Original Article

# Clinicopathological Findings of Adenocarcinoma of Ampulla of Vater: A Single Center Experience

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## ABSTRACT

**Background:**
Adenocarcinoma of the ampulla of Vater is a rare gastrointestinal cancer characterized by unique clinical and histopathological aspects. The annual incidence of ampullary adenocarcinoma has been increasing, and unlike pancreatic cancer, ampullary adenocarcinoma is often curable when diagnosed early. This study aimed to determine the clinicopathological features of ampullary adenocarcinomas based on a single-center experience.

**Materials and Methods:**
We conducted a retrospective study of patients diagnosed with ampullary lesions at our center from April 2020 to November 2024. A single pathologist reviewed all pathological reports and histopathological findings. Data on patient demographics, clinical presentations, histopathological subtypes, and tumor staging were systematically collected and analyzed.

**Results:**
A total of 47 patients were included, regarding tumor histology types, 43 patients had a pathological diagnosis of adenocarcinoma with a mean age of 55.81 years and a male-to-female ratio of 1.69 (P= 0.615). Obstructive jaundice was the most common presenting symptom, observed in 76.7% of cases with adenocarcinoma. Histopathological examination revealed 21(48.8%) intestinal and 22 (51.2%) pancreatobiliary subtypes. Survival and cure rates were higher in the intestinal type than in the pancreatobiliary type. Most adenocarcinomas (67.4%) were well differentiated and had better outcomes than those with moderately or poorly differentiated grades. Also, the cure rate was higher for negative lymph node involvement and limited tumor extension. Positive margins, advanced-stage tumors, and invasive characteristics correlated with poorer survival.

**Conclusion:**
We have found that adenocarcinomas are the most common type of tumors of the ampulla of Vater, followed by adenomatous polyps, gastrointestinal stromal tumor (GIST), and neuroendocrine tumor (NET) in the south of Iran from 2020 to 2024. Our findings emphasize the need for further research to deepen understanding of ampullary tumors and guide treatment and predict outcomes.

**Keywords:** Ampulla of Vater, Ampullary cancer, Adenocarcinoma, Clinical outcome, Histopathology

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## INTRODUCTION

The ampulla of Vater (AV), also regarded as the ampulla complex, is a significant anatomical point of connection where the pancreatic and common bile ducts join together to release their secretions into the duodenum (1).

Histologically, AV consists of cell types originating from three distinct locations: the pancreatic duct, the common bile duct, and the lining of the duodenum. The duodenal part of the ampulla is made up of a small intestinal lining, which has a transitional epithelium that shows a foveolar-like mucosa with sporadic goblet cells surrounding the ampulla's opening. In contrast, the end parts of both the pancreatic and common bile ducts are covered with pancreaticobiliary-type epithelium, showing a single mucinous layer of epithelial cells. Therefore, lesions in the AV can be associated with various medical conditions, and they are often categorized based on their nature (2-4). The AV can present different types of neoplasms, including carcinoma, adenoma, neuroendocrine tumor (NET), gangliocytic paraganglioma, and gastrointestinal stromal tumor (GIST) (5).

Ampullary carcinomas (AC) are rare, consisting just 0.2% of gastrointestinal cancers and about 7% of all periampullary cancers (6). Most of ampullary carcinomas are adenocarcinomas, but they can vary in other histological subtypes, including papillary, adenosquamous, and mucinous (7, 8). In contrast to pancreatic or biliary cancers, ampullary adenocarcinomas exhibit distinct clinicopathological features, frequently manifesting at an earlier stage due to symptoms of biliary obstruction, such as jaundice (9). Despite these unique characteristics, the rarity and histological heterogeneity of AC pose significant challenges for diagnosis and management (10).

Moreover, comprehensive data on ampullary carcinomas remain scarce, especially from single-center studies, which provide valuable insights into the complex clinicopathological features and their influence on treatment outcomes (11). There has been no published study regarding the pathological lesions of AV from Iran so far. In this study, we tried to extract and classify lesions of the AV from Abu Ali Sina Hospital, affiliated to Shiraz University of Medical Sciences, as the largest hepatobiliary surgery referral center in the south of Iran. The collected data provide valuable insights into the epidemiology and pathology of ampullary lesions, including their subtypes and their association with patient outcomes.

## MATERIAL AND METHODS

This retrospective cross-sectional study, conducted at Abu Ali Sina Hospital in Shiraz, Southern Iran, included patients clinically suspected of ampullary lesions who were referred for surgery or endoscopic retrograde cholangiopancreatography (ERCP) from April 2020 to November 2024. Information collected included the patients' age, sex, presenting symptoms, and biopsy findings. Surviving patients were telephoned to assess disease progression and any complications. Patient deaths have been determined through recorded information at Abu Ali Sina Hospital or by phone conversations with close relatives. Patients with ampullary tumors who we were unable to contact were excluded. This research was approved by the Ethics Committee for Human Research at the Medical University of Shiraz, and informed consent was obtained.

A single pathologist, unaware of the clinical reports, reassessed all tumor pathology slides. The slides were stained with hematoxylin and eosin, as well as immunohistochemistry, to determine the tumor's characteristics, including type, size, grade, depth of invasion, margins, lymphovascular or perineural invasion, involvement of the pancreatic head, lymph node involvement, and subtype (intestinal or pancreaticobiliary). Slides were accessible for evaluation for every patient. Clinical data and outcomes were extracted from patients' clinical charts.

Stata Statistical Software was utilized to perform statistical analysis (Release 17, College Station, TX: StataCorp LLC). Nominal variables were analyzed using the Pearson Chi-square test. The Shapiro test was employed to assess the normality of continuous variable distributions. Since the data did not follow a normal distribution, we utilized the Mann-Whitney U test (MWU) to compare continuous variables. The median was reported for variables in each group. The relationship between different mass characteristics and patients' prognosis was analyzed. Statistical significance was described as a P value $< 0.05$.

## RESULTS

### Patient characteristics

An overview of age, sex, size of the tumor (maximum diameter), and symptoms is provided in Table 1. We had a total of 47 cases. Regarding tumor histology types, 43 patients had a pathological diagnosis of adenocarcinoma. Two had adenomatous polyps (adenoma), one had GIST, and one had a NET. The mean age of all patients was 55.21± 9.91 years. Patients with adenocarcinoma had a mean age of 55.81, while patients with adenomatous polyps were older (mean age 60±16.97), and patients with GIST and NET were younger. Adenocarcinoma was more prevalent in male patients with a male-to-female ratio of 1.69 (P= 0.615).

The maximum mass diameter varied among the lesions.

Mean diameter was 2.26±1.27 cm, with a median size of 2.0 cm (range: 0.25–5.5 cm). Adenocarcinoma cases had a similar mean diameter of 2.28±1.22 cm, while adenomatous polyps were significantly smaller (median diameter: 0.48 cm). The largest diameters were observed in the GIST (4.5 cm) and NET (3.0 cm).

The most common presenting symptom across all cases was jaundice, reported in 70.2% of patients overall and 76.7% of those with adenocarcinoma. Pruritus was present in 44.7% of cases, exclusively among patients with adenocarcinoma. Weight loss was noted in 32% of patients, with 25.5% of those with adenocarcinoma.

Table 1. Overview of age, sex, and clinical status of patients diagnosed with ampullary lesions

| | | All (N=47) Adenocarcinoma (N=43) | | Adenomatous polyp (N=2) GIST (N=1) | | NET (N=1) | GIST (N=1) | NET (N=1) |
|---|---|---|---|---|---|---|---|---|
| | | Mean [SD] | Median (min, max) | Mean [SD] | Median (min, max) | Mean or median (min, max) | | |
| Age | | 55.21 ± 9.91 | 56 (27,72) | 55.81 ± 9.04 | 57 (27,69) | 60 (48, 72) | 30 | 45 |
| Durations of symptoms prior to admission (days) | | 3.58 ± 2.58 | 3 (1, 12) | 3.64 ± 2.69 | 3 (1, 12) | 3 (2, 4) | 2 | 4 |
| Max diameter of mass (cm) | | 2.26 ± 1.27 | 2 (0.25, 5.5) | 2.28 ± 1.22 | 2 (0.5, 5.5) | 0.48 (0.25, 0.70) | 4.50 | 3.0 |
| | | N (%) | | | | | | |
| Sex | Male | 29 (61.70) | | 27 (62.79) | | 0 (0.0) | 1 (100) | 1 (100) |
| | Female | 18 (38.30) | | 16 (37.21) | | 2 (100) | 0 (0.0) | 0 (0.0) |
| Symptoms | Jaundice | 33 (70.2) | | 33 (76.7) | | 2 (100) | 1 (100) | 1 (100) |
| | Pruritus | 21 (44.7) | | 21 (48.8) | | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Weight loss | 15 (32) | | 11 (25.5) | | 2 (100) | 1 (100) | 1 (100) |
| | Abdominal pain | 20 (42.5) | | 18 (41.8) | | 1 (50.00) | 0 (0.0) | 1 (100) |

**Characteristics of the adenocarcinoma cases**

Pathological findings of patients with adenocarcinoma and their relationship with prognosis are presented in Table 2. Most adenocarcinoma cases were well-differentiated (67.4%), followed by moderately (23.3%) and poorly differentiated (9.3%) grades. The prevalence of intestinal and pancreatobiliary subtypes were equal. Survival and cure rates in the intestinal type were higher than in the pancreatobiliary type. Well-differentiated grade also proved to have a higher survival rate.

Early-stage tumors (IA and IB) showed better outcomes, with 75% cure rates in stage IB. Advanced-stage tumors (III A and III B) were associated with higher mortality. Tumor extension beyond the ampulla was associated with poorer outcomes, particularly when it involved the peripancreatic soft tissue or extended beyond the sphincter of Oddi (P=0.094).

Patients without lymphovascular or perineural invasion had slightly better outcomes compared with those with invasion, but these differences were not statistically significant (P=0.338 and P=0.669, respectively).

Table 2. Pathological features of patients with resected ampullary adenocarcinoma (N=43)

| | | N (%) | Prognosis (%) | | | P value |
|---|---|---|---|---|---|---|
| | | | Cured | Under treatment | Expired | |
| Grade | Well-differentiated | 29 (67.4) | 15 (65.2) | 4 (17.4) | 4 (17.4) | 0.641 |
| | Moderately differentiated | 10 (23.3) | 2 (40) | 1 (40) | 1 (20) | |
| | Poorly differentiated | 4 (9.3) | 2 (66.6) | 0 (0.0) | 1 (33.3) | |
| Subtype | Pancreatobiliary | 22 (51.2) | 11 (57.9) | 3 (15.8) | 5 (26.3) | 0.440 |
| | Intestinal | 21 (48.8) | 8 (66.6) | 3 (25.0) | 1 (8.3) | |

Table 2. Pathological features of patients with resected ampullary adenocarcinoma (N=43)

| | | N (%) | Prognosis (%) | | | P value |
|---|---|---|---|---|---|---|
| | | | Cured | Under treatment | Expired | |
| Margins involvement | Yes | 3 (7.32) | 0 (0.0) | 1 (100) | 0 (0.0) | 0.153 |
| | No | 38 (92.68) | 19 (67.9) | 5 (17.9) | 4 (14.2) | |
| Lymph nodes involvement | Yes | 11 (26.8) | 5 (55.6) | 2 (22.2) | 2 (22.2) | 0.822 |
| | No | 30 (73.2) | 14 (66.6) | 4 (19.0) | 3 (14.3) | |
| Pancreatic head involvement | Yes | 24 (58.5) | 9 (56.3) | 4 (25.0) | 3 (18.8) | 0.674 |
| | No | 17 (41.5) | 10 (71.4) | 2 (14.2) | 2 (14.2) | |
| Stage | 0 | 1 (2.33) | 1 (100) | 0 (0.0) | 0 (0.0) | 0.101 |
| | I A | 5 (11.63) | 0 (0.0) | 0 (0.0) | 2 (100) | |
| | I B | 10 (23.26) | 6 (75.0) | 2 (25.0) | 0 (0.0) | |
| | II A | 11 (25.58) | 6 (75.0) | 1 (12.5) | 1 (12.5) | |
| | II B | 4 (9.30) | 0 (0.0) | 1 (100) | 0 (0.0) | |
| | III A | 10 (23.26) | 5 (62.5) | 1 (12.5) | 2 (25.0) | |
| | III B | 2 (4.65) | 1 (50.0) | 1 (50.0) | 0 (0.0) | |
| Tumor extension | Duodenal serosa | 2 (4.55) | 0 (0.0) | 1 (100) | 0 (0.0) | 0.094 |
| | No Invasion | 1 (2.27) | 1 (100) | 0 (0.0) | 0 (0.0) | |
| | Pancreas more than 0.5 cm | 4 (9.09) | 1 (50.0) | 0 (0.0) | 1 (50.0) | |
| | Pancreas up to 0.5 cm | 16 (36.36) | 8 (72.8) | 2 (18.2) | 1 (9.1) | |
| | All involved by tumor | 1 (2.27) | 0 (0.0) | 0 (0.0) | 1 (100) | |
| | beyond the sphincter of Oddi | 1 (2.27) | 0 (0.0) | 1 (100) | 0 (0.0) | |
| | Duodenal submucosa | 1 (2.27) | 1 (100) | 0 (0.0) | 0 (0.0) | |
| | Limited to the ampulla of Vater | 5 (11.36) | 1 (33.3) | 0 (0.0) | 2 (66.7) | |
| | Muscularis propria of the duodenum | 10 (22.73) | 7 (87.5) | 1 (12.5) | 0 (0.0) | |
| | Peripancreatic soft tissue | 3 (6.82) | 0 (0.0) | 1 (50.0) | 1 (50.0) | |
| Lymphovascular invasion | Yes | 10 (23.3) | 3 (60.0) | 1 (20.0) | 1 (20.0) | 0.338 |
| | No | 33 (76.74) | 16 (66.7) | 4 (16.7) | 4 (16.7) | |
| Perineural invasion | Yes | 12 (27.9) | 5 (50.0) | 3 (30.0) | 2 (20.0) | 0.669 |
| | No | 31 (72.1) | 14 (66.7) | 4 (19.0) | 3 (14.3) | |

**Characteristics of adenomatous polyp cases**

We had two patients with adenomatous polyps. One was a 48-year-old woman who presented with symptoms of weight loss and right upper quadrant abdominal pain for 4 months prior to her admission. She underwent Whipple's operation. In gross pathology, the serosal surface of the stomach and duodenum was normal. On pathology, an adenomatous polyp with low-grade dysplasia was found. There was no invasive component. Tumor size was 25 mm, and it was limited to the AV. All margins of the specimen were free of tumor. No lymphovascular or perineural invasion was seen. None of the 20 isolated regional lymph nodes was involved with the tumor.

The other case was a 72-year-old woman who presented with weight loss from 2 months prior to admission. Abdominopelvic sonography showed a dilated common bile duct (CBD). She underwent ERCP, and a biopsy of the ampullary mass was taken. Pathological evaluation of the biopsy revealed an ampullary adenomatous polyp with low-grade dysplasia with involvement of the margins. The patient underwent duodenal resection and cholecystectomy 1 month later. Pathological report of the second operation showed the same pathology with low-grade dysplasia and no associated invasive adenocarcinoma, with the duodenal margin uninvolved by carcinoma. No lymph node out of 13 isolated ones was involved. She received no chemotherapy or radiotherapy before or after her operation. She is now cured.

**Characteristics of the GIST (gastrointestinal stromal tumor) case**

There was one patient with the pathological diagnosis of GIST. The patient was a 30-year-old man who presented with weight loss, nausea, vomiting, and insomnia 2 months prior to his admission. The patient underwent Whipple's operation. The pathology report revealed a gastrointestinal stromal tumor, spindle cell type (C-KIT positive), with a size of 4.5X4.5X4 cm, at the ampullary site. The tumor was unifocal; the mitotic rate was <1 per 5.5 $mm^2$, and the Ki-67 index was <1%. Histological grade was well differentiated, and risk assessment was considered low. All surgical resected margins were free of tumor. There were seven free isolated lymph nodes. The stage was considered stage IA. Besides all these pathological evaluations, there was an immunohistochemical (IHC) study done on this case, which confirmed the diagnosis. After the surgery, the patient received neither chemotherapy regimen nor chemo-radiation therapy. The patient is now symptom-free 9 months following admission.

**Characteristics of the NET case**

We had only one patient with a diagnosis of NET. The patient was a 45-year-old man, known case of diabetes mellitus, hypertension, hypothyroidism, and with a history of coronary artery bypass graft (CABG) surgery, who presented with nausea and vomiting, weight loss, and abdominal pain, 4 months prior to admission. The patient underwent Whipple surgery. The pathology report revealed a well-differentiated neuroendocrine intra-ampullary tumor (low grade) with Ki67 (MIB-1): <3% and with invasion to the muscularis propria of the duodenum. The pancreatic neck and parenchymal margin were free of tumor. Other margins, including the bile duct, uncinate, proximal, and distal, were also free of tumor. Neither lymphovascular invasion nor perineural invasion had tumor cells. All 18 regional isolated lymph nodes were free. The stage was classified as Stage IB. Additionally, an IHC study was performed on the specimen, confirming the diagnosis. Now, 14 months after surgery, the patient is still receiving chemotherapy, but his condition is stable.

## DISCUSSION

Our study provides an overview of pathologically diagnosed cases at a single institution and was the first to investigate the pathological findings of tumors within the AV in Iran. We found that adenocarcinoma was the most prevalent histological type of ampullary lesions, followed by adenomatous polyps, GISTs, and NETs. Ampullary adenocarcinoma is a rare malignancy that accounts for just 0.2% to 0.5% of all gastrointestinal tract tumors (12, 13). Most ampullary carcinomas are thought to be adenocarcinomas (14, 15). The ampulla of Vater carcinoma (AVC) incidence rate is 0.49 per 105 people. Additionally, the incidence rate of AVC has increased (16, 17). Contrary to previous studies that showed ampullary adenoma to be the most common lesion in the AV (15), Carter and colleagues demonstrated that adenocarcinoma is the most common histological form of ampullary lesions (18). The typical age at diagnosis for sporadic ampullary cancers ranges from 60 to 70 years (19-21). We have found that adenocarcinoma is more common in men in their 50s. This finding was similar to findings by Albores-Saavedra and others, who also found that adenocarcinomas were the most common type; however, in their large sample, adenocarcinoma accounted for 65% of all the cases, compared to our 91.5% (13).

Earlier studies have demonstrated variations in the ratios of the intestinal and pancreaticobiliary subtypes in AVC. A large percentage of individuals with the pancreaticobiliary type of AVC were found in the global cohort research, but the proportion of patients with the intestinal type of AVC was minimal (22). A further retrospective analysis involving 45 individuals revealed that the pancreaticobiliary subtype was fewer than that of the intestinal subtype (23). Nevertheless, we found that the histological subtypes—intestinal and pancreatobiliary—in our study are roughly equivalent to what Carter and others found in their study (18). To better predict clinical outcomes, it is crucial to consider the histological subtypes and molecular changes in patients with AVC. The pancreaticobiliary subtype of AVC is clearly associated with poor clinical outcomes (24-26). Despite multiple institutional analyses showing no significant survival difference between the two subtypes in resected patients (27,28). Our study found that the intestinal subtype had higher survival and cure rates than the pancreatobiliary subtype.

No significant statistical correlation was found between tumor grade and prognosis, as the cure rates for well- and poorly differentiated tumors were nearly identical. This is probably due to the small population of cases in our study. However, the mortality rate for poorly differentiated tumors was higher (33%) than for either moderately or well differentiated tumors. Talamini and his co-workers discovered that poor survival was predicted by lymph node metastasis and poor differentiation (29). Howe and colleagues discovered that nodal metastasis was an independent predictor of survival, and also categorized patients based on their tumor subtype, either pancreaticobiliary or intestinal [30]. Most adenocarcinomas in our study showed no lymph node (LN) involvement. There was no LN involvement in any of the non-adenocarcinoma cases. LN involvement in our study failed

to predict prognosis or mortality, in contrast to the studies by Hornick and colleagues, who identified it as a significant poor prognostic factor in predicting mortality (31).

The most frequent reported symptom is obstructive jaundice caused by a tumor compressing the distal common bile duct (29, 32). Additionally, jaundice was the most common symptom in our research, followed by pruritus, abdominal pain, and weight loss, similar to findings in previous studies (33-35). We identified a patient with GIST and another patient with NET. These cases emphasize the significance of considering diagnoses other than adenoma and adenocarcinoma when assessing an ampullary lesion via a small biopsy.

We had some limitations in this research. This retrospective study was performed at a single center, with the main limitation being the small number of cases, so some comparisons were not statistically significant. This is probably because ampullary lesions are rare; therefore, larger multicenter studies are needed to address this issue. Another limitation was the lack of long-term follow-up; hence, we could not determine the 5-year survival rate of the patients.

In conclusion, the present study was the first to evaluate the prevalence and types of ampullary lesions in the south of Iran from 2020 to 2024. We have found that adenocarcinomas are the most common type of tumors of the AV, followed by adenomatous polyps, GIST, and NET in our area. Our findings emphasize the importance of conducting further research to gain a deeper understanding of ampullary tumors.

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## STATEMENTS AND DECLARATIONS

### ETHICAL APPROVAL:

Approval was obtained from the Ethics Committee of Shiraz University of Medical Sciences.

### CONSENT TO PARTICIPATE:

Informed consent was obtained from all participants prior to their inclusion in the study.

### CONSENT FOR PUBLICATION:

Written informed consent to publish was obtained from all participants.

### FUNDING:

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### AVAILABILITY OF DATA AND MATERIALS:

All datasets generated and analyzed are available in the article and on request from the corresponding author.

### CONFLICTING INTERESTS

The authors declare no conflict of interest related to this work.

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