

## Answers to the reviewers

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Title: Neoadjuvant chemotherapy for gastric cancer. Is it a must or a fake?

Science editor: Ze-Mao Gong

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Reviewer #1

**Reviewer's code:** 00502831

**Reviewer's country:** Japan

We have shorten the description of minor past RCTs in the section RESULTS, leaving more details for more significant and larger RCTs

Reviewer #2

**Reviewer's code:** 01558002

**Reviewer's country:** Greece

As concerns the **first comment**, I would reply that this paper is not simply a narrative review, and absolutely does not want to be educational, therefore it does not summarize the international guidelines and does not discuss the indications, benefit and harm of neoadjuvant chemotherapy because this is not the goal of this paper.

The main goal of the paper is provocative; it aims to raise doubts on the actual adoption of neoadjuvant chemotherapy in several national guidelines ( which are cited), because actual indications are based only on a couple of RCTs that have important limitations and biases when analyzed with attention. And this analysis was the goal of the paper..

The comment 2 concerns citations of abstracts and some clinical trials that, according to the reviewer, should be unsuitable for the analysis with the primary outcome of overall survival. We have considered all the 16 RCTs on NAC vs Surgery Alone published till here in literature; among these 16 trials there are many studies that are incomplete or only abstract, not well designed, not structured, with strange end points, and so on. All these reports are useful to underline how the evidence of NAC's effect on survival is based on very few reports; and, furthermore, that these few reports have limitations , biases.. as demonstrated in the trial. For example, the reviewer cites the study by Zhao (Ref 34) as a study not-relevant ; I would reply that this study has been cited in all meta-analyses published in literature till now.

**The comment 3**, finally, is absolutely not true. Actually, D2 gastrectomy does not include splenectomy except from cases of advanced cancer of the greater curvature, facing the splenic

hilum. Therefore we cannot understand the meaning of this comment. I have never mentioned spleno-Pancreasectomy during D2 gastrectomy in this Review.

Reviewer #3

**Reviewer's code:** 03002224

**Reviewer's country:** Japan

**Comment 1:** the title has been modified according to the suggestion of the reviewer. As the study is not a Meta-Analysis but a Review of the Literature in our conception, the title effectively contains a true question that we have tried to answer in the paper.

**Comment 2:** we have tried to demonstrate that in all 16 RCTs actually available in literature there is a consistent variability of chemotherapy regimens adopted, different criteria for patient selection mostly concerning the location of the tumor and no homogeneity of surgical procedures performed as concerns lymph node dissection. The aim of the study was to raise doubt upon the consistence of the actual indication to neoadjuvant chemotherapy.

**Comment 3:** IGCSG, MRC, NEJM, EJC abbreviation order has been modified and corrected and the explanation of each abbreviation has been introduced on the first time of their appearance.

Reviewer #4

**Reviewer's code:** 03017516

**Reviewer's country:** Italy

**Comment 1:** as already stated, we have obtained a language certificate by the American Journal Experts, which has been sent to the editor-in-chief of WJG at the moment of the manuscript sending.

**Comment 2:** The quality of the RCTs was assessed using modified Jadad's scoring system and Cochrane reviewers' handbook 5.0.1 RCT criteria. The assessment was based on the randomization methods, the report of dropout rates, allocation concealment, the use of intention-to-treat (ITT) analysis, and losses to follow-up, the extent to which valid results were depicted. Based on these criteria, the studies were divided into high quality group (score  $\geq 4$ ) and low quality group (score  $< 4$ ). (Table 1). A paragraph on "Quality assessment of the 16 RCTs available in Literature" has been added before the "RESULTS".

**Comment 3:** PRISMA guidelines are effective for proper systematic review. But this study was not intended as a systematic review in our conception but rather a review of the Literature. Therefore we did not consider Prisma guidelines essential for this review study.