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Original Article

Outcomes of Palliative Chemotherapy for Ampulla of Vater Adenocarcinoma: A Multicenter Cohort Study

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Background/Aims: Palliative chemotherapy (PC) is not standardized for patients with advanced ampulla of Vater adenocarcinoma (AA). This multicenter, retrospective study evaluated first-line PC outcomes in patients with AA.

Methods: Patients diagnosed with AA between January 2010 and December 2020 who underwent PC were enrolled from 10 institutions. Overall survival (OS) and progression-free survival (PFS) according to the chemotherapy regimen were analyzed.

Results: Of 255 patients (mean age, 64.0±10.0 years; male, 57.6%), 14 (5.5%) had locally advanced AA and 241 (94.5%) had metastatic AA. Gemcitabine plus cisplatin (GP) was administered as first-line chemotherapy to 192 patients (75.3%), whereas capecitabine plus oxaliplatin (CAPOX) was administered to 39 patients (15.3%). The median OS of all patients was 19.8 months (95% confidence interval [CI], 17.3 to 22.3), and that of patients who received GP and CAPOX was 20.4 months (95% CI, 17.2 to 23.6) and 16.0 months (95% CI, 11.2 to 20.7), respectively. The median PFS of GP and CAPOX patients were 8.4 months (95% CI, 7.1 to 9.7) and 5.1 months (95% CI, 2.5 to 7.8), respectively. PC for AA demonstrated improved median outcomes in both OS and PFS compared to conventional bile duct cancers that included AA.

Conclusions: While previous studies have shown mixed prognostic outcomes when AA was analyzed together with other biliary tract cancers, our study unveils a distinct clinical prognosis specific to AA on a large scale with systemic anticancer therapy. These findings suggest that AA is a distinct type of tumor, different from other biliary tract cancers, and AA itself could be expected to have a favorable response to PC. **(Gut Liver 2024;18:729-736)**

Key Words: Ampulla of Vater; Biliary tract neoplasms; Chemotherapy; Survival

INTRODUCTION

Cancer of the ampulla of Vater (AoV) is a rare malignancy.[1-3] Unfortunately, approximately 50% of patients with AoV cancer are not diagnosed until they are in an advanced stage, and as such, only 40% of patients can be treated surgically.[1,4] AoV adenocarcinoma (AA) is a predominant type of AoV cancer and can be classified into

intestinal, pancreaticobiliary, and mixed histologic subtypes.[1-3] Although the 5-year survival rate is approximately 50% following curative-intent resection, the 2-year survival rate is only 5% to 10% in patients with relapse or metastasis.[5-8] Therefore, appropriate chemotherapy is the most crucial factor for prognosis in patients with recurrence following surgery or initially palliative treatment. However, due to the rarity of AA, there is currently no standard chemotherapy in use, and it is difficult to select an appropriate chemotherapy regimen due to limited data.

Most of the research on palliative treatment of AA has been performed in concurrence with biliary tract cancer or small intestine cancer research.[9-14] The ABC-02 trial was the largest clinical trial of biliary tract cancer, including AA, in which gemcitabine plus cisplatin (GP) demonstrated an increased survival benefit compared with gemcitabine monotherapy (11.7 months vs 8.7 months, $p<0.001$).[15] The GP regimen was also effective compared to gemcitabine alone in Eastern patients with biliary tract cancer (median survival, 11.2 months vs 7.7 months).[16] Gemcitabine plus oxaliplatin (GEMOX) combination therapy can also be considered as an alternative option to GP therapy, but no large-scale study has been performed so far. The GEMOX regimen has been evaluated as a control group for some combination trials or in single-arm trials.[17-21] However, like the other studies mentioned above, most of the GEMOX studies included only small AAs, making it difficult to generalize the results.

Based on the ABC-02 trial, gemcitabine-platinum doublets were adopted in the international guidelines as the treatment of choice for advanced AA, as for the other primary sites of biliary tract cancer.[15,22,23] However, the evidence from this trial that suggests that GP treatment for AA is effective is tenuous, with only 20 (4.9%) participants with AA included in the study. While several studies on AA have been conducted based on either gemcitabine-based or fluorouracil-based regimens, a regimen more effective than GP has yet to be established.[8,15,24-26]

AA shows independent histological features and clinical courses compared with pancreaticobiliary or small intestine cancer.[9,27,28] When taking into consideration its complex histologic characteristics, even if the location of the AoV is near the biliary tract and small intestine, it is clear that a large-scale, independent study is required to evaluate the efficacy of specific chemotherapy regimens for AA. To date, there has been a limited number of studies regarding the effectiveness of the most common GP regimen for AA compared with other regimens. This study therefore aimed to evaluate the overall outcomes of palliative chemotherapy (PC) for AA in a large, multicenter, retrospective cohort.

MATERIALS AND METHODS

1. Study design and patients

The Korean Society of Gastrointestinal Cancer Research initially established a multicenter cohort of patients with AoV tumors in 2021. This retrospective cohort consisted of patients diagnosed with AoV tumors between January 2010 and December 2020 from nine institutions in Korea. A total of 1,607 patients with pathologically confirmed AoV tumors were included in the cohort. Patients diagnosed with the following diseases were excluded from those with AA: (1) neuroendocrine tumors (n=20); (2) adenomas (n=640); and (3) cancer types other than adenocarcinoma (n=34). A total of 913 patients with AA were identified, and patients with either of the following conditions were excluded as a means of identifying those who underwent PC for AA: patients who (1) did not receive chemotherapy (n=21) and (2) did not recur after resection (n=637). Ultimately, 255 patients who received PC for AA were included in the analysis (Fig. 1).

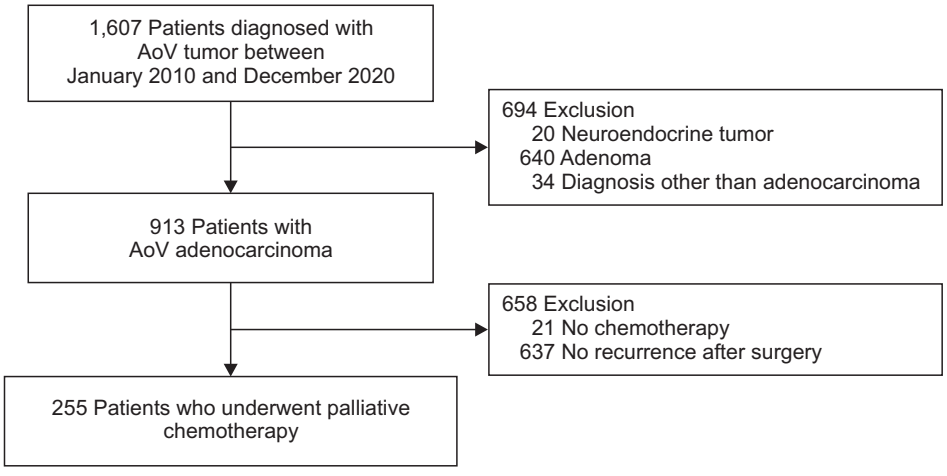

Fig. 1. Study flow. AoV, ampulla of Vater.

This study conformed with the ethical guidelines of the Declaration of Helsinki (1975), and the institutional review boards approved the studies conducted in all participating centers. The requirement for written informed consent was waived due to the retrospective nature of the study. The approval numbers from the institutional review boards of the participating hospitals are as follows: KC21RCDI0217 for Seoul St. Mary's Hospital, 2021-177-001 for Severance Hospital, 2020AN0078 for Korea University Anam Hospital, ISPAIK 2021-03-036-001 for Ilsan Paik Hospital, SMC 2021-3-202 for Samsung Medical Center, 2021-03-031 for Kyungpook National University Hospital, B-2104-689-104 for Seoul National University Bundang Hospital, DUIH 2021-04-012 for Dongguk University, and 2021-03-057 for Keimyung University.

2. Chemotherapy regimen

In GP chemotherapy, each cycle comprised cisplatin (25 mg/m^2 of body-surface area) followed by gemcitabine (1,000 mg/m^2), each administered on days 1 and 8 every 3 weeks.[15] In capecitabine plus oxaliplatin (CAPOX) chemotherapy, oxaliplatin 130 mg/m^2 was given on day 1 while capecitabine 750 mg/m^2 was given twice a day on days 1 through 14- as a 21-day cycle.[25] In Korea, the choice of regimen was left to the free decision of the clinicians, and the GP regimen has been approved for reimbursement since July 2012 and has been mainly used since then.

3. Clinical variables

We collected clinical and laboratory characteristics (age, sex, body mass index, serum carcinoembryonic antigen, carbohydrate antigen 19-9, and total bilirubin at diagnosis and follow-up period) and chemotherapy-related factors (chemotherapy indications, first-line regimen of chemotherapy, and second-line chemotherapy). Overall survival (OS) and progression-free survival (PFS) for each regimen, including GP and CAPOX, were evaluated. OS was defined as the number of days from the start date of chemotherapy until the last follow-up or death, and PFS was calculated as the number of days from the start date of chemotherapy until the confirmation of progression.

4. Tumor response

Based on the revised Response Evaluation Criteria in Solid Tumors guideline version 1.1, the overall best response to the first-line regimen of chemotherapy was divided into four categories: complete response, partial response, stable disease, and progressive disease.[29] The objective response was defined as the sum of the complete and partial responses. Disease control rate was defined as the sum of the rates of complete response, partial response, and stable disease.

5. Statistical analysis

All analyses were performed using IBM SPSS statistical software version 26 (IBM Corp., Armonk, NY, USA). The chi-square test was used to compare discrete variables, and the independent t-test was used to compare continuous variables. We performed the Kaplan-Meier analysis to compare OS and PFS.

Table 1. Baseline Characteristics

Characteristic	Total (n=255)	GP (n=192)	CAPOX (n=39)	p-value*
Age, yr	64.0±10.0	64.1±9.7	62.4±10.4	0.334
Male sex	147 (57.6)	113 (58.9)	20 (51.3)	0.383
BMI, kg/m^2	23.6±3.3	23.8±3.3	23.3±2.8	0.428
CEA, ng/mL	8.0±35.9	6.5±30.7	18.9±61.0	0.220
CA19-9, U/mL	949±5,211	1,023±5,920	962±2,178	0.949
Total bilirubin, mg/dL	5.0±5.8	4.9±5.6	4.8±6.6	0.921
Cancer status				0.526
Initial palliative				
Locally advanced	14 (5.5)	11 (5.7)	1 (2.6)	
Metastatic	45 (17.6)	34 (17.7)	10 (25.6)	
Recurrent	196 (76.9)	147 (76.6)	28 (71.8)	
First-line chemotherapy				
GP	192 (75.3)	192 (100)	0	-
CAPOX	39 (15.3)	0	39 (100)	-
Others	24 (9.4)	0	0	-
Second-line chemotherapy	122 (47.8)	91 (47.4)	16 (41.0)	0.467
Follow-up duration, mo	25.3 (16.1–38.1)	27.0 (17.3–39.1)	18.8 (13.5–32.0)	0.441

Data are presented as mean±SD, number (%), or median (interquartile range).
BMI, body mass index; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; GP, gemcitabine plus cisplatin; CAPOX, capecitabine plus oxaliplatin.
*Comparison between GP and CAPOX group.

RESULTS

1. Clinical and chemotherapy-related features of participants

A total of 255 patients who received PC for AA were analyzed. The mean age of the participants was 64.0±10.0 years, and 57.6% (147/255) were male. The initial palliative disease and recurrence following resection as chemotherapy indications were 23.1% and 76.9%, respectively. The median time to recurrence was 11.2 months (interquartile range, 6.6 to 18.9 months) in recurrent cases. With regard to first-line chemotherapy, 75.3% (192/255) of patients received GP therapy, 15.3% (39/255) received CAPOX therapy, and 9.4% (24/255) received other therapies. There was no significant difference between the GP and CAPOX groups in terms of baseline characteristics. Second-line chemotherapy was administered to 47.8% (122/255) of patients. The most common second-line regimen was CAPOX (63/122, 51.6%), followed by 5-fluorouracil/leucovorin combined with oxaliplatin or irinotecan (12/122, 9.8%). The median follow-up period was 25.3 months (interquartile range, 16.1 to 38.1 months) (Table 1).

2. Survival and disease progression

The median OS of all patients was 19.8 months (95% CI, 17.258 to 22.282), and the median PFS for first-line chemotherapy was 7.6 months (95% CI, 6.370 to 8.770) (Fig. 2). No difference in OS and PFS between the GP and

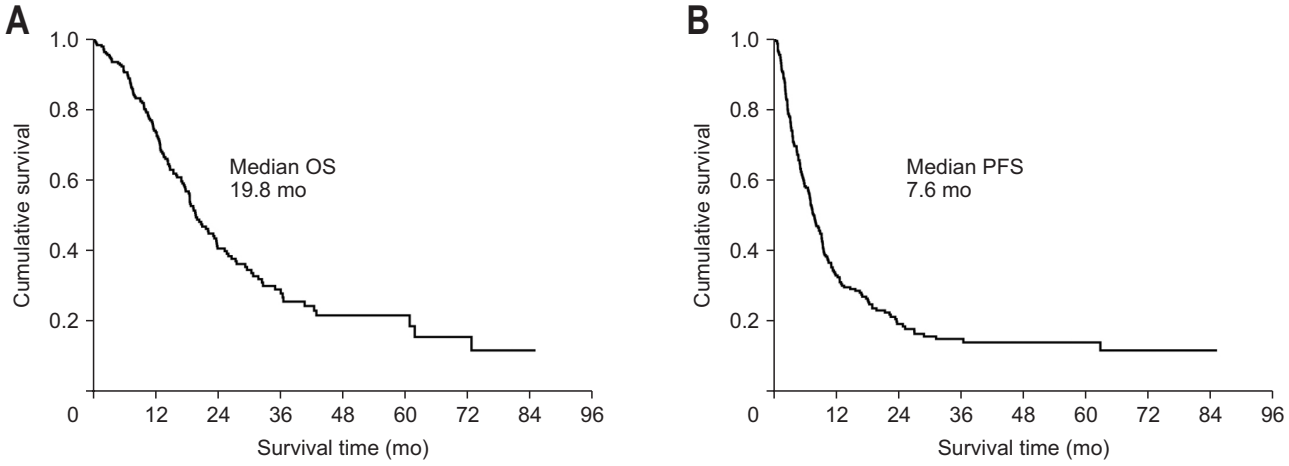

Fig. 2. Overall survival (OS) and progression-free survival (PFS) of the study group. (A) OS of the study group (median, 19.8 months; 95% confidence interval [CI], 17.258 to 22.282). (B) PFS of study group (median, 7.6 months; 95% CI, 6.370 to 8.770).

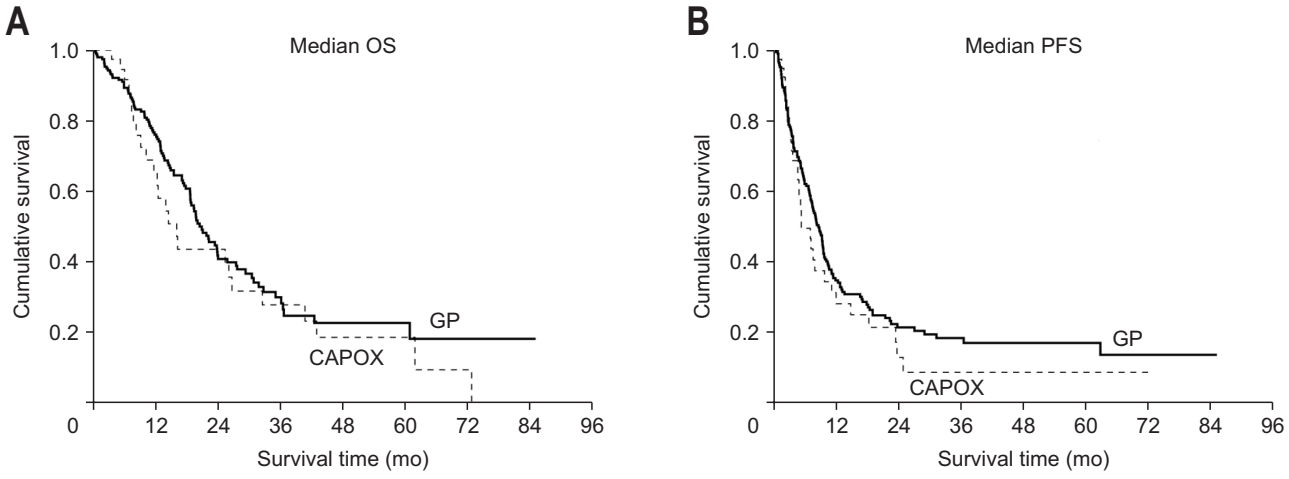

Fig. 3. Overall survival (OS) and progression-free survival (PFS), GP versus CAPOX. (A) OS of study group (GP median 20.4 months, 95% CI 17.213 to 23.587; CAPOX median 16.0 months, 95% CI 11.235 to 20.705; log rank test p=0.341). (B) PFS of the study group (GP median 8.4 months, 95% CI 7.139 to 9.721; CAPOX median 5.1 months, 95% CI 2.467 to 7.793; log rank test p=0.279). GP, gemcitabine plus cisplatin; CAPOX, capecitabine plus oxaliplatin; CI, confidence interval.

CAPOX groups (20.4 months vs 16.0 months, p=0.341; 8.4 months vs 5.1 months, p=0.279, respectively) was observed, despite the survival duration being longer in the GP group compared with the CAPOX group (Fig. 3).

3. Tumor response

The best tumor response was evaluated in 180 out of the 255 patients, allowing for exclusion of those who were lost to follow-up or were impossible to evaluate (n=75). A complete response was observed in four patients (4/180, 2.2%), all of whom received GP treatment. The objective response rate was 25.6% (46/180), and the disease control rate was 72.2% (130/180). No statistically significant differences were noted in the tumor response, objective response, and disease control rate between the GP and CAPOX groups (p=0.195, p=0.287, and p=0.287, respectively) (Table 2).

4. Comparison with previous clinical trials

Previous studies on AA included patients who were diagnosed with small bowel cancer and biliary tract cancer.[24-26] A CAPOX trial was conducted for advanced small bowel cancer, whereas the ABC-02 and FUGA-BT trials were conducted for advanced and recurrent biliary tract cancer. In contrast, our study focused only on unresectable AA. The number of patients with AA were 12 (40.0%), 20 (4.9%), and 13 (3.7%) in the CAPOX trial, ABC-02 trial, and FUGA-BT trial, respectively. Our study included 255 patients who were pathologically diagnosed with AA.[24-26]

Each study used the following regimens: (1) the CAPOX trial evaluated the CAPOX regimen only (single arm);[25] (2) the ABC-02 trial compared gemcitabine treatment and GP regimen;[15] and (3) the FUGA-BT trial compared GP regimen and gemcitabine in addition to S-1 therapy.[26] The current study evaluated various regimens including GP (75.3%), CAPOX (15.3%), and others (9.4%). The median OS observed in this study was similar to the CAPOX trial, which included patients with advanced small bowel cancer and AA, median OS of 16.0 and 20.4 months, respectively. In particular, the median OS of patients who underwent GP chemotherapy was the same as that of the CAPOX trial at 20.4 months. In addition, the median PFS of the GP regimen appeared low, as compared to those of previous trials, at 8.4 months in this study, 8.0 months in the ABC-02 trial, and 5.8 months in the FUGA-BT trial (Table 3).[15,25,26]

Table 2. Best Response According to Response Evaluation Criteria in Solid Tumors Version 1.1

	Total (n=180)	GP (n=141)	CAPOX (n=22)	p-value
Tumor response				0.195
CR	4 (2.2)	4 (2.8)	0	
PR	42 (23.3)	32 (22.7)	8 (36.4)	
SD	84 (46.7)	69 (48.9)	6 (27.3)	
PD	50 (27.8)	36 (25.5)	8 (36.4)	
Objective response	46 (25.6)	36 (25.5)	8 (36.4)	0.287
Disease control	130 (72.2)	105 (74.5)	14 (63.6)	0.287

Data are presented as number (%).
GP, gemcitabine plus cisplatin; CAPOX, capecitabine plus oxaliplatin; CR, complete response; PR, partial response; SD, stable disease; PD; progressive disease.

DISCUSSION

Biliary tract cancer has a high degree of heterogeneity in terms of clinical features and prognosis depending on location. Moreover, some types of advanced AA are similar to small intestine or pancreatic cancer and have very diverse clinical prognoses.[14,15,30,31] Therefore, research to confirm the independent characteristics of AA is urgently required. To date, existing studies on palliative treatment for AA have not included sufficient patients to allow for evaluation of the heterogeneous nature of its clinical course and to subsequently derive meaningful treatment options.[24-26] This study therefore aimed to determine independent clinical

Table 3. Comparison between the Present Study and Previous Clinical Trial Results

	Korean Society of Gastrointestinal Cancer	CAPOX[25]	ABC-02[15]	FUGA-BT[26]
Patients	Advanced and recurrent AoV cancer	Advanced small bowel and AoV cancer	Advanced and recurrent biliary tract cancer	Advanced and recurrent biliary tract cancer
Total patients	255	30	410	354
No. of AoV adenocarcinoma (%)	255 (100)	12 (40.0)	20 (4.9)	13 (3.7)
Regimen for AoV adenocarcinoma, No. (%)	GP 192 (75.3) CAPOX 39 (15.3)	CAPOX 12 (100)	Gem 11 (55.0) GP 9 (45.0)	GS 6 (46.2) GP 7 (53.8)
Median overall survival, mo	GP 20.4 CAPOX 16.0	CAPOX 20.4	Gem 8.1 GP 11.7	GS 15.1 GP 13.4
Median progression-free survival, mo	GP 8.4 CAPOX 5.1	CAPOX 11.3	Gem 5.0 GP 8.0	GS 6.8 GP 5.8

CAPOX, capecitabine plus oxaliplatin; AoV, ampulla of Vater; GP, gemcitabine plus cisplatin; Gem, gemcitabine; GS, gemcitabine plus S-1.

courses of PC for AA and propose reasonable treatment options based on a large patient cohort consisting entirely of AA.

AA is a disease with a recurrence rate of 40% to 50%.[1,4] Even after surgery, most patients with AA experience recurrence and undergo PC.[5-8] In this study, 76.9% of AA patients received PC due to recurrence. However, PC for AA resulted in longer OS and PFS compared to those of other biliary tract cancers. This suggests that PC for AA possesses distinct characteristics, different from other bile duct cancers. Further research is needed to elucidate this distinction.

Our results show that the GP regimen was most frequently used for our cohort of patients (75.3%), which indicates that most palliative treatments have potentially been administered based on the ABC-02 trial.[24,28] Notably, the median OS and PFS in the present cohort were high, as compared to the FUGA-BT and ABC-02 trials, which utilized the same regimen.[24,26] It is likely that this result could be attributed to the restriction of our study population to those patients with AA only. In addition, we included more patients who had recurrence or received second-line chemotherapy in our study, which ultimately may have contributed to an increased survival benefit.[24,26] This result therefore indicates the potential of the GP regimen as a standard treatment option for advanced or recurrent AA.

Moreover, we found that CAPOX was the second most commonly used therapy following the GP regimen. However, we were able to demonstrate that the prognosis for the CAPOX group, including OS, treatment response, and objective response, was not significantly different from that of the GP group. These results may have differed if more patients treated with CAPOX were included, as several studies have shown differences in therapeutic response as determined by a pathological subgroup.[9-14] Therefore, taking the diversity of AA into consideration, additional large-scale, comparative studies are required to provide appropriate treatment options.

Recently, it is essential to differentiate between the two primary histological subtypes, namely pancreatobiliary and intestinal in AA. The pancreatobiliary subtype is characterized by histological features that resemble pancreatic and biliary ducts. It often exhibits aggressive behavior and a poorer prognosis due to its invasive nature and a higher incidence of lymph node involvement. In contrast, intestinal subtype displays histological characteristics like the intestinal lining. It is generally associated with a more favorable prognosis and a better response to surgery and adjuvant therapies. Recognizing these histological subtypes is crucial for tailoring treatment strategies and predicting patient outcomes in the management of AA. In the updated National Comprehensive Cancer Network guidelines, pancreatic cancer regimens such as oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX) or gemcitabine-based chemotherapy are recommended for pancreatobiliary type, while CAPOX, FOLFOX (folinic acid, fluorouracil, and oxaliplatin), and FOLFOXIRI (folinic acid, fluorouracil, oxaliplatin, and irinotecan) are recommended for intestinal type. Although not included in this study, we believe that further analysis is needed to assess the treatment prognosis based on the histological classification of AA in the future.

Recently, two studies demonstrated putative associations between gene mutations and histological subtypes, with reported increases in the incidence of *KRAS*, *TP53*, and *SMAD4* mutations in the pancreaticobiliary type and *APC* mutations in the intestinal type.[32,33] More specifically, the presence of *KRAS* and *TP53* mutations is potentially associated with a more aggressive clinical course regardless of histology, which suggests that these mutations represent drivers of early cancer progression.[34] It is therefore possible for molecular and genetic studies to provide additional information on targeted therapy and immunotherapy as alternatives to conventional chemotherapy. Despite advances in targeted therapy and immunotherapy, conventional chemotherapy remains the primary treatment for unresectable or metastatic AA. As such, the present study is of particular significance as we analyzed the largest number of AA patients who received palliative conventional chemotherapy to date.

Despite our interesting results, this study had several limitations. First, given the rarity of AA, we were unable to plan a prospective study for our research and had to instead rely on a retrospective study. Second, subtyping and genetic and molecular profiling were not performed in this study. It was challenging to confirm the heterogeneous characteristics of AA in a multicenter study as each institution utilized a different evaluation method. Third, our study included a large number of recurrent cases, which may have resulted in a better prognosis. Nevertheless, we believe that this study reflects a more realistic clinical situation as we analyzed the results of conventional PC for AA over the past decade, which for the most part has been performed without additional subtyping. Lastly, in Korea, the choice of regimen is determined by the chemotherapy reimbursement policy, and the preferred regimens are different for each institution. Therefore, it is highly likely that there was selection bias in this study.

In conclusion, while previous studies have shown mixed prognostic outcomes when considering the combination of biliary tract cancer and AA, our study demonstrates the clinical prognosis specific to AA on a large scale with

systemic anticancer therapy. This result suggests that AA is a distinct type of tumor, different from other biliary tract cancers, and AA itself could be expected to have a favorable response to PC. Nevertheless, both conventional GP and CAPOX regimens proved effective in treating AA. Large-scale prospective studies are required in the future to identify more effective regimens targeting the individual characteristics of AA.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Study concept and design: J.K.P., H.S.L. Data acquisition: D.K.J., S.J.K., H.H.C., J.M.L., S.B.Y., J.C.L., D.W.S., J.H.H., M.K.J., Y.S.L., H.S.L., J.K.P. Data analysis and interpretation: D.K.J., S.J.K., H.H.C. Drafting of the manuscript: D.K.J., S.J.K., H.H.C. Approval of final manuscript: all authors.

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DATA AVAILABILITY STATEMENT

The data used to support the findings of this study are included within the article.

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