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^{18}F-FDG PET/CT for the early prediction of the response rate and survival of patients with recurrent or metastatic breast cancer

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Abstract. The present study aimed to explore the value of fludeoxyglucose F 18 positron emission tomography-computed tomography (PET/CT) for the early prediction of chemotherapy remission rates and survival in patients with recurrent and metastatic breast cancer. A total of 24 patients diagnosed with recurrent or metastatic breast cancer between 2009 and 2014 were enrolled. All patients underwent a PET/CT examination prior to (PET/CT1) and following (PET/CT2) chemotherapy. Differences of PET/CT1 maximal standardized uptake values (SUV_{max}), PET/CT2 SUV_{max}, ΔSUV_{max} and the ΔSUV_{max}% between objective remission (OR) and non-OR groups were measured. Survival differences between OR and non-OR groups and the overall survival (OS) between metabolic responsive and metabolic non-responsive groups were analyzed. In the present study, it was revealed that ΔSUV_{max} and ΔSUV_{max}% were significantly higher in the OR group compared with the non-OR group (P<0.001). Overall survival was significantly prolonged in the OR and metabolic responder groups compared with their respective control groups (P<0.001 and P<0.01, respectively). ΔSUV_{max}% were significantly positively associated with OS (r^2=0.266; P<0.01). In conclusion, PET/CT may be valuable for the early prediction of the chemotherapy efficacy and survival of patients with recurrent or metastatic breast cancer.

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Introduction

In the United States of America (USA), breast cancer is the most common malignant tumor type in women, and recurrence is the primary reason for the high mortality rates that result from this disease (1,2). A previous study demonstrated that 3-10% of patients with breast cancer present with metastatic disease at diagnosis in Europe and the United States (3). According to previously published, recurrent and metastatic rates of breast cancer are as high as 20-30% in USA (4). Assessment of tumor burden changes is an important feature used for the clinical evaluation of cancer therapeutic methods, and predicting the efficacy of direct individual therapy is a clinical challenge (5). Response evaluation criteria in solid tumors (RECIST), which is an anatomical assessment of tumor burdens using imaging methods including computed tomography (CT) and magnetic resonance imaging (MRI), has been used to evaluate therapeutic efficacy; however, its sensitivity and accuracy is limited (6). Tumor types with necrosis or fibrosis are difficult to distinguish from one another, and there is a time lag between tumor shrinking and tumor cell death as metabolic tissue changes precede morphological changes (7). Fluorine-18 fludeoxyglucose positron emission tomography-CT (^{18}F-FDG PET/CT) imaging may not only provide anatomical information, including tumor size, but may also reflect biochemical and metabolic changes in the body at the cellular and molecular level (8). This is important as these biochemical and metabolic changes occur earlier than anatomical changes (9). A key question considered by the RECIST Working Group in developing RECIST is whether it is appropriate to move from an anatomical unidimensional assessment of tumor burden to a functional assessment using PET/CT, as it still requires appropriate clinical validation (10).

^{18}F-FDG PET/CT has been documented to predict the curative effect of neoadjuvant chemotherapy in patients with breast cancer, however whether ^{18}F-FDG PET/CT may predict the curative effect of chemotherapy for patients with recurrent or metastatic breast cancer is unexplored (11-13). Therefore, the value of ^{18}F-FDG PET/CT for the early prediction of the response rate and survival for patients with recurrent or metastatic breast cancer was investigated in the present study.

Materials and methods

Patients. A total of 24 female patients (mean age, 49.54; age range, 31-73 years) were included in the present study between January 2009 and December 2014 at Suzhou Kowloon Hospital (Jiangsu, China) and Renji Hospital (Shanghai, China). Inclusion criteria included patients with biopsy-proven recurrent or metastatic breast cancer who were administrated anthracyclines or taxene regimens (capecitabine/docetaxel, or epirubicin/paclitaxel) as a first-line treatment. Exclusion criteria were as follows: Patients with pregnancy or known diabetes; aged younger than 18 years; not able to undergo serial PET/CT scans; no tumor uptake at baseline, or ineligibility for first-line chemotherapy with anthracyclines or taxene regimes. Ethical approval of the Human Clinical and Research Ethics Committees of Kowloon Hospital was obtained and all the patients provided written informed consent. Patient data are presented in Table I.

Objective remission (OR) patients included those who acquired complete remission and partial remission following chemotherapy, and the remaining patients were considered non-OR. Tumor response was determined clinically and radiographically based on CT or MRI data using RECIST1.1 criteria for every 2 courses of treatment (50 mg/m^2 D1 epirubicin and 150 mg/m^2 D1 paclitaxel i.v., every 21 days; or 1,000 mg/m^2 capecitabine bid po d1-14 and 75 mg/m^2 doxetaxel d1 i.v., every 21 days) (10).

^{18}F-FDG PET/CT imaging and image analysis. For PET/CT, a GE Discovery LS PET/CT scanner (Siemens AG, Munich, Germany) was used, and the half-high width of the PET horizontal space resolution was 4.8 mm. ^{18}F-FDG (purity >95%) was provided by Shanghai Kexin Biotech Co., Ltd. (Shanghai, China).

All patients were imaged prior to and following chemotherapy, and fasted for 6-8 h prior to imaging. Patients were administered ^{18}F-FDG (0.15 mCi/kg) through the contralateral elbow vein of the diseased breast. Patients were positioned and scanned using 16 row helical CT (160 kV; 100 mA; slice thickness 5 mm), and PET was conducted in the same range. For the whole body, 6-8 bed positions were scanned with 3 min per bed position and 3D data were collected. CT and PET fused images were reconstructed iteratively using a 3-dimensional row action maximum likelihood algorithm with a CT-derived attenuation correction, as previously described (11).

Image analysis. Maximal standard uptake values (SUV_{max}) were established by automatically drawing regions of interest using software (PET Syngo, version 4.1.1; Siemens AG), based on the plane with the SUV_{max} cross-section with a threshold of 50% SUV_{max}. The PET/CT1 examination was performed within 2 weeks prior to treatment initiation, and the PET/CT2 examination was performed at the end of the first treatment course. The SUV calculation was based on the following formula: SUV = C (kBq/g)/[ID (kBq)/W (g)], where C represents the radioactive concentration of local tissue, ID represents the injected dose, and W represents body weight. The change in SUV was calculated using the following formula: ΔSUV_{max} = PET/CT1 SUV_{max} - PET/CT2 SUV_{max}. The metabolic response was calculated using the following formula: SUV change rate (ΔSUV_{max}%) = [(PET/CT1 SUV_{max} - PET/CT2 SUV_{max})/PET/CT1 SUV_{max}] x100%. The SUVmax threshold between the tumor tissue and normal breast tissue was 2.5. The ΔSUV_{max} threshold was 20%. Sensitivity and specificity were 88 and 100%, respectively. Patients with a ΔSUV_{max} ≥20% were considered to be metabolic responding, and patients with a ΔSUV_{max} <20% were classed as metabolic non-responders.

Statistical analysis. The data were analyzed using SPSS 17.0 (SPSS, Inc., Chicago, IL, USA). Measurement data were presented as the mean ± standard deviation analyzed using an unpaired Student's t-test. A χ^2 test was used to analyze the metabolic response. The survival curve was produced using the Kaplan-Meier method. Cox regression analysis was used to analyze the association between SUV change rate and patient overall survival (OS). P<0.05 was considered to indicate a statistically significant difference.

Results

Comparisons of ΔSUV_{max}, ΔSUV_{max}%, and OS between OR and non-OR groups. Statistical analysis indicated that the difference in PET/CT1 SUV_{max} between OR and non-OR groups was not statistically significant (Fig. 1A; Table II). Although the PET/CT2 SUV_{max} of the OR group was lower compared with the non-OR group following chemotherapy, this difference was not statistically significant (Fig. 1B; Table II). The ΔSUV_{max} and ΔSUV_{max}% of the OR group were revealed to be significantly higher compared with the non-OR group (P<0.001; Fig. 1C and D; Table II). Survival analysis indicated that the survival time for the OR group was significantly longer compared with that of the non-OR group (P<0.001; Fig. 1E; Table III).

Comparison of OS between metabolic responders and metabolic non-responders. The ΔSUV_{max} threshold was 20%. Patients with a ΔSUV_{max} of ≥20% were classed as the metabolic responding group, and patients with a ΔSUV_{max} of <20% were classed as the metabolic non-responders group. The OS for the metabolic responders group was significantly better compared with the non-responders group (P<0.01; Fig. 2; Table IV).

Association between ΔSUV_{max}% and patient OS. ΔSUV_{max}% and OS of patients were revealed to be significantly positively associated (r^2=0.266, P<0.01; Fig. 3; Table V).

Case study

In March 2009, a 60-year-old female patient who presented with left breast masses and received a left breast modified radical operation was admitted to the Suzhou Kowloon Hospital, Shanghai

Table I. Clinical characteristics of patients with breast cancer.

Characteristic	Number of patients (%)
Number of patients	24 (100)
Mean age, years (range)	49.54 (31-73)
Organ metastasis	
Single organ metastasis	10 (41.67)
Multiple organ metastasis	14 (58.33)
Histological grade	
G2	8 (33.33)
G3	16 (66.67)
Estrogen/progesterone receptor status	
Positive	14 (58.33)
Negative	10 (41.67)
Her-2 status	
Positive	10 (41.67)
Negative	14 (58.33)
Treatment condition	
First-line treatment	20 (83.33)
Second-line treatment	4 (16.67)

Her-2, human epidermal growth factor receptor 2.

Jiaotong School of Medicine (Suzhou, China). Postoperative pathology indicated left breast infiltrating ductal carcinoma, and metastasis was identified in 3/12 ipsilateral axillary lymph nodes from the lymphadenectomy procedure. Immunohistochemistry analysis was performed as described in our previous study (14). The present study identified that the patient was estrogen receptor (ER) negative, progesterone receptor (PR) positive and human epidermal growth factor receptor (Her)2^{++}. Fluorescence *in situ* hybridization (FISH) confirmation for Her-2 and antigen Ki67 was not performed at this time. The patient was administered chemotherapy with a 5-fluorouracil, epidoxorubicin and cyclophosphamide regimen for 6 cycles and tamoxifen as endocrine therapy for 1.5 years. By March 2011, the patient had whole body bone pain and presented with redness and swelling, and nodular changes of the left chest wall. Physical examination confirmed multiple swollen superficial lymph nodes, an enlarged liver and multiple areas of bone pain. PET/CT indicated an increased FDG metabolism on the left side of the chest wall, left supraclavicular lymph nodes, left axillary lymph nodes, and lesions in the liver and the vertebra bones. The pathological results of a chest wall rebiopsy confirmed an infiltrating ductal carcinoma. Immunohistochemistry revealed that the patient was ER^{+}, PR^{-}, Her-2^{++} and FISH confirmation was performed for Her-2 (15). The patient was administered chemotherapy with a paclitaxel, carboplatin and Herceptin® regimen. At the end of the first cycle, PET/CT confirmed that the SUV of the patient's left chest wall, bone and liver metastases were significantly lower than before. In the first and second years following chemotherapy, PET/CT confirmed a normal SUV (Fig. 4A and B; Table VI). The patient remained in long-term follow-up, and was still alive with a stable disease status at 52 months post-evaluation and her overall survival was 76 months post-operative.

Therefore, following one cycle of chemotherapy, the SUV of the liver and bone metastases was notably decreased, the ΔSUV_{max} exceeded 50% and the SUV_{max} reached the threshold. Thus, tumor proliferation was inhibited. In the first year following chemotherapy, tumor proliferation continued to be strongly inhibited and metastases disappeared.

Discussion

In the past 20 years, ^{18}F-FDG PET/CT had been increasingly used for cancer imaging, diagnosis, staging, restaging and treatment monitoring (16). ^{18}F-FDG PET/CT scans may distinguish tumor necrosis from viable tumor types, so it was introduced for the sequential monitoring of the tumor response to treatment for breast cancer in 1993, and responding patients exhibited a rapid and significant decline in SUV, whereas non-responding patients did not (7). Since that report, numerous studies have confirmed that PET is useful for response assessment for various other tumor types (17-20). There is interest in using ^{18}F-FDG PET/CT to quickly assess tumor responses to therapy, and the fact that PET may identify patients that respond to treatment is attractive for personalized health care (16). A baseline PET scan prior to and following 1 or 2 cycles of treatment may be used to confirm effective treatment for that specific tumor and patient (21). Rapid readouts of the effect of treatment and prompt patient shifting to more suitable therapy types for that particular patient could save money, time and preserve the patient's health (12,16).

PET for the identification of patients who will respond to treatment for breast cancer has been investigated in several clinical studies. Previous studies reported that PET, following a single pulse of chemotherapy, may predict complete pathologic response (sensitivity 90%; specificity 74%) (20,22). A substudy from the NeoALTTO trial investigated the efficacy of ^{18}F-FDG PET/CT to identify patients with a greater likelihood of complete response following treatment with trastuzumab, lapatinib or the two drugs combined, and increased complete responses were associated with greater SUV_{max} reductions (23). In another trial, PET/CT assessments were used to identify Her-2-positive early responders to docetaxel plus trastuzumab therapy, and early PET assessment following two cycles helped identify non-responders to neoadjuvant therapy (24). Pathological complete responses were noted in 37 (53.6%, 95% CI 41.2-65.7) of the PET-predicted responders and 6 (24.0%, 95% CI 9.4-45.1) non-responders, so PET may be used to select treatment responders (24).

In contrast, a study of 98 women with stage II-III breast cancer indicated that PET/CT scans may not accurately predict neoadjuvant chemotherapy responses (25). However, a number of studies suggest that ^{18}F-FDG PET/CT may predict the curative effect of chemotherapy in patients with recurrent or metastatic breast cancer. Gennari *et al* (26) reported that semi-quantitative FDG-PET scanning of metastatic breast cancer sites revealed a rapid and significant decrease in tumor glucose metabolism soon following the first course of treatment in patients (N=6) responsive to first-line chemotherapy, but no significant decrease was observed in non-responding patients (N=3 with stable disease). Retrospective analysis performed with 102 women indicated that decreased SUV following treatment was an independent predictor of response duration

Table II. Comparisons of PET/CT1 SUV_{max}, PET/CT2 SUV_{max}, ΔSUV_{max} and ΔSUV_{max}% between OR and non-OR groups.

Groups	N	Mean ± standard deviation	P-value	95% CI
PET/CT1 SUV_{max}			0.5484	-1.370-2.510
OR	12	7.128±0.654		
Non-OR	12	6.558±0.668		
PET/CT2 SUV_{max}			0.0655	-3.519-0.119
OR	12	4.398±0.581		
Non-OR	12	6.098±0.657		
ΔSUV_{max}			0.0001	1.266-3.274
OR	12	2.730±0.241		
Non-OR	12	0.460±0.420		
ΔSUV_{max}%			0.0004	19.380-55.750
OR	12	41.190±4.318		
Non-OR	12	3.622±7.633		

PET/CT1, positron emission tomography-computed tomography prior to chemotherapy; PET/CT2, positron emission tomography-computed tomography following chemotherapy; SUV_{max}, maximal standardized uptake value; OR, objective remission; CI, confidence interval.

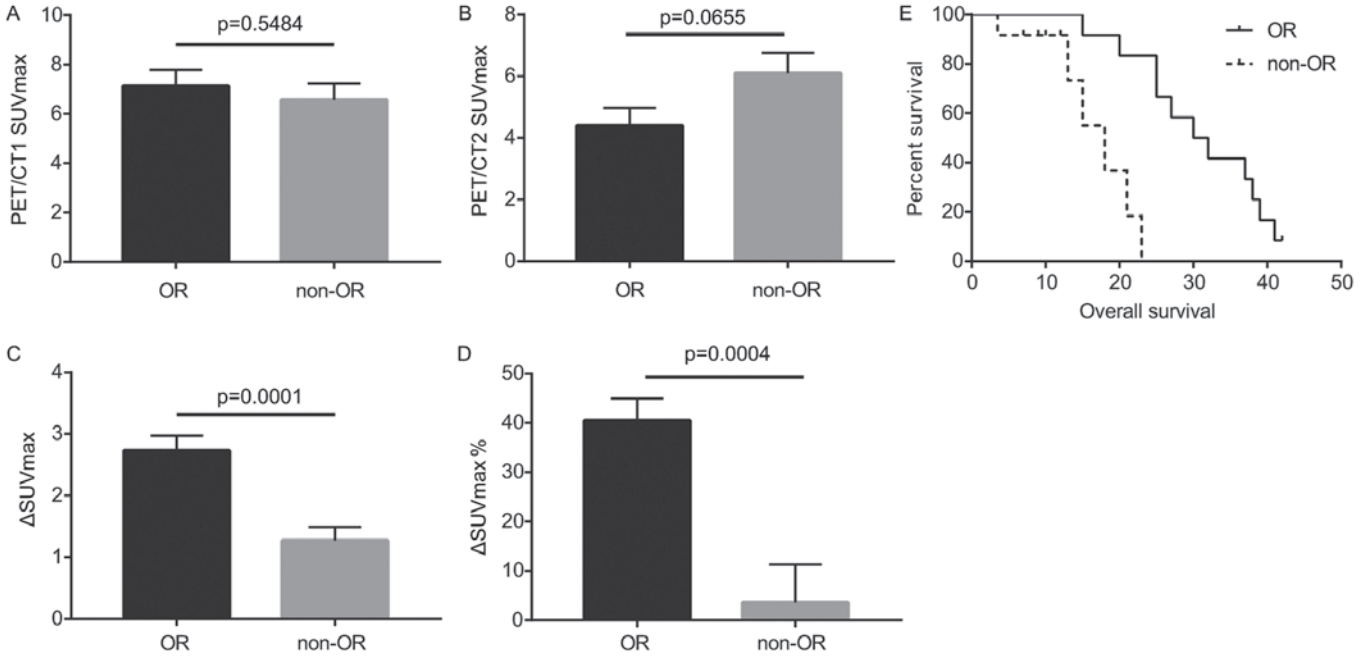

Figure 1. Comparisons of the PET/CT1 SUV_{max}, PET/CT2 SUV_{max}, ΔSUV_{max}, ΔSUV_{max}%, and OS between OR and non-OR groups. (A) Comparison of PET/CT1 SUV_{max} between OR and non-OR groups. (B) Comparison of PET/CT2 SUV_{max} between OR and non-OR groups. (C) Comparison of ΔSUV_{max} between OR and non-OR groups. (D) Comparison of ΔSUV_{max}% between OR and non-OR groups. Comparisons shown by lines. (E) Comparison of OS between OR and non-OR groups. PET/CT1, positron emission tomography-computed tomography prior to chemotherapy; PET/CT2, positron emission tomography-computed tomography following chemotherapy; SUV_{max}, maximal standardized uptake value; ΔSUV_{max}, change in standardized uptake value; OR, objective remission; OS, overall survival.

in patients with bone metastases (27), smaller decreases in SUV (or increases in SUV) were associated with a shorter time to progression, and that SUV_{max} tertiles are valuable as a prognostic variables (28,29). Another retrospective study with 122 patients with recurrent/metastatic breast cancer confirmed these results (30). Several studies have indicated that changes in PET/CT SUV are associated with changes in tumor volume as determined by bone scans, MRI and/or CT (9,11,31). However, to the best of our knowledge, no studies to evaluate comparative test performance between modalities have been performed, and associations between imaging results and subsequent clinical decisions are unclear. Evidence for imaging effectiveness in predicting treatment response amongst patients with metastatic breast cancer with visceral metastasis is limited, thus more rigorous research is required to confirm the value of imaging in this patient population. Here, ΔSUV_{max} and ΔSUV_{max}% were significantly higher in the OR group compared with the non-OR group (P<0.001). Survival was significantly prolonged in the

Table III. Comparison of the survival between OR and non-OR groups.

Groups	N	Survival time (months) (mean ± standard deviation)	P-value	95% CI
OR	12	30.917±2.411	0.0004	26.192-35.642
Non-OR	12	16.792±2.085		12.704-20.879
Overall	24	26.134±2.382		21.464-30.803

OR, objective remission; CI, confidence interval.

Table IV. Comparison of the overall survival between metabolic responders and non-responders.

Groups	N	Survival time (months) (mean ± standard deviation)	P-value	95% CI
Responder	14	29.923±2.421	0.0017	25.177-34.669
Non-rwesponder	10	16.550±2.582		11.489-21.611
Overall	24	26.134±2.382		21.464-30.803

CI, confidence interval.

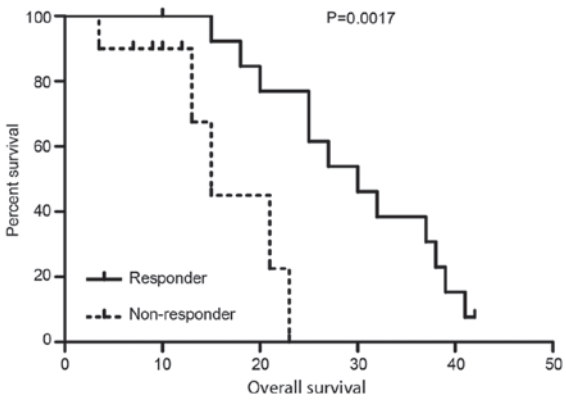

Figure 2. Comparison of the overall survival between metabolic responders and non-responders.

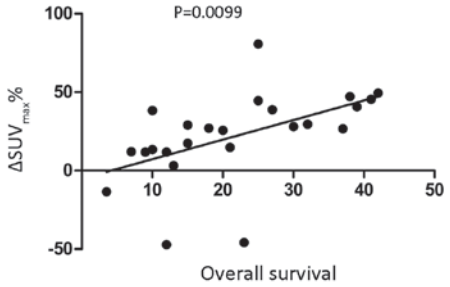

Figure 3. Association between ΔSUV_{max}% and patient overall survival. SUV_{max}, maximal standardized uptake value.

OR and the metabolic responders group compared with the respective control groups (P<0.001 and P<0.01, respectively) and the ΔSUV_{max}% was significantly positively associated with survival time (r^2=0.266, P<0.01). To the best of our knowledge, this is the first prospective study with a large population to confirm the early prediction of the response and survival of patients with non-bone metastatic breast cancer.

Table V. Association between SUV_{max} change rate and patient overall survival.

Variable	N	Mean ± standard deviation	r^2	P-value
SUV_{max} change rate (%)	24	22.058±28.319	0.266	0.0099
Survival time (months)	24	21.854±11.727		

SUV_{max}, maximal standardized uptake value.

Qualitative and quantitative approaches to ^{18}F-FDG PET response assessment have been applied and require a consistent PET methodology (9). The cutoff value used to distinguish responders from non-responders has been inconsistent between different studies (16,32,33). Statistically significant changes in tumor SUV occur in careful test-retest studies of high-SUV tumor types, with a change of up to 20% in SUVs of a region that is 1 cm or larger in diameter; however, medically relevant beneficial changes are often associated with a 30% or greater decline in SUVs (34). The more extensive the therapy, the greater the decline in SUVs with the most effective treatments (32). Important components of the proposed RECIST criteria requiring a 30% decline in SUVs for 'response' and criteria to define the progression of tumor-absent new lesions are uncertain (34). The optimum cutoff was 20% for the present study, and this value is not dissimilar from the 2-30% thresholds used by other studies (35-37).

The optimal method for standardizing PET assessment for response in breast cancer cases is not certain. Initially, women with newly diagnosed breast cancer exhibit a rapid and significant decline in SUVs within 8 d of the start of

Table VI. SUV and ΔSUV_{max} for fludeoxyglucose F 18 positron emission tomography-computed tomography imaging of metastases following chemotherapy.

Metastasis	SUV_{max}	SUV_{max} (following the first cycle chemotherapy)	ΔSUV_{max}	SUV change rate (%)	SUV_{max} (two years following chemotherapy)
Liver	8.4	4.1	-51.19	51.19	2.2
Bone	7.75	3.6	-53.55	53.55	2.3

SUV_{max}, maximal standardized uptake values.

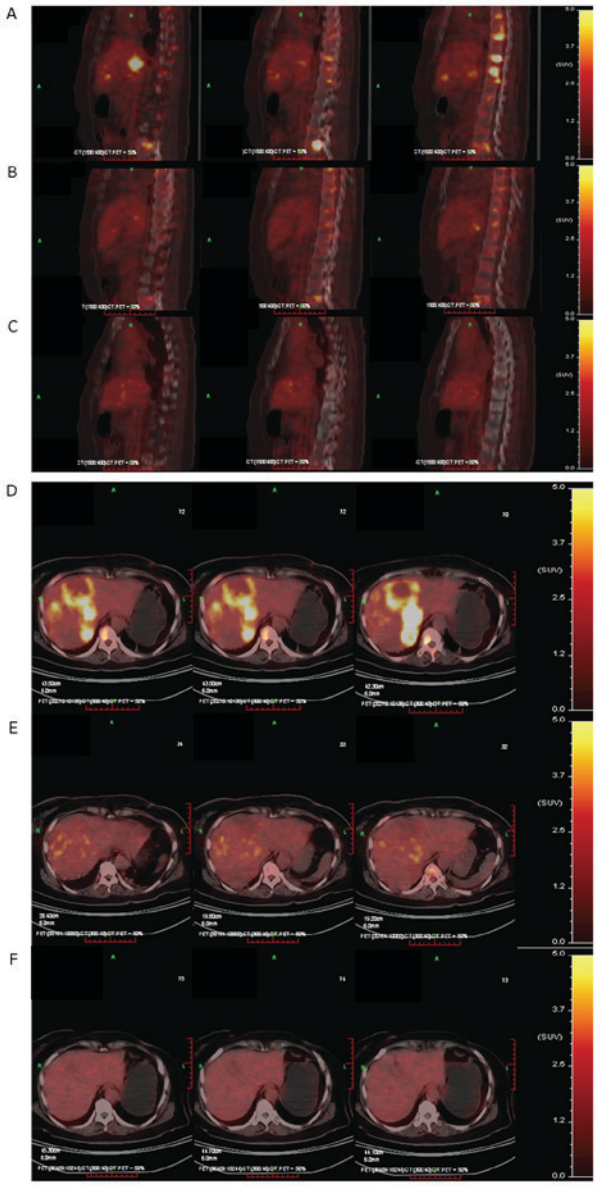

Figure 4. Changes in SUV imaging for ^{18}F-FDG PET/CT and thoracolumbar spine metastases at different times (1 week prior to chemotherapy, 1 week after the first cycle of chemotherapy and two years post chemotherapy) prior to and following chemotherapy. SUV of ^{18}F-FDG PET/CT imaging of baseline metastases (A) prior to chemotherapy, (B) subsequent to the first chemotherapy cycle and (C) two years following chemotherapy. Changes in SUV imaging of ^{18}F-FDG PET/CT and liver metastases at different times prior to and following chemotherapy. SUV of ^{18}F-FDG PET/CT imaging of baseline metastases (D) prior to chemotherapy, (E) subsequent to the first chemotherapy cycle and (F) two years following chemotherapy. ^{18}F-FDG PET/CT, fluorine-18 fludeoxyglucose positron emission tomography-computed tomography; SUV, standardized uptake value.

effective treatment. These parameters decline with each progressive treatment in responding patients, antedating changes in tumor size (34). Qualitative visual analysis for six responding patients revealed a decreased delineation of tumor masses from background activity soon following the first course of treatment (26) whereas other investigators used two, three and six cycles of chemotherapy for monitoring responses to chemotherapy in metastatic breast cancer cases or for targeted therapy (23,38-40). This raises the question on the optimal timing of assessment. The multi-center design, not compensated by a real standardization effort, and differences in assessment timing may explain the lower positive predictive value and the negative predictive value data recorded in the present study compared with single-center studies (16,32,33).

Therefore, there is a predictive value in PET/CT results and for an international consensus for standardizing PET/CT assessments. The results of the present study revealed that PET analysis two weeks following one cycle of salvage chemotherapy may be a viable option in this setting, but these results require validation with larger, randomized phase 3 trials. These data will help to design future studies and clarify the usefulness of PET/CT in treatment decisions and expand the arsenal of response-adaptive or risk-adaptive treatment approaches.

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Availability of data and materials

The datasets generated and analyzed during the current study are not publicly available due to unpublished data but are available from the corresponding author on reasonable request.

Author's contributions

All authors have seen the manuscript and approved submission. FCZ, HYX, YML and YCX designed the project, collected and analyzed the data and wrote the manuscript. JJL, YFX, BC, YJY, NNY and SLS were involved in selecting eligible patients. YML and YCX supervised the project and checked the manuscript.

Ethics approval and consent to participate

Ethical approval was obtained from the Human Clinical and Research Ethics Committees of Kowloon hospital and all patients signed written informed consent.

Consent for publication

Written informed consent for the publication of the patient's clinical details was obtained.

Competing interests

The authors declare that they have no competing interests.

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