Systematic review and trial sequential analysis of high-intensity focused ultrasound combined with chemotherapy versus chemotherapy in the treatment of unresectable pancreatic ductal adenocarcinoma

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ABSTRACT

Purpose: This study aimed to compare the survival benefits between high-intensity focused ultrasound (HIFU) combined with chemotherapy and chemotherapy alone in patients with unresectable pancreatic ductal adenocarcinoma (PDAC).

Methods: All randomized clinical trials (RCTs) and observational studies were systematically searched through the databases of PubMed, EMBASE, CNKi and CQVIP up to December 2020. Case reports, case series and nonsystematic reviews were excluded. A meta-analysis was conducted to generate combined hazard ratios (HRs) with 95% confidence intervals (CI) for overall survival (OS).

Results: Seven trials, containing a total of 992 patients, were included in this study. The meta-analysis showed that a combination of HIFU and chemotherapy increased overall survival compared with chemotherapy alone, with a pooled HR of 0.40 (95% confidence interval [CI], 0.28–0.58). The combined therapy group had a significant advantage in 1-year survival rate (OR: 0.35, 95% CI: 0.22–0.53, p = 0.00). The trial sequence analysis (TSA) showed that there were enough trials to control for random errors.

Conclusion: Our analysis suggests that HIFU combined with chemotherapy intravenously will prolong survival for unresectable PDAC patients. The TSA showed that the survival benefit of combined therapy was definitive and there was no need to expand the sample size for repetitive exploration.

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer death worldwide [1]. It is only curable in a minority of patients with resectable disease. About 80% of PDAC are unresectable at diagnose. The 5-year survival rate at the unresectable stage is only 2% with minimal improvement in prognosis observed for the past decades [2,3]. Despite the development of targeted therapy and immunotherapy [4–7], chemotherapy is still the main treatment for PDAC. According to different clinical trials, the median overall survival time is 8–11 months [8–11].

Because of its special tumor microenvironment and anatomical location, pancreatic cancer has poor sensitivity to treatment and limited local treatment methods. Pancreatic cancer cells are surrounded by a large amount of extracellular matrix, which forms a biological barrier that can cause ischemia, hypoxia [12] and increased osmotic pressure [13–15]. At the same time, the pancreas is located close to the intestinal tract and blood vessels, increasing the difficulty of local treatment such as radiofrequency ablation and irreversible electroporation [16–19].

High-intensity focused ultrasound (HIFU) uses ultrasound to penetrate tissues and focus ultrasonic heat on a tumor in vivo, so as to achieve tumor thermal ablation. HIFU provides a noninvasive and effective treatment for pancreatic cancer patients [20]. So far, there have been numerous studies on HIFU for PDAC. These studies have shown that HIFU plays a very effective role in pain relief and tumor size reduction [20–23]. Whether HIFU can prolong survival is still a matter of opinion.

Despite increasing evidence of the efficiency of HIFU, its status as a standard treatment remains unknown. Enhancing understanding of the role of HIFU in PDAC survival will improve clinical decision-making with respect to trial design and cancer treatment.

Methods

We followed the PRISMA Statement guidelines to design, analyze and report our meta-analytic findings [24,25].
Literature search

We reviewed PubMed, EMBASE, Web of science, Cochrane, CNKI and CQVIP databases for articles published before 10 December 2020. We identified studies by using Medical Subject Headings (MeSH) including pancreatic cancer, HIFU and chemotherapy. These terms were also combined with keywords and manual searches of references in all selected studies.

Selection criteria

The inclusion criteria were as follows: (i) survival comparisons were made between HIFU plus chemotherapy and chemotherapy alone in patients with pancreatic cancer; (ii) outcomes were related to overall survival; (iii) HR or survival curves were provided; (iv) articles were published in English or Chinese. In addition, articles were excluded if (i) no HRs or survival data were extracted; (ii) they were review articles; (iii) it was a single-arm study.

Study selection, data extraction and endpoints

Initial screening of potentially eligible records was performed by two investigators (Jing Guo, Yunbing Wang). Subsequent full-text record screening was performed independently by two investigators (Jing Guo, Jinyun Chen). Disagreements were resolved by consensus. Baseline characteristics and outcomes were extracted from the selected articles. We chose overall survival (OS) as our endpoint for meta-analysis.

Quality assessment

The quality of each study was independently rated by two investigators (Jing Guo, Wenzhi Chen), using the Newcastle-Ottawa Scale and Altman framework.

Statistical analysis

HR was used as a prognostic measurement. HRs and 95% confidence intervals (CI) were extracted from research studies. For studies without HRs and CIs, we used the extracted data from survival curves by Engauge Digitizer and calculated corresponding HRs and CIs using a method proposed by Parmar et al. (http://markummitchell.github.io/engauge-digitizer/). To improve accuracy, we excluded HRs derived from studies if the number of events in one group was less than 5. Heterogeneity was expressed by the $I^2$ index (25% corresponds to low heterogeneity, 50% medium, 75% high). Random effects models were initially used to estimate pooled HRs. If there was no heterogeneity between the results ($p > 0.05$), the fixed-effect model was used. Then, subgroup analyses were performed on the basis of administration route (by venous, by a venous plus artery or by oral administration), treatment mode (once or repeated) and randomization. Publication bias was assessed by inspecting the symmetry of the funnel plot and tested with Egger’s test.

Trial sequential analysis performance

Trial sequential analysis (TSA) is used to estimate the sample size of systematic review or meta-analysis, overcoming the shortcomings of classical systematic review or meta-analysis. First of all, when the number of cases included in the meta-analysis did not reach enough sample size, the application of TSA could minimize the false-positive results caused by random error. Secondly, meta-analysis is a retrospective study and the Required Information Size (RIS) obtained by TSA refers to the number of cases required for meta-analysis to obtain statistically significant differences. It is generally believed that the number of cases required for meta-analysis should not be less than the sample size required for a single well-designed randomized controlled trial with sufficient statistical certainty. Thirdly, meta-analysis aims to find evidence of the efficacy of medical interventions as early as possible. By estimating RIS, TSA provides a termination standard for clinical trials, that is, when the cumulative number of cases in meta-analysis reaches the expected information, similar clinical trials can be terminated, so as to avoid the waste of scientific research and medical resources.

TSA to assess for random errors and to calculate the required sample size by using an $\alpha$ of 0.05 (two-sided) and a $\beta$ of 0.20 (80% power). The control group proportions were calculated from the chemotherapy group of the trials [26–28].

According to our clinical experience, the truly effective treatments for reducing the risk of mortality had previously yielded a relative risk reduction of 35%, thus, an $\alpha$-spending monitoring boundary was used to detect an intervention effect with a relative risk reduction set at a level of 35%. We used two-tailed tests because it was unclear whether a combination of HIFU and chemotherapy performed better than chemotherapy in terms of one-year OS. We applied a random-effects model according to the calculated $I^2$ in the meta-analysis. TSA was performed by using TSA V.0.9.5.10 beta (http://www.ctu.dk/tsa/).

Results

Identification of relevant studies

Our initial search yielded 179 records. After reviewing the titles and abstracts, the full texts of 11 studies were examined. Four studies were further excluded for the following reasons: no comparisons between two groups or no survival data, such as HRs and survival curves. As a result, seven studies [29–35] were included in this meta-analysis (Figure 1).

Risk of bias within studies

Quality evaluation of selected literature is summarized in Figure 2. All of the trials were retrospective studies, not all of
Figure 1. Summarizes the identification of relevant studies [29–35].

Figure 2. Quality assessment of included studies with the Cochrane risk of bias assessment tool. (A) Overall and (B) study-level risk of bias.
the studies used randomization, only four did. Five studies reported using allocation concealment. The allocation concealment methods were inconsistent. Because HIFU is an operational treatment, it cannot be done in a blind way. Even though, two of the study mentioned blinding.

**Study characteristics**

Seven studies were included in this analysis. All these studies were conducted in China and published from 2006 to 2019. All patients enrolled had unresectable pancreatic cancer, classified as stage III and stage IV. In these studies, HIFU

**Table 1.** Study characteristics in this analysis.

| References | Type of study | HIFU | Stage | Period of study | Intervention regimen | Control regimen | Administration | Participants | Phase of treatment | HR (95% CI) |
|------------|---------------|------|-------|----------------|---------------------|----------------|----------------|--------------|-------------------|-------------|
| Zhang [30] | Random        | Once | Unresectable | 2009.3 to 2011.2 | HIFU + Gem | Gem | Venous | 21 vs 20 | 1st line | 0.49 (0.30–0.82) |
| Li [33]    | Not mentioned | Once | Metastic | 2012 to 2014 | HIFU + S-1 | S-1 | Venous | 61 vs 59 | 2nd line | 0.194 (0.012–0.336) |
| Lv [32]    | Random        | Once | Unresectable | 2008.3 to 2011.1 | HIFU + Gem | Gem | Venous | 23 vs 22 | 1st line | 0.5 (0.28–0.87) |
| Zhiqiang [34] | Random      | Once | Unresectable | 2007.12.20 to 2015.1.30 | HIFU + Gem | Gem | Venous + arterious | 347 vs 176 | 1st line | 0.65 (0.54–0.77) |
| Ning [35]  | Not mentioned | Once | Unresectable | 2007.12.20 to 2015.1.30 | HIFU + Gem | Gem | Venous + arterious | 347 vs 176 | 1st line | 0.65 (0.54–0.77) |
| Zhang [30] | Random        | Repeated | Unresectable | 2000.8 to 2003.8 | HIFU + Gem | Gem | Venous | 29 vs 23 | 1st line | 0.35 (0.17–0.71) |
| Zeng [29]  | Random        | Repeated | Unresectable | 2000.8 to 2003.8 | HIFU + Gem | Gem | Venous | 24 vs 22 | 1st line | 0.46 (0.25–0.84) |

**Figure 3.** Forest plots of studies comparing the overall survival between combined therapy and chemotherapy. Random: random-effects model.

**Figure 4.** Subgroup analysis of administrative way. Fixed: fixed effect model.
Ablation was performed once in five studies and more than once in two. Gemcitabine-based chemotherapy was conducted in six studies, which served as the first-line therapy, while S-1 was chosen as the second-line therapy in one study (Table 1).

**Effect of HIFU on the survival of PDAC patients**

Seven studies were included in the analysis of PDAC OS. The combination of HIFU and chemotherapy had better OS than chemotherapy alone, with a pooled HR of 0.40 (95% CI: 0.28–0.58) using random mode (Figure 3). Significant heterogeneity was found among these studies ($I^2 = 78\%$, $p = 0.0001$).

**Subgroup analysis of HIFU in PDAC**

To investigate potential sources of heterogeneity, we conducted a subgroup analysis.

**Subgroup analysis of administrative way**

Among the seven studies, five were given chemotherapy intravenously, one included both intravenous and arterial...
chemotherapy and the other one was administered orally. Combination therapy has a significant advantage in prolonging survival in all three subgroups. The venous administration subgroup showed a high degree of consistency, with a pooled HR of 0.39 (95% CI: 0.31–0.50, \( I^2 = 0\% \)) by the fixed effect model (Figure 4).

Randomization subgroup analysis

In five of the seven studies, patients were randomized and two did not mention how groups were formed. Therefore, we performed a subgroup analysis based on whether randomization was conducted (Figure 5). Randomization may be another main source of heterogeneity (HR = 0.39, 95% CI: 0.31–0.50, \( I^2 = 0\% \)).

HIFU ablation schedule subgroup analysis

At the same time, we are very concerned about the effect of different HIFU treatment modes on the survival of PDAC patients. Due to different mechanical principles, some HIFU treatment systems can be used for one-time ablation, while...
others require repeated treatment. This subgroup analysis shows high heterogeneity in HIFU treatments received (HR = 0.40, 95% CI: 0.26–0.63, $I^2 = 85\%$) (Figure 6).

**TSA**

Since most patient survival time has been less than 1 year, one-year survival rates were also analyzed in patients with PDAC. The forest pilot showed that combined therapy had a significant advantage in 1-year survival rate (OR 0.35, 0.22–0.53). Given the small number of existing studies and patients, random errors are possible, which can cause spurious results. For this reason, we conducted TSA. From Figure 6, we can see that the Z curve crossed the futility boundaries, but it did not reach the sequential monitoring boundary. This indicated that there are enough participants to confirm the survival benefit in HIFU (Figure 7).

**Publication bias**

Formal investigation using Egger’s tests indicated publication bias in the meta-analysis. The results showed that there was no publication offset, and Egger’s test showed no statistical significance ($p = 0.027$) (Figure 8).

**Discussion**

As far as we know, this is the first systematic review about the OS benefits of HIFU in PDAC patients by pooling HRs. We found HIFU plus chemotherapy will decrease the risk of death by 60%. To prevent the risk of random error and the multiplicity phenomenon due to repeated significance testing in the meta-analysis, we performed TSA. This further confirmed the deterministic effect of HIFU on prolonged survival.

HIFU has been applied in the treatment of pancreatic cancer for nearly 20 years [36,37]. A large number of studies have confirmed that HIFU has a significant effect on tumor shrinkage and pain relief [21,38,39]. As for the survival time, many current studies involved a single-arm cohort. The median OS in PDAC with HIFU is from 8 months to 16.72 months [40–43]. Holger et al. demonstrated that HIFU has an advantage in pancreatic cancers enveloping large mesenteric vessels [21]. Zeng et al. [29] firstly published a case-control study with an overall survival statistic in 2006. In the HIFU plus Gemcitabine cohort, the median survival time was 10.56 months, while it was 6.71 months in the controlled cohort. This result was less than the average result nowadays, taking into consideration the development of more chemotherapy regimens since 2010, such as nab-Paclitaxel and FOLFIRINOX. In 2019, Ning et al. [35] demonstrated the survival benefit of HIFU among PDAC patients treated with
Gemcitabine. The benefit was most obvious in PDAC patients treated with HIFU plus RIAC (regional intra-arterial chemotherapy) and systemic chemotherapy. However, the role of HIFU in the treatment of PDAC remains unclear due to a large number of uncontrolled studies. We hoped to provide clinicians with an exact treatment choice through meta-analysis.

There are several limitations to our study. First, most of the articles included in this meta-analysis were retrospectively small sample studies, lacking data from large-scale prospective clinical trials. Secondly, the included patients were all Chinese patients, which may be because HIFU technology was first developed and applied to clinical treatment in China, so a larger amount of patient data has been accumulated. However, further clinical research is needed to explore whether there are survival benefits for non-Chinese patients. Thirdly, in the excluded articles, we found that published abstracts or conference reports presented negative results [44]. Without HR data or a survival curve, we could not obtain the data for analysis. This may produce publication bias to our findings. Finally, the included articles neither distinguished between stages nor distinguished between treatment lines. This still needs to be further explored for making accurate clinical treatment decisions.

This meta-analysis and TSA showed that HIFU combined with the chemotherapy treatment group has long-term survival benefits in patients. Based on these data, HIFU has given us great confidence in the treatment of unresectable pancreatic cancer, which is worthy of further promotion and application in subsequent clinical work.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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