

Histopathologic differentiation as a prognostic factor in patients with carcinoma of the hepatopancreatic ampulla of Vater

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Abstract

Objective: Periampullary carcinomas are a group of neoplasms with variable histopathology that originate from the anatomical junction of different epithelial types including the bile duct, pancreatic duct, and duodenal mucosa. This study was performed to determine whether the histopathologic type of these tumors should be considered an independent prognostic factor.

Methods: We analyzed the specimen histopathology of 37 patients who underwent radical cephalic pancreatoduodenectomy for carcinoma of the ampulla of Vater during a 5-year period. We excluded patients with other tumors with an indication for Whipple's procedure and those in whom R0 resection was not achieved.

Results: The carcinomas of the hepatopancreatic ampulla were intestinal in 23 (62%) patients, pancreatobiliary in 13 (35%), and mixed type in 1 (3%). The analysis demonstrated significantly more advanced local tumor spread, a more aggressive lymph node metastasizing pattern, and more frequent lymphatic and perineural invasion in patients with pancreatobiliary than intestinal and mixed type tumors.

Conclusion: Pancreatobiliary type of ampullary carcinoma is associated with a poorer prognosis than intestinal and mixed types because of its more aggressive behavior. Histopathology should be

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regarded as an independent predictor of survival and may have therapeutic and prognostic implications for patients.

Keywords

Carcinoma, hepatopancreatic ampulla, histopathology, prognostic factor, pancreatoduodenectomy, survival

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Introduction

Carcinomas of the hepatopancreatic ampulla, most often referred to as periampullary carcinomas, are a group of neoplasms with a similar clinical presentation that originate from the anatomical junction of different epithelial types including the bile duct, pancreatic duct, and duodenal mucosa. Their histopathological differentiation is thus variable, with intestinal and pancreatobiliary being the most common and clinically significant types. These tumors also differ considerably in their prognosis and have a 5-year survival rate of 34% to 66%, reflecting the heterogeneity of their origin and pathogenesis.¹ These prognostic differences are probably due to histopathologic features rather than the anatomic site of origin of these lesions; i.e., the type of differentiation may be a more significant predictive factor for long-term survival. This study was performed to determine whether the histopathologic differentiation significantly and independently determines the lesion biology and thus prognosis. We analyzed and compared the elements of local tumor progression of different histopathologic types of ampullary carcinomas at the time of histological examination.

Methods

We analyzed the data of patients who underwent R0 pancreatoduodenectomy for

carcinoma of the ampulla of Vater from 2010 to 2015. We excluded patients with tumor-positive resection margins on specimen examination, periampullary lesions that could be morphologically differentiated as tumors not originating from within the ampulla (bile duct, pancreatic, or duodenal tumors), and remote metastases (liver or lung metastases) and ascites. The histopathological findings of the resected specimens, including the type of tumor differentiation and parameters of local progression (TN stage and lymphatic, perineural, and blood vessel invasion), were analyzed and compared.

Statistical analysis

Differences between the patients were examined by Fisher's exact test for all parameters except the T category, for which the chi-square test was used. Values of $p < 0.05$ were considered statistically significant. We used SigmaStat 2.0 (Systat Software, San Jose, CA, USA) for the statistical analysis.

Ethics statement

The authors did not seek institutional ethics committee approval because the study was retrospective, the analyzed data were obtained after the patients agreed to undergo standard therapeutic procedures by providing their signature, and no information that could enable the identification of any

person is included in the paper. The patients provided verbal informed consent that the data regarding the diagnostic and therapeutic procedures to which they were subjected may be used for scientific and educational purposes, provided that no identification is possible.

Results

The data of 37 patients (29 men, 8 women) were analyzed in this study. Their mean age was 63.1 years (range, 39–76 years). There were no perioperative deaths, the resection margins were tumor-free in all specimens, and two patients developed low-output pancreatic fistulas that were successfully treated conservatively. The histopathological evaluation was performed using the conventional classification proposed by

Kimura et al.² and revised by Albores-Saavedra et al.³ Of the 37 patients with carcinoma of the hepatopancreatic ampulla, 23 (62%) had intestinal tumors, 13 (35%) had pancreatobiliary tumors, and 1 (3%) had a mixed type tumor. There were no poorly differentiated, mucinous, signet ring cell, invasive papillary, or clear cell carcinomas. As shown in Table 1, further investigation and comparison of the data clearly demonstrated that the pancreatobiliary type was associated with significantly more advanced local tumor spread ($p=0.024$), a more aggressive lymph node metastasizing pattern ($p=0.035$), and more frequent lymphatic ($p=0.014$) and perineural ($p=0.034$) invasion than the intestinal type. No statistically significant difference in blood vessel invasion was found between these two histopathologic subtypes of carcinoma.

Table 1. Histopathological features of the hepatopancreatic ampulla carcinomas.

T category	Intestinal (n = 23)	Pancreatobiliary (n = 13)	Mixed (n = 1)
T1	4 (17.4)	0 (0.0)	0 (0.0)
T2	11 (47.8)	2 (15.4)	0 (0.0)
T3	6 (26.1)	6 (46.1)	1 (100.0)
T4	2 (8.7)	5 (38.5)	0 (0.0)
N-category	Intestinal (n = 23)*	Pancreatobiliary (n = 13)*	Mixed (n = 1)
N0	13	2	0
N1	10	11	1
Lymphatic invasion	Intestinal (n = 23)**	Pancreatobiliary (n = 13)**	Mixed (n = 1)
Yes	14	13	1
No	9	0	0
Blood vessel invasion	Intestinal (n = 23)	Pancreatobiliary (n = 13)	Mixed (n = 1)
Yes	20	12	1
No	3	1	0
Perineural invasion	Intestinal (n = 23)***	Pancreatobiliary (n = 13)***	Mixed (n = 1)
Yes	16	13	1
No	7	0	0

Data are presented as n or n (%)

*The proportion of observations in the different categories that define the contingency table is significantly different than that expected from random occurrence ($P=0.035$) (Fisher's exact test)

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Discussion

Carcinomas of the hepatopancreatic ampulla are rare tumors characterized by variable morphologic features owing to their origin at the meeting point of different epithelia. The conventional histopathologic classification proposed by Kimura et al.² and revised by Albores-Saavedra et al.³ acknowledged the heterogeneity of these tumors and introduced different subtypes: intestinal, pancreatobiliary, mixed, mucinous, signet ring cell, invasive papillary, clear cell, and poorly differentiated carcinomas. The prevalence of these different subtypes may vary, with intestinal (up to 49%) and pancreatobiliary (up to 45%) being the most common and clinically significant types.⁴ The microscopic features of these subtypes are presented in the microphotographs of the specimens from our patients. While the intestinal type typically consists of cribriform or tubular glands with an often pseudostratified columnar epithelium containing oval nuclei (Figure 1), the pancreatobiliary type has simple or branching glands with cuboidal to low columnar epithelium containing rounded nuclei (Figure 2). The mixed type is a combination of the former two (Figure 3). Previous studies have shown that this proposed histopathologic differentiation of carcinomas of the hepatopancreatic ampulla may have important therapeutic and prognostic implications for patient survival because of the different biology and progression patterns of each subtype.

This conventional histopathological classification system was applicable to the present study. Thirteen (35%) patients had pancreatobiliary tumors and one had a mixed type tumor; the majority of our patients (62%) had intestinal type carcinoma of the hepatopancreatic ampulla. These findings are consistent with previous reports.^{1,5} Although often described in similar studies, we did not identify any other

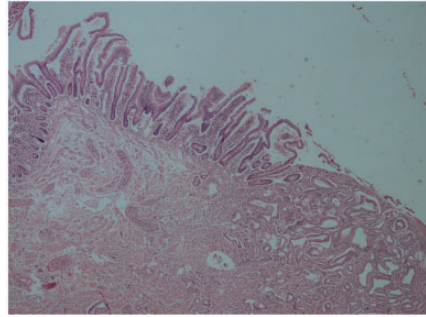


Figure 1. Intestinal type adenocarcinoma of the hepatopancreatic ampulla adjacent to normal mucosa. The neoplastic glands are composed of columnar cells with an intestinal phenotype (hematoxylin–eosin $\times 40$).

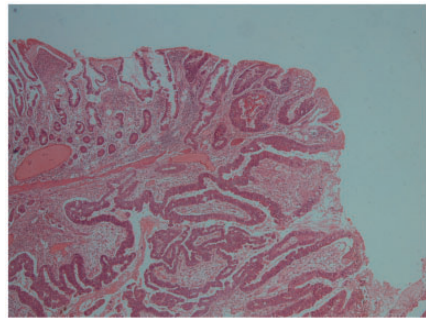


Figure 2. Pancreatobiliary type adenocarcinoma of the hepatopancreatic ampulla with a focal micropapillary pattern and cytological atypia (hematoxylin–eosin $\times 40$).

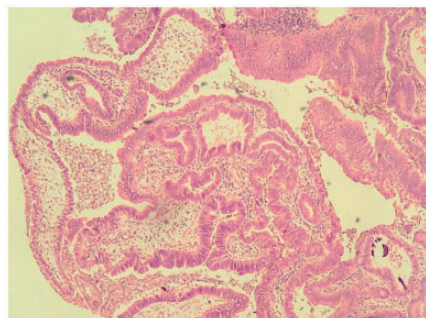


Figure 3. Mixed type infiltrative adenocarcinoma of the hepatopancreatic ampulla (hematoxylin–eosin $\times 100$).

tumor types because of the small number of patients analyzed. We further investigated the association between the type of tumor differentiation and the presence of other histopathologic features associated with a poor prognosis. The data analysis clearly revealed that compared with the intestinal type, pancreatobiliary type carcinomas demonstrated more aggressive local spread (advanced pT stage), more commonly metastasized to regional lymph nodes, and more frequently showed lymphatic and perineural involvement. No difference in blood vessel invasion was found among the histologic subtypes in our patients. Our results correspond with previously reported data.^{1,5,6} Tumor size is a well-known clinicopathologic factor associated with poorer survival after pancreaticoduodenectomy for ampullary cancer.⁷ The majority of our patients with pancreatobiliary type carcinomas had T2 and T3 lesions; no T1 tumors were present. This clearly suggests more advanced local tumor growth of this histopathological subtype. A study by Sudo et al.⁸ demonstrated that lymph node metastasis and perineural invasion were significant predictors of a poor prognosis, the latter being an independent predictor of poor prognosis. All pancreatobiliary ampullary cancers in the present study showed lymphatic and perineural invasion, and almost all (11 of 13) had positive lymph nodes, indicating their more invasive nature. We did not analyze survival data; we found such an analysis to be unnecessary for two reasons. First, the factors analyzed in this study (tumor size, lymph node status and lymphatic, vascular, and perineural invasion) are already well known to be significantly correlated with survival after surgery for ampullary cancer.⁹ Second, our results are consistent with previous findings that the intestinal type has a significantly better prognosis.^{1,10} The survival of patients with mixed type ampullary carcinoma lies somewhere

between that of patients with intestinal and pancreatobiliary types, which corresponds to the mixed morphology of these tumors.¹ Considering that the tumor progression parameters (local growth, lymph node metastasis, and lymphatic, vascular, and perineural invasion) are certain indicators of a poor prognosis and are significantly more common in patients with the pancreatobiliary type of carcinoma, it seems clear that the histopathologic type of differentiation is an independent predictor of survival. Additionally, a previous study showed that both intestinal and pancreatobiliary types of ampullary carcinoma histopathologically resemble carcinomas of corresponding tissues and are equal in their clinical evolution and survival.¹⁰ Therefore, regarding ampullary carcinomas as an independent entity may be questionable. Instead, emphasis might be more effectively placed on the histopathologic type of differentiation of these tumors as a more important survival factor than the point of origin. A precise histopathologic diagnosis is of utmost prognostic importance because it may have therapeutic implications necessitating both tumor- and patient-individualized therapy; i.e., histopathology-oriented and specific (neo)adjuvant oncologic treatment corresponding to different types of ampullary carcinomas.

Conclusion

Ampullary carcinomas are tumors with a uniform presentation. However, their prognosis differs depending on their histopathology and because of their diverse local growth and metastasizing features. The pancreatobiliary type of differentiation is associated with a poorer prognosis than the intestinal type because of its more aggressive behavior. Histopathologic differentiation should be regarded as an independent predictor of survival and may have

therapeutic and prognostic implications for patients.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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