Response Monitoring in Metastatic Breast Cancer: A Prospective Study Comparing ^{18}F-FDG PET/CT with Conventional CT

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This study aimed to compare contrast-enhanced CT (CE-CT) and ^{18}F-FDG PET/CT for response monitoring in metastatic breast cancer 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 metastatic breast cancer were enrolled prospectively and monitored using combined CE-CT and ^{18}F-FDG PET/CT every 9–12 wk 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 unmasked 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 versus ^{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 6 (1–11) follow-up scans. Progression was detected first by ^{18}F-FDG PET/CT in 43 (49.4%) of 87 patients and first by CE-CT in 1 (1.15%) of 87 patients ($P < 0.0001$). Excluding patients without progression ($n = 32$), progression was seen first on ^{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 6 mo (95% CI, 4.3–6.4 mo). At baseline, 76 (87.4%) of 87 patients had measurable disease according to PERCIST and 51 (58.6%) of 87 patients had measurable disease according to RECIST 1.1. Moreover, ^{18}F-FDG PET/CT provided 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 by CE-CT in most patients, with a potentially clinically relevant median 6-mo delay for CE-CT. More patients had measurable disease according to PERCIST than according to RECIST 1.1. The magnitude of the final benefit for patients is a perspective for future research.

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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*), and contrast-enhanced CT (CE-CT) is used widely in clinical practice. RECIST guidelines (RECIST 1.1) (*3*) are typically required when patients are monitored in clinical trials. However, CE-CT has low sensitivity for bone metastases and low specificity for liver metastases (*4–6*).

^{18}F-FDG PET/CT and PERCIST have been suggested to overcome the shortcomings of CE-CT (*4,6–8*). Changes in metabolic activity may appear before morphologic changes can be seen (*4,9*), giving ^{18}F-FDG PET/CT 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 that ^{18}F-FDG PET/CT is 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 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 (PD) was detected systematically earlier by one of the modalities, with the primary endpoint

TABLE 1
Time-Related Detection of Progression by CE-CT and ^{18}F-FDG PET/CT for 87 Patients

Distribution of progression	*n*	Difference
Progression seen first on ^{18}F-FDG PET/CT	43 (49.4%)	48%; 95% CI, 36%–60%; $P < 0.0001$
Progression on both modalities, seen first on ^{18}F-FDG PET/CT	26 (29.9%)	
Progression on ^{18}F-FDG PET/CT only	17 (19.5%)	
Progression seen first on CE-CT	1 (1.15%)	48%; 95% CI, 36%–60%; $P < 0.0001$
Progression on both modalities, seen first on CE-CT	0 (0.00%)	
Progression on CE-CT only	1 (1.15%)	
Progression on both modalities simultaneously	11 (12.6%)	
No progression on any modality	32 (36.8%)	

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, 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 gave written informed consent. The study was registered at ClinicalTrials.gov (NCT03358589) and followed the Declaration of Helsinki. Research Electronic Data Capture (RedCap; Vanderbilt University) and SharePoint (Microsoft) were used for data storage and management, and the results were reported using the Strengthening the Reporting of Observational Studies in Epidemiology guideline (*16*).

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

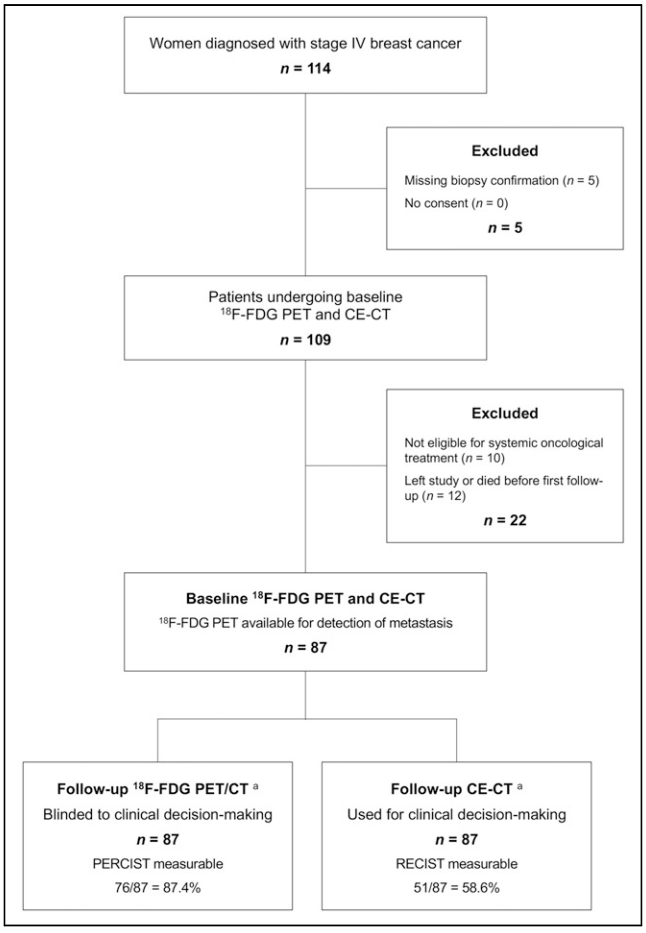

FIGURE 1. Flowchart of 87 women monitored by ^{18}F-FDG PET/CT and CE-CT during first-line treatment for MBC. [a]Combined ^{18}F-FDG PET/CT and CE-CT every 9–12 wk. ^{18}F-FDG PET images not available during study period.

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 the end of trial by November 30, 2020. Hence, in cases of change of oncologic treatment for reasons other than progression (i.e., toxicity or maximum dose of chemotherapy), the patient was still followed as mentioned. Data were derived from medical records, scan images, pathology, and scan reports.

Image Techniques

^{18}F-FDG PET/CT, including CE-CT imaging from top of skull to midthigh, was performed 60 ± 5 min after intravenous injection of 4 MBq of ^{18}F-FDG per kilogram of body weight. Blood sugar levels were measured routinely, and patients fasted at least 4 h before ^{18}F-FDG injection. All scans were performed according to the European Association of Nuclear Medicine guideline (*18*).

The PERCIST standardization criteria (*8*) were registered prospectively and are listed with supplemental image techniques in Supplemental Table 1 (supplemental materials are available at http://jnm.snmjournals.org).

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 masked ^{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 2 experienced radiologists made the CE-CT assessments used for clinical decision-making. In 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 unmasked at the end of the trial and assessed by one-lesion PERCIST (*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 3 nuclear medicine physicians assessed the scans. In cases of uncertainty, consensus was reached between the observer and a senior physician in nuclear medicine. Assessors of ^{18}F-FDG PET/CT were unaware of the CE-CT scan report and the clinical decision-making. The nadir scan was used as a reference in the PERCIST assessment to allow meaningful comparison with RECIST 1.1 (Supplemental Table 2).

Outcome Measures

The rate of earlier detection by one of the modalities was the primary endpoint. Progression was assigned in cases of new lesions, a 20% increase in the sum lesion diameter (CE-CT), a 30% increase in SUV normalized by lean body mass (SUL_{peak}, ^{18}F-FDG PET/CT), or unequivocal progression of nontarget 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 PD or progressive metabolic disease. In 18 instances (in 13 patients), progression was regarded as false-positive because PD was reported by CE-CT without clinical change of management and the following scan did not reveal further progression ($n = 9$) or because progressive metabolic disease was reported by ^{18}F-FDG PET/CT without further progression or resolution of ^{18}F-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 with medical records in June 2021. Change in treatment because of a clinically or image-guided identified progression or a confirmation on subsequent scans was considered a sign 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 1 of the 6 categories shown in Table 1. We report the 2 relative frequencies of ^{18}F-FDG PET/CT detecting progression first and CE-CT detecting progression first. We estimated the difference between them with a 95% CI and conducted a McNemar test for paired binary data (type I error, 5%, 2-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 2 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 between scans, 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 by 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-up, death, and final study scan as censoring events.

A preplanned interim analysis was conducted but had no impact on 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) and Excel (Microsoft).

TABLE 2
Baseline Characteristics of 87 Patients with MBC

Characteristic	Data
Age at diagnosis of MBC (y)	72.7 (41.1–89.4)
Time from primary breast cancer to MBC (y)	5.13 (0.00–38.1)
MBC diagnosis	
De novo MBC	27 (31.0%)
First distant relapse of MBC	60 (69.0)
ER status*	
Negative, 0%	12 (13.8)
Positive, 1%–100%	75 (86.2)
HER2 status*	
Normal	80 (92.0)
Positive	5 (5.75)
Unknown	2 (2.30)
Molecular subtype*	
ER+/HER2−	71 (81.6)
ER+/HER2 unknown	2 (2.30)
HER2+ (ER±)	5 (5.75)
Triple-negative	9 (10.3)
First-line treatment	
Endocrine therapy†	10 (11.5)
Endocrine therapy† + cyclin-dependent kinase 4/6‡	60 (69.0)
Chemotherapy§	12 (13.8)
Chemotherapy§ + trastuzumab + pertuzumab	4 (4.60)
Chemotherapy + pembrolizumab	1 (1.15)
Number of metastases‖	
1	1 (1.15)
2–4	7 (8.05)
≥5	79 (90.8)
Organs involved‖	
Bone only¶	23 (26.4)
Lymph node only	4 (4.60)
Visceral involvement	22 (25.3)
Mixed (not visceral)#	38 (43.7)

*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 ^{18}F-FDG PET/CT assessment.
¶Bone-only metastasis ± breast ± axillary lymph nodes.
#Mixed bone, lymph node, lung, skin, or other metastases.
ER = estrogen receptor; HER2 = human epidermal growth receptor 2. Qualitative data are number and percentage; continuous data are median and range.

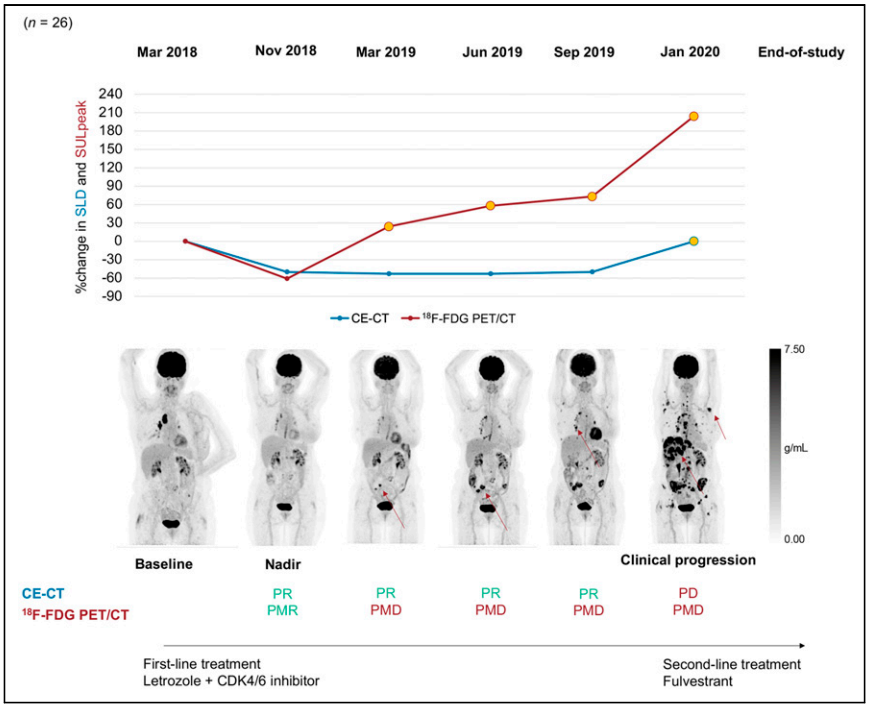

FIGURE 2. Illustration of progression detected by CE-CT and ^{18}F-FDG PET/CT but seen first on ^{18}F-FDG PET/CT. Shown are maximum-intensity projection images and percentage change in sum of diameters for CE-CT and RECIST 1.1 (blue line) and SUL_{peak} for ^{18}F-FDG PET/CT and PERCIST (red line). New lesions are shown as yellow dots. CDK4/6 = cyclin-dependent kinase 4/6; PMD = progressive metabolic disease; PMR = partial metabolic response; PR = partial response; SLD = sum of lesion diameter.

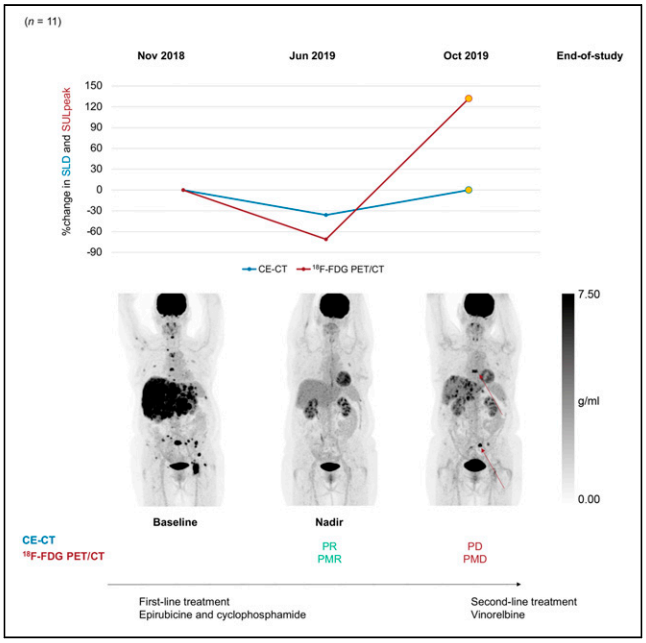

FIGURE 3. Illustration of progression detected by CE-CT and ^{18}F-FDG PET/CT simultaneously. Shown are maximum-intensity projection images and percentage change in sum of diameters for CE-CT and RECIST 1.1 (blue line) and SUL_{peak} for ^{18}F-FDG PET/CT and PERCIST (red line). New lesions are shown as yellow dots. PMD = progressive metabolic disease; PMR = partial metabolic response; PR = partial response; SLD = sum of lesion diameter.

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 (unaware of ^{18}F-FDG PET). A median of 6 scans (range, 1–11 scans) was performed per patient. The median follow-up time was 15.9 mo (range, 1.94–37.5 mo), 55 patients (63.2%) experienced a progression, and 1 patient died.

Baseline characteristics of included patients appear in Table 2 and Supplemental Table 4. HER2 was overexpressed in 5.75% of patients, 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 patients.

Detection of First Progression

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

Among 17 patients for whom progression was detected by ^{18}F-FDG PET/CT only, the consistency check after 7 mo revealed a subsequent change in treatment because of clinically or image-guided progression in 9 patients (52.9%; Fig. 4; Supplemental Fig. 2A). No treatment change had appeared in the remaining 8 patients, but (slow) progression could be confirmed on the subsequent scans (Supplemental Fig. 2B).

The detection of progression by CE-CT without detection by ^{18}F-FDG PET/CT in 1 patient led to a change in management (Fig. 5).

The median time to the detection of first progression was 24.3 mo (95% CI, 15.9 mo to infinity) and 14.9 mo (95% CI, 11.4–20.8 mo) for CE-CT and ^{18}F-FDG PET/CT assessment, respectively. Thus, a statistically significant difference was observed between the 2 modalities ($P < 0.001$; Fig. 6A). The median time from detection of progression by ^{18}F-FDG PET/CT to detection by CE-CT was 5.98 mo (95% CI, 4.27–6.41 mo; Fig. 6B).

Measurable Disease and Response Categories

Measurable disease at baseline was present in 51 (58.6%) and 76 (87.4%) of 87 patients for RECIST 1.1 and PERCIST, respectively. Of 11 patients not being measurable according to PERCIST, 7 patients (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, whereas stable disease was reported more often by CE-CT. Progression was detected by visual assessment in 18%

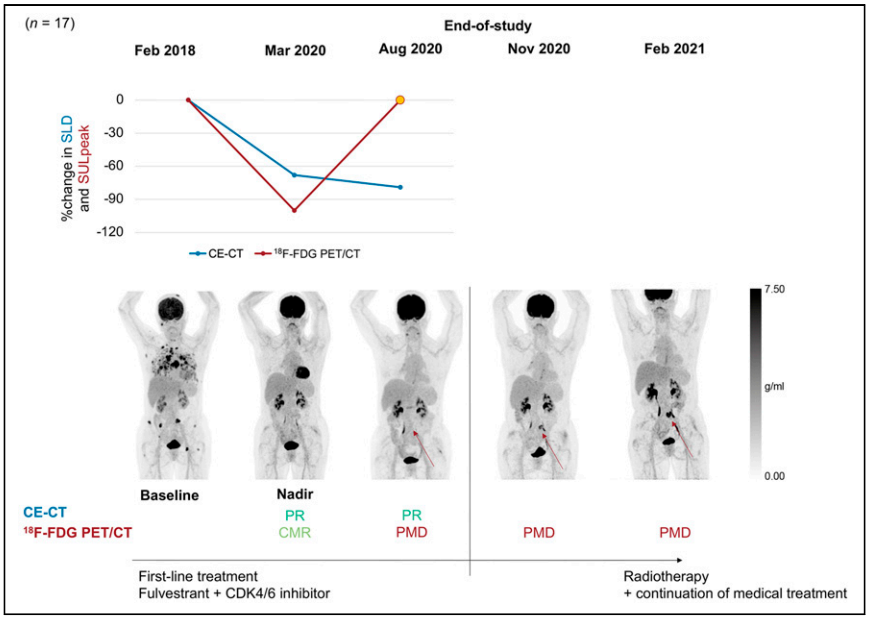

FIGURE 4. Illustration of progression detected by ^{18}F-FDG PET/CT only. Shown are maximum-intensity projection images and percentage change in sum of diameters for CE-CT and RECIST 1.1 (blue line) and SUL_{peak} for ^{18}F-FDG PET/CT and PERCIST (red line). New lesions are shown as yellow dots. CDK4/6 = cyclin-dependent kinase 4/6; PMD = progressive metabolic disease; PMR = partial metabolic response; PR = partial response; SLD = sum of lesion diameter.

(24/136) and 45% (21/47) of the total number of progressions detected by ^{18}F-FDG PET/CT and CE-CT, respectively.

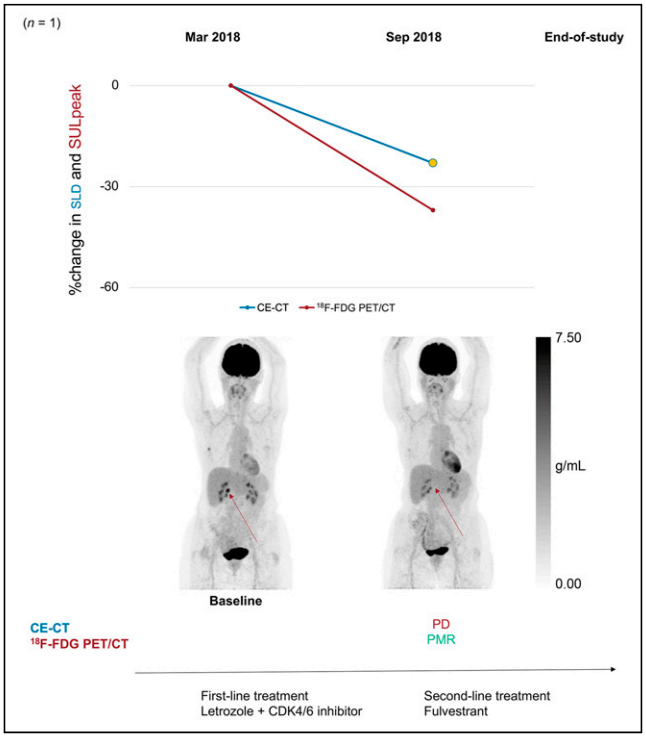

FIGURE 5. Illustration of progression detected by CE-CT only. Shown are maximum-intensity projection images and percentage change in sum of diameters for CE-CT and RECIST 1.1 (blue line) and SUL_{peak} for ^{18}F-FDG PET/CT and PERCIST (red line). New lesions are shown as yellow dots. CDK4/6 = cyclin-dependent kinase 4/6; PMR = partial metabolic response; SLD = sum of lesion diameter.

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 in MBC, progression was detected earlier by ^{18}F-FDG PET/CT than by CE-CT in most patients ($P < 0.0001$). A median delay of 6 mo 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 improved visualization of changes in response over time.

Detection of Progression

A high proportion of PET-detected PDs could be observed as continuous progression until detection by CE-CT. This implied that a true PD was present and that earlier detection could potentially impact clinical practice. In cases of progression seen only on ^{18}F-FDG PET/CT, a consistency check was made after the end of the trial. This revealed a clinical or image-guided change in management among half of these patients, thus suggesting true progression. The progression detected by ^{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 to indicate false progression since the progressing lesion resolved. The frequency of such findings was limited and equally distributed in both modalities.

TABLE 3
Reasons for First Progression Detected by CE-CT and ^{18}F-FDG PET/CT in Patients with Measurable Disease

Reason for first progression	CE-CT (*n*)	^{18}F-FDG PET/CT (*n*)
New lesions only	13 (48.1%)	24 (55.8%)
Increase in SLD* or SUL_{peak}† only	7 (25.9%)	10 (23.3%)
New lesions and increase in SLD* or SUL_{peak}† (combined)	5 (18.5%)	6 (14.0%)
Unequivocal progression of nontarget lesions	2 (7.40%)	3 (6.98%)
Total	27 (100%)	43 (100%)

*Increase of 20% in SLD.
†Increase of 30% in SUL_{peak}.
SLD = sum of lesion diameter.

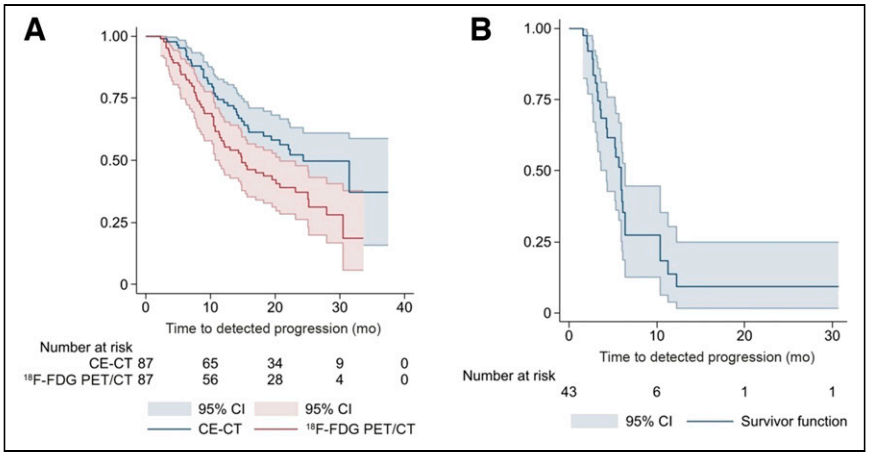

FIGURE 6. Kaplan–Meier estimates of time to detection of progression by CE-CT and ^{18}F-FDG PET/CT (n = 87) (A) and from detection of progression by ^{18}F-FDG PET/CT to detection by CE-CT (n = 43) (B).

^{18}F-FDG PET/CT for Response Monitoring

^{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 Ki-67 and low ^{18}F-FDG uptake (*22,23*), confirmed by this study with 7 of 11 patients who had no measurable disease of a lobular subtype.

The lack of standardization criteria has been suggested as a barrier to introducing ^{18}F-FDG PET/CT for response monitoring in 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 cutoff values of ±30% for PD or regressive disease, as suggested in PERCIST.

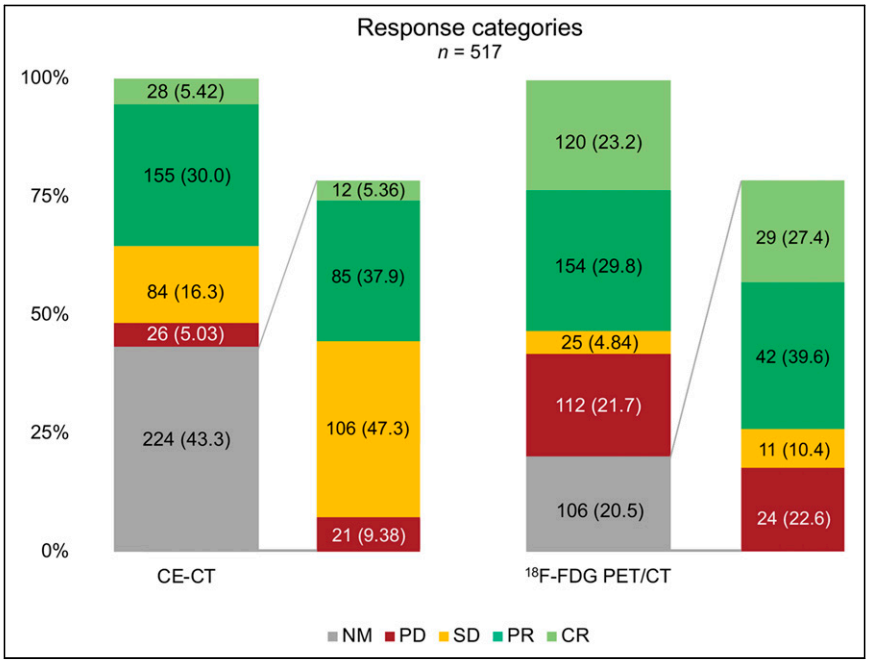

FIGURE 7. Response categories for CE-CT and ^{18}F-FDG PET/CT for 517 follow-up scans. Response categories from visual assessments are in gray. CR = complete (metabolic) response; NM = not measurable; PR = partial (metabolic) response; SD = stable (metabolic) disease.

Clinical Implications

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

Many patients with bone-only MBC are precluded from clinical trials because of nonmeasurability (*6*). ^{18}F-FDG PET/CT and PERCIST may allow more patients, including those with 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 markers of treatment efficacy (*29*), and treatment response is reported more frequently by ^{18}F-FDG PET/CT than by 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, in which 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 compares 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 nonrandomized single-center observational study. The nadir level of SUL_{peak} was used without international consensus. The follow-up time was relatively short such that no progression was observed in approximately 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 nonresponse earlier than conventional methods and preventing patients from receiving ineffective, potentially toxic treatments (*31,32*). In this study, progression was detected earlier by ^{18}F-FDG PET/CT. However, we cannot make firm conclusions about the long-term survival benefit of introducing ^{18}F-FDG PET/CT. We consider this and data on MR scans and circulation tumor DNA collected in the present study (NCT03358589) to be perspectives for

future research. Furthermore, stratified analyses within breast cancer–directed treatments could be relevant when comparing the 2 modalities.

CONCLUSION

Disease progression was detected earlier by ^{18}F-FDG PET/CT than by CE-CT in most patients, with a potentially clinically relevant 6-mo delay for CE-CT. More patients had measurable disease according to PERCIST than according to 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.

DISCLOSURE

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KEY POINTS

QUESTION: Is PD detected earlier by CE-CT or ^{18}F-FDG PET/CT used for response monitoring in MBC?

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

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

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