ISSN 1948-9366 (online)

World Journal of

Gastrointestinal Surgery

World J Gastrointest Surg 2022 January 27; 14(1): 1-77

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Surgery

Contents

Monthly Volume 14 Number 1 January 27, 2022

MINIREVIEWS

ORIGINAL ARTICLE

Retrospective Cohort Study

Retrospective Study

World Journal of Gastrointestinal Surgery

Monthly Volume 14 Number 1 January 27, 2022

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Surgery*, Ajaz Ahmad Rather, FACS, FICS, FRCS (Ed), MBBS, MS, Professor, Department of Surgery, SKIMS Medical College, Srinagar 190012, Jammu and Kashmir, India. drajazrather@gmail.com

AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Surgery* (*WJGS*, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, *etc*.

INDEXING/ABSTRACTING

The *WJGS* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2021 edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJGS* as 2.582; IF without journal self cites: 2.564; 5-year IF: 3.378; Journal Citation Indicator: 0.53; Ranking: 97 among 212 journals in surgery; Quartile category: Q2; Ranking: 73 among 92 journals in gastroenterology and hepatology; and Quartile category: Q4.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Rui-Rui Wu*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Ya-Juan Ma.*

NAME OF JOURNAL
World Journal of Gastrointestinal Surgery

ISSN
ISSN 1948-9366 (online)

LAUNCH DATE
November 30, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Peter Schemmer

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1948-9366/editorialboard.htm

PUBLICATION DATE
January 27, 2022

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Surg 2022 January 27; 14(1): 24-35

DOI: 10.4240/wjgs.v14.i1.24

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Survival after curative pancreaticoduodenectomy for ampullary adenocarcinoma in a South American population: A retrospective cohort study

Ramiro Manuel Fernandez-Placencia, Paola Montenegro, Melvy Guerrero, Mariana Serrano, Emperatriz Ortega, Mercedes Bravo, Lourdes Huanca, Stéphane Bertani, Juan Manuel Trejo, Patricia Webb, Jenny Malca-Vasquez, Luis Taxa, Alberto Lachos-Davila, Juan Celis-Zapata, Carlos Luque-Vasquez, Eduardo Payet, Eloy Ruiz, Francisco Berrospi

ORCID number: Ramiro Manuel Fernandez-Placencia 0000-0002-2450-5447; Paola Montenegro 0000-0002-1484-9537; Melvy Guerrero 0000-0002-3555-6338; Mariana Serrano 0000-0001-7830-4475; Emperatriz Ortega 0000-0003-0172-2972; Mercedes Bravo 0000-0002-6965-4841; Lourdes Huanca 0000-0003-0692-3864; Stéphane Bertani 0000-0002-0398-9745; Juan Manuel Trejo 0000-0003-0293-6569; Patricia Webb 0000-0002-8265-7561; Jenny Malca-Vasquez 0000-0003-2258-6113; Luis Taxa 0000-0002-0914-9149; Alberto Lachos-Davila 0000-0002-6190-1959; Juan Celis-Zapata 0000-0001-9687-6637; Carlos Luque-Vasquez 0000-0002-3871-5082; Eduardo Payet 0000-0001-9434-3888; Eloy Ruiz 0000-0001-5561-0752; Francisco Berrospi 0000-0002-0766-2520.

Author contributions: Fernandez-Placencia RM was the guarantor and designer of the study and carried out data acquisition, statistical analysis and interpretation, and drafting of the initial manuscript; Montenegro P, Serrano M and Ortega E participated in the acquisition, analysis and interpretation of the data and contributed to the initial

Ramiro Manuel Fernandez-Placencia, Juan Celis-Zapata, Eloy Ruiz, Francisco Berrospi, Hepato-Pancreato-Biliary Section, Department of Abdominal Surgery, Instituto Nacional de Enfermedades Neoplasicas, Lima 15038, Peru

Paola Montenegro, Mariana Serrano, Emperatriz Ortega, Department of Medical Oncology, Instituto Nacional de Enfermedades Neoplasicas, Lima 15038, Peru

Melvy Guerrero, Mercedes Bravo, Lourdes Huanca, Patricia Webb, Luis Taxa, Department of Pathology, Instituto Nacional de Enfermedades Neoplasicas, Lima 15038, Peru

Stéphane Bertani, International Joint Laboratory of Molecular Anthopological Oncology, Instituto Nacional de Enfermedades Neoplasicas, Lima 15038, Peru

Stéphane Bertani, Unite Pharmacochim & Pharmacol Dev, UMR152, F-31062 Toulouse, France

Juan Manuel Trejo, Jenny Malca-Vasquez, Alberto Lachos-Davila, Department of Radiation Oncology, Instituto Nacional de Enfermedades Neoplasicas, Lima 15038, Peru

Carlos Luque-Vasquez, Eduardo Payet, Department of Abdominal Surgery, Instituto Nacional de Enfermedades Neoplasicas, Lima 15038, Peru

Corresponding author: Ramiro Manuel Fernandez-Placencia, MD, FACS. Surgical Oncologist, Hepato-Pancreato-Biliary Section, Department of Abdominal Surgery, Instituto Nacional de Enfermedades Neoplasicas, 2520 E Angamos Ave. Office 216 Surquillo, Lima 15038, Peru. ramirofp02@gmail.com

Abstract

BACKGROUND

Ampullary adenocarcinoma (AAC) is a rare neoplasm that accounts for only 0.2% of all gastrointestinal cancers. Its incidence rate is lower than 6 cases per million people. Different prognostic factors have been described for AAC and are

draft of the manuscript; Guerrero M and Bravo M participated in the pathological reevaluation and contributed intellectual content; Bertani S participated in the design, data analysis and drafting of the initial manuscript; Huanca L, Trejo JM, Webb P, Taxa L, Lachos-Davila A, Celis-Zapata J, Luque-Vasquez C, Payet E and Ruiz E participated in the data analysis and contributed to the critical review of the manuscript along with important intellectual content; Berrospi F mentored, designed and critically revised the article for relevant intellectual content.

Institutional review board statement: Our institutional review board approved this study (Protocol Number 21-17), according to the Declaration of Helsinki19.

Informed consent statement: Informed consent was waived by the IRB (IRB No. 21-17).

Conflict-of-interest statement: No conflicts of interest to be declared.

Data sharing statement: According to the institutional policy, no data from our patients would be shared.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

Country/Territory of origin: Peru

Specialty type: Oncology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

associated with a wide range of survival rates. However, these studies have been exclusively conducted in patients originating from Asian, European, and North American countries.

AIM

To evaluate the histopathologic predictors of overall survival (OS) in South American patients with AAC treated with curative pancreaticoduodenectomy (PD).

METHODS

We analyzed retrospective data from 83 AAC patients who underwent curative (R0) PD at the National Cancer Institute of Peru between January 2010 and October 2020 to identify histopathologic predictors of OS.

RESULTS

Sixty-nine percent of patients had developed intestinal-type AAC (69%), 23% had pancreatobiliary-type AAC, and 8% had other subtypes. Forty-one percent of patients were classified as Stage I, according to the AJCC 8th Edition. Recurrence occurred primarily in the liver (n = 8), peritoneum (n = 4), and lung (n = 4). Statistical analyses indicated that T3 tumour stage [hazard ratio (HR) of 6.4, 95% confidence interval (CI) of 2.5-16.3, P < 0.001], lymph node metastasis (HR: 4.5, 95%CI: 1.8-11.3, P = 0.001), and pancreatobiliary type (HR: 2.7, 95%CI: 1.2-6.2, P = 0.025) were independent predictors of OS.

CONCLUSION

Extended tumour stage (T3), pancreatobiliary type, and positive lymph node metastasis represent independent predictors of a lower OS rate in South American AAC patients who underwent curative PD.

Key Words: Gastrointestinal neoplasms; Adenocarcinoma; Ampulla; Pancreaticoduodenectomy; Survival; South America

Core Tip: The pancreatobiliary type of ampullary adenocarcinoma, lymph node metastasis and T3 tumour stage (AJCC 8th Ed) are risk factors for lower overall survival in a South American population.

Citation: Fernandez-Placencia RM, Montenegro P, Guerrero M, Serrano M, Ortega E, Bravo M, Huanca L, Bertani S, Trejo JM, Webb P, Malca-Vasquez J, Taxa L, Lachos-Davila A, Celis-Zapata J, Luque-Vasquez C, Payet E, Ruiz E, Berrospi F. Survival after curative pancreaticoduodenectomy for ampullary adenocarcinoma in a South American population: A retrospective cohort study. *World J Gastrointest Surg* 2022; 14(1): 24-35
URL: https://www.wjgnet.com/1948-9366/full/v14/i1/24.htm
DOI: https://dx.doi.org/10.4240/wjgs.v14.i1.24

INTRODUCTION

Ampullary adenocarcinoma (AAC) is a rare neoplasm that represents 0.2% of all gastrointestinal cancers[1,2]. AAC has better prognosis and resection rates than pancreatic ductal adenocarcinoma (PDAC)[3,4]. This may be partly explained by the early symptom of jaundice caused by its location in the ampulla of Vater[5,6]. Nevertheless, three different epithelia (duodenal, biliary, and pancreatic) are present in the ampullary region[7], and their derived malignancies display different clinical behaviours[8]. Kimura and colleagues classified AAC into two histologic subtypes: Pancreatobiliary (PB) and intestinal (INT)[9]. Other features, such as preoperative CA 19-9[7], imaging[10], molecular phenotype[11,12], genetic mutations[13-15], and the diagnosis and classification of AAC[16], have been correlated with overall survival (OS). Consequently, the anatomic paradigm has shifted towards the interaction

Received: May 10, 2021
Peer-review started: May 10, 2021
First decision: August 9, 2021
Revised: September 28, 2021
Accepted: January 13, 2022
Article in press: January 13, 2022
Published online: January 27, 2022

P-Reviewer: Andrejic-Visnjic B, Mirshahi M, Yamada T
S-Editor: Wu YXJ
L-Editor: A
P-Editor: Wu YXJ

between genetic and epigenetic factors that determine OS and relapse-free survival (RFS)[14,17]. This may explain the wide range of outcomes reported in different centres (5-year OS: 30%-70%)[2].

However, most of these studies have been conducted in European, Asian, and North American countries. To the best of our knowledge, only one study has evaluated the impact of the lymph node ratio in predicting OS among AAC patients in Latin America[18]. Therefore, we evaluated the histopathologic predictors in AAC patients who underwent curative pancreaticoduodenectomy (PD) at the National Cancer Institute of Peru.

MATERIALS AND METHODS

Study design and patient selection

We conducted a retrospective cohort study in patients diagnosed with AAC who underwent curative (R0) PD between January 2010 and October 2020 at our tertiary centre. We specifically analysed histopathologic factors that influenced the patients' overall survival. Our institutional review board approved this study (Protocol Number 21-17), according to the Declaration of Helsinki[19].

Histopathology

Double reads in a blinded manner by pathologists specializing in hepatobiliary cancers were applied to ensure the diagnosis of AAC and classification into INT intestinal (INT)- and pancreatobiliary (PB)-type according to Kimura *et al*[9,20].

Morphologically, INT-type tumours are reminiscent of colorectal adenocarcinoma, with solid nests, tall columnar cells, and elongated pseudostratified nuclei[21]. A significant proportion of INT-type is related to intestinal adenomas, which correlates with the adenoma-carcinoma sequence[22]. Conversely, PB-type adenocarcinomas are similar to extrahepatic bile duct and pancreatic duct adenocarcinomas. The glandular units have more pleomorphism than the intestinal type, with no evident nuclear pseudostratification, and they are separated by stroma[21]. Additionally, a mixed subtype has been described as having more than 25% of each INT and PB differentiation or with hybrid features, such as intestinal architecture with pancreatobiliary cytology[23,24]. Immunohistochemistry has led to a better classification of this mixed subtype; nevertheless, a standard definition has not been established[24,25]. In the present study, the following antibodies were used to determine the dominant type: MUC1 (#6151, BioSB, California, United States), MUC2 (#6158, BioSB, California, United States), CDX2 (MAD-000645QD-12, Vitro S.A., Spain), CK20 (MAD-0005105QD-12, Vitro S.A., Spain), and MUC5AC (MAD-000434QD-12, Vitro S.A., Spain). In cases of no definite conclusion, the tumour was classified as tubular into "other subtypes".

Resection was classified as R0 when the 1-mm width of the surgical margin was free of neoplastic cells[26]. Tumour and nodal staging were categorized according to the AJCC 8th Edition.

PD

PD was considered the treatment of choice because it was demonstrated to be a more radical approach to achieve satisfactory lymph node clearance and tumour-free surgical margins[27]. Patients were eligible for surgery after a comprehensive evaluation. The clinical parameters included performance and nutritional status, anatomy, and tumour extension (evaluated with contrast-enhanced computed tomography scan or magnetic resonance imaging). CA19-9 Levels were monitored within one month before surgery. We also assessed the vascular structures of the mesenteric and celiac axes along the diameter of the pancreatic duct.

Our surgical approach has been described previously[28]. In brief, the procedure was carried out using level 2 mesopancreas resection[29], and the pancreatic stump was managed using Blumgart, duct-to-mucosa, or modified dunking (at the discretion of the surgeon). In all cases, two Blake drains were placed around the pancreaticojejunostomy. Prophylactic octreotide was not used. External stents were applied in patients with a high risk of postoperative pancreatic fistula[30].

Adjuvant therapy

Patients with adjuvant therapy (AT) were interpreted as those who received chemotherapy (two or more courses), radiotherapy (with or without a sensitizing

Table 1 Clinical, laboratory and operative patient characteristics (*n* = 83)

Clinical, laboratory and operative patient characteristics (*n* = 83)	
Age (yr), median (IQR)	59 (49–67)
Sex, male/female, *n* (%)	36 (43)/47 (57)
Perioperative transfusion, *n* (%)	21 (25)
Haemoglobin in g/L, median (IQR)	115 (108–127)
Platelet count in 10^9/L, median (IQR)	285 (243–372)
International Normalized Ratio, median (IQR)	1.06 (1.01–1.15)
Serum glucose in mmol/L, median (IQR)	5.1 (4.8–5.7)
Serum creatinine in mmol/L, median (IQR)	53 (47–65)
Serum albumin in g/L, median (IQR)	38.1 (32–41.1)
Serum total bilirubin in μmol/L, median (IQR)	23.9 (12.9–60)
Serum CA 19-9 in IU/mL, median (IQR)	26.3 (10–91.4)
Pancreaticoduodenectomy	
Pylorus-preserving PD, *n* (%)	69 (83)
Whipple procedure, *n* (%)	14 (17)

IQR: Interquartile range; PD: Pancreaticoduodenectomy.

chemotherapy drug), or a combination of both. The AT regimen was left at the discretion of treating physicians, according to the best evidence available and/or institutional protocol.

Patient follow-up

Follow-ups and patient check-ups were performed on postoperative days 15, 30, and 90. computed tomography (CT) scans and CA 19-9 tests were scheduled every 4 mo after the index procedure during the first year, every 6 mo during the second year, and annually from the third year onward. The National Database for Civil Status (RENIEC) was solicited to determine the fate of patients. OS (months) was monitored from the date of surgery to the date of death or last follow-up, and patients with no events were censored. Any event (recurrence or death) was recorded during the follow-up. The cut-off for the last follow-up was 60 mo.

Statistical analysis

Continuous variables were reported as medians (interquartile ranges), and categorical variables were reported as counts (percentages). For the univariate analysis, the log-rank test was used, and the histopathologically relevant variables were integrated into a Cox regression model. Statistical analyses were performed with an alpha significance level of 0.05 using IBM SPSS v.25 (IBM Corp., Armonk, NY, United States) and R software (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study population

From 2010 to 2020, 297 PDs were performed at the National Cancer Institute of Peru. Patients with R1/R2 resection, unavailable slides for revision, incomplete medical records, or synchronic neoplasms were excluded from the study. All patients included in the study underwent R0 resection. After a thorough revision of the medical files, 83 patients were included in the present study. Clinical, laboratory, and operative patient characteristics are presented in Table 1. The median age of the patient cohort was 59 years [interquartile range (IQR), 49-67], with a predominance of women (ratio = 1.3). The mean follow-up time was 39 mo. Twenty-five patients (30%) died during the follow-up period.

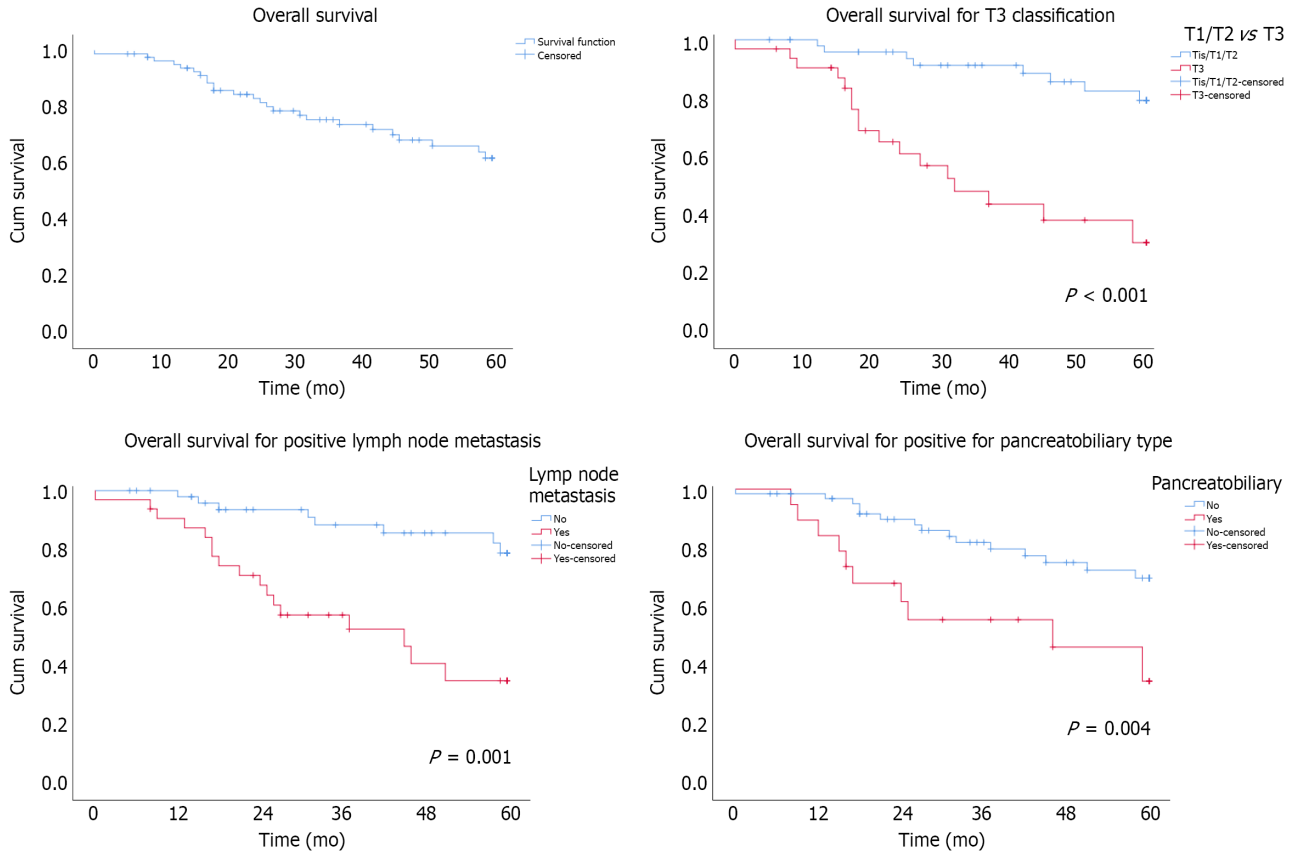

Figure 1 Survival probability of patients with adenocarcinoma of the ampulla of Vater undergoing pancreaticoduodenectomy.

Histopathologic characteristics

Sixty-nine percent of patients had developed INT-type AAC (69%), 23% PB-type AAC, and 8% other subtypes (including five patients with the tubular subtype and two patients with the tubular subtype with signet ring cells). Approximately 40% of cases demonstrated pancreatic invasion (T3 tumour stage), and 40% of patients had lymph node metastasis. Thirty-four (41%), 20 (24%), and 29 (35%) patients had stage I, II, and III disease, respectively. The histopathological characteristics of the cohort are shown in Table 2.

Use of AT

Twenty-four patients received AT (15 patients underwent chemotherapy, two patients underwent radiotherapy, and seven patients were subjected to both treatments). The most frequently employed chemotherapy regimen included gemcitabine, which was administered to 20 patients (24%). When chemoradiotherapy was applied, a dose of 4500 cGy in 25 sessions was administered using capecitabine as a sensitizing agent.

The evaluation of AT on OS was impaired by the heterogeneity of the AT regimen and the number of patients. Therefore, we decided not to include the AT variable in the survival analysis.

Patterns of recurrence

Recurrent distant metastases were diagnosed during the postoperative period in the liver (n = 12), peritoneum (n = 8), and lung (n = 7). Additionally, lymph node recurrences around the superior mesenteric artery and the retroperitoneal space were primarily observed in one and two patients, respectively (Table 3).

Overall survival and prognostic factors

The 5-year OS rate in the cohort was 62% (Figure 1). Applying the Cox regression model, three predictive factors were identified, *i.e.*, T staging, lymph node metastasis, and PB type. Time and outliers had no impact on these independent factors, according to the modelling Supplementary Figures (Table 4).

Table 2 Histopathologic characteristics (*n* = 83)

Histopathologic characteristics (*n* = 83)	
Tumour size in mm, median (IQR)	27 (17–40)
Subtype, *n* (%)	
Intestinal	57 (69)
Pancreatobiliary	19 (23)
Others	7 (8)
Tumour status, *n* (%)	
T1	7 (8)
T2	44 (53)
T3	32 (39)
Number of lymph nodes assessed, median (IQR)	17 (12–24)
Lymph node status, *n* (%)	
N0	50 (60)
N1	22 (26)
N2	11 (14)
Differentiation, *n* (%)	
Well differentiated	25 (30)
Moderately differentiated	53 (64)
Poorly differentiated	5 (6)
Lymphovascular invasion	30 (36)
Perineural invasion	26 (31)

IQR: Interquartile range.

Impact of the T tumour classification

Univariate analysis showed lower OS in patients with T3 classification ($P < 0.001$). The 5-year OS rates were 80% in T1/T2 patients and 30% in T3 patients, with a median OS of 30% in the latter group. According to the multivariate analysis, T3 patients had an HR of 6.4 (95%CI: 2.5-16.3, $P < 0.001$) (Figure 1).

Effect of lymph node invasion

Patients with lymph node metastases (N+) had a lower survival rate than those with no lymph node invasion (N0) ($P = 0.001$). The 5-year OS rates in the N+ and N0 groups were 38% and 80%, respectively. The median OS was 46 mo in the N+ group. The HR was 4.5 (95%CI: 1.8-11.3, $P = 0.001$) (Figure 1).

Influence of the histopathologic subtype

PB-type patients had a lower OS than patients with INT or other subtypes ($P = 0.004$). The 5-year OS rate for PB-type patients was 38%, whereas patients with INT or other subtypes had a 5-year OS rate of 70%. The median OS was 46 mo in PB-type patients, whereas the OS in the intestinal/other group was not reached during the follow-up period. The HR was 2.7 (95%CI: 1.2-6.2, $P = 0.025$) in PB-type patients (Figure 1).

DISCUSSION

To the best of our knowledge, the present study represents the first retrospective histopathologic work on AAC performed in a tertiary centre in South America, in which PD and the multimodal approach are standard. Our findings indicate that T3 tumour classification (pancreatic invasion), positive lymph node metastasis, and PB type are independent prognostic factors of OS in AAC patients treated with PD (R0).

Table 3 Recurrence patterns after pancreaticoduodenectomy (*n* = 19)

Organs involved					
Distant metastasis, *n* (%)	**(A) First organ**	**(B) Second organ**	**(C) Third organ**	**A + B + C**	**%**
Liver	8	3	1	12	32
Peritoneum	4	3	1	8	22
Lung	4	2	1	7	19
Supraclavicular lymph node	1			1	3
Bone		1		1	3
Suprarenal gland			1	1	3
Sub-table total				30	81
Lymph nodal recurrence, *n* (%)					
Celiac trunk		1		1	3
Hepatic hilum		1		1	3
Mesenteric lymph nodes	1	1		2	5
Retroperitoneal lymph nodes	2	1		3	8
Sub-table total				7	19
Total				37	100

Various factors have previously been described to be associated with AAC patient outcomes. In a meta-analysis, Zhou and colleagues identified age (> 65 years old), tumour size (> 20 mm), poor differentiation, PB-type, pT3-T4 stage diseases, lymph node metastasis, perineural invasion, lymphovascular invasion, pancreatic invasion, and positive surgical margins as independent factors associated with lower survival [32]. However, Koprowski and colleagues claimed that histotypes were not correlated with OS and concluded that disease stage was the primary determinant of patient outcomes[33]. In this study, the authors report 32% locoregional recurrence, despite the median number of retrieved lymph nodes and the low number of patients with R1 resection. Moreover, Quero and collaborators recently corroborated this finding about no difference between INT- and PB-types, but higher overall and recurrence-free survivals with excision of the mesopancreas[34].

Since AT allocation is based on tumour and nodal stages, we decided to consider these variables in the Cox model. We further stratified the patient cohort according to histopathologic subtypes (*i.e.*, INT, PB, and "others"). Of note, we did not observe the mixed subtype in our cohort from South America, contrasting with the studies published in other regions of the world[16,31].

Our model supports the predictive impact of the histology of AAC on survival in a patient cohort from South America. In our hands, PB type, pT3 stage, and lymph node metastases were associated with lower OS; other variables scrutinized were not significantly associated with OS. The low rate of locoregional recurrence reported in our cohort could be partly explained by the application of level 2 mesopancreas resection, in accordance with the data by Quero and collaborators[34].

AAC has been documented to have a better prognosis than PDAC. However, the present study suggests that there are detrimental factors associated with subgroups of AAC patients, with OS rates comparable to PDAC (Figure 2). In this regard, our data suggest that a better outcome would be primarily explained by the biology of the tumour and secondarily by its location. Hence, assessing the impact of AT in high-risk patients is of utmost relevance. In the ESPAC-3 study, which included 428 patients with periampullary adenocarcinoma, the use of chemotherapy (5-fluorouracil /leucovorin or gemcitabine) demonstrated a benefit in OS (HR 0.75) but no greater effectiveness based on the histological type[35]. Additionally, a multicentre retrospective analysis did not report any benefit of adjuvant chemotherapy in AAC patients, including those with high-risk criteria (N+ or advanced stages T3 and T4) [36]. Other studies have provided more contrasting results on the impact of adjuvant chemotherapy on OS[31,37-39]. Regarding adjuvant radiotherapy, benefits have essentially been analysed among PDAC patients, preventing definite conclusions in AAC patients[40-42]. A recent meta-analysis showed that AT, especially chemoradio-

Table 4 Cox regression model analysis for predictors of overall survival

Variables	Hazard ratio	95%CI		*P* value
		Lower	Upper	
Age in yr				0.355
Tumour size in mm	1.03	1	1.06	0.059
Histopathologic subtype				
Intestinal/other types				
Pancreatobiliary type	2.7	1.2	6.2	0.025
T classification				
T1-T2				
T3	6.4	2.5	16.3	< 0.001
Lymph node metastasis				
No				
Yes	4.5	1.8	11.3	0.001
Differentiation grade				0.54
Well differentiated				
Moderately differentiated				0.268
Poorly differentiated				0.755
Perineural invasion				0.517
Lymphovascular invasion				0.26

CI: Confidence interval.

therapy, was associated with increased OS among patients with PB-type or high-risk factors[43].

There is a lack of specific guidelines for AAC, except one that comprises the management of biliary tract and ampullary carcinomas[44]. The authors recommend AT in patients with high-risk features (pancreatic invasion, lymph node metastasis, and perineural invasion) but did not specify any regimen. The predictive ability of mutation driver mutations (*e.g.*, TP53, KRAS, and ELF3) in AAC histotypes has not been studied in great detail[45]. The characterization of AAC patient subgroups, based on their molecular alterations, would provide information on the choice of AT after radical surgery.

There are some limitations to recognize in the present study. Our primary AAC patient population displayed a high perioperative mortality rate (10 patients were excluded from this study), which we addressed and analysed previously[28]. We consider this a very important drawback, in addition to the retrospective design of the study. Another weakness was the heterogeneity in the multimodal management of the patients, which is reflected in international practices[31,39,46]. Therefore, we decided not to evaluate the impact of AT, as few patients would have been included in each group. Accordingly, further prospective studies are required because of the limited evidence available to date.

CONCLUSION

PB type, T3 tumour stage, and positive lymph node metastasis are independent predictors of lower survival in South American patients with ampullary adenocarcinoma treated by curative pancreaticoduodenectomy. Further evaluation of adjuvant and multimodal treatments is warranted, especially in patients with these high-risk factors.

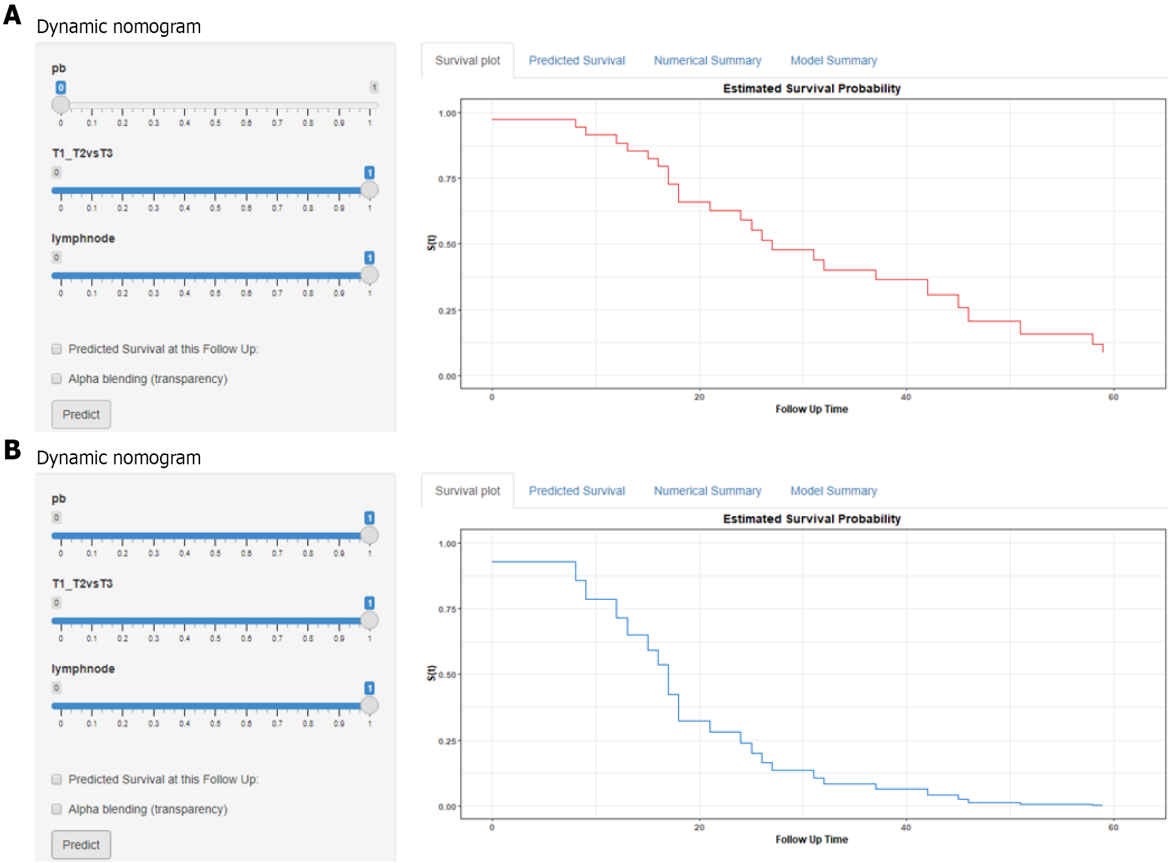

Figure 2 Comparison of survival probability between the intestinal/other (A) and pancreaticobiliary (B) types in patients with pT3 and pN+ adenocarcinoma of the ampulla of Vater.

ARTICLE HIGHLIGHTS

Research background

Ampullary adenocarcinoma (AAC) is a rare neoplasm that has not been studied previously in South American countries.

Research motivation

AAC might have different patterns of recurrence and overall survival than what has been reported in centres from Europe, Asia or North America.

Research objectives

To identify risk factors and their impact on overall survival in patients who underwent pancreaticoduodenectomy (PD) for AAC.

Research methods

We conducted a retrospective cohort study and analysed histopathologic predictors of survival in a Cox regression model.

Research results

Nearly two-thirds of patients had the intestinal-type AAC and around 25% had the Pancreatobiliary (PB)-type AAC. However, overall survival (OS) was lower for the latter subtype. Independently of the T3 and N+ tumour stage.

Research conclusions

Patients with PB-type AAC, T3 and N+ tumour stage are at higher risk of lower survival after curative PD.

Research perspectives

Identification of high-risk patients would guide the clinicians for the use of AT.

Further studies are warranted.

ACKNOWLEDGEMENTS

We would like to thank Pr. Lorenzo-Bermejo J for his valuable support in the review of the statistical methods.

REFERENCES

1 **Askew J**, Connor S. Review of the investigation and surgical management of resectable ampullary adenocarcinoma. *HPB (Oxford)* 2013; **15**: 829-838 [PMID: 23458317 DOI: 10.1111/hpb.12038]
2 **O'Connell JB**, Maggard MA, Manunga J Jr, Tomlinson JS, Reber HA, Ko CY, Hines OJ. Survival after resection of ampullary carcinoma: a national population-based study. *Ann Surg Oncol* 2008; **15**: 1820-1827 [PMID: 18369675 DOI: 10.1245/s10434-008-9886-1]
3 **Cameron JL**, He J. Two thousand consecutive pancreaticoduodenectomies. *J Am Coll Surg* 2015; **220**: 530-536 [PMID: 25724606 DOI: 10.1016/j.jamcollsurg.2014.12.031]
4 **Chandrasegaram MD**, Chiam SC, Chen JW, Khalid A, Mittinty ML, Neo EL, Tan CP, Dolan PM, Brooke-Smith ME, Kanhere H, Worthley CS. Distribution and pathological features of pancreatic, ampullary, biliary and duodenal cancers resected with pancreaticoduodenectomy. *World J Surg Oncol* 2015; **13**: 85 [PMID: 25890023 DOI: 10.1186/s12957-015-0498-5]
5 **Sommerville CAM**, Limongelli P, Pai M. Survival analysis after pancreatic resection for ampullary and pancreatic head carcinoma: An analysis of clinicopathological factors. *J Surg Oncol* 2009; **100**: 651-656 [PMID: 19722229 DOI: 10.1002/jso.21390]
6 **Morris-Stiff G**, Alabraba E, Tan YM, Shapey I, Bhati C, Tanniere P, Mayer D, Buckels J, Bramhall S, Mirza DF. Assessment of survival advantage in ampullary carcinoma in relation to tumour biology and morphology. *Eur J Surg Oncol* 2009; **35**: 746-750 [PMID: 19167859 DOI: 10.1016/j.ejso.2008.10.010]
7 **Okano K**, Oshima M, Yachida S, Kushida Y, Kato K, Kamada H, Wato M, Nishihira T, Fukuda Y, Maeba T, Inoue H, Masaki T, Suzuki Y. Factors predicting survival and pathological subtype in patients with ampullary adenocarcinoma. *J Surg Oncol* 2014; **110**: 156-162 [PMID: 24619853 DOI: 10.1002/jso.23600]
8 **Zheng-Pywell R**, Reddy S. Ampullary Cancer. *Surg Clin North Am* 2019; **99**: 357-367 [PMID: 30846039 DOI: 10.1016/j.suc.2018.12.001]
9 **Kimura W**, Futakawa N, Yamagata S. Different Clinicopathologic Findings in Two Histologic Types of Carcinoma of Papilla of Vater. *Japanese J Cancer Res* 1994; **85**: 161-166 [DOI: 10.1111/j.1349-7006.1994.tb02077.x]
10 **Yoen H**, Kim JH, Hur BY, Ahn SJ, Jeon SK, Choi SY, Lee KB, Han JK. Prediction of tumor recurrence and poor survival of ampullary adenocarcinoma using preoperative clinical and CT findings. *Eur Radiol* 2021; **31**: 2433-2443 [DOI: 10.1007/s00330-020-07316-4]
11 **Overman MJ**, Soifer HS, Schueneman AJ, Ensor J Jr, Adsay V, Saka B, Neishaboori N, Wolff RA, Wang H, Schnabel CA, Varadhachary G. Performance and prognostic utility of the 92-gene assay in the molecular subclassification of ampullary adenocarcinoma. *BMC Cancer* 2016; **16**: 668 [PMID: 27549176 DOI: 10.1186/s12885-016-2677-3]
12 **Schueneman A**, Goggins M, Ensor J, Saka B, Neishaboori N, Lee S, Maitra A, Varadhachary G, Rezaee N, Wolfgang C, Adsay V, Wang H, Overman MJ. Validation of histomolecular classification utilizing histological subtype, MUC1, and CDX2 for prognostication of resected ampullary adenocarcinoma. *Br J Cancer* 2015; **113**: 64-68 [PMID: 25989273 DOI: 10.1038/bjc.2015.172]
13 **Shroff S**, Overman MJ, Rashid A, Shroff RT, Wang H, Chatterjee D, Katz MH, Lee JE, Wolff RA, Abbruzzese JL, Fleming JB. The expression of PTEN is associated with improved prognosis in patients with ampullary adenocarcinoma after pancreaticoduodenectomy. *Arch Pathol Lab Med* 2013; **137**: 1619-1626 [PMID: 24168499 DOI: 10.5858/arpa.2012-0418-OA]
14 **Kim BJ**, Jang HJ, Kim JH, Kim HS, Lee J. KRAS mutation as a prognostic factor in ampullary adenocarcinoma: a meta-analysis and review. *Oncotarget* 2016; **7**: 58001-58006 [PMID: 27517148 DOI: 10.18632/oncotarget.11156]
15 **Valsangkar NP**, Ingkakul T, Correa-Gallego C, Mino-Kenudson M, Masia R, Lillemoe K. D, Ferná ndez-del Castillo C, Warshaw AL, Liss AS, Thayer SP. Survival in ampullary cancer: potential role of different KRAS mutations. *Surg (United States)* 2015; **157**: 260-268 [DOI: 10.1016/j.surg.2014.08.092]
16 **Asano E**, Okano K, Oshima M, Kagawa S, Kushida Y, Munekage M, Hanazaki K, Watanabe J, Takada Y, Ikemoto T, Shimada M, Suzuki Y; Shikoku Consortium of Surgical Research (SCSR). Phenotypic characterization and clinical outcome in ampullary adenocarcinoma. *J Surg Oncol* 2016; **114**: 119-127 [PMID: 27132476 DOI: 10.1002/jso.24274]
17 **Park HM**, Park SJ, Han SS, Hong SK, Hong EK, Kim SW. Very early recurrence following pancreaticoduodenectomy in patients with ampullary cancer. *Medicine (Baltimore)* 2019; **98**: e17711 [PMID: 31689805 DOI: 10.1097/MD.0000000000017711]

18 **Lino-Silva LS**, Gómez-Álvarez MA, Salcedo-Hernández RA, Padilla-Rosciano AE, López-Basave HN. Prognostic importance of lymph node ratio after resection of ampullary carcinomas. *J Gastrointest Oncol* 2018; **9**: 1144-1149 [PMID: 30603134 DOI: 10.21037/jgo.2018.07.04]

19 **World Medical Association**. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013; **310**: 2191-2194 [PMID: 24141714 DOI: 10.1001/jama.2013.281053]

20 **Kimura W**, Futakawa N, Zhao B. Neoplastic diseases of the papilla of Vater. *J Hepatobiliary Pancreat Surg* 2004; **11**: 223-231 [PMID: 15368105 DOI: 10.1007/s00534-004-0894-7]

21 **Bowitz Lothe IM**, Kleive D, Pomianowska E, Cvancarova M, Kure E, Dueland S, Gladhaug IP, Labori KJ. Clinical relevance of pancreatobiliary and intestinal subtypes of ampullary and duodenal adenocarcinoma: Pattern of recurrence, chemotherapy, and survival after pancreatoduodenectomy. *Pancreatology* 2019; **19**: 316-324 [PMID: 30713128 DOI: 10.1016/j.pan.2019.01.019]

22 **Lisita Rosa VD**, Maris Peria F, Ottoboni Brunaldi M. Carcinoma of Ampulla of Vater: Carcinogenesis and Immunophenotypic Evaluation. J Clin Epigenetics. 2017;03(03):1-5. DOI:10.21767/2472-1158.100059 [DOI: 10.21767/2472-1158.100059]

23 **Zimmermann C**, Wolk S, Aust DE, Meier F, Saeger HD, Ehehalt F, Weitz J, Welsch T, Distler M. The pathohistological subtype strongly predicts survival in patients with ampullary carcinoma. *Sci Rep* 2019; **9**: 12676 [PMID: 31481741 DOI: 10.1038/s41598-019-49179-w]

24 **Ang DC**, Shia J, Tang LH, Katabi N, Klimstra DS. The utility of immunohistochemistry in subtyping adenocarcinoma of the ampulla of vater. *Am J Surg Pathol* 2014; **38**: 1371-1379 [PMID: 24832159 DOI: 10.1097/PAS.0000000000000230]

25 **Liu F**, Shen D, Ma Y, Song Q, Wang H. Identification of ampullary carcinoma mixed subtype using a panel of six antibodies and its clinical significance. *J Surg Oncol* 2019; **119**: 295-302 [PMID: 30548547 DOI: 10.1002/jso.25311]

26 **Verbeke CS**, Menon KV. Redefining resection margin status in pancreatic cancer. *HPB (Oxford)* 2009; **11**: 282-289 [PMID: 19718354 DOI: 10.1111/j.1477-2574.2009.00055.x]

27 **Amini A**, Miura JT, Jayakrishnan TT, Johnston FM, Tsai S, Christians KK, Gamblin TC, Turaga KK. Is local resection adequate for T1 stage ampullary cancer? *HPB (Oxford)* 2015; **17**: 66-71 [PMID: 25395092 DOI: 10.1111/hpb.12297]

28 **Fernandez-Placencia R**, Berrospi-Espinoza F, Uribe-Rivera K, Medina-Cana J, Chavez-Passiuri I, Sanchez-Bartra N, Paredes-Galvez K, Luque-Vasquez Vasquez C, Celis-Zapata J, Ruiz-Figueroa E. Preoperative Predictors for 90-Day Mortality after Pancreaticoduodenectomy in Patients with Adenocarcinoma of the Ampulla of Vater: A Single-Centre Retrospective Cohort Study. *Surg Res Pract* 2021; **2021**: 1-9 [DOI: 10.1155/2021/6682935]

29 **Inoue Y**, Saiura A, Yoshioka R, Ono Y, Takahashi M, Arita J, Takahashi Y, Koga R. Pancreatoduodenectomy With Systematic Mesopancreas Dissection Using a Supracolic Anterior Artery-first Approach. *Ann Surg* 2015; **262**: 1092-1101 [PMID: 25587814 DOI: 10.1097/SLA.0000000000001065]

30 **Ecker BL**, McMillan MT, Asbun HJ, Ball CG, Bassi C, Beane JD, Behrman SW, Berger AC, Dickson EJ, Bloomston M, Callery MP, Christein JD, Dixon E, Drebin JA, Castillo CF, Fisher WE, Fong ZV, Haverick E, Hollis RH, House MG, Hughes SJ, Jamieson NB, Javed AA, Kent TS, Kowalsky SJ, Kunstman JW, Malleo G, Poruk KE, Salem RR, Schmidt CR, Soares K, Stauffer JA, Valero V, Velu LKP, Watkins AA, Wolfgang CL, Zureikat AH, Vollmer CM Jr. Characterization and Optimal Management of High-risk Pancreatic Anastomoses During Pancreatoduodenectomy. *Ann Surg* 2018; **267**: 608-616 [PMID: 28594741 DOI: 10.1097/SLA.0000000000002327]

31 **Moekotte AL**, Malleo G, van Roessel S, Bonds M, Halimi A, Zarantonello L, Napoli N, Dreyer SB, Wellner UF, Bolm L, Mavroeidis VK, Robinson S, Khalil K, Ferraro D, Mortimer MC, Harris S, Al-Sarireh B, Fusai GK, Roberts KJ, Fontana M, White SA, Soonawalla Z, Jamieson NB, Boggi U, Alseidi A, Shablak A, Wilmink JW, Primrose JN, Salvia R, Bassi C, Besselink MG, Abu Hilal M. Gemcitabine-based adjuvant chemotherapy in subtypes of ampullary adenocarcinoma: international propensity score-matched cohort study. *Br J Surg* 2020; **107**: 1171-1182 [PMID: 32259295 DOI: 10.1002/bjs.11555]

32 **Zhou YM**, Liao S, Wei YZ, Wang SJ. Prognostic factors and benefits of adjuvant therapy for ampullary cancer following pancreatoduodenectomy: A systematic review and meta-analysis. *Asian J Surg* 2020; **43**: 1133-1141 [PMID: 32249101 DOI: 10.1016/j.asjsur.2020.03.007]

33 **Affi Koprowski M**, Sutton TL, Brinkerhoff BT, Grossberg A, Sheppard BC, Mayo SC. Oncologic outcomes in resected ampullary cancer: Relevance of histologic subtype and adjuvant chemotherapy. *Am J Surg* 2021; **221**: 1128-1134 [PMID: 33883071 DOI: 10.1016/j.amjsurg.2021.04.001]

34 **Quero G**, Fiorillo C, De Sio D, Laterza V, Menghi R, Cina C, Schena CA, Rosa F, Galiandro F, Alfieri S. The role of mesopancreas excision for ampullary carcinomas: a single center propensity-score matched analysis. *HPB (Oxford)* 2021; **23**: 1557-1564 [DOI: 10.1016/j.hpb.2021.03.011]

35 **Neoptolemos JP**, Moore MJ, Cox TF, Valle JW, Palmer DH, McDonald AC, Carter R, Tebbutt NC, Dervenis C, Smith D, Glimelius B, Charnley RM, Lacaine F, Scarfe AG, Middleton MR, Anthoney A, Ghaneh P, Halloran CM, Lerch MM, Oláh A, Rawcliffe CL, Verbeke CS, Campbell F, Büchler MW; European Study Group for Pancreatic Cancer. Effect of adjuvant chemotherapy with fluorouracil plus folinic acid or gemcitabine vs observation on survival in patients with resected periampullary adenocarcinoma: the ESPAC-3 periampullary cancer randomized trial. *JAMA* 2012; **308**: 147-156 [PMID: 22782416 DOI: 10.1001/jama.2012.7352]

36 **Kim HS**, Jang JY, Yoon YS, Park SJ, Kwon W, Kim SW, Han HS, Han SS, Park JS, Yoon DS. Does

adjuvant treatment improve prognosis after curative resection of ampulla of Vater carcinoma? *J Hepatobiliary Pancreat Sci* 2020; **27**: 721-730 [PMID: 32652820 DOI: 10.1002/jhbp.801]

37 **Kamarajah SK**. Adjuvant radiotherapy following pancreaticoduodenectomy for ampullary adenocarcinoma improves survival in node-positive patients: a propensity score analysis. *Clin Transl Oncol* 2018; **20**: 1212-1218 [PMID: 29497964 DOI: 10.1007/s12094-018-1849-9]

38 **Ecker BL**, Vollmer CM Jr, Behrman SW, Allegrini V, Aversa J, Ball CG, Barrows CE, Berger AC, Cagigas MN, Christein JD, Dixon E, Fisher WE, Freedman-Weiss M, Guzman-Pruneda F, Hollis RH, House MG, Kent TS, Kowalsky SJ, Malleo G, Salem RR, Salvia R, Schmidt CR, Seykora TF, Zheng R, Zureikat AH, Dickson PV. Role of Adjuvant Multimodality Therapy After Curative-Intent Resection of Ampullary Carcinoma. *JAMA Surg* 2019; **154**: 706-714 [PMID: 31141112 DOI: 10.1001/jamasurg.2019.1170]

39 **Narang AK**, Miller RC, Hsu CC. Evaluation of adjuvant chemoradiation therapy for ampullary adenocarcinoma: The Johns Hopkins Hospital - Mayo Clinic collaborative study. *Radiat Oncol* 2011; **6**: 126 [DOI: 10.1186/1748-717x-6-126]

40 **Regalla DKR**, Jacob R, Manne A, Paluri RK. Therapeutic options for ampullary carcinomas. A review. *Oncol Rev* 2019; **13**: 440 [PMID: 31565197 DOI: 10.4081/oncol.2019.440]

41 **Bonet M**, Rodrigo A, Vázquez S, Carrizo V, Vilardell F, Mira M. Adjuvant therapy for true ampullary cancer: a systematic review. *Clin Transl Oncol* 2020; **22**: 1407-1413 [PMID: 31927720 DOI: 10.1007/s12094-019-02278-6]

42 **Miura JT**, Jayakrishnan TT, Amini A, Johnston FM, Tsai S, Erickson B, Quebbeman EJ, Christians KK, Evans DB, Gamblin TC, Turaga KK. Defining the role of adjuvant external beam radiotherapy on resected adenocarcinoma of the ampulla of vater. *J Gastrointest Surg* 2014; **18**: 2003-2008 [PMID: 25159502 DOI: 10.1007/s11605-014-2629-7]

43 **Vo NP**, Nguyen HS, Loh EW, Tam KW. Efficacy and safety of adjuvant therapy after curative surgery for ampullary carcinoma: A systematic review and meta-analysis. *Surg (United States)* 2021; 1-10 [DOI: 10.1016/j.surg.2021.03.046]

44 **Kondo S**, Takada T, Miyazaki M, Miyakawa S, Tsukada K, Nagino M, Furuse J, Saito H, Tsuyuguchi T, Yamamoto M, Kayahara M, Kimura F, Yoshitomi H, Nozawa S, Yoshida M, Wada K, Hirano S, Amano H, Miura F; Japanese Association of Biliary Surgery; Japanese Society of Hepato-Biliary-Pancreatic Surgery; Japan Society of Clinical Oncology. Guidelines for the management of biliary tract and ampullary carcinomas: surgical treatment. *J Hepatobiliary Pancreat Surg* 2008; **15**: 41-54 [PMID: 18274843 DOI: 10.1007/s00534-007-1279-5]

45 **Mafficini A**, Amato E, Cataldo I, Rusev BC, Bertoncello L, Corbo V, Simbolo M, Luchini C, Fassan M, Cantù C, Salvia R, Marchegiani G, Tortora G, Lawlor RT, Bassi C, Scarpa A. Ampulla of Vater Carcinoma: Sequencing Analysis Identifies TP53 Status as a Novel Independent Prognostic Factor and Potentially Actionable ERBB, PI3K, and WNT Pathways Gene Mutations. *Ann Surg* 2018; **267**: 149-156 [PMID: 27611608 DOI: 10.1097/SLA.0000000000001999]

46 **Chavez MT**, Sharpe JP, O'Brien T, Patton KT, Portnoy DC, VanderWalde NA, Deneve JL, Shibata D, Behrman SW, Dickson PV. Management and outcomes following pancreaticoduodenectomy for ampullary adenocarcinoma. *Am J Surg* 2017; **214**: 856-861 [PMID: 28285709 DOI: 10.1016/j.amjsurg.2017.01.029]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com