TCR TRANSLATIONAL CANCER RESEARCH
ADVANCES CLINICAL MEDICINE TOWARD THE GOAL OF IMPROVING PATIENTS' QUALITY OF LIFE
IMPACT FACTOR 1.241

Peer Review File

Article information: https://dx.doi.org/10.21037/tcr-21-2886

Reviewer A

Abstract

1. The authors should replace "macroscopic type" with "macroscopic type 4. Similarly, please revise it in the result section.

Reply 1: we have modified our text as advised (see Page 3, line 42；Page 8, line 156)

Introduction

2. Please update reference (Ref) 1. Now, the 2020 global cancer statistics are available as follows.

Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May;71(3):209-249. DOI: 10.3322/caac.21660.

Reply 2: we have modified our text as advised (see Page 4, line 49；reference 1)

3. The REGATTA trial was a trial of whether debulking surgery for advanced gastric cancer with a single incurable factor improved the overall survival or not but not a trial for the benefit of conversion surgery. Therefore, I recommend that the authors delete the description of the REGATTA trial in the introduction section to avoid confusing the reader.

Reply 3: we think the REGATTA trial describes the role of debulking surgery in advanced gastric cancer with a single incurable factor. The description of the REGATTA trial in the introduction aim to point out that patients underwent gastrectomy and subsequent systemic chemotherapy did not have survival benefit. The REGATTA trial is a pioneer, and we should to explore other choices of treatment. Of course, we can delete it if necessary.

4. Overall, Introduction is a little redundant. The authors should shorten it more, focusing on the purpose of this study.

Reply 4: we streamlined the content of introduction

Method

5. I understand that this study evaluated the efficacy of conversion surgery for HER2-positive advanced gastric cancer with Stage IV who was able to be feasible for chemotherapy. If so, I wonder why the authors analyzed the PFS and OS from the

time from diagnosis of stage IV, not after conversion therapy. Please provide the PFS and OS after the conversion surgery.

Reply 5: If the study population were locally advanced gastric cancer, we should to analyze the PFS and OS from the time after surgery therapy. Our study population were metastatic gastric cancer, so we think it is more reasonable to analyze the PFS and OS from the time from diagnosis of stage IV, not after conversion therapy. Of course, we can also provide the PFS and OS after the conversion surgery as advised if necessary.

6. Please provide the detail of treatment, such as second-line chemotherapy after conversion surgery, which strongly can affect the overall survival.

Reply 6: Various factors impact the treatment options of secend line therapy, such as recurrence pattern，socieconomical status，drug availability and so on. This study evaluated the efficacy of conversion surgery for HER2-positive advanced gastric cancer with Stage IV who was able to be feasible for chemotherapy. Describing posterior line therapy in too much detail may miss the purpose of the study. Of course, we can also add relevant information if necessary.

7. Please provide the detail of the first-line preoperative chemotherapy regimen in Table 1.

Reply 7: we provide the detail of the first-line preoperative chemotherapy regimen in Table 1.

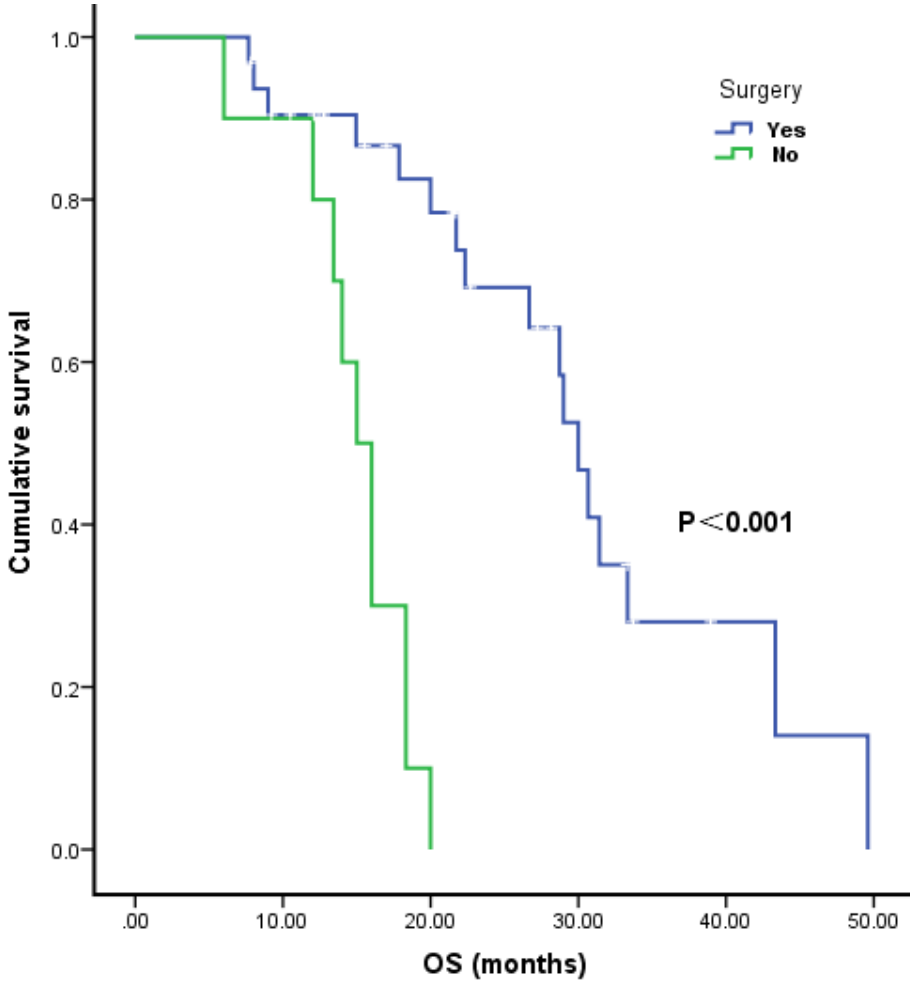
Discussion

8. The study revealed that prolonged inductive chemotherapy was an independent prognostic factor for OS from the diagnosis of stage IV gastric cancer. I wonder that strength of the inductive chemotherapy can affect the overall survival because the DCS regimen is stronger than S-1 alone.

Reply 8: univariate and multivariate analysis demonstrated that strength of the inductive chemotherapy was not independent prognostic factors of OS (see Table 3). Perhaps due to the small sample size, trastuzumab therapeutic effect may be more important, covered the differences between different chemotherapy regimens.

9. To evaluate the effect of conversion surgery, the authors should show the PFS and OS compared to the data of 10 patients who refused gastrectomy or mastectomy because their background was similar.

Reply 9: The median OS and PFS of the 10 patients that refused surgery were 14.8 and 7.8 months.



10. I do not understand what the loss of HER2-positivity means in this study about the third paragraph. If the author discussed this point, the authors should show the prognosis of five patients who were IHC2+ and FISH+ lost their HER2-positivity in this study and discuss it.

Reply 10: we discussed the loss of HER2-positivity means in this study (see Page 10, line 190-200) and pointed out re-evaluation of HER2 status when diseases recur or progress is warranted because several new drugs such as trastuzumab deruxtecan (T-DXd) (DS-8201a) have been established for later line use as an anti-HER2 treatment. we also show the prognosis of five patients who were IHC2+ and FISH+ lost their HER2-positivity in this study (see Page 10, line 189-190).

Reviewer B

In this retrospective single cohort analysis, the authors assessed the survival of patients with advanced Her2+ gastric cancer who were operated after treatment with

chemotherapy and Trastuzumab. Moreover, the authors attempted to investigate potential prognostic factors in this patient population. This manuscript joins a growing body of evidence supporting the multimodal approach for stage IV gastric cancer which combines perioperative chemotherapy/immunotherapy with surgery; this approach may offer an improved prognosis in selected patients.

I have the following questions/comments:

- It's not clear to me how what were the eligibility criteria for conversion surgery. The authors mention that it was assessed by a multidisciplinary team and that R-0 resection was the goal. Can the authors elaborate more on the eligibility criteria?
Reply 1: we have modified our text as advised (see Page 6, line 110-112).

- From a surgical point of view, it is quite interesting to read that there were only three complications in this cohort of 32 patients (two pulmonary infections and one wound infection). Those surgeries are usually more complex and include a non-negligible morbidity rate. Can the authors elaborate more on the post-operative course? Was the morbidity/mortality measured as 30/90/other days post op?
Reply 2: The Clavien-Dindo Classification of Surgical Classifications was used throughout surgery to grade adverse events (i.e., complications) that occurred as a result of surgical procedures. We only described complications above grade 3. Those surgeries are usually more complex, so surgeons are more careful during the operation and pay more attention to the changes of the disease after the operation. These may have contributed to a lower complication rate. Morbidity/mortality was measured during surgical hospitalization.

we have modified our text as advised (see Page 7, line 124-126).

- There were five patients with liver metastasis; was non-anatomic liver resection/ metastasectomy done? It is not clear from the text.
Reply 3: As conversion surgery is defined as a surgical treatment with the goal of curative resection of both primary and metastatic tumor, we showed the residual tumor classification of in this cohort of 32 patients.
- Table 2 is missing the number of total gastrectomies that were done.
Reply 4: I'm sorry, we missing the number of total gastrectomies that were done and accidentally switched the number of distal gastrectomy and total gastrectomy，we have modified our text as advised (see Table 2).

- When no cases/events are mentioned in a table as the number Zero, there should not be a percentage sign after it but rather as a stand-alone number (0).
Reply 5: we have modified our text as advised (see Tables).

- It would be interesting to see the survival of the 10 patients that refused surgery

Reply 6: The median OS and PFS of the 10 patients that refused surgery were 14.9 and 7.8 months.

- From a biological/oncological ponit of view it would be interesting to know whether in table 6, for the five patients who lost their Her2 positivity, was it checked only in the primary specimen or also in a metastatic site/paraaortic lymph nodes

Reply 7: it checked only in the primary specimen, we have modified our text as advised (see Page 9, line 165-166). This is a retrospective analysis with limited conditions. If necessary, we can supplement the data of metastatic site.

- Since the Yoshida classification is mentioned and measured in the manuscript, the authors should give a short description on the main components of the classification.

Reply 8: we have modified our text as advised (see Table 1). We think it is a little redundant, maybe we can delete it.