Author's response to reviews

Title: Lymph node enlargement after definitive chemoradiotherapy for clinical stage I esophageal squamous cell carcinoma

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Version: 3 Date: 9 August 2014

Author's response to reviews: see over
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Version: 3 Date: 9 August 2014

Author's response to reviews: see over
Dear Professors Michael and Solera:

Thank you very much for your letter dated July 21, 2014. We are very grateful for your encouraging review of our manuscript entitled “Lymph node enlargement after definitive chemoradiotherapy for clinical stage I esophageal squamous cell carcinoma”. We have carefully considered your comments and suggestions and used them to revise our manuscript. The changes are underlined and highlighted in red.

The reviewer’s comments and suggestions helped us to improve our manuscript. The point-by-point responses to the reviewers’ comments are given below. We hope that the revised manuscript is now suitable for publication in BMC Cancer.

Sincerely,

Tetsuo Takehara, MD, PhD
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Point-by-point responses to reviewers

Response to Reviewer 1:

Reviewer: 1
Reviewer’s report

Title: Lymph node enlargement after definitive chemoradiotherapy for clinical stage I esophageal squamous cell carcinoma

Version: 2 Date: 15 April 2014

Reviewer: Yuji Tachimori

Reviewer’s report:

This paper reported the clinical characteristics of lymph node enlargement after CRT. The aim of this study was quite unique and attractive. However, there are several points to be addressed.
1. The enlarged lymph nodes were diagnosed as a recurrence when they increased in size and number in the CT scan. The authors don’t include information from a currently used staging evaluation, PET, in their analysis. I suggest that this is an important deficiency.

Reply
According to your suggestion, we collected information of FDG uptake in PET-CT at the time when lymph node recurrence was suspected. We added the status of FDG accumulation in PET-CT to Table 3. We described these results in Results (page 11 line 22).

2. To elucidate the usefulness of CRT for patients with clinical stage I esophageal cancer won’t be the aim of this study.

Reply
As you pointed, the main objective of this study is the analysis of enlarged
lymph nodes after chemoradiotherapy. Previously, the usefulness of chemoradiotherapy for early esophageal carcinoma has been already reported as we described in Introduction. However, this is first report to discuss the enlarged lymph nodes including benign enlargement after chemoradiotherapy. We modified the last sentence of Introduction (page 5 line 15).

3. The planning target volume was limited to the primary tumor without prophylactic lymph node coverage. Metachronous recurrence out of the radiation field was not included in the present study. So, all the enlarged lymph nodes diagnosed as a recurrence were located in the radiation field limited within 2- to 3-cm margins above and below the tumor. However, in Table 3, LN locations spread from supraclavicular to cardia. Were all those nodes included in the radiation field?

Reply
Metachronous esophageal recurrence out of the radiation field was not included in the present study, because metachronous esophageal lesions were not caused to primary lesions. However, lymph node recurrences were thought to be metastatic lesions from primary lesions which had been treated with chemoradiotherapy. So, the enlarged lymph nodes were located both in and out of radiation field. Actually, the lymph node recurrences spread from supraclavicular to cardia. Because our description might cause misunderstanding, we added the word in Methods (page 7 line 20).

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.
Reviewer’s report

Title: Lymph node enlargement after definitive chemoradiotherapy for clinical stage I esophageal squamous cell carcinoma

Version: 2 Date: 15 July 2014

Reviewer: Edward Yu

Reviewer’s report:

Title: Lymph node enlargement after definitive chemoradiotherapy for clinical stage I esophageal squamous cell carcinoma
Yoshito Hayashi and co-workers, Department of Gastroenterology and Hepatology, Osaka University

This manuscript focuses on two issues: one of which is the clinical early stage of esophageal carcinoma treated with definitive chemoradiation treatment; the second is the characterization of lymph node enlargement of which benign enlargement complies more than 50% post chemoradiation therapy.

The concern about this paper is that although this may be common in the author’s country for stage I to receive combined chemoradiation treatment for those who refuse surgery, in other centres outside Japan it would actually be treated with radiation alone. The staging of clinical stage I can be assisted with PET scans which are available in most centres. It is understood that the research is a retrospective study from 2006 to 2011, the application of the finding to the literature may be questionable for the justification of combined chemoradiation in a very early clinical stage with potential curable disease. The short-term and long-term complications resulting from treatment could be difficult to justify in many other centres.

Reply
As you pointed out, we recognize the clinical stage I esophageal carcinoma is curable disease. Our results and previous studies
demonstrated that the overall survival rate of chemoradiotherapy was equivalent with surgery. Definitive chemoradiotherapy is more effective treatment in patients with advanced ESCC, compared with radiotherapy alone (Helskovic A, et al. N Engl J Med 1992, Cooper JS, et al. JAMA 1999) as described in Introduction (page 4 line 15). Moreover, our results showed acceptable feasibility, because our radiation field setting is limited as possible. However, we were not satisfied with the results of progression free survival rate. Today in Japan, randomized phase III trial of chemoradiotherapy compared with surgery is undergoing. To justify chemoradiotherapy is applied for stage I esophageal carcinoma, the result of this trial is required.

The use of combined chemoradiotherapy with radiation dose of 60 Gy is more than the convention of 50.4 Gy for esophagus ca with early stage concurrent with chemotherapy, treatment side effects are probably expecting to be more. In addition, it will be useful to identify the enlarged nodes whether they are within or outside the radiation port to eliminate the possibility of high dose radiation chemotherapy can have some potential effects on the lymph node enlargement in follow up. The availability of a PET scan for investigation in staging becomes quite trivial in many centres and that could be used for assisting in managing a follow up of benign lymph nodes or recurrence of disease.

**Reply**

As you suggested, the radiation dose of 60 Gy might cause the lymph node benign enlargement. We demonstrate the tumor location and enlarged lymph nodes location in Table 3, suggesting that lymph node enlargements did not depend on whether lymph nodes were included within or out of radiation field. According to your suggestion, we described the availability of a PET-CT in Results (page 11 line 22) and Table 3. All of the recurrent lymph nodes showed FDG accumulation in PET-CT. Regarding 11 benign lymph node enlargements, 1 patient showed positive and 5 patients showed negative. Other 5 patients were not performed.

Although this paper is written reasonably well, there is unusual information of clinical stage I with enlarged lymph nodes for esophagus agree treatments, the contribution to the literature from this finding is to a rather small patient subgroup
makes it less attractive to support the publication of this manuscript.

If other reviewers have strong feelings in supporting the publication of this paper, at least this paper requires major revisions as well as the above-mentioned concerns to be clarified and to address the limitation of the research work. Thank you for inviting me to provide my honest opinion for this manuscript

Reply
According to your recommendation, we added the limitation of this study in the Discussion (page 14 line 13).