Author's response to reviews

Title: Utility of 18F-fluorodeoxyglucose emission tomography/computed tomography fusion imaging in combination with ultrasonography for axillary staging in primary breast cancer

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Author's response to reviews: see over
March 31, 2008

Editor-in-Chief Melissa Norton, MD

Dear Dr. Melissa Norton,

RE: No.

Title: Utility of $^{18}$F-fluoro-deoxyglucose emission tomography / computed tomography fusion imaging in combination with ultrasonography for axillary staging in primary breast cancer.

Thank you very much for your E-mail. We have improved the contents of our manuscript according to the referee’s comments as follows.

Version: 1 Date: 10 March 2008

Reviewer: Christian Cohade

Reviewer’s report:

The authors prospectively evaluated diagnostic accuracies of PET/CT and US for detection of axillary node metastases in breast cancer patients. PET and CT demonstrated limited sensitivity. The authors concluded that candidates for SNB were more appropriately selected using combined US and PET/CT.
1. The reported sensitivities of PET/CT and US are limited (58% and 54% respectively). Even combined PET/CT and US showed a limited 64% sensitivity which is too low to make these modalities part of the routine evaluation of pre-operative breast cancer patients. 15% of patients had axillary node involvement when PET and US were negative.

2. The authors acknowledge that they use US to detect patients with massive tumor burden. The role of non-invasive in breast cancer patient would be to identify patients with massive tumor burden and to send these patients to axillary dissection instead of sentinel node biopsy. Since most recent studies demonstrated limited utility of PET/CT for axillary staging, what would be the added value of PET/CT for this role? Would not it be more appropriate to perform PET/CT only in patients in whom US showed massive tumor burden?

I agreed to your comments. Most recent studies revealed limitation of PET/CT for axillary staging.

We have corrected the last two sentences of the abstract in page 4, line 8-12 and the last sentence of the discussion in page 24, line 9-13. Instead, we have added the sentence that ‘Considering their limited sensitivities, the high radiation exposure by ¹⁸F-FDG PET/CT and also costs of the examination, it is likely that AUS will be more cost-effective in detecting massive axillary tumor burden. However, when we cannot judge the axillary staging using AUS alone, metabolic approach of ¹⁸F-FDG PET/CT for axillary staging would enable us a much more confident diagnosis.’
3. In the section describing PET/CT, essential technical details are lacking regarding PET/CT acquisition: (type of PET/CT camera, 2D vs. 3D mode, uptake time, and acquisition time per field position). Details on CT acquisition should also be provided (CT current, pitch, contrast enhancement).

We have corrected the paragraph of $^{18}$F-FDG PET/CT and quantification of $^{18}$F-FDG uptake in the axilla as below from page 10, line 2 to page 11, line 2.

All patients received $^{18}$F-FDG PET/CT scans (Biograph LSO Emotion, 3D model, Siemens, Germany) at Tokorozawa PET Diagnostic Imaging Clinic (Tokorozawa, Japan). Blood glucose level was measured in each patient and did not exceed 120 mg/dl.

Patients fasted at least 4 hours before $^{18}$F-FDG PET study. One hour after intravenous administration of 3.7Mbq/kg $^{18}$F-FDG, a transmission scan using CT (SOMATO Emotion, 16-slice configuration, pitch 1.83, Siemens, Germany) for attenuation correction and anatomical imaging was acquired for 90 sec. IV contrast was not administered to patients for the CT portion of the $^{18}$F-FDG PET/CT.

Back projection image was obtained after Gaussian filter was applied. The spatial resolution of the reconstructed images was 6.0-7.0 mm in cranio-caudal, 6.3-7.1 mm in right-left and 6.3-7.1 mm in anterior-posterior directions.

A regions of interest (ROI) was placed in the axillary lesion, including the highest uptake area (circle ROI, 2 cm in diameter), and SUV maximum in the ROI was calculated. The SUV was decay-corrected tissue activity divided by the injected dose per patient body, and was calculated using the following formula: SUV = activity in region of interest/decay factor of F-18 (MBq/ml)/injected dose (MBq/kg body weight).
CT images were also available for evaluation. Visual assessment of $^{18}$F-FDG uptake was carried out by at least two experienced nuclear medicine radiologists, and abnormal axillary uptake greater than background activity was interpreted as suspicious nodal involvement. Semiquantitative measurement of SUV was done on any axillary focus with abnormal uptake.

4. Blood sugar level should be indicated. We have added the sentence that ‘Blood glucose level was measured in each patient and did not exceed 120 mg/dl’ in page 10, lines 3-4.

5. The number of patients for categories 2 and 3 is limited. This restricts the conclusions that can be drawn for these two categories. As you pointed out, the number of patients for categories 2 and 3 is small. We have added the sentence that ‘The conclusions could not be determined because the number of patients for categories 2 and 3 have been limited, but we could indicate’, in page 21, lines 7-8.

6. Lobular and mucinous carcinomas are reported to show limited PET sensitivity due to low cellular density. What was the performance of US and PET/CT for these carcinomas?

In the present study, two (22%) of 9 ILCs had metastasis to sentinel lymph nodes. For these cases, neither FDG PET/CT nor AUS did detect the involved lymph nodes. In 2 mucinous carcinomas, no metastasis was not shown.
Therefore, it is probable that the performance of FDG PET/CT for these carcinoma appears relatively low, but it remains undetermined the conclusion because of small number of these cases.

MINOR ESSENTIAL REVISIONS

7. US is reported to be operator dependent. An experienced ultrasonographer performed the axillary examination. Can the conclusions apply to the average ultrasonographer?

As you pointed out, we think this is important. Because AUS is reported to be dependent on individual operators and/or types of ultrasound devices, the accurate axillary staging using AUS alone might be too much for the average ultrasonographer. Therefore, when we cannot judge the axillary stage using AUS alone, we suggest support by FDG PET would enable us a much more confident diagnosis.

This discussion has been added page 4, line 8-12 in the abstract and page 24, line 9-13 in discussion.

8. Table 1 Legend: ILC means Invasive Lobular carcinoma.

We have corrected ‘invasive lobular carcinoma’ instead of ‘invasive ductal carcinoma’ in Table 1.

9. Table 3: Line 8 Total should be written instead of total.
We have corrected ‘total’ instead of ‘tatal’

10. P 18. ‘AUS showed excellent sensitivity’. Limited would be more appropriate.

In page 19, line 7, we have corrected ‘AUS showed limited sensitivity’ instead of ‘AUS showed excellent sensitivity’.

11. SUV means Standardized Uptake Value not Standard Uptake Value.

In page 3, line 11, we have corrected ‘standardized uptake value’ instead of ‘standard uptake value’.

DISCRETIONARY REVISIONS

12. The authors could discuss the cost effectiveness of their proposed assessment of nodal status with PET/CT and US. Considering their limited sensitivities, it is more likely that US will be more cost-effective in detecting massive axillary tumor burden.

We agreed to your comments. In page 24, lines 9-13, we have added the sentence that ‘Considering their limited sensitivities, the high radiation exposure by $^{18}$F-FDG PET/CT and also costs of the examination, it is more likely that US will be more cost-effective in detecting massive axillary tumor burden. However, when we cannot judge the axillary staging using AUS
alone, metabolic approach of ¹⁸F-FDG PET/CT for axillary staging would enable us a much more confident diagnosis.’

13. There are numerous factors that will influence SUV results. The limited role of SUV in breast cancer staging could be indicated.

We have added the sentence that `However, there are numerous factors that will influence SUV results and we should take into considerations the limited value of SUV in breast’, in page 24, lines 4-6.

14. PET/CT could have a role in staging high risk breast cancer patients and in detecting other areas of lymph node metastases. The authors reported cases of parasternal and infraclavicular lymph node metastases. Did the authors detected distant metastases in the population.

We have added the following sentence in page 8, lines 4-7; ‘During the entry period, we experienced 15 patients who were diagnosed by ¹⁸F-FDG PET/CT to have breast cancer with distant metastases, comprising four distant lymph node metastases, nine bone metastases, and two lung metastases. Patients having distant metastases were also ineligible for this study.’

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article whose findings are important to those with closely
related research interests

Quality of written English: Needs some language corrections before being published

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: Utility of 18F-fluorodeoxyglucose emission tomography/computed tomography fusion imaging in combination with ultrasonography for axillary staging in primary breast cancer

Version: 1 Date: 6 March 2008
Reviewer: Siroos Mirzaei

Reviewer's report:

The authors discuss an interesting issue comparing the preoperative diagnostic accuracies of 18-FDG PET/CT and axillary ultrasonography (AUS).

Major Compulsary Revisions:

The specificity of AUS alone was 99%. Regarding the high radiation exposure by PET-CT and also costs of the examination it should be discussed whether in the patients with positive results by AUS additional PET/CT would be necessary, or more preferably not.

We deleted the last sentence of the abstract in page 4, lines 8-12 and the last sentence of the discussion in page 24, lines 9-13 and added ‘Considering their limited sensitivities, the high radiation exposure by $^{18}$F-FDG PET/CT and also costs of the examination, it is true that US will be more cost-effective in detecting massive axillary tumor burden. However, when we cannot judge the axillary staging using AUS alone, metabolic approach of $^{18}$F-FDG PET/CT
for axillary staging would enable us a much more confident diagnosis.

At this stage of literature and also due to the limited results of this study we could not in general recommend the combination of PET/CT and AUS for the preoperative staging of the breast cancer patients. Therefore, the conclusion of the study should be accordingly adapted.

We agreed to your comments. We added the paragraph above in the conclusion.

Minor Essential Revisions:

It could be interesting for the reader to know whether the positive lymph nodes found by FDG-PET matched the SNB results.

In the present study, 6 patients (50%) had involved sentinel nodes (SNs) among 12 patients with axillary FDG uptake who underwent sentinel node biopsy. All of these 6 patients had involved SNs without non-SNs metastases. These results suggest that axillary FDG uptakes in these 6 cases were involved SNs.

We have added novel Table 6 and the following paragraph in page 18, lines 5-10.

‘Diagnostic performance of SNB in 18F-FDG positive and AUS-negative patients’

Table 6 shows diagnostic performance of SNB for axillary staging in 18F-FDG-positive and AUS-negative patients of category 2. Six (50%) of 12 patients had involved SNs and others
(50%) had no involved SNs in spite of 18F-FDG uptake. No metastases were found in non-SNs in all patients that had involved SNs and received subsequent axillary dissection.

Furthermore, we have added the sentence that ‘We confirmed the positive lymph nodes found by 18F-FDG-PET matched the SNB results in all patients of category 2 that had involved SNs and received subsequent axillary dissection (shown in Table 6)’, in 21 page, lines 14-16.

What next?: Accept after minor essential revisions

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.

In response to the reviewer’s comment, Yukihiro Hama supported us to improve this paper as to technical issues of FDG PET/CT. We have added his name as a one of the co-authors in this paper.

There are 6 tables and a total of 4942 words in this report.

We are looking forward to hearing from you again.

Sincerely,

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