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Long-term oncologic benefit of postoperative chemotherapy in the resected ampulla of Vater cancer: hope or hype? A propensity score matching analysis

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Purpose: The oncologic benefits of adjuvant chemotherapy for resected ampulla of Vater cancer (AoVCa) remain contentious. This study aimed to evaluate the long-term oncologic effects of postoperative adjuvant chemotherapy (PACT) in patients who underwent radical surgery for AoVCa.
Methods: From 2005 to 2019, clinical and pathological data of 306 AoVCa patients who underwent pancreatoduodenectomy were retrospectively reviewed. Patients were divided into the PACT (+) and PACT (–) groups. Propensity score matching (PSM) was conducted to adjust for clinical factors.
Results: The PACT (+) group (n = 124) and PACT (–) group (n = 182) showed significant differences in cancer stage, lymph node metastasis, perineural invasion, lymphovascular invasion, and cancer differentiation. Lower overall survival (OS) ($P < 0.001$) and disease-free survival (DFS) ($P < 0.001$) were observed in the PACT (+) group. After PSM, no significant differences in OS or DFS were found between the groups. Multivariate analysis identified lymph node metastasis and perineural invasion as significant prognostic factors, while PACT did not significantly impact long-term survival. Paradoxically, PACT was associated with worse outcomes in patients with favorable prognostic factors.
Conclusion: This study suggests that PACT does not provide a clear oncologic benefit for resected AoVCa patients and may even be detrimental for those with favorable prognostic factors. There is an urgent need to develop effective anticancer treatments and consider tailored therapeutic approaches based on individual patient profiles. Future research should focus on long-term follow-up and the integration of precision medicine to improve outcomes for AoVCa patients.
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Key Words: Ampulla of Vater, Drug therapy, Neoplasms, Pancreaticoduodenectomy, Survival

INTRODUCTION

Ampulla of Vater cancer (AoVCa) is a rare malignant neoplasm that occurs in the ampulla of Vater complex, located at the terminal portion of the confluence of the common bile duct and pancreatic duct. AoVCa accounts for 0.2% of gastrointestinal malignancies and 7% of periampullary cancers, with an incidence rate of 0.5 cases per 100,000 persons [1,2]. The only established treatment for AoVCa is complete resection [3]. Generally, AoVCa has a better prognosis than other periampullary cancers due to the early detection of the disease, which is often prompted by early clinical manifestations caused

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by biliary obstruction [4]. Additionally, the fact that R0 resection is performed in more than 80% of patients is recognized as a reason for better outcomes compared to other periampullary cancers [5].

However, the likelihood of recurrence in AoVCa is high, especially in advanced cancers of T3 stage or higher or with lymph node (LN) involvement, which is directly related to decreased survival rates [6,7]. Due to the rarity of AoVCa, there are currently no clear guidelines for postoperative adjuvant chemotherapy (PACT), with existing recommendations often based on guidelines for treating cancers in similar anatomic sites, such as pancreatic cancer [8]. Consequently, many research institutes have conducted numerous studies to evaluate the effectiveness of adjuvant chemotherapy for AoVCa patients, but the results are still controversial [6,9-11]. In addition, it is difficult to confirm the effectiveness of adjuvant chemotherapy with a simple comparison due to several factors that can affect the prognosis of patients with AoVCa [11,12]. Therefore, this study evaluated the oncologic role of PACT in resected AoVCa.

METHODS

Ethics statement

This study was approved by the Institutional Review Board of Severance Hospital (No. 4-2024-0731). It was performed in accordance with the Declaration of Helsinki and written informed consent was waived due to its retrospective nature.

Patients and data collection

This study was conducted through a retrospective review of the electronic medical records of Severance Hospital (Seoul, Korea). From January 2005 to December 2019, 312 patients who underwent radical resection as the primary treatment for AoVCa were enrolled as study subjects. Among them, 6 patients were excluded from the study and analysis due to distant metastasis (n = 4) and neoadjuvant chemotherapy (n = 2). Finally, a total of 306 patients were enrolled in the study (Fig. 1). Clinical data such as patient age, sex, body mass index (BMI), past medical history, American Society of Anesthesiologists physical status (ASA PS) classification, serum level of CA 19-9, surgery-related data (operation method, time required, conversion status), administration of adjuvant chemotherapy, chemotherapy regimen used, and biopsy information such as the survival period and recurrence through the pathology and follow-up were collected and analyzed. Postoperative outcomes were also collected; major complications were defined as Clavien-Dindo classification (CDC) grade III or higher, and clinically relevant postoperative pancreatic fistula (CR-POPF) was defined as grade B or C as defined by the International Study Group of Pancreatic Fistulae [13,14]. In addition, diagnoses of delayed gastric emptying (DGE), and postoperative pancreatic hemorrhage (PPH) were defined according to the International Study Group of Pancreatic Surgery [15,16]. According to PACT, patients were categorized into 2 groups: the PACT (+) group and the PACT (–) group. The cancer stage was classified according to the Cancer Staging Manual of American Joint Committee on Cancer, 8th edition. The primary outcome measures of the study were

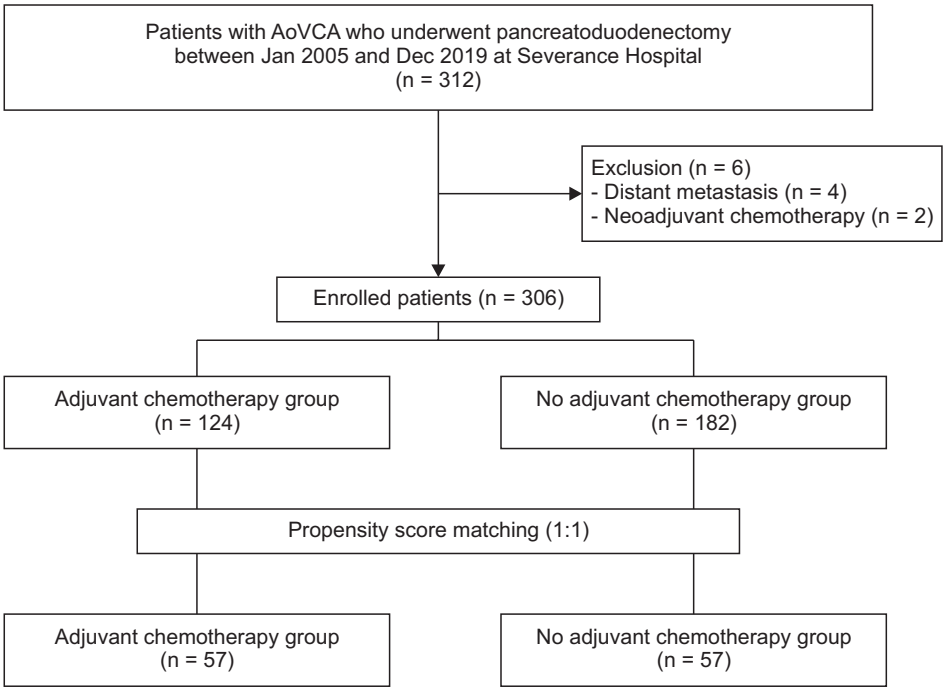

Fig. 1. Flow chart of the study population. AoVCa, ampulla of Vater cancer.

overall survival (OS) and disease-free survival (DFS), both of which were calculated from the date of surgery. Follow-up data was collected through December 2021.

Treatment

All patients underwent pylorus-preserving pancreaticoduodenectomy with standard LN dissection, which included the dissection of stations 8 (common hepatic artery), 12 (hepatoduodenal ligament), 3 (lesser curvature of the stomach), 5 (suprapyloric), 13 (retropancreatic area), and 16 (paraaortic area). Radical R0 resection was performed to achieve complete tumor clearance. Postoperatively, patients were managed according to our center's protocol. Adjuvant chemotherapy was generally considered for patients with high-risk pathological features such as LN metastasis, lymphovascular invasion (LVI), perineural invasion (PNI), or poorly differentiated (PD) tumors, as these factors are associated with an increased risk of recurrence. However, adjuvant chemotherapy was not administered in cases where patients refused treatment due to personal limitations such as cost, had poor general conditions, or were of advanced age. Even in early-stage cases, adjuvant chemotherapy was considered for patients with high-risk pathological features (LVI+, PNI+, PD tumors) if they opted for treatment after discussion with their physician. Patients were categorized into the PACT (+) group if they received at least one cycle of adjuvant chemotherapy, following the intention-to-treat principle. Adjuvant chemotherapy was given within 6–8 weeks of surgical resection. Historically, 5-fluorouracil (5-FU)–based regimens were predominantly used at our institution. More recently, chemotherapy selection has been increasingly guided by National Comprehensive Cancer Network recommendations, with 5-FU–based regimens preferred for the intestinal type and gemcitabine-based regimens for the pancreatobiliary type. However, a standardized institutional guideline for adjuvant chemotherapy in ampullary cancer has not yet been established. Patients who were not treated with adjuvant chemotherapy received follow-up only after surgical resection. All patients were followed up with a comprehensive physical examination, serum tumor marker testing (CEA and CA 19-9), and regular surveillance imaging, including CT. The follow-up schedule consisted of every 3 months during the first 6 months postoperatively, followed by every 6 months thereafter. This schedule was designed to ensure the early detection of recurrence and to monitor treatment outcomes.

Statistical analysis

Statistical analysis for this study was performed using IBM SPSS Statistics ver. 27.0 (IBM Corp.). Continuous variables were presented as means with their associated standard deviations. Categorical variables were compared and analyzed using the chi-square test, and quantitative data were analyzed using the Student t-test. Patient survival analysis was performed using the Kaplan-Meier method and was compared with a log-rank test. Multivariate survival analysis was performed using Cox proportional hazards regression models to identify independent predictors of death and recurrence. All variables with a P-value less than 0.1 in the univariate analysis were entered into the multivariate analysis. Results were reported as hazard ratios (HRs) and 95% confidence intervals (CIs). A P-value less than 0.05 was considered statistically significant.

Propensity score matching

We performed propensity score matching (PSM) using the MatchIt package in R statistical software ver. 4.4.1(The R Foundation) to reduce selection bias between patients who received adjuvant chemotherapy and those who did not, hypothesizing that patients with more advanced disease were more likely to receive adjuvant chemotherapy. Propensity scores were calculated using a logistic regression model that included key clinicopathological factors known to influence oncologic outcomes, specifically age (years), sex, histologic differentiation, LN metastasis, TNM stage, LVI, PNI, and preoperative serum CA 19-9 level. These variables were selected based on their established prognostic significance in the existing literature and their relevance to the research question. Intraoperative variables, such as blood transfusion, severe complications, and hospital stay, were not included as covariates to avoid adjusting for factors that may themselves be influenced by treatment or surgical outcomes. After estimating propensity scores, we used a 1:1 nearest neighbor matching algorithm to match 57 pairs of patients in the PACT (+) group and the PACT (–) group. We calculated the standardized mean difference of each covariate and set it at less than 0.2 to ensure appropriate PSM.

RESULTS

General characteristics of the patients

The characteristics of the patients designated for the study are summarized in Table 1. The mean age of the patients was 65 years (range, 33–91 years), and 54.6% of the patients were male. The mean BMI was 22.80 kg/m^2. A total of 246 patients (80.4%) underwent open pancreaticoduodenectomy, while 60 (19.6%) received minimally invasive pancreaticoduodenectomy (robot-assisted or laparoscopic). Among the patients, 125 (40.8%) were stage I, 58 (19.0%) were stage II, 119 (38.9%) were stage III, and 4 (1.3%) were stage IV. LN metastasis was present in 111 patients (36.3%), PNI in 162 (52.9%), and LVI in 153 (50%). Histologically, 71 patients (23.2%) had well-differentiated (WD) tumors, 204 (66.7%) had moderately differentiated (MD) tumors, and 31 (10.1%) had PD tumors. A total of 124 patients (40.5%) were in the PACT (+) group, while the remaining 182 (59.5%) were PACT (–) group. Among the 124 patients in the PACT (+) group,

Table 1. General characteristics of the patients

Characteristic	Data
No. of patients	306
Age (yr)	65 (33–91)
Sex	
Male	167 (54.6)
Female	139 (35.4)
Body mass index (m^2/kg)	22.80 ± 4.02
ASA PS classification	
I	88 (28.8)
II	150 (49.0)
III	68 (22.2)
CA 19-9	301.80 ± 1,540.47
Operation time (min)	437.00 ± 105.25
Estimated blood loss (mL)	437.00 ± 355.60
Intraoperative transfusion	
Done	36 (11.8)
Not done	270 (88.2)
Operation method	
Open	246 (80.4)
Laparoscopy	60 (19.6)
Major complication	57 (18.6)
TNM stage	
I	125 (40.8)
II	58 (19.0)
III	119 (38.9)
IV	4 (1.3)
LN metastasis	
LN+	111 (36.3)
LN–	195 (63.7)
PNI	
Present	162 (52.9)
Absent	144 (47.1)
LVI	
Present	153 (50.0)
Absent	153 (50.0)
Differentiation	
WD	71 (23.2)
MD	204 (66.7)
PD	31 (10.1)

Values are presented as number only, mean (range), number (%), or mean ± standard deviation.
ASA PS, American Society of Anesthesiologists physical status; LN, lymph node; PNI, perineural invasion; LVI, lymphovascular invasion; WD, well differentiated; MD, moderated differentiated; PD, poor differentiated.

10 (8.1%) discontinued chemotherapy prematurely due to side effects such as neutropenia, while 114 (91.9%) completed the planned chemotherapy schedule. The average operation time was 437 minutes, with an average estimated blood loss of 437 mL. Intraoperative blood transfusions were required for 36 patients (11.8%). The mean preoperative serum CA 19-9 level was 301.80 U/mL.

Overall comparative analysis between the PACT (+) group and PACT (–) group

Table 2 presents the comparative analysis according to PACT in resected AoVCa. It was found that patients with more aggressive biologic behavior of AoVCa received PACT. In the PACT (+) group, the proportion of advanced cancer stages was significantly higher (stage I, 7.3% *vs.* 63.7%; stage II, 18.5% *vs.* 19.2%; stage III, 71.8% *vs.* 16.5%; and stage IV, 2.4% *vs.* 0.6%; P < 0.001). The frequency of LN metastasis (68.5% *vs.* 14.3%, P < 0.001), PNI (58.1% *vs.* 39.6%, P < 0.001), and LVI (68.5% *vs.* 41.8%, P < 0.001) were also significantly higher in the PACT (+) group. Additionally, the degree of differentiation of cancer tissues was significantly poorer in the PACT (+) group (WD, 14.5% *vs.* 29.1%; MD, 71.0% *vs.* 63.8%; and PD, 14.5% *vs.* 7.1%; P = 0.010). However, there were no significant differences in the baseline characteristics between the 2 groups in the matched cohort. Table 3 compares the operative outcomes between the PACT (+) group and PACT (–) group before and after PSM. Before matching, the PACT (+) group had a significantly longer operation time (455.3 minutes *vs.* 423.8 minutes, P = 0.010) and higher estimated blood loss (507.9 mL *vs.* 389.5 mL, P = 0.004) compared to the PACT (–) group. However, major complications, including CDC grade III or higher, as well as specific complications such as CR-POPF, PPH, DGE, and length of stay, were not significantly different between the 2 groups. After PSM, no significant differences in operative outcomes were observed between the 2 groups across all categories.

Survival analysis between the PACT (+) group and PACT (–) group

In survival analysis, the mean OS was estimated to be 110.3 months (95% CI, 103.2–117.4 months), and the mean DFS period was 97.9 months (95% CI, 90.5–105.2 months). The PACT (+) group showed lower long-term survival outcomes compared to the PACT (–) group (OS: 79.7 months *vs.* 120.7 months, P < 0.001; DFS: 63.8 months *vs.* 112.6 months, P < 0.001).

After PSM, there were no significant differences between the groups in OS (84.5 months *vs.* 65.5 months, P = 0.966) and DFS (67.1 months *vs.* 58.2 months, P = 0.388) (Fig. 2, Supplementary Table 1).

Determining independent prognostic factors to predict long-term survival in patients with resected ampulla of Vater cancer

In univariate analysis, adjuvant chemotherapy (OS, P < 0.001; DFS, P = 0.001), TNM stage (P < 0.001), LN metastasis (P < 0.001), PNI (P < 0.001), LVI (P < 0.001), differentiation (OS, P = 0.010; DFS, P < 0.001), and CA 19-9 >37 U/mL (OS, P = 0.029; DFS, P = 0.022) were found to be significantly associated with poor OS and DFS. Subsequent multivariate analysis identified LN metastasis (HR, 4.249; 95% CI, 2.467–7.318; P < 0.001) and

Table 2. Distribution of characteristics before and after propensity score matching (PSM)

Characteristic	Before PSM				After PSM			
	Adjuvant CTx (n = 124)	No adjuvant CTx (n = 182)	P-value	SMD	Adjuvant CTx (n = 57)	No adjuvant CTx (n = 57)	P-value	SMD
Age (yr)	63.19 ± 11.31	65.97 ± 9.96	0.024	0.260	64.96 ± 11.23	65.14 ± 11.69	0.698	0.015
Sex			0.875	0.018			>0.999	0.036
Male	67 (54.0)	100 (54.9)			35 (61.4)	35 (61.4)		
Female	57 (46.0)	82 (45.1)			22 (38.6)	22 (38.6)		
BMI (m^2/kg)	23.22 ± 5.29	22.52 ± 2.83	0.134	0.166	22.94 ± 2.73	22.56 ± 2.70	0.461	0.138
ASA PS classification			0.525	0.074			0.256	0.192
I	36 (29.0)	52 (28.6)			22 (38.6)	20 (35.1)		
II	64 (51.6)	86 (47.3)			27 (47.4)	22 (38.6)		
III	24 (19.4)	44 (24.2)			8 (14.0)	15 (26.3)		
CA 19-9	298.59 ± 1,108.50	304.06 ± 1,778.69	0.976	0.004	394.35 ± 1,412.11	437.00 ± 1,761.83	0.890	0.027
Operation method			0.841	0.023			0.771	<0.001
Open	99 (79.8)	147 (80.8)			51 (89.5)	50 (87.7)		
Laparoscopy	25 (20.2)	35 (19.2)			6 (10.5)	7 (12.3)		
TNM stage			<0.001	1.614			0.907	<0.001
I	9 (7.3)	116 (63.7)			9 (15.8)	14 (24.6)		
II	23 (18.5)	35 (19.2)			23 (40.4)	13 (22.8)		
III	89 (71.8)	30 (16.5)			25 (43.9)	29 (50.9)		
IV	3 (2.4)	1 (0.6)			0	1 (1.8)		
LN metastasis			<0.001	1.298			0.852	0.035
LN+	85 (68.5)	26 (14.3)			26 (45.6)	25 (43.9)		
LN–	39 (31.5)	156 (85.7)			31 (54.4)	32 (56.1)		
PNI			0.001	0.375			0.710	0.070
Present	72 (58.1)	72 (39.6)			32 (56.1)	30 (52.6)		
Absent	52 (41.9)	110 (60.4)			25 (43.9)	27 (47.4)		
LVI			<0.001	0.414			0.710	0.035
Present	77 (62.1)	76 (41.8)			32 (56.1)	30 (52.6)		
Absent	47 (37.9)	106 (58.2)			25 (43.9)	27 (47.4)		
Differentiation			0.001	0.398			0.734	0.064
WD	18 (14.5)	53 (29.1)			10 (17.5)	8 (14.0)		
MD	88 (71.0)	116 (63.8)			37 (64.9)	43 (75.4)		
PD	18 (14.5)	13 (7.1)			10 (17.5)	6 (10.5)		

Values are presented as mean ± standard deviation or number (%).
CTx, chemotherapy; SMD, standardized mean difference; BMI, body mass index; ASA PS, American Society of Anesthesiologists physical status; LN, lymph node; PNI, perineural invasion; LVI, lymphovascular invasion; WD, well differentiated; MD, moderated differentiated; PD, poor differentiated.

Table 3. Operative outcomes before and after propensity score matching (PSM)

Characteristic	Before PSM			After PSM		
	Adjuvant CTx (n = 124)	No adjuvant CTx (n = 182)	P-value	Adjuvant CTx (n = 57)	No adjuvant CTx (n = 57)	P-value
Operation time (min)	455.34 ± 111.52	423.81 ± 99.04	0.010	416.51 ± 94.38	428.25 ± 114.02	0.384
Estimated blood loss (mL)	507.90 ± 405.82	389.48 ± 308.93	0.006	474.39 ± 393.00	468.25 ± 381.76	0.863
Intraoperative transfusion	19 (15.3)	17 (9.3)	0.112	9 (15.8)	6 (10.5)	0.410
Major complication[a]	22 (17.7)	35 (19.2)	0.744	7 (12.3)	11 (19.3)	0.309
CR-POPF	12 (9.7)	26 (14.3)	0.217	3 (5.3)	5 (8.8)	0.468
PPH	2 (1.6)	7 (3.8)	0.222	1 (1.8)	4 (7.0)	0.174
DGE	16 (12.9)	28 (15.4)	0.545	8 (14.0)	10 (17.5)	0.611
Intra-abdominal infection	14 (11.3)	29 (15.9)	0.240	4 (7.0)	7 (12.3)	0.346
Reoperation	5 (4.0)	2 (1.1)	0.132	2 (3.5)	2 (3.5)	>0.999
Length of stay (day)	20.65 ± 9.76	22.34 ± 16.22	0.300	21.09 ± 10.02	22.42 ± 12.53	0.532

Values are presented as mean ± standard deviation or number (%).
CTx, chemotherapy; CR, clinically relevant; POPF, postoperative pancreatic fistula; PPH, postpancreatectomy hemorrhage; DGE, delayed gastric emptying.
[a]Clavien-Dindo classification ≥III.

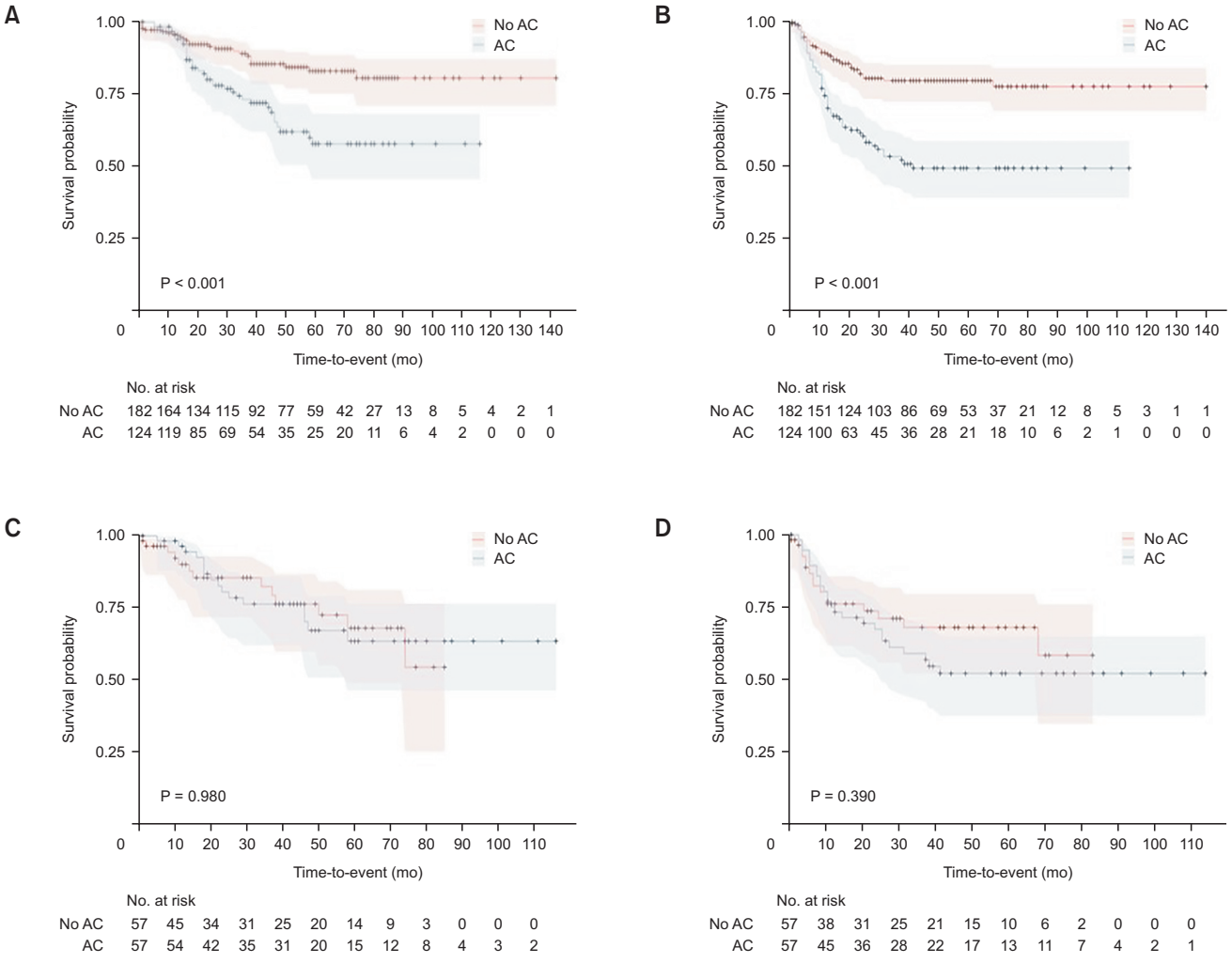

Fig. 2. Long-term oncologic impact of postoperative adjuvant chemotherapy (AC) in resected ampulla of Vater cancer before and after propensity score matching (PSM). (A) Overall survival before PSM. (B) Disease-free survival before PSM. (C) Overall survival after PSM. (D) Disease-free survival after PSM.

Table 4. Univariate and multivariate analysis of overall survival and disease-free survival

Variable	Overall survival				Disease-free survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR 95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Adjuvant CTx	2.475 (1.479–4.141)	0.001	0.652 (0.344–1.237	0.191	2.757 (1.788–4.249)	<0.001	0.863 (0.504–1.477)	0.590
Age >65 yr	1.519 (0.904–2.552)	0.115			1.037 (0.679–1.582)	0.867		
Male sex	0.748 (0.449–1.246)	0.265			0.943 (0.620–1.433)	0.783		
Body mass index	0.952 (0.876–1.036)	0.254			0.961 (0.897–1.029)	0.249		
ASA PS classification								
I	1				1			
II	0.790 (0.457–1.365)	0.398			0.792 (0.491–1.279)	0.341		
III	0.682 (0.316–1.474)	0.331			0.936 (0.524–1.672)	0.823		
TNM stage		<0.001		0.455		<0.001		0.098
I	1		1		1		1	
II	2.716 (1.125–6.560)	0.026	1.949 (0.785–4.838)	0.150	3.281 (1.607–6.698)	0.001	2.205 (1.066–4.560)	0.033
III	7.012 (3.377–14.558)	<0.001	1.920 (0.489–7.549)	0.350	6.770 (3.690–12.419)	<0.001	1.544 (0.481–4.955)	0.465
IV	6.278 (1.355–29.084)	0.018	1.614 (0.257–10.150)	0.610	2.267 (0.296–17.332)	0.430	0.526 (0.055–5.052)	0.578
LN metastasis	5.057 (2.964–8.626)	<0.001	4.249 (2.467–7.318)	<0.001	4.307 (2.787–6.654)	<0.001	3.239 (1.152–9.111)	0.026
PNI+	2.894 (1.669–5.020)	<0.001	1.955 (1.091–3.503)	0.024	2.915 (1.860–4.567)	<0.001	2.358 (1.491–3.728)	<0.001
LVI+	3.142 (1.775–5.562)	<0.001	1.832 (0.995–3.376)	0.052	2.547 (1.626–3.992)	<0.001	1.291 (0.790–2.111)	0.308
Differentiation		0.010		0.416		<0.001		0.002
WD	1		1		1		1	
MD	2.937 (1.327–6.502)	0.008	1.683 (0.741–3.821)	0.213	4.731 (2.053–10.903)	<0.001	3.134 (1.344–7.305)	0.008
PD	2.682 (0.900–7.992)	0.077	1.831 (0.601–5.577)	0.288	6.747 (2.562–17.765)	<0.001	4.521 (1.696–12.051)	0.003
CA 19-9 >37 U/mL	1.755 (1.061–2.903)	0.029	1.193 (0.709–2.009)	0.506	1.630 (1.073–2.477)	0.022	1.099 (0.713–1.693)	0.668
Operation method, open	0.589 (0.268–1.295)	0.188			0.680 (0.377–1.225)	0.199		
Intraoperative transfusion	1.238 (0.628–2.441)	0.538			1.358 (0.766–2.405)	0.295		

HR, hazard ratio; CI, confidence interval; CTx, chemotherapy; ASA PS, American Society of Anesthesiologists physical status; LN, lymph node; PNI, perineural invasion; LVI, lymphovascular invasion; WD, well differentiated; MD, moderated differentiated; PD, poor differentiated.

PNI (HR, 1.955; 95% CI, 1.091–3.503; P = 0.024) as independent prognostic factors for estimating OS. Similarly, LN metastasis (HR, 3.239; 95% CI, 1.152–9.111; P = 0.026), PNI (HR, 2.358; 95% CI, 1.491–3.728; P < 0.001), and differentiation (P = 0.002) were determined to be independent prognostic factors affecting DFS. However, PACT did not have a significant impact on the long-term oncologic outcomes of resected AoVCa (Table 4). In the univariate analysis, adjuvant chemotherapy was associated with an increased hazard ratio (HR > 1). However, after adjusting for confounding variables in the multivariate model, the HR direction changed, suggesting that the observed univariate effect was confounded by factors such as TNM stage, LVI, and tumor differentiation.

Oncologic impact of postoperative adjuvant chemotherapy in resected ampulla of Vater cancer according to subgroup analysis

It was also found that PACT did not provide long-term oncologic benefit even in resected AoVCa patients with independent poor prognostic factors, such as LN metastasis, TNM stage, PNI, LVI, differentiation, and CA 19-9 level (Fig. 3). Paradoxically, the adverse oncologic impact of PACT was noted in resected AoVCa with favorable independent prognostic factors. Patients with TNM stage I who received PACT showed inferior OS (HR, 4.988; P = 0.047) and DFS (HR, 7.574; P = 0.001). Similarly, PACT impaired OS (HR, 3.118; P = 0.024) and DFS (HR, 4.119; P < 0.001) in patients without LVI. Patients with CA 19-9 <37 U/mL who were treated with PACT had significantly worse OS (HR, 4.266; P < 0.001) and DFS (HR, 3.636; P < 0.001). In addition, DFS was worse in the group that received PACT in patients without PNI (HR, 2.664; P = 0.010) and patients who had WD tumors (HR, 6.094; P = 0.037). And while patients without LN metastases had a non-significant, tendency for worse DFS in the group that received PACT (HR, 1.498; 95% CI, 0.945–4.019; P = 0.071), there was no difference in OS.

DISCUSSION

The current study presents an in-depth analysis of the long-term oncologic benefits of PACT in patients who underwent resection for AoVCa. Our results indicate that PACT does not significantly enhance long-term survival outcomes, suggesting a need for reassessment of its role in the management of resected AoVCa.

Despite its rarity, AoVCa poses significant clinical challenges due to high recurrence rates, particularly in advanced stages

A

Subgroup	HR (95% CI)	P-value
All patients	2.475 (1.479–4.141)	<0.001
LN metastasis		
LN−	1.517 (0.588–3.911)	0.388
LN+	0.625 (0.296–1.319)	0.217
TNM stage		
I	4.988 (1.019–24.410)	0.047
II	0.499 (0.138–1.802)	0.289
III	0.674 (0.320–1.423)	0.301
PNI		
PNI−	1.380 (0.535–3.562)	0.505
PNI+	2.641 (1.371–5.090)	0.004
LVI		
LVI−	3.118 (1.158–8.395)	0.024
LVI+	1.721 (0.939–3.152)	0.079
Differentiation		
WD	2.097 (0.469–9.372)	0.332
MD	2.479 (1.379–4.457)	0.002
PD	1.499 (0.274–8.197)	0.641
CA 19-9 (U/mL)		
CA 19-9 ≥ 37	1.256 (0.624–2.528)	0.523
CA 19-9 < 37	4.266 (1.980–9.193)	<0.001

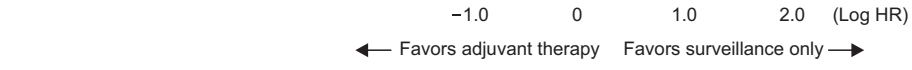

Fig. 3. Forest plot of subgroup analysis of overall survival and disease-free survival. (A) Overall survival. (B) Disease-free survival. HR, hazard ratio; CI, confidence interval; LN, lymph node; PNI, perineural invasion; LVI, lymphovascular invasion; WD, well differentiated; MD, moderated differentiated; PD, poor differentiated.

B

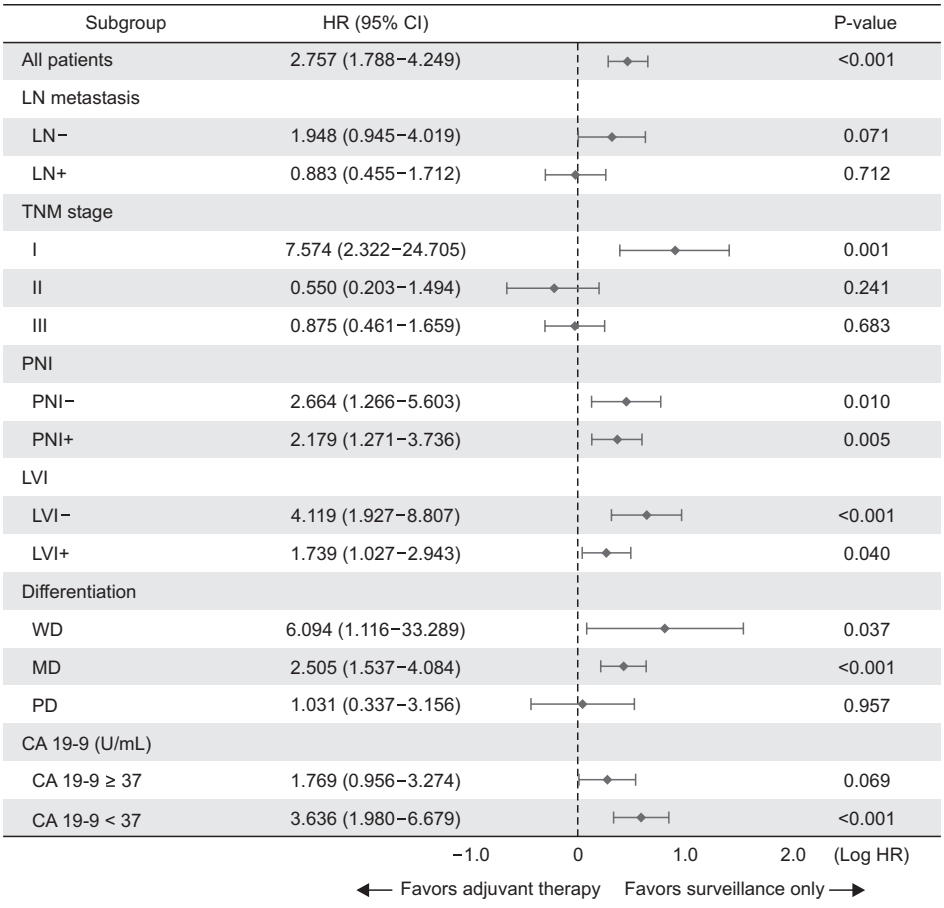

Fig. 3. Continued.

with LN involvement [1,2,4,6]. Historically, treatment approaches have been heavily influenced by established protocols for similar malignancies, such as pancreatic cancer [8]. Adjuvant chemotherapy in patients with AoVCa is an ongoing topic of debate, with studies providing conflicting results regarding its efficacy. A recently published meta-analysis found no significant difference in OS or recurrence-free survival between patients who received adjuvant chemotherapy and those who did not in the overall pooled data [17]. However, a subgroup analysis of this study suggested that AoVCa patients with nodal metastasis may benefit from PACT as they had favorable outcomes. This is supported by other studies that have shown better outcomes with PACT in patients with nodal metastasis [18]. Other studies have also suggested a potential, albeit limited, benefit for PACT but emphasized that stronger evidence is needed before this can be universally claimed [6,9].

Our retrospective study involving 306 patients who underwent pancreaticoduodenectomy reveals several critical insights. To analyze independent prognostic factors affecting long-term survival of resected AoVCa, the following factors were included in the analysis: adjuvant chemotherapy administration, age, sex, ASA PS classification, surgical method, TNM stage, presence of LN metastasis, PNI, LVI, cancer differentiation, serum CA 19-9 level, intraoperative transfusion, and BMI. The impact of factors such as LN metastasis, PNI, and LVI on OS and DFS in resected AoVCa has been demonstrated in previous studies [19], and in this study, multivariate analysis confirmed that they had a significant impact on the prognosis of resected AoVCa. However, PACT did not affect prognosis. The PSM analysis was employed to mitigate selection bias, ensuring a balanced comparison between patients who received PACT and those who did not. Despite the rigorous methodology, the results did not demonstrate significant differences in OS or DFS between the 2 groups post-PSM.

Interestingly, our subgroup analysis revealed paradoxical results, where PACT appeared to adversely affect survival in patients with favorable prognostic factors. This finding necessitates a cautious approach to administering adjuvant chemotherapy, particularly in early-stage AoVCa patients with low-risk profiles. Considering that cancer survival is generally determined by the patient's immunity and the biological behavior of the tumor itself [20,21], the paradoxical effect of chemotherapy in AoVCa patients with favorable factors may be due to the fact that chemotherapy is not only ineffective but

also decreases the patient's immune function. Therefore, the strategy of PACT in patients with resected AoVCa with favorable survival factors might be reevaluated, focusing on enhancing patients' immune function and developing more potent and effective anticancer drugs for aggressive AoVCa.

Chemotherapy can significantly weaken the immune system, which can have a negative impact on cancer prognosis. Studies have shown that chemotherapy not only kills cancer cells but also fast-growing healthy cells, including bone marrow cells responsible for producing white blood cells [20]. Given these issues, boosting a patient's immune function before and during chemotherapy can help mitigate these side effects and improve treatment outcomes. In fact, one study reported that boosting immune function while undergoing chemotherapy was associated with a favorable cancer outcome [22]. Immunotherapies that harness and enhance the body's immune response to cancer include a number of specific drugs (e.g., omega-3 fatty acids, antioxidants, vitamins, red ginseng, etc.), immune checkpoint inhibitors, cancer vaccines, and adoptive cell transplants [23-25]. These treatments have shown promise for a variety of cancers by improving the immune system's ability to fight cancer cells. In patients with AoVCa, too, especially those with favorable factors, implementing these immune-boosting strategies may help patients better tolerate treatment and improve their overall prognosis.

Recent research has emphasized the importance of precision medicine, which is tailored to specific patient groups [26]. Precision medicine aims to provide optimal care by taking into account an individual patient's genetic, molecular, environmental, and lifestyle factors. Genomic and biomarker-based research is essential to implementing this precision medicine approach. Genomic analysis plays an important role in developing tailored, personalized therapies for cancer. For example, targeted therapies are being developed based on genes such as *KRAS*, *CDKN2A*, *TP53*, and *SMAD4*, which are mutated genes found in pancreatic ductal adenocarcinoma [27]. Similarly, AoVCa can have pathogenic germline mutations in genes such as *BRCA2*, *ATM*, *RAD50*, and *MUTYH*, and targeted therapies for these genes are also conceivable [28].

In addition, AoVCa can be histologically divided into the intestinal type and pancreatobiliary type. Patients with the intestinal type had the longest survival times, while those with the pancreatobiliary type had shorter survival times [1]. The response to chemotherapy varies significantly between these subtypes. Recent studies indicate a significant survival benefit from adjuvant chemotherapy in pancreatobiliary-type patients, but not in those with the intestinal type, likely due to the differing efficacy of chemotherapy regimens [3,29]. However, the data on chemotherapy responses are controversial, primarily due to the lack of large-scale prospective studies. Some retrospective studies suggest no significant survival benefit from adjuvant chemotherapy for either subtype, highlighting the need for more tailored and prospective research [30]. These findings underscore the necessity for individualized treatment plans and further investigation to improve outcomes for all AoVCa patients.

The retrospective nature and single institution setting of the study are notable limitations, potentially affecting the generalizability of the findings. Additionally, the inclusion of patients who discontinued chemotherapy prematurely (n = 10) in the PACT (+) group, based on the intention-to-treat principle, introduces variability in the actual treatment exposure. This may have influenced the results, as patients who discontinued treatment early may have experienced different oncologic outcomes compared to those who completed the planned chemotherapy cycles. Furthermore, variability in chemotherapy regimens and treatment duration across patient cohorts may have influenced survival outcomes. While 5-FU–based chemotherapy was historically predominant at our institution, treatment patterns evolved to include gemcitabine-based regimens for pancreatobiliary-type tumors. However, the extended study period and absence of a standardized institutional protocol led to individualized regimen selection, limiting the ability to assess the precise oncologic benefit of specific treatments (Supplementary Table 2).

Among the total cohort, histological subtypes were identified in 123 patients (intestinal type, 62; pancreatobiliary type, 61). Subgroup analysis showed no significant differences in OS or DFS between the PACT (+) and PACT (–) groups for the intestinal type ($P > 0.05$, data not shown). However, for the pancreatobiliary type, both OS and DFS were significantly worse in the PACT (+) group compared to the PACT (–) group ($P < 0.001$), consistent with the findings of the overall cohort. Nonetheless, histological subtype data were often unavailable in earlier pathology reports, preventing consistent regimen differentiation based on subtype across the entire study period. Additionally, the relatively small sample size of each subgroup limits the statistical power of this analysis, and caution is needed in interpreting these results. While we conducted this preliminary analysis, this study primarily focused on the overall oncologic impact of adjuvant chemotherapy. Future prospective studies with larger, multi-institutional cohorts and standardized treatment protocols are necessary to better assess the oncologic benefit of chemotherapy according to histological subtype and to refine optimal treatment strategies for AoVCa.

In conclusion, the current study underscores the complex and nuanced role of PACT in resected AoVCa. The lack of clear survival benefits from PACT calls for a reevaluation of existing treatment guidelines and emphasizes the need for tailored therapeutic approaches. The development of more effective adjuvant treatments and the identification of reliable biomarkers for risk stratification remain critical to improving

outcomes for AoVCa patients. Continued research and collaborative efforts are imperative to advance the management of this challenging malignancy.

SUPPLEMENTARY MATERIALS

Supplementary Tables 1 and 2 can be found via https://doi.org/10.4174/astr.2025.109.1.15.

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