



RESEARCH ARTICLE

Assessment of the Relapse Patterns Following Surgical Resection of Adenocarcinoma of the Ampulla of Vater in a Third Level Care Hospital: A 5 Years Analysis

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Abstract

Background: Relapse of adenocarcinoma of ampulla of Vater (CAV) and its presentation after surgery continues to be a main issue and its patterns is unknown in our population.

Objectives: To describe the relapse patterns after radical surgery and to identify the associated risk factors in a mexican population at a Tertiary Care Center.

Methods: Retrospective Study. Patients with CAV who underwent surgery from January 2016 to December of 2020. Relapse: demonstrable disease by means of radiological studies after 3 months of surgery. Main outcomes: patterns of relapse and associated clinical and pathological factors.

Results: 72 patients CAV included. Relapse developed in 50% (36), 21 men (58.3%), mean age 60 years (range, 56.9 to 63), 18 in clinical stage III (50%), the procedure mostly performed: Traverso 29 (80.6%), the mean procedure duration: 353 minutes and surgical mortality 9.7%. Pancreatic fistula 33.3% of relapse. CAV relapse: Regional lymph node 19.4%, liver metastasis 52.8%, lung metastasis 27.8%. Mean survival in each relapse pattern: pulmonary metastasis 27.5 months, liver metastasis 25.4 months and lymph nodes metastasis 23.6 months with P=0.002 (95% CI). Mean survival for local relapse 23.6 months and for distant relapse 25.9 months (95%, CI), P=0.29. Identified pancreatic fistula as independent risk factor associated with relapse (HR=2.4, 1.16-4.96, P=0.02).

Conclusions: Relapse patterns: liver (52.8%), pulmonar (27.8%) and regional lymph nodes (19.4%) of which regional lymph node relapse seems to have the worst survival prognosis. Pancreatic fistula was related to relapse and survival deterioration. Local or systemic recurrence have similar prognosis.

Keywords: Adenocarcinoma, Ampulla of Vater, Fistula, Metastasis, Prognosis

Introduction

Pancreatic adenocarcinoma (PA) is one of the most aggressive cancers and one of the leading causes of cancer related mortality worldwide, with an estimated 5-year overall survival rate of 5% [1-4]. In our country, it is the twelfth leading cause of cancer with 4,489 cases diagnosed per year and represents 4.9% of cancer related deaths [2]. Ampulla of Vater adenocarcinoma (CAV) is a very rare condition in our media and worldwide, corresponding the 0.5% of all gastrointestinal malignancies [5].

In PA as well as in CAV, the only potentially curable treatment is the radical resective surgery (pancreatoduodenectomy) with or without adjuvant chemotherapy depending on the stage [2,4,6-8]. The oncological outcome of CAV is known to have a better prognosis compared to PA and cholangiocarcinoma. The 5-year survival of CAV after curative surgical resection was reported to be 40 to 65% and R0 resection is achieved in 80% of cases. Since the incidence of CAV is low compared to other periampullary malignancies, reports of the prognosis and relapse of this disease are scarce, at present a recurrence of 26 to 46% is reported after curative surgical resection [7-10]. The poor survival in CAV is mainly due to relapse and the fact that not all cases have the same biological behavior, even among patients who develop metastases, which can be limited to isolated organs such as: liver, lung or peritoneum or in more than one organ at a time. The most common relapse patterns described in the literature for CAV are liver (53-67%), lymph nodes (28-60%) peritoneal carcinomatosis (20-21%), lung (21-22%) and bone (13-17%).

While in ductal adenocarcinoma of the pancreas relapse is reported in several studies; Van den Broeck *et al* [11] and Sperti *et al.* [12] classify these as: local relapse (17% to 33%), distant relapse (28 to 60%) and distant and local relapse (23 to 39%), there are few studies focused on the relapse patterns in CAV and in both cases, recurrence significantly affects patient survival.

Knowing the relapse patterns in CAV in our population after the initial treatment, has made it possible to prepare an adequate selection of patients in whom follow-up and/or surgical treatment is possible to which the relapse is unique or to identify cases. in which recurrence occurs as systemic disease in multiple organs that are given palliative treatment. The objective of this study is to identify the pattern of recurrence of ampulla of Vater adenocarcinoma surgically treated by pancreaticoduodenectomy, corporocaudal pancreatectomy, and total pancreatectomy during the period from January 2016 to December 2020, at an Oncology High Specialty Medical Unit.

Material and Methods

A cohort of all consecutive patients who underwent pancreaticoduodenectomy (PD), pylorus-sparing pancreaticoduodenectomy or Traverso-Longmire procedure (PPPP), corporocaudal pancreatectomy (PCC) or total pancreatectomy (TP) with histological diagnosis of ampulla of Vater adenocarcinoma (CAV) were enrolled from January 2016 to December 2020 in the Oncology Hospital of a Tertiary Care Center, to obtain the clinical, pathological and characteristics of recurrences. And to guarantee the accuracy of the data, those patients with incomplete records were excluded, as well as those with neoadjuvant treatment, metastasis at the time of surgery,

patients with perioperative mortality within 90 days after the intervention. The main objective of the study was the recurrence patterns, as well as the survival associated with them, and the risk factors potentially associated with recurrence. The present study was conducted in accordance with the guidelines stipulated in the Declaration of Helsinki in 1975 (revised in 2013).

This retrospective research study was approved to be carried out by the institutional review board and ethics committee on April 11, 2023 with folio number F-2023-3602-051.

Patient Demographics

The selection of patients for surgical resection was elaborated within a multidisciplinary committee done in our department in a weekly meeting and with an imaging study protocol using triphasic multiplanar axial tomography to assess resectability by the surgical staff of surgical oncologists with experience in pancreatic and hepatobiliary surgery who performed all resections. The Surgical Oncologists who performed the surgeries had the same hospital training. The surgical specimens were delivered for analysis by the specialized staff of the Pathology department who reported the diagnosis, histological type, margins, size, lymph node invasion, grade and the main histopathological characteristics that served to define the clinical stage using the staging system of the American Joint Committee on Cancer eighth edition and the postoperative appearance of pancreatic fistula was documented, defined as an amylase level measured in the postoperative drainage greater than three times the normal serum value [13].

Recurrence was defined as the reappearance of the disease 3 months after the surgical event, verified by imaging, clinical, and biochemical evidence.

Statistic Analysis

Means, interquartile ranges, among other quantitative variables were used. In qualitative variables, frequencies and percentages were used. For the comparison of categorical variables, the Chi-square was used, and for the estimation of total survival was calculated using Kaplan Meier curves according to the type of recurrence that occurs. To evaluate the factors associated with recurrence, we used the Cox Multivariate analysis. For all tests, a $P < 0.05$ was considered statistically significant, which corresponds to a 95% confidence interval (CI). The analysis was carried out using the SPSS version 23 (IBM) statistical package.

Results

Demographic Characteristics and Treatment

From January 2016 to December 2020, 72 postoperative patients for Vater ampulla adenocarcinoma (CAV) were included for analysis. Those who presented recurrence were 36 (50%) and those who did not experience it were similar in number and percentages. It stands out in the relapse group that clinical stage III, 23 (24.5%). The main demographic and treatment characteristics are reported in Table 1.

Table 1: Analysis of the demographic characteristics and treatment and comparison Non-Recurrence and Recurrence (Adenocarcinoma Ampulla of Vater).

Characteristics (n=72)	Non-recurrence (n=36)	Recurrence (n=36)	P-value
Age: Mean (SD)	61.94(SD:11.17)	59.92(SD:9.05)	0.40
Sex			0.99
Women	16(44.4)	15(41.7)	
Men	20(55.6)	21(58.3)	
Clinical Stage n (%)			0.05
IA	4(11.1)	0(0)	
IB	6(16.7)	1(2.8)	
IIA	7(19.4)	7(19.4)	
IIB	8(22.2)	10(27.8)	
III	11(30.6)	18(50)	
Type of surgery			0.07
Whipple Procedure	8(22.2)	7(19.4)	
Traverso-Longmire	27(75)	29(80.6)	
Total Pancreatectomy	1(2.8)	0(0)	
Time QX Minutes: Mean (SD)	365.72(111.33)	352.61(95.04)	0.59
Bleeding ml: Median (Interquartile Range)	870.83(RI:638)	904.17(RI:488)	
Transfusion	13(36.1)	10(27.8)	0.61
Surgical Approach			0.67
Opened	34(94.4)	32(88.9)	
Laparoscopic	2(5.6)	4(11.1)	

Factors Associated with Recurrence

No significant differences were identified between the non-recurrence and recurrence groups, when analyzing the patients with CAV, regarding the variables age, sex, AJCC clinical stage, type of surgical procedure, duration of surgery, need for transfusion, type of surgical approach, number of erythrocytes concentrates and number of fresh frozen plasma transfused, and the use of adjuvant radiotherapy. While in the group of patients with CAV that recurred, 63% (23 patients) received adjuvant chemotherapy, while those who did not recur were only 33.3% (12 patients) (P=0.02). There was a statistically significant difference between fistula events between patients in the non-recurrence group with 5 cases (14%) and the recurrence group with 12 cases (33.3%) (P=0.04).

The number of patients who died secondary to the complication of surgery were exclusively from the non-recurrence group, which corresponded to 19.4% of that group, and globally to 9.72% (7 patients). No patient received neo-adjuvant chemotherapy (Tables 1 and 2).

In the univariate analysis of the variables, it was shown that the postoperative pancreatic fistula was the only variable that was potentially associated with recurrence. While in the multivariate confirmed the postoperative fistula as a risk factor for recurrence, in addition to the decrease in survival due to it.

Outcome	Non-Recurrence n/ (%) 36(100)	Recurrence (%) 36(100)	P-value
Recurrence site	-		
Lung	-	10(27.8)	
Liver	-	19(52.8)	
Locoregional	-	7(19.4)	
Death due to surgery complication	7(19.4)	0(0)	0.00
Died by disease	0(0)	27(75)	0.00
Pancreatic fistula	5(14)	12(33.3)	0.04
Chemotherapy	12(33.3)	23(63.9)	0.02
Radiotherapy	4(11.1)	6(16.7)	0.74

Table 2: Analysis of the outcome in comparison Non-recurrence y Recurrence (Ampulla of Vater adenocarcinoma).

(Univariate: P=0.02; HR=5.4. Multivariate: P=0.02; HR=2.4; 95% CI: 1.16-4.96) (Table 3).

VARIABLES	Univariate P-value(HR)
Age: Mean (SD) 0.39 (0.73)	0.39 (0.73)
Sex	0.53 (0.40)
Clinical Stage n (%)	0.07(8.70)
Time QX Minutes: Mean (SD)	0.18 (1.79)
Bleeding ml: Median (Interquartile Range)	0.92 (0.01)
Transfusion	0.91(0.11)
Surgical Approach	0.11(2.55)
Transfused Packed Red Cells	0.36 (0.83)
Transfused Fresh Plasmas	0.48(0.51)
Chemotherapy	0.18(1.79)
Radiotherapy	0.83 (0.05)

Variable	Univariate P-value(HR)	Multivariate P-value(HR)	Multivariate CI 95%
Pancreatic fistula	P=0.02(5.4)	P=0.02(2.4)	1.16-4.96

Table 3: Analysis of the factors associated with recurrence in ampulla of Vater adenocarcinoma. Univariate/Multivariate analysis Cox.

Analysis of Relapse Patterns

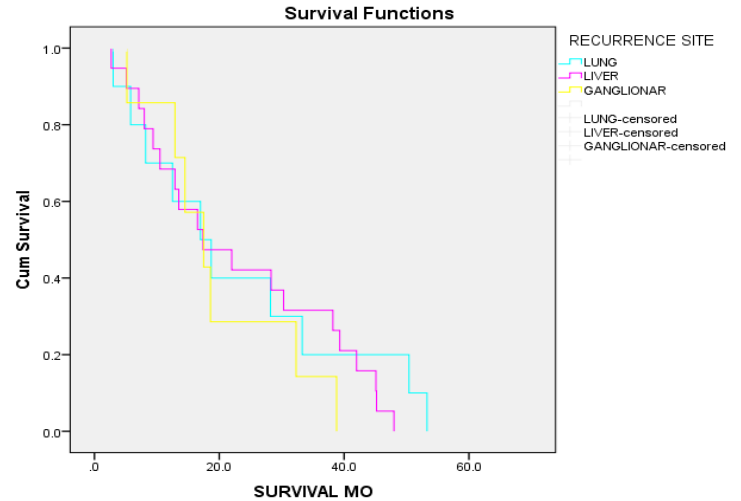
Regarding locoregional relapse (nodal), they were 19.4% (7) in CAV. Pulmonary recurrence was 27.8% (10) in CAV. At the level of the hepatic gland, the relapse of 52.8% in CAV corresponded to nineteen patients. It is important to mention that in CAV there were 4 (11.1%) patients with two or more sites of synchronous recurrence: one patient with pulmonary-hepatic recurrence, two patients with pulmonary-nodal recurrence, and one patient with pulmonary-hepatic and nodal recurrence.

Survival of Patients with CAV

Patients without recurrence survived a median of 38 months (31.79-44.39; 95% CI). The survival of patients with CAV who did not receive and those who received adjuvant radiotherapy were 27.66 (23-32; 95% CI) and 35.69 (23-47; 95% CI) months, respectively, but without a significant difference (P= 0.14). It was also observed that patients who received adjuvant chemotherapy survived longer compared to those who did not receive it, but no significant difference was found either (No chemotherapy=26.43 months; 20.2-32.7; 95% CI and If chemotherapy=31.05; 25.32 -36.78; 95% CI) (P=0.32). Patients with pancreatic fistula had a median survival of 18.76 months (11.64-25.88; 95 CI); against those who did not with 33.06 (28.28-37.85; 95% CI) months on average and a statistically significant difference with a P=0.003.

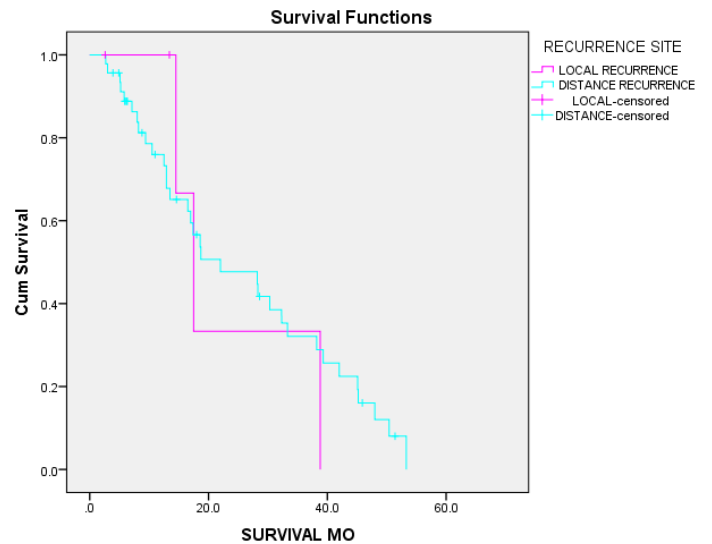
Regarding survival by location of recurrence, pulmonary had the highest survival with 27.5 months (16.55-38.41 months) followed by liver with 25.4 months (18.56-32.27 months) and lymph node survival of 23.6 months (8.61-38.6) with a P (0.002) with significant difference (95%, CI). See Graph 1.

GRAPHIC 1: Kaplan Meier curves showing survival over time. By organ of recurrence. Pulmonary 27.5 months (16.55-38.41 months) followed by hepatic 25.4 months (18.56-32.27 months) and lymph node 23.6 months (8.61-38.6), P (0.002) (95%, CI). (Figure 1)



The relapse pattern was also analyzed, grouping the patients into: local (tumor bed and regional lymph nodes) and distant (hepatic, pulmonary, peritoneal) as a way of facilitating the explanation of the recurrence process in terms of survival; thus, a survival of 23.6(8.6-38.6) months was obtained for the first and 25.9(20.6-31.3) months for the second, where no significant difference was found (P=0.29) (Log Rank, Mantel- Cox). See Graph 2.

GRAPHIC 2: Kaplan Meier curves showing survival over time. Local disease 23.6(8.6-38.6) months and distance 25.9(20.6-31.3) months. No significant difference (P=0.29) (95% CI). (Figure 2)



When analyzing survival by histological subtypes, we found months were similar, in the intestinal subtype with 36.9 months (30.1-43.8) and in the pancreatobiliary 35.7 months (25.5-45.9), P=0.72, 95%. I.C.

Discussion

Ampullary adenocarcinoma of Vatter is a rare condition in our environment and worldwide, corresponding to 0.5% of all

gastrointestinal malignancies, which is reflected in the size of our sample and in the almost non-existent prospective studies and very few retrospective ones [14].

Surgical mortality of 9.7% found in our environment was found within the current range that occurred in reference hospitals (5 to 10%, Buchler 2003, Cameron 2015) and high surgical volume of the procedure, defined as that which occurred within the first thirty postoperative days. Noting that regardless of the type of surgery, whether Whipple or Traverso (Already described by Huttner, [8]) there was no significant difference regarding morbidity and mortality between them, although it is important to mention the difficulty in assuming this inference given our size of study sample.

In world literature, the definition of pancreatic fistula varies widely, even more so its frequency, from figures of 8.8% to 9.3% (Whipple and Traverso respectively [8]), or they can go from 10 to 28% according to Buturini depending on its definition (2006) and the Oncological treatment group (30 to 45% Bassi 2001, Cameron 2015, Buchler 2003) [7]. According to our definition, we found its presence in 24% of patients (17), which is not far from the range of presentation in the literature.

Regarding the recurrence presented in our population, 50% is like what is reported in the literature (43.5%, Park; 44.8%, Zhang) [8,15] corroborating the aggressive nature of the disease. We add that the recurrence in our study was similar regardless of the histological subtype, be it pancreatobiliary, or intestinal (P=0.72), without having any information in this regard to contrast with the literature.

Regarding the recurrence patterns, even though very few studies have focused on them, the one that predominated in our study was the hepatic in 19 patients (52.8%), followed by the pulmonary with 10 (27.8%) and the regional lymph nodes being the lowest with 7 (19.4%), these results are comparable to the results of Hsu *et al.* [16] With a mean total overall survival in CAV of the cohort of 36.1 months (29.6-42.6). While the mean survival according to the recurrence pattern was in our cohort: 27.5 months (16.6-38.4) pulmonary, followed by hepatic with 25.4 months (18.6-32.3) and lymph node 23.6 (8.6-39.6) with a P (0.04) of statistically significant difference (95%, CI).

Mean survival in local relapse was of 23.6(8.6-38.6) months and in distance 25.9(20.6-31.3), (95%, CI), P=0.29.

Notably, we identified pancreatic fistula as a risk factor associated with recurrence by uni-multivariate analysis (HR=2.4, 1.16-4.96, P=0.02) in our study. Nagai *et al* in 2011 described the above association especially with peritoneal recurrence with HR=3.97, 1.35-11.74, 95% CI [5]. Without detracting from our finding, given the retrospective nature of the current study, we must question whether this result could somehow reflect the immunological depletion secondary to the fistulous event, the sample size, the effect of the adjuvant delay until the fistula is resolved. or lack of randomization.

Conclusions

Given the analytical exploratory nature of our retrospective study, it confirms that the clinical-demographic presentation modality of

ampullary adenocarcinoma is like that reported in medical literature.

Recurrence in our environment is also a cause of impaired survival in patients with CAV. Its recurrence patterns do not differ from what has already been reported. Among patients with postoperative CAV, the development of pancreatic fistula may be related to the probability of recurrence and deterioration in survival, a group to be monitored more frequently. Lymph node recurrence showed the worst prognosis after its detection. The impact of survival is similar, be it local or systemic recurrence. Additional randomized multicenter prospective studies will be needed to corroborate these findings.

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Conflict of Interest Statment

Authors declare no conflict of Interest for this article.'

Authors Contribution:

A.V.G., L.G.R. and R.M.G.: Study design. **A.V.G.:** Literature review. **A.V.G. and L.G.R.:** Collected the data. **A.V.G. and L.G.R.:** Conceived and designed the analysis. **A.V.G., L.G.R. and M.L.C.:** Analysis and/or interpretation. **M.L.C., A.M.M., A.G.A. and M.V.O.:** Critical review. **R.M.G.:** Supervision. **A.V.G.:** Wrote the paper. **M.V.O.:** Edition of research article in English.

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