Surgical Oncology 27 (2018) 563–574

Contents lists available at ScienceDirect

Surgical Oncology

journal homepage: www.elsevier.com/locate/suronc

Comparative effectiveness of preoperative, postoperative and perioperative treatments for resectable gastric cancer: A network meta-analysis of the literature from the past 20 years

Zhaolun Cai[a,1], Yuan Yin[a,1], Chaoyong Shen[a], Jian Wang[a], Xiaonan Yin[a], Zhixin Chen[a], Ye Zhou[b], Bo Zhang[a,*]

[a] Department of Gastrointestinal Surgery, West China Hospital, Sichuan University, Chengdu, 610041, Sichuan, China
[b] Department of Gastric Surgery, Fudan University Shanghai Cancer Center, Shanghai, 200032, China

ARTICLE INFO

Keywords:
Gastric cancer
Adjuvant
Neoadjuvant

ABSTRACT

Background: Different preoperative, postoperative or perioperative treatment strategies, including chemotherapy or chemoradiotherapy, are available for patients with gastric cancer, but conventional meta-analyses that assess two alternative treatments are unable to compare differences in overall survival. Thus, we performed a network meta-analysis to identify the best treatment strategy.

Methods: We systematically searched and assessed studies for eligibility and extracted data. We then pooled the data and conducted a Bayesian network meta-analysis to combine direct comparisons with indirect evidence. The node-splitting method was used to assess the inconsistency. Rank probabilities were assessed by the probability of treatment rankings.

Results: Thirty-three eligible randomized controlled trials were included in the network meta-analysis. Four treatments that had significantly improved prognoses when compared with surgery only were postoperative chemotherapy [HR = 0.80 with 95% CrI: (0.73, 0.88)], postoperative chemoradiotherapy [HR = 0.73 with 95% CrI: (0.61, 0.87)], preoperative chemoradiotherapy [HR = 0.77 with 95% CrI: (0.62, 0.98)] and perioperative chemotherapy [HR = 0.69 with 95% CrI: (0.55, 0.84)]. Preoperative chemotherapy, however, did not significantly improve survival when compared with surgery alone [HR = 0.94 with 95% CrI: (0.71, 1.2)]. There was no statistically significant difference between postoperative chemotherapy, postoperative chemoradiotherapy, preoperative chemoradiotherapy and perioperative chemotherapy in terms of overall survival. Chemoradiotherapy after D2 lymphadenectomy did not significantly improve OS when compared with postoperative chemotherapy [HR = 0.95 with 95% CrI: (0.73, 1.3)].

Conclusion: Among patients with operable gastric cancer, perioperative chemotherapy had the highest probability of being the best treatment. Further clinical resources may be required to assess the efficacy and safety of perioperative chemotherapy for patients with gastric cancer.

1. Introduction

As the fourth most common cancer and one of the leading causes of cancer death worldwide, gastric cancer (GC) accounts for 8% of total cases and 10% of total deaths, with 989,600 new cases and 738,000 deaths in 2008 [1]. The general prognosis of GC is poor, with a 5-year survival of 25.1% [2]. Surgery is the main treatment for patients with GC. However, a large number of patients develop recurrence or metastases even after curative resection [3]. Therefore, various preoperative, postoperative and perioperative treatment strategies, including chemotherapy (CT) or chemoradiation therapy (CRT), have been investigated to improve the surgical outcomes and prevent relapse for the disease. These strategies are recommended in the National Comprehensive Cancer Network (NCCN) guidelines for the treatment of GC [4].

Previous randomized controlled trials (RCTs) and meta-analyses have assessed the outcomes of preoperative, postoperative and perioperative treatments, producing conflicting results that make optimal

* Corresponding author.
E-mail addresses: caizhaolun@foxmail.com (Z. Cai), Yinyuan10@gmail.com (Y. Yin), scyshenchaoyong@163.com (C. Shen), wj66220@126.com (J. Wang), yxnyinxiaonan@163.com (X. Yin), chenzhixin@medmail.com.cn (Z. Chen), zhouye79@yahoo.com (Y. Zhou), hxwcwk@126.com (B. Zhang).
[1] These authors contributed equally to the research.

https://doi.org/10.1016/j.suronc.2018.07.011
Received 13 February 2018; Received in revised form 14 June 2018; Accepted 15 July 2018

treatments unknown. Postoperative adjuvant chemotherapy is one of the most common therapies for patients with GC. Several meta-analyses confirmed the effectiveness of postoperative adjuvant chemotherapy for GC [5–7]. Meanwhile, the ACTS-GC trial [8] and CLASSIC trial [9] verified the effectiveness of adjuvant chemotherapy after gastrectomy with D2 lymphadenectomy (D2 gastrectomy). The survival benefits of adjuvant chemoradiotherapy were confirmed by the INT-0116 trial [10] and several meta-analyses [11,12], establishing postoperative adjuvant CRT as part of the standard of care for the treatment of GC. For neoadjuvant CT, the role of the treatment for GC remains controversial. Several meta-analyses that analyzed preoperative CT and perioperative CT together indicated that neoadjuvant CT contributes to the survival benefit [13,14]. The EORTC 40954 trial suggested that preoperative CT might increase the R0 resection rate, which may result from the downstaging of the tumor, but failed to demonstrate a survival benefit [15]. Regarding adding radiotherapy to the neoadjuvant treatment of GC, several RCTs and meta-analyses have proven the survival benefits of neoadjuvant CRT therapy [16,17] in addition to surgery alone. However, previous studies failed to obtain a statistically significant difference between preoperative CT and preoperative CRT [18,19]. Perioperative CT is recommended for resectable GC after two trials [20,21] verified the effectiveness of the treatment.

Despite the advances in the treatment strategies of GC, a definitive statement on the optimum treatment in terms of overall survival is still missing, and some of the treatments have never been compared to each other because of the limitations of traditional meta-analysis methods and the lack of head-to-head trials. Thus, the optimum treatment for patients with operable GC is still unknown. Furthermore, D2 lymphadenectomy has been widely performed. Thus, an analysis of the best treatment for patients undergoing D2 lymphadenectomy is urgently needed.

We used a Bayesian network meta-analysis to investigate this problem. In network meta-analyses, comparisons between treatments can be made using indirect comparisons when no head-to-head studies are available, and direct and indirect comparisons can be combined to compare several factors while preserving individual randomization trials [22–24]. The aim of our network meta-analysis was to investigate and summarize the direct and indirect evidence for the comparative overall survival (OS) of various treatments, including preoperative, postoperative and perioperative CT or CRT in patients with operable GC and to derive the comparative efficacy of the treatments.

2. Methods

2.1. Search strategy

Two investigators performed a systematic literature search in PubMed, EMBASE (Ovid), and Cochrane Library (Ovid) (last updated on May 8, 2017) without language restrictions using combinations of the following terms: (((((“stomach neoplasms"[MeSH Terms] OR (“stomach"[All Fields] AND “neoplasms"[All Fields]) OR “stomach neoplasms"[All Fields] OR (“gastric"[All Fields] AND “cancer"[All Fields]) OR “gastric cancer"[All Fields]) OR “stomach cancer")) OR (“esophagogastric junction"[MeSH Terms] OR (“esophagogastric"[All Fields] AND “junction"[All Fields]) OR “esophagogastric junction"[All Fields] OR (“gastroesophageal"[All Fields] AND “junction"[All Fields]) OR “gastroesophageal junction"[All Fields])) AND (((((((((neoadjuvant) OR neoadjuvant chemotherapy) OR Perioperative)) or adjuvant)) OR Pre-operative)) OR Post-operative)) AND (((((((((“Randomized Controlled Trial” [Publication Type]) OR “Controlled Clinical Trial” [Publication Type]) OR “randomized” [tiab]) OR “placebo” [tiab]) OR “Clinical Trials as Topic"[Mesh:NoExp]) OR “randomly” [tiab]) OR “trial” [ti])) NOT ((“Animals” [mh]) NOT ″ humans” [mh])) in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* [25].

The reference lists were also checked for relevant studies, and all studies were carefully evaluated to identify duplicate data.

2.2. Study selection

The following criteria were used for study selection: (1) Participants (P): Patients were eligible if they had histologically proven carcinoma of gastric tissue or the gastroesophageal junction (GEJ) with no evidence of distant metastases. The GEJ segment encompasses the distal 5 cm of the lower esophagus, GEJ and proximal 5 cm of the stomach [26]. (2) Interventions (I) and comparisons (C): The study should compare two or more of six treatment strategies (surgery alone, postoperative CRT, postoperative CT, preoperative CRT, preoperative CT and perioperative CT) (3) Outcomes: OS; (4) Study design (S): Published RCTs; (5) Provided enough information to estimate the hazard ratio (HR) and 95% confidence intervals (CIs) of OS.

Conference abstracts, letters, case reports, reviews, studies without randomization for treatment allocation and studies without usable data were excluded. Studies published before 1997 were excluded because changes in CRT and CT strategies during recent decades are likely to influence the results. Studies concerning intraperitoneal chemotherapy or immunotherapy were excluded. Studies enrolling patients with esophageal cancer were excluded if data for gastric and gastroesophageal cancer were not extractable.

2.3. Assessment of risk of bias and data collection

Qualitative assessment and data extraction were completed by two investigators independently, and disagreements were resolved in discussion with a third investigator. The two researchers used the same standardized collection form to extract information from each enrolled study. Data concerning study quality, population characteristics and year of publication as well as interventions and outcomes (OS) were extracted. We also extracted the HR with 95% CI to assess the survival benefit.

The quality and the risk of bias in RCTs were assessed by Cochrane Collaboration's tool [27].

2.4. Statistical analysis

The PRISMA checklist [28] was used as the guideline for the meta-analysis. The primary endpoint of our network meta-analysis was OS. HRs with the 95% CI, which take the number and timing of events into consideration, were used to assess time-to-event outcomes. We obtained the survival data directly from the studies or used Kaplan–Meier survival curves to estimate the HRs of OS as reported by Tierney et al. [29]. An HR below 1 indicated a better prognosis with the experimental treatment. Heterogeneity within each pairwise comparison when two or more trials were available for the comparison was assessed by Cochran's Q test and measured by the I^2 statistic, and interpretation of the I^2 values was made by assigning attributes of low, moderate, and high in cases of 0–25%, 25–50% and above 75%, respectively [30,31]. The pooled HRs and 95% CIs were calculated by the random effects models (DerSimonian–Laird method [32]).

First, we performed a traditional pair-wise meta-analysis with Stata 12 (Stata Corp, College Station, TX) for direct comparisons. Second, a network meta-analyses using the Bayesian Methods [23] with a random-effect model concerning multiple treatments [33] was performed with Stata 12 (Stata Corp, College Station, TX), JAGS and R (version x64 3.3.3) with the gemtc package (version: 0.8–2) and rjags package (version: 4–6).

Furthermore, the direct comparison HRs from the network meta-analysis and the pair-wise meta-analyses were compared to estimate the consistency between direct and indirect comparisons. In addition, the inconsistency of our results was evaluated by the node-splitting method and the Bayesian P value [34], which compares the direct and the indirect estimates for each comparison. The 95% credible intervals (Crl)