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Original contribution

Clinicopathological features related to survival in adenocarcinoma of the Vaterian system in a Mexican population ☆

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Summary Adenocarcinomas of the ampulla of Vater account for 0.5% of malignant neoplasms of the gastrointestinal tract and 6% to 20% of malignant periampullary neoplasms, with most patients being candidates for elective surgery. Our objective was to evaluate the clinicopathological prognostic factors of ampullary adenocarcinomas after surgical resection in a Mexican population. From the records of the Department of Pathology at the Instituto Nacional de Cancerología, México, cases diagnosed as adenocarcinomas of the ampulla of Vater were selected over a period of 11 years, from January 2005 to September 2015. Cases with a pancreaticoduodenectomy report were included, and from each case, demographic and pathological data of the surgical specimen were obtained. Univariate and multivariate statistical analyses were performed using the log-rank test and Cox regression. Of 157 cases diagnosed as ampullary adenocarcinomas, 104 patients were excluded as not eligible for surgical treatment at the time of diagnosis. In the remaining 53 patients, a pancreaticoduodenectomy was performed. The mean age of the entire group was 55.4 years, and most were men. Intestinal-type adenocarcinomas were more frequent (77.4%) than pancreatobiliary-type (15.1%), with most being without perineural invasion, well to moderately differentiated, and less than 3 cm in size. Lymph node metastasis and age greater than 65 years had a negative impact on overall survival of the patients. The most convenient classification of malignant epithelial tumors of the Vaterian system is according to the histopathologic phenotype grouped into intestinal-, pancreatobiliary-, and mixed-type adenocarcinomas, as well as uncommon variants.

1. Introduction

The ampulla of Vater is strictly the anatomical region formed by the confluence of the common bile duct and the major pancreatic duct at distinct levels. It is separated from the duodenal

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aspect of the papilla of Vater by the Oddi sphincter; thus, these assembled structures constitute the Vaterian system. Because of this complex convergence, 3 types of mucosal epithelium can be distinguished: pancreatobiliary-type (ampulla of Vater), intestinal-type (duodenum), and between them, transitional foveolar-like mucosa (papilla of Vater) [1]. Adenocarcinomas arising from this anatomic region have been indistinctly called ampullary carcinomas, irrespective of the site of origin. According to their location, carcinomas were formerly classified as intra-ampullary, periampullary, and mixed carcinomas, without consideration of the histologic phenotype. Up to now, no specific risk factors for ampullary carcinoma have been clearly evidenced, but based on morphologic, histochemical, immunohistochemical, and molecular observations [2], pathogenesis could be related to chemical carcinogens due to the mix of the pancreatic juice and bile, predominantly in the common channel of the papilla of Vater (ampullopancreatobiliary common duct), where atypical epithelial changes are most frequently seen.

According to the Surveillance, Epidemiology, and End Results program of the US National Cancer Institute, carcinomas of the ampulla of Vater represent a small portion of the gastrointestinal malignant neoplasms, accounting for only 0.5% of all cases [3]. Contrary to pancreatic and common bile duct carcinomas, which remain steady, ampullary carcinoma shows a significant and sustained annual rise, probably due to improved surveillance methods and early diagnosis. Therefore, surgical treatment at the time of diagnosis is possible in most patients (85%-96%), with 5-year survival rate between 32% and 61% of these cases [4]. Moreover, ampullary adenocarcinomas have better prognosis than those originated in the pancreatic head, common distal bile duct, and duodenum, with overall and disease-free survivals largely dependent on the extension of the disease. Several clinical and tumor characteristics as obstructive jaundice on presentation, lymphovascular and perineural invasion, pancreatobiliary phenotype, and tumor (T), node (N) metastasis (M), and overall stages have been studied and considered as predictors of survival. In this study, we thoroughly analyzed several of these factors to establish reliable criteria for prognostic stratification after surgical resection in a Mexican population harboring adenocarcinoma of the Vaterian system (AVS). To the best of our knowledge, there are no similar studies in Latin American population.

2. Materials and methods

This is a cross-sectional, descriptive, observational, and retrolective study conducted in accordance with the institutional research and ethical requirements of the Helsinki Statement, Good Clinical Practices, and Mexican General Health Law Guidelines at the Instituto Nacional de Cancerología, México. Cases with pathological diagnosis of adenocarcinoma of the ampulla of Vater were retrieved from the files of the Department of Surgical Pathology from January 2005 to September 2015. Eligible cases were selected according to the following inclusion criteria: patients with clinical and pathological diagnosis of adenocarcinoma of the ampulla of Vater in whom a Whipple procedure or a pancreaticoduodenectomy had been performed and whose clinical digital record, including the pathologic report, as well as glass slides with histologic sections and paraffin blocks, were completely available. Demographic (sex and age), clinical (diagnosis and surgery dates, outcome), gross (localization and tumor size, number of dissected lymph nodes), and histologic (morphologic phenotype and grade, lymphovascular and perineural invasion, margin status, lymph node metastasis) data were properly registered. The seventh edition of the pathological (p)TNM staging system for ampullary carcinoma issued by Union for International Cancer Control (UICC) was used as reference [5]. Gross localization was recorded as intra-ampullary, periampullary, and mixed.

Histologic classification into intestinal and pancreatobiliary major phenotypes, as well as tumor grading, was made on a morphologic basis, without the use of immunohistochemistry, considering cytological and architectural features according to the criteria established by Kimura et al [6] and revised by Albores-Saavedra et al [7]. Briefly, intestinal-type adenocarcinomas are composed of irregular glands with central necrosis accompanied with inflammatory cells, lined by columnar cells with similar and regular oval nuclei, arranged in a pseudostratified configuration; atypical mitotic figures are frequently present. According to the histologic grade, cribriform and solid areas may be seen, and in general terms, the desmoplastic stroma around neoplastic tissue is scarce. On the other hand, pancreatobiliary-type adenocarcinoma has irregular branching glands lined by cuboidal to low columnar cells, arranged in a single layer, without nuclear pseudostratification; nuclei are usually rounded, displaying a high degree of pleomorphism; and small solid nests of neoplastic cells may be found. The most striking feature of pancreatobiliary adenocarcinoma is

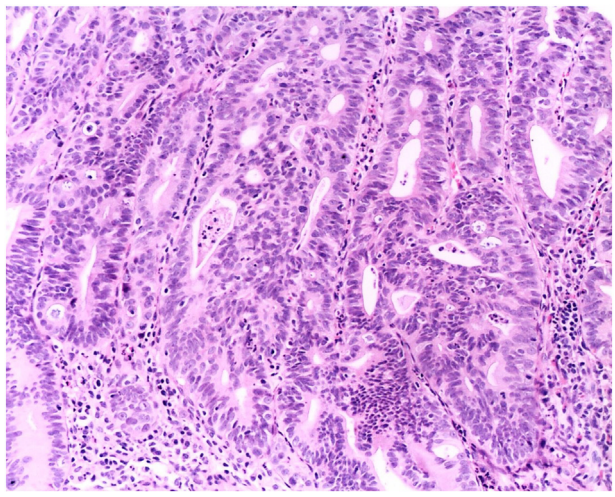


Fig. 1 Intestinal-type adenocarcinoma. Back-to-back tubular structures with an evident cribriform pattern are lined by columnar cells with hyperchromatic and pseudostratified elongated nuclei. Dirty-type necrosis is seen inside the lumens of neoplastic glands. The stroma is scarce, with some inflammatory cells (hematoxylin and eosin, original magnification ×20).

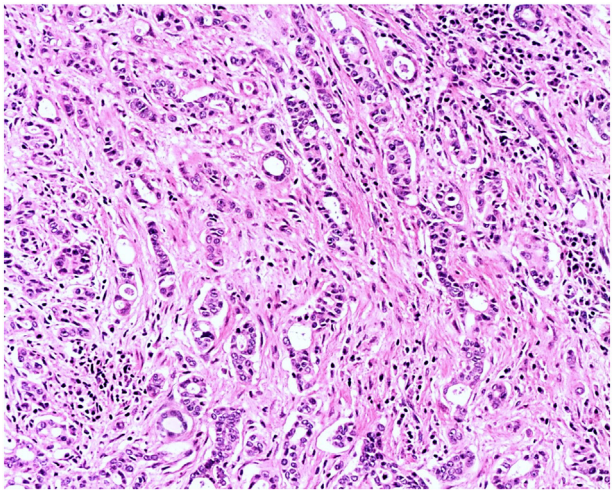


Fig. 2 Pancreatobiliary-type adenocarcinoma. Dispersed neoplastic glands lined by a single layer of polyhedral cells are surrounded by abundant desmoplastic stroma (hematoxylin and eosin, original magnification ×20).

the abundance of desmoplastic stroma (Figs. 1 and 2). Some ampullary adenocarcinomas may exhibit features of both (at least 10%) intestinal and pancreatobiliary phenotypes classified as mixed-type adenocarcinomas.

Statistical analysis was performed using the SPSS software package, version 25 (SPSS, Chicago, IL). Continuous variables were summarized as arithmetic means with SD and medians with interquartile ranges for descriptive analysis, whereas categorical variables were expressed as frequencies and percentages. Either Student *t* test or Mann-Whitney *U* test was used for 2 group comparisons according to data distribution evaluated by using the Kolmogorov-Smirnov and Shapiro Wilk tests. Comparisons between categorical variables were assessed using the χ^2 or Fisher exact test. A *P* value of less than .05 was accepted as statistically significant for 2-tailed tests.

All variables were dichotomized for survival curve analysis. Overall survival (OS) was measured from the day of diagnosis to the date of death or last follow-up, and comparisons among survival times were performed using a log-rank test as well as univariate and multivariate Cox regression analysis. X-tile software (version 3.6.1) [8] from the Yale University was used to evaluate the optimal cutoffs contrasted versus OS in numeric variables including age, tumor size, number of dissected lymph nodes, and lymph node ratio (LNR), whereas the optimal cutoffs to establish relationships between these and other clinical variables were assessed with the freely available online tool "Cutoff Finder," based on R programming, developed by Budczies et al [9].

3. Results

A total of 157 cases diagnosed as adenocarcinomas of the ampulla of Vater were retrieved from the files of the

Table 1 Clinicopathological features of 53 adenocarcinomas of the Vaterian system

	n (%)
Age (y)	
Mean (SD)	55 (11)
<65	41 (77)
≥65	12 (23)
Sex	
Female	22 (41.5)
Male	31 (58.5)
Location	
Periampullary	19 (36)
Intra-ampullary	27 (51)
Mixed	7 (13)
Histologic phenotype	
Intestinal	
Pure intestinal	34 (64)
Mucinous component (30%)	1 (2)
Mucinous component (15%)	1 (2)
Mucinous component (5%)	3 (6)
Cribriform pattern	2 (4)
Pancreatobiliary	
Pure pancreatobiliary	7 (13)
Pancreatobiliary/signet ring cells	1 (2)
Other	
Pure mucinous	1 (2)
Intestinal/pancreatobiliary (mixed)	2 (4)
Poorly differentiated	1 (2)
Histologic grade	
1	15 (28)
2	34 (64)
3	4 (8)
Tumor size (cm)	
Median (range)	2.0 (0.4–6.2)
<3	32 (68)
≥3	15 (32)
Dissected LN	
Median (range)	14 (7–39)
<12	11 (22)
≥12	40 (78)
Affected LN	
No	32 (60)
Yes	19 (36)
No. of metastatic LN	
1	8 (15)
≥2	11 (21)
TNM (T)	
T1	7 (13)
T2	28 (53)
T3	18 (34)
Lymphatic permeation	
No	41 (77)
Yes	12 (23)
Vascular permeation	
No	50 (94)
Yes	3 (6)
Perineural invasion	
No	39 (74)
Yes	14 (26)

Abbreviation: LN, lymph nodes.

Table 2 Univariate Cox regression analysis of OS for adenocarcinomas of the Vaterian system

	n	Survival (mo), median (SE) (95%CI)	Hazard ratio (95% CI)	*P*
Age (y)				
<65	41	59.1 (20.1) (19.8-98.5)		
≥65	12	7.2 (6.9) (0.0-20.7)	2.740 (1.102-6.813)	.030 *
Sex				
Female	22	–		
Male	31	39.1 (10.6) (18.4-59.8)	2.064 (0.812-5.246)	.128
Location				
Periampullary	19	–		
Intra-ampullary	27	39.1 (16.3) (7.2-70.9)	2.534 (0.909-7.066)	.076 **
Mixed	7	–	1.370 (0.326-5.764)	.668
Histopathologic subtype				
Intestinal	41	40.7 (13.4) (14.5-66.9)		
Pancreatobiliary	8	16.4	1.323 (0.375-4.668)	.664
Other	4	–	0.445 (0.059-3.348)	.445
Histologic grade				
1	15	113.3 (71.9) (0.0-254.4)		
2	34	35.9 (8.9) (18.4-53.4)	2.607 (0.865-7.854)	.089 **
3	4	39.1 –	0.999 (0.111-9.025)	.999
Tumor size				
<3 cm	32	113.3 (0.0) –		
≥3 cm	15	40.7 –	0.831 (0.309-2.232)	.713
Dissected LN				
<12	11	40.7 (13.7) (13.9-67.5)		
≥12	40	59.1 (24.2) (11.7-106.6)	0.828 (0.300-2.284)	.715
LNR cutoff[a]				
<0.05	35	113.3 (55.7) (3.9-222.6)		
≥0.05	16	39.1 (6.7) (26.0-52.2)	1.814 (0.744-4.423)	.190
<0.10	40	113.3 (53.8) (7.9-218.7)		
≥0.10	11	40.7 (11.9) (17.4-63.9)	1.551 (0.594-4.050)	.370
<0.15	44	113.3 (40.6) (33.7-192.9)		
≥0.15	7	59.1 (0.0) –	1.141 (0.333-3.904)	.834
<0.20	46	40.7 (20.2) (1.1-80.3)		
≥0.20	5	59.1 (0.0) –	0.885 (0.205-3.818)	.870
<0.25	46	40.7 (20.2) (1.1-80.3)		
≥0.25	5	59.1 (0.0) –	0.885 (0.205-3.818)	.870
<0.30	48	59.1 (19.3) (21.4-96.9)		
≥0.30	3	19.9 –	0.827 (0.110-6.200)	.853
TNM(T)				
T1	7	–		
T2	28	40.7 (18.2) (5.1-76.3)	2.764 (0.612-12.493)	.186
T3	18	39.1 (10.0) (19.5-58.7)	2.359 (0.482-11.537)	.289
TNM(N)1				
N0	32	113.3 (55.7) (4.1-222.4)		
N1	19	39.1 (14.4) (10.8-67.4)	2.490 (1.016-6.102)	.046 *
TNM(N)2				
N0	32	113.3 (55.7) (4.1-222.4)		
N1	8	39.1 (12.1) (15.3-62.9)	2.930 (1.100-7.802)	.031 *
N2	11	59.1 (0.0)-	1.812 (0.489-6.716)	.374
Lymphatic permeation				
No	41	59.1 (13.6) (32.4-85.8)		
Yes	12	25.8 –	1.175 (0.430-3.210)	.753
Vascular permeation				
No	50	40.7 (12.8) (15.5-65.8)		
Yes	3	–	0.645 (0.086-4.841)	.670
Perineural invasion				
No	39	113.3 (43.5) (28.0-198.6)		
Yes	14	40.7 (7.8) (25.3-56.0)	1.649 (0.662-4.103)	.283

Department of Surgical Pathology. One hundred four patients were excluded because they were not suitable for surgical treatment at the time of diagnosis, because they clinically presented at an advanced disease stage, with direct invasion to adjacent organs and anatomic structures, and/or with one or more distant metastases. In a few cases, the surgical procedure was canceled at the time of the initial laparotomy because of the extensive disease; occasionally, patients refused the surgical procedure. In the remaining 53 patients, a pancreaticoduodenectomy was performed, and the clinical and pathological information, as well as pathological material, was complete; therefore, they met the inclusion criteria.

There were 31 men (58.5%) and 22 women (41.5%; male-to-female ratio, 1.4:1), and the mean age for the entire group was 55 ± 11 years (range, 35-79 years). In 45 (85%) patients, panendoscopic biopsies were obtained from the ampullary lesions before the surgical procedure; in the remaining 8 cases (15%), external reports supported surgical treatment. Forty-five cases had previous panendoscopic biopsies diagnosed as follows: there were 31 (68.9%) intestinal-type adenocarcinomas (2 with cribriform areas, 1 with papillary pattern, and 1 with both cribriform and papillary patterns), 3 (6.7%) pancreatobiliary-type adenocarcinomas, 2 (4.4%) mixed adenocarcinoma (intestinal and pancreatobiliary), 1 (2.2%) poorly differentiated adenocarcinoma, 5 (11.1%) cases diagnosed as high-grade intraepithelial neoplasia/dysplasia, and 3 (6.7%) adenomas (data not shown).

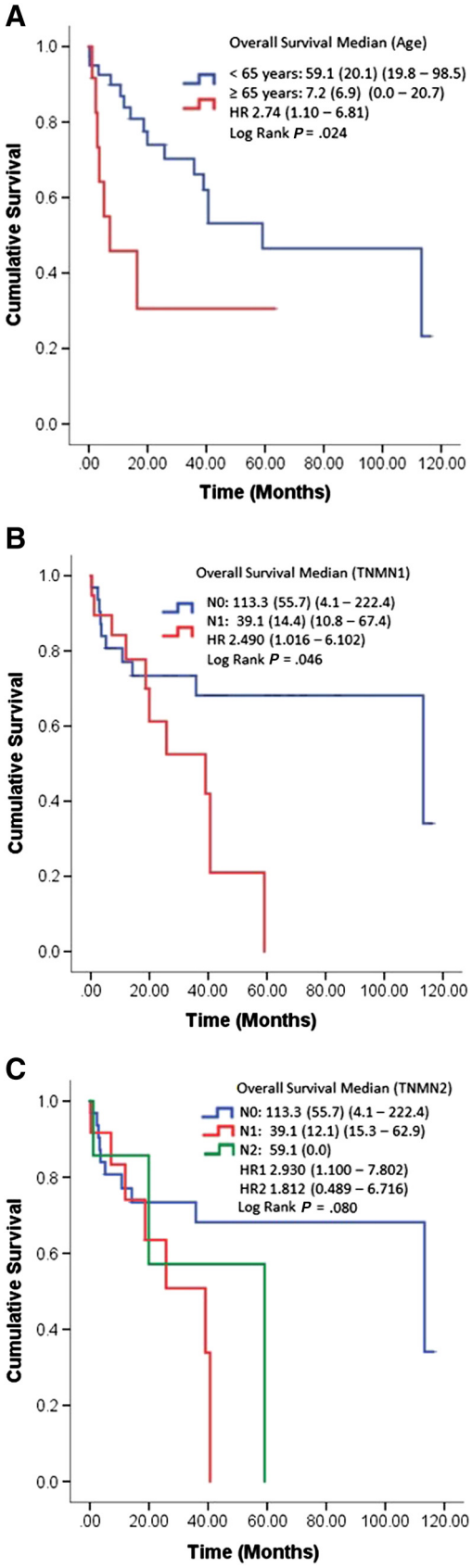
On pancreaticoduodenectomy, 13 cases showed neighboring premalignant lesions: villous (6 cases), tubulovillous (1 case), and tubular (1 case) adenomas, as well as pancreatic intraepithelial neoplasia (PanIN) grades 3 (2 cases) 2 (1 case), and 1 (2 cases). There was a good concordance regarding histopathologic diagnosis before and after surgical procedure ($P = .028$; data not shown). The median tumor size was 2.0 cm (0.4-6.2 cm); in 6 patients (11%), tumor size was not recorded. The number and location of the dissected lymph nodes were specified in 51 patients; in 2 cases, the lymph node status was unknown. Nineteen cases had lymph node metastasis (36%). The median number of dissected lymph nodes was 14 (range, 7-39), whereas the median number of metastatic lymph nodes was 2 (range, 1-8). Resection margins were tumor-free in all 53 patients. Metastatic disease was absent in all patients at the time of diagnosis. According to degree of differentiation, there were 14 (34%) well-differentiated (G1) intestinal-type adenocarcinomas; 26 (63%) and 6 (75%) moderately differentiated intestinal-type and pancreatobiliary-type (G2) adenocarcinomas, respectively; and 1 (3%) and 2 (25%) poorly differentiated (G3) intestinal-type and pancreatobiliary adenocarcinomas, respectively. The clinicopathological features of the 53 cases are summarized in Table 1. There were no patients with clinical history of familial adenomatous polyposis.

Univariate analysis was performed by means of Cox regression (Table 2). Patients' age (<65 or ≥65 years) and lymph node involvement (yes or no) showed statistically significant differences in OS; the median survival in patients younger than 65 years was 59.1 months, whereas that in patients 65 years or older was 7.2 months ($P = .030$; Fig. 3A). On the other hand, periampullary location and well-differentiated (G1) adenocarcinomas showed a trend toward better OS. The median survival in patients without regional lymph node metastases was 113.3 months after surgery compared with 39.1 months in patients with metastatic cancers ($P = .046$; Fig. 3B and C). The LNR did not show statistically significant differences. In the multivariate analysis, age remained as an independent prognostic factor (hazard ratio, 3.47; $P = .027$; Table 3). The relationships between clinicopathological characteristics in patients with adenocarcinoma of ampulla of Vater are shown in Table 4. The N stages showed a significant association with perineural invasion ($P = .0025$) because in 84.4% of cases at N0 stage, perineural invasion was not demonstrated. The presence of metastatic lymph nodes correlated ($P = .005$) with histologic grade; tumor grades G2 and G3 showed higher frequency of affected lymph nodes compared with G1 (84.2% and 10.5% versus 5.3% respectively). Most adenocarcinomas with intestinal phenotype lacked perineural invasion and were well to moderately differentiated. For multiple comparisons, we used the Bonferroni correction in post hoc analyses.

4. Discussion

AVS (formerly ampulla of Vater) is among the periampullary cancers including those originated within 2 cm of the papilla of Vater, such as pancreatic, biliary, and duodenal carcinomas. Although these neoplasms share a common embryonic origin (distal foregut), a similar surgical approach, and a potential field of cancerization [10], they display significant differences regarding survival outcome and incidence [11]. Adenocarcinomas originated in the Vaterian system are among the periampullary malignant neoplasms with best survival rates, despite their greater frequency, after pancreatic cancer. AVS can originate from intestinal or pancreatobiliary epithelia, and the biological behavior largely depends on this condition. Since the original characterization of adenocarcinoma of the ampulla of Vater by Outerbridge in 1913 (referred by Carter et al [12]), several schematic classifications have been proposed, including those by gross and growth pattern

Footnotes to Table 2:
NOTE. The P values presented are from the Cox regression analysis. Dash (–) refers to data not available.
[a] All possible cutoff values for LNR and other numeric variables were tested by the X-tile software.
* $P < .05$ was considered statistically significant.
** $P < .1$ was considered borderline significant.



[7], histopathologic [6], histoanatomical [13], immunohistochemical [14], and histomolecular classification [15] (morphology plus immunohistochemistry) as pathological prognostic variables. The biological significance of such distinction between intestinal and pancreatobiliar phenotypes has been recently emphasized in a joint genomic project [16]. AVS is more frequent in men, with a ratio of 1.5:1; as in our study, the low-grade intestinal phenotype has better prognosis, and OS depends on the extent of neoplasm (local, regional, or systemic). In this study, patients with AVS were on average 10 years younger (mean age, 55.4 years) than those reported in other similar series, and older patients (>65 years) had worse prognosis. This adverse outcome could be attributed to the natural process of aging associated with more clinical, medical, and surgical risk factors, plus less predictable convalescence. Schueneman et al [17] also found in a multivariate analysis that age was associated with poor survival, although they did not explain such finding.

Our results are in accordance with those published in other series; we found that histomorphologic assessment is reproducible, reliable, and predictive, thus emphasizing the proper functioning of this straightforward stratification approach. Immunohistochemistry is a powerful ancillary tool, which should be used whenever possible, but mainly in panendoscopic biopsies and when morphologic features are superimposed or not well defined, such as mixed-type, poorly differentiated, and undifferentiated adenocarcinomas. From our point of view, in daily practice, morphologic classification does not represent a major challenge. Ang et al [18] reported a good agreement (overall κ value = 0.53; $P < .00001$) for histologic typing, and most of the discordant cases were within the group of mixed adenocarcinomas. Westgaard et al [19] reported an almost perfect interobserver agreement (κ = 0.90; 95% confidence interval, 0.82-0.99) for determination of histologic type of differentiation. In a study of 108 cases of periampullary carcinomas by Kumari et al [20], including 91 cases of ampullary carcinomas, 84.2% of cases could be differentiated into intestinal and pancreatobiliary type by morphology alone, and in 4 more cases (3.7%; 2 mixed-type, 1 signet ring cell, and one undifferentiated carcinomas), immunohistochemistry solved the differentiation phenotype.

Pancreatobiliary-type adenocarcinomas are among the most frequent ampullary carcinomas worldwide [21], but we found a high prevalence of intestinal-type adenocarcinoma. The prevalence of intestinal type in those series reporting a higher frequency than pancreatobiliary-type ampullary adenocarcinomas is 46% to 68.3% [12,19]. Differences in this figure have been mostly attributed to an inaccurate interpretation of the histomorphologic features; therefore, the use of immunohistochemical and molecular markers would be advisable. However, the inherent population characteristics have been

Fig. 3 Kaplan-Meier survival curves of adenocarcinomas of the Vaterian system according to age less than 65 years (A), former TNM staging (TNM[N]1; B), and current TNM staging (TNM[N]2; C). The *P* values correspond to the log-rank test.

Table 3 Multivariate Cox regression analysis of OS for adenocarcinomas of the Vaterian system

	B	SE	Wald	*P*	Hazard ratio (95% CI)
Age (y)					
<65					
≥65	1.245	.561	4.922	.027 [a]	3.474 (1.156-10.440)
Location					
Periampullary					
Intra-ampullary	0.952	0.689	1.913	.167	2.592 (0.672-9.995)
Mixed	0.350	0.830	0.178	.673	1.420 (0.279-7.219)
Histologic grade					
1					
2	0.532	0.708	0.564	.453	1.702 (0.425-6.818)
3	−0.186	1.174	0.025	.874	0.830 (0.083-8.285)
TNM(N)					
N0					
N1	0.251	0.808	0.096	.757	1.285 (0.264-6.263)
TNM(N)2					
N0					
N1	0.190	0.705	0.072	.788	1.209 (0.304-4.814)
N2					

[a] Statistically significant.

underestimated, and the participation of yet-unknown predisposing factors and conditions (ie, nutritional, local environment, and genetics) might contribute to this contrast.

Several immunochemical markers are now considered for differential diagnosis between intestinal and pancreatobiliary phenotypes, as in predicting response to adjuvant chemotherapy and long-term survival. Cytokeratin (CK) 20, mucin (MUC) 2, and caudal-type homeobox 2 are characteristically expressed in intestinal-type adenocarcinomas, whereas CK7, CK17, MUC1, MUC4, and the gastric MUC5AC are expressed in

Table 4 Relationship between pathological variables in adenocarcinomas of the Vaterian system

	TNM (N0)			
Perineural invasion	N0 (%)	N1 (%)		*P*
No	27 (84.4)	9 (42.9)		
Yes	5 (15.6)	12 (57.1)		.0025 [a]
	Histologic grade			
Involved LN	G1 [b]	G2	G3	*P*
No	14 (43.8)	16 (50)	2 (6.2)	
Yes	1 (5.3)	16 (84.2)	2 (10.5)	.005 [a]
	Histologic type			
Perineural invasion	Intestinal	Pancreatobiliary		*P*
No	35 (85.4)	3 (37.5)		
Yes	6 (14.6)	5 (62.5)		.003 [a]
	Histologic type			
Histologic grade	Intestinal	Pancreatobiliary		*P*
G1	14 (34%)	0 (0%)		
G2	26 (63%)	6 (75%)		
G3	1 (3%)	2 (25%)		.017 [a]

χ^2 test or Fisher exact test ($n < 5$).

[a] Statistically significant.

[b] Statistically significant after post hoc test with Bonferroni correction.

pancreatobiliary-type adenocarcinomas [21-24]. Moreover, in a recent report, MUC5AC was strongly associated with prognosis [12]. However, according to some authors [25], objectivity of immunohistochemistry to the classification of ampullary cancers is questionable.

Precursor lesions (ie, adenomas) of intestinal-type adenocarcinomas have been described in a wide range of cases (36%-91%) [21]; in this study, we found only 8 cases (19.5%) with evidence of a precursor lesion, a figure below the lower side of the spectrum, that could be a sampling error, engulfment of the precursor lesion by the growing carcinoma, and occasionally development of the carcinoma through a mechanism of intestinal metaplasia. In the case of pancreatobiliary-type adenocarcinomas, high-grade PanIN has been found in 22% to 41% of the resected specimens [21]; in our series, the prevalence of high-grade PanIN was 25% (2 cases), within the range of previously reported frequency. PanIN is frequently associated with benign and malignant neoplasms of the ampulla of Vater [26].

Although we found low-risk pathological variables among intestinal-type adenocarcinomas, in comparison to pancreatobiliary-type adenocarcinomas, there was no improvement in OS, a controversial issue in the literature where the clinical significance of pathologic subtype is debated [27]. Further studies are warranted to determine the role and prognostic value of the intestinal subtype.

In this study, the presence of lymph node metastases had impact on OS independently of LNR. In several studies, LNR has predicted survival among patients with ampullary adenocarcinoma. In studies by Chen et al [28] and Roland et al [29], a LNR of 0.15 or greater correlated with lower survival after surgical resection with curative intent, whereas Kwon et al [30] found that a LNR of 0.17 or greater was associated with poor overall and locoregional relapse-free survival, the same as Tol et al [31], with a LNR of greater than 0.18.

Our results are in accordance with Sakata et al [32], who reported the number of metastatic lymph nodes, but not LNR, as an independent factor of worse prognosis. These controversial results could be attributable to unsuitable lymph node retrieval and downstaging of the disease, as discussed by Sakata et al [32]. Our results regarding the lack of significance of the LNR to discriminate OS agree with this statement supported by the fact that the median of harvested lymph node was 14; thus, the best way to assess the lymph node status (N) is the number of metastatic lymph nodes instead of LNR. According to those authors, LNR is particularly useful when the number of dissected lymph nodes is less than 12. Noteworthy, Falconi et al [33] reported that the risk of local recurrence was proportionally associated with progressive increase of LNR, whereas a higher number of dissected lymph nodes (mean, 16) correlated with less probability of tumor recurrence. On the other hand, some authors [34,35] have proposed to stratify the N stage of the TNM system into N1 (1-2 metastatic lymph nodes) and N2 (≥3metastatic lymph nodes) because it has higher prognostic value. This stratification has been recently adopted in the eighth edition of the TNM classification of malignant tumors [36]. Nevertheless, in this study, substaging of metastatic lymph nodes into N1 and N2 was no different from the classification of metastatic (N1), and no metastatic (N0) (Fig. 3C). Interestingly, in a very recent study in Germany, Schlitter et al [37] confirmed this finding in pancreatic adenocarcinoma, where nodal staging into categories N0/N1 had prognostic value in contrast to N0/N1/N2 substages. N1 and N2 categories did not improve the prognostic appraisal.

5. Conclusions

In conclusion, adenocarcinomas of the Vaterian system with intestinal phenotype are associated with low-risk pathological variables after curative-intent resection, whereas the pancreatobiliary phenotype is more aggressive. In this study, AVS with intestinal phenotype was related to a low histologic grade and absence of perineural invasion. Conversely, the presence of lymph node metastases and the pancreatobiliary phenotype had adverse prognosis. The most convenient classification of malignant epithelial tumors of the Vaterian system is according to the histopathologic phenotype grouped into intestinal-, pancreatobiliary, and mixed-type adenocarcinomas, as well as uncommon variants. Further studies are warranted to clearly define the applicability of immunohistochemistry and molecular methods, as well as the stratification of lymph node status, in planning the personalized adjuvant therapeutic approach and to estimate middle- and long-term prognosis for pancreaticoduodenectomy with curative intent.

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