Dual-time FDG-PET/CT in patients with potential breast cancer recurrence: head-to-head comparison with CT and bonescintigraphy

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Purpose

Breast cancer is the most common type of cancer in women. After primary treatment, approx. 30% of women experience recurrence [1,2]. Conventional imaging in the diagnostic work-up of recurrence often includes CT and bone scintigraphy in order to either verify or rule out distant metastasis. FDG-PET/CT has been suggested as an alternative to conventional imaging and recent studies have shown interesting results by performing dual-time-point FDG-PET/CT in other cancer types. The aim of this prospective study was to examine the value of dual time-point FDG-PET/CT in women suspected of breast cancer recurrence compared with conventional imaging. These data are based on an interim analysis of the first 39 patients.

For accurate diagnosis of organ and lymph node metastases contrast-enhanced computed tomography (CT) of the thorax and the upper abdomen is often used and if osseous metastasis is suspected, bone scintigraphy is the preferred modality. Other modalities such as magnetic resonance imaging (MRI) are often used as a supplement to confirm or refute equivocal findings [3-5]. Whole body positron emission tomography/computed tomography (PET/CT) with $^{18}$fluorodeoxyglucose (FDG) is able to supply functional information with morphology. The literature shows that some breast carcinomas have low metabolic activity which can lead to false negatives when the study technique involves a single time-point acquisition [6].

Several studies have demonstrated that FDG uptake continues to increase for several hours after injection in various malignant lesions while benign lesions, such as inflammatory lesions, decrease [7-9]. See also figure 1.

Due to the difference in the time-activity curves for malignant and benign processes late imaging should hypothetically increase the accuracy of the modality in detecting recurrent BC.

Multiple time-point or delayed single time-point FDG PET/CT imaging has the potential to become a one-stop-shop for diagnosing recurrence and thereby optimize the work-up in this patient group.

This poster presents the results of the interim analysis of the first 39 patients in our study designed to evaluate the diagnostic accuracy of FDG PET/CT performed one and three hours after injection compared with CT and bone scintigraphy in patients suspected of BC recurrence.
**Fig. 1:** The principle in dual-time PET/CT. The two grey bars illustrate time point 1 and time point 2. Figure adapted from Basu S et al [7].

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Methods and Materials

Thirty-nine patients suspected of BC recurrence were included. All patients underwent FDG PET/CT (with imaging 1 and 3 hours after injection of FDG), routine bone scintigraphy and routine CT of the chest and upper abdomen, figure 2. The PET/CT images were evaluated independently and blinded to the other examinations by a nuclear medicine physician experienced in PET/CT. The bone scintigraphy was evaluated by another nuclear medicine physician true to the routine in the department and was also blinded to other modalities. The CT images were evaluated by a radiologist with experience in BC-radiology according to department guidelines. Positive findings by any of the three modalities were generally verified by biopsy. For ethical reasons this was not possible for all lesions. In these cases a composite reference comprising all available imaging procedures and follow-up data was used as gold standard.

For the FDG PET/CT the patients fasted for a minimum of six hours and had a blood glucose level no higher than 8 mmol/l prior to injection of 4 MBq/kg of FDG. Imaging was performed 1 and 3 hours (±5 mins) after injection. At both time-points a low-dose CT from the skull to the proximal femur was obtained followed by a 3D PET-scan of the same area. The duration of the PET-scan was adjusted according to body mass index (BMI) i. e. 2½ min/bed position. At the late time-point the scan time was prolonged by 1 min/bed position. The images of the two PET/CT scans were evaluated independently and blinded by an experienced nuclear medicine physician.

Contrast-enhanced diagnostic CT of the thorax and the upper abdomen was performed at the Department of Radiology according to their current guidelines. The patients were scanned from the seventh cervical vertebra to the upper abdomen including the liver. 100 ml of Optiray 300 mg I/ml were administered with a flow of 3.0 ml/s and a delay of 60 seconds. The images were evaluated by a radiologist with experience in BC-radiology according to department guidelines.

For the bone scintigraphy the patients were injected with 700 MBq $^{99m}$Tc-DPD 3 to 4 hours prior to whole body imaging. The images were evaluated by a nuclear medicine physician.

For the data analysis sensitivity, specificity, positive and negative predictive values (PPV/NPV), accuracy and likelihood ratio of positive and negative test (LRpos/LRneg) were calculated for PET/CT, CT and bone scintigraphy for both a patient based and a lesion based analysis. Comparison between modalities was performed true to the methodology and field-of-view of the respective modality. Hence, bone scintigraphy was only compared with bone lesions found in CT and FDG PET/CT in the comparable field-of-view and likewise for comparison of the other modalities.
**Fig. 2:** Patient flow in the study.

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Results

Thirty-nine patients with a total of 119 lesions were eligible for inclusion in the study. Seventeen patients (44%) showed recurrence verified by biopsy with a total of 79 true positive lesions. Bone metastases were verified in 9 of 17 patients with positive lesions. CT had a correct diagnose in 13 patients (77%). PET/CT correctly diagnosed 15 patients (88%) and showed similar data between the 1 and 3 hour scan and the overall PET/CT evaluation on a patient basis. Bone scintigraphy correctly identified 7 out of the 9 patients (78%) with bone metastasis. On a patient basis, FDG-PET/CT had a sensitivity and specificity of 88% and 95%. The corresponding values for CT were 76% and 100%, respectively, and for bone scintigraphy 78% and 70%, respectively.

On a lesion basis, sensitivity and specificity were 81% and 84% for 1-hour FDG-PET/CT and 89% and 82%, respectively, for the 3-hour scan. The overall PET/CT had a sensitivity and specificity of 89% and 76%. CT and bone scintigraphy had sensitivities of 69% and 85% and specificities of 100% and 78%, respectively. The completed statistical analyses are shown in table 1 and 2. The location of the true positive findings on the different modalities can be seen in table 3.
### Table 1: The different modalities compared on a patient basis. BS = bone scintigraphy, PET/CT = FDG PET/CT.

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
<th>LR&lt;sub&gt;pos&lt;/sub&gt;</th>
<th>LR&lt;sub&gt;neg&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PET/CT</strong></td>
<td>88%</td>
<td>95%</td>
<td>94%</td>
<td>91%</td>
<td>92%</td>
<td>19.41</td>
<td>0.12</td>
</tr>
<tr>
<td><em>(95% CI)</em></td>
<td>(73% - 100%)</td>
<td>(87% - 100%)</td>
<td>(82% - 100%)</td>
<td>(80% - 100%)</td>
<td>(84% - 100%)</td>
<td>(2.84 - 132.78)</td>
<td>(0.03 - 0.45)</td>
</tr>
<tr>
<td><strong>BS</strong></td>
<td>78%</td>
<td>70%</td>
<td>44%</td>
<td>91%</td>
<td>72%</td>
<td>2.59</td>
<td>0.32</td>
</tr>
<tr>
<td><em>(95% CI)</em></td>
<td>(51% - 100%)</td>
<td>(54% - 96%)</td>
<td>(19% - 64%)</td>
<td>(80% - 100%)</td>
<td>(58% - 96%)</td>
<td>(1.30 - 4.96)</td>
<td>(0.09 - 1.10)</td>
</tr>
<tr>
<td><strong>CT</strong></td>
<td>76%</td>
<td>100%</td>
<td>100%</td>
<td>85%</td>
<td>90%</td>
<td>-</td>
<td>0.25</td>
</tr>
<tr>
<td><em>(95% CI)</em></td>
<td>(56% - 97%)</td>
<td>-</td>
<td>-</td>
<td>(71% - 98%)</td>
<td>(80% - 99%)</td>
<td>-</td>
<td>(0.10 - 0.55)</td>
</tr>
</tbody>
</table>

### Table 2: The different modalities compared on a lesion basis. BS = bone scintigraphy, PET/CT = FDG PET/CT.

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
<th>LR&lt;sub&gt;pos&lt;/sub&gt;</th>
<th>LR&lt;sub&gt;neg&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PET/CT 1h</strong></td>
<td>81%</td>
<td>84%</td>
<td>92%</td>
<td>68%</td>
<td>82%</td>
<td>5.16</td>
<td>0.22</td>
</tr>
<tr>
<td><em>(95% CI)</em></td>
<td>(73% - 90%)</td>
<td>(73% - 96%)</td>
<td>(85% - 100%)</td>
<td>(55% - 81%)</td>
<td>(76% - 89%)</td>
<td>(2.46 - 10.83)</td>
<td>(0.14 - 0.35)</td>
</tr>
<tr>
<td><strong>PET/CT 3h</strong></td>
<td>89%</td>
<td>82%</td>
<td>91%</td>
<td>78%</td>
<td>87%</td>
<td>4.83</td>
<td>0.14</td>
</tr>
<tr>
<td><em>(95% CI)</em></td>
<td>(82% - 96%)</td>
<td>(69% - 94%)</td>
<td>(85% - 100%)</td>
<td>(65% - 90%)</td>
<td>(80% - 93%)</td>
<td>(2.46 - 9.46)</td>
<td>(0.07 - 0.26)</td>
</tr>
<tr>
<td><strong>PET/CT, overall</strong></td>
<td>89%</td>
<td>76%</td>
<td>89%</td>
<td>76%</td>
<td>85%</td>
<td>3.75</td>
<td>0.15</td>
</tr>
<tr>
<td><em>(95% CI)</em></td>
<td>(82% - 96%)</td>
<td>(63% - 90%)</td>
<td>(82% - 99%)</td>
<td>(63% - 90%)</td>
<td>(78% - 91%)</td>
<td>(2.11 - 6.68)</td>
<td>(0.08 - 0.28)</td>
</tr>
<tr>
<td><strong>BS</strong></td>
<td>85%</td>
<td>78%</td>
<td>65%</td>
<td>91%</td>
<td>80%</td>
<td>3.76</td>
<td>0.20</td>
</tr>
<tr>
<td><em>(95% CI)</em></td>
<td>(73% - 96%)</td>
<td>(68% - 88%)</td>
<td>(52% - 76%)</td>
<td>(84% - 98%)</td>
<td>(73% - 87%)</td>
<td>(2.45 - 5.77)</td>
<td>(0.09 - 0.42)</td>
</tr>
<tr>
<td><strong>CT</strong></td>
<td>69%</td>
<td>100%</td>
<td>100%</td>
<td>63%</td>
<td>79%</td>
<td>-</td>
<td>0.31</td>
</tr>
<tr>
<td><em>(95% CI)</em></td>
<td>(58% - 80%)</td>
<td>-</td>
<td>-</td>
<td>(50% - 75%)</td>
<td>(72% - 87%)</td>
<td>-</td>
<td>(0.22 - 0.45)</td>
</tr>
</tbody>
</table>
Table 3: True positive findings with the three modalities compared to the gold standard. *GS consists of biopsy in combination with the composite reference standard. GS = gold standard, tp = time point, BS = bone scintigraphy.

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Fig. 3: 1h FDG-PET/CT in patient with multiple metastases.

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Fig. 4: 3h FDG-PET/CT in the same patient as in figure 3. Compared with the 1h image, the 3h image shows increased uptake of FDG in the malignant foci.

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Conclusion

In conclusion, these interim results suggest that FDG PET/CT may have a role in the diagnostic work-up of patients with suspected recurrent breast cancer. The 3-hour FDG-PET scan may be diagnostically superior to the other modalities. However, these results are preliminary and further research is needed to be able to draw safe conclusions.

In both the patient and the lesion based analysis BS shows a higher number of false positives than false negatives resulting in a better sensitivity and a poorer specificity. This is a result of the methodology of the BS and is caused by changes in the bone homeostasis which results in tracer accumulation in benign lesions such as degenerative changes and inflammation as well as in lesions of a malignant origin.

In this study CT shows no false positives in either the patient or the lesion based analysis. During follow-up of the patients in this study it has come to our attention, however, that when deciding whether or not to do a biopsy the physicist tends to lean more towards the results from the CT scan than both bone scintigraphy or FDG-PET/CT. This has the potential to increase the number of false positives in regards to the two latter scans thus decreasing the specificity of those modalities and bias the results.

FDG-PET/CT has the advantage of the larger field-of-view compared to CT and this modality also benefit from the high spatial resolution of CT. Combined with the functional information from the PET scan this results in a higher number of true positive lesions compared with both BS and CT. On a lesion basis this is reflected in the higher sensitivity of FDG-PET/CT compared to CT. In addition the quantitative information from the PET/CT scan can in some cases contribute with important information regarding the glucose metabolism for the specific cancer type. Several studies have shown a connection between the quantitative measurements of standard uptake values (SUV) and the treatment and prognosis of the patient [6].

As can be seen in table 3 neither CT nor FDG-PET/CT identifies all local recurrent lesions correctly. Local recurrent lesions are often small in size and can appear blurred by radiation sequel and thus not classified as malignant on CT. Small lesions can similarly be missed on the FDG-PET/CT due to partial volume artifacts and low metabolism of some breast cancer tumor types.

The addition of a late FDG-PET/CT does not change the number of true positive local breast lesions. The late scan, however, appears to have a positive effect on the detection of lymph node metastases. This could suggest that FDG-PET/CT is not the appropriate choice in the diagnostic work-up of locally recurrent BC - a finding which correlates with other studies [8,10].
References


