



A meta-analysis of the association between adjuvant chemoradiotherapy and disease-free survival in gastric cancer according to the histology

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Abstract

Background There are biological distinctions between gastric cancers from Eastern and Western nations, and therapeutic strategies may differ regionally. Perioperative chemotherapy, adjuvant chemotherapy, and adjuvant chemoradiotherapy (CRT) have all been demonstrated to be effective in the treatment of gastric cancer. The goal of this study was to do a meta-analysis of published studies that were eligible to see if adjuvant chemoradiotherapy was helpful for gastric cancer based on the cancer's histology.

Method From inception to May 4, 2022, manual searches were conducted to identify all eligible literature using the PubMed database for the published phase III clinical trial and a randomize-controlled trial testing the role of adjuvant chemoradiotherapy in operable gastric cancer.

Results Two trials with a total of 1004 patients were selected as a result. Adjuvant CRT was found to have no effect on disease-free survival (DFS) in gastric cancer patients treated with D2 surgery (HR: 0.70 (0.62–1.02), $p = 0.07$). However, patients with intestinal-type gastric cancers exhibited significantly longer DFS (HR: 0.58 (0.37–0.92), $p = 0.02$).

Discussion After D2 dissection, adjuvant CRT improved DFS in patients with intestinal-type gastric cancers but not in those with diffuse-type gastric cancers.

Keywords Adjuvant chemoradiotherapy · Gastric cancer · Lauren classifications

Background

The prevalence of gastric cancer has decreased over the several decades, but it is still a common malignancy and the fourth leading cause of cancer-related death worldwide [1]. Although the treatment strategy varies geographically, perioperative chemotherapy, adjuvant chemotherapy, or adjuvant chemoradiotherapy are the treatment options that can be used as adjuncts to surgery [2–4]. In Asia, the preferred method is surgery with D2 dissection followed by adjuvant chemotherapy. In Europe, on the other hand, perioperative chemotherapy is usually done. Adjuvant chemoradiotherapy has been the cornerstone of adjuvant therapy since the pivotal Int 116 trial; however, results of the recent

adjuvant chemoradiotherapy (CRT) trials in patients with D2 dissected gastric cancer were negative, thus questioning the role of adjuvant chemoradiation [3, 4].

Many studies have found that the presence of R1 resection, lymph node involvement, diffuse histology, lymphovascular invasion, tumor grade, and resection type are associated with poor disease-free survival in gastric cancer patients [5–8].

According to Lauren's classification, gastric cancers are histologically classified as diffuse and intestinal subtypes [9]. These two subtypes exhibit many differences in epidemiology, biology, and prognosis.

In this study, we aimed to assess the benefit of adjuvant CRT according to Lauren's histological classification by conducting a meta-analysis of phase III trials that reported disease-free survival (DFS) outcomes according to histological subtype.

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Method

Literature search

We performed this meta-analysis following the Preferred Items for Systematic Reviews and Meta-Analysis guidance.

We systematically searched the PubMed database for published clinical trials from inception until April 4, 2022. The inclusion criteria were as follows: (1) phase III clinical trial evaluating the role of adjuvant radiotherapy in operable gastric cancer, (2) hazard ratio (HR) for disease-free survival (DFS), (3) separate reporting for the intestinal and diffuse subtypes, and (4) only English-language studies. The exclusion criteria were as follows: (1) articles other than clinical trials (real-world data, commentaries, reviews, and opinion papers); (2) studies without separate reporting for Lauren subtypes; and (3) lack of data regarding HRs.

Two authors independently extracted the available data (HCY and DCG), and any discrepancies were resolved by the senior author (OD). The following data was extracted for the included studies: year of the study, study arms, sample size, study arms, and HR for DFS in the intestinal and diffuse subtypes. The risk of bias was evaluated with the Risk of Bias Tool v.2.

Our search strategy retrieved a total of 743 records. Of the 743 records, 39 articles (phase 3 clinical trials and randomized trials) with full texts were evaluated, and after duplicates were removed, 31 articles were evaluated. Twenty-nine of the articles were excluded: lack of DFS outcomes ($N:11$), neoadjuvant chemoradiotherapy ($N:9$), other primary tumors ($N:3$), recurrent disease treatment ($N:2$), phase 2 trial ($N:2$), no D2 surgery ($N:1$), and article not in English ($N:1$). Two articles were included in the systematic review. The PRISMA diagram for article selection is shown in Fig. 1.

Meta-analysis

The primary objective was to evaluate the benefit of adjuvant radiotherapy according to intestinal and diffuse subtypes. The meta-analysis was conducted using the generic inverse variance with a fixed-effect model, considering the low degree of heterogeneity across studies. The principal summary measure was the HR with a 95% confidence interval (CI).

We conducted meta-analyses with the Review Manager software, version 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark), and considered p values below 0.05 statistically significant.

Result

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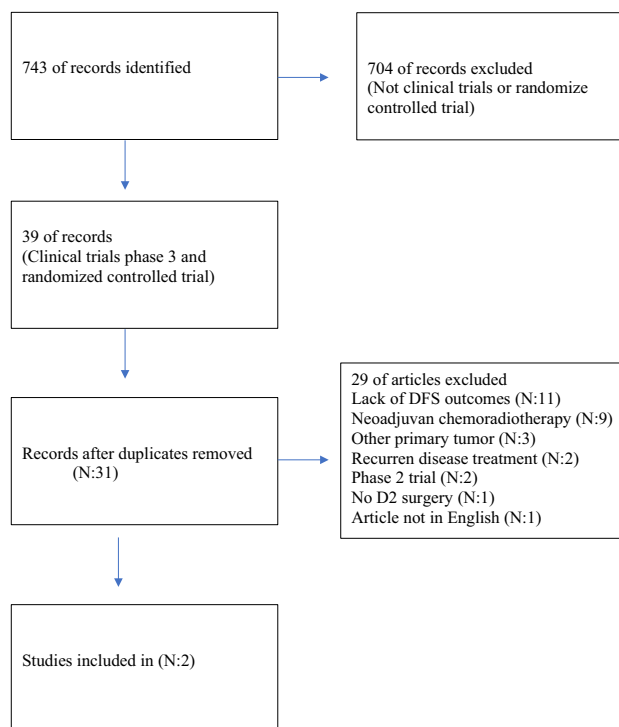


Fig. 1 PRISMA flow diagram

The ARTIST and ARTIST 2 studies were included in the analysis. Table 1 outlines the main characteristics of both trials. A total of 1004 patients were included in the two studies. Of these patients, 328 had intestinal-type tumors, 534 had diffuse-type tumors, and 142 had mixed or unclassified tumors.

Meta-analysis including the two studies showed that adjuvant CRT did not improve DFS in gastric cancer patients treated with D2 surgery in the entire patient population (HR: 0.70 (0.62–1.02), p 0.07). However, the benefit of CRT varied with the histological subgroup. Adjuvant CRT significantly prolonged DFS in intestinal-type gastric cancers (HR: 0.58 (0.37–0.92), $p=0.02$), but no DFS benefit was observed in patients with diffuse gastric cancer (HR: 0.91 (0.67–1.22), $p=0.52$) (Fig. 2).

Discussion

Our study showed that adjuvant CRT improved DFS in patients with intestinal-type gastric cancer but not in those with diffuse-type gastric cancer after D2 dissection.

Int 116 was the first randomized phase III trial showing the benefit of adjuvant CRT in patients with gastric cancer, but most of these patients had D0 or D1 surgery [10]. Although the trial was overall positive, updated OS analysis showed that the OS benefit of CRT was limited to patients with intestinal-type GC. This was an unplanned subset analysis, and the histologic

Table 1 Characteristics of the ARTIST and ARTIST-2 trials

	ARTIST	ARTIST-2
Stage	1B–4(M0)	2–3, LN positive
Patient number	458	546
Concept	Adjuvant CT with or without CRT	Adjuvant CT with or without CRT
Surgery	D2 LND	D2 LND
CT	Six cycles of XP (capecitabine 2000 mg/m ² per day on days 1 to 14 and cisplatin 60 mg/m ² on day 1, repeated every 3 weeks)	S-1 for 1 year (Arm A); SOX for 6 months (Arm B)
CRT	Two cycles of XP followed by 45-Gy XRT (capecitabine 1650 mg/m ² per day for 5 weeks) and two cycles of XP	45 Gy in 25 fractions of 1.8 Gy with SOX
Primary endpoint	DFS	DFS
Survival outcomes	3-year DFS: XP/XRT/XP arm vs XP arm 78.2% vs 74.2% (P = .0862)	3-year DFS: S-1 versus SOX versus SOX–RT 64.8%, 74.3%, and 72.8% (HR: SOX versus S-1 0.692 (0.409–0.987; P = 0.042); HR: SOX–RT versus S-1 0.724 (0.507–1.032; P = 0.074); HR: SOX–RT versus SOX 0.971 (0.663–1.421; P = 0.879)]

HR hazard ratio, CT chemotherapy, CRT chemoradiotherapy, DFS disease-free survival, OS overall survival, RR response rate, XP capecitabine plus cisplatin, XRT capecitabine plus radiotherapy, SOX S1 plus oxaliplatin, SOX-RT S1 plus oxaliplatin plus radiotherapy

type was unknown in 23% of the patients in this trial. The authors stated that it was not known whether the difference in DFS benefit was random or depended on biology; however, subsequent trials suggested that this effect was not random.

We could not include this study in our meta-analysis because we did not have the subgroup analysis of DFS according to histology in this study. The CRITICS trial compared the efficacy of adjuvant CT vs. CRT in patients with gastric cancer treated with neoadjuvant CT [11]. In the per-protocol analysis of the patients who started the assigned postoperative treatment, which was about 60% of the whole study population, CRT was worse than CT in terms of 5-year OS.

There was no difference between CT and CRT in patients with diffuse-type gastric cancer in this study. CT performed better in intestinal-type tumors. The study’s differences were that all of the patients had received neoadjuvant CT, and postoperative CRT was not added to but instead replaced adjuvant CT.

ARTIST1 and ARTIST2 trials were designed to assess the benefit of adjuvant CRT in addition to adjuvant CT in patients with gastric cancer treated with D2 surgery [3, 4]. In ARTIST1,

subgroup analysis showed lower recurrence rates with CRT in patients with node-positive tumors [3]. Subsequently, ARTIST2 was initiated in node-positive tumors, which did not show any benefit from CRT [4]. However, subgroup analysis of both trials showed a strong signal of benefit with CRT in patients with intestinal-type tumors, and our meta-analysis confirmed these findings. Current NCCN guidelines do not recommend adjuvant CRT for people who have had their gastric cancer removed but did not get any treatment before surgery.

The inclusion of only two phase 3 clinical trials in our study is our most important limitation, and it also prevented us from evaluating other prognostic parameters.

We suggest that patients with diffuse-type tumors definitely do not need CRT, but those with intestinal-type tumors may still derive some benefit from adjuvant CRT, and this issue should be investigated in future trials.

Declarations

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest The authors declare no competing interests.

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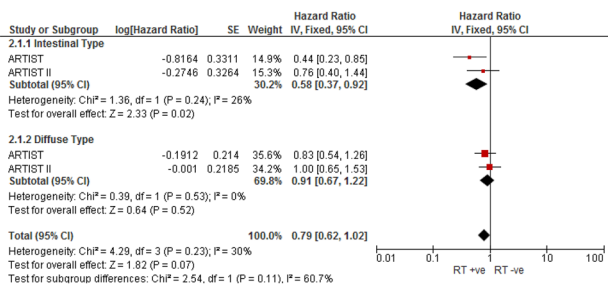


Fig. 2 Meta-analysis of the association between histological type and disease-free survival (DFS) in localized-stage gastric cancer

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