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ORIGINAL ARTICLE

Retrospective Study

Survival benefit of concurrent chemoradiotherapy for advanced ampulla of Vater cancer

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Abstract

BACKGROUND

Currently, there is no standard adjuvant therapy for patients with resected ampulla of Vater (AoV) cancer.

AIM

To evaluate the effectiveness of adjuvant concurrent chemoradiotherapy (CCRT) in patients with advanced AoV cancer who underwent curative resection.

METHODS

This single-centered, retrospective study included 29 patients with advanced AoV cancer who underwent pancreaticoduodenectomy between 2006 and 2018. The impact of CCRT on advanced AoV cancer was analyzed.

RESULTS

The 1-, 3-, and 5-yr recurrence-free survival (RFS) rates for patients with advanced AoV cancer were 82.8%, 48.3%, and 40.8%, respectively, and the overall survival (OS) rates were 89.7%, 62.1%, and 51.7%, respectively. Lymphovas -cular invasion was found to be a significant risk factor for RFS and OS in patients with advanced AoV cancer in the univariate analysis, whereas T stage and lymph node metastasis were significantly associated with OS in the multivariate analysis. Compared to the patients who did not receive adjuvant CCRT, those who received adjuvant CCRT did not show statistically significant improvements in the RFS and OS, although they had a significantly lower average age and significantly higher platelet-to-lymphocyte ratio.

CONCLUSION

Adjuvant CCRT did not improve survival outcomes in patients with advanced AoV cancer. These findings contribute to existing knowledge on the effectiveness of CCRT in this patient population and provide important insights for clinical decision-making.

Key Words: Advanced ampulla of Vater cancer; Adjuvant concurrent chemoradiotherapy; Recurrence; Survival; Vater cancer

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Core Tip: We examined the potential survival benefits of adjuvant concurrent chemoradiotherapy (CCRT). Our findings indicated that adjuvant CCRT may not provide any survival advantage to patients with ampulla of Vater (AoV) cancer who had T3/T4 or lymph node-positive tumors. Therefore, the use of adjuvant CCRT as a standard approach in the treatment of advanced AoV cancer patients should be reconsidered.

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INTRODUCTION

Although ampulla of Vater (AoV) cancer has a relatively good prognosis among periampullary cancers, it still has a 5-yr survival rate of only 37%-51% after resection[1,2]. Advanced stage and lymph node involvement were identified as significant prognostic factors[3,4]. Thus, adjuvant treatment is required for patients at advanced stages with a high risk of recurrence. However, previous studies have suggested that radiotherapy alone has no survival benefit[5,6]. Further, Miura *et al*[6] reported minor benefits of radiotherapy in patients with lymph node (LN) metastases. Consequently, the most commonly used adjuvant treatment is chemotherapy or concurrent chemoradiotherapy (CCRT).

Several trials have demonstrated that adjuvant chemotherapy is associated with improved survival compared with observation alone, with a benefit greater in patients with advanced T3/T4 lesions or LN metastases[4,7,8]. However, some studies have reported contrasting opinions[9,10]. Despite the controversy surrounding the benefits of adjuvant chemotherapy after resection for AoV cancer and the lack of consensus guidelines, adjuvant chemotherapy tends to be used clinically[11]. Currently, the combination of adjuvant chemotherapy and radiation is the standard approach. However, evidence supporting the use of CCRT in AoV cancer is limited, and further research is needed to determine the best treatment approach. Therefore, this study aimed to retrospectively evaluate the efficacy of adjuvant CCRT in patients with advanced AoV carcinoma who underwent curative-intent resection.

MATERIALS AND METHODS

Patients

A total of 92 patients with AoV cancer, confirmed by histological examination, underwent pancreaticoduodenectomy between January 2006 and December 2018 at a single tertiary hospital by a single surgeon. Of these, 11 patients with advanced AoV cancer (T3/T4 or LN metastases) who underwent adjuvant CCRT, and 18 patients who did not receive adjuvant therapy and who did not meet the following exclusion criteria were included: exclusive adjuvant chemotherapy or radiotherapy, treatment-associated mortality, significant decline in post-surgery physical strength, variants of adenocarcinoma, neuroendocrine carcinoma, regional LN metastasis beyond LN, total pancreatectomy, incomplete medical records, and cause of death not recurrence but a different medical cause. The clinicopathologic characteristics of the patients are showed in Supplementary Table 1. TNM staging was performed according to the 8th edition of the American Joint Committee Staging System. Demographic, adjuvant treatment, and survival outcome data were retrospectively obtained from the medical records. This study was approved by the Institutional Review Board of Clinical Trial Center in our hospital (IRB No. 2303-007-124).

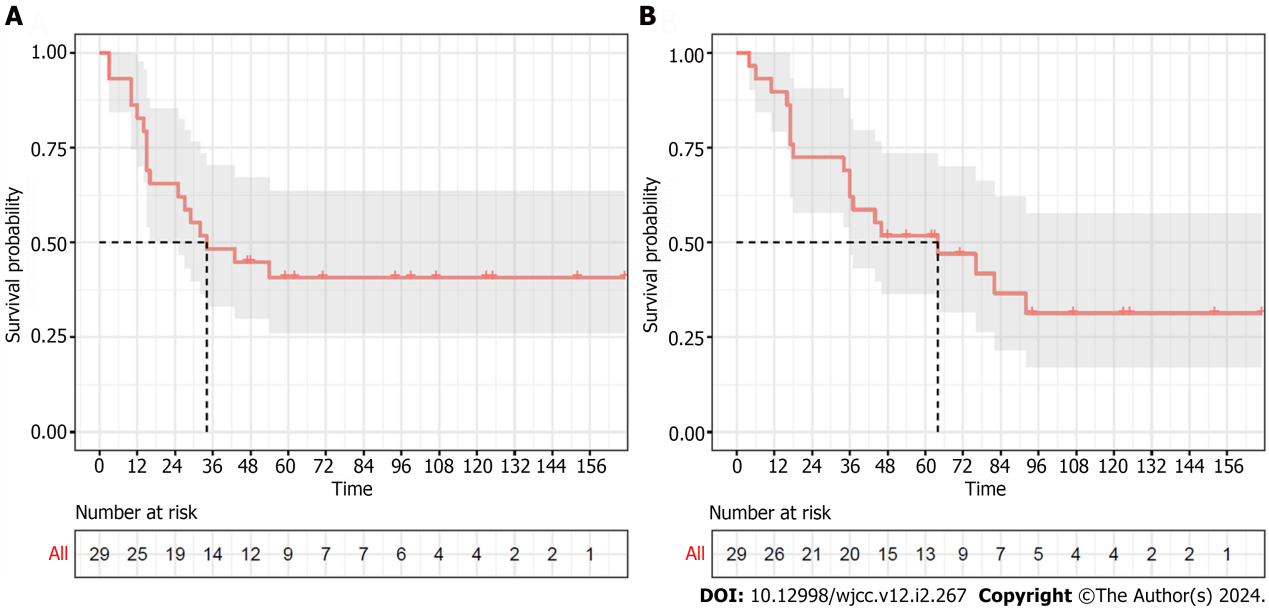

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Figure 1 Kaplan-Meier curves of 29 AoV cancer patients. A: Recurrence-free survival; B: Overall survival. The dashed line indicates the median survival time.

Adjuvant CCRT

Adjuvant CCRT was recommended for patients with LN metastasis regardless of the T stage and was administered 4-8 wk after surgery according to the patient's voluntary decision. The chemotherapy regimen consisted of six cycles of fluoropyridine- or gemcitabine-based chemotherapy [5-FU plus leucovorin (FLv) or gemcitabine plus cisplatin (GP)] for 6 cycles, with a radiation dose of 50.4 Gy. One patient died of gastric infarction and was excluded from the study.

Follow-up

Patients underwent tumor marker (CA19-9 and CEA) testing every 3 mo, with additional imaging tests (abdominal and chest computed tomography) performed if abnormalities were detected. If there were no abnormalities, imaging tests were performed every 6 mo. Palliative treatment was administered to patients who experienced recurrence. One patient died from complications due to radiofrequency ablation and was excluded from the study.

Statistical analysis

The clinical and pathological characteristics of the CCRT and non-CCRT groups were compared and analyzed using the Mann-Whitney *U* and chi-square tests for continuous and categorical variables, respectively. Univariate and multivariate analyses were performed using Cox proportional hazard models. Statistical analyses were performed using the R software (version 4.2.1). The R packages "moonbook," "survminer" and "survival," were used. Statistical significance was set at $P < 0.05$. The statistical methods of this study were reviewed by Kim JM from Biomedical Research Institute, Pusan National University Hospital.

RESULTS

The 1-, 3-, and 5-yr recurrence-free survival (RFS) rates for advanced AoV cancer were 82.8%, 48.3%, and 40.8%, respectively, and the overall survival (OS) rates were 89.7%, 62.1%, and 51.7%, respectively. The median RFS and OS durations were 34 and 64 mo, respectively (Figure 1). Tables 1 and 2 show the results of the univariate and multivariate analyses for RFS and OS in patients with advanced AoV cancer. Patients with positive lymphovascular invasion (LVI) had a significantly higher risk of RFS [hazard ratio (HR): 2.971, confidence interval (CI): 1.123-7.861, $P = 0.028$) and OS (HR: 3.35, CI: 1.226-9.153, $P = 0.018$, respectively). However, other factors such as age; tumor size; T stage; LN metastasis; perineural invasion (PNI); differentiation, and CCRT; and biochemical markers such as, bilirubin, CEA, CA19.9, CRP, albumin, platelet-to-lymphocyte ratio (PLR), and neutrophil-to-lymphocyte ratio (NLR), were not significantly associated with RFS or OS in the univariate analysis. In the multivariate analysis, while LVI did not have a statistically significant impact on RFS or OS, T stage and LN metastasis were significant prognostic factors for OS (HR: 3.015, CI: 0.989-9.095, $P = 0.052$; HR: 3.702, CI: 1.116-12.283, $P = 0.032$, respectively).

Patients with advanced AoV cancer were divided into two groups according to whether they received CCRT: patients who received adjuvant CCRT (CCRT, $n = 11$) and those who did not (non-CCRT, $n = 18$). The clinical features were then compared between these two groups. As shown in Figure 2A, the 3-yr and 5-yr RFS rates were 55.6% and 50.0%, respectively, in the non-CCRT group, and 36.4% and 27.3%, respectively, in the CCRT group. The median RFS in the non-CCRT and CCRT groups was 43 and 32 mo, respectively. The 3-yr and 5-yr OS rates were 55.6% and 55.6% in the non-

Table 1 Univariate and multivariate analyses for recurrence-free survival

	Univariate		Multivariate	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Sex (male)	1.988 (0.568-6.955)	0.282		
Age	0.976 (0.939-1.014)	0.215		
Size	0.816 (0.530-1.255)	0.354		
T stage	1.808 (0.485-6.743)	0.378	1.952 (0.499-7.628)	0.326
LN metastasis (positive)	2.026 (0.747-5.498)	0.166	1.848 (0.522-6.541)	0.341
LVI (positive)	2.971 (1.123-7.861)	0.028[a]	2.002 (0.589-6.806)	0.266
PNI (positive)	1.026 (0.395-2.663)	0.958		
Differentiation (poor)	1.366 (0.504-3.706)	0.540		
CCRT	1.543 (0.594-4.006)	0.373		
Bilirubin	0.935 (0.864-1.01)	0.089		
CEA (≥ 5 ng/mL)	0.429 (0.056-3.288)	0.416		
CA19.9 (≥ 39 U/L)	0.635 (0.225-1.796)	0.392		
CRP (≥ 0.5 mg/mL)	1.139 (0.367-3.536)	0.822		
Albumin (< 3.3 or > 5.2 mg/dL)	0.903 (0.119-6.831)	0.922		
PLR	1.001 (0.997-1.005)	0.661		
NLR	0.999 (0.871-1.144)	0.983		

[a]$P < 0.05$.

LN: Lymph node; LVI: Lymphovascular invasion; PNI: Perineural invasion; CCRT: Concurrent chemoradiotherapy; CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9; CRP: C-reactive protein; PLR: Platelet-to-lymphocyte ratio; NLR: Neutrophil-to-lymphocyte ratio; HR: Hazard ratio; CI: Confidence interval.

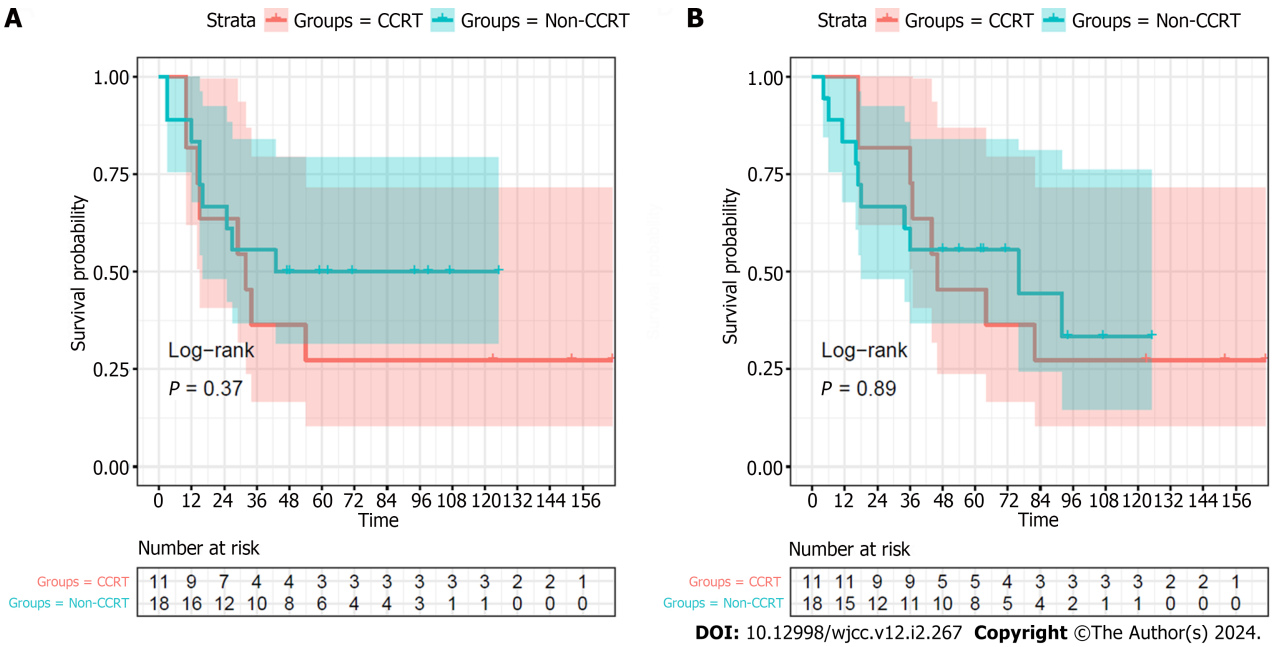

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Figure 2 Kaplan-Meier curves between concurrent chemoradiotherapy (*n* = 11) and non-concurrent chemoradiotherapy groups (*n* = 18). A: Recurrence-free survival; B: Overall survival. CCRT: Concurrent chemoradiotherapy.

Table 2 Univariate and multivariate analyses for overall survival

	Univariate		Multivariate	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Sex (male)	1.752 (0.5667-5.416)	0.33		
Age	0.992 (0.9545-1.031)	0.693		
Size	0.924 (0.6395-1.334)	0.672		
T stage	2.102 (0.6376-6.927)	0.222	3.015 (0.989-9.159)	0.052
LN metastasis (positive)	2.596 (0.967-6.968)	0.058	3.702 (1.116-12.283)	0.032[a]
LVI (positive)	3.35 (1.226-9.153)	0.018[a]	1.806 (0.549-5.941)	0.33
PNI (positive)	1.344 (0.5331-3.39)	0.531		
Differentiation (poor)	1.398 (0.5406-3.617)	0.489		
CCRT	1.073 (0.423-2.724)	0.881		
Bilirubin	0.966 (0.8975-1.04)	0.359		
CEA (≥ 5 ng/mL)	0.423 (0.0555-3.226)	0.407		
CA19.9 (≥ 39 U/L)	1.372 (0.475-3.963)	0.559		
CRP (≥ 0.5 mg/mL)	3.503 (0.7991-15.35)	0.096		
Albumin (< 3.3 or > 5.2 mg/dL)	3.088 (0.6807-14.01)	0.144		
PLR	1.003 (0.9991-1.007)	0.128		
NLR	1.061 (0.9529-1.18)	0.282		

[a]$P < 0.05$.

LN: Lymph node; LVI: Lymphovascular invasion; PNI: Perineural invasion; CCRT: Concurrent chemoradiotherapy; CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9; CRP: C-reactive protein; PLR: Platelet-to-lymphocyte ratio; NLR: Neutrophil-to-lymphocyte ratio; HR: Hazard ratio; CI: Confidence interval.

CCRT group and 72.7% and 45.5% in the CCRT group, respectively. The median OS durations of the non-CCRT and CCRT groups were 76 and 46 mo, respectively (Figure 2B). The patients who had received CCRT showed worse RFS and OS than those who did not receive CCRT, but the difference was not statistically significant ($P = 0.37$, $P = 0.89$, respectively). Table 3 shows the patient characteristic in the CCRT and non-CCRT groups. The average of age was significantly lower in the CCRT group than in the non-CCRT group (59.0 ± 8.3 *vs* 71.22 ± 12.17, $P = 0.007$). Additionally, the PLR was significantly higher in the CCRT group ($P = 0.044$). However, there were no significant differences in sex, tumor size, LN metastasis, LVI, PNI, CEA, CA19.9, CRP, albumin, NLR, American Society of Anesthesiologists grade, or transfusion between the two groups.

DISCUSSION

After tumor resection, the prognosis of patients with AoV cancer is generally better than that of patients with pancreatic cancer; however, poor survival rates have been observed in patients with advanced-stage cancer. Adjuvant treatment is often used in these cases, and this study evaluated the effectiveness of adjuvant CCRT in patients with AoV cancer with poor prognostic factors, such as high T stage or LN metastases. However, our findings suggest that adjuvant CCRT may not provide any survival benefits in patients with advanced AoV cancer.

While some studies suggest that adjuvant chemotherapy (ACT) provides a survival benefit for patients with advanced AoV cancer, studies such as the ESPAC-3[7] and Al Abbas *et al*[12] have some limitations, including heterogeneity in the study population and variations in the chemotherapy drugs used. To date, most studies have used 5-FU- or gemcitabine-based chemotherapy as ACT. In this study, FLv or GP regimens were used, but no difference in the survival benefit was observed. Some studies have compared the efficacy of 5-FU- and gemcitabine-based regimens. In a subgroup analysis of the ESPAC-3 study population, the patients who received gemcitabine showed a survival benefit, whereas no benefit was observed among those who received 5-FU with folinic acid[7]. Conversely, in a study by Al Abbas *et al*[12], 5-FU led to better survival rates than gemcitabine in patients with advanced-stage disease. Therefore, an optimal treatment regimen for patients with AoV cancer is yet to be established.

Recent studies have evaluated the different effects of ACT regimens on survival outcomes based on histological subtypes of AoV cancer[9,12,13]. While 5-FU- and gemcitabine-based regimens may be useful for certain histological subtypes, Al Abbas *et al*[12] reported that 5-FU-based ACT improved survival regardless of the subtype. However, Ecker

Table 3 Baseline characteristics between the ampulla of Vater cancer patients with and without concurrent chemoradiotherapy

Characteristics	CCRT (*n* = 11)	Non-CCRT (*n* = 18)	Total (*n* = 29)	*P* value
Sex (%)				0.647
Male	9 (81.8)	12 (66.7)	21 (72.4)	
Female	2 (18.2)	6 (33.3)	8 (27.6)	
Age, median (IQR)	60 (52; 63)	75.5 (63.3; 79.5)	65 (60; 76)	0.007[b]
Size, median (IQR)	2.9 (1.9; 3.8)	2.7 (2.2; 3.0)	2.7 (2.1; 3.2)	0.928
T stage (%)				0.200
2	3 (27.3)	2 (11.1)	5 (17.2)	
3	7 (63.6)	16 (88.9)	23 (79.3)	
4	1 (9.1)	0 (0.0)	1 (3.4)	
LN metastasis (%)				1.000
Negative	5 (45.5)	9 (50.0)	14 (48.3)	
Positive	6 (54.5)	9 (50.0)	15 (51.7)	
LVI (%)				1.000
Negative	7 (63.6)	12 (66.7)	19 (65.5)	
Positive	4 (36.4)	6 (33.3)	10 (34.5)	
PNI (%)				0.661
Negative	5 (45.5)	11 (61.1)	16 (55.2)	
Positive	6 (54.5)	7 (38.9)	13 (44.8)	
Differentiation (%)				0.076
Well-to-moderate	4 (36.4)	14 (77.8)	18 (62.1)	
Poor	6 (54.5)	3 (16.7)	9 (31.0)	
Unknown	1 (9.1)	1 (5.6)	2 (6.9)	
Bilirubin	4.6 (1.3; 11.9)	2.8 (0.5; 13.7)	4.1 (0.9; 12.9)	0.515
CEA (%)				1.000
< 5 ng/mL	8 (88.9)	14 (87.5)	22 (88.0)	
≥ 5 ng/mL	1 (11.1)	2 (12.5)	3 (12.0)	
CA19.9 (%)				0.866
< 39 U/L	3 (30.0)	7 (41.2)	10 (37.0)	
≥ 39 U/L	7 (70.0)	10 (58.8)	17 (63.0)	
CRP (%)				0.297
< 0.5 mg/dL	1 (11.1)	7 (38.9)	8 (29.6)	
≥ 0.5 mg/dL	8 (88.9)	11 (61.1)	19 (70.4)	
Albumin (%)				1.000
3.3-5.2 g/dL	10 (90.9)	17 (94.4)	27 (93.1)	
< 3.3 or > 5.2 g/dL	1 (9.1)	1 (5.6)	2 (6.9)	
PLR, median (IQR)	277.0 (215.1; 291.7)	159.8 (124.1; 237.9)	202.0 (133.9; 287.5)	0.044[a]
NLR, median (IQR)	4.1 (3.3; 4.5)	2.7 (2.2; 4.7)	3.6 (2.3; 4.6)	0.334
ASA				0.105
I	3 (27.3)	0 (0.0)	3 (10.3)	
II	6 (54.5)	11 (61.1)	17 (58.6)	
III	2 (18.2)	6 (33.3)	8 (27.6)	

IV	0 (0.0)	1 (5.6)	1 (3.4)

[a]$P < 0.05$.
[b]$P < 0.01$.
LN: Lymph node; LVI: Lymphovascular invasion; PNI: Perineural invasion; CCRT: Concurrent chemoradiotherapy; CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9; CRP: C-reactive protein; PLR: Platelet-to-lymphocyte ratio; NLR: Neutrophil-to-lymphocyte ratio; ASA: American Society of Anesthesiologists.

et al[9] found no survival benefit of ACT regardless of the histological type or advanced stage. The lack of an association between chemotherapeutic agents and histological type presents a challenge in evaluating the efficacy of ACT. Although the benefits of different chemotherapy regimens according to histologic type have been suggested, the small number of patients in each subset and poor reproducibility of histologic typing are considerable limitations. In this study, most of the patients had not undergone phenotypic classification when receiving adjuvant therapy; therefore, treatment decisions were not based on histological subtypes.

The effectiveness of CCRT in patients with advanced-stage AoV cancer is controversial, despite some studies demonstrating its benefits. The Mayo Clinic reported improved disease relapse and survival rates following CCRT[4]. In addition, Nassour *et al*[11] showed that CCRT was associated with improved survival compared with observation only. In contrast, studies by Ecker *et al*[9] and Kim *et al*[10,14] found no significant differences in survival or recurrence rates, regardless of the addition of radiotherapy. Therefore, the use of CCRT in clinical practice should be carefully considered, as this study highlights that CCRT does not have survival benefits for patients with advanced AoV cancer.

Our study found that age and PLR were correlated with the administration of adjuvant CCRT, with older patients and those with a low PLR being less likely to receive this treatment. These findings are consistent with those reported by the Mayo Clinic regarding age. However, these factors should not be used as the criteria for selecting patients for CCRT, as our study results did not show a significant difference in the survival outcomes between the CCRT and non-CCRT groups.

This study had limitations. First, this was a single-center, retrospective, non-randomized study with a small sample size, which should be taken into consideration when interpreting the results. The limited sample size is attributed to the specificity of the disease, and particularly in advanced stages, the target group inevitably diminishes. Therefore, further confirmation of the findings is warranted through multi-institutional research. Second, the chemotherapy regimens used were not standardized and the histological type was not evaluated. Third, a large proportion of the patient population received palliative treatment, which may have influenced the OS outcomes.

CONCLUSION

In conclusion, our study provides some evidence that CCRT may not provide a survival benefit to patients with advanced AoV cancer. Therefore, further research is required to address the limitations of the current study and provide definitive answers regarding the role of CCRT in the treatment of advanced AoV cancer.

ARTICLE HIGHLIGHTS

Research background

Although ampulla of Vater (AoV) cancer has a relatively favorable prognosis among periampullary cancers, the 5-yr survival rate after resection remains poor. The benefits of adjuvant treatment for AoV cancer is still controversial, leading to the prevalent use of chemotherapy or concurrent chemoradiotherapy (CCRT).

Research motivation

Despite clinical use of adjuvant treatment, there are no consensus guidelines for patients with AoV carcinoma. This study aims to contribute valuable insights into the survival benefits of CCRT in patients with advanced AoV cancer, providing evidence to guide treatment decisions.

Research objectives

The study aims to retrospectively assess the efficacy of adjuvant CCRT in patients with advanced AoV carcinoma who underwent curative resection.

Research methods

Eleven patients with advanced AoV cancer [T3/T4 or lymph node (LN) metastases] who underwent adjuvant CCRT, and 18 patients who did not receive adjuvant therapy were retrospectively reviewed.

Research results

The study found 1-, 3-, and 5-yr RFS rates of 82.8%, 48.3%, and 40.8%, and OS rates of 89.7%, 62.1%, and 51.7%, respectively, for advanced AoV cancer. T stage and LN metastasis were significantly associated with OS in the multivariate analysis. However, CCRT did not show a statistically significant survival advantage.

Research conclusions

This study suggests that adjuvant CCRT may not provide survival benefits for patients with advanced AoV cancer.

Research perspectives

Additional multi-institutional studies with larger sample sizes, standardized regimens, and histological evaluations are recommended to identify the optimal options for patients with advanced AoV cancer.

FOOTNOTES

Author contributions: Seo HI contributed design of the study; Kwon CH contributed analysis of data; Seo HI and Kwon CH contributed interpretation of data and drafting the article; Kim DU and Han SY contributed review the manuscript; Kim S, Lee NK, Hong SB, Ahn JH, Par YM and Noh BG contributed acquisition of data; all authors have read and approved the final manuscript.

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Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: The authors have no financial relationships to disclose.

Data sharing statement: The data that support the findings of this study are available from the corresponding author.

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