

Answers to the reviewers' comments

Reviewer 1 (no particular comment to answer to)

Thank you very much for your interest in your review.

Reviewer 2

There are some review, systematic review and meta-analysis about therapy for gastroesophageal adenocarcinoma. Authors can refer to some of these papers in their manuscript instead of referring to trilas when we have some updated reports in review articles.

Thank you very much for your interest in our review.

Reviewer 2 is right. Reviews on the topic have been published recently. We have added a reference to the Cohen and Leichman review (JCO, 2015) in the introduction section (reference n°8).

Reviewer 3

Overall good review with some comments and suggestions below:

Thank you very much for your interest in our review and for your comments.

1. Abstract: clearly chemoradiation without surgery is potentially curative for esophageal cancer (as proven by 2 randomized trials looking at chemoRT +/- surgery, including FFCD trial referenced in text). Stating that surgery is necessary for cure for both esophageal and gastric cancers is not accurate or appropriate. If you want to make this assertion, please limit the discussion to gastric cancers, specifically Siewert III only.

Reviewer 3 is right. Esophageal cancers can be treated with exclusive radiochemotherapy. We have replaced "only" with "major" in the sentence of the abstract which stated that surgery was the only curative treatment.

2. Abstract: citing MAGIC trial for esophageal cancer doesn't particularly make sense. Please reference the POET trial looking at the importance of radiotherapy for GE junction cancer.

Reviewer 3 is right; the POET trial shows the importance of radiotherapy for GE junction cancer. In the abstract, we have chosen to reference the MAGIC and the FNCLCC-FFCD trials because we point out the benefits of perioperative chemotherapy. We chose to reference the POET trial in the "Combination of neoadjuvant induction chemotherapy and chemoradiotherapy" section (p.12-13).

3. Introduction: again surgery is not the only curative treatment for esophageal cancers

Again, reviewer 3 is right. In addition to correcting the abstract, we have corrected the same sentence in the introduction replacing "only" with "major". We have also added in the

introduction a sentence stating clearly that our review will only focus on neoadjuvant therapies. We will not discuss exclusive radiochemotherapy treatment of esophageal cancers in our review.

4. Adjuvant therapies:

a) Please discuss any data comparing chemotherapy alone vs. chemoRT - ie., POET trial for GE junction cancer.

Reviewer 3 is right, it is important to discuss data comparing chemotherapy alone versus chemoradiotherapy before surgery, i.e. the POET trial. We have discussed it in the "Combination of neoadjuvant induction chemotherapy and chemoradiotherapy" section, referencing the POET trial (reference 42 in our manuscript). We have also referenced another study comparing neoadjuvant chemoradiotherapy versus neoadjuvant chemotherapy alone, which reported a significant reduction of the R1 resection rate for patients treated with chemoradiotherapy (reference 43 in our manuscript).

b) Please comment why the INT-0116 (MacDonald trial) had a higher numerical 5 year survival than the MAGIC trial for gastric cancer.

Comparing two studies to one-another is difficult. Indeed, the MacDonald and the MAGIC trials assess two different therapeutic strategies (postoperative radiochemotherapy and perioperative chemotherapy) in different patients.

When asked for the comparison, the MAGIC trial reported 5-year survival rates of 36% and 23%, and the Mac Donald study, rate of about 42% versus 25%, which seem of the same order.

c) Please discuss metaanalyses comparing induction chemotherapy vs. chemoRT for esophageal cancer.

Reviewer 3 is right, meta-analyses comparing induction chemotherapy versus chemoradiotherapy have been published. To our knowledge, they all include squamous cell carcinomas, which we do not wish to discuss in our review.

d) Finally, please comment on why the absolute survival advantage for chemotherapy alone in the metaanalyses was ~6% while the CROSS trial had a more robust 13% survival advantage.

As said in answer 4b, comparing two studies to one-another is difficult, such is comparing meta-analyses and trial results. The CROSS trial compares radiochemotherapy versus surgery alone, which is too difficult to compare to the 6% survival advantage for chemotherapy alone reported in the meta-analyses referenced by reviewer 3.

5. Conclusions: I might be biased but it appears that trimodality therapy is superior to bimodality therapy. However, I completely agree that intensifying chemotherapy in chemoRT regimens makes intuitive sense - but needs to be validated in randomized trials. You should acknowledge that CALGB 80101 tried this but failed. Also comment on Her-2/neu inhibitors. Again great job overall! I would actually suggest including one of your radiotherapy colleagues to this manuscript.

To our knowledge, the superiority of trimodality therapy over bimodality therapy has not yet been shown in randomized trials. We discuss this point in the "Perspectives in the GEA

management: unanswered questions” section, citing some ongoing studies (the FLOTT study, a study of the ICORG group), including a phase III study focusing on the question. As addressed before, the POET study seemed promising but cannot be considered as a standard without further studies confirming these results.

Concerning the CALGB trial, the CALGB 80101 trial considered adjuvant and not preoperative treatment. We have referenced instead in the “Neoadjuvant chemoradiotherapy” section the CALGB 9781 which tried to show a benefit of neoadjuvant chemoradiotherapy with 5FU-CDDP regimen, but failed due to a poor accrual.

Finally, concerning the Her2/neu inhibitors, to our knowledge, no relevant data on the use of these treatments as neoadjuvant setting in the management of GEA cancers have been published. We do not wish to discuss this therapeutic strategy in our review.