Response monitoring in metastatic breast cancer – a prospective study comparing $^{18}$F-FDG PET/CT with conventional CT

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Financial support:
Qvesehls grant, Mrs. Astrid Thaysens grant, The Independent Research Fund Denmark, University of Southern Denmark, Odense University Hospital, and Center for Personalized Response Monitoring in Oncology (PREMIO)

Running title
$^{18}$F-FDG PET/CT or CE-CT in breast cancer
ABSTRACT

PURPOSE This study aimed to compare contrast-enhanced CT (CE-CT) and $^{18}$F-FDG PET/CT for response monitoring in metastatic breast cancer (MBC) using the standardized response evaluation criteria RECIST 1.1 and PERCIST. The objective was to examine whether progressive disease was detected systematically earlier by one of the modalities.

METHODS Women with biopsy-verified MBC were enrolled prospectively and monitored using combined CE-CT and $^{18}$F-FDG PET/CT every 9-12 weeks to evaluate response to first-line treatment. CE-CT scans and RECIST 1.1 were used for clinical decision-making without accessing the $^{18}$F-FDG PET/CT scans. At study completion, $^{18}$F-FDG PET/CT scans were unblinded and assessed according to PERCIST. Visual assessment was used if response criteria could not be applied. The modality-specific time to progression was defined as the time from the baseline scan until the first scan demonstrating progression. Paired comparative analyses for CE-CT vs. $^{18}$F-FDG PET/CT were applied, and the primary endpoint was earlier detection of progression by one modality. Secondary endpoints were time to detection of progression, response categorization, visualization of changes in response over time, and measurable disease according to RECIST and PERCIST.

RESULTS In total, 87 women were evaluable with a median of six (1-11) follow-up scans. Progression was detected first by $^{18}$F-FDG PET/CT in 43/87 patients (49.4%) and by CE-CT first in 1/87 (1.15%) ($p < 0.0001$). Excluding patients without progression (n=32), progression was seen first by $^{18}$F-FDG PET/CT in 78.2% (43/55) of patients. The median time from detection of progression by $^{18}$F-FDG PET/CT to that of CE-CT was six months (95% CI 4.3-6.4). At baseline, 76 patients (76/87, 87.4%) had measurable disease according to PERCIST and 51 (51/87, 58.6%) according to RECIST 1.1. Moreover, $^{18}$F-
FDG PET/CT provided an improved visualization of changes in response over time, as seen in the graphical abstract.

**CONCLUSION** Disease progression was detected earlier by $^{18}$F-FDG PET/CT than CE-CT in most patients with a potentially clinically relevant median six-month delay for CE-CT. More patients had measurable disease according to PERCIST compared with RECIST 1.1. The magnitude of the final benefit for patients is a perspective for future research.

**KEYWORDS**

Metastatic breast cancer; response monitoring; $^{18}$F-FDG PET/CT; CE-CT; PERCIST; RECIST 1.1
INTRODUCTION

Response monitoring modalities are used to guide clinical decision-making to optimize treatment strategy. However, no specific modalities for monitoring response in metastatic breast cancer (MBC) are recommended by clinical guidelines (1,2), contrast-enhanced CT (CE-CT) being used widely in clinical practice. The response evaluation criteria in solid tumors (RECIST 1.1) (3) are typically required when patients are monitored in clinical trials. However, CE-CT has a low sensitivity for bone metastases and low specificity for liver metastases (4-6).

$^{18}$F-fluorodeoxyglucose-positron emission tomography / computed tomography ($^{18}$F-FDG PET/CT) and the PET response criteria in solid tumors (PERCIST) have been suggested to overcome the shortcomings of CE-CT (4,6-8). Changes in metabolic activity may appear before morphological changes can be seen (4,9), giving $^{18}$F-FDG PET/CT an excellent potential to monitor treatment response in bone and liver metastases and detect treatment failure early (4,10,11). Further, more patients may be classified as having measurable disease using $^{18}$F-FDG PET/CT and PERCIST than CE-CT and RECIST 1.1 (6).

Studies have demonstrated $^{18}$F-FDG PET/CT promising for measuring and detecting early response in MBC (4,12-14), and its use for monitoring may improve survival for patients with MBC (15). But to our knowledge, no prospective studies have compared CE-CT and RECIST 1.1 with $^{18}$F-FDG PET/CT and PERCIST for longitudinal response monitoring in MBC.

Several treatment options are available for women with MBC, and their priorities concerning survival, quality-of-life, and toxicity influence the shared decision-
making (1). A precondition for any clinical decision-making is accurate diagnosis of disease progression – the earlier this can be achieved, the more a patient can benefit from treatment adaptations.

This study compared $^{18}$F-FDG PET/CT and CE-CT for longitudinal response monitoring in women with MBC. The objective was to examine whether progressive disease was detected systematically earlier by one of the modalities, with the primary endpoint being the first detection of progression. Secondary endpoints were comparisons of time until detection of progression, response categorization, measurable disease according to RECIST 1.1 and PERCIST, respectively, and visualization of changes in response over time.

MATERIALS AND METHODS

Study Design and Patients

A prospective cohort study compared response assessment using CE-CT and $^{18}$F-FDG PET/CT in MBC patients who served as their own controls. The institutional review board (the Danish Ethics Committee, S-20170019) approved this study and all subjects signed written informed consent. The study was registered at Clinical.Trials.gov (NCT03358589) and followed the Declaration of Helsinki. REDCap (Research Electronic Data Capture) and SharePoint were used for data storing and management, and the results were reported using the STROBE guideline (16).

Women were eligible if diagnosed with de novo or recurrent MBC (17) and fit for systemic oncological treatment. They were excluded if MBC was not biopsy-verified or if they left the study or died before the first follow-up scan.
Data Collection

Patients were included before initiating first-line treatment. They were followed until progression leading to change to second-line treatment, death, loss of follow-up, or until the end of trial by November 30, 2020. Hence, in cases of change of oncological treatment due to other reasons than progression (i.e., toxicity or maximum dose of chemotherapy), the patient was still followed as mentioned above. Data derived from medical records, scan images, pathology, and scan reports.

Image Techniques

$^{18}$F-FDG PET/CT, including CE-CT imaging from the top skull to mid-thigh, was performed 60 ± 5 min p.i. with intravenous injection of 4 MBq $^{18}$F-FDG per kg. Blood sugar levels were measured routinely, and patients fasted at least four hours before $^{18}$F-FDG injection. All scans were performed following the European Association of Nuclear Medicine guideline (18).

The PERCIST standardization criteria (8) were registered prospectively and listed with supplemental image techniques in Supplemental Table 1.

Image Interpretation

A diagnostic $^{18}$F-FDG-PET combined with CE-CT was performed with $^{18}$F-FDG-PET images available at baseline (19,20). $^{18}$F-FDG PET/CT and CE-CT scans were performed simultaneously for each follow-up scan, but treatment decisions were based on CE-CT with blinded $^{18}$F-FDG PET images. Hence, women were monitored with CE-CT using RECIST 1.1 (3) if the disease was measurable at baseline; otherwise, a visual assessment was used based on the radiologist's discretion. One of two experienced radiologists (FH, JTA) made the CE-CT assessments used for clinical decision-making.
cases of uncertainty, consensus on the response category was reached in a multidisciplinary conference.

The response categorization from CE-CT scans used in daily clinical practice was registered for research purposes. Follow-up $^{18}$F-FDG PET/CT scans were unblinded at the end of the trial and assessed by PERCIST one-lesion (8) in patients with measurable disease at baseline and when follow-up scans were comparable according to PERCIST (Supplemental Table 2). Otherwise, a visual assessment based on the discretion of the nuclear medicine specialist was used. One of three nuclear medicine physicians (NMJ, HJN, SEDW) assessed the scans. In cases of uncertainty, consensus was reached between the observer and a senior physician in nuclear medicine (MGH). Assessors of $^{18}$F-FDG PET/CT were blinded to the CE-CT scan report and the clinical decision-making. The nadir scan was used as reference in the PERCIST assessment to allow a meaningful comparison with RECIST 1.1 (Supplemental Table 2).

Outcomes Measures

The rate of earlier detection by one of the modalities was the primary endpoint. Progression was assigned in cases of new lesions, +20% increase in sum lesion diameter (CE-CT) or +30% increase in SULpeak ($^{18}$F-FDG PET/CT), or unequivocal progression of non-target lesions, (Supplemental Table 2).

The secondary endpoint of modality-specific time until detection of the first progression was defined as the time from baseline until the first scan with an assessment of progressive disease (PD) or progressive metabolic disease (PMD). In 18 instances (in 13 patients), progression was regarded as false-positive because 1) PD was reported by CE-CT without clinical change of management, and the following scan did not reveal any further progression ($n = 9$), or 2) PMD was reported by $^{18}$F-FDG PET/CT without further
progression or resolving of FDG-uptake on the following scan \((n = 9)\). A detailed description of these instances is provided in Supplemental Figure 1. They were not counted as progressions in the time-related analyses of detection of progression.

For patients with progression on one modality only, a consistency-check was performed by follow-up in medical records in June 2021. Change in treatment due to a clinically or image-guided identified progression or a confirmation on subsequent scans were considered signs of consistency.

The distribution of patients with measurable disease at baseline and response categories on follow-up scans were registered as secondary endpoints. Changes in treatment response over time were visualized in selected patients.

**Statistical Analysis**

Descriptive statistics are presented as frequencies and respective percentages. The relative timing of progression was classified by assigning each patient to one of the six categories shown in Table 1. We report the two relative frequencies of \(^{18}\text{F-}
FDG PET/CT detecting progression first and CE-CT detecting progression first. We estimated the difference between them with a 95\% confidence interval (95\% CI) and conducted McNemar’s test for paired binary data (type I error: 5\%, two-sided).

The modality-specific time until detection of progression for both modalities was visualized by a Kaplan-Meier plot. The significance of the difference between the two modalities was analyzed using a shared-frailty model. Censoring was performed at the time point of the last available scan for patients reaching the end of follow-up (November 2020) without progression, loss to follow-up in between, or death. As the data were paired, this was the same time point for both modalities.
For patients in whom progression was detected earlier by $^{18}$F-FDG PET/CT than CE-CT, the median time from detection by $^{18}$F-FDG PET/CT until detection by CE-CT was estimated with 95% CI. Results were visualized by a Kaplan-Meier plot treating loss to follow, death, and final study scan as censoring events.

A preplanned interim analysis was conducted but had no impact on the further study conduct. It can be seen with the sample size calculation in Supplemental Table 3.

Analyses were performed using Stata/IC 15.0 (StataCorp, College Station, Texas, USA) and Microsoft Excel (Microsoft, Redmond, WA, USA).

RESULTS

Between September 1, 2017, and August 31, 2019, 114 patients were diagnosed with MBC at Odense University Hospital, Denmark. As seen in Figure 1, 27 patients were excluded. In total, 87 patients had 517 follow-up CE-CT scans performed as part of $^{18}$F-FDG PET/CT scans ($^{18}$F-FDG PET blinded). A median of six scans (range 1-11) was performed per patient. The median follow-up time was 15.9 months (range 1.94-37.5), 55 (63.2%) patients experienced a progression, and one patient died.

Baseline characteristics of included patients appear in Table 2 and Supplemental Table 4. HER2 was overexpressed in 5.75%, and most metastases were estrogen receptor-positive, compatible with most patients (80.5%) receiving endocrine therapy. Bone-only disease was present in 26.4% of the patients.

Detection of First Progression

Progression was detected first by $^{18}$F-FDG PET/CT in 43 of 87 patients (49.4%) and first by CE-CT in one of 87 (1.15%) ($p < 0.0001$). Excluding 32 patients with no progression while on study, progression was seen first by $^{18}$F-FDG PET/CT in 78.2%
(43/55) and by CE-CT in 1.82% (1/55). Further results on time-related detection of progression for the two modalities are seen in Table 1 and Figures 2-5. Reasons for the first progression were almost equally distributed between the two modalities (Table 3).

Among 17 patients for whom progression was detected by $^{18}$F-FDG PET/CT only, the consistency-check after seven months revealed a subsequent change in treatment due to clinically or image-guided progression in nine patients (52.9%) (Figure 4 and Supplemental Figure 2A). No treatment change had appeared in the remaining eight patients, but (slow) progression could be confirmed on the subsequent scans (Supplemental Figure 2B).

The detection of progression by CE-CT without detection by $^{18}$F-FDG PET/CT in one patient led to a change in management (Figure 5).

The median time to the detection of first progression was 24.3 months (95% CI 15.9-infinity) and 14.9 months (95% CI 11.4-20.8) for CE-CT and $^{18}$F-FDG PET/CT assessment, respectively. Thus, a statistically significant difference was observed between the two modalities ($p < 0.001$, Figure 6A).

The median time from detection of progression by $^{18}$F-FDG PET/CT to detection by CE-CT was 5.98 months (95% CI 4.27-6.41, Figure 6B).

**Measurable Disease and Response Categories**

Measurable disease at baseline was present in 51 (51/87, 58.6%) and 76 (76/87, 87.4%) for RECIST 1.1 and PERCIST, respectively. Of 11 patients not being measurable according to PERCIST, seven (63.4%) had invasive lobular carcinomas.

Figure 7 illustrates the distribution of response categories during the study period. Complete metabolic responses and progressive metabolic disease were reported
more frequently by $^{18}$F-FDG PET/CT, while stable disease was reported more often by CE-CT. Progression was detected by visual assessment in 18% (24/136) and 45% (21/47) of the total number of progressions detected by $^{18}$F-FDG PET/CT and CE-CT, respectively.

Changes in response over time are illustrated in Figure 2 and Supplemental Figure 3 for patients with measurable disease at baseline for whom progression was detected by both modalities but seen first on $^{18}$F-FDG PET/CT.

**DISCUSSION**

In this prospective study of longitudinal response monitoring of metastatic breast cancer, progression was detected earlier by $^{18}$F-FDG PET/CT than CE-CT in most patients ($p < 0.0001$). A median delay of 6 months was observed for CE-CT compared with $^{18}$F-FDG PET/CT, which seems clinically relevant. In addition, more patients had measurable disease by PERCIST than RECIST 1.1, and $^{18}$F-FDG PET/CT provided an improved visualization of changes in response over time.

**Detection of Progression**

A high proportion of PET-detected progressive diseases could be observed as continuous progression until it was detected by CE-CT. This implied that true progressive disease was present and that earlier detection could potentially impact clinical practice. In cases of progression seen only by $^{18}$F-FDG PET/CT, a consistency-check was made after end-of-trial. This revealed clinical or image-guided change in management among half of these patients, thus suggesting true progression. The progression detected on $^{18}$F-FDG PET/CT in the remaining patients generally presented as small, solitary, but slow-progressing lesions of which the long-term clinical impact could not be assessed.
We considered lesions that could not be confirmed on the subsequent scan as false progression since the progressing lesion resolved. The frequency of such findings was limited and equally distributed in both modalities.

\textbf{\textsuperscript{18}F-FDG PET/CT for Response Monitoring}

\textsuperscript{18}F-FDG PET/CT has been suggested to be less useful in patients with invasive lobular cancers with a predilection site for metastatic spread in the gastrointestinal tract, peritoneal carcinomatosis, and bones (21). These subtypes often encounter low Ki67 and low FDG-uptake (22,23), confirmed by this study with seven of 11 patients with no measurable disease being of lobular subtype.

The lack of standardization criteria has been suggested as a barrier to introducing \textsuperscript{18}F-FDG PET/CT for response monitoring MBC in clinical trials (4,24), but PERCIST has been suggested as promising and feasible (6,25-27). In this study, PERCIST was applied using the one-lesion method with cut-off values of \pm 30\% for progressive/regressive disease as suggested in PERCIST.

\textbf{Clinical Implications}

Earlier detection of progression offers the opportunity of earlier treatment alterations, which may improve overall survival for MBC patients monitored by \textsuperscript{18}F-FDG PET/CT (15).

Many patients with bone-only MBC are often precluded from clinical trials due to non-measurability (6). \textsuperscript{18}F-FDG PET/CT and PERCIST may allow more patients, including bone-only disease, to enter clinical trials because more patients meet the measurability criteria. These patients have prolonged overall survival (28), with important implications for evaluating treatment effects. Response rates are often used as a marker of
treatment efficacy (29), and treatment response is reported more frequently by $^{18}$F-FDG PET/CT than CE-CT (14). Therefore, treatment effect might be underestimated by CE-CT and RECIST 1.1 in current clinical practice (8,14).

**Strengths and Limitations**

A major strength is the prospective, paired study design, where patients served as their own controls. The study included patients from daily clinical practice with no strict inclusion criteria regarding measurability or molecular subtypes. The study provides clinically relevant knowledge and novelty as the first to compare the standardized response evaluation criteria RECIST 1.1 and PERCIST for longitudinal response monitoring in MBC. We used the PERCIST criteria with strict acquisition to the suggested image conditions, allowing images to be compared between baseline and follow-up $^{18}$F-FDG PET/CT scans (8).

With other limitations, this was a non-randomized single-center observational study. The nadir level of SULpeak was used without international consensus. The follow-up time was relatively short such that no progression was observed in approx. one-third of the patients. This could be explained by most patients having estrogen receptor-positive disease, for whom new treatment options have improved survival (30).

**Perspectives**

$^{18}$F-FDG PET/CT has been suggested to improve treatment decisions by detecting non-response earlier than conventional methods and preventing patients from receiving ineffective, potentially toxic treatments (31-32). In this study, progression was detected earlier on $^{18}$F-FDG PET/CT. However, we cannot make any firm conclusions about the long-term survival benefit of introducing $^{18}$F-FDG PET/CT. We consider this and
data on magnetic resonance scans and circulation tumor DNA collected in the present study (NCT03358589) perspectives for future research. Further, stratified analyses within breast cancer-directed treatments could be relevant when comparing the two modalities.

CONCLUSION

In conclusion, disease progression was detected earlier by $^{18}$F-FDG PET/CT than CE-CT in most patients with a potentially clinically relevant six-month delay for CE-CT. More patients had measurable disease according to PERCIST compared with RECIST 1.1, and visualization of changes over time was improved by $^{18}$F-FDG PET/CT. The magnitude of the final benefit for patients is a perspective for future research.

SUPPORT

Qvøsehls grant, Mrs. Astrid Thaysens grant, The Independent Research Fund Denmark (DFF – 7016-00359), by University of Southern Denmark, Odense University Hospital, and by Center for Personalized Response Monitoring in Oncology (PREMIO), Odense University Hospital, Odense, Denmark.

CLINICAL TRIAL INFORMATION

NCT03358589 (MESTAR)

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGMENT

We want to share our deepest acknowledgments to Marie Lykke Rasmussen and Susanne Geneser, who served as patient representatives and co-researchers in this study.
KEY POINTS

QUESTION: Is progressive disease detected earlier by CE-CT or 18F-FDG PET/CT used for response monitoring in metastatic breast cancer?

PERTINENT FINDINGS: Disease progression was detected earlier by 18F-FDG PET/CT than CE-CT in most patients (p < 0.0001).

IMPLICATIONS FOR PATIENT CARE: 18F-FDG PET/CT may improve treatment decisions by detecting progression earlier than CE-CT, preventing patients from receiving ineffective, potentially toxic treatments.

REFERENCES


**TABLES**

**TABLE 1.** Time-related detection of progression by CE-CT and $^{18}$F-FDG PET/CT (n = 87)

<table>
<thead>
<tr>
<th>Distribution of progression</th>
<th>n (%)</th>
<th>n (%)</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Progression seen first on $^{18}$F-FDG PET/CT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progression on both modalities, seen first on $^{18}$F-FDG PET/CT</td>
<td>26 (29.9)</td>
<td>43 (49.4)</td>
<td></td>
</tr>
<tr>
<td>Progression on $^{18}$F-FDG PET/CT only</td>
<td>17 (19.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Progression seen first on CE-CT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progression on both modalities, seen first on CE/CT</td>
<td>0 (0.00)</td>
<td>1 (1.15)</td>
<td></td>
</tr>
<tr>
<td>Progression on CE/CT only</td>
<td>1 (1.15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Progression on both modalities simultaneously</strong></td>
<td>11 (12.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>No progression on any modality</strong></td>
<td>32 (36.8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval
TABLE 2. Baseline characteristics of 87 patients with metastatic breast cancer

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>Age at diagnosis of MBC</td>
<td></td>
</tr>
<tr>
<td>Years, median (range)</td>
<td>72.7 (41.1-89.4)</td>
</tr>
<tr>
<td>Time from primary breast cancer to MBC</td>
<td></td>
</tr>
<tr>
<td>Years, median (range)</td>
<td>5.13 (0.00-38.1)</td>
</tr>
<tr>
<td>MBC diagnosis</td>
<td></td>
</tr>
<tr>
<td>De novo MBC</td>
<td>27 (31.0%)</td>
</tr>
<tr>
<td>First distant relapse of MBC</td>
<td>60 (69.0%)</td>
</tr>
<tr>
<td>ER status</td>
<td></td>
</tr>
<tr>
<td>Negative (0%)</td>
<td>12 (13.8%)</td>
</tr>
<tr>
<td>Positive (1-100%)</td>
<td>75 (86.2%)</td>
</tr>
<tr>
<td>HER2 status</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>80 (92.0%)</td>
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<tr>
<td>Positive</td>
<td>5 (5.75%)</td>
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<tr>
<td>Unknown</td>
<td>2 (2.30%)</td>
</tr>
<tr>
<td>Molecular subtype</td>
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</tr>
<tr>
<td>ER+ / HER2−</td>
<td>71 (81.6%)</td>
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<tr>
<td>ER+ / HER2 unknown</td>
<td>2 (2.30%)</td>
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<tr>
<td>HER2+ (ER±)</td>
<td>5 (5.75%)</td>
</tr>
<tr>
<td>Triple-negative</td>
<td>9 (10.3%)</td>
</tr>
<tr>
<td>First-line treatment</td>
<td></td>
</tr>
<tr>
<td>Endocrine therapy †</td>
<td>10 (11.5%)</td>
</tr>
<tr>
<td>Endocrine therapy † + cyclin-dependent kinase 4/6 ‡</td>
<td>60 (69.0%)</td>
</tr>
<tr>
<td>Chemotherapy §</td>
<td>12 (13.8%)</td>
</tr>
<tr>
<td>Chemotherapy § + Trastuzumab and Pertuzumab</td>
<td>4 (4.60%)</td>
</tr>
<tr>
<td>Chemotherapy § + Pembrolizumab</td>
<td>1 (1.15%)</td>
</tr>
<tr>
<td>Number of metastasis *</td>
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</tr>
<tr>
<td>1</td>
<td>1 (1.15%)</td>
</tr>
<tr>
<td>2-4</td>
<td>7 (8.05%)</td>
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<tr>
<td>≥5</td>
<td>79 (90.8%)</td>
</tr>
<tr>
<td>Organs involved *</td>
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<tr>
<td>Bone-only</td>
<td>23 (26.4%)</td>
</tr>
<tr>
<td>Lymph node only</td>
<td>4 (4.60%)</td>
</tr>
<tr>
<td>Visceral involvement</td>
<td>22 (25.3%)</td>
</tr>
<tr>
<td>Mixed (not visceral)</td>
<td>38 (43.7%)</td>
</tr>
</tbody>
</table>

Abbreviations: MBC, metastatic breast cancer; ER, estrogen receptor; HER2, human epidermal growth receptor 2

* Biomarker profile of metastatic lesion or concurrent local recurrence

† Aromatase inhibitor or Fulvestrant
‡ Palbociclib, Ribociclib, or Abemaciclib

§ Epirubicin, cyclophosphamide, taxanes, carboplatin, gemcitabine, vinorelbine, or capecitabine

* Combined CE-CT and ¹⁸F-FDG PET/CT assessment

* Bone-only metastasis ± breast ± axillary lymph nodes

** Mixed bone, lymph-node, lung, skin, or other metastases
**TABLE 3.** Reasons for first progression detected on CE-CT and $^{18}$F-FDG PET/CT in patients with measurable disease.

<table>
<thead>
<tr>
<th>Reasons for first progression</th>
<th>CE-CT $n$ (%)</th>
<th>$^{18}$F-FDG PET/CT $n$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>New lesions only</td>
<td>13 (48.1)</td>
<td>24 (55.8)</td>
</tr>
<tr>
<td>Increase in SLD$^\dagger$ or SULpeak$^\ddagger$ only</td>
<td>7 (25.9)</td>
<td>10 (23.3)</td>
</tr>
<tr>
<td>New lesions and increase in SLD$^\dagger$ or SULpeak$^\ddagger$ (combined)</td>
<td>5 (18.5)</td>
<td>6 (14.0)</td>
</tr>
<tr>
<td>Unequivocal progression of non-target lesions</td>
<td>2 (7.40)</td>
<td>3 (6.98)</td>
</tr>
<tr>
<td>Total</td>
<td>27 (100)</td>
<td>43 (100)</td>
</tr>
</tbody>
</table>

Abbreviations: SLD, sum of lesion diameter; SULpeak, standardized uptake value normalized by lean body mass

$^\dagger$ Increase of 20% in SLD

$^\ddagger$ Increase of 30% in SULpeak
Flowchart of 87 women monitored by $^{18}$F-FDG PET/CT and CE-CT during first-line treatment for metastatic breast cancer.
Combined ¹⁸F-FDG PET/CT and CE-CT every 9-12 weeks. ¹⁸F-FDG PET images not available during the study period.

FIGURE 2

Illustration of progression detected on CE-CT and ¹⁸F-FDG PET/CT but seen first on ¹⁸F-FDG PET/CT. The maximum intensity projection images and percentage change in the sum of diameters for CE-CT and RECIST 1.1 (blue line) and SULpeak for ¹⁸F-FDG PET/CT and PERCIST (red line). New lesions are shown as yellow dots.

Abbreviations: SULpeak, standardized uptake value normalized by lean body mass; P(M)D, progressive (metabolic) disease; P(M)R, partial (metabolic) response
Illustration of progression detected on CE-CT and $^{18}$F-FDG PET/CT simultaneously. The maximum intensity projection images and percentage change in the sum of diameters for CE-CT and RECIST 1.1 (blue line) and SULpeak for $^{18}$F-FDG PET/CT and PERCIST (red line). New lesions are shown as yellow dots.

Abbreviations: SULpeak, standardized uptake value normalized by lean body mass; P(M)D, progressive (metabolic) disease; P(M)R, partial (metabolic) response
Illustration of progression detected on $^{18}$F-FDG PET/CT only. The maximum intensity projection images and percentage change in the sum of diameters for CE-CT and RECIST 1.1 (blue line) and SULpeak for $^{18}$F-FDG PET/CT and PERCIST (red line). New lesions are shown as yellow dots.

Abbreviations: SULpeak, standardized uptake value normalized by lean body mass; PMD, progressive metabolic disease; PR, partial response; CMR, complete metabolic response
Illustration of progression detected on CE-CT only. The maximum intensity projection images and percentage change in the sum of diameters for CE-CT and RECIST 1.1 (blue line) and SULpeak for $^{18}$F-FDG PET/CT and PERCIST (red line). New lesions are shown as yellow dots.

Abbreviations: SULpeak, standardized uptake value normalized by lean body mass; PD, progressive disease; PMR, partial metabolic response
Kaplan-Meier estimate of time to detection of progression on A) CE-CT and $^{18}$F-FDG PET/CT ($n = 87$) and B) on $^{18}$F-FDG PET/CT to detection of progression on CE-CT ($n = 43$).

Abbreviations: CI, confidence interval
Response categories for CE-CT and $^{18}$F-FDG PET/CT for 517 follow-up scans. Response categories from visual assessments are in grey.

Abbreviations: NM, not measurable; PD, progressive (metabolic) disease; SD, stable (metabolic) disease; PR, partial (metabolic) response; CR, complete (metabolic) response
GRAPHICAL ABSTRACT
Women diagnosed with stage IV breast cancer  
\[ n = 114 \]

Excluded  
Missing biopsy confirmation \( (n = 5) \)  
No consent \( (n = 0) \)  
\[ n = 5 \]

Patients undergoing baseline  
\(^{18}\text{F-FDG PET and CE-CT} \)  
\[ n = 109 \]

Excluded  
Not eligible for systemic oncological treatment \( (n = 10) \)  
Left study or died before first follow-up \( (n = 12) \)  
\[ n = 22 \]

Baseline  
\(^{18}\text{F-FDG PET and CE-CT} \)  
\(^{18}\text{F-FDG PET available for detection of metastasis} \)  
\[ n = 87 \]

Follow-up  
\(^{18}\text{F-FDG PET/CT}^a \)  
Blinded to clinical decision-making  
\[ n = 87 \]  
PERCIST measurable  
\[ 76/87 = 87.4\% \]

Follow-up  
\(^{CE-CT}^a \)  
Used for clinical decision-making  
\[ n = 87 \]  
RECIST measurable  
\[ 51/87 = 58.6\% \]
(n = 11)

<table>
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<tr>
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<th>Nov 2018</th>
<th>Jun 2019</th>
<th>Oct 2019</th>
<th>End-of-study</th>
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<tbody>
<tr>
<td>% change in SLD and SULpeak</td>
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- CE-CT
- $^{18}$F-FDG PET/CT

**Baseline**

**Nadir**

**PD**

PR

PMR

PMD

First-line treatment
Epirubicine and cyclophosphamide

Second-line treatment
Vinorelbine
(n = 17)

End-of-study


% change in SLD and SULpeak

CE-CT  

\[ \text{Baseline} \quad \text{Nadir} \quad \text{PR} \quad \text{CMR} \]

\[ \text{PR} \quad \text{PMD} \]

\[ \text{PMD} \quad \text{PMD} \]

\[ \text{First-line treatment} \quad \text{Radiotherapy} \quad + \text{continuation of medical treatment} \]

Fulvestrant + CDK4/6 inhibitor
(n = 1)

Mar 2018  Sep 2018  End-of-study

% change in SLD and SUV\text{peak}

0  -30  -60

CE-CT  $^{18}\text{F}-\text{FDG PET/CT}$

Baseline

First-line treatment
Letrozole + CDK4/6 inhibitor

Second-line treatment
Fulvestrant

PD  PMR