abdominal abscess (n=4), and postoperative bleeding (n=3).

Survival outcomes. During the follow-up period, 35 patients (61.4%) in the AC group, and 26 (53.6%) in the non-AC group died. In the AC group, the MST and 5-year OS rate were 50.4 months and 40.8%, respectively; in comparison, MST and OS in the non-AC group were 37.3 months and 44.6% (p=0.916, Figure 2).

Relapse was observed in 37 patients (64.9%) in the AC group and in 28 (57.1%) in the non-AC group. The most frequent site of initial relapse in both groups was the liver (in 18 (48.6%) *vs*. 16 (57.1%), in AC and non-AC groups, respectively], followed by the lymph nodes [in 13 (35.1%) *vs*. six (21.4%), respectively]. In the AC group, the median RFS and 5-year RFS rate were 17.5 months and 30.9%, respectively; this compares to 25.9 months and 38.4%, in non-AC patients (p=0.794, Figure 3). There were no significant differences in OS and RFS between the AC and non-AC groups.

Univariate and multivariate analyses for OS are shown in Table II. Multivariate analysis identified lymph node metastasis (HR=2.93, 95% CI=1.69-5.23, p<0.001) as a prognostic factor. In subgroup analysis based on selected clinical variables, AC was significantly associated with an improved prognosis in two following variables; evidence of lymph node metastasis (32.1 *vs*. 14.9 months; p=0.040) and without postoperative complication (50.4 *vs*. 25.2 months; p=0.040).

Adverse events. Toxicity grade was not evaluated for 12 patients as they received adjuvant gemcitabine chemotherapy at other hospitals. Adverse events observed during treatment are listed in Table III. Patients who received gemcitabine displayed grade 3/4 hematological toxicity more frequently than patients administered S 1 (in 16 *vs*. one, p=0.033). There were no treatment-related deaths. Thirty-two patients (56.1%) completed treatment. The main reasons for discontinuation were adverse events (in 12 patients,

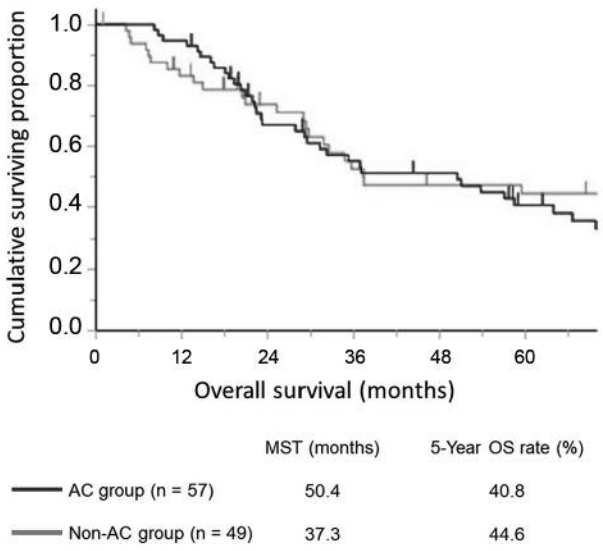

Figure 2. *Kaplan–Meier estimates of overall survival (OS) in the adjuvant chemotherapy (AC) and non-AC groups (p=0.916; generalized Wilcoxon method). MST: Median survival time.*

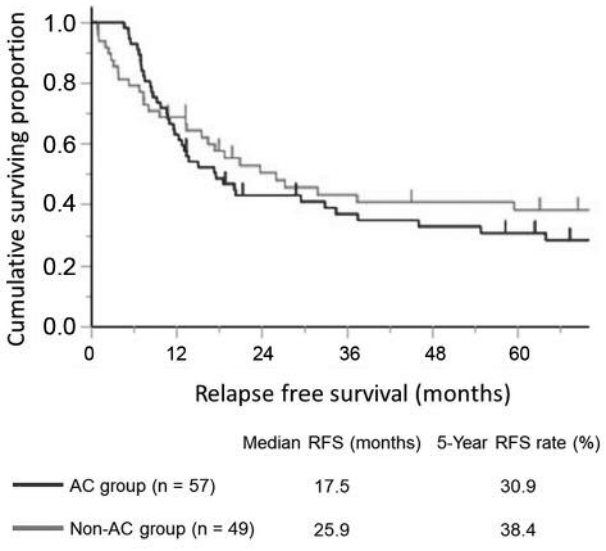

Figure 3. *Kaplan–Meier estimates of relapse-free survival (RFS)in the adjuvant chemotherapy (AC) and non-AC groups (p=0.794; generalized Wilcoxon method).*

Table II. *Assessment of factors associated with overall survival using univariate/multivariate Cox proportional hazards analysis.*

Variable	Univariate		Multivariate	
	HR (95 % CI)	*p*-Value	HR (95 % CI)	*p*-Value
CA19-9				
<37 U/ml	Ref		Ref	
≥37 U/ml	1.86 (1.08-3.37)	0.023	1.65 (0.90-3.12)	0.103
Tumor stage				
T1/T2	Ref		Ref	
T3/T4	1.56 (0.92-2.72)	0.094	1.44 (0.80-2.71)	0.221
Lymph node metastasis				
Negative	Ref		Ref	
Positive	3.07 (1.80-5.40)	<0.001	3.00 (1.73-5.36)	<0.001
Tumor grade				
Well/moderate	Ref		Ref	
Poor	1.61 (0.81-2.93)	0.159	1.45 (0.71-2.77)	0.285
Surgical margin				
Negative	Ref		Ref	
Positive	1.17 (0.69-1.95)	0.553	0.90 (0.51-1.57)	0.736

CI: Confidence interval; HR: hazard ratio.

including six with cholangitis), followed by recurrence in nine and refusal in three.

Discussion

In this study, we evaluated the impact of AC on ECC outcomes. AC tended to be utilized most frequently in patients with fewer complications and those who were at high risk for tumor recurrence. AC treatment did not significantly improve the clinical outcomes of patients with ECC. However, it was associated with a survival benefit for patients with ECC with lymph node metastasis and without postoperative complication. In addition, lymph node metastasis was identified as a prognostic factor. As a result, AC may be effective for patients with ECC with lymph node metastasis.

Table III. *Adverse events according to adjuvant chemotherapy received. Adverse events were defined according to the Common Terminology Criteria for Adverse Events version 4.0 (15).*

	Gemcitabine (n=34), n (%)			S-1 (n=11), n (%)			All (n=45), n (%)			
	Grade			Grade			Grade			*p*-Value*
Adverse event	Any	3	4	Any	3	4	Any	3	4	Grade 3/4
Hematological toxicity	30 (88.2%)	12 (35.3%)	6 (17.6%)	8 (72.7%)	1 (9.1%)	0	38 (84.4%)	13 (28.9%)	6 (13.3%)	0.033
Leukopenia	25 (73.5%)	6 (17.6%)	0	3 (27.3%)	0	0	28 (62.2%)	6 (13.3%)	0	0.311
Neutropenia	25 (73.5%)	10 (29.4%)	5 (14.7%)	4 (36.4%)	0	0	29 (64.4%)	10 (22.2%)	5 (11.1%)	0.089
Anemia	14 (41.1%)	2 (5.9%)	0	2 (18.2%)	0	0	16 (35.6%)	2 (4.4%)	0	>0.99
Thrombocytopenia	13 (38.2%)	1 (2.9%)	1 (2.9%)	6 (54.5%)	1 (9.1%)	0	19 (42.2%)	2 (4.4%)	1 (2.2%)	0.560
AST/ALT elevation	11 (32.4%)	0	0	2 (18.2%)	0	0	13 (28.9%)	0	0	>0.99
Non-hematological toxicity	32 (94.1%)	4 (11.8%)	3 (8.8%)	8 (72.7%)	4 (36.4%)	0	40 (88.9%)	8 (17.8%)	3 (6.7%)	0.421
Fatigue	13 (38.2%)	0	0	3 (27.3%)	0	0	16 (35.6%)	0	0	>0.99
Anorexia	6 (17.6%)	0	0	3 (27.3%)	0	0	9 (20.0%)	0	0	>0.99
Nausea	6 (17.6%)	0	0	4 (36.4%)	0	0	10 (22.2%)	0	0	>0.99
Diarrhea	4 (11.8%)	0	0	2 (18.2%)	0	0	6 (13.3%)	0	0	>0.99
Stomatitis	3 (8.8%)	0	0	4 (36.4%)	0	0	7 (15.6%)	0	0	>0.99
Fever	17 (50.0%)	0	0	4 (36.4%)	0	0	21 (46.7%)	0	0	>0.99
Biliary tract infection	6 (17.6%)	4 (11.8%)	2 (5.9%)	4 (36.4%)	4 (36.4%)	0	10 (22.2%)	8 (17.8%)	2 (4.4%)	0.228
Pancreatic infection	1 (2.9%)	0	1 (2.9%)	0	0	0	1 (2.2%)	0	1 (2.2%)	>0.99

AST: Aspartate aminotransferase; ALT: alanine aminotransferase. *Gemcitabine *vs*. S-1.

Currently, whether administering AC is beneficial for patients with resectable BTC remains unclear. Some retrospective studies (5, 6) and a recent phase III trial failed to show any positive impact on survival from AC for patients with ECC (16). Indeed, meta-analysis of AC in patients with BTC (8), and results from the BILCAP trial (9), both identify non-significant improvements in OS. Even so, as surgical resection alone carries such a poor prognosis, many institutions are choosing to administer AC for patients with resectable BTC. Based on this, and the improvements in survival seen in some studies (albeit non-significantly), AC may become a standard treatment for BTC in the near future.

A small percentage (~30%) of our cohort were able to complete adequate AC. About half of the patients (46.2%, 49/106) were not submitted to AC primarily due to postoperative complications (long hospital stays plus sequelae). Furthermore, a high proportion of the AC group (43.9%, 25/57) had to discontinue chemotherapy due to adverse events. In addition, a number of patients either experienced relapse before (n=6) or during (n=9) the administration of AC. Although we have identified that AC seemed to be beneficial in patients with lymph node metastasis, complications related to surgery restrict its full implementation. Our analysis has identified not only a specific population for whom AC may be beneficial, but also that this treatment modality is inadequate as a standard strategy to improve survival for all patients with ECC.

Although surgical techniques continue to improve, postoperative complications still limit the implementation of AC. Among gastrointestinal cancer types for instance, the surgical techniques for pancreatic and esophageal cancer are particularly invasive, especially when compared to those used for either gastric or colon cancer. Ironically, types of cancer which require less invasive surgery have powerful well-evidenced postoperative treatments available, such as doublet AC (*e.g.* FOLFOX, capeOX) (17,18); those which require more invasive surgery generally do not. However, there are some encouraging results for adjuvant (and neoadjuvant) chemotherapy in the context of other surgically difficult cancer types. In a trial comparing neoadjuvant and AC for esophageal cancer (19), patient survival was improved as a result of neoadjuvant chemotherapy; in this study, the authors suggest this improvement may result from down-staging, improved suitability for resection, and an improved suitability for chemotherapy. For pancreatic cancer, it has been shown that postoperative complications are associated with the omission of AC and treatment delays (20). In addition, there are clinical trials that describe the efficiency of neoadjuvant therapy for pancreatic cancer (21, 22). Currently, the standard treatment for advanced esophageal cancer is neoadjuvant therapy (19, 23) and the treatment strategy for advanced pancreatic cancer is gradually moving towards neoadjuvant therapy. Likewise, for ECC, neoadjuvant chemotherapy may be a promising approach to increase the potential for successful therapeutic intervention.

Our study has a number of limitations. Firstly, as a retrospective study, it was not possible to directly measure the direct effects of AC. In addition, the study does include some selection bias, primarily as a result of the clinical

variables (namely age, nodal status, and complications) that relate to the administration of AC. Therefore, we are not able to definitively conclude that AC is beneficial for patients with lymph node metastasis; nevertheless, our results appear promising and warrant further study.

In conclusion, AC for ECC might be inadequate as a standard strategy owing to low implementation and completion rates because postoperative complications often hamper the application of AC and thus limit its potential efficacy.

Conflicts of Interest

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

Authors' Contributions

Koshiro Morino mainly acquired and analyzed the data, and wrote the draft. Koshiro Morino, Satoru Seo, and Tomoaki Yoh designed the research. Satoru Seo, Kenya Yamanaka, and Kojiro Taura interpreted the data, and contributed to writing and editing the article. Koshiro Morino, Satoru Seo, Tomoaki Yoh, Hiroto Nishino, Ken Fukumitsu, Takamichi Ishii, Kojiro Taura, Hideaki Okajima, and Toshimi Kaido participated in the data acquisition. Shinji Uemoto supervised the research design, interpretation of the data, and contributed to editing the article. All Authors participated in critical revision of the article for important intellectual content.

Acknowledgements

The Authors would like to thank Editage (www.editage.jp) for English language editing.

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Received February 6, 2019
Revised March 18, 2019
Accepted March 20, 2019