

Responses to the reviewer's comments:

Reviewer #1:

Specific Comments to Authors: this topic is interesting but i have comments to the authors:

1. the number of patients is small

Reply: Yes, the number of patients is small because this is a phase II study with small sample size.

2. please add degree of freedom for each p value

Reply: Thank you for your suggestion. We agree with you and have revised accordingly.

c

3. in th first sentence of the inclusion criteria remove either inclusion or the following

Reply: Thank you for your suggestion. We agree with you and have revised accordingly.

4. patients with either total or partial gastrectomy had problems with feeding, how they tolerate oral capecitabine

Reply: According to our follow-up, the patient had no difficulty swallowing soft food or capecitabine, unless anastomotic stenosis occurred after surgery.

5. how you define recurrence, relapse and metastasis

Reply: The definition of recurrence was shown in Paragraph 2 in the Statistical analysis.

6. did you use upper digestive endoscopy in the follow up of your patients and how many and what is the findings:

Reply: Yes. We suggest the patients who had gastrectomy use digestive endoscopy at least once a year or any time when CT/PET-CT indicated any signs of recurrence around or in the anastomoses or gastric remnant. Normally, it helps to diagnose whether regional lymph node recurrence involves anastomotic or residual stomach and to find cancer of gastric remnant.

Reviewer #2:

Specific Comments to Authors: In this study, the authors investigated the efficacy and toxicity of oral capecitabine and IMRT based on their own phase I study. Although adjuvant CRTx is not routinely applied in Japan and South Korea, CRTx may be a useful treatment option in patients who underwent D1 gastrectomy or pts with N3 patients. This study showed acceptable safety and efficacy of CRTx following gastrectomy with D1/2 LND for locally advanced

gastric cancer. Therefore, this study is valuable in that it can be a reference in western countries. The followings are my specific comments for this article;

1. The authors hypothesized the 3-year DFS rate would improve from 50% to 70% based on INT 0116 trial (surgery alone vs. CRTx= 31% vs. 48%). In this study, does “3-yr DFS of 50%” mean 3-yr DFS in surgery-alone group, or that in adjuvant CTx group? Currently, adjuvant CTx is essential worldwide in locally advanced gastric cancer. Therefore, I think it is reasonable to consider 3-yr DFS in adjuvant CTx group as a baseline. However, regarding phase II trial, authors should clarify the character of baseline DFS in study protocol.

Reply: Thank you for your suggestion. The 3-yr DFS of 50% was from the result of adjuvant CRTx based on INT 0116 trial. We have clarified the character of baseline DFS in study protocol.

2. Was a patient, who died of gastric bleeding, associated with recurrence, or RTx? Because gastric bleeding can be controlled with endoscopic ablation or remnant gastrectomy, more specific descriptions are needed.

Reply: Thank you for your rigorous and serious working attitude. One patient died of severe gastric bleeding after nearly 7 years after surgery without any signs of recurrence. So I think it may be due to RTx or some other benign disease of the stomach, such as gastric ulcer. However, we could not make clear the cause of death because he died in local hospital.

3. Locoregional recurrence occurred in 7 patients (17.5%), which is considerably high, regarding CRTx with D1/2 gastrectomy. How many patients were with solitary locoregional recurrence? Were there subsequent treatments such as reoperation or intensive RTx for local control?

Reply: Solitary locoregional recurrence developed in only three patients (7.5%), including one patient at regional lymph node at the gastric trunk area, one at the anastomosis, and one at the gastric stump. Chemotherapy is the main subsequent treatment for these patients with locoregional recurrence unless the site of recurrence is outside the irradiation field. Reoperation was rarely performed in patients with relapse at anastomosis or gastric remnant in our hospital.

4. The rate of R0/R1 resection should be presented in Table 2 because R1 resection is strongly associated with locoregional or peritoneal recurrence.

Reply: No patients underwent R1 resection in this study. All of them had R0 resection.

5. This study consists of 18 pts with D1 gastrectomy and 22 pts with D2 gastrectomy. Therefore, it can be meaningful that authors show the results of D1 group and D2 group.

Reply: We agree with your comment. However, for a small sample size study enrolled only 40 patients, we think that the analysis of subsequent group would be not meaningful.

6. It is natural to change the arrangement of present/absent as absent/present in Table 2. AJCC 6th stage is unnecessary in Table2, despite authors wanted to emphasize the proportion of advanced disease.

Reply: Thank you for your suggestion. We agree with you and have revised accordingly.

7. Survival analysis in Table 4 should be presented as a figure along with number at risk. 7-yr OS was lower than 7-yr DFS in Table 4. It does not make sense.

Reply: Thank you for your suggestion. We agree with you and have revised the manuscript accordingly. As for why 7-yr OS was lower than 7-yr DFS, we check the data again. The patient who died of gastric bleeding seven years after surgery was not recorded as tumor recurrence, which resulted in an opposite survival outcome for this study. That is to say, with a very long-term follow-up time, very few patients relapse and die of the tumor 5 years after surgery.

Reviewer #3:

Specific Comments to Authors: While overall quality is good I wish to express some doubts

1. potential inclusion of D0 patients is strange as I consider them non oncological treatments in advanced gastric cancer.

Reply: Patients with D0 lymph node dissection was not enrolled in this study. All patients underwent radical D1/2 lymphadenectomy.

2. D1 in advanced gastric cancer is problematic and writing recommended D2 is not really good enough. Still only 55% had a D2 resection and there are patients with 5 LNs resected. That is not even D1. A ugly nonhomogenous group as much as surgery is concerned will created a major bias.

Reply: Thank you for your rigorous and serious working attitude. We sincerely apologize for the errors. We wrote the minimum number of LNs resected wrong. We have corrected these mistakes in our revised manuscript.

3-4. You should be more specific regarding CTV and PTV. I personally do not understand the benefit of including LNs stations in CTV after radical gastrectomy (eg station 3 irrespective of location). Basically you overtreat an area that should have been resected plus add high dosage on the stomach. I believe you need to explain why you need to treat LN areas that are meant to be resected. If you assume bad surgery than it is a major problem and you need to selected other surgeons. RT may not compensate bad surgery. In your inclusion criteria all patients were required to have a D2 beta resection. please explain why do you decide to irradiate same areas. You will have to indicate if recurrences developed in such sites or RT prevented that

Reply: Question No. 4 was not completed so I combined No. 3 & 4 to answer. We totally agree with you. This study was performed from 2011 to 2013. At that time, CTV contouring guidelines was from Smalley et al ^[1], which included the tumor bed, anastomotic stumps, gastric remnant, and regional lymphatics at high risks. After that, we excluded gastric remnant from the target volume according to the conclusion made by Nam et al ^[2]. Nowadays, with the development of D2 lymphadenectomy, it has been found that locoregional recurrence rate is getting lower and lower, especially in perigastric lymphatic area (station 1-6). Moreover, interim results of ARTIST II showed no difference in DFS between SOX and SOXRT (HR 0.910, P = 0.667) ^[3]. Thus, postoperative CRT was only used to treat some patients at high risk such as (y)pN3 without neoadjuvant RT. Accordingly, CTV was modified to cover station 7-9, 11-12 and 16a. Even tumor bed or anastomotic stumps were not irradiated again.

References

- [1] Smalley SR, Gunderson L, Tepper J, et al. Gastric surgical adjuvant radiotherapy consensus report: rationale and treatment implementation. *Int J Radiat Oncol Biol Phys.* 2002. 52(2): 283-93.
- [2] Nam H, Lim do H, Kim S, et al. A new suggestion for the radiation target volume after a subtotal gastrectomy in patients with stomach cancer. *Int J Radiat Oncol Biol Phys.* 2008. 71(2): 448-55.
- [3] ARTIST 2: Interim results of a phase III trial involving adjuvant chemotherapy and/or chemoradiotherapy after D2-gastrectomy in stage II/III gastric cancer (GC). Presented at: ASCO Annual Meeting; May 31-June 4, 2019; Chicago, IL.; Abstract 4001 .

5. I would like to have examples of PTVs and describes the changes associate with organ movements between sessions.

Reply: The PTV typically includes the CTV plus a 5–7 mm margin in the radial direction and a 10mm margin in the superior-inferior direction. We designed a study to investigate the intrafractional and interfractional anastomosis motion during postoperative RT in gastric cancer by four-dimensional CT. It showed that the intrafractional and interfractional anastomosis motion should be considered during postoperative adjuvant radiotherapy in gastric cancer patients who have undergone partial gastrectomy. The internal margins required for anastomosis in right-left, anterior-posterior and superior-inferior directions are 24. 2 mm, 10. 3 mm and 18. 3 mm, respectively.

References

- Liu WY, Jin J, Tian Y, et al. Four-dimensional CT-based evaluation of intrafractional and interfractional anastomosis motion during postoperative radiotherapy in gastric cancer: a prospective study. *Chin J Radiat Oncol.* 2015;24(2):163-167.

6 You state that stomach was not routinely included, but LN station 3 was included. That in the context of a large majority of partial gastrectomy (which you need to develop - what kind of partial gastrectomy and LN territory resected)

Reply: LN station 3 is the LNs along the lesser curvature, which attached to station 7-9. The area of this station is different from remnant stomach. If you included remnant stomach, sometimes you have to include station 4 (the greater curvature). Partial gastrectomy comprises proximal or distal subtotal gastrectomy (Billroth I or II gastrectomy). We have revised the manuscript accordingly.

7. ACT and ARCT are used in a very liberal manner and may influence the results. There are too many variables in a small cohort.

Reply: We agree with your comments. That is also the limitation of this small-sample study.

8. While peritoneal and distant metastasis are obvious, you need to discuss more about the local and regional recurrences. I have some major doubts regarding gastric stump recurrence and anastomotic recurrence (assuming correct surgery). I would like to know if the location for recurrences are inside PTV or not. A table should be provided with locations, LNs area removed at surgery (if known), nr LNs and LNindex, LN areas inside PTV or not and time to recurrence. I think it would be essential to make it clear if regional recurrence is inside or outside D2 resection area.

Reply: Solitary locoregional recurrence developed in three patients, including one patient at regional lymph node at the gastric trunk area, one at the anastomosis, and one at the remnant stomach. Locoregional recurrence combined with distant metastasis developed in four patients, including two patients at the anastomosis and two at lymph node around the abdominal aorta. The remnant stomach was not in the target volume, but the other recurrent sites are within the irradiation field.

We appreciate for your constructive comments that have helped us to improve the quality of our manuscript.