Author's response to reviews

Title: Capecitabine in combination with either cisplatin or weekly paclitaxel as a first-line treatment for metastatic esophageal squamous cell carcinoma: a randomized phase II study

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Author's response to reviews: see over
Dear Editor,

BMC Cancer

Re: MS: 1202356651651272

Capecitabine in combination with either cisplatin or weekly paclitaxel as a first-line treatment for metastatic esophageal squamous cell carcinoma: a randomized phase II study

Su Jin Lee, Sungmin Kim, Moonjin Kim, Jeeyun Lee, Yeon Hee Park, Young-Hyuck Im and Se Hoon Park

In response to your kind review, we are glad to provide the revised manuscript here. You can find our answers to the reviewers’ comments, and attached the edited (changes are underlined) manuscript files. Again we state that this study is not under consideration for publication elsewhere and that all named authors have read and approved this manuscript to its submission for your journal.

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Reviewer 1’s report:

This is an interesting paper. The question is well defined by the authors, and the writing is acceptable. However, here are some comments.

Major Compulsory revisions:

1. In page 5 line 14, the author told us all the patients were chemotherapy naïve, but in table 1, which showed 19 patients had prior chemotherapy. Please indicate that

-> All patients enrolled in the present study had to receive no prior chemotherapy for metastatic or recurrent disease. They may be treated with neoadjuvant or adjuvant chemotherapy in perioperative setting. We described patient eligibility more clearly in Methods as "Patients with no prior chemotherapy or only adjuvant chemotherapy that had been completed more than 6 months before registration, and no radiotherapy within 4 weeks before study registration were eligible.", and edited Table 1 “chemotherapy -> adjuvant or neoadjuvant chemotherapy”. Thanks.

2. This is a randomized trial, but the author did not tell us how to randomize.

-> Thanks for the comment. Randomization was done with the permuted random method with a block size of 4. Stratification factor included performance status. We think it a bit redundant to include how to assign treatment in more detail.

Minor Essential Revisions

1. Although response rates are explained in the manuscript, it will be better to add graphs describing them. Please check the data in page 9 from line 13 to 20, some data were not complied with fig1., the result of disease control in CC group is wrong which 57% plus 22% equal to 79%#Page 9#line 15#

-> As your kind comments, we are able to provide Table 3, and edit Figure 1. Thanks.
2. Add some comments like groups#median months and P values in the chart of PFS and OS.

-> We edited figures 2 and 3 as your suggestion.

3. Why use chest x-ray and chest computed tomography (CT) scan as the baseline evaluation?#Page 6#line 17#Evaluation of Response should use the same method as that in the baseline period.#Page 6#line 22#

-> Chest x-ray and CT scans are the standard methods for evaluating disease extent in esophageal cancer. Responses were assessed using chest CT or by the same tests that were initially used to stage the tumor, as stated in the Methods.

4. 4. Why not choose factors like “Prior Chemotherapy” #“LN metastasis” in the analysis of Cox model for PFS and OS, which might be the prognostic factors for PFS and OS.

-> Actually these baseline factors were included in the Cox model for PFS and OS. We revised the Table 4 to include more details.

5. Limitations of the work have not been stated in the manuscript

-> Thanks again for the suggestion. We described in more detail the potential limitations of the present randomized phase II study in Discussion. Please be considerate this was a small, phase II study, and the direct comparison between the two arms was not possible. “The results of the present phase II study should be interpreted with caution. We do not intend for these data to be interpreted as stating that one regimen is better than another. It should be kept in mind that only a small group of patients with metastatic squamous cell esophageal carcinoma was represented in this study, and the study was not adequately powered to compare the two treatment arms.”
Reviewer 2's report:

In this RCT study, the author compared cisplatin and paclitaxel in the treatment of metastatic esophageal cancer during 2008 to 2012, and analyzed the patients' QoL and follow-up results. It is a well written study. The volume of cases and hospital admissions for thoracic disease are impressive, emphasizing the authors' abilities to write and comment about this disease and procedure. I have the following questions and suggestions.

1. In the conclusions, the author claimed that 2 regiments were equal. The question is whether they are equally good or bad?

-> Great comment. It should be stated that the purpose of a randomized phase II study is not draw a conclusion that one treatment regimen is superior (or inferior) to another. We described the limitation in the Discussion “The results of the present phase II study should be interpreted with caution. We do not intend for these data to be interpreted as stating that one regimen is better than another. It should be kept in mind that only a small group of patients with metastatic squamous cell esophageal carcinoma was represented in this study, and the study was not adequately powered to compare the two treatment arms.”

2. The study chose to include patients with metastatic esophageal cancer patients. However, a metastatic case did not equally mean patients with tumor metastasis (M1): Some are locally advanced cases with lymph node invasion to the cervical station or abdominal station, and some are metastasis to the lung, liver or bone. While the author had all patients included, was there any bias contributed to the patients' selection?

-> In fact, according to the protocol, only patients with recurrent or metastatic disease were eligible. We edited the sentences to make it clear.

3. Why not use the radio therapy? As evidence collected, CRT was clinically better in compared with chemo alone in advanced staged esophageal cancer, the study could better discussed this issue.

-> In NCCN guideline 2015, for locally recurrent or metastatic disease, systemic therapy is recommended. Our institutional guidelines recommend no radiotherapy unless there are obstructing
4. How the metastatic diseases were found? Just according to the radiographic findings? Is there any possibility that false-positive cases included to the study due to lack of pathologic findings?

-> Good point. Metastases or recurrences are, in most cases, detected by using radiologic findings. In some cases with suspicious, single metastatic lesion, histologic confirmation is strongly recommended.

5. Actually, the application of cisplatin was less welcomed in clinical practice due to its toxicity towards renal function, so why did the author chose to do the comparison between the 2 regimens?

-> Another good question. As we described in Introduction and again in Discussion, cisplatin-based chemotherapy is one of the most widely accepted standard of care in esophageal cancer. It was one of the main objectives in the present study to circumvent cisplatin-related toxic effects by replacing it with paclitaxel. Thanks.

6. Why QoL was close in the 2 groups? More discussion is required other than re-state it in the
discussion part. And why survival was close? Please explain it in the discussion part.

-> For evaluation of QoL, we checked the only EORTC-QLQ-OES18, which is specific for esophageal cancer. Similar QoL results between two groups might suggest that they had similar efficacy in esophageal cancer. But, as this study is not for comparison between two arms, we cannot directly compare two regimens.

7. The limitation of the study was not mentioned.

-> Thanks again for the suggestion. We described in more detail the potential limitations of the present randomized phase II study in Discussion. Please be considerate this was a small, phase II study, and the direct comparison between the two arms was not possible. “The results of the present phase II study should be interpreted with caution. We do not intend for these data to be interpreted as stating that one regimen is better than another. It should be kept in mind that only a small group of patients with metastatic squamous cell esophageal carcinoma was represented in this study, and the study was not adequately powered to compare the two treatment arms.”