Revision for World Journal of Gastroenterology

Title: **Predictors of Post-Treatment Stenosis in Cervical Esophageal Cancer Undergoing High-dose Chemoradiotherapy** (Manuscript No. 37402)

Reviewer #1 (03552525)

The stenosis after chemoradiotheray for esophageal cancer was very important, and this report is interesting, but I would like authors to revise some points.

Answer)

Thank you for your review and comments. We tried to answer your comments as thoroughly as possible. The changes made in the manuscripts are highlighted in yellow.

1. If authors would like to use "Predictors of Post-Treatment Stenosis" in title, you should show results about stenosis before treatment outcome in abstract and results.

Answer)

In the RESULTS, we placed the *Toxicity and risk factors* section ahead of the *Treatment outcome and prognostic factors* section. Table positions and numbers are changed accordingly.

2. Authors said "chemoradiotherapy" in title, but there were 2 patients who did not receive concurrent chemotherapy. If they did not receive any chemotherapy including

adjuvant and neoadjuvant, authors should exclude them, or change title.

Answer)

We changed the title of the article as follows:

Predictors of Post-treatment Stenosis in Cervical Esophageal Cancer Undergoing High-dose Radiotherapy

We also change the AIM of the Abstract as follows:

To evaluate toxicity and treatment outcome of high-dose radiotherapy (RT) for cervical esophageal cancer (CEC).

3. If possible, could authors show correlation between stenosis and chemotherapy cycle.

Answer>

The number of patients receiving consolidation chemotherapy of 0, 1, 2, 3, 4, 5, and 6 cycles was 18, 12, 9, 4, 17, 1, and 1, respectively. A higher number of consolidation chemotherapy (≥3 cycles vs. <3 cycles) did not show a significant correlation with occurrence of post-treatment stenosis ($p = 0.369$) or TE fistula ($p = 0.584$). We did not add the information regarding the correlation between stenosis and the number of consolidation chemotherapy cycles in the manuscript because it was not statistically significant. In METHODS, we corrected the number of consolidation chemotherapy cycles from 1-4 cycles to 1-6 cycles as follows:

Two cycles of chemotherapy were administered concurrently with RT, followed by 1–6 cycles of consolidation chemotherapy.

4. I also think more than 50Gy is necessary to treat CEC, but more than 80Gy was too high. Authors should explain why there were some patients received more than 80Gy irradiation.

Answer>

It is unusual to prescribe a total dose higher than 63 Gy for cervical esophageal cancer at our institution. Two of the patients received 81 Gy and 90 Gy each because they received a boost dose of radiation to the residual tumor 1~2 months after receiving 63 Gy. We added the following sentence in the *Patient characteristics* section of RESULTS:

Two of the patients received a total dose of 81 Gy and 90 Gy each because a boost RT (18~27 Gy) was delivered to the residual tumor 1~2 months after 63 Gy.

5. Authors should show explain median follow-up time of survival patients for readers to know how long you follow up them.

Answer)

The following sentence was added to the *Treatment outcome and prognostic factors* section of RESULTS:

Twenty-seven patients were alive at the time of diagnosis. The median follow-up was 24.3 (range, 3.4–152) months for all patients and 67.8 (range, 17.8–152) months for surviving patients.

6. I think authors would like to show predictive factors for post treatment stenosis, as you write in title. If you so, "Factors influencing occurrence of post-RT stenosis" should be written in not supplementary file but table, instead of table 2. This supplementary table 2 is much more important than table 2 in this article.

Answer)

We placed *Supplementary table 2 Factors influencing occurrence of post-RT stenosis* as Table 3 in the manuscript. *Table 2 Factors influencing overall survival* is now placed in the manuscript as *Supplementary table 4*. We placed *Table 4 Factors influencing occurrence of post-RT stenosis or TEF* in the manuscript as *Supplementary table 1* because it was somewhat redundant to place both tables, *Factors influencing occurrence of post-RT stenosis* and *Factors influencing occurrence of post-RT stenosis or TEF* as main tables in the manuscript. Figures 1A and 1B are rearranged to show LFFS first and then OS. The order of the tables is as follows:

Table 1 Demographic and treatment data (n = 62)

Table 2 Post-RT toxicity profile

Table 3 Factors influencing occurrence of post-RT stenosis

Table 4 Patients with post-RT stenosis or TEF (n = 19)

Supplementary table 1 Factors influencing occurrence of post-RT stenosis or TEF

Supplementary table 2 Patients with initial esophageal stenosis (n = 17)

Supplementary table 3 Factors influencing local failure-free survival

Supplementary table 4 Factors influencing overall survival

7. Paragraph 1 in discussion is introduction. So, authors should delete it, or rewrite it.

Answer)

We removed the following paragraph from DISCUSSION and placed it in INTRODUCTION:

Organs at risk for RT planning depend on the site of treatment. Radiation pneumonitis and fibrosis are of major concern when planning for the thoracic esophagus but are of less importance for CEC. Esophageal toxicity information from hypopharyngeal cancer treatment is of limited value; the radiation field for hypopharyngeal cancer includes only a small segment of the cervical esophagus, while RT for CEC includes a large segment of the esophagus because of expansion of the craniocaudal margins from the gross tumor and the entire esophageal circumference.

Reviewer #2 (02546235)

This manuscript has been well-written. Accordingly, this would be worthy of publication in World Journal of Gastroenterology.

Answer)

Thank you very much for your review and the positive result.

Reviewer #3 (00503563)

The authors investigated predictors of post-treatment stenosis in cervical esophageal cancer undergoing high-dose chemoradiotherapy. There are some queries and comments.

Answer)

Thank you for your review and comments. We tried to answer your comments as thoroughly as possible. The changes made in the manuscripts are highlighted in yellow.

1. The authors should indicate about the future perspectives of the clinical management in patients with cervical esophageal cancer undergoing high-dose chemoradiotherapy.

Answer)

We modified the last paragraph in DISCUSSION as follows:

Our study showed that, although pre- and post-RT stenosis was a prognostic factor for patients' survival, complete circumference involvement rather than a higher radiation dose was the key contributing factor. In clinical practice, physicians are often tempted to prescribe a higher-than-standard dose of 50 Gy for esophageal cancer, especially when it is expected that the patient is unable to undergo surgical resection because of tumor location, poor generalized condition, or patient's refusal for surgery. Our data suggests that patients with cervical esophageal cancer may undergo radiotherapy of up to 63 Gy without increasing the risk of radiation-induced toxicities. Since prospective data is lacking, our study warrants a prospective trial to investigate toxicity and efficacy of high-dose radiotherapy for cervical esophageal cancer.

2. In the present study, a higher dose was not associated with post-RT stenosis. How do the authors discuss about this finding?

Answer)

In our study, the median dose was 63 (range, 45-90 Gy). In fact, the highest dose we prescribed was 63 Gy except for the 2 patients who received a boost dose of 18 Gy and 27 Gy to the residual tumor 1 and 2 months after completing 63 Gy. The total dose of 90 Gy resulted in stenosis, and the other patient who received a total dose of 81 Gy experienced malignant stenosis. Although prospective data is lacking, 60 Gy or higher dose is often prescribed for definitive radiotherapy of cervical esophageal cancer in clinical settings. We believe 63 Gy, compared with 50 Gy, can increase local control without increasing radiation-induced toxicity in treating patients with cervical esophageal cancer. We added the following paragraph in DISCUSSION:

In the current study, the highest dose we prescribed was 63 Gy except for the 2 patients who received a boost dose of 18 Gy and 27 Gy to the residual tumor. Although this is not a dose-escalation study, 63 Gy may be safely delivered to the cervical esophagus without causing severe toxicities.

Additional changes

1. We added a title to Supplementary figure 1: “Patterns of failure”

2. We added another funding source in the title page as follows:

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