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The histopathologic type predicts survival of patients with ampullary carcinoma after resection: A meta-analysis

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ABSTRACT

Objectives: The results of studies on the prognostic value of histopathologic differentiation of the intestinal and pancreatobiliary types of ampullary carcinoma after resection are conflicting. A meta-analysis was undertaken to investigate this issue.
Methods: A systematic literature search was performed to identify articles published from January 2000 to August 2016. Data were pooled for meta-analysis using Review Manager 5.3.
Results: Twenty three retrospective studies involving a total of 2234 patients were identified for inclusion, of whom 1021 (45.7%) had intestinal type tumors and 899 (40.2%) had pancreaticobiliary type tumors. Patients with the pancreaticobiliary type had high rates of poor tumor differentiation ($P < 0.001$), lymph node metastasis ($P < 0.001$), vascular invasion ($P < 0.001$), perineural invasion ($P < 0.001$), and positive resection margins ($P = 0.004$), as compared with those with the intestinal type. The pancreaticobiliary type predicted a worse overall survival (hazard ratio [HR] 1.84, 95% CI 1.49–2.27; $P < 0.001$) and disease-free survival (HR 1.93, 95% CI 1.23–3.01; $P = 0.004$).
Conclusion: The histopathologic type has major impact on survival in patients with ampullary carcinoma after resection, and the pancreaticobiliary type reflects a more aggressive tumor biology and is associated with worse survival.
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1. Introduction

Periampullary carcinoma may originate from the mucosa of the ampulla of Vater, the pancreatic duct, the distal common bile duct, or the duodenum. Carcinoma of the ampulla of Vater is a relatively rare neoplasm, accounting for approximately 0.2% of gastrointestinal malignancies or 7% of periampullary carcinomas [1]. Although patients with ampullary carcinoma have a more favorable prognosis than those with other periampullary malignancies, a subset of these patients eventually succumb to the disease after resection. Identification of predictors associated with poor prognosis would help stratify patients for appropriate management categories. Ampullary carcinomas can be classified histologically into two main subgroups: intestinal type and pancreatobiliary type [2]. In tumorigenesis, the former type arises from the intestinal mucosa of the papilla and evolves through an adenoma-carcinoma sequence, and the latter type originates from the epithelium of the common ampullary channel, the distal pancreatic duct, or the distal common bile duct and evolves from precursor large-duct pancreatic intraepithelial neoplasia [3]. Many studies have tried to determine whether or not this classification has a prognostic value. However, the study results are often conflicting or inconclusive mainly because of the relatively small sample sizes [4–13]. To increase the statistical power and allow reliable assessment of data available in published studies, this meta-analysis was undertaken to compare the clinicopathologic characteristics and long-term survival for intestinal-type and pancreatobiliary-type of ampullary carcinoma after resection.

2. Methods

2.1. Study selection

The present study was performed by following the

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recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [14]. Medline and EMBASE databases from January 2000 to August 2016 were searched by using the following Mesh search headings: "ampulla of Vater," "carcinoma," and "cancer." The reference lists of all retrieved articles were manually reviewed in order to identify additional studies.

2.2. Criteria for inclusion and exclusion

To be eligible for inclusion, a study needed to report on the impact of intestinal and pancreatobiliary differentiation on overall survival (OS) or disease-free survival (DFS) in patients with ampullary carcinoma after resection. Abstracts, letters, editorials and expert opinions, reviews without original data, case reports, nonhuman studies, non-English language studies, and studies that included other periampullary carcinomas (pancreatic, duodenal, and biliary) in the same study cohort without separate assessments were excluded.

2.3. Data extraction

Two independent investigators (YZ and LW) reviewed each study using standardized data extraction forms. Parameters extracted included first author, study origin, year of publication, study design, intestinal or pancreatobiliary type of differentiation, other pathologic variables such as lymph node, vascular and perineural invasion, available long-term outcomes, multivariable effect estimates for OS and DFS. Disagreement regarding extracted data was resolved by discussion and consensus.

2.4. Assessment of methodological quality

The methodological quality of the included studies was assessed by using the Newcastle-Ottawa Scale Scores were assigned for patient selection, comparability of the study groups, and outcome assessment [14].

2.5. Statistical methods

The differences in clinicopathologic features were estimated as a pooled odds ratio (OR) or weighted mean difference (WMD) with 95% confidence intervals (CI). Data for OS and DFS were analyzed using hazard ratios (HR) with 95% CI, and a HR > 1 represents a worse outcome. Between-study heterogeneity was assessed with I^2 statistics, and a value of >50% was considered significant heterogeneity. A funnel plot based on the OS outcome was conducted to evaluate the presence of publication bias. All analyses were performed using the Review Manager 5.3 (Cochrane Collaboration, Software Update, Oxford). A value of $P < 0.05$ was considered statistically significant.

The study was approved by the ethics committee of each contributing institution.

3. Results

3.1. Selection of studies

Of the 2384 publications retrieved from the initial search, 23 retrospective studies involving a total of 2234 patients were identified for inclusion (Fig. 1). The main characteristics of the 23 studies [4–13,16–29] are summarized in Table 1. Histologically, 1021 (45.7%) cases were classified as intestinal type, 899 (40.2%) as pancreatobiliary type, and 147 (6.6%) as other types (86 mixed type, 26 mucinous adenocarcinoma, 20 poorly differentiated-adenocarcinoma, 7 invasive-papillary carcinoma, 5 colloid carcinoma, one adenosquamous carcinoma, and one clear cell adenocarcinoma, and one carcinosarcoma). The histological subtype was unknown in 167 (7.5%) cases.

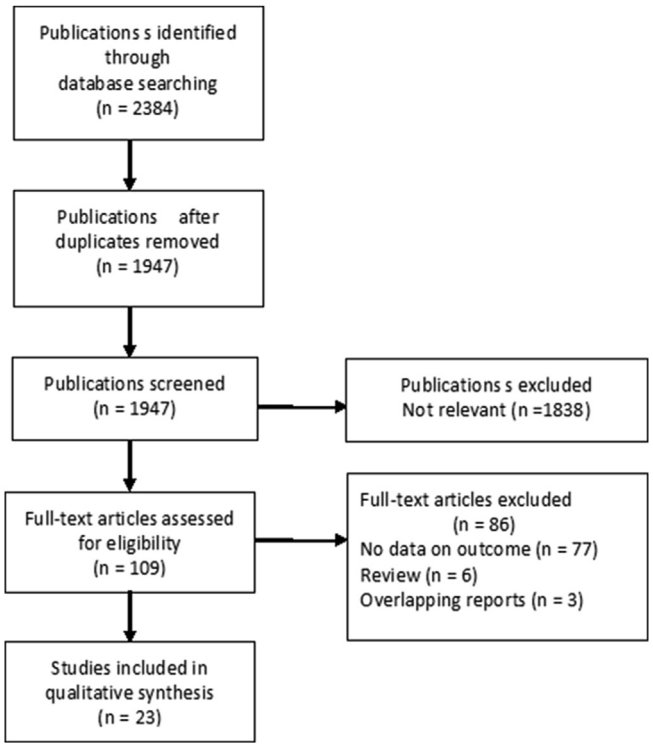

Fig. 1. Flowchart of the study selection.

3.2. Meta-analysis

Seventeen studies reported comparison of clinicopathological factors between intestinal and pancreaticobiliary ampullary carcinomas [4,7,10–13,16–29]. Pooled analysis showed that patients with the pancreaticobiliary type had higher rates of poor tumor differentiation ($P < 0.001$), lymph node metastasis ($P < 0.001$), vascular invasion ($P < 0.001$), perineural invasion ($P < 0.001$), and positive resection margins ($P = 0.004$), as compared with patients with the intestinal type (Table 2).

All the 23 studies reported OS after resection of ampullary carcinomas stratified by the histopathologic type. The median and 5-year OS ranged from 19 to 47.1 months and 11%–60.5% for patients with the pancreaticobiliary type *versus* 51–115 months and 43%–100% for those with the intestinal type, respectively. Thirteen [4,6,7,10,17–19,21,23,25,27–29] of the 23 studies performed multivariable analyses for OS, and the HR data were pooled in a separate meta-analysis. Results from these 13 studies revealed that the pancreaticobiliary type was negatively correlated with a shorter OS (HR 1.84, 95% CI 1.49–2.27; $P < 0.001$) with no heterogeneity ($I^2 = 0\%$) (Fig. 2a). Removal of any single study from the analysis did not change the results significantly in a sensitivity test (data not shown).

Only three studies included DFS data of the patients. In one study [21], the median DFS for patients with the pancreaticobiliary type and intestinal type was 25.3 months and 58.9 months, respectively (P = 0.0013). Kwon et al. [27] reported a similar 5-year DFS between the two groups (pancreaticobiliary 38% *versus* intestinal 57%). In contrast, Yun and Seo [26] found that there was a

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