MEDICAL IMAGING—ORIGINAL ARTICLE

Diagnostic value of ^{68}Ga-DOTATATE PET-CT imaging for staging of ER^{+}/PR^{+} HER2- breast cancer patients with metastatic disease: Comparison with conventional imaging with bone scan, diagnostic CT and ^{18}F-FDG PET-CT in a prospective pilot trial

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Abstract

Introduction: ^{18}F-Fludeoxyglucose PET-CT (FDG) is increasingly used to stage breast cancer. Most breast cancers express the Oestrogen Receptor (ER) and Progesterone Receptor (PR), and this subtype demonstrates lower activity on FDG imaging. Somatostatin receptors (SSTR) offer a potentially improved radiotracer target for ER^{+}/PR^{+} breast cancer. We present the first *in vivo* clinical study comparing ^{68}Ga-DOTATATE PET-CT (DOTA) to FDG and conventional imaging (bone scan and diagnostic CT), in metastatic ER^{+}/PR^{+} human epidermal growth factor receptor 2 (HER2) negative breast cancer.
Methods: Patients with clinically progressive metastatic ER^{+}/PR^{+} HER2- breast cancer underwent restaging with DOTA, FDG and conventional imaging. Scans were analysed visually, and semi-quantitatively. Wilcoxon-Rank Scoring was used to assess significance.
Results: Ten women (mean age 57 years) underwent imaging. 8/10 demonstrated disease on both DOTA and FDG. 2/10 positive on conventional imaging, but DOTA^{-}/FDG^{-}, and had no disease progression at 1-year follow-up. Heterogeneity of uptake was seen between DOTA and FDG with 5 bone lesions DOTA^{+}/FDG^{-} and 1 bone lesion FDG^{+}/DOTA^{-}. Twenty-one visceral lesions were FDG^{+}/DOTA^{-} (2 patients), with 10/21 identified on conventional imaging. Maximum standard uptake values (SUV max) of DOTA were greater than FDG (10.9 vs. 6.6, P = ns). Four sites were biopsied (3 patients). 3/4 had high ER/PR expression (mean DOTA SUV max 9.4) and 1/4 low ER/PR expression (DOTA SUV max 3.1).
Conclusion: Whilst we have not demonstrated DOTA to be superior to FDG in staging of ER^{+}/PR^{+} breast cancers, DOTA may have a role in assessing HR status and treatment decisions; further evaluation of this is warranted.

Key words: ^{68}Ga-DOTATATE; metastatic breast cancer; PET-CT.

Introduction

Breast cancer is the most commonly diagnosed neoplasm in women worldwide and the leading cause of cancer-related mortality in women.[1] The majority of breast cancer tumours express hormone receptors (HR), including Oestrogen Receptor (ER) and Progesterone Receptor (PR).[2] Human epidermal growth factor receptor 2 (HER2) is expressed in only 20% to 25% of breast cancer. Consequently, HR^{+}/HER2^{-} subtype accounts for around three quarters of all breast cancer tumours.[3]

The prognosis of metastatic breast cancer is poor, with an estimated five-year survival of 26%.[2] New diagnostic and therapeutic techniques are needed to improve

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outcome. Conventional imaging in metastatic breast cancer includes diagnostic CT and bone scan. ^{18}F-Fludeoxyglucose PET-CT (FDG) is increasingly used for the detection of distant metastasis in patients with breast cancer.[4] However, tumours expressing HR have significantly lower FDG uptake than tumours that do not express HR.[5] Somatostatin receptors (SSTR) are variably expressed in primary breast cancer tumours, and there is a positive correlation between several receptor subtypes (SSTR1, SSTR2 and SSTR4) and HR$^+$ tumours.[6,7] ^{68}Ga-DOTATOC has also been shown to be more efficient than FDG in detecting breast tumours in an animal model of breast cancer expressing SSTR subtype SSTR2.[8]

There is currently no published literature evaluating the clinical utility of SSTR imaging in metastatic breast cancer in humans. This study therefore aims to produce preliminary evidence for the diagnostic value of ^{68}Ga-DOTATATE PET-CT (DOTA) compared with FDG and conventional imaging in women undergoing staging for metastatic HR$^+$/HER2$^-$ breast cancer.

Methods

Study design

This prospective pilot study was undertaken at a single Australian institution (St Vincent's Hospital Sydney, Australia). Enrolment criteria included clinically progressive metastatic ER$^+$/PR$^+$ HER2$^-$ breast cancer requiring restaging (FDG, bone scan and CT chest, abdomen and pelvis). The receptor status was confirmed on histology reports of a primary or metastatic tumour. Informed written consent was obtained from all patients and Institutional Human Research Ethics Committee approval was obtained (HREC/18/SVH/56). Clinical information regarding age, time since diagnosis, initial pathology including pathological stage, previous and current treatments, sites of disease, histology of subsequently biopsied metastatic lesions if performed, and available serum tumour biomarkers were collected. All imaging studies were undertaken between October 2018 and June 2019. FDG, DOTA, ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP) bone scan and diagnostic CT chest, abdomen and pelvis were performed within a three-week period (median days between scans 3, IQR 1.25–7).

FDG protocol

FDG scans were performed using a standardised protocol with a Philips Ingenuity TOF-PET/64-slice CT scanner. Following a 6-hour fast, patients were injected with ^{18}F-FDG intravenously (3.5 MBq/kg, median dose 237.5 MBq). The blood sugar levels (BSL) were <11 mmol/L (median BSL 5.5 mmol/L) prior to injection. One hour after injection (median time 62 min), the non-contrast low dose CT scan was obtained using the following CT parameters: slice thickness of 2 mm, with 2-mm slices, soft-tissue reconstruction kernel, 120 kV and 50 mAs, pitch of 0.828, 600 mm field of view and a 512 matrix. Non-contrast low dose CT scan was followed by a whole body PET scan (skull vertex to mid-thigh) at 2 min per bed position. Emission data were corrected for randoms, scatter and decay using the Phillips Body-dynamic.xml and body.xml reconstruction protocol.

DOTA protocol

^{68}Ga-DOTATATE was produced on-site compliant to the Good Laboratory Practices procedure using a TRASIS-automated radiopharmacy cassette. Radiopharmacy quality control was undertaken using a high-pressure liquid chromatography method. Following completion of the bone scan, patients were injected with ^{68}Ga-DOTATATE intravenously (2.6 MBq/kg, median dose 178 MBq). One hour after the injection (median time 62.5 min), low dose CT and PET scan were performed using the same PET-CT scanner and with similar parameters to FDG.

Bone scan

Bone scan was performed using dual-head gamma cameras (Discovery 670) equipped with a low energy general-purpose collimator. Patients were injected with 900 MBq of ^{99m}Tc-MDP (median dose 920 MBq) and imaging was performed 3–4 h after tracer injection. Whole body sweeps, high-count oblique views and SPECT-CT of the spine were acquired.

Diagnostic CT scan

Diagnostic CT scan of the chest, abdomen and pelvis with contrast (75 mL of Omnipaque 300 mgI/mL) was performed using the following CT parameters: slice thickness of 1 mm, with 0.5-mm slices, soft-tissue reconstruction kernel, 120 kV, 80 mAs (chest) and 127 mAs (abdomen and pelvis), pitch of 1.172 (chest) and 0.798 (abdomen and pelvis), 600 mm field of view, and a 512 × 512 matrix.

Image interpretation

All PET-CT images were viewed and reported using the Philips Fusion Viewer. All studies were interpreted by three credentialed nuclear medicine physicians with experience in reporting FDG and DOTA images. Interpretation of both PET studies for each patient was performed by the same physician. Data for all scans were analysed both visually and quantitatively. Visual analysis included a four-point certainty scoring scale (definitely negative, equivocal probably negative, equivocal probably positive, definitely positive), as well as anatomical site of lesions. Equivocal lesions were subsequently reviewed by a second nuclear medicine physician for consensus scoring as positive or negative. Quantitative analysis was

undertaken using MIM software to measure standardised uptake value (SUV) max and SUV mean. Bone scans were interpreted by the same nuclear medicine physicians. CT scans were interpreted by two experienced oncology radiologists using RECIST criteria.

Statistical analysis

Quantitative PET results were compared at per patient level and all measurable lesions between the two PET tracers were compared using Wilcoxon Rank Scoring. All results were reported using Median (IQR).

Results

Demographics

Baseline characteristics are summarised in Table 1. Ten patients were enrolled, and undertook DOTA imaging at the time of FDG and conventional imaging to restage for clinically suspected progressive disease. Eight patients presented with recurrent breast cancer following initial surgery for their primary breast tumour, while two patients first presented with *de novo* metastatic disease and therefore had their breast tumours still in situ at the time of the study. All patients had prior lines of systemic therapy in the metastatic setting.

DOTATATE and FDG patient analysis

Eight out of the 10 patients demonstrated positive findings on both DOTA and FDG, while two patients were negative on both PET tracers. No patient was positive on DOTA or FDG alone. Two patients without detectable disease on both DOTA and FDG had multiple positive osteoblastic and sclerotic lesions on conventional imaging. They both had clinically stable disease at 1-year follow-up, and no change in systemic therapy.

Table 1. Patient characteristics

Variable	Number	IQR
Median age (years)	57	48–64
Median time from diagnosis (years)	2	1–6
Type of primary cancer		
Invasive ductal carcinoma	8	
Invasive lobular carcinoma	1	
Unknown	1	
Stage at diagnosis		
Localised	8	
Metastatic (*de novo*)	2	
Number of lines of prior therapy		
1	4	
2	2	
3	2	
>3	2	
Most recent therapy		
CDK4/6 inhibitor +/− aromatase inhibitor	5	
Selective oestrogen receptor degrader (SERD)	3	
Aromatase inhibitor alone	1	
PARP inhibitor	1	

Quantitative per patient analysis

Whole body quantitative analysis demonstrated that SUV max was higher for DOTA than FDG though not statistically significant (10.9 vs. 6.6, $P = 0.08$). SUV mean was not different (3.1 vs. 2.9, P = ns).

Per-lesion analysis

The number of visually detectable lesions on DOTA, FDG, and conventional imaging is summarised in Table 2. A similar total number of lesions were visually identified on DOTA, FDG and conventional imaging (96 vs. 113 vs. 104, P = ns). Five bone lesions were identified on DOTA not present on FDG ($DOTA^+/FDG^-$) (Fig. 1) and one bone lesion detected on FDG not present on DOTA ($FDG^+/DOTA^-$). There were 34 bone lesions identified on DOTA that were not detectable on conventional imaging and 35 bone lesions were identified on conventional imaging not present on DOTA. There were 21 visceral lesions that were $FDG^+/DOTA^-$, including 16 liver metastases (Fig. 2) from one patient and five pleural metastases from another patient. Of these, eight of the liver metastases and two of the pleural metastases were identified on CT ($CT^+/DOTA^-$). DOTA, FDG and CT were concordant in detecting two primary breast lesions (Fig. 3), one chest wall lesion and six nodal metastases. DOTA and FDG identified three additional nodal metastases not detected on CT.

Biopsy of metastatic lesions

Three patients had biopsies of metastases performed (four metastatic sites biopsied in total) and receptor status reassessed. Three of the metastatic sites (right hilar node, sub-carinal node and right chest wall) had high expression of ER/PR (95%/80%, 95%/80% and 95%/50%, respectively) and demonstrated significant DOTA avidity (SUV max 8.9, 5.8 and 13.5, respectively) (Fig. 4a). In contrast, the pleural metastasis showed low ER/PR expression (2%/0% compared with 98%/90% in its initial primary tumour) and demonstrated lower DOTA avidity (SUV max 3.1) (Fig. 4c).

Table 2. Visualised lesions on DOTA vs. FDG vs. conventional imaging

Site	DOTA	FDG	Conventional Imaging
Node	9	9	6
Bone	78	74	79
Visceral (liver, pleura and lung)	6	27	16
Muscle (chest wall)	1	1	1
Breast primary	2	2	2
Total number of lesions	96	113	104

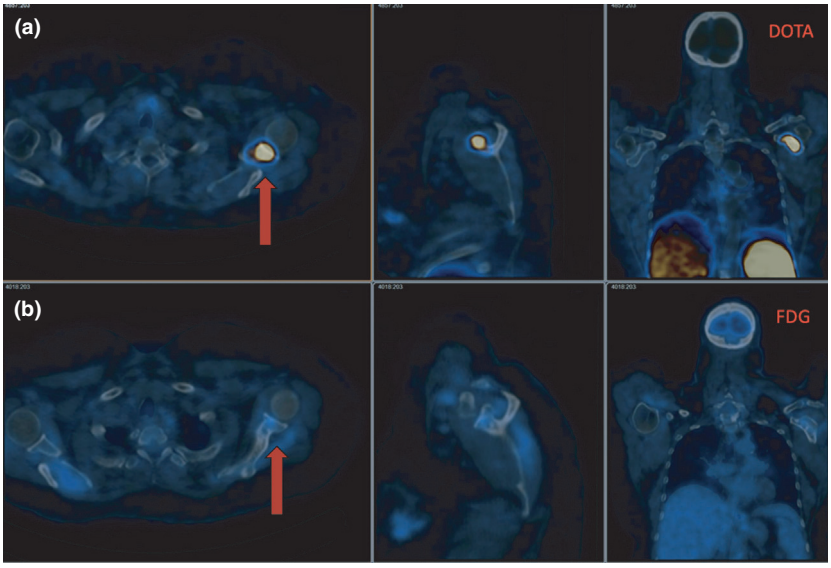

Fig. 1. Left glenoid metastatic lesion (red arrow) is intensely avid on DOTA (a) but non-avid on FDG (b).

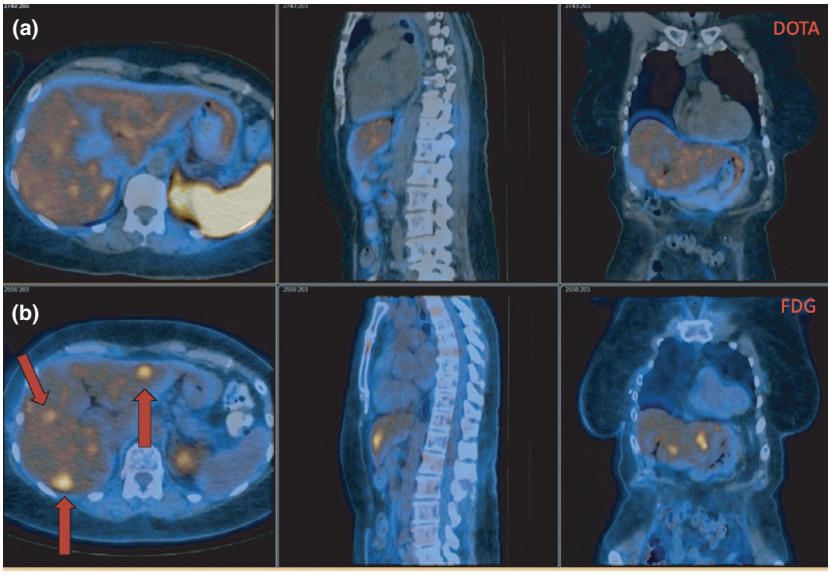

Fig. 2. Hepatic metastases (red arrows) not detected on DOTA (a) but moderately avid on FDG (b).

Discussion

FDG PET-CT is used increasingly in the staging of breast cancer. The subtype ER^+/PR^+ however demonstrates lower FDG avidity than ER^-/PR^- $HER2^+$ or triple negative subtypes. The SSTR has been suggested as an alternative radiotracer target of ER^+/PR^+ subtypes. Our study compared the use of DOTA with FDG PET and conventional imaging in staging of metastatic ER^+/PR^+ HER2- breast cancer.

Our study has not demonstrated superiority of DOTA over FDG in staging patients with metastatic ER^+/PR^+ $HER2^-$ breast cancer. DOTA and FDG were equally sensitive in detecting metastatic disease in a majority of the patients (8/10) and there were no patients whose disease was positive on FDG or DOTA alone. Two out of 10 patients had negative findings on both DOTA and FDG, but positive bone lesions on conventional imaging (Fig. 5). These lesions probably represent inactive/treated disease, as reflected by stable tumour markers and their clinical status at 1-year follow-up.

The total lesional detection rate of DOTA was comparable to FDG and conventional imaging for primary breast tumours, nodal and bone metastases. Although total

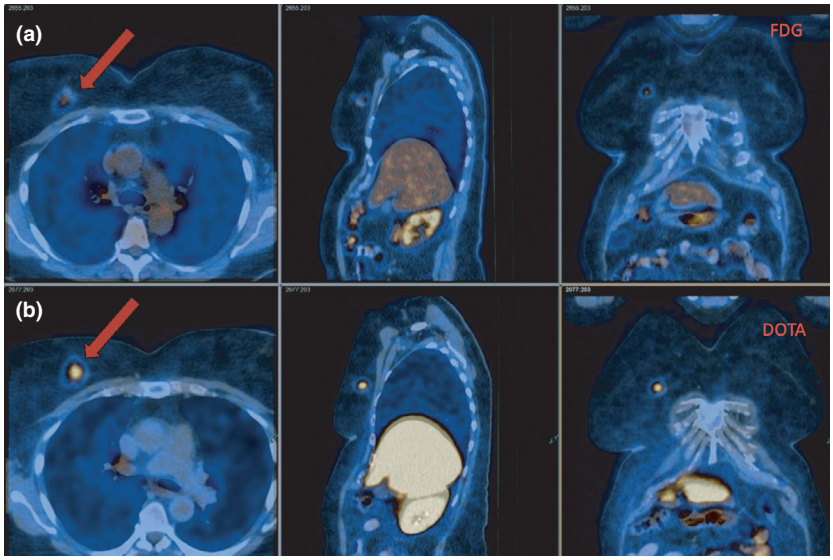

Fig. 3. Primary breast lesion (red arrow) mildly avid on FDG (a) and moderately avid on DOTA (b).

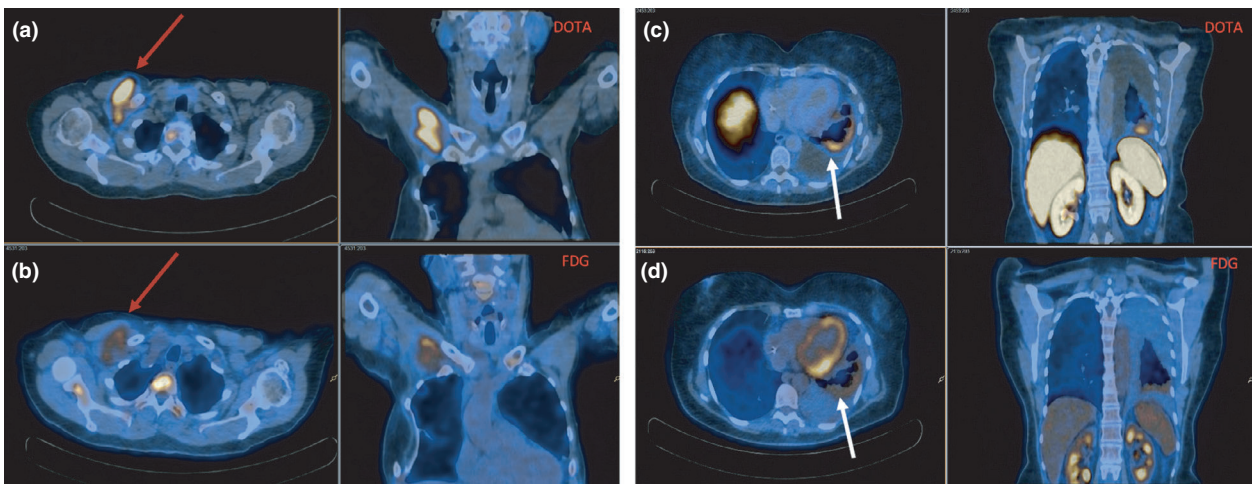

Fig. 4. Intensity of DOTA uptake and ER/PR expression on biopsy of metastatic lesions. The right chest wall metastasis (red arrow) which has high expression of ER (95%) and PR (50%) is intensely avid on DOTA (a). It is less avid on FDG (b). The left pleural metastasis (white arrow) with very low expression of ER (2%) and negative PR expression (0%) is only mildly avid on DOTA (c) and minimally avid on FDG (d).

lesion detection rate between PET tracers and conventional imaging in bony metastases was comparable, site detection differed between the two modalities to a large extent (34 bone lesions DOTA^{+}/conventional imaging-, 35 bone lesions conventional imaging^{+}/DOTA^{-}). The discordant findings between PET tracers and conventional imaging are likely related to whether the bony lesions are lytic, sclerotic, mixed or invisible types on CT, as previously reported by Nakai et al.[9]

DOTA demonstrated a lower detection rate of visceral lesions compared with FDG. However, lesions that were FDG^{+}/DOTA^{-} (21 in total), originated from only two patients, potentially reflecting two common clonal mutations with reduced SSTR expression. Two primary breast lesions in our study were positive on both DOTA and FDG. DOTA avidity in a breast primary has been previously reported by Elegeti et al.[10] In their retrospective study, 33 ^{68}Ga-DOTATOC PET/CT scans were undertaken for staging of neuroendocrine tumours. Analysis identified four breast lesions with abnormal tracer uptake both visually and semi-quantitatively. Histological evaluation of the suspicious lesions revealed two with neuroendocrine metastases and two primary breast malignancies.

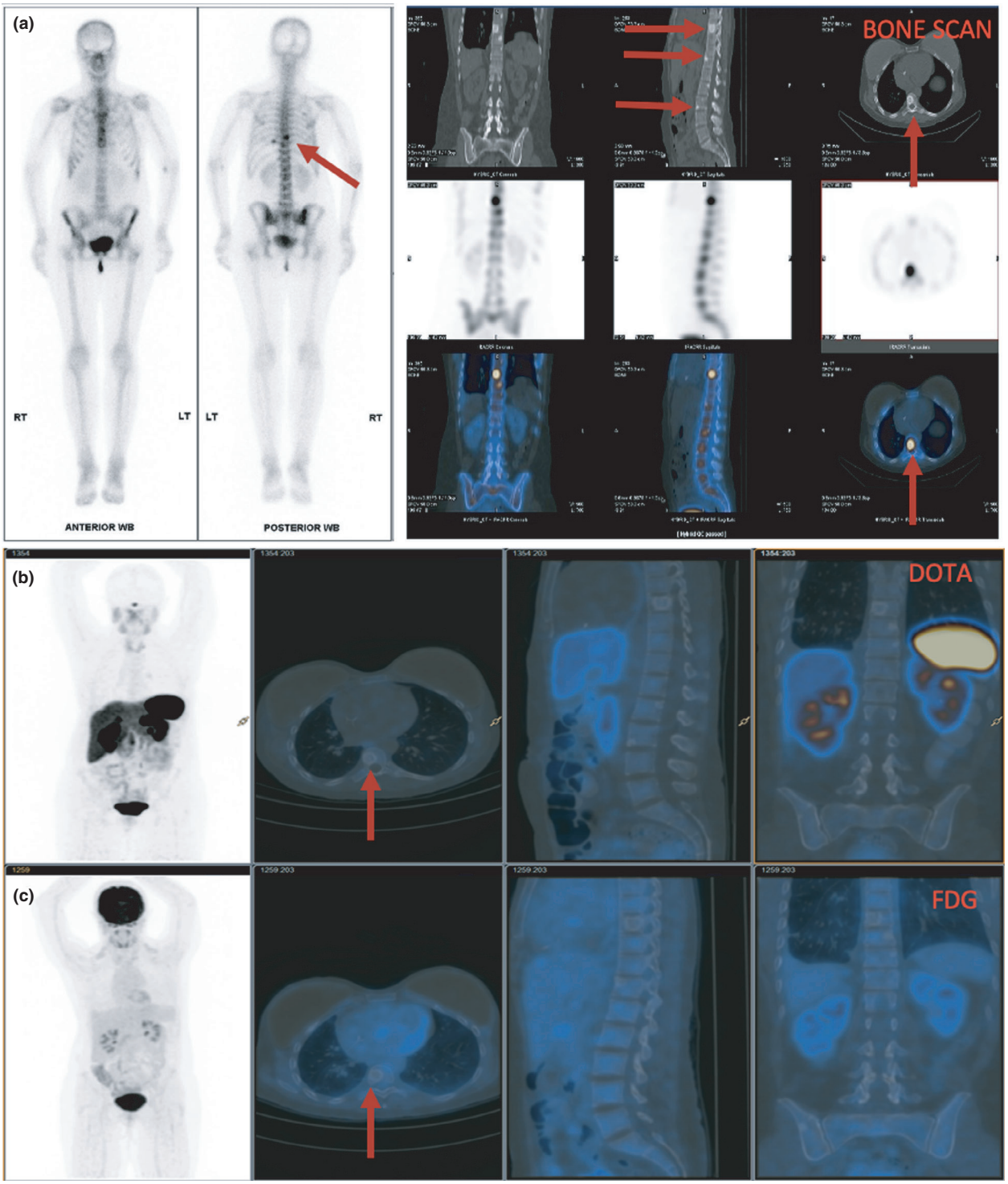

Fig. 5. Patient with positive findings on conventional imaging but negative on PET studies. Whole body bone scan with SPECT/CT (a) showed multiple osteoblastic and sclerotic lesions (arrows) which are negative on both DOTA (b) and FDG (c).

Within each DOTA and FDG image, we found significant heterogeneity of inter-lesional tumour intensity. This is not a surprising finding given the high heterogeneity of the primary tumour, the cellular plasticity driving metastatic breast cancer,[11,12] and previously reported genomic evolution in breast cancer metastases and relapse.[13]

Overall, the mean SUV max for DOTA was higher than FDG, though did not reach statistical significance.

A novel aspect of our study was the comparative histological and imaging evaluation of four metastatic sites. The three tumour sites with high level of ER/PR expression (>90%) demonstrated high DOTA intensity. By contrast, a metastatic site with only low ER/PR positivity (2%/0%) had low DOTA avidity (Fig. 4). Loss of hormone receptors in metastases has been well described in breast cancer and is associated with resistance to endocrine therapy and poor outcomes.[14] Our findings suggest that DOTA avidity may be a non-invasive means of assessing the HR expression in metastatic sites, an advantage it would have over conventional imaging and FDG PET. Information on HR expression may help determine the optimum treatment modality for the individual patient.

While this study is limited by the small numbers of participants, this pilot study is the first study in humans investigating the diagnostic value of DOTA imaging in staging of metastatic ER^+/PR^+ $HER2^-$ breast cancer and provides some novel insights into its utility and the biology of SSTR in breast cancer.

In conclusion, DOTATATE PET-CT was not shown to be superior to FDG in staging patients with metastatic ER^+/PR^+ $HER2^-$ breast cancer. However, findings from metastatic biopsies in our study suggest that the strength of HR^+ status may have an association with avidity seen on DOTA. DOTA may have a future role in assessing HR status to help guide treatment. Further evaluation with greater patient numbers is required.

Acknowledgements

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Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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