Comparing [18F]FACBC and [18F]FES as high potential non-FDG PET tracers in ILC: Don't forget about the forgotten tracer FACBC!

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Abstract
A 64-year-old woman presented with a palpable mass in her left breast and palpable axillary lymph nodes in the left axilla. Mammography and ultrasound-guided biopsy revealed metastasis of invasive lobular carcinoma (ILC) in a left axillary lymph node, but no primary tumour in the left breast. [18F]FACBC PET/CT and [18F]FES PET/CT were performed for staging purposes with an interval of approximately 1 week. [18F]FACBC demonstrated intense focal uptake in the left breast, suspicious for primary tumour, and in multiple left axillary lymph nodes, suspicious for metastases, with a SUVmax of 5.7 and 15.2, respectively. Similar uptake was found in the same area of the left breast and in left axillary lymph node metastases with [18F]FES, however with lower SUVmax: 4.7 and 9.8 respectively. Nowadays most attention is drawn towards [18F]FES as promising tracer in (ER positive) low grade breast tumours including ILC. However, our case suggests equal performance of [18F]FACBC and [18F]FES in ILC. To our knowledge this is the first case comparing performance of [18F]FACBC and [18F]FES in a patient with ILC. Our case indicates that [18F]FACBC may have added value for staging ILC and might perform similar or even superior to [18F]FES.

Case
A 64-year-old woman, referred from the breast cancer screening program, presented with a palpable mass in the lateral lower quadrant of the left breast and a suspicious axillary lymph node. Mammography and ultrasound of the left breast showed no pathology in the aforementioned region, however an irregularity of 11 mm was found cranio-centrally in the same breast. Ultrasound-guided biopsy showed mastopathic changes but no (pre)malignancy. The lymph node biopsy revealed a metastasis of invasive lobular breast carcinoma (ILC). Immunohistochemistry was applied to evaluate the receptor expression and showed an estrogen receptor (ER)-positive (100%), progesterone receptor (PR)-positive (100%) and human epidermal growth factor receptor 2 (HER2)-negative tumour. 18F-labeled 1-amino-3-fluorocyclobutane -1-carboxylic acid (18F-fluciclovine), also known as [18F]FACBC PET/CT was performed, instead of 18F-fluorodeoxyglucose ([18F]FDG) PET/CT, as ILC is difficult to visualize with [18F]FDG PET/CT (1-4). The [18F]FACBC PET/CT showed focal intense uptake in an area of 13 mm, approximately 20 mm medial to the biopsy marker (figure 1). A second area with increased [18F]FACBC uptake was seen anteriorly of the marker. In the left axilla multiple lymph nodes with intense [18F]FACBC uptake were noticed (figure 2). However, differentiation between lymph node metastases and reactive lymph nodes could not be made with certainty since our patient was vaccinated for COVID-19 in the left arm a few weeks earlier. This clinical dilemma was approached by performing a 4-fluoro-11β-methoxy-16α-[(18)F]fluoroestradiol ([18F]FES) PET/CT with the expectation that the specificity of the ER tracer would elucidate this dilemma. The [18F]FES PET/CT showed a similar focus with high ER density cranio-centrally in the left breast (figure 1). The second suspicious region anteriorly of the marker showed slightly higher receptor density compared to the rest of the left breast tissue. Intense tracer uptake was seen in multiple lymph nodes in the left axilla (figure 2), hence, confirming the malignant nature of all [18F]FACBC-avid lymph nodes. In addition, MRI of the breast was performed, confirming the suspicious lesion (BIRADS 5) in the left breast corresponding to the focal pathology as seen on functional imaging. The second suspicious area, anteriorly of the marker, showed non-mass enhancement, suspicious for malignancy, preferentially DCIS. Based on these findings, our patient was treated with neoadjuvant chemotherapy. A I-125 marker was placed in one of the lymph node metastases. Surgical treatment combined with MARI-procedure and sentinel node biopsy is planned afterwards.

Discussion
Primary ILC consists of discohesive neoplastic cells causing an infiltrative growth pattern, making it difficult to visualise on mammography, ultrasound and MRI. Furthermore, ILC lacks aggressive pathologic features such as high mitotic index or high

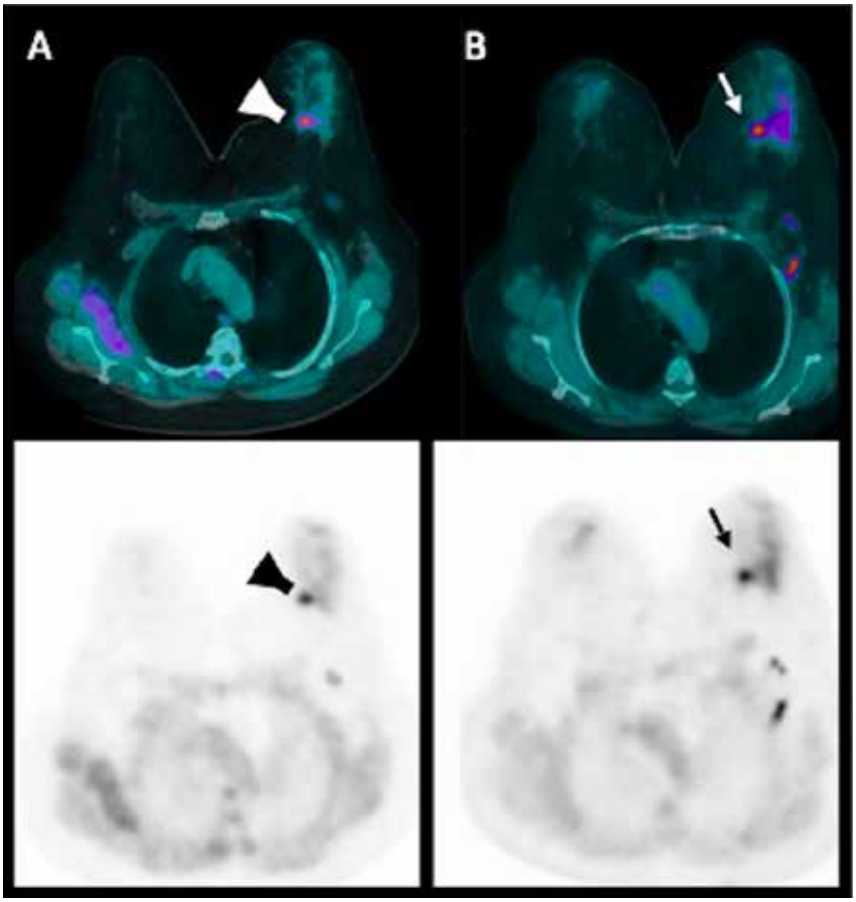

Figure 1. **A.** Axial fused [^{18}F]FACBC PET/CT (top) and [^{18}F]FACBC PET(bottom) demonstrating suspicious increased focal uptake in the left breast (arrowhead); **B.** Axial fused [^{18}F]FES PET/CT(top) and [^{18}F]FES PET (bottom) showing suspicious focal increased ER-expression in the left breast (arrow).

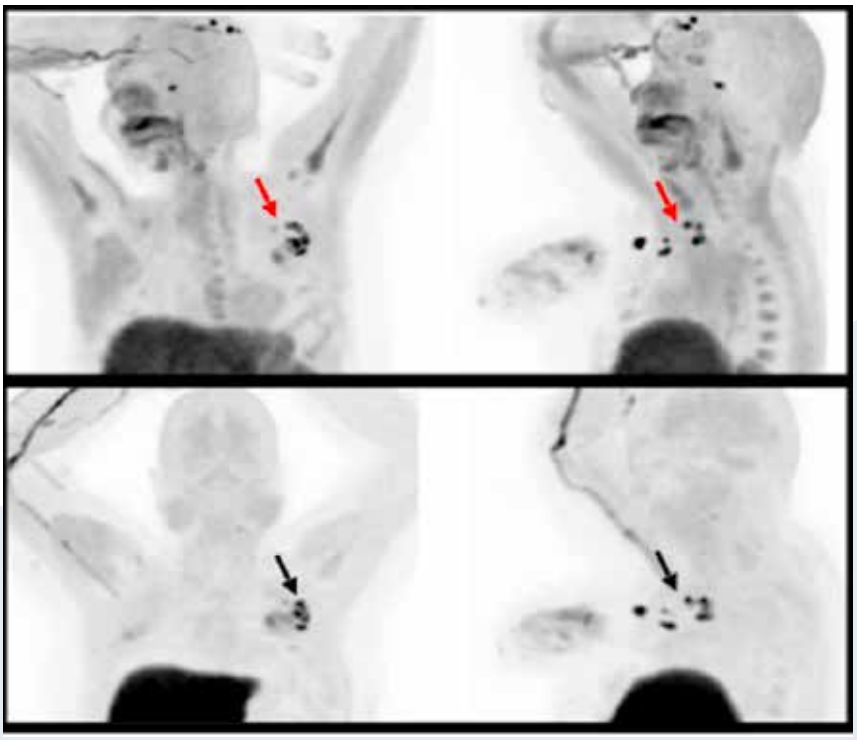

Figure 2. Maximum Intensity Projection (MIP). **Upper row**: [^{18}F]FACBC PET anterior (left) and lateral (right) view showing FACBC avid lymph nodes in left axilla (red arrow). **Lower row**: [^{18}F]FES PET anterior (left) and lateral (right) view showing lymph nodes with high ER-expression in left axilla (black arrow).

histologic grade, and therefore lacks the characteristics for high [18F]FDG uptake (1). However, [18F]FDG PET/CT is still first choice imaging modality for staging breast carcinoma. Although guidelines still recommend [18F]FDG PET/CT for systemic staging, the impact of [18F]FDG PET/CT on staging is substantially lower in patients with ILC compared to patients with IDC (5). Hence, there is a need for alternative tracers for staging ILC. [18F]FACBC, is a leucine analog. Leucine is transported across the cell membrane via LAT1 and ASCT2 transporters (6). [18F]FACBC visualises amino acid metabolism, which is highly upregulated in breast cancer (7). Ulaner et al compared [18F]FACBC and [18F]FDG uptake in both IDC and ILC and reported higher SUVmax and SUVmean values for [18F]FACBC (4). Moreover, in case of ILC, all lesions showed structurally higher SUV values with [18F]FACBC compared to [18F]FDG. In addition, both IDC and ILC show substantially higher [18F]FACBC uptake in malignant lesions compared to benign breast tissue (3). In our patient a high target-to-background ratio was found as well using [18F]FACBC, supporting the findings of the Emory group (3).

A second promising tracer for imaging ILC is [18F]FES, since 95% of the ILCs are ER positive. Ulaner et al compared [18F]FES PET/CT with [18F]FDG PET/CT in metastatic ILC; [18F]FES PET/CT showed higher SUVs and more metastatic lesions compared to [18F]FDG PET/CT (8). Three case reports observed metastatic lesions only with [18F]FES PET/CT but not with [18F]FDG PET/CT (9).

Our patient showed intense uptake at the site of the ILC lesions both with [18F]FACBC and [18F]FES, although [18F]FACBC uptake was higher as compared to [18F]FES (SUVmax in focal breast lesion 5.7 versus 4.7, SUVmax in lymph node metastases 15.2 versus 9.8, respectively).

Although available literature is limited concerning the clinical value of [18F]FACBC and [18F]FES in ILC, both tracers seem promising in this type of breast cancer. Nowadays, however, it seems that most attention is drawn towards [18F]FES PET/CT for application in low grade breast tumours including ILC, while our case shows that [18F]FACBC and [18F]FES have at least comparable potency. In our patient, the tumour showed 100% ER expression. Since a positive correlation exists between ER expression and [18F]FES uptake (10), it might be assumed that tumours with lower ER positivity will show lower [18F]FES uptake, while ER expression is not influencing the uptake of [18F]FACBC. Furthermore, ER expression can change over time, leading to discordant expression between primary tumour and metastases. Hence, in our opinion, for staging purposes the independency on ER expression favours the use of [18F]FACBC over [18F]FES.

Breast cancer is a highly heterogeneous disease. In this era of precision medicine, further research on tailoring tracer application according to breast cancer subtype and (immuno)histological features is needed. We hypothesise that [18F]FDG might perform adequately for staging high grade ILC due to the positive correlation between [18F]FDG uptake and Ki-67 expression as well as with tumour grade (11,12). On the other hand, [18F]FACBC might play an important role in staging low grade invasive ductal carcinoma (IDC), as low grade IDC is difficult to visualise with [18F]FDG as well, due to its low aggressive histological features. Precision medicine in nuclear medicine is trending, especially as the availability of specific PET tracers is growing. However, within this exploration of patient-based choices, one should not forget about the forgotten tracer FACBC!

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