의학석사 학위논문

성향점수 매칭을 통한 바터팽대부 암의 보조 항암치료에서의 종양학점 이점에 대한 논란

Controversial oncologic benefit of adjuvant therapy for ampullary cancer:

A propensity score matched analysis

울 산 대 학 교 대 학 원

의 학 과

강 재 철

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이 논문을 의학석사 학위 논문으로 제출함

2022 년 2 월

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ABSTRACT

Background: Although surgery is the primary treatment for ampullary cancer (AC), the benefit of adjuvant chemotherapy (CTx) has not yet been confirmed.

Methods: AC patients who were administered fluoropyrimidine-based CTx after curative intent surgery between 2011 and 2019 were included. Prognosis was compared between the observation (OB) and CTx groups after propensity score matching (PSM) using perioperative variables to control for differences in patient characteristics.

Results: Before PSM, of 475 patients, those in the CTx group (n = 194) had worse 5-year overall survival (OS) (82.1% vs. 78.5%, p = 0.017) and worse 5-year recurrence-free survival (RFS) (75.7% vs. 54.9%, p < 0.001) than those in the OB group (n = 281). In addition, the CTx group had a higher rate of poor prognostic factors such as a high T stage (p < 0.001), node metastasis (p < 0.001), and poor differentiation (p < 0.001). After PSM, perioperative outcomes were comparable. In addition, there were no significant differences in OS (hazard ratio [HR], 1.085; 95% confidence interval [CI], 0.688–1.710; p = 0.726) or RFS (HR, 0.883; 95% CI, 0.613 1.272; p = 0.505) between the CTx (n = 123) and OB (n = 123) groups even after stratification by TNM stage. Intestinal subtype showed better 5-year OS (83.7 % vs 33.2 %, p = 0.015) and RFS (46.5 % vs 24.9%, p = 0.035) rate compared with pancreatobiliary/mixed subtype.

Conclusion: Patients who received adjuvant chemotherapy based on fluoropyrimidine showed comparable oncologic outcomes to patients in the OB group even after stratification by tumor stage. The patients with intestinal subtype showed better OS, RFS for fluoropyrimidine based chemotherapy compared with pancreatobiliary or mixed subtypes.

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Introduction

Ampullary cancer (AC) occurs within the ampullary complex, distal to the bifurcation of the distal common bile duct and the pancreatic duct. AC is a rare malignancy, comprising only 0.2% of gastrointestinal cancers and 7% of all periampullary cancers (1). Approximately 50% of patients who are diagnosed with AC are candidates for curative surgery. Curative intent surgery involves pancreaticoduodenectomy, including regional lymph node dissection (LND) with or without pylorus resection (2). Although patients diagnosed at an early stage have a good prognosis, R0 resection with sufficient LND is recommended because lymph node metastasis is common (up to 45%, even in T1 AC) (3). Furthermore, 20–50% of patients experience locoregional or hepatic recurrence, even after curative resection. This is especially common in patients with advanced disease, R1 resection, lymphovascular/perineural invasion, or a high level of CA19-9. Therefore, surgical treatment in these patients is insufficient. Many studies have argued the need for adjuvant chemotherapy after surgery. Some studies [2-4] showed that adjuvant chemotherapy after curative surgery in AC improved overall survival (OS), while others [7,11] came to the opposite conclusion. These controversial results may be due to heterogeneity in patient characteristics and chemotherapy regimens. The survival benefit of adjuvant chemotherapy is therefore not confirmed. Clinically, the higher the pathologic stage of the tumor, the more likely it is that the patient will undergo adjuvant chemotherapy. Conversely, patients who are diagnosed at a lower stage are less likely to be given chemotherapy. In addition, the timing of the chemotherapy regimen may be affected by postoperative complications, compromising its efficacy. These retrospective studies included all patients, without proper selection, because of the rarity of the disease. Furthermore, chemotherapy regimens are often determined by the patients' insurance or enrollment in clinical trials. These potential sources of bias may be the cause of the conflicting previous data on the benefit of adjuvant chemotherapy in AC. This study aimed to compare oncologic outcomes in patients with or without adjuvant chemotherapy after curative intent surgery for AC.

Patients and Methods

Patients, study design, and data collection

This study was a retrospective single center study, and it was approved by the Institutional Review Board of Asan Medical Center (IRB No: 2019-1007), and the requirement for informed consent was waived because of the retrospective nature of the study.

Patients who underwent curative intent surgery for AC at tertiary referral center(Asan medical center) between January 2011 and October 2019 were identified. Patients who received chemotherapy before surgery or palliative surgery, or whose medical records were incomplete, were excluded. Surgical procedures consisted of pancreaticoduodenectomy with or without pylorus resection, including LND around the common hepatic artery, hepatoduodenal ligament, and retropancreatic area.

The patients with ampullary mass were performed enhanced computed tomography and endoscopic biopsy, and the patients with adenocarcinoma were referred for curative surgery. Pathologic reevaluation was performed for referred patients from another institution. Pathologists who are specialized for hepatobiliary pancreatic diseases evaluated specimen after surgery. They used immunohistochemistry staining including CK20, CDX2, MUC1, and MUC2 as well as hematoxylin and eosin staining. Tumor and lymph node status were classified and described based on WHO guideline and AJCC 8th edition. Pathologic review was performed in some patients in this study because classification including intestinal and hepatobiliary type were reported recently.

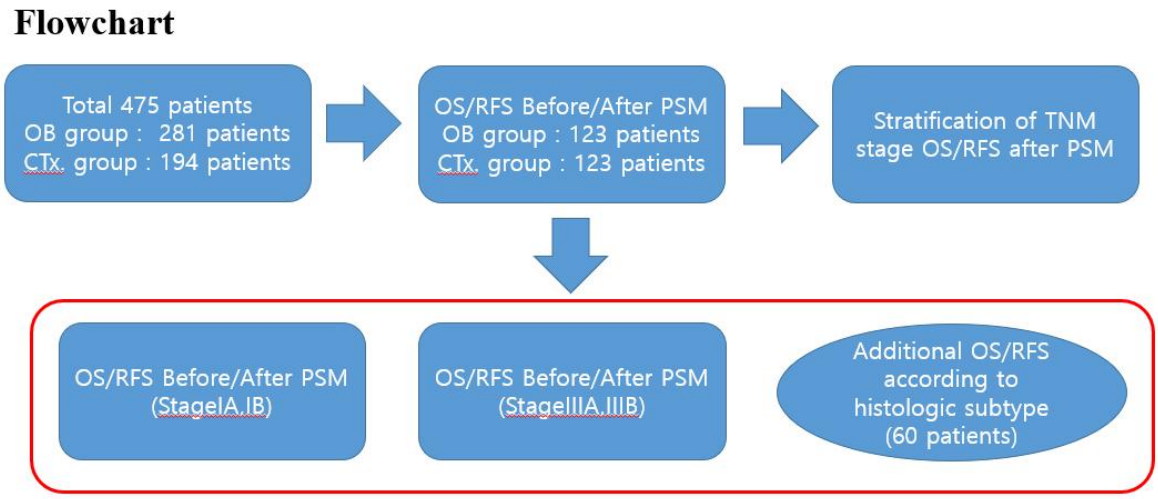
Overall Survival(OS) and recurrence-free survival (RFS) were compared between patients who received adjuvant chemotherapy (CTx group) after surgery and those who received observation alone (OB group). OS was determined from the date of initial surgery to the date of death from any cause and censored at the date of the last follow-up for patients who were still alive at the time of analysis. RFS was measured from the date of initial surgery to the date of local recurrence or metastasis, and censored at the last follow-up or death for patients without recurrence. Because there were differences in patient characteristics, including the TNM stage, between the OB and CTx group, survival analysis after propensity score matching (PSM) was performed. Clinical data were collected from medical records,

and parameters including preoperative data (age, sex, body mass index [BMI], Charlson comorbidity index [CCI], and laboratory findings, including tumor markers), intraoperative data (type of surgery, duration of the surgery, intraoperative transfusion, and estimated blood loss), pathologic data (tumor differentiation, depth of invasion, node metastasis, and presence of lymphovascular or perineural invasion), postoperative data (duration of hospital stay, postoperative complications), and oncologic outcomes (recurrence, recurrence site, and survival) were analyzed. (Figure 1.)

Statistical analysis

Data are presented as the mean and standard deviation for continuous variables, and as the count and percentage for categorical variables. The χ^2 test was used to compare categorical variables, and the Student's *t*-test was used to compare continuous variables between the subgroups. Before matching, the multivariable Cox proportional hazards model was used to determine prognostic factors for OS and RFS. The variables were selected based on clinical significance and statistical significance in univariate Cox proportional hazards analyses, taking care to avoid overfitting and ensure generalizability. Matching variables were age, sex, BMI, CCI, preoperative total bilirubin, preoperative carbohydrate antigen (CA) 19-9, TNM stage (using the criteria of the 8th Edition of the American Joint Committee on Cancer [AJCC]), tumor differentiation, lymphovascular invasion, perineural invasion, minimally invasive surgery, operation time, intraoperative transfusion, estimated blood loss, and postoperative complications. The propensity score model was built using logistic regression with matching variables as independent variables, and the CTx group as the response variable. The standardized mean difference (SMD) was calculated for each matched variable to confirm the accuracy of the matching between two groups. After PSM, the Cox proportional hazards model was used to model survival time, using a sandwich estimator, with and without stratification by pathologic stage. OS and RFS were estimated using the Kaplan–Meier method and compared using log-rank tests. In all analyses, a p-value of < 0.05 (two-sided) was considered statistically significant. SPSS version 22.0 (SPSS Corp., Chicago, IL, USA) and R 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) were used for all analyses.

Figure 1. Flowchart



Results

Patient characteristics

This study included data from 476 patients who were diagnosed with AC and underwent curative intent pancreaticoduodenectomy. The mean age and female proportion were 63.5 and 47.8%, respectively. The mean CCI was 2.3, and 108 (22.7%) patients underwent minimally invasive surgery. The mean operation time and estimated blood loss were 313.9 minutes and 232.3 ml, respectively. The mean hospital stay was 16.2 days, and 118 (32.8%) patients experienced postoperative complications. Among pathologic data, duodenal or pancreatic invasion was detected in 198 (41.7%) and 126 (26.5%) patients, respectively. Lymph node metastasis was found in 163 (34.3%) patients. After surgery, 194 (40.8%) patients received adjuvant chemotherapy, and fluoropyrimidine were the most common chemotherapeutic agents (Table 1). At the time of data collection, there were 476 patients, but it was not confirmed whether one patient had chemotherapy of not. That patient did not come to the outpatient clinic after surgery, so we excluded one patient and analyzed total 475 patients.

We used fluoropyrimidine monotherapy as adjuvant chemotherapy regimen in almost all cases. This therapy was administered with oral agent or intravenous injection fluoropyrimidine for 6 months. In 58 cases of total 194 cases, patients took UFT/Leucovorin for 4weeks, then took a rest for 1week, and they

received total 6cycles of treatment for 6 months. In 57 cases, patients were administered intravenous fluoropyrimidine medication once every 2 weeks, and 12 cycles were performed for 6 months.(sLV5FU2) In 38 cases, patients were administered intravenous fluoropyrimidine medication daily for 5 days, took a month off, and 6 cycles were performed for 6 months.(LF-1) In 16 cases, patients received UFT-E/Leucovorin adjuvant chemotherapy in the same form of UFT/Leucovorin. And mFOLFIRINOX was 1 case. In 24 cases, Some patients received adjuvant chemotherapy at a nearby hospital. In our study, in very few cases, gemcitabine monotherapy, XELOX(Capecitabine+Oxaliplaatin) therapy, Cisplatin + Gemcitabine were used as adjuvant chemotherapy for ampullary cancer.

Table 1. Patient characteristics (*n* = 475)

	n (%) or mean ± SD
Age (years)	63.5 ± 9.1
Sex (M/F)	162 (52.2) / 227 (47.8)
Charlson comorbidity index	2.3 ± 1.3
Body mass index (kg/m2)	23.7 ± 2.9
Preoperative CA19-9 (U/ml)	299.8 ± 2668.9
Preoperative CEA (ng/ml)	2.9 ± 6.6
Operative manners (MIS/open)	108 (22.7) / 367 (77.3)
Operation time (min)	313.9 ± 91.9
Intraoperative transfusion	55 (15.3)
Estimated blood loss (ml)	232.3 ± 285.8
Postoperative complication	118 (32.8)
Hospital stay (days)	16.2 ± 15.5
T stage (1/2/3/4), AJCC 8th	139 (29.3) / 198 (41.7) / 126 (26.5) / 12 (2.5)
N stage (0/1/2), AJCC 8th	312 (65.7) / 126 (26.5) / 37 (7.8)

Differentiation (WD/MD/PD)	137 (28.8)/ 281(59.2) / 57 (12.0)	
LVI/PNI	229 (48.2)/ 111 (23.4)	
Adjuvant Chemotherapy	194 (40.8)	
Chemotherapeutic agent(194cases)	UFT(-E)/LV(74cases), LF-1(38cases), Others(24cases)	sLV5FU2(57cases), mFOLFIRINOX(1case),

SD; standard deviation, , CA 19-9; carbohydrate antigen 19-9, CEA; carcinoembryonic antigen, MIS; minimally invasive surgery, AJCC; American Joint Committee on Cancer, WD; well differentiated, MD; moderate differentiated, PD; poorly differentiated, LVI; lymphovasvular invasion, PNI; perineural invasion

Prognostic factors for survival and recurrence, and propensity score matching

The median follow-up period was 29.5 months. The 5-year OS and RFS rates were 70.3% and 59.4%, respectively. A prognostic model was established in all patients with AC. In the survival model, a high CCI (hazard ratio [HR], 1.263; 95% confidence interval [CI], 1.608–1.494; p = 0.006), large tumor size (HR, 1.294; 95% CI, 1.044–1.605; p = 0.019), high N stage (N0 vs. N2; HR, 3.592; 95% CI, 1.822–7.082, p < 0.001), lymphovascular invasion (HR, 2.126; 95% CI, 1.180–3.830; p = 0.012), and perineural invasion (HR, 1.935; 95% CI, 1.206–3.103; p = 0.006) were independent prognostic factors for worse survival (Table 2). In the recurrence model, high N stage (N0 vs. N2; HR, 3.147; 95% CI, 1.704–5.814; p < 0.001), lymphovascular invasion (HR, 4.140; 95% CI, 2.232–7.679; p < 0.001), and perineural invasion (HR, 2.169; 95% CI, 1.421–3.309; p < 0.001) were independent prognostic factors for early recurrence (Table 3).

Table 2. Univariate and multivariate analysis of overall survival in all patients with ampullary cancer

		Univariate analysis			*Multivariate analysis*		
Variables		HR	95% CI	p-value	HR	95% CI	p-value
Age > 60		0.626	0.390-1.005	0.052			
Sex		0.618	0.396-0.966	0.035			
Charlson comorbidity index		1.327	1.127-1.562	0.001	1.263	1.608-1.494	0.006
Preop. CA19-9 > 37IU/ml		1.071	0.669-1.716	0.775			
Preop. total bilirubin		1.017	1.004-1.031	0.011			
Preop. WBC count		1.006	0.991-1.020	0.449			
Intraoperative transfusion		1.428	0.838-2.432	0.190			
R1 resection		2.643	0.834-8.373	0.099			
Tumor size		1.498	1.222-1.837	< 0.001	1.294	1.044-1.605	0.019
T stage (AJCC 8th)	T1 (ref)	1		< 0.001			
	T2	2.113	1.044-4.277	0.038			
	T3	3.675	1.809-7.464	< 0.001			
	T4	6.096	2.316-16.055	< 0.001			
N stage (AJCC 8th)	N0 (ref)	1		< 0.001	1		0.001

	N1	2.932	1.828-4.703	< 0.001	1.791	1.047-3.064	0.033
	N2	1.496	1.222-1.837	< 0.001	3.592	1.822-7.082	< 0.001
Differentiation	WD (ref)	1	1.340-2.717	0.002			
	MD	2.469	1.352-4.508	0.003			
	PD	3.643	1.688-7.863	0.001			
Lymphovascular invasion		4.001	2.437-6.569	< 0.001	2.126	1.180-3.830	0.012
Perineural invasion		2.953	1.907-4.572	< 0.001	1.935	1.206-3.103	0.006
Adjuvant CTx		0.557	0.361-0.861	0.008			

Preop., preoperative; CA 19-9, carbohydrate antigen 19-9; HR, hazard ratio; CI, confidence interval; CT, computed tomography; WD, well-differentiated; MD, moderately differentiated; PD, poorly differentiated; AJCC 8th, 8th Edition of the American Joint Committee on Cancer; WBC, white blood cell; CTx, chemotherapy.

Table 3. Univariate and multivariate analysis of recurrence-free survival in all patients with ampullary cancer

		Univariate analysis			*Multivariate analysis*		
Variables		HR	95% CI	p-value	HR	95% CI	p-value
Age > 60		1.062	0.726-1.552	0.757			
Sex		0.760	0.523-1.103	0.149			
Charlson comorbidity index		0.932	0.807-1.077	0.342			
Preop. CA19-9 > 37IU/ml		1.731	1.183-2.532	0.005			
Preop. total bilirubin		1.024	1.013-1.035	< 0.001			
Preop. WBC count		1.002	0.990-1.014	0.774			
Intraoperative transfusion		0.868	0.512-1.473	0.601			
R1 resection		2.472	0.785-7.785	0.122			
Tumor size		1.360	1.140-1.624	0.001			
T stage (AJCC 8th)	T1 (ref)	1					
	T2	2.021	1.083-3.772	0.027			
	T3	5.196	2.832-9.533	< 0.001			
	T4	4.919	1.958-12.357	0.001			
N stage (AJCC 8th)	N0 (ref)	1		< 0.001	1		0.001

	N1	3.617	2.421-5.404	< 0.001	1.783	1.110-2.864	0.017
	N2	8.315	4.860-14.227	< 0.001	3.147	1.704-5.814	< 0.001
Differentiation	WD(ref)	1					
	MD	3.344	1.895-5.902	< 0.001			
	PD	6.196	3.127-12.278	< 0.001			
Lymphovascular invasion		7.693	4.694-12.607	< 0.001	4.140	2.232-7.679	< 0.001
Perineural invasion		3.527	2.438-5.103	< 0.001	2.169	1.421-3.309	< 0.001
Adjuvant CTx		2.640	1.824-3.822	< 0.001			

Preop., preoperative; CA 19-9, carbohydrate antigen 19-9; HR, hazard ratio; CI, confidence interval; CT, computed tomography; WD, well-differentiated; MD, moderately differentiated; PD, poorly differentiated; AJCC 8th, 8th Edition of the American Joint Committee on Cancer; WBC, white blood cell; CTX, chemotherapy.

Perioperative outcomes in the OB and CTx groups before and after propensity score matching

To control for differences between the two groups that could affect outcomes, PSM was performed using perioperative variables and prognostic factors. Perioperative and oncologic outcomes were compared between the OB and CTx groups. Before PSM, the CTx group was younger (61.6 vs. 64.8, $p < 0.001$), had a higher BMI (24.1 vs. 23.5, $p = 0.038$), a shorter operation time (300.1 min vs. 323.4 min, $p = 0.007$), a lower postoperative complication rate (39.2% vs. 52.0%, $p = 0.008$), a higher T ($p < 0.001$) and N stage ($p < 0.001$), a higher proportion of poorly differentiated tumors (18.6% vs. 7.5%, $p < 0.001$), a higher lymphovascular invasion rate (66.5% vs. 35.6 %, $p < 0.001$), and a higher perineural invasion rate (33.5% vs. 16.4 %, $p < 0.001$) (Table 4). After PSM, the SMD of each of these variables was < 0.2, indicating accurate matching.

Table 4. Distribution of covariance before and after propensity score matching

	Before PSM				After PSM			
	Observation (n=281)	Adjuvant (n=194)	P-value	SMD*	Observation (n=123)	Adjuvant (n=123)	P-value	SMD*
Age	64.84 ±9.47	61.60 ± 8.42	<0.001	0.362	62.52 ± 9.30	62.46 ± 7.97	0.057	0.008
Male (%)	142 (50.5)	106 (54.6)	0.431	0.082	65 (52.8)	75 (61.0)	0.198	0.165
BMI	23.52 (2.81)	24.10 (3.23)	0.038	0.192	24.07 (3.02)	23.75 (3.16)	0.5666	0.104
CCI	2.48 (1.31)	2.24 (1.29)	0.046	0.187	2.22 (1.24)	2.25 (1.11)	0.271	0.028
log.Preoperative bilirubin	-0.18 ±0.82	0.02 ±0.84	0.008	0.249	-0.03 ±0.85	0.06 ±0.84	0.753	0.108
log.CA19-9	2.81 ±1.61	3.14 ± 2.17	0.063	0.174	3.01 ± 1.65	3.10 ± 1.83	0.409	0.051
Minimally invasive surgery	65 (23.1)	43 (22.2)	0.892	0.023	23 (18.7)	24 (19.5)	0.026	0.021
Operation time (min)	323.44 (93.11)	300.18 (88.64)	0.007	0.256	303.46 (81.01)	315.01 (90.27)	0.336	0.135
log.EBL (ml)	3.77 (2.64)	4.21 (2.26)	0.058	0.180	3.96 (2.63)	3.78 (2.60)	0.934	0.069
Intraoperative transfusion	40 (14.2)	17 (8.8)	0.097	0.172	15 (12.2)	16 (13.0)	247.037	0.024
Postoperative complication	146 (52.0)	76 (39.2)	0.008	0.259	59 (48.0)	64 (52.0)	0.407	0.081
T stage AJCC 8th			<0.001	0.642			0.433	0.084
1	109 (38.8)	30 (15.5)			21 (17.1)	20 (16.3)		
2	117 (41.6)	81 (41.8)			56 (45.5)	55 (44.7)		
3	50 (17.8)	76 (39.2)			42 (34.1)	42 (34.1)		
4	5 (1.8)	7 (3.6)			4 (3.3)	6 (4.9)		
N stage AJCC 8th			<0.001	0.792			0.492	0.089
0	225 (80.1)	87 (44.8)			73 (59.3)	70 (56.9)		
1	47 (16.7)	79 (40.7)			41 (33.3)	41 (33.3)		
2	9 (3.2)	28 (14.4)			9 (7.3)	12 (9.8)		
Cell Differentiation			<0.001	0.577			0.634	0.102

Well differentiated	107 (38.1)	30 (15.5)			26 (21.1)	23 (18.7)		
Moderate differentiated	153 (54.4)	128 (66.0)			81 (65.9)	80 (65.0)		
Poorly differentiated	21 (7.5)	36 (18.6)			16 (13.0)	20 (16.3)		
Lymphovasular invasion	100 (35.6)	129 (66.5)	<0.001	0.650	70 (56.9)	74 (60.2)	0.268	0.066
Perineural invasion	46 (16.4)	65 (33.5)	<0.001	0.404	33 (26.8)	37 (30.1)	0.319	0.072

PSM; propensity score matching, SMD; Standardized Mean Difference, BMI; body mass index, CCI; Charlson comorbidity index, CA 19-9; carbohydrate antigen 19-9, EBL; estimated blood loss, WD; well differentiated, MD; moderate differentiated, PD; poorly differentiated, AJCC; American Joint Committee on Cancer.

Worse oncologic outcomes were observed in the CTx group before PSM

The CTx group showed worse 5-year OS (82.1% vs. 78.5%; p = 0.017; 95% CI, 72.1–79.7; Figure 2-A) and RFS (75.7% vs. 54.9%; p < 0.001; 95% CI, 60.2–68.4; Figure 2-B) than the OB group. These results were likely due to differences in patient characteristics between the two groups, as patients in the CTx group had a higher rate of poor prognostic factors. In patients with stage IA and IB disease, before PSM, there was no significant difference in the 5-year OS rate between the OB group (n = 199) and the CTx group (n = 45) (86.6% vs. 75.2%, p = 0.971; Figure 3-A); however, patients in the CTx group showed early recurrence compared with the OB group (59.3% vs. 44.5%, p = 0.007; Figure 3-B). In stage IIIA and IIIB patients, there was no significant difference in the 5-year OS rate (50.7% vs. 57.5%, p = 0.391; Figure 4-A) or RFS rate (36.0% vs. 37.1%, p = 0.638; Figure 4-B) between the OB group (n = 56) and the CTx group (n = 109). After PSM, in patients with stage IA and IB disease, the OB group (n = 55) and the CTx group (n = 40) had similar OS (86.4% vs. 74.7%, p = 0.995; Figure 5-A) and RFS rates (79.8% vs. 64.6%, p = 0.517; Figure 5-B). In stage IIIA and IIIB patients, the OS rate (40.7% vs. 41.4%, p = 0.889; Figure 6-A) and the RFS rate (29.2% vs. 35.2%, p = 0.301; Figure 6-B) were also similar between the OB (n = 50) and CTx (n = 55) groups.

Figure 2. Worse oncologic outcomes in patients receiving adjuvant chemotherapy before PSM. The chemotherapy group showed worse 5-year OS (82.1% vs. 78.5%, p = 0.017) and RFS (75.7% vs. 54.9%, p < 0.001) compared with the observation group before PSM.

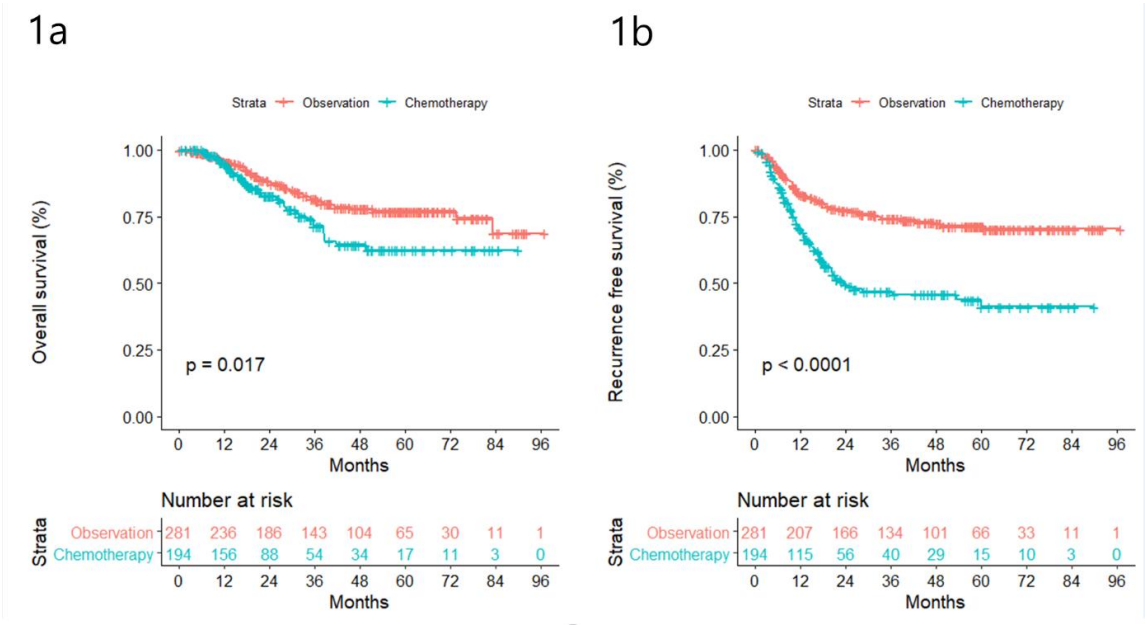


Figure 3. In patients with stage IA and IB disease, the OS rate (86.6% vs. 75.2%, p = 0.971; 1a) was comparable between the observation and chemotherapy groups. The RFS rate (59.3% vs. 44.5%, p = 0.007; 1b) showed early recurrence in the CTx. group compared with the OB group before PSM.

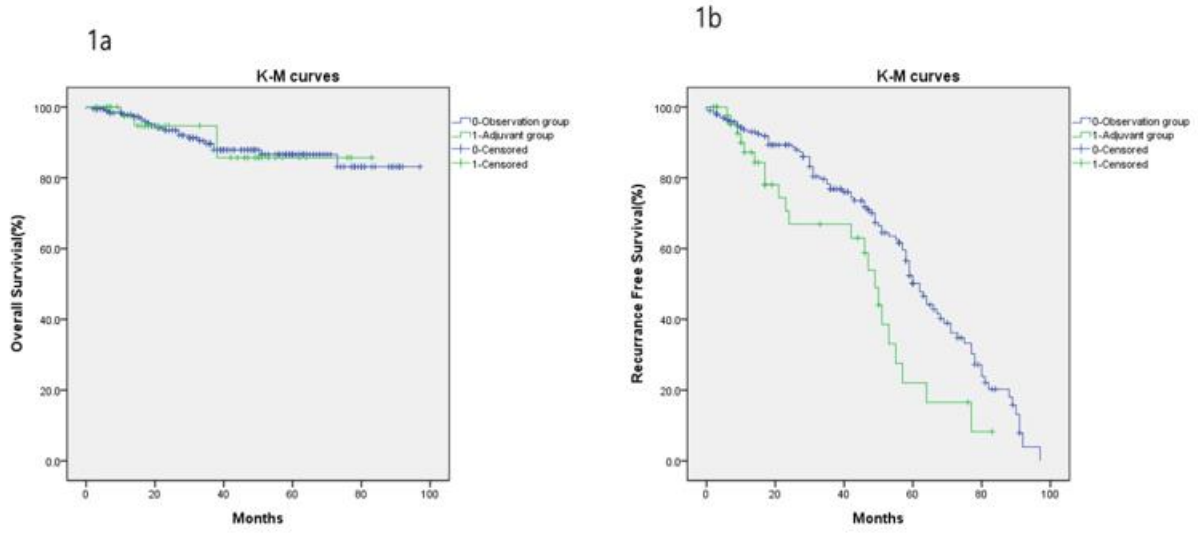


Figure 4. In patients with stage IIIA and IIIB disease, the OS rate (50.7% vs. 57.5%, p = 0.391; 1a) and RFS rate (36.0% vs. 37.1%, p = 0.638; 1b) were comparable between the observation and chemotherapy groups before PSM.

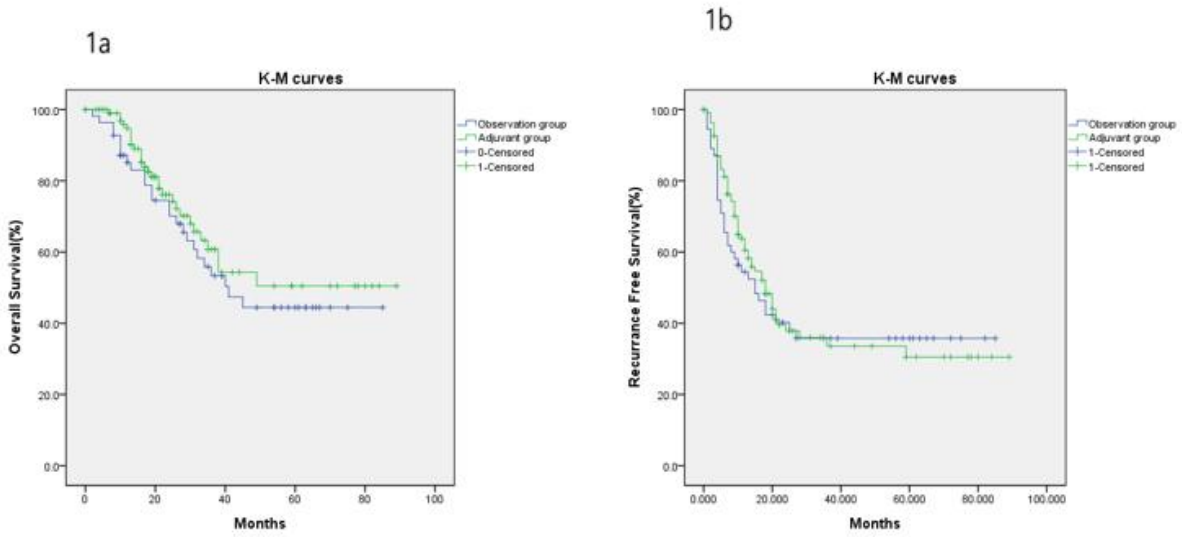


Figure 5. In patients with stage IA and IB disease, the OS rate (86.4% vs. 74.7%, p = 0.995; 1a) and RFS rate (79.8% vs. 64.6%, p = 0.517; 1b) were comparable between the observation and chemotherapy groups after PSM.

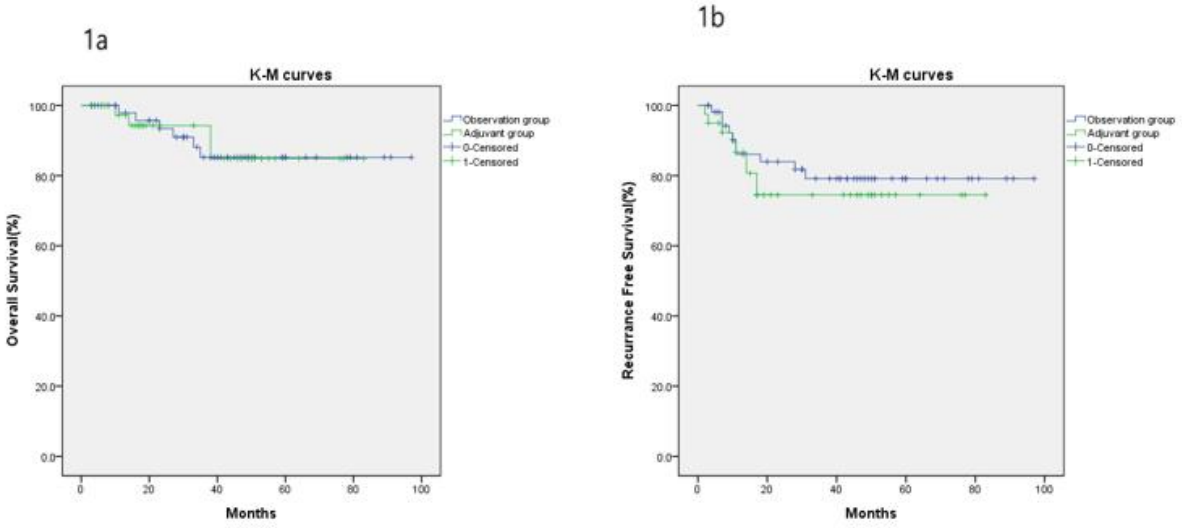
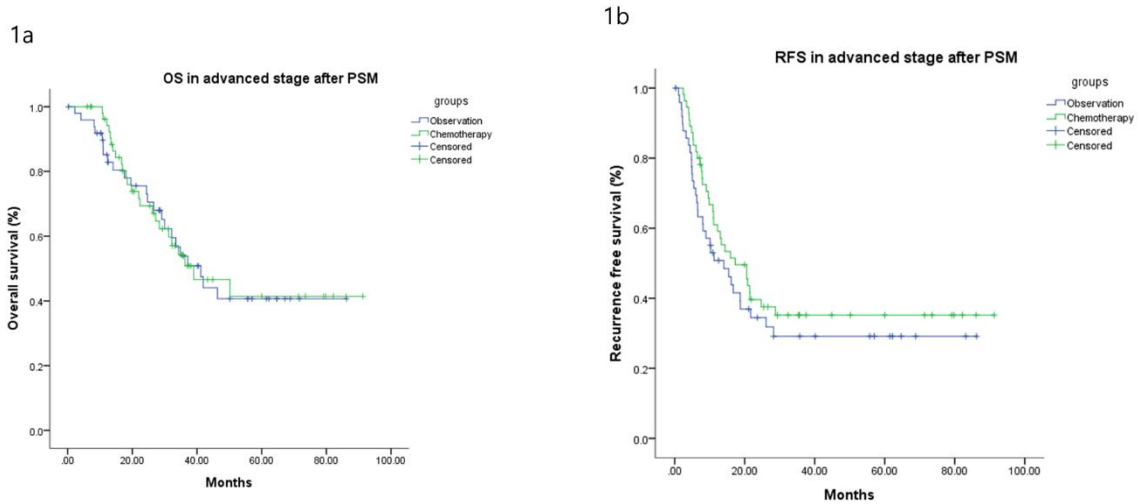


Figure 6. In patients with stage IIIA and IIIB disease, the OS rate (40.7% vs. 41.4%, p = 0.889; 1a) and RFS rate (29.2% vs. 35.2%, p = 0.301; 1b) were comparable between the observation and chemotherapy groups after PSM.



Comparable oncologic outcomes between the OB and CTx groups after PSM

After PSM, there was no significant difference of the 5-year OS rate between OB and CTx groups. (65.4% [OB group] vs. 58.7% [CTx group]; HR, 1.208, 95% CI, 0.770–1.894; p = 0.412; Figure 7-A), and there was no significant difference in RFS between the two groups (51.1% [OB] vs. 46.3% [CTx]; HR, 1.117; 95% CI, 0.796–1.567; p = 0.522; Figure 7-B). Prognosis was analyzed according to the use of adjuvant chemotherapy after stratification by TNM stage because the CTx group included patients with a higher TNM stage before PSM. After PSM, a stratified Cox proportional hazards model showed no significant differences in OS (HR, 1.085; 95% CI, 0.688–1.710; p = 0.726) or RFS (HR, 0.883; 95% CI, 0.613–1.272; p = 0.505) between the CTx and OB groups (Table 5). This result demonstrates comparable oncologic outcomes in patients who did or did not receive CTx, regardless of TNM stage.

Figure 7. Comparable oncologic outcomes between the observation and adjuvant chemotherapy groups after PSM. After PSM, there was no significant difference of the 5-year OS rate between OB and CTx groups. (65.4% [OB group] vs. 58.7% [CTx group]; HR, 1.208, 95% CI, 0.770–1.894; p = 0.412; Figure 2-A), and there was no significant difference in RFS between the two groups (51.1% [OB] vs. 46.3% [CTx]; HR, 1.117; 95% CI, 0.796–1.567; p = 0.522; Figure 2-B).

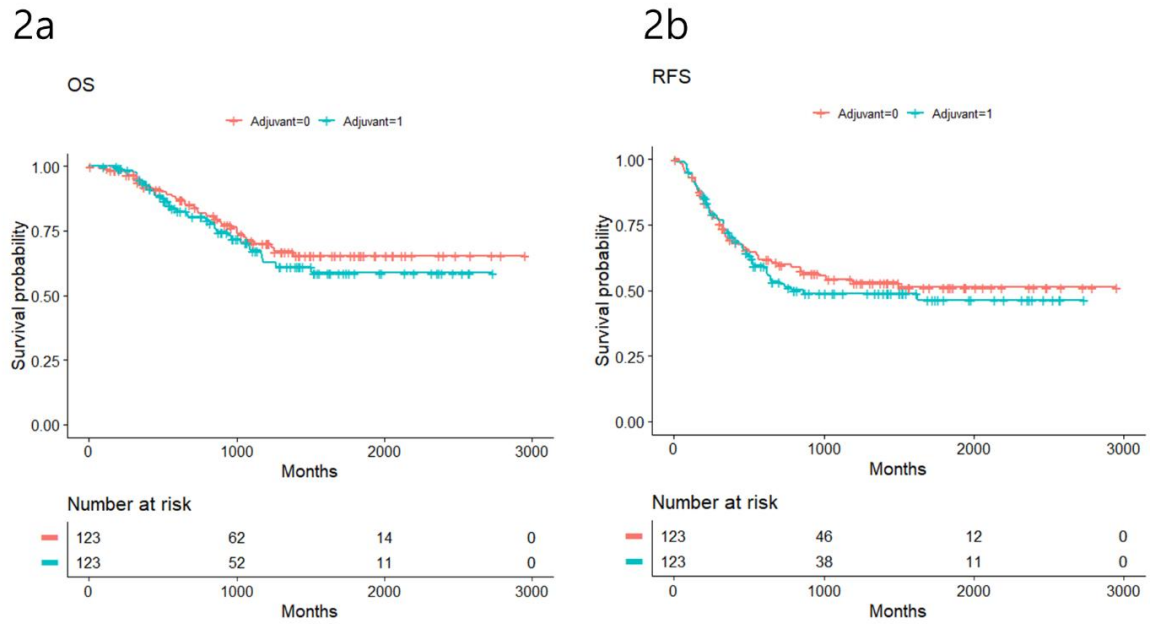


Table 5. Stratified Cox proportional hazard model and stratified log rank test for propensity score matched data

		HR	95%CI	*P value*
Matched patients	Overall survival	1.208	0.770-1.894	0.412
	Recurrence free survival	1.117	0.796-1.567	0.522
Stratification of TNM stage	Overall survival	1.085	0.688-1.710	0.726
	Recurrence free survival	0.883	0.613-1.272	0.505

HR; hazard ratio, CI; confidence interval, Strata; TNM stage

Oncologic benefit of fluoropyrimidine based adjuvant chemotherapy according to the histologic subtype

To compare oncologic benefit based on histologic subtype, consecutive 60 patients who were administered chemotherapy were reviewed pathologically. Intestinal, pancreatobiliary, and mixed subtypes were diagnosed in 31, 19, and 10 cases, respectively. Otherwise, 10 cases were classified with mucinous subtype. We compared perioperative and oncologic outcome between intestinal (n = 31) and pancreatobiliary/mixed (n = 29) subtype. Median survival in this subgroup was 30 months. Intestinal subtype showed better 5-year OS (83.7 % vs 33.2 %, p = 0.015; figure 7-A) and RFS (46.5 % vs 24.9%, p = 0.035; figure 7-B) rate compared with pancreatobiliary/mixed subtype for similar chemotherapeutic regimen.

Table 6-1. Intestinal subtype patient characteristics (n = 31)

	n (%) or mean ± SD
Age (years)	59.39 ± 13.122
Sex (M/F)	14 (45.2) / 17 (54.8)
Charlson comorbidity index	1.97 ± 0.948
Body mass index (kg/m2)	23.66 ± 3.482
Preoperative CA19-9 (U/ml)	126.30 ± 470.123
Preoperative CEA (ng/ml)	2.93 ± 3.192
Operative manners (MIS/open)	11 (35.5) / 20 (64.5)
Operation time (min)	313.00 ± 78.938
Intraoperative transfusion	1 (3.2)
Estimated blood loss (ml)	270.12 ± 310.451
Postoperative complication	15 (48.4)
Hospital stay (days)	11.29 ± 2.807
T stage (1/2/3/4), AJCC 8th	5 (16.1) / 12 (38.7) / 11 (35.5) / 3 (9.7)
N stage (0/1/2), AJCC 8th	15 (48.4) / 12 (38.7) / 4 (12.9)
Differentiation (WD/MD/PD)	5 (16.1) / 26 (83.9) / 0 (0)
LVI/PNI	20 (64.5)/ 9 (29.0)

SD; standard deviation, , CA 19-9; carbohydrate antigen 19-9, CEA; carcinoembryonic antigen, MIS; minimally invasive surgery, AJCC; American Joint Committee on Cancer, WD; well differentiated, MD; moderate differentiated, PD; poorly differentiated, LVI; lymphovasvular invasion, PNI; perineural invasion

Table 6-2. Pancreatobiliary/Mixed subtype patient characteristics (*n* = 29)

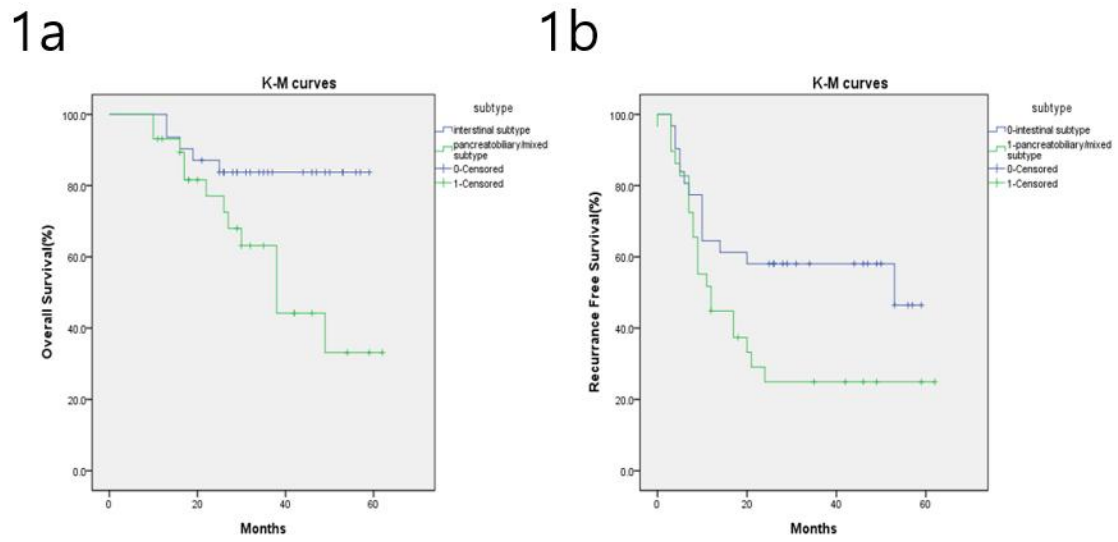
	n (%) or mean ± SD
Age (years)	61.21 ± 9.469
Sex (M/F)	10 (34.5) / 19 (65.5)
Charlson comorbidity index	2.31 ± 1.339
Body mass index (kg/m2)	23.67 ± 3.134
Preoperative CA19-9 (U/ml)	200.24 ± 506.367
Preoperative CEA (ng/ml)	7.15 ± 21.527
Operative manners (MIS/open)	6(20.7) / 23 (79.3)
Operation time (min)	321.31 ± 74.510
Intraoperative transfusion	7 (24.1)
Estimated blood loss (ml)	383.50 ± 386.542
Postoperative complication	17 (58.6)
Hospital stay (days)	14.59 ± 5.454
T stage (1/2/3/4), AJCC 8th	4 (13.8) / 9 (31.0) / 15 (51.7) / 1 (3.5)
N stage (0/1/2), AJCC 8th	8 (27.6) / 17 (58.6) / 4 (13.8)
Differentiation (WD/MD/PD)	4 (13.8) / 16 (55.2) / 9 (31.0)
LVI/PNI	24 (82.8)/ 15 (51.7)

SD; standard deviation, , CA 19-9; carbohydrate antigen 19-9, CEA; carcinoembryonic antigen, MIS; minimally invasive surgery, AJCC; American Joint Committee on Cancer, WD; well differentiated, MD; moderate differentiated, PD; poorly differentiated, LVI; lymphovasvular invasion, PNI; perineural invasion

Table 6-3 Comparison characteristics between intestinal and pancreatobiliary/mixed subtype

	Histologic subtype		
	Intestinal (n=31)	Pancreatobiliary/mixed (n=29)	P-value
Age (years)	59.39 ± 13.122	61.21 ± 9.469	0.543
Sex (M/F)	14 (45.2) / 17 (54.8)	10 (34.5) / 19 (65.5)	0.440
Charlson comorbidity index	1.97 ± 0.948	2.31 ± 1.339	0.255
Body mass index (kg/m2)	23.66 ± 3.482	23.67 ± 3.134	0.986
Preoperative CA19-9 (U/ml)	126.30 ± 470.123	200.24 ± 506.367	0.560
Preoperative CEA (ng/ml)	2.93 ± 3.192	7.15 ± 21.527	0.285
Operative manners (MIS/open)	11 (35.5) / 20 (64.5)	6(20.7) / 23 (79.3)	0.258
Operation time (min)	313.00 ± 78.938	321.31 ± 74.510	0.677
Intraoperative transfusion	1 (3.2)	7 (24.1)	0.024
Estimated blood loss (ml)	270.12 ± 310.451	383.50 ± 386.542	0.214
Postoperative complication	15 (48.4)	17 (58.6)	0.451
Hospital stay (days)	11.29 ± 2.807	14.59 ± 5.454	0.004
T stage AJCC 8th			0.554
1	5 (16.1)	4 (13.8)	
2	12 (38.7)	9 (31.0)	
3	11 (35.5)	15 (51.7)	
4	3 (9.7)	1 (3.5)	
N stage AJCC 8th			0.231
0	15 (48.4)	8 (27.6)	
1	12 (38.7)	17 (58.6)	
2	4 (12.9)	4 (13.8)	
Cell Differentiation			0.003
Well differentiated	5 (16.1)	4 (13.8)	
Moderate differentiated	26 (83.9)	16 (55.2)	
Poorly differentiated	0 (0)	9 (31.0)	
Lymphovasular invasion	20 (64.5)	24 (82.8)	0.148
Perineural invasion	9 (29.0)	15 (51.7)	0.113

Figure 8. In patients with fluoropyrimidine based chemotherapy, the OS rate (52.2% vs. 40.6%, p = 0.015; 1a) and RFS rate (37.0% vs. 23.3%, p = 0.035; 1b) were no significant difference between intestinal and pancreatobiliary/mixed subtype.



Discussion

In this study, the CTx group had worse OS and RFS than the OB group before PSM, and most patients were administered CTx based on fluoropyrimidine as the first line chemotherapy because of national reimbursement system. Patient characteristics were different between the OB and CTx groups, as patients in the CTx group were more likely to have poor prognostic factors. We therefore used PSM to normalize differences between the two groups. However, the CTx group did not show a significant improvement in OS or RFS even after PSM. The results were similar after stratification by TNM stage. Oncologic outcomes were compared in patients with CTx group according to the pathologic subtypes. Intestinal subtype showed better prognosis for fluoropyrimidine CTx than pancreatobiliary/mixed subtypes.

Although the role of adjuvant chemotherapy in AC is not clear because of the rarity of the disease and the limited number of previous studies, clinicians prefer to use adjuvant CTx in patients with stage IB or higher disease in current practice. Patients with a higher pathologic stage usually experience early recurrence even after curative intent resection, suggesting the need for adjuvant CTx. However,

controversial effect of adjuvant chemotherapy were reported in previous studies (4-6). Zhou et al. (7) showed that adjuvant chemoradiotherapy did not improve survival. Another multinational, retrospective cohort study with PSM matching included data from 12 institutions and concluded that adjuvant therapy was more frequently used in patients with poor prognostic factors, but was not associated with significant improvements in survival, regardless of the CTx regimen or the tumor histologic subtype (1). Another large study came to the same conclusion (8). In the current study, oncologic outcomes were similar in patients who received OB or fluoropyrimidine based CTx even after PSM. Only patients with higher-stage disease showed a better RFS rate, although this did not reach statistical significance. Similar results have been shown in two prospective studies, including the fluoropyrimidine subgroup in the ESPAC-3 trial and a separate comparison of adjuvant fluoropyrimidine and mitomycin C, although the possibility of type II error was suggested (9, 10). This study showed similar results. CTx group has poor prognostic factors and clinician tended to select CTx for these patients. However, prognosis was not changed regardless of fluoropyrimidine based CTx even after PSM. There is a different result compared with previous studies. The patients with intestinal subtype showed better prognosis than pancreatobiliary/mixed subtypes in patients with fluoropyrimidine based CTx. Although fluoropyrimidine based CTx is considerable regimen for the patients with intestinal subtype, the same regimen is insufficient for the patients with pancreatobiliary/mixed subtype.

Several studies have demonstrated the effectiveness of adjuvant chemotherapy (6, 11, 12). Bhatia et al. (11) divided patients by disease stage and concluded that` adjuvant chemotherapy was effective in advanced disease. That study included various CTx regimens. A retrospective cohort study based on the National Cancer Database using PSM concluded that CTx significantly improved OS (13). That study used PSM to exclude bias but included the chemotherapy regimen and histologic type. A recent study showed that gemcitabine-based adjuvant CTx for pancreatobiliary or mixed-type AC resulted in a better OS rate than OB. The authors concluded that histologic type should be considered for selection of the CTx regimen (14, 15). Previous studies have shown that pancreaticobiliary tumors are more aggressive and have worse outcomes than intestinal tumors (16-18). Gemcitabine-based CTx has been recommended in pancreatobiliary subtype AC (15). Several studies have evaluated the response to

adjuvant CTx according to the histologic subtype, although the results remain controversial (1, 19, 20). Furthermore, a nomogram study including age, margin, differentiation, and TNM stage, which predict prognosis, showed that adjuvant therapy confers a survival benefit in patients with a very high risk of recurrence.(21)

At the time of our study, our center HBP pathologists did not analyze pathological specimens for subtypes. So, we asked the pathology department subtype analysis of some of our study cases. Total 75 cases were reviewed, Intestinal subtype were 31 cases, pancreatobiliary subtype were 19 cases, mixed subtype were 10 cases and the other cases such as mucinous subtype were 10cases. All of cases received fluoropyrimidine based monotherapy (sLV5FU2, LF-1, UFT). And we excluded other cases such as mucinous subtype to properly evaluate the effectiveness of adjuvant chemotherapy of intestinal and pacreatobiliary subtype. There was no significant difference in overall survival and recurrence free survival according to each subtype. But, It could be seen that intestinal subtype was more effective and significant difference in fluoropyrimidine based adjuvant chemotherapy than the others.(Table6, Figure7)

There are several limitations to this study. A retrospective study at a single institution may include potential bias. This study included a small number of patients, which limits the interpretation of subgroup analyses. This study also included patients with fluoropyrimidine based CTx, while a gemcitabine-based CTx regimen has been recently recommended. The benefit of gemcitabine-based CTx. Is therefore unknown. Although we performed subgroup analysis according to the histologic subtype, we need to study with more cases and controlling for other variables.

Conclusion

The oncologic outcomes in AC patients who received adjuvant CTx based on fluoropyrimidine was comparable to that of patients who did not receive CTx. The patients with intestinal subtype showed better OS, RFS for fluoropyrimidine based chemotherapy compared with pancreatobiliary or mixed subtype. Further randomized controlled trial should be conducted to investigate if adjuvant CTx should be recommended for these patients or not.

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국문요약

연구배경 : 바터팽대부 암은 드문 악성질환으로 췌두부십이지장절제술을 통한 수술적 치료가 주된 치료이며 5년 생존율이 약 30~60%로 비교적 낮고 재발율이 20~50%로 높으며 연구자료마다 큰 편차를 보이고 있다. 아직 보조항암치료의 효과에 대해 논란이 있지만, 일반적으로 stage IB 이상의 환자군에서 보조항암치료를 시행하고 있다. 하지만 환자수가 적고 이에 대한 연구들이 많지 않아 명확한 원칙이 있지 않은 상태로 바터팽대부 암에서 술 후 보조항암치료의 효과에 대해 추가적 연구가 필요하다.

연구방법 : 바터팽대부 암 환자들의 술 후 보조항암치료를 받은 환자와 경과관찰을 한 환자들간의 특징을 비교하고 성향점수 매칭을 통해 5년 생존율과 재발율을 비교하여 보조항암치료가 생존율과 재발률에 영향을 주는 요인인지 확인하고자 한다.

연구결과 성향점수 매칭을 하기 전 475 명의 환자들 중 보조항암치료군(194 명)에서 경과관찰군(281 명)보다 5년 생존율(p=0.017), 재발율(p<0.001)에서 좋지 않은 결과를 보였다. 게다가 보조항암치료군에서 심한 국소 침범, 림프절 전이, 나쁜 분화도 일수록 나쁜 예후인자들이 더 높은 비율로 나타났다. 성향점수 매칭 후, 수술 전후 결과는 보조항암치료군(123 명)과 경과관찰군(123 명)에서 차이 없이 비슷했다. 게다가 TNM stage 에서 계층화를 한 뒤에도 5년 생존율(0.726)과 재발율(p=0.505)에서 유의한 차이가 없었다. 장형 아형은 플루오로피리미딘 보조항암치료에서 췌장담도형/혼합형에 비해 5년 생존율(p=0.015), 재발율(p=0.035) 모두 더 좋은 경과를 보였다.

연구결론 : 플루오로피리미딘 보조항암치료를 받은 환자군에서 종양 병기를 계층화를 한 뒤에도 항암치료를 받은 군과 경과관찰한 군에서 생존율과 재발율의 유의한 차이가 없었다. 플루오로피리미딘 보조항암치료는 장형 아형을 가진 환자군에서 췌장담도형/혼합형 환자군보다 좋은 생존율과 재발율의 유의한 차이를 보였다.