Author's response to reviews

Title: Diagnostic performance of contrast enhanced CT and 18F-FDG PET/CT in suspicious recurrence of biliary tract cancer after curative resection

Authors:

Yun-Gyoo Lee (gosciny@gmail.com)
Sae-Won Han (saewonhan@medimail.co.kr)
Do-Youn Oh (phdoyoun@snu.ac.kr)
Eui Kyu Chie (ekchie93@snu.ac.kr)
Jin-Young Jang (jangjy4@snu.ac.kr)
Seock-Ah Im (moisa@snu.ac.kr)
Tae-You Kim (kimty@snu.ac.kr)
Sun-Whe Kim (sunkim@snu.ac.kr)
Sung Whan Ha (swha@snu.ac.kr)
Yung-Jue Bang (bangyj@snu.ac.kr)

Version: 2 Date: 28 February 2011

Author's response to reviews: see over
28 Feb, 2010

Dear Editor-in Chief of *BioMed Central Cancer*

We deeply appreciate your careful comments for our manuscript entitled, “*Diagnostic performance of contrast enhanced CT and 18F-FDG PET/CT in suspicious recurrence of biliary tract cancer after curative resection*”. Your comments were really helpful for revising our manuscript. We totally agree with the comments of reviewers. We have revised our manuscript regarding to reviewers’ comments. The changes and responses to specific comments will follow at the Author Response. We hope that these changes may satisfy the editors and reviewers.

Thank you again for giving us important comments on our work. We hope you to consider this paper for publication in *BioMed Central Cancer*.

Sincerely,

Do-Youn Oh, M.D., Ph.D.

Assistant Professor

Department of Internal Medicine, Seoul National University Hospital

101 Daehang-ro,Jongno-gu,

Seoul 110-744, Korea

Tel: +82-2-2072-0701

Fax: +82-2-762-9662

E-mail: ohdoyoun@snu.ac.kr
Author Response to Reviewers’ Specific Comments

Referees’ comments:

Referee 1

Referee’s Comments for the Author

This study treats about the diagnostic performance of suspicious recurrence by ceCT and 18F-FDG PET-CT in patients treated by curative resection of biliary tract cancer.

1. In the background (at line 10), authors should cite the tumor markers realized in routine.

⇒ Thank you for your comment. We think your comment is helpful to make our manuscript more reasonable. The role of tumor marker (CA19-9) as surveillance is not clear, but constantly rising levels often precede radiologic evidence of recurrence by a number of months. So, in clinical practice, we usually check the tumor marker for surveillance of biliary tract cancer.

⇒ We further described this point in background section as per the reviewer’s comment (page 5, line 15-17).

: The role of tumor marker (CA19-9) as surveillance is not clear, but constantly rising levels often precede radiologic evidence of recurrence by a number of months.

2. Moreover, aims have to be explained more clearly and could be divided in two parts.

First: overall (and by specific sites) sensitivity, specificity, PPV, NPV and accuracy of ceCT and FDG-PET/CT.

Second: search for correlation between SUVmax in FDG-PET/CT and tumor markers

⇒ We totally agree to your opinion on this point. We divided aims in two parts and explained them more clearly as per the reviewer’s comment (page 6, line 11–15).

: Therefore, we conducted this study to evaluate and compare the diagnostic validity of ceCT and 18F-FDG PET/CT in the assessment of BTC recurrence after curative surgery. In addition, we searched for correlation between maximal standardized uptake value (SUV_max) in 18F-FDG PET/CT and tumor markers.
3. Concerning materials, authors should explain the ceCT method. Were all exams performed on the same system? Is the number of slice different for each exam?

⇒ Thank you for your keen comment. We totally agree to your comments. So, we have explained this information in the method part as per the reviewer’s comment. (page 7, line 12-19)

: Contrast enhanced CT

All CT images were obtained using a multidetector-row computed tomography (MDCT) scanner (Mx 8000, Philips Healthcare; or LightSpeed Ultra, GE Healthcare; Sensation 16, Simens Healthcare). Each patient received 90 mL of nonionic contrast material that was administered at a rate of 3.0-4.0 mL/s using a mechanical injector. For the MDCT examinations, 3- to 5-mm slice thickness, and 3- to 5-mm reconstruction interval were used. CT images were obtained during the arterial and portal venous phases.

4. How do you confirm recurrence by imaging?

⇒ Thank you for your comment. We think your question is very reasonable and important point.

The step to confirm recurrence is critical in our study. Because there are no specific criteria for the identification of new radiographic malignant lesions it could be arbitrary. After curative resection the appearance of new malignant lesions denotes disease recurrence. However, if a new lesion is equivocal, for example because of its small size, follow-up evaluation will clarify if it represents truly disease recurrence. As we mentioned in the methods section (page 9, line 8-12), we resorted to a clinical confirmation via radiologic correlation with subsequent ceCT with a minimum 3-month follow-up. If there is a significant increase in size of lesion of interest, we can confirm the lesion is malignant. Thus, no significant interval change for at least 3-months of follow-up by ceCT was required to confirm the lesion of interest as clinically benign. We additionally described in the method section (page9, line 12-13)

If there is a significant increase in size of lesion of interest, we can confirm the lesion is malignant.
5. In the results section (at line 3), authors forget to cite ampulla Vater cancer (28%) for primary site of tumor. No reference about AJCC classification were given.

⇒ Thank you for your delicate comment. We have additionally mentioned the proportion of ampulla of Vater cancer in the results section (page 11, line 5) and added the reference about AJCC classification (page 11, line 7). [Ref. 15]

: (page 11, line 5) : ampullar of Vater, 28%

: (page 11, line 7) : in AJCC 6th classification

6. What is median delay between the end of treatment and suspicion of recurrence?

⇒ We have calculated the time interval between the end of post-operative adjuvant treatment and suspicion of recurrence; median time was 10.7 months (range 0.5-97.3 months). We have included this information in Table 1 as per the reviewer’s comment.

: Table 1:

| Interval between post-operative treatment and suspicion of recurrence | Median (range) | 10.7 months (0.5-97.3) |

7. Figure 1 title is badly readable

⇒ Thank you for your delicate comment. We have edited the Figure 2 and changed to the larger font. (In subsequent editing, we have changed the original Figure 1 to Figure 2)
8. Have all patients benefit from pathologic confirmation of recurrence? If not, how many was inconclusive.

⇒ As we discussed in the background section, an acceptable biopsy is not always possible because the lesion of interest is often small in size and located deep adjacent to large vessels or vital structures. Among 50 patients, only 6 patients were eligible for the pathologic confirmation of recurrence (Table 3): 4 lesions were recurred malignancies and 1 lesion was benign. However, a biopsy of the other 1 lesion was inconclusive because of limited gain of specimen. We have added this information in results section as per the reviewer’s comment (page 12, line 1-4).

: Only 6 patients were eligible for pathologic confirmation (5 by biopsy, 1 by surgery): 4 lesions were recurred malignancies and 1 lesion was benign. However, a biopsy of the other 1 lesion was inconclusive because of limited gain of specimen.
9. What is the patient's overall survival?

Thank you for your comment. Your comment was helpful to make our manuscript more informatively. We have updated the patient information and calculated the median overall survival of study cohort (50 patients). Median overall survival was 52.5 months (95% CI 41.1, not reached). We have added this information to the result section as per the reviewer’s comment (page 11, line 11-12).

In all 50 patients, median overall survival was 52.5 months (95% CI:41.1, -).

10. Are RECIST criteria used (progressive disease) to confirm recurrence by ceCT?

Yes. For the confirmation of recurrence during surveillance, the RECIST criteria were used. We have described this information in the method section as per the reviewer’s comment (page 8, line 16-17).

The appearance of new malignant lesions in locoregional area or distant site denotes disease recurrence. For the confirmation of recurrence by ceCT, the RECIST criteria were used [14].

11. Was pathologic confirmation realized by biopsy (guided by imaging?) or by new surgery?

Among relevant 6 patients of pathologic confirmation, 5 patients were realized by biopsy and 1 patient by new surgery. We added this result in the result part as per the reviewer’s comment (page 12, line 1~3).

Only 6 patients were eligible for pathologic confirmation (5 by biopsy, 1 by surgery): 4 lesions were recurred malignancies and 1 lesion was benign.

12. In the discussion it will be interesting to explain the clinical impact of the six false negative cases identified by additional PET/CT.

Thank you for your comment. We totally agree with your opinion. So, we further reviewed clinical records on this point. Of these six false-negative cases by ceCT, five patients could receive palliative chemotherapy, whereas the other patient could not receive chemotherapy because of poor performance status. We have additionally explained this issue in the discussion as per the reviewer’s comment (page 15, line 17~19).
From this information, five patients could receive palliative chemotherapy, whereas the other patient could not receive chemotherapy because of poor performance status.

13. Are the confirmed recurrent lesion correlated with the absence of adjuvant treatment?

Rightarrow We have further analyzed on this point. 15 of 22 patients of observation group (68.2%) were recurred. Interestingly, 19 of 28 patients of adjuvant treatment group (67.9%) were recurred. Our data showed that there was no correlation between the absence of adjuvant treatment and recurrence. We additionally described this information in the result section (page 11, line 7-9).

14. Another limitation is the probable different characteristics of ceCT imaging between the period of 2003 to 2008 (spatial resolution).

Rightarrow We agree with you on this concern. Though all ceCT images were obtained using a MDCT, there is another limitation from the different characteristics between 3 MDCT scanners. We have added this limitation in discussion section as per the reviewer’s comment (page 16, line 21-23).

15. Moreover authors should precise if image analysis was independently reviewed by two experts.

Rightarrow Yes, your comment on the independent review of image analysis by two experts is important. In our university hospital, CT images were analyzed during three different reading sessions. One session was for consensus reading to find significant CT features and two sessions were for independent reviewing with and without information about those significant features. After the consensus reading, two other board-certified radiologists independently interpreted CT images for the recurrence. We have added this information in method section (page 8, line 13-14).

Two other board-certified radiologists, who were blinded to the diagnosis, independently interpreted
ceCT images for the recurrence.

16. Prognostic value of FDG-PET in initial staging BTC is not related in the start of discussion. A prognostic value of SUVmax in recurrent disease could also be research in you study and discuss with the following reference:


⇒ We agree with your valuable comments and reviewed the reference.

⇒ Furukama et al. evaluated the prognostic significance of FDG uptake on PET in patients with biliary tract cancer and demonstrated a maximum SUV of 6.3 to be the optimal cutoff point for survival. In addition, their data showed that the maximum SUV was one of the significant prognostic factors for overall survival in univariate analysis.

⇒ After your valuable comments, we further analyzed our data. Among 34 patients with recurrent disease, we calculated the median value of SUVmax (3.35) and generated Kaplan-Meier survival curves for patients with a SUVmax less than 3.35 and greater than 3.35.

⇒ However, the logrank test showed that the survival probability for patients with SUVmax less than 3.35 was not significantly higher than patients with SUVmax greater than 3.35 (p=0.40). The low number of patients and selection bias could explain these results do not reach statistical significance.
We briefly described these results in the results and discussion section (page 13, line 9-13; page 16, line 10-15).

Among 34 patients with recurrent disease, we calculated the median value of SUVmax (3.35) and compared overall survival between patients with SUVmax of 3.35 or less and greater than 3.35. However, the survival probability for patients with SUVmax of 3.35 or less was not significantly higher than patients with SUVmax greater than 3.35 (p=0.40).

Furukama et al. evaluated the prognostic significance of FDG uptake on PET in patients with biliary tract cancer and demonstrated the SUVmax of 6.3 to be the optimal cutoff point for survival [1]. In addition, their data showed that the SUVmax was one of the significant prognostic factors for overall survival in univariate analysis. However, our data did not show that the SUVmax was the significant prognostic factor for overall survival, probably due to the low number of patients and selection bias.

The title could be changed to: “Diagnostic performance of ceCT and 18F-FDG PET-CT in suspicious recurrence of biliary tract cancer after curative resection”

We agree to your suggestion. So we have changed the title of our paper according to your suggestion.
Referees’ comments:

Referee 2

Referee’s Comments for the Author

In this manuscript, the authors describe the potential role of FDG-PET/CT in comparison to ceCT in detection of recurrence of biliary tract cancer after curative resection. An additional FDG-PET/CT after a ceCT significantly improved the sensitivity for detecting tumour recurrence.

1. In general this is a relevant and interesting topic. Some methodological aspects should be addressed. Especially, blinded reading should be performed for all studies and the level of confidence for each finding should be noted for each modality and the combination of ceCT and PET, e.g. using a 5 point scale. By doing so, a ROC analysis could be performed and the AUC for all modalities could be compared.

⇒ Thank you for your smart comment. We totally agree with your opinion. Your comments that blinded reading should be performed for all studies and the level of confidence for each finding should be noted are very important.

⇒ In our university hospital, CT images were analyzed during three different reading sessions. One session was for consensus reading to find significant CT features and two sessions were for independent reviewing with and without information about those significant features. After the consensus reading, two other board-certified radiologists independently interpreted CT images for the recurrence. We have added this information in methods section as per the reviewer’s comment (page 8, line 13-14).

: Two other board-certified radiologists, who were blinded to the diagnosis, independently interpreted ceCT images for the recurrence.

⇒ After three reading sessions, the level of confidence for each finding was noted: 1, definitely benign; 2, probably benign; 3, equivocal finding; 4, probable malignance; 5, definitely malignance. By doing so, we have performed a ROC analysis and compared the AUC for each modality as follows. Because the combination of ceCT and PET/CT was not actual combination, we did not perform a ROC analysis. We have described this result in methods section and results section as per the reviewer’s comment (page 9, line 18-21, page 12, line 19-21, Figure 1). Accordingly, we have changed the original figure 1 to figure 2.

: (page 9, line 18-21)
Receiver operating characteristics (ROC) analysis was performed for the detection of recurrent lesions of ceCT and 18F-FDG PET/CT. All p values were two-sided in tests and p values less than or equal to 0.05 were considered to be statistically significant.

The ROC analysis indicated that a PET/CT had the higher overall accuracy for the detection of recurrence than ceCT (AUC 0.788 in PET/CT vs. AUC 0.603 in ceCT; Figure 1).

Figure 1.

2. Moreover, the % change in patient management should be noted which was achieved by adding PET to ceCT

⇒ We appreciate your important comment. Your comment was helpful to make our manuscript more informatively. Among 14 patients with discordant results, 11 patients (11/14, 79%) was treated regarding to the results of PET/CT. We have additionally described this information in the discussion section (page 15, line 21-22).

: Among 14 patients with discordant results, 11 patients (11/14, 79%) was treated regarding to the results of PET/CT.
3. Abstract:

One could mention that FDG-PET/CT showed higher sensitivity and accuracy compared to CT, but the results did not reach statistical significance, probably due to the low number of patients.

⇒ We agree to your comment. We have added this comment in the results section as well as abstract (page 3, line 17-19; page 4 line 4-5; page 12, line 8-9; page 14 line 6-8).

PET/CT showed higher sensitivity (88% vs. 76%, p=0.16) and accuracy (82% vs. 66%, p=0.11) for recurrence compared to ceCT, even though the difference was not significant.

⇒ These results do not reach statistical significance, probably due to the low number of patients.

PET/CT showed higher sensitivity and accuracy compared to ceCT, but the results did not reach statistical significance.

⇒ However, these results do not reach statistical significance, probably due to the low number of patients. On the other hand,

4. Methods:

- Patients: concerning the criteria for a FDG-PET/CT: was one of the four sufficient? because it says “any combination” of these criteria, which would mean at least two have to be present? Please clarify.

⇒ As we can find the concerning criteria in Table 2, one of the four criteria is sufficient for undergoing 18F-FDG PET/CT. According to your comments, we have deleted “any combination” and clarified the meaning (page 7 line 8). We appreciate your sharp comment.
5. - blinded reading should definitely be performed for all scans

⇒ Yes, your comment on the independent review of image analysis by two experts is important. In our university hospital, CT images were analyzed during three different reading sessions. One session was for consensus reading to find significant CT features and two sessions were for independent reviewing with and without information about those significant features. After the consensus reading, two other board-certified radiologists independently interpreted CT images for the recurrence. We have added this information in method section (page 8, line 13-14).

: Two other board-certified radiologists, who were blinded to the diagnosis, independently interpreted ceCT images for the recurrence.

6. - what is the definition of a benign finding?

⇒ During postoperative surveillance, the appearance of new malignant lesions in locoregional area or distant site denotes disease recurrence. When a postoperative image finding was uneventful: no locoregional recurrence and no distant metastasis, we can define a benign finding. If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly recurrence. We have additionally described this explanation in the method section (page 8 line 17-20)

: When a postoperative image finding was uneventful: no locoregional recurrence and no distant metastasis, we can define a benign finding. If we cannot differentiate recurrence from benign, the lesion of interest is a equivocal finding.

7. - please show exact data for the follow up: mean, min, max, std-deviation;

⇒ We further calculated the median follow-up time with 95% confidence interval and standard error. The median follow-up time was 49.1 months (range 5.1-86, standard error 11.5). We
have added this information in the results section as per the reviewer's comment (page 1, line 12-13).

: The median follow-up time was 49.1 months (range 5.1-86, standard error 11.5).

8.- what is recurrence in “vascular areas”?

⇒ Thank you for your delicate comment. Originally, a recurrence in “vascular area” means a recurrence in lymph nodes around mesenteric vessels. However, we found this differentiation could give confusion to readers. To avoid confusions, after receiving advices from experts in radiology, we have combined two categories (lymph node, vascular area) and recalculated the relevant diagnostic validity in main text as well as Table 3 and 5 (page 11 line 2; page 12 line 6).

( page 12 line 5) 16 were recurrent in the lymph nodes

( page 13 line 9) (4.53 in locoregional areas, 4.4 in lymph node areas)

9.- how is the site-specific specificity calculated? What were the negative reference areas / lesions? Please clarify

⇒ When there are multiple recurrent legions we calculated site-specific efficacy of ceCT and PET/CT. If we count each recurrent lesion as an independent lesion, ceCT detected 39 lesions and PET/CT detected 42 lesions. After removing the overlapping lesions, there are remaining 59 lesions of interest. Among 59 lesions of interest there were 16 recurred lesions. Benign 43 (59-16) legions were the negative reference lesions.

10. Results:

- how can the low specificity of combined ceCT and PET/CT be explained? This is also contradictory to the discussion.

⇒ When we evaluate the findings of PET/CT on ceCT as recurrence, at least one image finding of recurrence was necessary. However, benign findings on both ceCT and PET/CT were necessary to interpret the lesions of interest as benign (page 9, line 4-5). Therefore, among 7 patients identified as benign in ceCT and 11 patients identified as benign in PET/CT, only 6 patients
with benign findings from both PET/CT and ceCT were evaluated as benign in case of combination of PET/CT and ceCT. We analyzed this pre-defined condition can lead to the lower specificity in combination of ceCT and PET/CT. To clarify this uncertainty, we have added a clear expression in method section (page 9, line 4) and explained this in results section as per the reviewer’s comment (page 12, line 12-16).

: (page 9, line 4)

benign findings on both 18F-FDG PET/CT and ceCT were necessary to interpret the lesions of interest as benign

(page 12, line 12-16).

: The lower specificity in combination of ceCT and PET/CT than ceCT or PET/CT alone can be explained that benign findings from both ceCT and PET/CT were necessary to interpret the lesions of interest as benign: among 7 patients identified as benign in ceCT and 11 patients identified as benign in PET/CT, only 6 patients with benign findings from both ceCT and PET/CT (Table 4).

11.- how many patients had a larger interval than 3 weeks for CT and PET/CT? This might influence the results.

⇒ We further look at our data and found 17 patients had a longer interval than 3 weeks for ceCT and PET/CT. We totally agree with this longer time interval between ceCT and PET/CT might influence the results. In fact, 13 of these 17 patients (76.5%) showed recurrence, but 22 of remaining 33 patients (66.6%) showed recurrence. Though the difference in proportions is not statistically significant (p=0.47), your concern about the influence of longer time interval was reasonable. We described this aspect in the result section as well as discussion section as per the reviewer’s comment (page 11 line 10-11, page 16 line 21-23).

: (page 11 line 10-11)

Median time interval between ceCT and 18F-FDG PET/CT was 17 days (range 1-70) and 17 patients had the longer interval than 3 weeks.

: (page 16 line 21-23)

Lastly, the longer time interval between ceCT and PET/CT and the different characteristics of 3 CT scanners between the period of 2003 to 2008 might influence the results.
12. Please clarify what a “vascular area” is

⇒ As we discussed above, a recurrence in “vascular area” means a recurrence in lymph nodes around mesenteric vessels. However, we found this differentiation could give confusion to readers. To avoid confusions, after receiving advices from experts in radiology, we have combined two categories (lymph node, vascular area) and recalculated the relevant diagnostic validity in main text as well as Table 3 and 5 (page 12 line 5; page 13 line 9).

(page 12 line 5) 16 were recurrent in the lymph nodes

(page 13 line 9) (4.53 in locoregional areas, 4.4 in lymph node areas)

13. Discussion:

- there is definitely a trend that PET/CT is better than ceCT in my opinion, probably the number of patients is just too low to reach statistical significance

⇒ Yes. We agree to your opinion that our data suggested a tendency that PET/CT was better than ceCT. However, the limited number of patients is one of our limitations not to reach statistical significance. As we discussed above, we have described this aspect in abstract and discussion section (page 3, line 17-19; page 4 line 4-5; page 12, line 8-9; page 14 line 6-8).

: (page 3, line 17-19)

PET/CT showed higher sensitivity (88% vs. 76%, p=0.16) and accuracy (82% vs. 66%, p=0.11) for recurrence compared to ceCT, even though the difference was not significant.

: (page 4 line 4-5)

These results do not reach statistical significance, probably due to the low number of patients.

: (page 12, line 8-9)

PET/CT showed higher sensitivity and accuracy compared to ceCT, but the results did not reach statistical significance.

: (page 14 line 6-8)
However, these results do not reach statistical significance, probably due to the low number of patients. On the other hand,

14. - it should be mentioned at some point, that most modern PET/CT scanners allow for fully diagnostic ceCT scans as well, so would the authors recommend contrast enhanced diagnostic PET/CT as the primary modality of choice in case of suspected recurrence?

⇒ We agree with your opinion. According to your opinion, we have mentioned that as follows (page 17, line 3-6).

: Additionally, as the most modern PET/CT scanners allow for fully diagnostic ceCT scans, contrast enhanced diagnostic PET/CT could be recommended as the primary modality of choice in case of suspected recurrence.

15. - 5 false positives in ceCT were correctly identified as negative in PET/CT, so how comes the low specificity of ceCT plus PET/CT in table 4? Please clarify.

⇒ As we discussed above, the lower specificity in combination of ceCT and PET/CT than ceCT or PET/CT alone can be explained that benign findings from both ceCT and PET/CT were necessary to interpret the lesions of interest as benign. In case of 5 false positives in ceCT which were correctly identified as benign in PET/CT, the higher specificity of PET/CT than ceCT (69% vs. 44%) can explain your question.

⇒ Your essential question guided us to the clearer understanding. It is grateful to your essential question about diagnostic validity.