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Review

Dose surgical resection of hepatic metastases bring benefits to pancreatic ductal adenocarcinoma? A systematic review and meta-analysis

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ABSTRACT

Objective: The objectives of this systematic review and meta-analysis were to examine morbidity, mortality, and long-term survival after surgical resection of hepatic metastases from pancreatic ductal adenocarcinoma (PDAC) patients.

Background: Patients with hepatic metastases from pancreatic ductal adenocarcinoma are facing a dilemma of whether to make hepatic resection.

Methods: A systematic literature research was undertaken through computerized databases as well as manually research from unpublished data. A meta-analysis was performed to investigate the differences in the efficacy of liver resection and non-surgical treatments based on the evaluation of morbidity, 30-day mortality, and 1-, 3-, or 5-year survival.

Results: 11 cohort studies with 1147 patients were identified in the pool. Compared with the non-surgical approach, hepatic resection can be performed in a safe and feasible manner for all pancreatic cancer patients with liver metastases ($p = 0.13$ for overall morbidity; $p = 0.63$ for mortality). For surgical group, the median 1-year, 3-year, and 5-year survival were 40.9%, 13.3%, 2.9%, respectively, with a median survival of 9.9 months. Surgical resection of hepatic metastases was associated with a significantly improved overall 1-year and 3-year survival ($p < 0.001$).

Conclusions: Hepatic resection is a safe procedure; furthermore, it is worth doing such an extended surgery for PDAC patients due to additional survival benefit in the medium-term (less than 3 years). However, further randomized, controlled trials are urgently needed.

1. Introduction

Distant metastases often represent the last stage of tumor evolvement, which directly leading to the irreversible outcome or even death. Due to the central role in the portal circulation, liver is a frequent disseminate site for metastatic tumor, especially for digestive tract tumors such as colorectal, gastric, and pancreatic tumors [1]. The most common pathological pattern of pancreatic tumor is pancreatic ductal adenocarcinoma (PDAC), which accounts for approximately 90% of all cases.

Treatments of hepatic metastases including: surgery (hepatic resection), intervention (embolization [HAE] and transcatheter arterial chemoembolization [TACE]), systemic chemotherapy, and radiofrequency ablation. Among them, only hepatic resection for metastatic disease has gained general acceptance as a potentially curative option in patients with colorectal cancer. The role of surgery for metastases from neuroendocrine tumors on long-term outcome is also well-documented [2,3]. Recently, Markar et al. [4] and co-workers made a systematic review and pooled analysis: surgical resection of hepatic metastases from gastric adenocarcinoma was associated with a significantly improved overall survival ($p < 0.001$). In addition, they confirmed the additional survival benefit of solitary compared with multiple hepatic metastases (odds ratio = 0.31; $p = 0.011$). For pancreatic neuroendocrine tumor (PNET) patients, Yuan et al. drew a conclusion based on meta-analysis: liver resection had a favorable prognostic outcome in terms of higher postoperative symptom relief rates and longer survival rates [5]. However, historical results in regarding to hepatic resection from PDAC were in conflicts and remained controversial. Furthermore, rare systematic review or meta-analysis was ever reported focusing on PDAC as a separate group. While large published series on non-colorectal, non-neuroendocrine hepatic metastasectomy may include a heterogeneous array of tumor histology, [6] these studies frequently do not distinguish PDAC among the various types of tumors. In this study, we sought to investigate the role of hepatic resection for metastatic PDAC patients. As far as we know, this is the first systematic review and meta-analysis trying to answer this key

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question in the field.

The primary aim of this systematic review and meta-analysis was to examine overall survival (OS) following surgical resection of hepatic metastases from PDAC patients. The secondary aim was to study mortality and morbidity from these patients and to compare above parameters between liver resection group and non-surgical group. Accordingly, this study would assist clinicians in filling this knowledge gap.

2. Methods

2.1. Search strategy

A computerized search was made of the Medline/PubMed, EM base, Cochrane Library from January 1990 to May 2017. Languages including but not limited to English. The following search headings were used: “pancreatic cancer”, “pancreatic ductal adenocarcinoma”, “pancreatic neoplasm”, “hepatic metastases resection”, “liver metastases resection”, “synchronous hepatectomy”, “simultaneous hepatectomy”, “synchronous hepatic resection,” “synchronous liver resection” “synchronous liver resection” “simultaneous hepatic resection,” “simultaneous liver resection.” We used “AND” “OR” “NOT” for combination of these headings to avoid missing and wrong articles. To maximize our search results, we also did manual research by reading 2nd literature database and consulting manual search books. If there was any doubt about the suitability after reading the abstract, the full manuscript was obtained. Details please see the flowchart of search history in Fig. 1.

2.2. Criteria for inclusion and exclusion

For inclusion in the meta-analysis, a study had to meet the following criteria: (1) Cohort or comparative studies of patients undergoing hepatectomy for hepatic metastases from pancreatic ductal adenocarcinoma; (2) Including more than 10 patients; (3) Survival data for at least 1-year following surgical resection were available; (4) NOS score ≥ 6, in other words, at least 6 stars should be allocated in terms of selection, comparability and outcome.

Abstracts, letters, editorials and expert opinions, animal experiments, reviews without original data, case reports, and studies lacking control groups were excluded.

Authors from the same institution published two or more similar studies, the most recent or the larger publication was included in the analysis.

2.3. Data extraction

Abstracts of all articles identified by the electronic search were scrutinized by two reviewers (Xinzhe Yu & Jichun Gu) independently to determine their suitability for inclusion in the pooled analysis. Any discrepancies between the two authors were settled in discussion with a third independent author (Chen Jin). Once we confirmed all the included articles, we extracted all articles on following categories: first author, year of publication, study population characteristics, study design, inclusion and exclusion criteria, tumor characters and histopathology, intra-operation parameters, resection margin, procedure-related morbidity and mortality, and OS. All relevant texts, tables, and figures were reviewed for data extraction. In addition, we wrote emails to original authors of inclusive studies in request of some key data we really need.

2.4. Quality assessment

To assess the overall strength/quality of evidence for the various parameters in this meta-analysis, a quality assessment was carried out in the form of Newcastle-Ottawa Quality Assessment Scale (NOS System) for cohort studies [7]. We assessed each inclusive article by looking at such aspects: Selection, Comparability and follow-up of the exposed cohort. Any study can obtain a score ≥ 8 may be recognized as high quality study for inclusion.

2.5. Heterogeneity analysis

It is well-known that the ability to draw meaningful comparisons in a meta-analysis is largely dependent on the degree of heterogeneity present [8]. Among the 11 studies deemed eligible, baseline data were found to be quite homogeneous. Based on tolerable heterogeneity, fixed effects models were used in this analysis.

2.6. Statistical analysis

The meta-analysis was performed in line with Cochrane recommendations, following the MOOSE guidelines, [9] using the Review Manager 5.3 software. We analyzed dichotomous variables with estimation of odds ratios (OR) together with a 95% CI, and continuous variables with weighted mean difference (WMD) and a 95% CI if available. Pooled effect was calculated using either the fixed effects model or the random effects model based on I^2 at the threshold of 75%. Statistical heterogeneity among trials was evaluated by I^2 and p value, with significance being set at $p < 0.05$ and $I^2 > 75\%$. Survival was calculated from the time of resection of the hepatic metastases or time of diagnosis of hepatic metastases in the nonsurgical group. Sensitivity analysis was also performed by excluding some unique studies and testing with total studies. Publication bias was assessed visually with a funnel plot [10].

3. Results

3.1. Baseline description of eligible studies

A total of 47 articles were retrieved for the full-text. Among them, 6 studies got a NOS score ≥ 8 being recognized as high quality studies, another 5 studies got 6 or 7 points because of lacking some of the key data or small sample size but still can meet the selection criteria. At the meantime, other 36 studies with NOS scores below 6 or lacking key data were deleted finally [11–16]. To sum up, 11 cohort studies [17–27] were included in this systematic review and meta-analysis, more details of the included studies please refer to Table 1.

This meta-analysis evaluated 1147 patients in 11 cohort studies, of whom 217 patients underwent hepatic resection and were included into the surgical group, while other 930 patients received non-surgical therapies and used as the control group. As shown in Table 1: baseline data such as publication year, time for study, the median age, gender ratio was listed. Beyond that, 5 studies [17–20,22] gave information on the quantity of hepatic metastases (solitary/multiple); 3 studies [17,18,27] gave information on the site of hepatic metastases (unilobar/bilobar); 3 studies [19,20,27] gave information on the occurrence time of hepatic metastases (synchronous/metachronous).

Next, we performed a further literature review of the included 11 cohort studies. All 11 studies were limited to PDAC patients. Overall, 9 studies yielded a median R0 resection rate (primary tumor) of 81.8% (31.8%–100%), and a median chemotherapy rate of 81.8% (15.4%–100%). For surgical group, the median 1-year, 3-year, and 5-year survival were 40.9%, 13.3%, 2.9%, respectively, with a median survival of 9.9 months. On the other hand, for non-surgical group, the median 1-year, 3-year, and 5-year survival were 40%, 3.4%, 0%, respectively, with a median survival of 7.5 months. Generally, for PDAC patients: 4 studies, [21,23,27] chose hepatic resection as the optimal option for liver metastases, whereas 3 studies [20,24,26] gave a negative opinion on surgical approach, the other 4 studies [17–19,22] kept in neutral position. Finally, 3 studies [19,21,25] also made a subgroup analysis, and concluded that primary tumor site, R0 resection, lymph nodes status, and the occurrence time of hepatic metastases were the