Imaging hormone receptors in metastatic breast cancer patients
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Chapter 4

$^{18}$F-fluoroestradiol positron emission tomography (FES PET) has added value in staging and therapy decision making in patients with disseminated lobular breast cancer

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Abstract
Lobular breast cancer (LBC) is the second most common type of invasive breast cancer, accounting for almost ten percent of the invasive lesions. LBC lesions are often difficult to detect with conventional imaging, as they tend to grow less cohesively than the more common ductal cancer. In this case series we present four patients with LBC, in whom confirmation of metastatic disease would make the crucial difference between curative or non-curative treatment. Staging with conventional imaging, however, yielded equivocal results, and a biopsy was not feasible. In contrast, $16\alpha$-$^{18}$F-fluoro-17β-estradiol (FES) PET provided a decisive contribution to clinical decision making in these patients with LBC. This indicates that FES-PET may have added value in relation to conventional staging in LBC and may support in clinical decision making.

Keywords: FES-PET, lobular breast cancer, estrogen receptor
Chapter 4

Lobular breast cancer (LBC) accounts for almost 10% of the invasive breast cancer lesions. These tumors originate from lobules and have different appearances than ductal carcinoma. Patients with LBC tend to have a better prognosis than patients with ductal breast cancers (DBC), at similar disease stages [1]. LBC is more difficult to detect compared to DBC, as LBC usually does not present as a lump. Loss of cell adhesion protein E-cadherin in LBC induces diffuse growth, often into the stroma without a significant desmoplastic reaction [2]. This diffuse growth pattern also applies to metastasis in the gastrointestinal tract, which makes LBC metastases often difficult to detect by physical examination and conventional imaging. The abundant expression of the estrogen receptor (ER) by nearly all LBCs renders molecular imaging of the ER particularly suitable for detection of LBCs metastases. The estrogen derivative 16α-[18F]fluoro-17β-estradiol (FES) is a tracer used for positron emission tomography (PET) imaging in several studies to detect ER expression in tumors. FES PET has a high sensitivity (84%) and specificity (98%) for ER-positive tumors [3]. At the University Medical Center Groningen we often perform FES-PET in patients with a clinical dilemma [5].

Here we present four patients with LBC and inconclusive standard work-up, in whom confirmation of metastatic disease would make the crucial difference between curative and non-curative treatment. The examples demonstrate the important contribution FES PET can have in diagnostic work-up of LBC. FES-PET images were all obtained from the skull to mid-thigh with a 64-slice PET/CT camera (Biograph mCT, Siemens Medical Systems, Knoxville, TN). A low-dose CT-scan was used for attenuation correction. The whole body PET-scan was acquired 60 minutes after intravenous injection of approximately 200 MBq FES.

Case 1 A 72 year old patient was diagnosed with LBC 12 years prior to referral, for which she underwent breast amputation and consecutive radiotherapy. At the time of referral, a local recurrence in the amputation scar was excised. Excision margins were focally positive for tumor cells. The patient could be treated with a curative intent by hyperthermia and radiotherapy if no distant metastases were present. Contrast enhanced CT revealed sclerosis of thoracic vertebra 7 and the iliac bone, suggesting
metastatic lesions. These lesions, however, were not confirmed by bone scintigraphy or $^{18}$F-fluorodeoxyglucose (FDG) PET. The bone scan did show one skull lesion, which could not be confirmed by FDG PET (Fig 1). FDG-PET showed only increased uptake at the excision site due to the recent surgery. Because of the discrepancy between the different conventional imaging modalities, a FES-PET was performed, which showed high tracer uptake in multiple bone lesions and lymph nodes throughout the body (Fig. 1). FES-PET could not detect remnants of the local recurrence. The focally present cells were either below the detection limit of the FES-PET or FDG PET was false positive due to tissue repair after surgery. The skull lesion visible on the bone scan was not visible on the FES-PET scan. Since FDG-PET was also negative, this was presumably a non-malignant hyperostosis lesion.

![Figure 1](image_url)

**Figure 1:** whole body conventional bone scan (left, anterior and posterior view) of case 1 showing one focal lesion in the skull (arrow 1): a bone metastasis cannot be excluded. FDG PET (A) shows only uptake at the site of the recently excised local recurrence (arrow 2). FES PET (B) shows multiple bone metastases and lymph node metastases in the mediastinum (arrow 3), but no uptake at the site of the local recurrence (arrow 2).
In conclusion, FES-PET findings were compatible with LBC metastases in lymph nodes and bone. Anastrozole treatment was started as first line palliative hormone therapy. Treatment evaluation was based on clinical findings and biochemical evaluations, because lesions were not visible on conventional imaging. At follow-up after eight months of treatment, the patient showed good clinical response.

**Case 2** A 70 year old patient had been diagnosed with an occult LBC with axillary lymph node metastases prior to referral. She had complaints of back pain and laboratory results showed anemia (6.4 mmol/l). On a diagnostic CT-scan of the thorax and abdomen diffuse inhomogeneous skeletal findings were found and considered non-malignant. FDG-PET scan showed slightly elevated uptake at the malignant lymph nodes and multiple bone foci, of which further differentiation between malignancy and degenerative or traumatic changes was not possible. More lymph nodes and bone lesions were detected by FES-PET than by FDG-PET. Furthermore diffuse uptake was visible in the bone marrow. Based on the FES-PET findings an additional bone marrow biopsy was performed. The bone marrow was diffusely infiltrated with LBC (Fig. 2). In conclusion, the FES-PET was compatible with bone marrow and bone metastases from LBC, in addition to the known lymph node metastases. The patient received tamoxifen after which she showed good biochemical and clinical response for more than one year.
Figure 2: FDG PET of case 2 (part A) shows pathological lymph nodes, as well as diffuse bone uptake, considered to be either degenerative, traumatic or metastatic disease. FES PET shows uptake in axillary, hilar, and mediastinal lymph nodes and diffuse bone uptake indicating ER-positive uptake.

Case 3 A 54 year old patient was diagnosed with T2N0M0 LBC one year prior to referral. She underwent breast amputation and consecutive chemo-radiation therapy, and was on adjuvant hormonal treatment at time of referral. She had complaints of her left hip, which on additional imaging showed a solitary lesion of uncertain significance in the left femur on both bone scintigraphy and the MRI scan. Because of this diagnostic uncertainty, the patient was referred for a FES-PET. This scan was performed one month after the MRI scan and showed no uptake in the femur lesion nor any other lesions (Fig. 3). Therefore, the FES-PET did not support the presence of ER-positive metastases, and the patient continued her adjuvant hormonal treatment. Complaints resolved spontaneously and a follow-up MRI could no longer identify the femur lesion (Fig 3C).
Figure 3: FES PET of case 3 shows physiological uptake, but no abnormal uptake in hip area or any other part of the body (A). MRI shows a lesion in the left caput femoris prior to FES PET (B, arrow), which spontaneously resolved after 3 months (C, arrow)

Case 4: A 72 year old patient was diagnosed with T3N2M0 LBC 8 years prior to referral. She underwent breast amputation and consecutive chemo-radiation therapy, followed by adjuvant hormonal treatment. After 5 years of treatment, adjuvant hormonal treatment was stopped according to the guidelines. After cessation of adjuvant treatment she started suffering from diffuse skeletal pain. Restaging with CT showed one lesion in the eighth thoracic vertebral body, but no other sites suspect for metastases. A biopsy of this lesion was considered unsafe due to the location. Therefore, a FES-PET was requested to assess the presence of ER-positive disease. In line with the CT, the FES-PET showed uptake in the vertebral lesion, without uptake anywhere else (Fig. 4). She was considered to have an oligometastasis and underwent curative radiation treatment (16 Gy) of the lesion. Now 2 years later, there is still no evidence of disease.
Figure 4: FES PET of case 4 shows high uptake in one vertebral lesion (A, arrow), indicating oligometastasis. CT scan showed a single sclerotic bone lesion at thoracic vertebra (B, arrow).

Staging lobular breast cancer patients with conventional imaging

Although it is more difficult to detect LBC, current Comprehensive Cancer Network Guidelines (NCCN) on screening and staging breast cancer patients do not differentiate between LBC and DBC [6]. Mammography has a high false negative rate of about 30% to detect LBC [7]. LBC lesions mostly manifest as architectural distortions and calcifications are detected less frequently [7-9]. At the time of diagnosis, patients with LBC often present with a larger tumor size and higher stage compared to patients with ductal breast cancer [10]. Ultrasound is performed for staging tumors when lesions are found by mammography or when a lump is palpable, and ultrasound therefore has a sensitivity of 98%, similar to ductal breast cancer [7]. MRI has a sensitivity up to 96% to detect LBC, similar to the overall detection of primary breast cancer [8]. FDG uptake in LBC primary lesions is lower compared to ductal breast cancer and may result in false-negative results in LBC patients [11,12].

In Table 1 more details on sensitivity for detection of breast cancer overall and LBC are provided.
Metastatic LBC tends to spread mostly to the bone, similar to ductal breast cancer, resulting in both sclerotic and lytic bone lesions. Sclerotic lesions can be detected by conventional bone scintigraphy, but for lytic lesions, FDG-PET is preferable [13]. However bone metastases in LBC patients have lower FDG uptake compared to those with ductal breast cancer [14,15]. Apart from bone lesions, LBC also causes metastases in gastrointestinal tract, peritoneum and reproductive organs more often than ductal breast cancer. On CT, gastrointestinal tract metastases usually are observed as general wall thickening rather than a solid mass. With the conventional imaging modalities it is thus difficult to recognize LBC both in early disease- and in the metastatic setting.

**Table 1**: Sensitivity of imaging modalities for detection of breast cancer overall and lobular breast cancer in particular

<table>
<thead>
<tr>
<th>Imaging</th>
<th>Setting</th>
<th>Sensitivity overall breast cancer</th>
<th>Sensitivity lobular breast cancer</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammography</td>
<td>Primary</td>
<td>60-98%</td>
<td>11-81%</td>
<td>7, 8</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>Primary</td>
<td>68-98%</td>
<td>90%</td>
<td>7, 8</td>
</tr>
<tr>
<td>MRI breast</td>
<td>Primary</td>
<td>90-98%</td>
<td>93-95%</td>
<td>8, 9</td>
</tr>
<tr>
<td>FDG PET</td>
<td>Primary</td>
<td>78-91%</td>
<td>75%</td>
<td>11, 12, 20</td>
</tr>
<tr>
<td>FDG PET</td>
<td>Metastatic</td>
<td>93-95%</td>
<td>43% -100%</td>
<td>13, 14</td>
</tr>
<tr>
<td>Bone scintigraphy</td>
<td>Metastatic</td>
<td>82-91%</td>
<td>Unknown</td>
<td>15, 16</td>
</tr>
</tbody>
</table>

**Discussion**

Since LBC is usually ER-positive, FES-PET could be of help to assess bone and nodal metastases. Due to high physiological uptake of FES in the liver, and excretion via the bile, FES-PET is not the optimal imaging technique to detect liver and intestinal metastases. However, in case of equivocal lesions or suspected metastatic disease outside of the liver and intestines, FES-PET could be of help in staging the patient with LBC, for better understanding the course of the disease and to guide treatment decision making. This is to our knowledge the first case series indicating that FES-PET can have clear impact on clinical decision making in LBC, when other imaging
techniques show equivocal results. This early clinical finding will have to be confirmed in larger prospective studies.

Conclusion
FES PET can provide crucial information for patients with LBC and referring physicians regarding disease stage, which can profoundly affect treatment decisions and thus prognosis.

List of abbreviations:
FES: 16α-[18F]fluoro-17β-estradiol
FDG: 2′-[18F]fluoro-2′-deoxyglucose
LBC: lobular breast cancer
DBC: ductal breast cancer
SUV: standardized uptake value
References

