Author's response to reviews

Title: Prospective study of daily low-dose nedaplatin and continuous 5-fluorouracil infusion combined with radiation for the treatment of esophageal squamous cell carcinoma

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Author's response to reviews: see over
Dear Dr. Norton,

Enclosed please find our revised manuscript entitled “Prospective study of daily low-dose nedaplatin and continuous 5-fluorouracil infusion combined with radiation for the treatment of esophageal squamous cell carcinoma” which we are resubmitting for publication in the BMC Cancer. We made a reply to the reviewer’s comments to respond one by one and modified the manuscript accordingly.

All coauthors have agreed to resubmit this manuscript to the Journal. We hope that you and the reviewers find it suitable for publication and we look forward to your reply.

Sincerely yours,

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Response to the Referees
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We wish to resubmit our paper which has been revised, based on the reviewer’s comments. We anticipated to response to all the comments from the reviewers. In the following section, we note the revised points one by one.

Response to Referee 2: Ate van der Gaast

Reviewer’s report:

Abstract
In the abstract is not mentioned that 78.8% received additional chemotherapy. The fact that 27.3% of the patients did not complete the planned therapy is not included in the abstract.

-------We thank very much for the reviewer’s kind and critical comment. We added the completion rate of the planned therapy and the rate of the patients received additional chemotherapy in abstract section (Page 3, Line 13-15; Page3, Line 19; Page 4, Line 2-3).

Page 6
Patients and pretreatment evaluation. As a rule patients with disease limited to the mucosal layer and those with metastases to distant organs were excluded from this study. However 6 of the 33 patients had stage 1 disease.

-------According to the TNM classification (sixth edition) of the International Union against Cancer (UICC), patients with disease limited to the mucosal layer were classified as either Stage 0: TisN0M0 or Stage 1: T1(depth m)N0M0. And, both of those were excluded in this study. All of the 6 patients classified as Stage 1 (T1N0M0) in this study had tumor with submucosal invasion (depth sm) and evaluated to be eligible for the chemoradiotherapy. To clarify this point, we added the note for Stage1 in Table 1 in the revised manuscript (Page 25, Line 7).

Page 7
Spraclavicular = supraclavicular
Supraclavicular nodes or celiac nodes were included in the fields. Was there a maximum field length? Was the length of the field altered during
treatment? Two patients were treated with brachytherapy. Are these patients eligible?

-------- We corrected this spelling mistake (Page 7, Line 7).
-------- We thank very much for the reviewer’s critical comments.

Supraclavicular nodes were included in the treatment portals for the upper and the middle thoracic tumors; celiac nodes were included for the lower and the middle thoracic tumors as described in our manuscript. However, if the primary tumor located in lower esophagus with supraclavicular node metastasis, we planned the field as “long T-shape” from bilateral supraclavicular nodes to celiac nodes. After completion of 40 Gy, the field was modified to avoid the spinal cord irradiation, and only macroscopic lesions were irradiated with a margin of at least 1 cm. Two patients with stage I disease (depth sm, N0M0) were also eligible and given 12 Gy/3 fractions of high-dose-rate intraluminal brachytherapy (HDRIBT) after 40 Gy of external irradiation. Dose variation of radiation therapy among the enrolled patients was presented in Table 2.

Page 9

Was there a sample size calculation?

------- Since this study was performed as single institutional setting, we could not enroll enough number of patients who had same clinical stage disease as we calculated the sample size. We allowed several variations of stage and radiation therapy. Therefore, to our regret, the sample size calculation could not be described in this study.

Discussion

The discussion focuses extensively on the comparison with other studies this can be shortened.

------- According to reviewer’s criticism, we deleted following sentences to avoid some redundancy.

1. (Page 13, Line 5-6) 1- and 2-year overall survival rates were 41% and 31.5%, respectively [24], and

2. (Page 13, Line 24---Page14, Line 2) Only 1 pilot study of definitive chemoradiotherapy using the protracted low-dose nedaplatin and continuous infusion of 5-FU regimen has been conducted with reported response and CR rates of 80 and 50%, respectively [31].

3. (Page 14, Line 6-8) Differences in anticancer and adverse effects between
cisplatin and nedaplatin if daily low-dose administration is combined with radiation may account for this finding.

4. (Page 14, Line 10-11) Esophageal cancer surgery alone is still the standard treatment for resectable stage I and IIA. For stages IIB and III, surgery with neoadjuvant chemotherapy or chemoradiotherapy may become the most frequently performed treatment, because

5. (Page 15, Line 3-5) A valid concern, however, is the possible occurrence of delayed complications, since patients are surviving longer due to the improved therapeutic outcome with chemoradiotherapy.

We hope that this revised manuscript is appropriate to requirement for the publication. Again, we thank you very much for both of your help on our work and the publication.

Sincerely yours,

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