

## Prognostic analysis of carcinoma of the ampulla of Vater: pancreaticoduodenectomy versus local resection

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### Abstract

**Background and Aim:** Pancreaticoduodenectomy (PD) is considered to be the optimal treatment for carcinoma of the ampulla of Vater, but the trauma caused by PD is often severe and extensive. Local resection (LR) for ampullary tumors has been performed for a century but remains controversial. The use of this procedure for benign conditions is clear, but its place, if any, in the management of ampullary carcinoma is debated. The aim of this study was to investigate the outcomes and analyse the prognostic factors of LR of carcinoma of the ampulla of Vater by comparison with PD.

**Patients and Methods:** A retrospective analysis of 71 patients of carcinoma of the ampulla of Vater was conducted at Zhejiang Cancer Hospital from January 1995 to December 2005. We investigated the differences of the baseline characteristics and the intra- and postoperative data of patients who underwent PD and LR. Prognostic factors for recurrence and survival of carcinoma of the ampulla of Vater between PD and LR was also analysed.

**Results:** Among the 71 patients of ampullary carcinoma who underwent surgical resection, a PD was performed in 46 (64.8%) patients while a LR was performed in 25 (35.2%) patients. The 30-day mortality rate associated with PD (6.5%) was not different from that with LR (0%;  $p=0.547$ ) while the morbidity following PD (30.4%) and LR (8.0%) was statistically different ( $p=0.031$ ). The complications were also significantly higher in the PD group than the LR group (34.8% vs 6.5%;  $p=0.013$ ). In a univariate Cox regression analysis of survival, there were significant differences in tumor size ( $p=0.031$ ), TNM (Tumor Node Metastasis) stage ( $p=0.000$ ), pT (pathologic Tumor) stage ( $p=0.010$ ), pN (pathologic Node) stage ( $p=0.000$ ), differentiation ( $p=0.026$ ), and surgical margin ( $p=0.031$ ). Multivariate Cox regression analysis showed that TNM stage (HR=3.640, 95% CI 1.428~9.282;  $p=0.007$ ), pT stage (HR=3.090, 95% CI 1.230~7.762;  $p=0.016$ ), and pN stage (HR=4.479, 95% CI 1.524~13.161;  $p=0.005$ ) remained as independent predictors of survival rates. According to the method of Kaplan-Meier, the five-year survival rate in the PD group was 53.5% and that in the LR group was 48.0%, no significant differences were found between the two groups in overall survival rates ( $p=0.540$ ). Compared with the PD, the 5-year survival of patients with the TNM stage-III/IV who undergoing LR was statistically lower (11.1% vs 38.1%;  $p=0.040$ ). As expected, the overall survival were significant differences between the two groups in pT stage-T3/T4 (47.4% vs 18.2%,  $p=0.018$ ) and pN stage-N1 (36.8% vs 11.1%,  $p=0.004$ ), respectively. Tumor recurrence was diagnosed in 10/43 (23.3%) patients after PD and 12/25 (48.0%) patients after LR ( $p=0.035$ ). Logistic regression analysis of recurrence showed that TNM stage-III/IV ( $p=0.004$ ), pT stage-T3/T4 ( $p=0.034$ ), and pN stage-N1 ( $p=0.007$ ) were associated with a 2.444, 1.943, and 2.111-fold increased risk of recurrence, respectively.

**Conclusions:** PD is the preferred operation for carcinoma of the ampulla of Vater. LR is less mortal and morbid than PD, which is a suitable treatment in patients with a low-risk cancer in stages I/II or pT1/T2 N0 with a maximum diameter of 2 cm or less. TNM stage, pT stage, and pN stage remained as independent predictors of survival rates. Hippokratia. 2012; 16 (1): 23-28

**Key words:** ampullary carcinoma, ampulla of Vater, pancreaticoduodenectomy, local resection; prognosis, recurrence, survival

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Carcinoma of the ampulla of Vater is a relatively uncommon malignancy, but it is the second most common cancer of the periampullary region with a proportional incidence of 0.2% of gastrointestinal cancers and 6%~20% of periampullary tumors<sup>1-3</sup>. The prognosis for patients with carcinoma of the ampulla of Vater is improved relative to other periampullary tumors<sup>4</sup>. Pancreaticoduodenectomy (PD) is considered to be the optimal treatment for ampullary carcinomas, but the trauma caused by PD for ampullary carcinoma of Vater is often severe and

extensive<sup>5,6</sup>. Local resection (LR) is a less invasive and potentially equally effective alternative for cancers with favourable prognostic features<sup>7</sup>.

LR of ampullary tumors has been performed for a century but remains controversial. The use of this procedure for benign conditions is clear, but its place, if any, in the management of ampullary carcinoma is debated. The aim of this study was to investigate the outcomes and analyse the prognostic factors of LR of carcinoma of the ampulla of Vater by comparison with PD.

## Patients and Methods

A retrospective analysis of 71 patients of ampullary carcinoma was conducted at Zhejiang Cancer Hospital from January 1995 to December 2005. All patients underwent the surgical treatment, and a final diagnosis of adenocarcinoma was confirmed by histopathology. Tumor staging was performed according to the 7th edition of the American Joint Committee on Cancer Staging Manual. The mean follow-up duration was 4.5 years.

Based on the medical records, the following data were collected for each patient: age, gender, tumor size, preoperative symptoms, tumor staging (TNM stage, pT stage and pN stage), differentiation, surgical method and surgical margin. The surgical technique of PD and details regarding perioperative management of carcinoma of the ampulla of Vater has been previously described<sup>6,8</sup>. Patients were considered for LR only if the tumors were smaller than 2 cm. It was consisted of resection of the ampulla through a transduodenal approach in conjunction with a pancreaticobiliary sphincteroplasty<sup>9</sup>. We investigated the differences of the intra- and postoperative data of patients who underwent PD and LR. Perioperative morbidity and mortality was defined as any complication or death that occurred within 30 days of surgery or during the same admission as the operation.

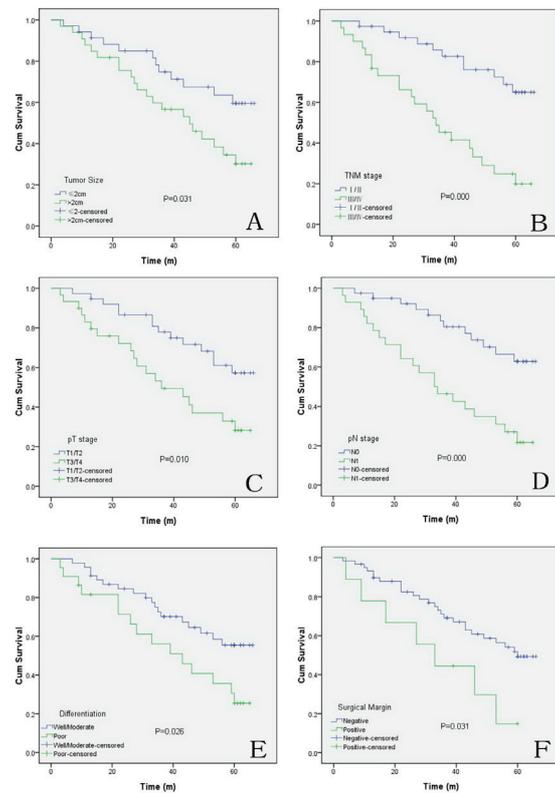
The impact factors of patients with ampullary carcinoma, such as age, gender, tumor size, Jaundice, tumor staging (TNM stage, pT stage and pN stage), differentiation, surgical method, and surgical margin were analysed. Prognostic factors (TNM stage, pT stage and pN stage) for recurrence and survival of ampullary carcinoma between PD and LR was also analysed.

## Statistical Analysis

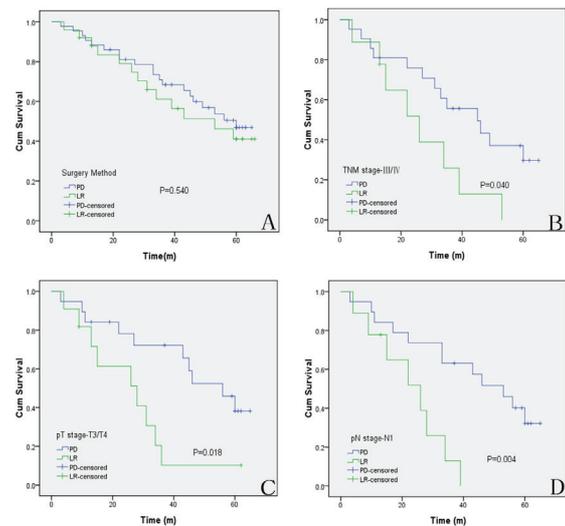
Statistical evaluation was conducted with SPSS 17.0 (SPSS Inc., Chicago, IL, USA). The distribution of baseline characteristics and intra- and postoperative data of patients between PD and LR were evaluated using either Fisher's exact or  $\chi^2$  tests in the case of categorical variables or student's t-test in the case of continuous variables. The overall cumulative probability of survival was calculated by the Kaplan-Meier method, and the difference was assessed by the Log-rank test. Univariate and multivariate analyses of Cox regression proportional hazard model were performed to evaluate the prognostic parameters for survival. Logistic regression analysis was also performed to evaluate the prognostic parameters for recurrence. P-value less than 0.05 was considered to be statistically significant.

## Results

Among the 71 patients with an ampullary carcinoma who underwent surgical resection, a PD was performed in 46 (64.8%) patients while a LR was performed in 25 (35.2%) patients. The baseline characteristics of two groups were presented in Table 1. The mean age of the LR group was  $62.0 \pm 11.4$  years, which was significant higher comparing with the PD group ( $p=0.013$ ). Among the subjects,



**Figure 1:** Kaplan-Meier survival curves according to the tumor size (Figure. 1A;  $p=0.031$ ), TNM stage (Figure. 1B;  $p=0.000$ ), pT stage (Figure. 1C;  $p=0.010$ ), pN stage (Figure. 1D;  $p=0.000$ ), differentiation (Figure. 1E;  $p=0.026$ ), and surgical margin (Figure. 1F;  $p=0.031$ ).



**Figure 2:** The overall survival of patients between PD and LR (Figure. 2A;  $p=0.540$ ). Kaplan-Meier survival curves according to TNM stage-III/IV (Figure. 2B;  $p=0.040$ ), pT3/T4 (Figure. 2C;  $p=0.018$ ), and pN1 (Figure. 2D;  $p=0.004$ ) between patients who underwent PD and LR.

**Table 1:** The clinicopathologic characteristics of ampullary carcinoma

	<i>PD (n=46)</i>	<i>LR (n=25)</i>	<i>P-value</i>
Age (year)	56.3±9.8	62.0±11.4	0.013
Gender (n,%)			0.966
Male	26 (56.5)	14 (56.0)	
Female	20 (43.5)	11 (44.0)	
Tumor size (cm)	2.8±1.1	1.3±0.5	0.000
Preoperative symptoms (n, %)			
Obstructive Jaundice	36 (78.3)	23 (92.0)	0.140
Abdominal pain	17 (37.0)	11 (44.0)	0.562
Nausea or vomiting	13 (28.3)	9 (36.0)	0.501
Chill or fever	11 (23.9)	7 (28.0)	0.705
Weight loss	21 (45.7)	8 (32.0)	0.264
Asymptomatic	3 (6.5)	0 (0)	0.547
TNM stage (n,%)			0.103
I/II	22 (47.8)	17 (68.0)	
III/IV	24 (52.2)	8 (32.0)	
pT stage (n, %)			0.894
T1/T2	25 (54.3)	14 (56.0)	
T3/T4	21 (45.7)	11 (44.0)	
pN stage (n, %)			0.337
N0	24 (52.2)	16 (64.0)	
N1	22 (47.8)	9 (36.0)	
Differentiation (n, %)			0.813
Well/Moderate	30 (65.2)	17 (68.0)	
Poor	16 (34.8)	8 (32.0)	
Surgical margin (n, %)			0.034
Negative	43 (93.5)	19 (76.0)	
Positive	3 (6.5)	6 (24.0)	

**Table 2:** The intra- and postoperative data of ampullary carcinoma

	<i>PD (n=46)</i>	<i>LR (n=25)</i>	<i>P-value</i>
Intraoperative data (median, range)			
Blood loss (ml)	645 (120~8500)	220 (100~750)	0.000
Operative time (min)	342 (215~968)	178 (126~355)	0.000
Postoperative mortality (n, %)	3 (6.5)	0 (0)	0.547
Postoperative morbidity (n, %)	14 (30.4)	2 (8.0)	0.031
Postoperative complications (n, %)			
Pancreatic fistula	7 (15.2)	0 (0)	0.047
Wound infection	3 (6.5)	1 (4.0)	1.000
Abdominal abscess	3 (6.5)	0 (0)	0.547
Bleeding	2 (4.3)	0 (0)	0.537
Bile leak	1 (2.2)	1 (4.0)	1.000

41 cases (57.7%) were male and 30 cases (42.3%) were female, there was no significant difference between the two groups ( $p=0.966$ ). The tumor size was significantly higher in the PD group than the LR group ( $2.8\pm 1.1$  cm vs  $1.3\pm 0.5$  cm;  $p=0.000$ ). The positive surgical margin was significantly higher in the LR group than the PD group (24.0% vs 6.5%;  $p=0.034$ ). The preoperative symptoms, TNM stage, pT stage, pN stage, and differentiation were not different between the two groups.

The intra- and postoperative data were presented in

Table 2. Median blood loss was higher among patients who underwent PD compared with LR (645 ml vs 220 ml;  $p=0.000$ ). As expected, operative time was also longer for PD (342 min) compared with LR (178 min;  $p=0.000$ ). The 30-day mortality rate associated with PD (6.5%) was not different from that with LR (0%;  $p=0.547$ ), while the morbidity following PD (30.4%) and LR (8.0%) was statistically different ( $p=0.031$ ). The postoperative complications were significantly higher in the PD group than the LR group (34.8% vs 6.5%;  $p=0.013$ ). The incidence

**Table 3:** Univariate Cox regression analysis of overall survival for ampullary carcinoma

	Cases (n, %)	Survival (m, mean) (95% CI)	Hazard Ratio (95%CI)	P-value
Age (years)				0.313
≤60	28 (41.2)	50.0±4.1 (41.9~58.1)	1.000	
>60	40 (58.8)	45.0±3.3 (38.5~51.5)	1.280 (0.636~2.574)	
Gender				0.649
Male	38 (55.9)	45.8±3.4 (39.2~52.4)	1.000	
Female	30 (44.1)	48.4±4.1 (40.4~56.4)	0.691 (0.335~1.427)	
Tumor size (cm)				0.031
≤2	35 (51.5)	52.2±3.5 (45.4~59.1)	1.000	
>2	33 (48.5)	41.9±3.6 (34.7~49.1)	2.138 (1.050~4.356)	
Jaundice				0.735
No	11 (16.2)	49.8±6.9 (36.3~63.3)	1.000	
Yes	57 (83.8)	46.5±2.8 (41.0~51.9)	1.197 (0.420~3.407)	
TNM stage				0.000
I/II	38 (55.9)	56.2±2.8 (50.8~61.6)	1.000	
III/IV	30 (44.1)	36.0±3.9 (28.4~43.6)	3.879 (1.868~8.056)	
pT stage				0.010
T1/T2	38 (55.9)	53.2±3.0 (47.3~59.1)	1.000	
T3/T4	30 (44.1)	39.0±4.1 (30.9~47.1)	2.413 (1.207~4.882)	
pN stage				0.000
N0	40 (58.8)	55.2±2.8 (50.0~60.1)	1.000	
N1	28 (41.2)	36.5±4.1 (28.5~44.5)	3.365 (1.650~6.862)	
Differentiation				0.026
Well/Moderate	46 (67.6)	50.8±3.0 (44.9~56.7)	1.000	
Poor	22 (32.4)	39.7±4.8 (30.4~49.1)	2.127 (1.071~4.222)	
Surgical method				0.540
PD	43 (63.2)	48.1±3.2 (41.8~54.3)	1.000	
LR	25 (36.8)	44.9±4.5 (36.1~53.7)	1.242 (0.617~2.499)	
Surgical margin				0.031
Negative	59 (86.8)	49.2±2.8 (43.8~54.6)	1.000	
Positive	9 (13.2)	33.6±6.6 (20.7~46.4)	2.442 (1.054~5.659)	

**Table 4:** Multivariate Cox regression analysis of overall survival for ampullary carcinoma

	B value	SE	Wald	P value	Hazard Ratio (95%CI)
Age (>60 years vs ≤60 years)	0.081	0.473	0.030	0.864	1.085 (0.429~2.741)
Gender (Female vs Male)	-0.374	0.468	0.639	0.424	0.688 (0.275~1.721)
Tumor size (>2 cm vs ≤2 cm)	0.439	0.449	0.958	0.328	1.552 (0.644~3.742)
Jaundice (Yes vs No)	0.316	0.472	0.447	0.504	1.372 (0.543~3.462)
TNM stage (III/IV vs I/II)	1.292	0.478	7.320	0.007	3.640 (1.428~9.282)
pT stage (T3/T4 vs T1/T2)	1.128	0.470	5.762	0.016	3.090 (1.230~7.762)
pN stage (N1 vs N0)	1.499	0.550	7.430	0.005	4.479 (1.524~13.161)
Differentiation (Poor vs Well/Moderate)	0.476	0.501	0.899	0.343	1.609 (0.602~4.299)
Surgical method (LR vs PD)	0.082	0.506	0.026	0.872	1.085 (0.403~2.923)
Surgical margin (Positive vs Negative)	0.841	0.485	3.005	0.083	2.318 (0.896~5.996)

of pancreatic fistula was higher (15.2%) among patients who underwent PD compared with LR (0%;  $p=0.047$ ). The other complications were not statistically different between the two groups.

In a univariate Cox regression analysis of survival (Table. 3), there were significant differences in tumor size (Figure. 1A;  $p=0.031$ ), TNM stage (Figure. 1B;

$p=0.000$ ), pT stage (Figure. 1C;  $p=0.010$ ), pN stage (Figure. 1D;  $p=0.000$ ), differentiation (Figure. 1E;  $p=0.026$ ), and surgical margin (Figure. 1F;  $p=0.031$ ). Multivariate Cox regression analysis (Table. 4) showed that TNM stage (HR=3.640, 95% CI 1.428~9.282;  $p=0.007$ ), pT stage (HR=3.090, 95% CI 1.230~7.762;  $p=0.016$ ), and pN stage (HR=4.479, 95% CI 1.524~13.161;  $p=0.005$ )

**Table 5:** Survival of different tumor stages between PD and LR

	PD		LR		P-value
	Survival(95%CI)	5-year survival (%)	Survival(95%CI)	5-year survival (%)	
TNM stage					
I/II	57.1±3.4 (50.3~63.7)	76.2	54.8±4.5 (46.1~63.5)	70.6	0.600
III/IV	41.4±4.8 (32.0~50.7)	38.1	26.4±5.5 (15.7~37.1)	11.1	0.040
pT stage					
T1/T2	52.0±3.5 (45.1~59.0)	66.7	54.4±4.8 (45.0~63.8)	64.3	0.918
T3/T4	46.2±5.0 (36.3~56.0)	47.4	26.2±5.0 (16.5~36.0)	18.2	0.018
pN stage					
N0	52.6±3.5 (45.8~59.4)	70.8	56.2±4.2 (48.0~64.5)	68.8	0.967
N1	43.9±4.5 (34.2~53.6)	36.8	22.7±4.1 (14.7~30.7)	11.1	0.004

**Table 6:** Recurrence of different tumor stages between PD and LR

	Recurrence		Hazard Ratio (95%CI)	P-value
	PD (n, %)	LR (n, %)		
Total	10/43 (23.3)	12/25(48.0)	1.476 (0.978~2.226)	0.035
TNM stage				
I/II	1/21 (4.8)	4/17 (23.5)	1.245 (0.941~1.649)	0.083
III/IV	9/22 (40.9)	8/8 (100)	2.444 (1.479~4.039)	0.004
pT stage				
T1/T2	2/24 (8.3)	3/14 (21.4)	1.167 (0.865~1.573)	0.249
T3/T4	8/19 (42.1)	9/11 (81.8)	1.943 (1.070~3.528)	0.034
pN stage				
N0	1/24 (4.2)	3/16 (18.8)	1.179 (0.919~1.514)	0.132
N1	9/19 (47.4)	9/9 (100)	2.111 (1.314~3.391)	0.007

remained as independent predictors of survival rates. According to the method of Kaplan-Meier, the five-year survival rate in the PD group was 53.5% and that in the LR group was 48.0%, no significant differences were found between the two groups in overall survival (Figure. 2A;  $p=0.540$ ). Compared with the PD, the 5-year survival of patients with the TNM stage-III/IV who undergoing LR was statistically lower (11.1 vs 38.1%;  $p=0.040$ ; Figure. 2B). As expected, the overall survival were significant differences between the two groups in pT stage-T3/T4 (47.4% vs 18.2%,  $p=0.018$ ; Figure. 2C) and pN stage-N1 (36.8% vs 11.1%,  $p=0.004$ ; Figure. 2D), respectively.

Tumor recurrence was diagnosed in 10/43 (23.3%) patients after PD and 12/25 (48.0%) patients after LR (HR=1.476, 95% CI 0.978~2.226,  $p=0.035$ ). Logistic regression analysis of recurrence showed that TNM stage-III/IV ( $p=0.004$ ), pT stage-T3/T4 ( $p=0.034$ ), and pN stage-N1 ( $p=0.007$ ) were associated with a 2.444, 1.943 and 2.111-fold increased risk of recurrence in LR by comparison with PD, respectively (Table 6).

## Discussion

The results of the present retrospective analysis showed a 6.5% hospital mortality after PD and 0% after LR for carcinoma of the ampulla of Vater ( $p=0.547$ ). Postoperative morbidity was significantly higher in the PD group (30.4%) than in the LR group (8.0%;  $p=0.031$ ). These results were in agreement with several other previ-

ous reports<sup>2,6,10-12</sup>. Despite the marked reduction in hospital mortality after PD in recent years, postoperative complications continue to be a problem<sup>12</sup>. In our study, the postoperative complications was 34.8% after PD, which was significantly higher than LR (6.5%;  $p=0.013$ ).

More and more researchers have proposed several specific criteria to identify which patients may be appropriate for LR<sup>7,9,11</sup>. In a study conducted with 171 consecutively surgically treated ampullary carcinoma patients reported that in patients with a low-risk cancer in stages pTis and pT1 N0 M0, G1 or G2, a surgical treatment of LR with ampullectomy including local lymph node dissection was justified<sup>13</sup>. Nikfarjam et al<sup>14</sup> showed that LR was a suitable alternative to PD in patients with T1 and T2 adenocarcinomas with a maximum diameter of 3 cm or less. Lagoudianakis et al<sup>15</sup> showed that LR for periampullary tumors was a viable option and was well suited for medically unfit patients or those who refused more radical treatment options. However, there are still controversies on the effects of LR on outcomes in patients with ampullary carcinoma. Lindell et al<sup>16</sup> analysed 92 patients with cancer of the ampulla of Vater, the 5-year survival of patients undergoing LR was only 10%. He concluded that LR played a limited role in carefully selected patients. While in our study, we suggested that LR was a suitable treatment in patients with a low-risk cancer in stages I/II or pT1/T2 N0 with a maximum diameter of 2 cm or less.

Many studies showed that the survival of ampullary car-

cinoma is related to tumor stage, lymphatic metastasis, and tumor grade<sup>3,5,12,17-19</sup>. In our study, the TNM stage ( $p=0.007$ ), pT stage ( $p=0.016$ ), and pN stage ( $p=0.005$ ) remained as independent predictors of survival rates. Lindell et al<sup>16</sup> showed that the 5-year survival following PD for ampullary cancer was 35%, while the the 5-year survival following LR was only 10%. In our study, the 5-year survival rate in the PD group was 53.5% and that in the LR group was 48.0%, no significant differences were found between the two groups ( $p=0.540$ ). The relatively short survival in our patients undergoing PD may reflected that the tumor stage was fairly advanced, 51.2% being in TNM stage III/IV. Otherwise, patients in this study were considered for LR only if the tumors were smaller than 2 cm. Therefore, as many as 76.7% of patients with tumor size larger than 2 cm were performed with PD. Compared with the PD, the 5-year survival of patients with the TNM stage-III/IV who underwent LR was statistically lower (11.1 vs 38.1%;  $p=0.040$ ). As expected, the overall survival were significant differences between the two groups in pT stage-T3/T4 (47.4% vs 18.2%,  $p=0.018$ ) and pN stage-N1 (36.8% vs 11.1%,  $p=0.004$ ), respectively.

There are very few previous studies in the literature which have focused on the recurrence of ampulla of Vater carcinoma after surgical resection, despite the fact that it has a major impact on the outcome for patients. Park et al<sup>20</sup> showed that lymph node metastasis was the most important risk factor for recurrence after a curative resection. Branum et al<sup>9</sup> reported that six of eight patients developed a recurrence following local ampullectomy. Lindell et al<sup>16</sup> showed that local recurrence was diagnosed in 11/49 (22%) patients after PD and 8/10 (80%) patients after LR ( $p=0.001$ ). In our study, tumor recurrence was diagnosed in 23.3% patients after PD and 48.0% patients after LR ( $p=0.035$ ). Recurrence of different tumor stages showed that TNM stage-III/IV ( $p=0.004$ ), pT stage-T3/T4 ( $p=0.034$ ), and pN stage-N1 ( $p=0.007$ ) were significantly higher in LR, associated with a 2.444, 1.943 and 2.111-fold increased risk of recurrence of ampulla of Vater carcinoma.

There were several potential limitations in our study, the number of patients was relatively small, the prognostic analysis was retrospective, the mean follow-up duration was short, and the study was conducted by a single institution. As such, direct intra- and postoperative data between patients who underwent PD and LR have limited statistical power. Moreover, it did not provide enough information on the details of the endoscopic treatment on patients.

In conclusion, PD is the preferred operation for carcinoma of the ampulla of Vater. LR is less mortal and morbid than PD, which is a suitable treatment in patients with a low-risk cancer in stages I/II or pT1/T2 N0 with a maximum diameter of 2 cm or less. TNM stage, pT stage, and pN stage remained as independent predictors of survival rates.

#### Conflict of interest:

The authors declare no conflicts of interest

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