Author's response to reviews

Title: The Role of PET/CT for the Detection of Gastric Cancer Recurrence

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Dear, Editor in Chief

We wish to express our gratitude to you and the reviewers for the consideration and thorough review of our manuscript entitled “The Role of PET/CT in Detection of Gastric Cancer Recurrence”. We have made some corrections and clarifications in the manuscript. Here I summarized the changes to the paper below, as well as our responses to specific comments.

We hope the revised manuscript will better meet the requirements of the BMC cancer for publication.

Sincerely yours,

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Reviewer #1.

General remarks
1. the study design is unclear: retrospective-prospective; blinded-not blinded, randomised-non randomised, sequence of CT and PET/CT

Answer and Revision:
This was a retrospective study. We revised manuscript to clarify this in Materials and Methods section as follows

All information was collected and analyzed retrospectively. We screened all the patients with gastric cancer who received curative resection and had subsequently undergone contrast CT and PET/CT for the surveillance of recurrence between Apr. 2004 and Dec. 2006 in Seoul National University Hospital.

2. The quality of the PET/CT applied has to be discussed, if no additional information compared to the normal CT scan can be provided. Nowadays PET/CT are available with diagnostic CT scans, in which the CT scan has the same quality as a normal diagnostic CT: probably your results occur due to technical problems.

Answer and Revision:
The diagnostic CT used in the study has the parameters of 150mA, 120kVp, and 5mm thickness with 90ml contrast media and the parameters of CT which used in PET/CT were described in Materials and Methods. These parameters are similar to those of PET/CT we used in the study except contrast media use. Basically, PET/CT shows metabolic images and the principle role of CT in PET/CT is adding anatomical information to PET images. Therefore, quality of images would not make a big difference.

We added some diagnostic CT information to Material and Method section as follows

The patients were enrolled when the cancer recurrence can be validated by tissue confirmation or by the change of lesions on contrast CT follow up of at least 5-month interval. Basically, all the patients had undergone routine follow up with 3 to 6 month interval after curative resection. The diagnostic contrast CT scan was performed with 5mm thickness and 90ml contrast media, which were adjusted to body weight.

Introduction
1. focus on the problem recurrence of gastric cancer->include literature focused on recurrence of gastric cancer
   -> recurrence rate
   -> localization at different sites, problem esp petitoneal Dx
   -> available diagnostic tools for the diagnosis of recurrences of gastric cancer

Revision:
Thank you for your kind comments. We rearranged the order of paragraph and revised introduction section with literature, generally.

2. Describe the problem of PET in the Diagnosis of gastric cancer

Revision:
Following your comments, we revised the introduction as follows

However, in contrast to the other cancer, it has been reported that FDG uptake of gastric cancer cell is relatively poor and the PET image has a limitation on the detection of recurred gastric cancer

3. Define the aim of your study and your primary and secondary endpoint at the end of your introduction
To clarify the aim, we revised the manuscript as follows

In clinical practice, it is hard to make a treatment decision when gastric cancer recurrence is suspicious in contrast CT but tissue confirmation is difficult. In this case, additional PET/CT could give us more information on the detection of recurrence. Therefore, we conducted this study to evaluate efficacy and usefulness of PET/CT for the detection and confirmation of recurred gastric cancer after curative resection.

Methods and Materials
1. Describe your study design exactly.

Revision:
This study was a retrospective study. Following your comment, we added an explanation about our study design to the manuscript clearly. (Materials and Methods section)

All information was collected and analyzed retrospectively. We screened all the patients with gastric cancer who received curative resection and had subsequently undergone contrast CT and PET/CT for the surveillance of recurrence between Apr. 2004 and Dec. 2006 in Seoul National University Hospital.

2. At what time points routine follow up was performed?
Revision:
Routine follow up was performed at 3 to 6 month intervals. We revised the manuscript as follows (materials and Methods page …추가예정.)

The patients were enrolled when the cancer recurrence can be validated by tissue confirmation or by the change of lesions on contrast CT follow up of at least 5-month interval. Basically, all the patients had undergone routine follow up with 3 to 6 month interval after curative resection. The diagnostic contrast CT scan was performed with 5mm thickness and 90ml contrast media, which were adjusted to body weight.

3. Define localization of recurrence -> local recurrence: distant metastasis: PC

Answer and Revision:
Peritoneal carcinomatosis (PC) is regarded as distant metastasis/recurrence generally and we think there is no reason to classify the peritoneal carcinomatosis as an isolated category.
Therefore, we classified recurrence sites as local recurrence and distant recurrence (Table 2).

<table>
<thead>
<tr>
<th>Variables</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Pathological confirmation</td>
<td>17</td>
</tr>
<tr>
<td>Clinical confirmation by image</td>
<td>35</td>
</tr>
<tr>
<td>Recurrence site</td>
<td></td>
</tr>
<tr>
<td>Locoregional recurrence</td>
<td>7</td>
</tr>
<tr>
<td>Remnant stomach or anastomosis</td>
<td></td>
</tr>
<tr>
<td>site</td>
<td></td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>37</td>
</tr>
<tr>
<td>Lymph-node</td>
<td>20</td>
</tr>
<tr>
<td>Liver</td>
<td>6</td>
</tr>
<tr>
<td>Other site (bone, lung, etc.)</td>
<td>3</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>15</td>
</tr>
</tbody>
</table>

4. Why a sequential examination was performed, was the evaluation blinded, was the quality of CT scan in
PET/CT and CT equal?

Answer:
This study was retrospective study. When performing CT or PET/CT, patients’ information was given to interpreters. So the evaluation was not blinded.
For some patients, dates of diagnostic CT and PET/CT were different. Simultaneous examination at the same day was not easy for us. On the other hand, suspicious CT findings lead patients to undergo PET/CT. However, the median time interval between diagnostic CT and PET/CT was only 9 days (Table 1).
As we mentioned above, the principle role of CT in PET/CT is adding anatomical information to PET images. Therefore, quality of images would not make a big difference.

Results
1. The recurrence rate 38/52 is extremely high: how do you explain it? 50% of the patients were stage I and II

Answer and Revision:
It may be because the early stage patients who were suspicious of recurrence underwent PET/CT more than the advanced stage patients. In advanced stage patients, the risk of recurrence is high. Therefore, they underwent PET/CT less than early stage patients. This could mean that the early stage patients who had high risk of recurrence were selected in this study.
However, in the patients with discordant findings between CT and PET/CT, recurrence to non-recurrence ratio revealed the increasing trend of recurrence rate with the stage. That means the possibility of selection bias is small. We mentioned this in the discussion section as follows

In our data, although about a half of total patients was early stage patients, the recurrence rate was extremely high. It may be because the early stage patients who were suspicious of recurrence underwent PET/CT more than the advanced stage patients. This could mean that the early stage patients who had high risk of recurrence were selected in this study. However, although the possibility of selection bias, recurrence to non-recurrence ratio showed the increasing trend of recurrence rate as the stage get advanced in the patients with discordant findings (Table 5).

2. How do you explain that the sensitivity of PET/CT is lower than contrast CT in general?

Answer and Revision:
This might be attributed to the low metabolic activity of recurred gastric cancer. However, as you mentioned, we don’t know the exact FDG avidity of recurred gastric cancer yet. The other explanation would be due to the small number of study population and the method of CT validation that could make the ability of contrast CT overestimated. However, the difference between sensitivity of PET/CT and that of contrast CT was found ‘not significant’. We discussed this in the discussion section as follows

These might be attributed to the method of CT validation that could make the ability of contrast CT overestimated. The other explanation would be due to the low metabolic activity of recurred gastric cancer. It is well known FDG avidity depends on histologic type. Signet ring cell type or mucinous type is known to have low FDG avidity. However, only a small portion of signet ring cell cancer patients was included in the study population. And the FDG avidity has not been known yet in recurred gastric cancer.

3. analyse your results based on your endpoints./what were the aims of the study:
- to identify recurrences correctly: sensitivity and PPV
- is there a difference in the correct identification of the different sites of recurrence : distal / local/ PC?
These two questions would be clinically relevant and should be addressed and analysed.

Answer and Revision
Based on recurrence sites, PPV were analyzed.
We think there is no reason to classify the peritoneal carcinomatosis as an isolated category. And the localization of recurrence sites as distal/local/PC is too simple. Some patients had multiple recurrence sites and the analysis based on the localization could not reflect the sensitivity precisely.
The important aim of this study is to evaluate the efficacy and usefulness of additional PET/CT on contrast CT for detecting recurred gastric cancer after curative resection. Therefore, Table 4 and Figure 1 are the most important figures. In our opinion, site-specific analysis is more informative. Therefore, we didn’t revise these Table and Figure.

Table 3. Overall and site specific sensitivity and specificity of contrast CT and fusion PET/CT

<table>
<thead>
<tr>
<th>Site</th>
<th>Contrast CT</th>
<th>Fusion PET/CT</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity (%)</td>
<td>specificity (%)</td>
<td>PPV(%)</td>
</tr>
<tr>
<td>Overall</td>
<td>89.4(34/38)</td>
<td>68.4(26/38)</td>
<td>0.057*</td>
</tr>
<tr>
<td>Remnant stomach or anastomosis</td>
<td>42.85(4/7)</td>
<td>100(7/7)</td>
<td>0.13*</td>
</tr>
<tr>
<td>Lymph node</td>
<td>90(18/20)</td>
<td>70(14/20)</td>
<td>0.21*</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>86.6(13/15)</td>
<td>46.6(8/15)</td>
<td>0.039*</td>
</tr>
<tr>
<td>Liver</td>
<td>50.0(3/6)</td>
<td>66.6(4/6)</td>
<td>1.0*</td>
</tr>
</tbody>
</table>

Discussion

1. Include the available literature for gastric cancer and PET and recurrence and gastric cancer. The FDG non-avidity is a well known problem in gastric cancer. In most countries gastric cancer is not an accepted tool for the initial staging of gastric cancer and is not recommended in the diagnosis of recurrences. Because we know that 20-50% of the gastric cancers are FDG avid, we do not know at all, the percentage of FDG avid recurrences in gastric cancer.

Revision

We included some literatures about gastric cancer recurrence and PET in appendix as you recommended. Most literatures mentioned about FDG inavidity according to histologic types or differentiation of tumor. However, it seems unclear to declare overall inavidity of FDG to stomach cancer based on previous studies.


2. Discuss the high recurrence rate n=27 for stage III patients in your study population.

Answer and Revision

It may be because the early stage patients who were suspicious of recurrence underwent PET/CT more than the advanced stage patients. There may be a selection bias. However, in the patients with discordant findings between CT and PET/CT, recurrence to non-recurrence ratio revealed the increasing trend of recurrence rate with the stage. That means the possibility of selection bias is small.

We added this to discussion section and added the ratio of recurrence to non-recurrence to the Table 5.

In our data, although about a half of total patients was early stage patients, the recurrence rate was extremely high. When the early stage patients were suspicious of recurrence, they underwent PETCT more than the
advanced stage patients to get more information. These might mean the patients who had high risk of recurrence were selected in this study. However, in the patients with discordant findings, recurrence to non recurrence ratio showed the increasing trend of recurrence rate with the stage (Table 5) That means the possibility of selection bias is small.

Table 5. Age and stage distribution in patients with discordant findings but no tissue confirmation

<table>
<thead>
<tr>
<th>Stage</th>
<th>Recurrence</th>
<th>Yes</th>
<th>Ratio(Yes/No)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IX</td>
<td>4</td>
<td>7</td>
<td>1.75(7/4)</td>
</tr>
<tr>
<td>II</td>
<td>2</td>
<td>6</td>
<td>3(6/2)</td>
</tr>
<tr>
<td>IIIx</td>
<td>1</td>
<td>11</td>
<td>11(11/1)</td>
</tr>
<tr>
<td>IV</td>
<td>2</td>
<td>2</td>
<td>1(2/2)</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>26</td>
<td></td>
</tr>
</tbody>
</table>

2. The percentage of signet cell cancer in your study population is rather small-is there a bias or subselection? 
This might bias your results, because we know that intestinal tumors are more frequently FDG avid.

Answer

Signet ring cell type or mucinous type is known to have low FDG avidity
Unfortunately due to the retrospective study characteristics, only a small portion of signet ring cell cancer patients was included in the study population. Although, our data showed the inferior tendency of PET/CT. And the FDG avidity of cancer cells in the recurrence is not well known although the histological type before operation was signet ring cell type. Further studies are needed to define FDG avidity of stomach cancer.

**Literature**

Included the literature available for recurrence and gastric cancer

Revision:Following your comments, we included some literatures in the manuscript.


**FIGURES:**

correct please figure 1

Revision: We corrected the figure 1: changed 1 to 11

Reviewer #2.

Difficulties with detecting gastric cancer lesions in the regional lymph nodes and peritoneum are well known, in-spite of high avidity of gastric cancer for FDG. The FDG-PET scanning may be suboptimal in identifying locoregional disease and recurrence. PET/CT is better than PET alone. This paper can be of interest to readers if it is revised. My main reservations are with the writing style and lack of any PET/CT images. The authors
should consider revising and re-submitting.

Revision
Thank you for your kind comments.
Following your comments, we added some images and revised the paper generally.