ORIGINAL ARTICLE

Comparison of the two histological subtypes of ampullary adenocarcinoma: a retrospective study

Comparación de los dos subtipos histológicos del adenocarcinoma ampular: un estudio retrospectivo

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Abstract

Objectives: *This study aimed to compare the intestinal and pancreatobiliary subtypes of ampullary adenocarcinoma in a large patient group due to limited data on survival and risk factors.* **Methods:** *A retrospective analysis of the clinical and pathological findings and the survival of 184 patients with ampullary adenocarcinoma who underwent curative operation between 2007 and 2018 was performed.* **Results:** *Pancreatobiliary subtype had a higher prevalence of jaundice before operation than the intestinal subtype ($p < 0.05$). Pancreatobiliary subtype had a larger tumor size (> 2 mm) ($p < 0.01$) and poorer differentiation ($p < 0.05$) than the intestinal subtype. Perineural invasion more frequently occurred in pancreatobiliary subtype than the intestinal subtype ($p < 0.01$) and pancreatobiliary subtype had a higher prevalence of positive dissected lymph nodes ($p < 0.05$) with an advanced disease stage ($p < 0.01$) than the intestinal subtype. Patients of the pancreatobiliary subtype had poorer disease-free and overall survival than patients of the intestinal subtype. No survival benefit of adjuvant chemotherapy was found in either patients of the intestinal subtype or pancreatobiliary subtype. No significant difference was found in any subtypes regarding the recurrent regions.* **Conclusions:** *Pancreatobiliary subtype exhibited a higher recurrence rate and a poorer overall survival rate with more unfavorable pathological characteristics than the intestinal subtype.*

Keywords: *Ampullary adenocarcinoma. Histological subtype. Survival, prognosis.*

Resumen

Objetivos: *Los datos sobre la supervivencia y los factores de riesgo del adenocarcinoma ampular son limitados debido a su rareza. Este estudio buscó comparar el subtipo intestinal y el subtipo pancreático-biliar en pacientes con adenocarcinoma ampular.* **Métodos:** *Análisis retrospectivo de hallazgos clínicos y patológicos y la supervivencia de 184 pacientes con adenocarcinoma ampular tratados entre 2007 y 2018.* **Resultados:** *El subtipo pancreático-biliar tuvo una mayor prevalencia de ictericia antes de la operación y un tamaño de tumor mayor, y una peor diferenciación, que el subtipo intestinal. La invasión perineural fue más frecuente en el subtipo pancreático-biliar, con una mayor prevalencia de linfonodos disecados positivos y un estadio avanzado de la enfermedad. Los pacientes del subtipo pancreático-biliar tuvieron una supervivencia libre de enfermedad y una supervivencia general peores que los pacientes del subtipo intestinal. No se encontró ningún beneficio de la quimioterapia adyuvante en pacientes del subtipo intestinal o pancreático-biliar. No hubo diferencia significativa en las regiones recurrentes.* **Conclusión:** *El subtipo pancreático-biliar mostró una tasa de recurrencia y una tasa de supervivencia general peores, con características patológicas más desfavorables que el subtipo intestinal.*

Palabras clave: *Adenocarcinoma ampular. Subtipo histológico. Supervivencia. Pronóstico.*

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Introduction

The ampullary adenocarcinoma is a malignancy arising from the periampullary region[1]. It has been classified as intestinal and pancreatobiliary subtypes in histopathology[2]. The previous studies suggested that the prognosis was directly correlated with subtypes of ampullary adenocarcinoma[3,4]. Since the disease is rare, data on survival and the risk factors are limited. Most studies focusing on the histopathological predictors of ampullary adenocarcinoma have a small study population. The aim of this study is to compare the intestinal subtype and the pancreatobiliary subtype of ampullary adenocarcinoma in a large cohort of patients.

Methods

Patients

The findings on 184 consecutive patients who were operated on for ampullary adenocarcinoma from January 2007 and December 2018 at Shanghai Jiao Tong University Affiliated Sixth People's Hospital and Heilongjiang Provincial Hospital Affiliated to Harbin Institute of Technology were retrospectively reviewed. The population of this study consisted of 34 patients undergoing curative Whipple procedure and 150 patients undergoing curative pylorus-preserving procedure (PPPD). This study was approved by the ethics committee of Shanghai Jiao Tong University and was conducted according to the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from each patient.

Surgical procedure and chemotherapy

Curative resection was regarded as a negative resection margin and the complete resection of all metastatic lymph nodes. All patients underwent surgery with standard regional lymphadenectomy including the peripancreatic lymph nodes, the common and proper hepatic artery lymph nodes, the hepatoduodenal ligament lymph nodes, and those along the right lateral area of the superior mesenteric vessel. The aortocaval or paraaortic lymph nodes were dissected when they were enlarged seen in pre-operative imaging. Referral for adjuvant chemotherapy was done based on a consensus of the local multidisciplinary team. The chemotherapy regime was chosen at the discretion of the treating oncologist. No patients received radiotherapy. Chemotherapy regimens were extremely heterogeneous, but gemcitabine-based regimens were the most frequently adopted.

Pathological examination

One experienced pathologist in each center independently made the diagnoses and classified the histopathological subtypes. The classification was conducted as described previously[2,4]. Protein expression of CDX2, CK20, CK7, MUC2, MUC1, and MUC5a was detected by immunochemistry. The intestinal subtype was defined as positive immunostaining of CDX2, CK20, and MUC2, whereas the pancreatobiliary subtype was defined as positive immunostaining of MUC1, MUC5a, and CK7. TNM staging was performed according to the American Joint Committee on Cancer 8th edition[5].

Follow-up

Follow-up at 3-month intervals comprised of physical examination, laboratory tests, and tumor markers. CT or MR was arranged every 3 months in the 1st year and then every 6 months in the 2nd year. CT of the thorax, bone scan, and MR of the brain were performed if clinical examination led to a suspicion of metastasis or PET-CT was performed if other metastasis was suspected. The primary endpoint of the study was recurrence. The secondary endpoints were and disease-free survival and overall survival.

Statistical analysis

Continuous variables were expressed as median and range or mean ± standard deviation. Categorical variables were expressed as numbers and percentages. Normally distributed data were expressed as mean ± standard deviation and those that are not normally distributed were expressed as median and range. Chi-squared test was used for normal data. Univariate analysis was performed using the χ^2 test or Fisher's exact test for categorical variables. When the data did not normally distribute, the non-parametric Mann–Whitney U test was used. The survival was analyzed by Kaplan–Meier method with a log-rank test. Significant factors in univariate analysis were subjected to multivariate analysis by cox proportional hazard regression. Data were considered significant for $p < 0.05$. SPSS 20 statistical software (SPSS, Chicago, IL) was used for analyses.

Results

Comparison of the characteristics of intestinal and pancreatobiliary subtypes

The characteristics of intestinal and pancreatobiliary subtypes of ampullary adenocarcinoma were compared in table 1. Pancreatobiliary subtype had a higher prevalence of jaundice before operation than the intestinal subtype (58.3% vs. 45.7%, $p < 0.05$) whereas the pancreatobiliary subtype had a larger tumor size (> 2 mm) ($p < 0.01$) and poorer differentiation ($p < 0.05$) than intestinal subtype. Perineural invasion more frequently occurred in pancreatobiliary subtype than the intestinal subtype ($p < 0.01$). In addition, pancreatobiliary subtype had a higher prevalence of positive dissected lymph nodes ($p < 0.05$) with a more advanced disease stage (T, N, and TNM stages) ($p < 0.01$) than the intestinal subtype.

Comparison of survivals of intestinal and pancreatobiliary subtypes

Patients with pancreatobiliary subtype had poorer disease-free and overall survival than patients with the intestinal subtype ($p < 0.05$ and $p < 0.01$) (Fig. 1A and B). In multivariate analysis, jaundice, N stage, and perineural invasion were independently associated with disease-free and overall survival in patients with intestinal subtype. Meanwhile, T stage, N stage, and perineural invasion were independently associated with disease-free and overall survival in patients with pancreatobiliary subtype (Table 2). In addition, adjuvant chemotherapy was administered to 34.6% of the patients with the intestinal subtype and 26.2% of the patients with the pancreatobiliary subtype. No survival benefit of adjuvant chemotherapy was found in either patients with intestinal subtype or pancreatobiliary subtype ($p > 0.05$) (Table 3).

Comparison of recurrent patterns of intestinal and pancreatobiliary subtypes after curative resection

Eighty-eight patients experienced tumor recurrence. The patterns of recurrence are shown in table 4. Distant recurrence was found more frequently occurred than locoregional recurrence in both intestinal and pancreatobiliary subtypes. In distant recurrence patients, liver metastasis was identified as the most frequent occurrence, followed by distant lymph node metastasis and lung metastasis. No significant difference was found in any subtypes regarding recurrent regions ($p > 0.05$) (Table 4).

Discussion

Ampullary adenocarcinoma is a rare cancer. It is proven to have a better prognosis than bile duct cancer and pancreatic cancer. A 5-year survival rate of 45% was found in ampullary adenocarcinoma patients[6]. It is reasonable that an early symptom occurred due to obstructive jaundice caused by distal bile duct occlusion explains partially the better prognosis of ampullary carcinoma. It seems that tumor biological characteristics contribute to the favorable prognosis.

Noticeably, ampullary adenocarcinoma may arise from duodenal, pancreatic, or biliary epithelia. Two distinct histological subtypes (intestinal and pancreatobiliary) were identified based on the original epithelium. In this study, 81 carcinomas were classified into the intestinal (44.0%) and 103 into pancreatobiliary subtypes (56.0 %). We found that patients of pancreatobiliary subtype had poorer disease-free and overall survival than patients of the intestinal subtype. Furthermore, the pepancreatobiliary subtype was associated with a bigger tumor size, an advanced tumor stage, poorer differentiation, and more lymph node metastasis and perineural invasion, consisting with Kim's findings[7]. This could explain the poor prognosis of the pancreatobiliary subtype. Furthermore, jaundice, N stage, and perineural invasion were independently associated with disease-free and overall survival in patients of the intestinal subtype. Meanwhile, T stage, N stage, and perineural invasion were independently associated with disease-free and overall survival in patients of the pancreatobiliary subtype.

The effect of adjuvant chemotherapy remains indistinct for ampullary adenocarcinoma. Kurihara found that adjuvant chemotherapy did not show any survival benefits[8]. Although histological subtypes of ampullary adenocarcinoma have been widely admitted, the impact of subtypes on the response to chemotherapy is not clear. Ecker reported that there was no correlation between adjuvant chemotherapy and survival, regardless of histological subtypes[9]. In this study, no survival benefit of adjuvant chemotherapy was found in either patients of the intestinal subtype or pancreatobiliary subtype. In line with the previous reports[8,9].

In addition, patterns of recurrence after curative resection are not well known. We analyzed 88 patients experiencing tumor recurrence in the present study.

Table 1. Characteristic comparison between intestinal and pancreatobiliary subtypes of ampullary adenocarcinoma

Characteristic	Intestinal (n = 81)	Pancreatobiliary (n = 103)	p value
Gender, n (%)			NS
Male	42 (51.9%)	56 (54.4%)	
Female	39 (48.1%)	47 (45.6%)	
Mean age (years), (± SD)	64.7 ± 11.7	67.6 ± 11.6	NS
Mean BMI, (± SD)	23.6 ± 3.6	23.6 ± 3.6	NS
CA199 (U/ml), (median [range])	51 (1.5-559)	62.2 (1.5-728)	NS
Bilibubin (mg/dL), (median [range])	5.6 (1.4-10.5)	8.1 (1.5-13.8)	NS
Jaundice, n (%)			< 0.05
Absent	44 (54.3%)	43 (41.7%)	
Present	37 (45.7%)	60 (58.3%)	
Type of surgery, n (%)			NS
Whipple	17 (21.0%)	17 (16.5%)	
PPPD	64 (79.0%)	86 (83.5%)	
Tumor size (cm), (± SD)	2.2 ± 1.2	2.6 ± 1.2	< 0.01
T stage, n (%)			< 0.01
T1 + T2	81 (100.0%)	0 (0.0%)	
T3 + T4	0 (0.0%)	103 (100.0%)	
N stage, n (%)			< 0.01
Node negative	65 (80.2%)	67 (65.0%)	
Node positive	16 (19.8%)	36 (35.0%)	
TNM stage, n (%)			< 0.01
I + II	81 (100.0%)	79 (76.7%)	
III + IV	0 (0.0%)	24 (23.3%)	
Differentiation, n (%)			< 0.05
Well	30 (37.0%)	27 (26.2%)	
Moderate	46 (56.8%)	64 (62.1%)	
Poor	5 (6.2%)	12 (11.7%)	
Perineural invasion, n (%)			< 0.01
Absent	69 (85.2%)	73 (70.9%)	
Present	12 (14.8%)	30 (29.1%)	
Lymphovascular invasion, n (%)			NS
Absent	54 (66.7%)	65 (63.1%)	
Present	26 (33.3%)	38 (36.9%)	
Total lymph node harvested, n (median range)	10 (0-38)	12(0-43)	NS
Positive lymph node, n (median range)	1 (0-11)	1(0-14)	NS
Lymph node ratio, (median range)	0.05 (0.00-0.50)	0.09(0.00-1.00)	< 0.05
Adjuvant chemotherapy, n (%)			NS
Absent	53 (65.4%)	76 (73.8%)	
Present	28 (34.6%)	27 (26.2%)	

NS: not significant; PPPD: pylorus-preserving pancreaticoduodenectomy.

Distant recurrence was found more frequently occurred than locoregional recurrence in both the intestinal subtype and pancreatobiliary subtype. In distant recurrent patients, liver metastasis was identified as most frequently occurring, followed by distant lymph node metastasis and lung metastasis. No significant difference was found in any subtypes regarding recurrent regions.

In the queue of patients we studied, all patients were eligible for pancreaticoduodenectomy or PPPD after evaluation, compared to endoscopic papillectomy and transduodenal local resection, pancreaticoduodenectomy

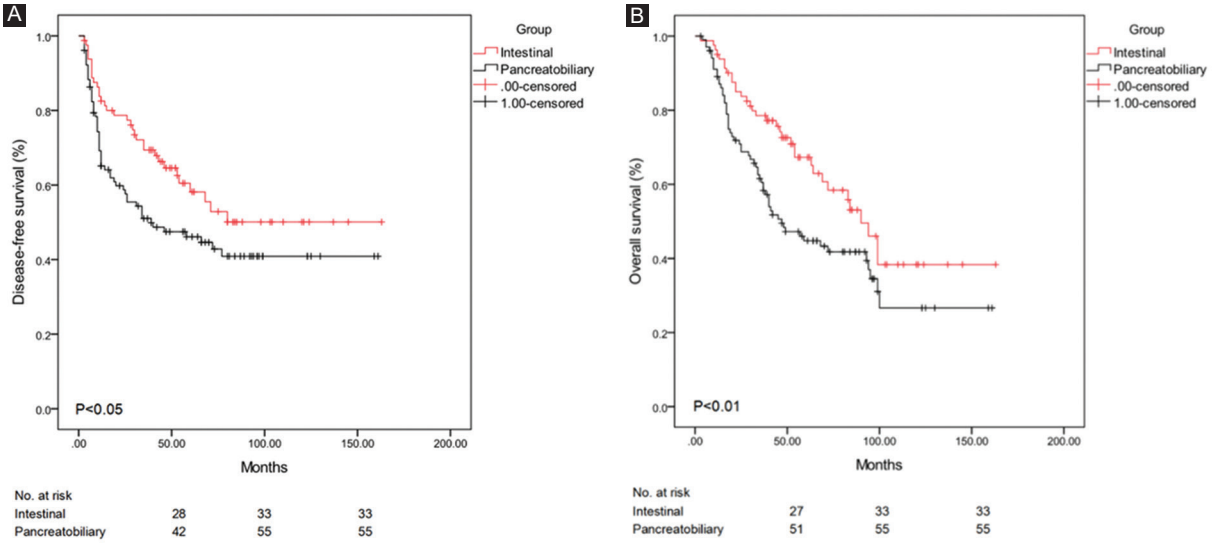

Figure 1. *Diseaese-free survival and overall survival of patients.* **A:** *patients of pancreatobiliary subtype had poorer disease-free than patients of intestinal subtype (p < 0.05).* **B:** *patients of pancreatobiliary subtype had poorer overall survival than patients of intestinal subtype (p < 0.01).*

Table 2. Multivariate analysis for predictive factors influencing survival in patients with intestinal and pancreatobiliary subtypes of ampullary adenocarcinoma

Subtype	Disease-free survival			Overall survival		
	HR	95% CI	p value	HR	95% CI	p value
Intestinal						
Jaundice	2.4	1.2-4.8	< 0.05	3.4	1.6-7.0	< 0.01
N stage	2.6	1.4-4.1	< 0.01	2.7	1.2-4.2	< 0.01
Perineural invasion				3.1	1.4-7.1	< 0.01
Pancreatobiliary						
T stage	2.3	1.2-3.9	< 0.01	2.6	1.3-4.4	< 0.01
N stage	3.1	1.6-4.6	< 0.01	2.0	1.2-3.1	< 0.01
Perineural invasion	2.0	1.1-3.4	< 0.01	1.9	1.1-3.2	< 0.05

Table 3. Univariate analysis for adjuvant chemotherapy influencing intestinal and pancreatobiliary subtypes of ampullary adenocarcinoma

Subtype	Disease-free survival			Overall survival		
	HR	95% CI	p value	HR	95% CI	p value
Intestinal (n = 81) Absent (n = 53) Present (n = 28)	0.8	0.4-1.7	> 0.05	1.0	0.5-1.9	> 0.05
Pancreatobiliary (n = 103) Absent (n = 76) Present (n = 27)	1.4	0.8-2.4	> 0.05	1.4	0.8-2.3	> 0.05

has a more thorough surgical margin and lower recurrence rate, but with slightly higher perioperative morbidity and mortality rates[10]. In addition, whether adjuvant chemotherapy was used had no impact on DFS and OS in either intestinal or pancreatobiliary subtypes. Although the choice of chemotherapy drugs may differ, the most commonly used drug in our center is gemcitabine, which is contradictory to the research results of Duke University, which showed that adjuvant radiotherapy and chemotherapy had a significant effect on the 3-year local recurrence (88% vs. 55%, p = 0.001) and was beneficial for disease-free survival (66% vs. 48%, p = 0.09) and overall survival (62% vs. 46%, p = 0.074)[11]. In addition, there is evidence to suggest that gemcitabine-based regimens may be particularly useful for patients with

Table 4. Patterns of recurrence after curative resection

Site	No of recurrence (n = 88)		p value
	Intestinal (n = 33)	Pancreatobiliary (n = 55)	
Locoregional, n (%)	8 (24.2%)	14 (25.5%)	NS
Distant, n (%)	25 (75.8%)	41 (74.5%)	
Liver	12 (48.0%)	20 (48.8%)	NS
Lymph node	5 (20.0%)	8 (19.5%)	NS
Lung	5 (20.0%)	6 (14.6%)	NS
Seeding	3 (12.0%)	3 (7.3%)	NS
Bone	0 (0.0%)	2 (4.9%)	NS
Brain	0 (0.0%)	2 (4.9%)	NS

NS: not significant

pancreaticobiliary-type ampullary carcinoma, while 5-fluorouracil-based regimens may be beneficial for those with intestinal-type ampullary carcinoma[12]. It is possible that differences in the selection of chemotherapy agents and the histological composition of patient populations may have led to different conclusions in different research centers.

In addition, molecular alterations in ampullary adenocarcinoma are receiving increasing attention. Different histological subtypes involve different molecular changes, which can also lead to differences in prognosis. Studies have shown that chromosomal 17p deletion is an indicator of poor prognosis and can help determine whether patients need adjuvant therapy beyond surgery. In addition, molecular changes involving TP53, K-RAS, APC, ELF-3, and ERBB2 in ampullary cancer are being increasingly discovered[10,13]. These molecules activate pathways such as WNT and PI3K, and increase microsatellite instability, which is becoming increasingly important for treatment and prognosis[14].

This study had some limitations due to its retrospective character. Although there were limitations in this study, the differences between the groups were dramatic.

Conclusions

Patients of pancreatobiliary subtype exhibited a higher risk of recurrence and disease-related death with more unfavorable pathological characteristics than patients of the intestinal subtype. Therefore, it is important to strengthen the pre-operative classification and post-operative follow-up of these patients, select the most appropriate treatment method according to different subtypes, and improve the prognosis of patients, which can greatly reduce the risk of death from ampullary adenocarcinoma.

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Conflicts of interest

The authors state no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective and observational study.

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