Author's response to reviews

Title: Is there a role of whole-body bone scan in patients with esophageal squamous cell carcinoma

Authors:

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Author's response to reviews: see over
Reply to the reviewers’ and editor’s comments

We thank the editor and the reviewers for valuable suggestions, and for consideration of publication of our revised manuscript. We have carefully addressed the reviewers’ comments by including additional descriptions. During resubmission, we have attached the non-marked revised manuscript and marked revised manuscript for your reference. Here, we have indicated the changes made to the manuscript to account for the comments from the four reviewers. Our point-by-point replies to each comment from the reviewers are as follows:

Reviewer 1: Xian-shu GAO
1. Major Compulsory Revisions
   -Comment 1: I do not think Comments 3 of Major Compulsory Revision in my previous report was well defined by author. In the manuscript the author retrospectively evaluated the radiographic and scintigraphic images of 360 esophageal squamous cell carcinoma patients, in which 33 cases were confirmed to have bone metastases eventually and 327 cases were not (in Figure 1). Please supplement survival data comparatively between 33 cases and 327 cases.
   -Answer: Sorry for our misunderstanding during previous reply. The median overall survivals of 33 patients with confirmed bone metastasis and 327 patients without confirmed bone metastasis were 219 days and 419 days, respectively (P<0.001). The 3-year overall survival rates of 33 patients with confirmed bone metastasis and 327 patients without confirmed bone metastasis were 3% and 27%, respectively. We have added the descriptions in the revised manuscript. Please see the figure as below. (The figures are only showed in the reply to reviewers’ and editor’s comments as your reference because there are already 6 tables/figures in the revised manuscript. But, if reviewers think this part is necessary, we are pleased to add the figures in the revised manuscript.)
   -Change: We have modified the manuscript on page 13, paragraph 2.
Comment 2: “For patients with equivocal findings during initial radiological examination, further radiological follow-up is necessary to confirm bone metastasis” (Line 3-5 of Confirmation of Bone Metastases in Methods). Please clearly indicate the time interval between the “equivocal finding” and “further radiological follow-up”. And please explain the reason of adopting that time interval.

Answer: Thanks for your comment. In our hospital, bone scan follow-up was performed at 5-6 months after initial bone scan for most patients with equivocal bone scan findings. Computed tomography (CT) or magnetic resonance imaging (MRI) scans were performed at 3-6 months after initial CT or MRI scans for most patients with equivocal CT or MRI scan findings. In Taiwan, it is difficult to repeat the same radiological follow-up within 3 months after initial radiological examination because it is not allowed by Taiwan’s health-insurance system. Therefore, we usually performed the radiological follow up at 3-6 months after initial radiological examination. In the series of Kato et al[1] studying patients with esophageal cancer, bone metastasis was assessed by radiological follow up for 6 months (CT scan, MRI scan, or bone scan). In the series of Lecouvet et al[2] studying patients with high risk prostate cancer, bone metastasis was also assessed by radiological follow up for 6 months (MRI scan or bone scan). In the series of Lauenstein et al[3] studying the role of MRI in cancer patients with metastases, the radiological follow-up examinations (CT scan, MRI scan, or bone scan) were performed 3–9 months after the initial radiological examinations. In the revised manuscript, we rephrased our descriptions as follows: “…For patients with equivocal findings during initial radiological examination, further radiological follow-up within 6 months is necessary to confirm bone metastasis….” Please evaluate it.

Change: We have modified the manuscript on page 10, paragraph 1.

2. Minor Essential Revisions

Comment 1: Since bone recurrence was clearly defined at Line 6-9 in Confirmation of Bone Metastases in Methods, bone “recurrence-free survival” is recommended instead of “freedom from bone recurrence”.

Answer: Thanks for your suggestion. We took the advice from the reviewer and used “bone recurrence-free survival” instead of “freedom from bone recurrence” throughout the revised manuscript.

Change: We have modified the manuscript on page 3, paragraph 1; page 4, paragraph 1; page 4, paragraph 2; page 8, paragraph 3; page 10, paragraph 2; page 14, paragraph 1; page 14, paragraph 2; page 15, paragraph 1; page 15,
paragraph 2; page 16, paragraph 1; page 16, paragraph 2; page 19, paragraph 2; page 20, paragraph 1; page 20, paragraph 2; page 21, paragraph 2; revised table 3; and page 32, paragraph 2.
Reviewer 2: Chen Chun

-The authors have answered my points sufficiently well, and I allow their manuscript to be published.

-Answer: Thanks a lot.
Reviewer 3: Hongcheng Shi

1. Minor Essential Revisions

-Comment 1: The limitations of the work did not state clearly. So the authors should state the limitation clearly.

-Answer: Thanks for your valuable suggestion.

<1>We took the advice from the reviewer and described our limitations in the discussion as follows: “Our study has important limitations. First, our results are based on the retrospective analysis. The retrospective design of this analysis further justifies the conclusion that a prospective study in the future is needed to define our findings. Second, most of the patients in this study did not have fluorodeoxyglucose positron emission tomography (FDG-PET) as comparison because it is not routinely supported by Taiwan’s health-insurance system. Third, the patients in the present study were staged based on the CT of the chest or/and EUS. The bone scan findings were not integrated into staging. Therefore, the disease staging in the present study may be understaged.

-Change: We have modified the manuscript on page 20, paragraph 3; and page 21, paragraph 1.
Reviewer 4: Li Wang

1. Minor Essential Revisions

In the Cover letter, the authors demonstrated that “The bone scan findings were not integrated into staging in the present study. For example, one patient had T3N1M0 disease by chest CT & EUS. He also had positive bone scan with confirmed bone metastasis. In the present study, his pretreatment clinical staging was stage IIIA, not stage IV.” This study method with the wrong disease staging increased the possibility of misleading the conclusion of the study because disease stage is a very important factor for prognosis. Also, Kato H, et al. already reported that “FDG-PET scans were superior to bone scintigraphy in detecting bony metastases of esophageal carcinomas” back to 2005. Thus, the authors need make the following changes for the publication purpose for this retrospective study:

-Comment 1. The limitations of this work need to be clearly addressed in the discussion.

-Answer: Thanks for your suggestions.

<1>We took the advice from the reviewer and described our limitations in the discussion as follows: “Our study has important limitations. First, our results are based on the retrospective analysis. The retrospective design of this analysis further justifies the conclusion that a prospective study in the future is needed to define our findings. Second, most of the patients in this study did not have fluorodeoxyglucose positron emission tomography (FDG-PET) as comparison because it is not routinely supported by Taiwan’s health-insurance system. Third, the patients in the present study were staged based on the CT of the chest or/and EUS. The bone scan findings were not integrated into staging. Therefore, the disease staging in the present study may be understaged.

-Change: We have modified the manuscript on page 20, paragraph 3; and page 21, paragraph 1.

<2>Indeed, there is a promising role of FDG-PET in the staging of esophageal cancer and detecting bone metastasis in several types of cancers. We did not add the detailed discussion about FDG-PET in the revised manuscript and only described it briefly in the limitations part because we took the advice from one of the reviewers (First version of reviewer’s comment: This paper title is “Is there a role of whole-body bone scan in patients with esophageal squamous cell carcinoma”. In discussion part authors talk something about PET/CT. It has nothing to do with bone scan in this paper) and deleted the detailed discussion about FDG-PET which has been described in the first version of manuscript. But, if reviewers think this part is necessary, we are pleased to add it in the revised
manuscript. We also attached the discussion about FDG-PET in the first version of manuscript for your reference as follows: “Novel imaging modalities such as FDG-PET have been examined over the last decade, and several studies [4, 5] showed their promising results for detection of bone metastasis. The only published study from Kato, et al[1] comparing FDG-PET with bone scan for patients with esophageal cancer revealed that FDG-PET was slightly superior to bone scan in detecting bony metastases, but the differences were not statistically significant. However, the diagnostic accuracy of FDG-PET, and the extent of FDG-PET’s clinical impact on patients’ outcome, and finally the cost effectiveness of FDG-PET are important considerations when justifying the allocation of health care resources.[6] If FDG-PET is not available, our results suggest that bone scan should be included in the staging investigations for patients with esophageal squamous cell carcinoma before esophagectomy. Moreover, for most tumor types including esophageal cancer, FDG-PET is typically acquired from the external auditory meatus to the mid-thigh region [7, 8]. Among patients with confirmed bone metastasis in the present study, there were one patient with fibula metastasis and one patient with left parietal skull metastasis which may not be detected by FDG-PET.” Please evaluate it.

-Comment 2. Bone scan status is a part of disease staging. Thus, disease stage should be a confounding factor to the roles that bone scan status played in prognosis predicting. Add the interaction statistic analysis between disease stage and bone scan status to the influence of the two study endpoints.
-Answer: Thanks for your comments.

<1> We took the advice from the reviewer and performed the interaction statistic analysis between disease stage and bone scan status. Among 288 patients receiving bone scan, bone scan was positive in 46 patients and negative in 242 patients. Positive bone scan was significantly associated with T3+4 disease (P=0.023) and stage IV disease (P=0.017). We have added the above descriptions in the revised manuscript. Please evaluate it. The following table is only showed in the reply to reviewers’ and editor’s comments as your reference because there are already 6 tables/figures in the revised manuscript. But, if reviewers think this part is necessary, we are pleased to add the table in the revised manuscript.

-Change: We have modified the manuscript on page 12, paragraph 2.

<p>| Table: The association between disease stage and bone scan status in 288 esophageal squamous cell carcinoma patients receiving bone scan |</p>
<table>
<thead>
<tr>
<th>Parameters</th>
<th>No. of patients</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive bone scan (n=46)</td>
<td>Negative bone scan (n=242)</td>
</tr>
<tr>
<td>Primary tumor</td>
<td>T1+2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>T3+4</td>
<td>43</td>
</tr>
<tr>
<td>Lymph node</td>
<td>Negative</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>34</td>
</tr>
<tr>
<td>7th AJCC stage</td>
<td>I+II</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>III+IV</td>
<td>34</td>
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<tr>
<td>7th AJCC stage</td>
<td>I+II+III</td>
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<tr>
<td></td>
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<td>21</td>
</tr>
</tbody>
</table>

χ² test or Fisher’s exact test was used for statistically analyzed

<2> Indeed, disease stage is a confounding factor to the roles that bone scan status played in prognosis predicting. Therefore, we have performed the multivariate analysis to reduce the confounding factor. In multivariate comparison, absence of preoperative bone scan (P=0.012, odds ratio: 5.053, 95% confidence interval: 1.419-17.986) and 7th AJCC stage III (P=0.010, odds ratio: 7.891, 95% confidence interval: 1.630-38.190) represented the independent adverse prognosticator for bone recurrence-free survival in 161 patients receiving esophagectomies. For 133 stages II+III patients receiving esophagectomies, multivariate analysis also showed that absence of preoperative bone scan (P=0.009, odds ratio: 5.832, 95% confidence interval: 1.509-19.195) was the independent negative factor of bone recurrence-free survival. In multivariate comparison, absence of preoperative bone scan (P=0.029, odds ratio: 1.603, 95% confidence interval: 1.048-2.450), and 7th AJCC stage III (P=0.002, odds ratio: 1.926, 95% confidence interval: 1.262-2.937) represented the independent adverse prognosticators for overall survival in 133 stages II+III patients receiving esophagectomies. The above multivariate results were described in the manuscript (page 15, paragraph 1; page 16, paragraph 1; and page 17, paragraph 1). Please evaluate it.

Finally, we thanks you again for your patience and valuable time

Sincerely,
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Reference: