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Original Article

Malignant transformation and overall survival of morphological subtypes of intraductal papillary mucinous neoplasms of the pancreas: A network meta-analysis

Xiaolong Qi [a,b,1], Xin Zhao [a,1], Junlei Su [c,1], Mingxin Xu [c], Weifeng Zhang [d], Hui Sheng [c], Zhiwei Li [a,*], Jiping Wang [b,**]

[a] Department of General Surgery, 302 Hospital of PLA, Beijing 100039, China
[b] Division of Surgical Oncology, Brigham and Women's Hospital, Boston, MA, USA
[c] Department of Endocrinology, Shanghai Tenth People's Hospital, Tongji University, Shanghai 200072, China
[d] Department of Gastroenterology, The First Affiliated Hospital with Nanjing Medical University, Nanjing, 210029 China

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ABSTRACT

Background: Emerging evidence suggests the predictive role of morphological subtypes (gastric, intestinal, pancreatobiliary, and oncocytic) of intraductal papillary mucinous neoplasms (IPMNs) in malignant transformation and overall survival. But results of these studies are currently discordant.
Methods: A comprehensive literature search in MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) was conducted for eligible studies. Network meta-analysis using the random-effect model was carried out to detect differences in incidences of invasive IPMNs and hazard ratios from survival curves among four morphological subtypes.
Results: 19 studies were included in the network comparison. The outcomes showed that pancreatobiliary-type (OR for odds ratio = 25.87, 95% CI: 12.11–52.10, compared with gastric-type) and oncocytic-type (OR = 18.59, 95% CI: 7.18–42.74) IPMNs had the highest risks of progressing to invasive IPMNs, followed by intestinal-type (OR = 5.71, 95% CI: 2.85–10.61) and gastric-type IPMNs. With the gastric type as the baseline, pancreatobiliary-type IPMNs were found to have the worst prognosis (HR for hazard ratio = 5.05, 95% CrI: 1.33–13.47) while no significant differences were found for the intestinal type (HR = 1.90, 95% CrI: 0.59–4.58) and the oncocytic type (HR = 3.29, 95% CrI: 0.75–9.71).
Conclusion: It is suggested that pancreatobiliary-type IPMNs are the most likely to become invasive and are associated with poor prognosis. In contrast, the other three subtypes have similar overall survivals even though the oncocytic- and intestinal-type IPMNs are predisposed to be more invasive than gastric-type IPMNs.

1. Introduction

Intraductal papillary mucinous neoplasm (IPMN) is the most prevalent cystic tumor of the pancreas, accounting for approximately 8–20 % of all resected pancreatectomy specimens [1]. It is characterized by dilated pancreatic ducts (main or branch) and mucin-producing atypical epithelium present in a papillary fashion [1–5]. Considered to be precursor of invasive carcinoma, these lesions can undergo malignant transformation from low-grade or intermediate-grade dysplasia to high-grade dysplasia, and culminate in the development of invasive colloid, tubular or oncocytic carcinoma with poor prognosis [6–11]. The prevalence of IPMNs with an associated invasive carcinoma reportedly ranges from 64% to 92% in the main-duct and mixed IPMNs and 18% to 25% in the branch-duct IPMNs [3,12–16]. And the 5-year survival rate of invasive IPMNs (28%–62%) is significantly lower than noninvasive IPMNs (higher than 75%) [17–20].

Morphological type may be an independent predictor of patient prognosis [21–23]. But IPMNs belong to a heterogeneous group which exhibits a wide spectrum of morphological variations. Efforts have been made for the classification [24–27]. In 2003, a unified classification was proposed and this new criteria divided IPMNs into four subtypes: gastric (GF), intestinal (IN), pancreatobiliary (PB), and oncocytic (Onc) primarily based on their morphology and immunohistochemistry for mucin core proteins (MUCs) as confirmatory marker [28]. Approximately, IN-type IPMNs account for 54% of IPMNs, GF subtype 26%, PB subtype 7% and Onc subtype 13% [29].

Emerging evidence has implied diversity in histologic and clinical characteristics among the four subtypes. Although many studies showed a general consensus, the malignant potential and overall survival of the four subtypes remain an issue of controversy. In addition, studies investigating the correlation between malignant transformation, overall

* Correspondence to: Z. Li.
** Correspondence to: J. Wang.
E-mail addresses: lzw302@163.com (Z. Li), jipingwangbwh@126.com, wanglongwood@gmail.com (J. Wang).
[1] Equal contributor.

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survival and morphological subtypes of IPMNs usually had small number of patients included and were hard to obtain a robust creditability. Nevertheless, it is of vital importance for clinical management to determine which subtype of patients is prone to developing invasive IPMNs and facing higher risks to have lower overall survival. Therefore, we present this network comparison combing all direct and indirect evidence to illustrate a clear-cut picture for morphological subtypes of IPMNs in terms of malignant potential and overall survival.

2. Methods

2.1. Search strategies

We conducted a thorough search in the Cochrane Controlled Trials Registry, PubMed and EMBASE databases up to January 2015. The following terms were used to identify possible candidates: "intraductal papillary mucinous neoplasm," "intraductal papillary mucinous tumor," "mucinous cyst," "pancreatic cyst," "cystic neoplasm of the pancreas" and "IPMN". All eligible studies were retrieved, and their reference lists were checked for additional relevant publications.

2.2. Study selection criteria

Complete texts were retrieved based on their abstracts for possible inclusion. Studies that satisfied all of the following criteria were included: (1) English articles; (2) study population of histology-confirmed IPMNs; (3) study designs of retrospective cohorts and prospective cohorts; and (4) sufficient data on histologic classification or overall survivals corresponding to morphological subtypes.

2.3. Exclusion criteria

The exclusion criteria were as follows: (1) case reports; (2) review articles; (3) editorials; (4) duplicate reports; and (5) studies not within the field of interest of this study.

2.4. Data extraction

For each study, the following baseline information was extracted: the first author's surname, year of publication, study design, period of data collected, the number of subjects, the percentage of male, age, and macroscopic type of IPMN.

2.5. Invasive IPMNs

We extracted numbers of patients with invasive IPMNs corresponding to each morphological subtype. "Unclassified type", "mixed type" or "no description" that cannot be categorized into the aforementioned four types was excluded. Considering the various criteria of different studies for histologic grading, we defined invasive IPMN as follows based on the mainstream of included studies: in studies using the Word Health Organization (WHO) classification in which the epithelial dysplasia was graded as low, intermediate, high (or carcinoma in situ) and associated invasive carcinoma [30,31], we collected patients' number of invasive carcinoma; in studies using the Japan Pancreas Society (JPS) in which IPMNs were classified as intraductal papillary mucinous adenoma (IPMA) and intraductal papillary mucinous carcinoma (IPMC, sub-classified as non-invasive, minimally invasive and invasive) [32,33], we collected minimally invasive (refers to IPMC with "slight stromal invasion" beyond the pancreatic duct) and invasive IPMC as invasive IPMN in this report.

2.6. Overall survival

We used the Engauge Digitizer 4.1 to digitalize survival curve data, and then estimated log hazard ratios (HR) and corresponding standard errors from the overall survival curves of each subtypes with methods described by Tierney et al. [34] Data extraction was performed by 2 independent reviewers (XMX and ZXD) and disagreements were resolved by discussion and consensus among study investigators.

2.7. Statistical analysis

Network meta-analysis was conducted using an R2WINBUGS package based on a Bayesian framework, to incorporate all direct and indirect evidence, for assessing whether there were differences in subtypes in malignant transformation among the four morphologies. Moreover, we applied a network comparison to evaluate HRs estimated from the overall survival curves, using a random-effect model with methods described by Woods et al. [35] The model was conducted using WinBUGS (version 1.4.3), also within a Bayesian framework. HR was calculated with gastric subtype as baseline subtype as the endpoint and the 95% CrI for each result were computed. We analyzed models using one chain and 40,000 iterations after a burn-in of 10,000 iterations. Convergence was evaluated by monitoring trace plots, autocorrelations, and Monte Carlo error which describes the variability of each estimate due to the simulations.

3. Results

3.1. Literature search

Our identification process for eligible studies was shown in Fig. 1. The initial search yield 2138 article candidates that included our search terms. Of those, 1920 were excluded based on the title and abstract: 223 non-English articles; 235 reviews; 97 letters, editorials, or abstracts; 300 case reports; and 1065 articles that were not in the field of interest of this study. The remaining 218 articles were retrieved for full-text review, from which 199 were excluded: 172 not containing morphological data, 15 not including the whole histologic grades (for example, studies only included invasive IPMNs), 10 not having corresponding message between morphological subtypes and histologic grading and 2 duplicates. Finally, 19 studies including 1954 patients who met the inclusion criteria and were included in the meta-analysis [20–23,27,36–49].

The characteristics of the 19 included trials are summarized in Table 1. All the studies were retrospective and were published after the Sendai criteria except one [27]. Of all included studies, the three macroscopic types of IPMN (main-duct, branch-duct and combined or mixed type) were involved except that one study investigated main-duct and combined IPMNs and another investigated main-duct IPMNs only [44,48]. 1 study had 2 arms of subtypes and 3 studies had 3 arms while the rest all had 4 arms. Overall, the patients were mostly in their 60s, and more males were involved than females.

3.2. Network meta-analysis

3.2.1. Association between morphological subtypes and invasive IPMNs

All 19 studies were incorporated in the analysis of correlation between morphological subtypes and invasive IPMNs. Definitions of morphological subtypes varied between studies, but the majority of them were based on cytomorphological features of the papillae and, when available, immunohistochemical demonstration according to Furukawa et al. [28]

Pooling of ORs of harboring invasive IPMNs for individual morphological subtypes showed significant differences in pair-wise comparisons, except the comparison between PB and Onc (Fig. 2). The results revealed that gastric subtype was with the lowest risk in terms of evolving into invasive IPMN, while pancreatobiliary subtype (OR = 25.87, 95%CI: 12.11–52.10; compared with gastric subtype) and oncocytic subtype (OR = 18.59, 95%CI: 7.18–42.74; compared with gastric subtype) were associated with the highest malignant transformation rate of all, with no significant difference found between the two