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
Editor-in-Chief, BMC Cancer  
Melissa Norton, M.D.

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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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We wish to resubmit our paper which has been completely revised, based on the reviewers' critical and kind comments. We anticipated to response to all the comments from the reviewers. In the following section, we will note the revised points one by one.

**Response to the Referee 1: K Jingu**

**Major Compulsory Revisions**

1) *In Methods, authors should show endpoint of this study. What is primary endpoint? Response rate? CR rate? Toxicity?*

-------We thank for the reviewer's helpful comment. The primary end-point of this study was to evaluate the tumor response, and the secondary end-point was to evaluate the toxicity and the overall survival. We added the descriptions according to the reviewer's comment in the Abstract section (Page 3, Line 13-15) and the Methods section (Page 8, Line 10-12).

2) *In Methods, although I saw ClinicalTrials.gov (NCT00197444), I do not know the additional chemotherapy was also prospective treatment initially? Authors said that patients who showed an objective response to the treatment was performed the additional chemotherapy, but when were the patients evaluated response? 1 or 2 months after chemoradiotherapy? Authors should show it in Methods.*

-------We thank very much for the reviewer's kind and critical comment. Additional chemotherapy in this study was optional, and out of the ClinicalTrials.gov (NCT00197444) because the response evaluation was before or during this therapy, which was similar setting to the previous other study (Ohtsu A, et al. J Clin Oncol 1999). Tumor response was assessed according to the RECIST and initially evaluated within 1 month after chemoradiotherapy. Confirmation of CR and PR were reevaluated 3 months after initial evaluation. In this study additional chemotherapy started after initial evaluation. We added the descriptions for this issue in the Methods section (Page 8, Line 17-23).

3) *In Methods, authors should describe radiation therapy in more detail. For*
example, the irradiated field, the direction of irradiation and energy of X-ray. And, in brachytherapy, authors should describe where was prescribed 4Gy per fraction and how often treat with brachytherapy? Once per week? Why were there variations in radiation therapy? Furthermore, authors show how many patients were performed in each total irradiation dose. It is difficult to evaluate the toxicities if not the irradiation method is kept uniform or similar, I think.

-------We thank very much for the reviewer’s critical comments. In revised manuscript, we described detail of the radiation therapy according to the comment (Page 7, Line 4-20). We added a table to describe the variation of irradiation protocol, and show the number of patients for each therapy (Table 2).

4) Because of above 2) and 3), I do not know that the prospective study is acceptable as phase II study. I guess authors had better change the title to “Prospective study of daily ~ ”.

-------We concur the reviewer’s critical comment. Since we recognized the several issues existing to state our study as “phase II” in the title, we altered it as “Prospective study of daily low-dose nedaplatin and continuous 5-fluorouracil infusion combined with radiation for the treatment of esophageal squamous cell carcinoma”.

5) In Results, Why were performed salvage surgery after recurrence? Was this protocol of this study? Please describe in Discussion about it. And what treatment was performed after recurrence? Other chemotherapy? Re-irradiation?

-------The protocol of this study had not any restriction of the salvage surgery for locoregional recurrence. Although we were always worth considering the salvage surgery after recurrence, there was no patient in this series who was able to tolerate to and agree to the salvage surgery due to circumstances. Therefore, all of the patients who had locoregional recurrence were treated with chemotherapy in this series. We added the description on this issue in the Discussion section (Page 15, Line 10-17).

6) In Results, is the acute toxicities included adverse effects in additional chemotherapy? If the endpoint in the present study was results of concurrent chemoradiation, authors have to except the toxicities,
especially hematologic toxicities, from the results.

-----We thank very much for the reviewer’s kind and critical comment. The acute toxicities in this study did not involve the adverse effects in additional chemotherapy. All of the hematologic toxicities represented in the manuscript were related with chemoradiotherapy and observed before additional chemotherapy. We added the description of this in the Methods section (Page 8, Line 24 - Page 9, Line 2).

7) In Results (also in Discussion), authors described that the 5-year survival tended to be better for the adjuvant chemotherapy group (Figure 2B). But, because the significant value p was more than 0.1, authors cannot say better.

-----We thank very much for the reviewer’s kind suggestion. We deleted the description according to the reviewer’s comment (Page 12, Line 6, Page 16, Line 2-4).

8) In Results, authors showed the initial response rate. And CR was showed in 20/33 patients, but 26/33 patients were performed additional chemotherapy. When is evaluated initial response?

-----We thank very much for the reviewer’s kind and critical comment. In this study, evaluation of the initial response according to RECIST is based on both the initial evaluation after chemoradiotherapy and second evaluation to confirm of CR and PR. We initially evaluated response rate within 4 weeks after chemoradiotherapy, and confirmation of CR and PR according to RECIST criteria (≥4 weeks) were usually evaluated 3 months after initial evaluation, irrespective of any additional therapies (Page 8, Line 17-23).

Minor Essential Revisions

1) Some authors do not show their affiliations. Do those authors belong to First Department of Medicine?

-----We have added their affiliations in the revised manuscript.

2) Some regions were written in red. For example, “:” in results in abstract.

-----We have corrected our mistakes.

3) Conclusion in abstract was written “Conclusione”.

-----We made the correction.

4) In methods, in eligibility criteria, authors wrote white blood cells>3*10^3
and platelets>1*10^5.

------ We made the corrections.

5) In methods, authors should show the name of statistical software.

------ We have added the name of statistical software (Methods section: Page 9, Line 8-10)

6) At 5 lines on page 11, authors should add “,” before respectively.

------ We have added “,” according to the comment.

Response to Referee 2: Ate van der Gaast

Reviewer's report:

1) This is a small phase II trial with radiotherapy combined with daily low dose nedaplatin and continuous 5FU for patients with squamous cell carcinoma of the esophagus. This trial had a slow accrual and a total of 33 patients were included over a period of 5 years. What was the primary objective of this study and what was the power calculation? In 31 patients the radiotherapy doses range from 50.4 to 66 Gy. What was the reason for this variation and was this specified in the study protocol? Two patients received a combination of external radiotherapy and brachytherapy. This is an essential different treatment? Was this according to the protocol? Although this is acknowledged by the authors it is not clear what the reasons for this variation were. Besides the total dose and dose fraction details about how the radiotherapy was delivered are lacking.

------ We thank very much for the reviewer's kind and critical comment. The most important aim of this study was to evaluate the efficacy and the toxicity of the daily use of low dose CDGP and 5-FU in chemoradiotherapy for squamous esophageal cancer. Thus, the protocol allowed some variations of the radiation therapy although the total dose of irradiation was fixed to 50.4~66Gy (the dose of definitive chemoradiotherapy). Since this study was performed as single institutional setting and we could not enroll many patients who had same clinical stage disease, we allowed several variations of stage and radiation therapy. However, since we recognized the several issues existing to claim our study as “phase II” in the title, we altered the title as “Prospective study of daily low-dose nedaplatin and continuous 5-fluorouracil infusion combined with radiation for the treatment of esophageal squamous cell carcinoma” in the revised manuscript. Also we
described variation of irradiation and procedures of irradiation in detail (Page 7, Line 4-20, and Table 2).

2) About 12 patients had “early” disease (stage I and II) and 3 patients had distant metastases (stage IVB). Why were patients with distant metastases included in this trial? Was there any restriction for the field margins?

-------In the present study, patients with disease limited to the mucosal layer and those with metastasis to distant organs were excluded, but patients who had distant lymph node metastasis that could be encompassed in a single radiation field were included [M1 lymph node metastasis (M1 lym)] (Page 6, Line 16-20). Supraclavicular and celiac nodes metastasis were involved in M1 lym that could be irradiated in a single radiation field; for example, if the primary tumor was located in the middle or the lower esophagus with metastasis to supraclavicular nodes, the stage was IVB according to the TNM classification (UICC classification).

3) Had all patients EUS or were there also a number of patients with no pass?

-------We thank for the reviewer’s comment. In the present study, endoscopic ultrasonography was performed to determine the depth of the primary tumor invasion for the patients with suspected Stage I disease. We added the description in the revised manuscript (Page 6, Line14-16).

4) Response evaluation after chemoradiotherapy is often not very reliable this is not discussed by the authors. Were all complete responses biopsy proven?

-------We thank for the reviewer’s kind comment. RECIST does not refer to CR criteria for primary lesions by endoscopy in detail, and endoscopic methods of evaluation have not yet been fully validated. Since response evaluation after chemoradiotherapy is often not very reliable, CR for the primary tumor was defined by endoscopy when all visible tumors, including ulceration, disappeared with negative biopsy and lasted for ≥4 weeks according to the previous studies (Tahara M, et al. Jpn J Clin Oncol 2005; Ohtsu A, et al. J Clin Oncol 1999). Confirmation of CR was usually reevaluated 3 months after initial evaluation. We added the
description on this issue in the revised manuscript (Page 8, Line 18-23).

5) 27.3% of the patients did not receive planned treatment. What was the actual delivered treatment in these patients. What was the median and minimum follow-up in these patients? The survival curves suggest that more than 50% of the patients were censored before 24 months. A number of patients received additional chemotherapy. The authors state that additional chemotherapy did not significantly influence survival. However one should realize that the total numbers were very small.

-------We thank for the reviewer’s critical comment. In this study, the median follow-up period for all patients was 19 months (range, 6–66 months). No patient was lost to follow-up (Page 9, Line 20-22). Nine patients (27.3%) did not complete the regimen of chemoradiotherapy because of adverse events in the acute phase. Among these, one patient did not complete both of the radiation therapy (at the dose of 36 Gy) and chemotherapy due to severe bone marrow suppression and febrile condition. Another patient did not complete the radiation therapy at the dose of 46 Gy due to the Grade 3 leukopenia and patient’s refusal of the continuation of therapy due to depressive mental condition. The other 7 patients could not continue the chemotherapy suffered from hematological toxicities (Page 11, Line 13-20).

We recognized the total number of the enrolled patients was small, and the follow-up period was not enough to evaluate the value of adjuvant chemotherapy as the survival benefit. Thus, we think that our results do not deny the value of adjuvant chemotherapy completely. Further long-term observation is also required to clarify this issue. We added the sentences to the Discussion section as a comment of the study limitation (Page 16, Line 2-4).

6) In the conclusion the author's stat that daily low dose nedaplatin and continuous 5-FU infusion combined with radiotherapy is tolerable and may yield a higher CR rate and better survival for patients with esophageal squamous cell carcinoma. What is the definition of tolerable since 27.3% of the patients did not receive the planned treatment. Whether a treatment results in a higher response rate and/or survival can only be assessed in a randomized trial.

-------We thank for the reviewer’s criticism. According to the suggestion,
we deleted the description of “tolerable” and stated “higher CR rate and better survival” in the Conclusion section in revised manuscript (Page 16, Line 15-18).

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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