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Brief Communication

Long-term survival and pattern of recurrence in ampullary adenocarcinoma patients after curative Whipple's resection: a retrospective cohort study in the National Cancer Center in China

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Abstract: Due to the low incidence of ampullary adenocarcinoma (AA), the recurrence patterns, risk factors for recurrence and post-recurrence treatment are still debated. The purpose of this study is to clarify such clinical issues based on the retrospective data at the National Cancer Center in China. Finally, one hundred and eighty-two AA patients after curative Whipple's resection from 1998 to 2019 were retrospectively reviewed. Among them, 27 patients had locoregional recurrence and 61 patients had systemic recurrence. However, no significant difference of clinicopathological features and survival were found between locoregional recurrence and distant metastasis. In the recurrence group, the 1-year, 2-year, and 3-year recurrence-free survival and overall survival were 59.1%, 29.5%, 10.2%, 88.6%, 61.6%, and 37.6%, respectively. AA patients with recurrence have a worse prognosis than those without recurrence, regardless of stage. In addition, we found that advanced T stage and lymphovascular invasion were two independent risk factors for RFS in AA patients after curative Whipple's resection. In conclusion, AA patients with recurrence have a poor prognosis. Advanced T stage and lymphovascular invasion were two independent risk factors for recurrence-free survival in AA patients after curative Whipple's resection. Nevertheless, further studies with larger sample sizes are needed to fully validate.

Keywords: Ampullary adenocarcinoma, recurrence, risk factors, survival, Whipple

Introduction

Ampullary adenocarcinomas (AA) are uncommon malignancies and account for only 0.5% of gastrointestinal cancers [1, 2]. Even following potentially curative Whipple's resection, the prognosis of AA patients remains unsatisfactory [3-6]. It is reported that the 5-year survival rates after surgical resection ranges from 37% to 68% [7]. Recurrence is one of the most important prognostic factors in AA patients. Despite comprehensive management, more than 50% AA patients experienced recurrence after curative resection [8]. However, due to the low incidence, the risk factors of recurrence for AA patients after curative resection are still debated. Meanwhile, a consensus about the recurrence pattern and the post-recurrence treatment of AA patients has not yet been reached.

Therefore, the aim of this study was to explore the recurrence patterns, identify potential risk factors for recurrence, and further assess the impact of the post-recurrence treatment on post-recurrence survival time in AA patients after curative Whipple's resection.

Methods

Patient selection and study design

Clinicopathologic characteristic of patients between 1998 and 2019 were retrospectively col-

lected from the National Cancer Center in China. This was a retrospective, observational cohort study, therefore a waiver from informed consent was obtained. The major including criteria were: (a) Patients with a pathologic diagnosis of ampullary adenocarcinoma; (b) Patients treated with potential curative Whipple's surgery, including open approach, laparoscopic approach, and robotic approach. The major excluding criteria were: (a) Patients who died during the perioperative period; (b) Patients with the missing detailed data of first recurrence sites and date; (c) Patients whose detailed information of post-operative treatments and post-recurrence treatment was not available; (d) Patients whose other important clinicopathologic data was missing.

Study variables

The variables included in this study included demographic characteristics and clinical variables. The major covariates include gender, age, preoperative jaundice, intraoperative transfusion, operation time, tumor size, differentiation, number of regional lymph nodes examined, AJCC TNM stage (8th edition), Lymphovascular invasion, postoperative complications, and adjuvant treatment. For age and tumor size, we converted them into categorical variables according to X-tile software (version 3.6.1) to further discover possible effects on survival and recurrence. Patients were followed-up by outpatient clinic visits every three months within two years after surgery, and every six months thereafter.

Definition of outcomes

The primary patient outcome was recurrence status. AA recurrence were identified through confirmative imaging, which including contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET). Recurrence was defined as relapse of tumor in the surgical bed or the systemic organs. According to the sites of first recurrence, the patients were divided into locoregional recurrence group and systemic recurrence group. The locoregional recurrence was defined as recurrence in the surgical region, which contained the hepatic and mesenteric areas [9]. The systemic recurrence was defined as distant metastasis and intraperitoneal space metastasis [9, 10].

The secondary outcomes were recurrence-free survival time (RFS), post-recurrence survival time (PRS), and overall survival time (OS). The RFS was defined as the time between complete resection and the first recurrence. The PRS was defined as the time from recurrence date to the end of follow-up or the date of death. The OS was calculated as the period from operation date to the end of follow-up or the date of death. The survival information was obtained through outpatient review and telephone interview.

Statistical analysis

Statistical analysis was conducted using SPSS program version 22.0 for Windows (SPSS Inc., Chicago, IL, USA). Categorical variables for different groups were compared by the Chi-squared test or Fishers exact test. Univariate and multivariate analyses were performed with the Cox proportional hazards regression model to identify the independent affecting factors for RFS. Only factors with $P<0.1$ were included in the multivariate model. Odds ratios (OR), hazard ratios (HR) and their 95% confidence interval (95% CI) were presented. Survival curves were depicted by the Kaplan-Meier method in the GraphPad Prism software (GraphPad Software version 8.0.2, La Jolla, CA, USA). Statistically significant difference was defined as the $P<0.05$.

Results

Baseline characteristics

In all, 314 AA patients were treated in our center, and the perioperative death occurred in 11 patients. Moreover, 121 patients were lost to follow-up. Finally, 182 AA patients received curative Whipple's surgery (male to female ratio = 1.39:1) were included in the study. All the patients received the open pancreaticoduodenectomy. The detailed demographic information was illustrated in **Table 1**. In the current cohort, none of patients had received neoadjuvant therapy. According to the Clavien-Dindo system for complication grading, 47 patients had Clavien-Dindo complications graded <3, and 21 patients had Clavien-Dindo complications grade ≥3. In addition, 48 patients (26.4%) were confirmed to have lymph nodes metastasis in the postoperative pathologic examination. However, only 39 patients (21.4%)

Table 1. Clinicopathological characteristics of patients with recurrence and recurrence-free

Characteristic	Total		Recurrence-free		Recurrence		*P*-value
	n=182	100%	n=94	100%	n=88	100%	
Sex							0.706
Male	106	58.2%	56	59.6%	50	56.8%	
Female	76	41.8%	38	40.4%	38	43.2%	
Age							0.269
≤48	46	25.3%	27	28.7%	19	21.6%	
>48	136	74.7%	67	71.3%	69	78.4%	
Jaundice							0.316
No	41	22.5%	24	25.5%	17	19.3%	
Yes	141	77.5%	70	74.5%	71	80.7%	
Intraoperative transfusion							0.116
No	70	38.5%	31	33.0%	39	44.3%	
Yes	112	61.5%	63	67.0%	49	55.7%	
Operation time							0.673
≤6 hours	139	76.4%	73	77.7%	66	75.0%	
>6 hours	43	23.6%	21	22.3%	22	25.0%	
Tumor size							0.301
≤2.2 cm	92	50.5%	51	54.3%	41	46.6%	
>2.2 cm	90	49.5%	43	45.7%	47	53.4%	
Differentiation							0.013
Poor	54	29.7%	21	22.3%	33	37.5%	
Moderate	81	44.5%	41	43.6%	40	45.5%	
Well	47	25.8%	32	34.0%	15	17.0%	
Regional nodes examined							0.085
≤11	113	62.1%	64	68.1%	49	55.7%	
>12	69	37.9%	30	31.9%	39	44.3%	
T stage							0.007
T1	25	13.7%	18	19.1%	7	8.0%	
T2	72	39.6%	42	44.7%	30	34.1%	
T3	85	46.7%	34	36.2%	51	58.0%	
N stage							0.011
N0	134	73.6%	78	83.0%	56	63.6%	
N1	40	22.0%	14	14.9%	26	29.5%	
N2	8	4.4%	2	2.1%	6	6.8%	
TNM stage							0.001
I	81	44.5%	54	57.4%	27	30.7%	
II	53	29.1%	24	25.5%	29	33.0%	
III	48	26.4%	16	17.0%	32	36.4%	
Lymphovascular invasion							<0.001
No	156	85.7%	90	95.7%	66	75.0%	
Yes	26	14.3%	4	4.3%	22	25.0%	
Postoperative complications							0.377
No	114	62.6%	56	59.6%	58	65.9%	
Yes	68	37.4%	38	40.4%	30	34.1%	
Adjuvant treatment							<0.001
No	143	78.6%	84	89.4%	59	67.0%	
Yes	39	21.4%	10	10.6%	29	33.0%	

Table 2. The specific site of recurrence for the ampullary adenocarcinoma patients after curative Whipple's resection

Recurrence sites	n=88	%
Locoregional recurrence	27	30.7%
Systemic recurrence	61	69.3%
Liver metastasis	44	50.0%
Lung metastasis	3	3.4%
Bone metastasis	2	2.3%
Distant lymph nodes metastasis	21	23.9%
Peritoneal seeding	7	8.0%

received adjuvant treatment. During the follow-up period, 88 patients (48.4%) experienced recurrence. The median age at diagnosis in the recurrence-free group and recurrence group were 56.3 years and 55.5 years. The recurrence group contained more patients with poor differentiation (37.5%), T3 stage (58.0%), lymph nodes metastasis (36.4%), lymphovascular invasion (25.0%), and postoperative treatment (33.0%) compared with patients without recurrence.

Recurrence pattern

Regarding the site of recurrence, 27 patients (30.7%) presented locoregional recurrence, while 61 patients (69.3%) presented systemic recurrence. The liver was the most common site of distant metastasis (44 patients), followed by distant lymph nodes (21 patients) and peritoneal (7 patients). The detailed results for recurrence were displayed in **Table 2**. In addition, no difference was found with respect to the clinicopathologic characteristics between locoregional recurrence and systemic recurrence (**Table 3**).

Post-recurrence treatment

Overall, 74 patients received post-recurrence treatment and 14 patients abandoned therapy after recurrence. (**Table 4**) Among these 74 patients, the majority patients received chemotherapy (43 patients) and interventional therapy (17 patients). One patient received resection of distant metastatic lesion and one patient underwent second resection of local recurrence lesion. Moreover, two patients received immunotherapy and one patient received targeted therapy with bevacizumab. Details of the post-recurrence treatment of patients were not available.

Long-term survival analysis

The median follow-up time was 30 months, and the longest follow-up time was 240 months. Overall, the median RFS and OS for all patients in this study were 20 months and 30 months, respectively. The 1-year, 3-year, and 5-year RFS were 75.7%, 46.2%, and 42.3%, respectively. The 1-year, 3-year, and 5-year OS were 90.5%, 61.2%, and 46.0%, respectively. The survival curves were demonstrated in **Figure 1A**, **1B**.

For the patients occurred recurrence, the median RFS was 14.5 months, the median OS was 27 months, and the median PRS was 10 months. The 1-year, 2-year, and 3-year RFS were 59.1%, 29.5%, and 10.2%, respectively. The 1-year, 2-year, and 3-year OS were 88.6%, 61.6%, and 37.6%, respectively. The 6-month, 12-month, and 18-month PRS were 79.2%, 49.1%, and 23.8%, respectively. Furthermore, we conducted the survival analysis on different stages and recurrence, the results demonstrated that patients developed recurrence had worse prognosis in any stage (**Figure 2**). We also compared the survival time between locoregional recurrence and systemic recurrence. The Kaplan-Meier survival curves showed that the RFS and PRS were similar between different recurrence patterns (**Figure 3A**, **3B**).

Furthermore, we conducted Cox regression survival analysis to find out the independent risk factors for RFS in all patients. The univariate analysis revealed that the tumor size, differentiation, T stage, N stage, lymphovascular invasion, and adjuvant treatment were potential prognostic factors for RFS. However, the multivariate analysis demonstrated that only T3 stage (HR: 2.656, 95% CI: 1.079-6.541, P=0.034) and lymphovascular invasion (HR: 1.953, 95% CI: 1.050-3.633, P=0.035) were independent risk factors for RFS (**Table 5**). From a therapeutic perspective, we found that patients who underwent postoperative treatments had poorer RFS, while patients who received post-recurrence treatments had better PRS (**Figures 3B** and **4**).

Discussion

The recurrence was one of the most crucial prognostic risk factors for AA patients. At present, few studies were designed to exactly address this issue [3, 7-9, 11-16]. In the pres-

Table 3. Comparisons of the clinicopathologic characteristics between locoregional recurrence and systemic recurrence

Characteristic	Locoregional recurrence		Systemic recurrence		*P*-value
	n=27	%	n=61	%	
Sex					0.275
Male	13	48.1%	37	60.7%	
Female	14	51.9%	24	39.3%	
Age					0.641
≤48	5	18.5%	14	23.0%	
>48	22	81.5%	47	77.0%	
Jaundice					0.675
No	4	14.8%	13	21.3%	
Yes	23	85.2%	48	78.7%	
Intraoperative transfusion					0.360
No	10	37.0%	29	47.5%	
Yes	17	63.0%	32	52.5%	
Operation time					0.350
≤6 hours	22	81.5%	44	72.1%	
>6 hours	5	18.5%	17	27.9%	
Tumor size					0.232
≤2.2 cm	10	37.0%	31	50.8%	
>2.2 cm	17	63.0%	30	49.2%	
Differentiation					0.108
Poor	8	29.6%	25	41.0%	
Moderate	11	40.7%	29	47.5%	
Well	8	29.6%	7	11.5%	
Regional nodes examined					0.653
≤11	16	59.3%	33	54.1%	
>12	11	40.7%	28	45.9%	
T stage					0.174
T1	2	7.4%	5	8.2%	
T2	13	48.1%	17	27.9%	
T3	12	44.4%	39	63.9%	
N stage					0.381
N0	20	74.1%	36	59.0%	
N1	6	22.2%	20	32.8%	
N2	1	3.7%	5	8.2%	
TNM stage					0.157
I	12	44.4%	15	24.6%	
II	8	29.6%	21	34.4%	
III	7	25.9%	25	41.0%	
Lymphovascular invasion					0.083
No	24	88.9%	42	68.9%	
Yes	3	11.1%	19	31.1%	
Postoperative complications					0.698
No	17	63.0%	41	67.2%	
Yes	10	37.0%	20	32.8%	
Adjuvant treatment					0.960
No	18	66.7%	41	67.2%	
Yes	9	33.3%	20	32.8%	

Table 4. The post-recurrence treatment patterns for the ampullary adenocarcinoma patients after curative Whipple's resection

Post-recurrence treatment	n=88	%
Observation	14	15.9%
Chemotherapy	43	48.9%
Radiotherapy	5	5.7%
Chemoradiotherapy	3	3.4%
Interventional therapy	17	19.3%
Operation	2	2.3%
Other (Chinese medicine, Targeted therapy, Immunotherapy)	4	4.5%

ent study, we found that the mainly recurrence pattern of AA patients was systemic recurrence. The common sites of metastasis in AA patients were liver and distant lymph nodes. However, no significant difference of clinicopathological features and survival were found between locoregional recurrence and distant metastasis. In addition, we found that advanced T stage and lymphovascular invasion were two independent risk factors for RFS in AA patients after curative Whipple's resection. With respect to treatment, we found that post-recurrence treatment could improve the survival time of AA patients after recurrence.

The present study demonstrated that the predominant pattern of postoperative recurrence in AA patients was systemic recurrence and the liver metastasis was the most common site of distant recurrence, which were in line with previous results [9, 14, 17]. However, the locoregional recurrence rates diverge somewhat in the different institutional series. In the Duke University Medical Center, the 5-year local recurrence rate was 50% [8], in addition, a previous study in Taiwan demonstrated that the locoregional recurrence rate were 45.6% (26/57) [18]. However, in the Seoul National University College of Medicine, the locoregional recurrence rate was much lower with 20.2% [9]. In the present study based on the database of National Cancer Center in China, the locoregional recurrence rate was 30.7%, which was similar to a reported result of 37.8% in the Yonsei University College of Medicine [14]. We speculated that such the discrepancies among these studies might be related to the following reasons. Firstly, the number of patients with recurrence had a relatively large variation, ranging from 37 patients to 89 patients. Secondly, locoregional recurrence might be overlooked as soon as the patients developed systemic recurrence. However, the locoregional recurrence might play an important role in systemic recurrence [8]. Thirdly, some patients in the current cohort may have inadequate lymph nodes resection. However, enough lymph nodes dissection might reduce the locoregional recurrence, especially recurrence in regional lymph nodes. Fourthly, the previous study revealed that the recurrence was detected in most AA patients within two years after surgery [14]. However, some patients had a relatively short follow-up time, which might account for the low incidence of recurrence.

Thus far, large tumor size [11], poor differentiation [15, 19], advanced tumor stage [9, 11, 15, 20-22], and lymphovascular invasion [13, 15, 23] have been reported to be risk factors for postoperative recurrence in AA patients. This being said, there is no consensus as to the risk factors for postoperative recurrence in AA patients. In a retrospective cohort study based on the patients treated at The Johns Hopkins Hospital, the researchers found that lymph nodes metastasis was significant predictor of recurrence in for pancreatic, distal bile duct and duodenal adenocarcinoma but not for ampullary cancer [24]. In the current study, lymphovascular invasion was identified by multivariate analysis as an independent risk factor for recurrence in AA patients after curative Whipple's resection. A possible explanation for our observation was that lymphovascular invasion might be related with the tumor micro metastases. The previous studies have demonstrated that the tumor cells initially entered in the blood circulation and generate micro metastases by invading the local microvascular network [25, 26]. The micro metastasis has been reported to be significantly related with locoregional and systemic recurrence [27].

The current study revealed that T3 stage was independent risk factor for RFS in AA patients after curative Whipple's surgery, which was in line with the previous studies [3, 15]. However, according to a recent international multicenter

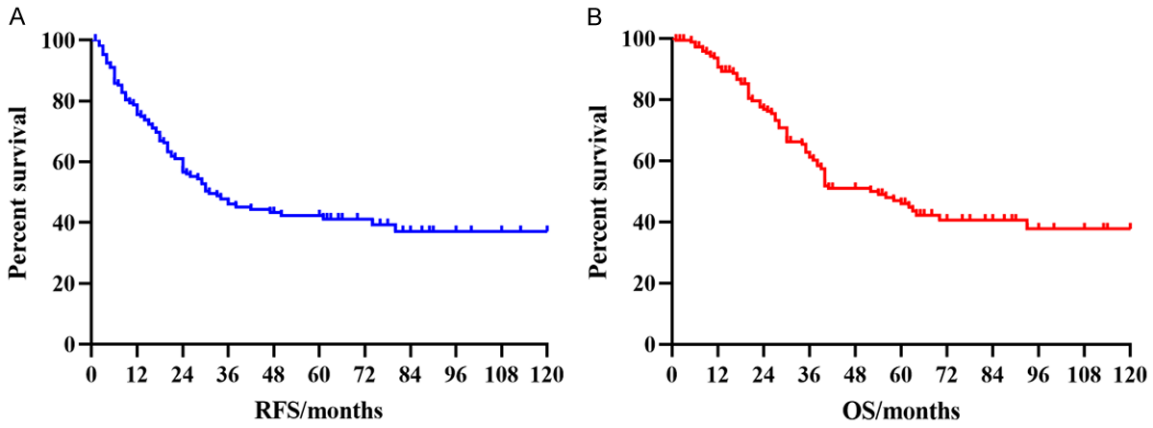

Figure 1. The Kaplan-Meier survival curves for the ampullary adenocarcinoma patients after Whipple's resection. A. RFS curve in all patients; B. OS curve in all patients.

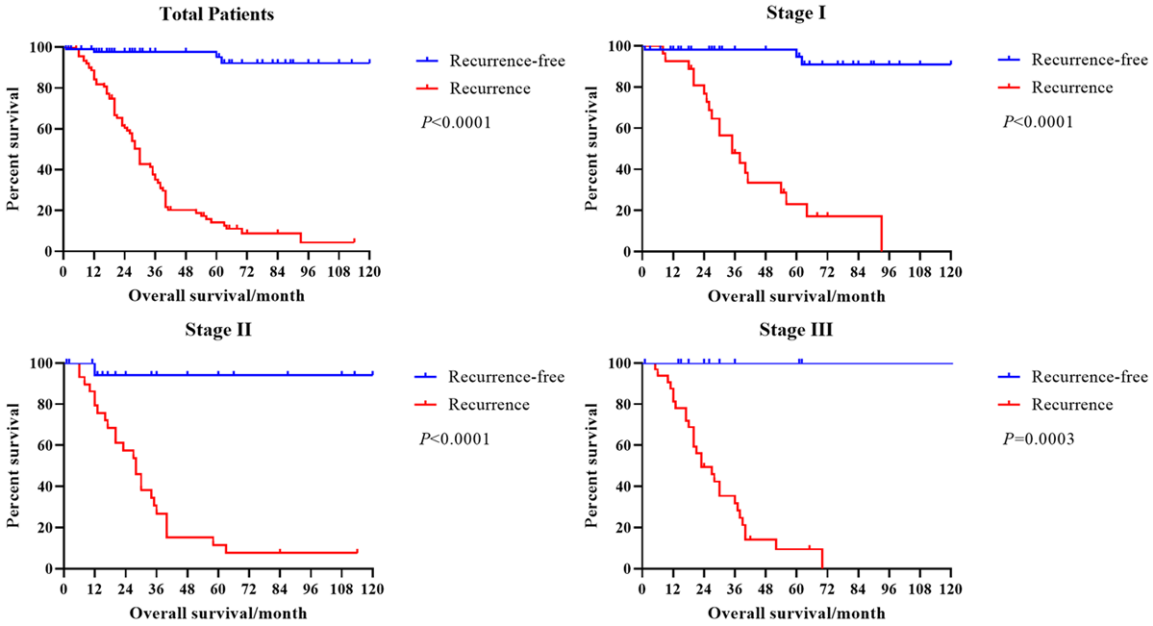

Figure 2. The comparison of OS curves between different stages.

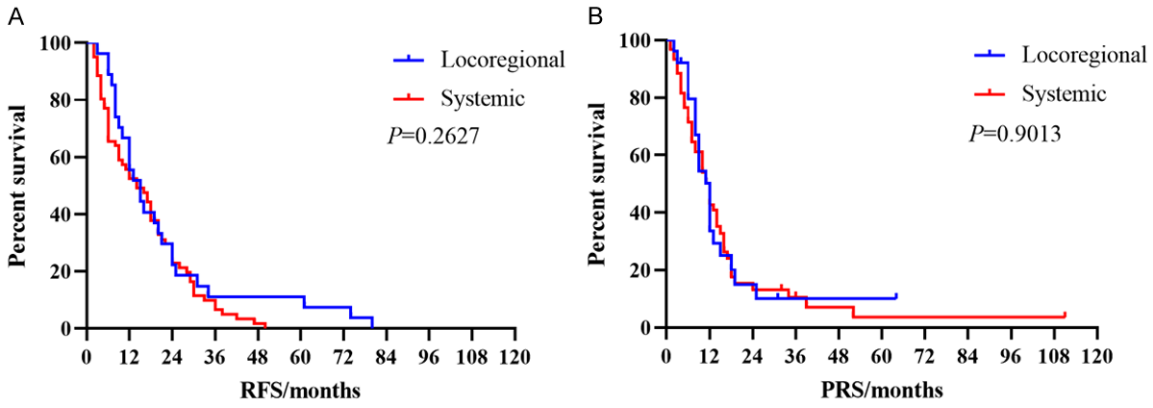

Figure 3. The comparison of RFS curves and PRS curves between locoregional recurrence and systemic recurrence. A. RFS curves between different recurrence patterns; B. PRS curves between different recurrence patterns.

Table 5. Univariate and multivariate Cox regression analyses for recurrence-free survival time in ampullary adenocarcinoma patients after Whipple's resection

Characteristic	Univariable analysis		Multivariable analysis	
	HR [95% CI]	*P*-value	HR [95% CI]	*P*-value
Sex				
Male	Reference			
Female	1.180 [0.774-1.800]	0.442		
Age				
≤48	Reference			
>48	0.796 [0.479-1.323]	0.379		
Jaundice				
No	Reference			
Yes	1.279 [0.753-2.171]	0.363		
Intraoperative transfusion				
No	Reference		Reference	
Yes	0.683 [0.448-1.042]	0.077	0.668 [0.430-1.040]	0.074
Operation time				
≤6 hours	Reference			
>6 hours	1.097 [0.677-1.777]	0.708		
Tumor size				
≤2.2 cm	Reference		Reference	
>2.2 cm	1.611 [1.059-2.453]	0.026	1.330 [0.845-2.091]	0.217
Differentiation				
Poor	Reference		Reference	
Moderate	0.720 [0.454-1.144]	0.164	1.063 [0.633-1.786]	0.817
Well	0.350 [0.189-0.649]	0.001	0.807 [0.381-1.706]	0.574
Regional nodes examined				
≤11	Reference		Reference	
>12	1.524 [0.996-2.333]	0.052	0.980 [0.595-1.615]	0.937
T stage				
T1	Reference		Reference	
T2	1.969 [0.864-4.488]	0.107	1.696 [0.704-4.084]	0.239
T3	4.205 [1.898-9.312]	<0.001	2.656 [1.079-6.541]	0.034
N stage				
N0	Reference		Reference	
N1	2.071 [1.294-3.316]	0.002	1.105 [0.616-1.985]	0.737
N2	2.888 [1.240-6.728]	0.014	1.523 [0.543-4.274]	0.424
Lymphovascular invasion				
No	Reference		Reference	
Yes	3.310 [2.005-5.463]	<0.001	1.953 [1.050-3.633]	0.035
Postoperative complications				
No	Reference			
Yes	1.026 [0.660-1.594]	0.911		
Adjuvant treatment				
No	Reference		Reference	
Yes	2.481 [1.579-3.900]	<0.001	1.243 [0.658-2.348]	0.502

cohort study, only lymph nodes metastasis was independent risk factors for RFS [28]. In our previous study, we demonstrated that the positive lymph nodes ratio (LNR, LNR=number of

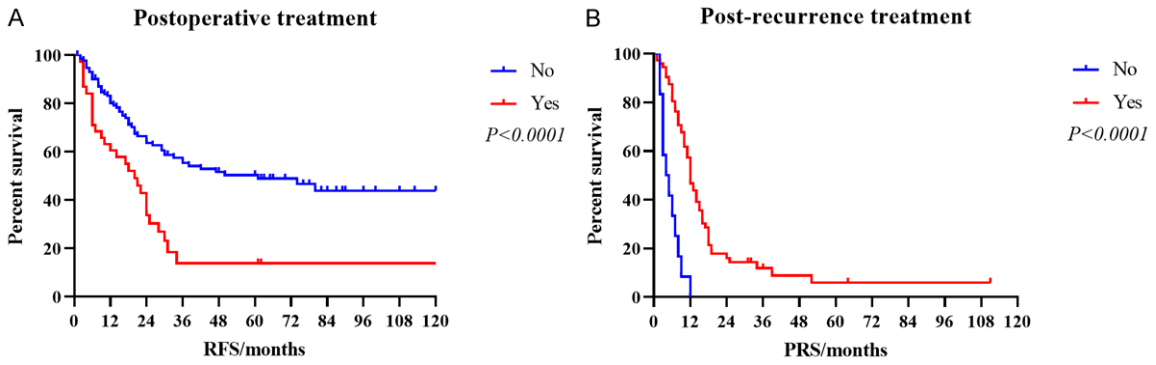

Figure 4. The Kaplan-Meier survival curves of postoperative and post-recurrence treatment. A. RFS curves of postoperative treatment; B. PRS curves of post-recurrence treatment.

positive lymph nodes/number of resected lymph nodes) was an independent prognostic factor of AA patients, which indicted that sufficient lymph nodes dissection might give patients a better survival [29].

Currently, whether the postoperative treatment could reduce the recurrence rate and prolong the survival is still debated. Despite several retrospective study revealed that adjuvant treatment was associated with better prognosis in AA patients after curative surgery [30-34], in the present study, we found that the adjuvant treatment did not reduce the recurrence rate and bring the survival benefit. Notably, a few previous reported multicenter cohort study and randomized controlled trials also suggested that AA patients might not drive a survival benefit from postoperative treatment [35-39]. We speculated that this disparity in outcome might be associated with the chemotherapeutic drugs and histological subtypes. In the present study, we found that post-recurrence treatment might potentially prolong the post-recurrence survival time. For the patients who adopted observation after recurrence, half of the patients died within three months. Unfortunately, clinical decisions are currently being made mainly based on clinical experience. Clearly, further studies required to investigate this issue.

In the current study, we explored the recurrence and several relevant clinical issue of AA patients after curative Whipple's surgery based on the twenty years retrospective data in the National Cancer Center in China. Nevertheless, we acknowledge that our study has some potential limitations. Firstly, the current study is a single-center study, and thus the results may not be universally representative. Secondly, this is a retrospective study over a long time period, therefore it is inevitable that there is certain heterogeneity among patients in lymph node dissection and postoperative treatment strategies. Thirdly, other potential confounding factors, such as blood biochemical indicators or tumor marker indicators, and patient's nutritional status, were not involved in the present study, which might also affect the postoperative recurrence and long-term survival in AA patients. Fourthly, the number of patients enrolled in the current study is small and some patients have a relatively short follow-up time, which may lead to some potential bias. Fifthly, many patients were followed by other oncological centers, therefore, the adjuvant treatment strategies were not well recorded.

Conclusions

In conclusions, we found that T3 stage and lymphovascular invasion were independent risk factors for recurrence-free survival in ampullary adenocarcinoma patients after curative Whipple's surgery. The clinicopathologic characteristics and survival outcomes were comparable between locoregional recurrence and systemic recurrence. In addition, post-recurrence treatment could potentially prolong the post-recurrence survival.

Disclosure of conflict of interest

None.

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