ORIGINAL ARTICLE

Comparison of Clinical Outcomes for Adjuvant Chemoradiation versus Adjuvant Chemotherapy Following Resection Biliary Tract Cancer: A Retrospective Cohort Study

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Background: Biliary tract cancer (BTC) has a poor treatment outcome and a high mortality rate because after curative resection, local and distant recurrences are frequent. The benefit of adjuvant chemotherapy (AC) for overall survival (OS) is evident when compared with no AC treatment, but there is limited data on the comparison between AC and adjuvant chemoradiation (CCRT).

Objective: To assess the clinical outcomes of CCRT versus AC in patients with resected BTC. The end point was to determine the median overall survival time (mOS) and median recurrence-free survival time (mRFS) in the CCRT compared with the AC group.

Materials and Methods: A retrospective study was conducted on patients diagnosed with BTC who underwent curative resection and received CCRT or AC between January 2016 and December 2021at Khon Kaen Cancer Center, Khon Kaen Hospital.

Results: Fifty patients received CCRT and 80 received AC. The mRFS for the CCRT and AC groups were 15.0 and 10.0 months ($p<0.011$), respectively. The mOS for the CCRT and AC groups were 29.0 and 22.0 months ($p<0.001$), respectively. CCRT had a significantly better RFS and OS than did AC. Univariable analysis showed patterns of recurrences, and types of adjuvant treatments were independent prognostic factors on RFS and OS. Additionally, multivariable analysis showed that type of adjuvant treatment and recurrence status were statistically significant improvement in OS.

Conclusion: Adjuvant CCRT showed statistically significant benefits both RFS, and OS compared to AC in patients who underwent curative resection for BTC.

Keywords: Biliary tract cancer; Adjuvant chemotherapy; Adjuvant chemoradiation

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Biliary tract cancer (BTC) is a heterogenous group of neoplasms that includes cholangiocarcinoma of intrahepatic, hilar bile duct, distal bile duct, perihilar bile duct and gall bladder[1]. The prognosis for BTC is poor, which has a 5-year survival rate of less than 20%[2]. Surgery is currently the standard of care for patients with localized disease, but even those with localized disease have survival rates of 15% to 30% at five years from registry data, and outcomes from surgical series report 18% to 63% survival at five years[3-8]. Recurrence patterns after curative surgery can be found both locally and at a distance, and the likelihood of recurrence depends on tumor location and surgical outcome. Current data support adjuvant treatment including chemotherapy, radiation, and chemoradiation (CCRT) to potentially control both systemic and local recurrence and may improve overall survival (OS)[9-11]. Adjuvant chemotherapy (AC) has been shown to improve OS in comparison to not receiving AC[12]. However, the comparison between adjuvant CCRT and AC's effectiveness is controversial[13]. The current National Comprehensive Cancer Network (NCCN) guidelines recommend all options including systemic treatment and CCRT for resected BTC[14]. The aim of this study was to assess the clinical outcomes of adjuvant CCRT versus AC in patients with resected BTC.

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Objective

The aim of the present study was to assess the clinical outcomes of CCRT versus AC in patients with resected BTC. The end point was to determine median overall survival time (mOS) and median recurrence-free survival time (mRFS) in CCRT compared with AC group.

Material and Methods

Study design and patients' eligibility

The present study was a single-center retrospective, including patients diagnosed with BTC, intrahepatic bile duct cancer (IHBDC), perihilar bile duct cancer (PBDC), distal bile duct cancer (DBDC), or gall bladder cancer (GBC) who had undergone curative resection between January 1, 2016, and December 31, 2021, at Khon Kaen Cancer Center, Khon Kaen Hospital. The inclusion criteria were patients age older than 18 years who underwent curative resection, which was defined as a total excision of entire tumor, including the primary tumor and associated lymph node drainage fields. Exclusion criteria included patients with active second-primary cancer within the past five years.

All patients were classified into two groups, the AC group, which included those who received postoperative chemotherapy and the CCRT group, which included those who received post operative CCRT.

Demographic data, type of treatment and treatment outcome were collected from electronic medical recorded (EMR) and outpatient department (OPD) card. Recurrence-free survival (RFS) was calculated from the time from initial surgery until disease recurrence or death. OS is defined from the time from complete surgery until death from any cause or last follow up. Investigators evaluated tumor recurrence by computed tomography (CT) or magnetic resonance imaging (MRI) at intervals according to local practice.

The present study was reviewed and approved by the Khon Kaen Hospital Institutional Review Board in Human Research, Khon Kaen, Thailand (KEXP67013).

Sample size

The study included 130 patients, comprising 50 individuals receiving adjuvant CCRT and 80 individuals receiving adjuvant AC. The sample size was determined using the sealed envelope program. Statistical calculations were based on predefined parameters. A significant level (alpha) of 0.05, a power (1-beta) of 0.8, and a success rate of 65% in both the control and experimental groups, leading to the final sample size of 130 participants[15].

Statistical analysis

The patients baseline characteristics were reported using descriptive statistics. The RFS and OS were presented by Kaplan-Meier method and compared using the log-rank test. The Cox proportional hazard model was used for multivariable analyses to adjust for potential confounding factors. The results are presented as hazard ratios (HR) and 95% confidence intervals (CI). The chi-square test and Fisher's exact test were used to compare baseline characteristics among patients grouped by categorical variables. Continuous variables were compared using Student's t-test. The level of critical significance was assigned at p-value of less than 0.05. The statistical analyses were performed by using IBM SPSS Statistics, version 20.0 (IBM Corp., Armonk, NY, USA).

Results

Patients' characteristics and tumor data

One hundred thirty curatives resected BTC patients were enrolled. The patient's characteristics are presented in Table 1. Fifty patients received CCRT, and 80 patients received AC. The baseline characteristic and tumor data had significant differences in tumor location, tumor grade, lymph node involvement, pathological stage, surgical margin, CA19-9 level before surgery, regimen chemotherapy and pattern of tumor recurrence. The median follow-up period in CCRT and AC groups were 30.00 and 22.0 months, respectively. Death had occurred in 99 of 130 patients (76%) during the follow-up period.

The mRFS was assessed for two groups, the CCRT group and the AC group. The mRFS for the CCRT group was found to be 15.0 months. In contrast, the mRFS for the AC group was determined to be 10.0 months. A statistically significant difference was observed between these two groups, with a p-value of less than 0.011. Univariable analysis revealed that adjuvant CCRT significantly contributed to prolonging RFS. Furthermore, the absence of recurrence was also identified as a significant factor. The findings were corroborated through multivariable analysis, reinforcing their importance (Table 2, Figure 1A).

The mOS was evaluated in two distinct cohorts, the CCRT group and the AC group. The CCRT group

Table 1. Baseline characteristics and tumor data of resected BTC patients, according to treatment group

Characteristic	Total (n=130)	Adjuvant chemoradiation (CCRT) (n=50)	Adjuvant chemotherapy (AC) (n=80)	p-value
Age (years); median (IQR)	63 (56 to 67)	62.5 (56 to 66)	63.8 (58 to 67)	0.848
Men; n (%)	84 (64.6)	31 (62.0)	53 (66.3)	0.620
Smoking; n (%)	65 (50)	25 (50)	40 (50)	1.000
Alcohol consumption; n (%)	42 (32.3)	14 (28)	28 (35.0)	0.406
Body wight (kg); median (IQR)	51 (44.2 to 60.5)	50 (44.2 to 59.7)	52 (46.5 to 60.5)	0.943
BMI (kg/m^2); median (IQR)	20.13 (17.9 to24.1)	19.5 (17.9 to 24.1)	20.7 (17.9 to 22.6)	0.680
ECOG performance status; n (%)				0.139
ECOG 0	84 (71.8)	38 (79.2)	46 (66.7)	
ECOG 1	33 (28.2)	10 (20.8)	23 (33.3)	
Tumor location; n (%)				<0.001
Intrahepatic bile duct	53 (40.8)	8 (16.0)	45 (56.3)	
Perihilar bile duct	32 (24.6)	19 (38.0)	13 (16.3)	
Distal bile duct	26 (20.0)	8 (16.0)	18 (22.5)	
Gallbladder	19 (14.6)	15 (30.0)	4 (5.0)	
Histology feature; n (%)				0.890
Adenocarcinoma	107 (82.3	42 (84.0)	65 (81.3)	
Papillary carcinoma	18 (13.8)	6 (12.0)	12 (15.0)	
Tubular carcinoma	5 (3.8)	2 (4.0)	3 (3.8)	
Tumor grade; n (%)				0.016
Well	33 (25.4)	19 (38.0)	14 (17.5)	
Moderate	52 (40.0)	20 (40.0)	32 (40.0)	
Poor	29 (22.3)	9 (18.0)	20 (25.0)	
NA	16 (12.3)	2 (4.0)	14 (17.5)	
Perineural invasion; n (%)				0.444
Yes	44 (33.8)	17 (34.0)	27 (33.8)	
No	64 (49.2)	24 (48.0)	40 (50.0)	
NA	21 (16.2)	8 (16.0)	13 (16.3)	
Lymphovascular invasion; n (%)				0.273
Yes	78 (60.0)	27 (54.0)	51 (63.7)	
No	41 (31.5)	18 (36.0)	23 (28.7)	
NA	21 (16.2)	8 (16.0)	13 (16.3)	
pT stage; n (%)				0.164
1	6 (4.7)	1 (2.0)	5 (6.3)	
2	46 (35.9)	13 (26.5)	33 (41.8)	
3	58 (45.3)	27 (55.1)	31 (39.2)	
4	18 (14.1)	8 (16.3)	10 (12.7)	
pN stage; n (%)				<0.001
0	32 (24.6)	4 (8.0)	28 (35.0)	
1	83 (63.8)	35 (70.0)	48 (60.0)	
2	15 (11.5)	11 (22.0)	4 (5.0)	
Pathological stage; n (%)				<0.001
1	3 (2.3)	1(2.0)	2(2.5)	
2	21 (16.2)	1 (2.0)	20 (25.0)	
3	58 (44.6)	30 (60.0)	28 (35.0)	
4	48 (36.9)	18 (36.0)	30 (37.5)	
Surgical margin; n (%)				<0.001
Negative	68 (52.3)	14 (28.0)	54 (67.5)	
Positive	62 (47.7)	36 (72.0)	26 (32.5)	

BMI=body mass index; ECOG=Eastern Cooperative Oncology Group; NA=not available; IQR=interquartile range

Table 1. (continued)

Characteristic	Total (n=130)	Adjuvant chemoradiation (CCRT) (n=50)	Adjuvant chemotherapy (AC) (n=80)	p-value
CA 19-9 level before surgery; n (%)				0.002
CA 19-9 ≥37 U/mL	44 (34.1)	25 (50.0)	19 (24.1)	
CA 19-9 <37 U/mL	85 (65.9)	25 (50.0)	60 (75.9)	
CA 19-9 level post-surgery; n (%)				0.227
CA 19-9 ≥37 U/mL	113 (87.0)	46 (92.0)	67 (83.0)	
CA 19-9 <37 U/mL	17 (13.0)	4 (8.0)	13(17.0)	
Regimen chemotherapy; n (%)				<0.001
Fluoropyrimidine (5FU)	67 (52.3)	26 (52.0)	41 (52.6)	
Capecitabine	36 (28.1)	24 (48.0)	12 (15.4)	
Gemcitabine	7 (5.5)	0 (0.0)	7 (9.0)	
S-1	5 (3.9)	0 (0.0)	5 (6.4)	
Gemcitabine and cisplatin	10 (7.8)	0 (0.0)	10 (12.8)	
5FU and cisplatin	3 (2.3)	0 (0.0)	3 (3.8)	
Pattern of recurrence; n (%)				<0.001
No	30 (23.1)	22 (44.0)	8 (10.0)	
Local	28 (21.5)	5 (10.0)	23 (28.7)	
Distance	55 (42.3)	17 (34.0)	38 (47.5)	
Both	17 (13.1)	6 (12.0)	6 (12.0)	

BMI=body mass index; ECOG=Eastern Cooperative Oncology Group; NA=not available; IQR=interquartile range

Table 2. Relapse free survival outcome

Factor	Univariable analysis			Multivariable analysis		
	HR	95% CI	p-value	Adjusted HR	95% CI	p-value
Age (years): ≤60 (ref: >60)	0.99	0.96 to 1.02	0.636			
Tumor location: intrahepatic bile duct (ref: other)	0.93	0.75 to 1.16	0.772			
Tumor grade: well/moderate (ref: poor)	1.49	0.79 to 2.80	0.211			
Lymphovascular invasion: yes (ref: no)	1.08	0.56 to 2.08	0.812			
Perineural invasion: yes (ref: no)	0.75	0.42 to 1.35	0.354			
pT stage: 1 to 2 (Ref: 3 to 4)	1.00	0.60 to 1.80	0.878			
Lymph node involvement: yes (ref: no)	0.99	0.64 to 1.52	0.969			
Pathological stage: 1 to 2 (ref: 3 to 4)	0.80	0.40 to 1.60	0.537			
Surgical margin: positive (ref: negative)	0.66	0.40 to 1.07	0.930			
Recurrence status: no (ref: yes)	0.35	0.25 to 0.49	<0.001	0.12	0.07 to 0.05	0.003
Adjuvant treatment: chemoradiation (ref: chemotherapy)	0.34	0.27 to 0.51	0.001	0.24	0.13 to 0.31	0.002

HR=hazard ratio; CI=confidence interval

exhibited an mOS of 29.0 months, while the AC group demonstrated a lower mOS of 22.0 months. This difference was statistically significant, with a p-value of less than 0.001. Univariable analysis indicated that adjuvant CCRT was a significant contributor to improved OS outcomes. Additionally, the absence of recurrence was identified as a crucial variable influencing survival. These findings were further validated through multivariable analysis, highlighting their clinical relevance. Overall, the results underscore the effectiveness of adjuvant CCRT in enhancing survival in these patient populations (Table 3, Figure 1B).

Discussion

BTC is frequently recurring following surgery and has poor prognosis and short survival. Adjuvant treatment in BTC after resection is the standard of care. Nevertheless, the role of AC and CCRT therapy in patients with resected BTC is poorly defined, with lack of data from phase III RCTs[16]. AC, according to the BILCAP study protocol for those who received adjuvant capecitabine had better OS and RFS compared with observation at 53 versus 36 months

Table 3. Overall survival outcome

Factor	Univariable analysis			Multivariable analysis		
	HR	95% CI	p-value	Adjusted HR	95% CI	p-value
Age (years): ≤60 vs. >60	0.99	0.96 to 1.01	0.443			
Tumor location: intrahepatic bile duct vs. other	0.83	0.42 to 1.64	0.451			
Tumor grade: well/moderate vs. poor	1.91	1.05 to 3.46	0.320			
Lymphovascular invasion: yes vs. no	1.05	0.55 to 1.99	0.876			
Perineural invasion: yes vs. no	0.53	0.29 to 0.97	0.734			
pT stage: 1 to 2 vs. 3 to 4	0.79	0.47 to 1.32	0.374			
Lymph node involvement: yes vs. no	1.02	0.64 to 1.63	0.913			
Pathological stage: 1 to 2 vs. 3 to 4	0.58	0.29 to 1.15	0.122			
Surgical margin: positive vs. negative	0.75	0.47 to 1.21	0.242			
Recurrence status: no vs. yes	0.35	0.25 to 0.49	<0.001	0.18	0.08 to 0.44	<0.001
Adjuvant treatment: chemoradiation vs. chemotherapy	0.42	0.24 to 0.30	<0.001	0.43	0.01 to 0.63	<0.001

HR=hazard ratio; CI=confidence interval

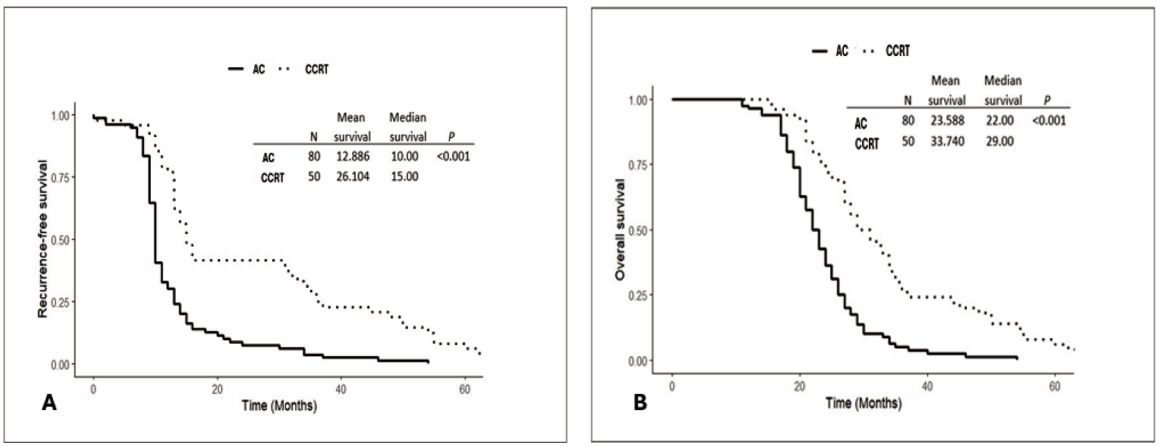

Figure 1. Recurrence-free survival (RFS) and overall survival (OS) by adjuvant chemoradiation (CCRT) and chemotherapy (AC). Patients treated with adjuvant CCRT had better RFS (A) and OS (B) as compared to those treated with adjuvant chemotherapy.

(p=0.028) and at 24.4 versus 17.5 months (p=0.033), respectively)[17]. Several studies and the systematic review and meta-analysis of BTC by Horgan et al.[18] in 2012 in patients with resected cholangiocarcinoma compared AC to CCRT, which had significantly improved OS when compared with surgery alone but there was no difference survival in gallbladder cancer and bile duct cancers. A retrospective study from McNamara et al.[19] compares the effects of adjuvant CCRT and AC on BTC. Both adjuvant treatments are associated with OS benefit (p=0.020, HR 0.41). particularly, positive surgical margin (p<0.005, HR 0.23), and lymph node involvement (p<0.005, HR 0.46). In data by Nassour er al.[13] that compare treatment between those who had received adjuvant CCRT compared with chemotherapy, there was marginal benefit of CCRT in term of OS at 25 versus 31 months (p=0.040, HR 0.80). In 2020, Kim et al.[15] compare effective of adjuvant CCRT and chemotherapy for resected BTC. The present study demonstrated the effectiveness of CCRT over AC in RFS (p=0.001) but not significant in OS (p=0.222). In 2023, Zhu et al.[20] verified data from SEER data base showed adjuvant CCRT improved OS when compared with AC and favorable prognosis in GBC and benefit of CCRT especially in older than 60 years, female, lymph node positive, tumor size greater than 5 cm, and none removed lymph node. Adjuvant CCRT may have a significant survival benefit in patients with T3 or T4 tumor, lymph node involvement and positive surgical margin[21,22]. The NCCN guidelines recommend adjuvant treatment for lymph node involvement and positive surgical margin[14].

The findings in the present study demonstrate that adjuvant CCRT is superior in terms of RFS and OS compared with adjuvant AC in resected BTC

even with the baseline characteristic difference of tumor location, tumor grade, pN stage, pathological stage, surgical margin, CA 19-9 before surgery, and regimen chemotherapy.

The tumor location affects RFS and OS. In the adjuvant CCRT group, the location associated with long survival is intrahepatic bile duct (IHD), while in AC group, the location associated with long survival is gallbladder. This is consistent with previous study[20]. The majority of patients presented with locally advanced disease, AJCC stage 3 and 4 for 81% of all patients, posing challenges in selecting the surgical strategy, thereby influencing both surgical results and survival outcomes. For the present study, the positive surgical margin was 47%. Factors to consider for selecting adjuvant treatment include lymph node involvement, positive surgical margin, and liver reserve after surgery, as adjuvant CCRT can increase the risk of liver failure. In the present study locoregional RFS for adjuvant CCRT and AC group was 53.79 and 34.13 months ($p<0.001$), respectively[15]. The distant RFS for the adjuvant CCRT and AC group was 49.19 and 30.58 months, respectively. For recurrence pattern, in the CCRT group, there was no tumor recurrence more than in the AC group, and longer survival is expected if there was no tumor recurrence.

The locoregional RFS and distant RFS had significantly higher survival in the adjuvant CCRT group compared to the AC group. For multivariate analysis, the pattern of adjuvant treatment with CCRT, well differentiated tumor grade, lymphovascular invasion (LVI), positive surgical margin, well differentiated tumor grade, and recurrence were the significant prognostic factors for RFS. Prognostic factors for OS are adjuvant treatment CCRT, well differentiated tumor grade, LVI, positive surgical margin, and tumor recurrence.

Ther are limitations of the present study. As this study is a retrospective cohort study with non-random distribution of adjuvant treatment, the results may be affected by selection bias. The variance in chemotherapy regimen between CCRT and AC could potentially impact on the survival result. However, the present study confirms a survival benefit in RFS and OS of adjuvant CCRT compared to AC treatment in resected BTC.

Conclusion

The present study findings demonstrate that adjuvant CCRT is more effective than adjuvant AC in increasing OS and RFS. The favorable prognostic factor RFS and OS included well-differentiated tumor grade, absence of LVI, clear surgical margins, and absence any tumor recurrence.

What is already known about this topic?

Adjuvant CCRT provided statistically and clinically meaningful improvement of RFS and OS in patients with resected early-stage BTC when compared to AC.

What does this study add?

This study focused on adjuvant treatment in resected BTC. The authors report on the real-world clinical outcome of adjuvant CCRT compared with AC. This might be the largest real-world evidence of adjuvant treatment in Asia population.

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Conflicts of interest

The authors declare no conflict of interest.

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