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REVIEW ARTICLE

Long-term outcome following neoadjuvant therapy for resectable and borderline resectable pancreatic cancer compared to upfront surgery: a meta-analysis of comparative studies by intention-to-treat analysis

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Abstract
The aim of the study was to evaluate the effect of neoadjuvant therapy on long-term survival in patients with resectable and borderline resectable pancreatic cancer. A meta-analysis was conducted using the reported randomized, controlled trials and retrospective studies using an intention-to-treat analysis to compare upfront surgery and neoadjuvant therapy in resectable or borderline resectable pancreatic cancer patients. Six comparative studies consisting of two randomized, controlled trials and four retrospective studies were included. The overall pooled hazard ratio was 0.66 (95% confidence interval: 0.50–0.87, $P = 0.003$), indicating that patients in the neoadjuvant group had better long-term survival than those in the upfront surgery group. However, considerable inter-study heterogeneity was observed ($I^2 = 62\%$). This meta-analysis focusing on comparative studies analyzed by intention-to-treat analysis showed that neoadjuvant therapy for resectable and borderline resectable pancreatic cancer tends to improve patients' long-term outcomes. However, the evidence level remains too low for a firm conclusion. The well-designed, randomized, controlled trials now ongoing will provide the definite evidence needed in the future.

Keywords Pancreatic cancer · Neoadjuvant · Meta-analysis

Introduction

Pancreatic cancer still has a dismal prognosis all over the world and is the fourth leading cause of death from cancers [1]. In fact, most pancreatic cancer patients (~ 80%) are diagnosed with unresectable disease due to locally advanced and/or distant metastatic disease at initial diagnosis. The remaining 10–20% are diagnosed with resectable or borderline resectable disease that can be considered for surgery. Upfront curative resection followed by adjuvant chemotherapy is well-accepted as standard treatment for resectable or borderline resectable pancreatic cancer [2]. Adjuvant chemotherapy has been improved by several randomized, controlled trials (RCTs) [3, 4]; however, the improved prognosis with adjuvant chemotherapy was seen only in patients with curative resection and full recovery after pancreatic surgery. From the perspective of intention-to-treat (ITT) analysis, cases with incidentally detected metastases at the time of surgery or insufficient recovery after surgery should be included in the RCTs comparing neoadjuvant therapy with upfront surgery.

In recent years, neoadjuvant therapy has emerged as a new alternative approach for pancreatic cancer treatment, especially for patients with resectable and borderline resectable disease [5]. Numerous preoperative treatment protocols including chemotherapies and chemoradiotherapies have been performed and evaluated in high-volume referral centers [6–8]. Neoadjuvant therapy before surgery might be expected to provide several benefits, including: better patient selection by excluding patients with undetected distant metastasis or rapid progressive disease who will not receive the benefit of subsequent resection; a higher possibility of curative resection with a negative surgical margin as a result of tumor size shrinkage [9]; and almost all patients

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can receive an active systemic treatment in the neoadjuvant setting compared with the adjuvant setting, which is associated with surgical complications and delayed recovery after surgery.

Although recent large cohort studies actually suggested the feasibility and usefulness of neoadjuvant therapy for resectable or borderline resectable pancreatic cancer [10–12], almost all studies evaluated the outcomes among only the cases who underwent surgical resection in a retrospective manner, which might lead to wrong conclusion because of patient selection bias excluding cases who did not undergo resection due to tumor progression or worsened general condition after the neoadjuvant therapy. To obtain strong evidence for the benefits of neoadjuvant therapy, ITT analysis should be performed including all enrolled or allocated cases [13]. Actually, recent meta-analyses investigating the prognostic benefits of neoadjuvant therapy for pancreatic cancer patients reported controversial results with considerable inter-study heterogeneities, which might be caused by their different analytic methods [14–16]. Theoretically, ITT analysis should be performed as an RCT design. So far, only several RCTs with a small sample size have been reported [17–19].

Taken together, to clarify the impact of neoadjuvant therapy on long-term outcomes for resectable and borderline resectable pancreatic cancer patients, a meta-analysis was performed using the comparative studies with an ITT analysis.

Methods

This meta-analysis was performed in accordance with guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) group [20].

Literature search strategy

A computerized MEDLINE (through PubMed) search was conducted for relevant and original publications on the relationship between preoperative therapy and resectable and borderline resectable pancreatic cancer outcomes. The following search terms were used: ("pancreatic neoplasms" [MeSH]) AND (preoperative OR neoadjuvant OR neoadjuvant) AND ("drug therapy" [MeSH] OR chemotherapy OR chemoradiotherapy OR radiochemotherapy OR chemoradiation OR irradiation). In addition, the ''related articles'' function on PubMed was used. Relevant publication references were manually searched in an effort to identify additional studies overlooked using the search strategy. The original search was conducted in August 2017, and the last update was made on March 5, 2018.

Inclusion and exclusion criteria

All studies were restricted to those involving human subjects, published in English, reporting predefined long-term outcomes such as overall survival and disease-specific survival, and with ITT analysis. This study focused only on articles published after 2001 to best reflect modern surgical practice and perioperative management. Studies that failed to fulfill the above inclusion criteria were excluded. Exclusion criteria were publication in a language other than English; review articles, editorials, letters, comments, case reports, and conference abstracts; single-arm analysis; and studies that did not evaluate long-term outcomes. Studies of pancreatic cancer with locally advanced disease and distant metastases were also excluded.

Data extraction and statistical analysis

Study characteristics and outcome parameters for all included studies were extracted using a standardized data form. The primary outcome was the survival rate. Crude or adjusted hazard ratios (HRs) were extracted for survival. If the available data were presented as a Kaplan–Meier curve, the survival rates at some specified times were extracted to reconstruct the HR estimate and its variance, with the assumption that the rate of patients censored was constant during study follow-up [21]. Pooled HRs were calculated using the random-effect model (DerSimonian–Laird method) because of the possibility of clinical heterogeneity among studies. An HR < 1 indicated that the neoadjuvant group was favored. A two-sided P value < 0.05 was considered significant. Heterogeneity among the studies was assessed with the I^2 statistic. Data are presented in a forest plot for each outcome parameter with pooled estimates presented at the lower end. Publication bias analysis was not performed because the number of studies was too small (< 10) to detect an asymmetric funnel [22]. All statistical analyses were performed using Review Manager 5.3.5 (Cochrane Collaboration, Oxford, UK).

Results

Literature search and study selection

Details of the literature search are shown in Fig. 1. A total of 1283 articles were identified. After preliminary elimination of 1128 articles, 155 original articles remained. As a secondary screening, 146 articles with non-ITT analyses and single-arm studies were excluded to meet the inclusion criteria of the present study. Only one article was manually

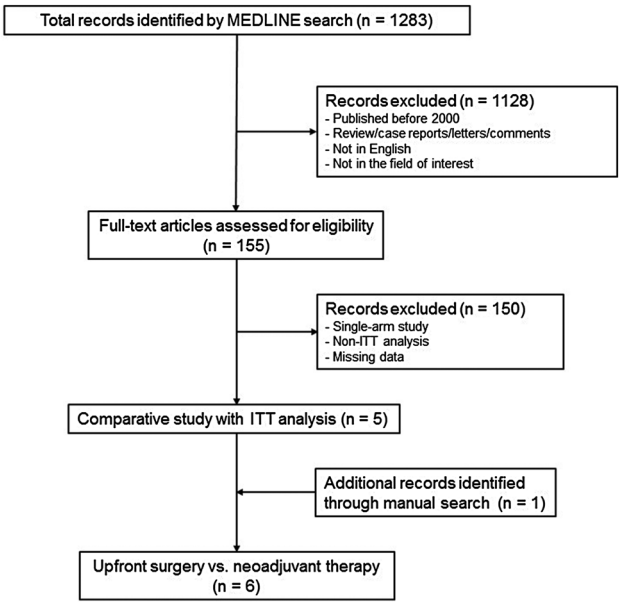

Fig. 1 Flow chart showing the meta-analysis literature selection process. *ITT* intention-to-treat

added because it was the most recent publication during the literature search period. Finally, six studies were suitable for inclusion in the present study and subsequent meta-analysis [18, 19, 23–26].

Characteristics of included studies

The study characteristics of the included studies in the present meta-analysis are summarized in Fig. 2. A total of six studies (two RCTs and four retrospective studies) comparing upfront surgery with neoadjuvant chemotherapy and chemoradiotherapy by ITT analysis for long-term survival outcomes were included. Only one study was based on a national cancer data base for clinical Stage III pancreatic cancer and, therefore, the preoperative and postoperative treatment protocols were not definitely applicable [26]. The preoperative treatment arms of the remaining studies consisted of four with chemoradiotherapy (CRT) [18, 19, 23, 24] and one with chemotherapy (CT) [25]. The median survival time (MST) in the upfront surgery groups ranged from 11.6 to 17.0 months after patient allocation.

Outcome evaluation

As shown in Fig. 2, the overall pooled HR for all six studies was 0.66 (95% confidence interval 0.50–0.87, $P = 0.003$), which means that patients in the neoadjuvant group had better overall survival than those in the resection group. However, significant heterogeneity was observed ($I^2 = 62\%$).

Sensitivity analysis

A sensitivity analysis to examine the intervention effects after excluding studies with lower methodological quality would have been conducted if appropriate. Unfortunately, the limited numbers of trials for the same intervention did not permit a sensitivity analysis.

Discussion

In the present study, the resectable and borderline resectable pancreatic cancer patients who underwent neoadjuvant therapy had significantly longer survival than those who underwent upfront surgery. Two recent reports of a systematic review and meta-analysis emphasized the importance of ITT analysis to eliminate patient selection bias [27, 28]. Actually, these two systematic reviews demonstrated that the overall survival by ITT analysis including all allocated patients was much shorter than the overall survival including only resected patients. Therefore, this meta-analysis was designed focusing on the comparative studies analyzed by ITT to maintain the quality of the included studies to avoid potential inter-study heterogeneities. Nevertheless, considerable heterogeneity still existed, and, therefore, the pooled

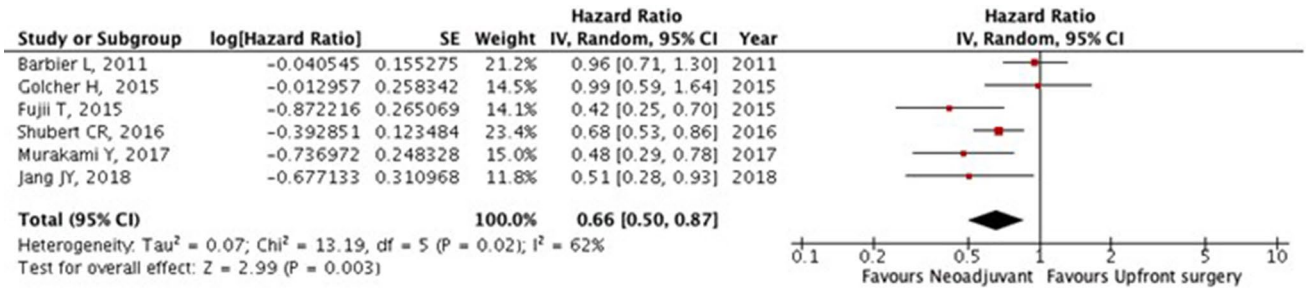

Fig. 2 Forest plot of long-term survival outcomes. Point estimates from individual studies are illustrated as solid squares, with the size presenting the statistical weight of each study. Diamonds indicate the estimated pooled odds ratios. Horizontal error bars are 95% confidence intervals (CIs)

HR in favor of the neoadjuvant group should be interpreted carefully.

Among the studies included in the present meta-analysis, two RCTs comparing neoadjuvant CRT and upfront surgery by ITT analysis had apparently different conclusions. One was the worldwide first prospective phase II RCT that was terminated early due to slow enrollment and non-significant results. On the other hand, a recent RCT reported from the Republic of Korea demonstrated significantly better oncological outcomes, such as R0 resection rate and overall survival, for the neoadjuvant CRT group at the interim analysis, which resulted in early termination. In both of the RCTs, even though there were differences, such as tumor resectability and CRT regimens, there is no specific reason to explain their opposite outcomes.

Recent reports showed the association between hospital volume and long-term outcomes after pancreatic cancer surgery [29, 30]. In the present study, the hospital volumes of the hospitals involved in the studies could not be analyzed because of a lack of data. The MST in the upfront surgery group, which might be a surrogate marker for the quality of surgical treatment, looked similar across the included studies. These results suggest that facility differences have a minimal effect on long-term outcomes. In contrast, a considerable difference of MSTs was seen in the neoadjuvant therapy group.

Another potential factor affecting inter-study heterogeneities is postoperative management for the neoadjuvant group. In one included study, postoperative adjuvant therapy was not performed because it was considered that medical treatment was completed prior to surgery [23]. Actually, this study showed the shortest MST (15.0 months from allocation) among the neoadjuvant therapy groups of the included studies. Furthermore, the treatment regimens for postoperative adjuvant therapy differed across the included studies. In brief, orally administered S-1-based therapies were used in the two studies reported from Japan [24, 25], and intravenous gemcitabine based on CONKO-01 was used in the other remaining studies [18, 19, 23]. Taken together, postoperative adjuvant chemotherapy can be strongly associated with long-term outcomes, and future studies should be designed to include adjuvant chemotherapy in both groups.

On the basis of the current meta-analysis, the hypothesis is that neoadjuvant therapy might improve overall survival in cases with resectable or borderline resectable pancreatic cancer. Although previous RCTs from Italy and Germany were terminated early due to difficulty in recruiting patients [17, 18], strong evidence comes only from RCTs; therefore, future RCTs with well-designed protocols and larger cohorts are needed. In fact, several RCTs investigating the usefulness of neoadjuvant therapy for resectable or borderline resectable pancreatic cancer are now ongoing [31–34]. Based on the results of these RCTs, the treatment strategy for pancreatic cancer should be drastically changed in the future.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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