18F-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 ASUV 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 ASUV 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=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.

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 (18F-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).
18F-FDG PET/CT has been documented to predict the curative effect of neoadjuvant chemotherapy in patients with breast cancer; however whether 18F-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 18F-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 inability 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 radio graphically based on CT or MRI data using RECIST1.1 criteria for every 2 courses of treatment (50 mg/m2 D1 epirubicin and 150 mg/m2 D1 paclitaxel i.v., every 21 days; or 1.000 mg/m2 capecitabine bid po d1-14 and 75 mg/m2 doxetaxel d1 i.v., every 21 days) (10).

18F-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. 18F-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 18F-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 (SUVmax) were established by automatically drawing regions of interest using software (PET Syngo, version 4.1.1; Siemens AG), based on the plane with the SUVmax cross-section with a threshold of 50% SUVmax. 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: \( \Delta \text{SUV}_{\text{max}} = \frac{\text{PET}_{\text{CT2}} \text{SUV}_{\text{max}} - \text{PET}_{\text{CT1}} \text{SUV}_{\text{max}}}{\text{PET}_{\text{CT1}} \text{SUV}_{\text{max}}} \times 100\% \). The SUVmax threshold between the tumor tissue and normal breast tissue was 2.5. The \( \Delta \text{SUV}_{\text{max}} \) threshold was 20%. Sensitivity and specificity were 88 and 100%, respectively. Patients with a \( \Delta \text{SUV}_{\text{max}} \geq 20\% \) were considered to be metabolic responding, and patients with a \( \Delta \text{SUV}_{\text{max}} < 20\% \) 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 \( \chi^2 \) 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 \( \Delta \text{SUV}_{\text{max}} \), \( \Delta \text{SUV}_{\text{max}}\% \), and OS between OR and non-OR groups. Statistical analysis indicated that the difference in PET/CT1 SUVmax between OR and non-OR groups was not statistically significant (Fig. 1A; Table II). Although the PET/CT2 SUVmax 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 \( \Delta \text{SUV}_{\text{max}} \) and \( \Delta \text{SUV}_{\text{max}}\% \) 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 \( \Delta \text{SUV}_{\text{max}} \) threshold was 20%. Patients with a \( \Delta \text{SUV}_{\text{max}} \geq 20\% \) were classed as the metabolic responding group, and patients with a \( \Delta \text{SUV}_{\text{max}} < 20\% \) 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 \( \Delta \text{SUV}_{\text{max}}\% \) and patient OS. \( \Delta \text{SUV}_{\text{max}}\% \) and OS of patients were revealed to be significantly positively associated (r=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.
Therefore, following one cycle of chemotherapy, the SUV of the liver and bone metastases was notably decreased, the ΔSUV\textsubscript{max} exceeded 50% and the SUV\textsubscript{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, \(^{18}\text{F}-\text{FDG}\) PET/CT had been increasingly used for cancer imaging, diagnosis, staging, restaging and treatment monitoring (16). \(^{18}\text{F}-\text{FDG}\) 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 \(^{18}\text{F}-\text{FDG}\) 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 pathological response (sensitivity 90%; specificity 74%) (20,22). A substudy from the NeoALTTO trial investigated the efficacy of \(^{18}\text{F}-\text{FDG}\) 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\textsubscript{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 \(^{18}\text{F}-\text{FDG}\) 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 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 (Her2)+++. 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, epodoxorubicin and cyclophosphamide regimen for 6 cycles and tamoxifen as endocrine therapy for 1.5 years. By March 2011, the patient had whole 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.
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

| Groups | N | Mean ± standard deviation | P-value | 95% CI  |
|--------|---|--------------------------|---------|--------|
| PET/CT1 SUV_max | | | | |
| OR | 12 | 7.128±0.654 | 0.5484 | -1.370-2.510 |
| Non-OR | 12 | 6.558±0.668 | | |
| PET/CT2 SUV_max | | | | |
| OR | 12 | 4.398±0.581 | 0.0655 | -3.519-0.119 |
| Non-OR | 12 | 6.098±0.657 | | |
| ΔSUV_max | | | | |
| OR | 12 | 2.730±0.241 | 0.0001 | 1.266-3.274 |
| Non-OR | 12 | 0.460±0.420 | | |
| ΔSUV_max% | | | | |
| OR | 12 | 41.190±4.318 | 0.0004 | 19.380-55.750 |
| 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.
OR and the metabolic responders group compared with the respective control groups (P<0.001 and P<0.01, respectively) and the ΔSUVₘₐₓ% was significantly positively associated with survival time (r²=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.

Qualitative and quantitative approaches to ¹⁸F-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 SUVₘₐₓ 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 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                                    | 1.2704  | 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-responder      | 10 | 16.550±2.582                                    |         | 11.489-21.611 |
| Overall            | 24 | 26.134±2.382                                    |         | 21.464-30.803 |

CI, confidence interval.

Table V. Association between SUVₘₐₓ change rate and patient overall survival.

| Variable                      | N  | Mean ± standard deviation | r²    | P-value |
|-------------------------------|----|---------------------------|-------|---------|
| SUVₘₐₓ change rate (%)        | 24 | 22.058±28.319             | 0.266 | 0.0099  |
| Survival time (months)        | 24 | 21.854±11.727             |       |         |

SUVₘₐₓ, maximal standardized uptake value.

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

Figure 3. Association between ΔSUVₘₐₓ% and patient overall survival. SUVₘₐₓ, maximal 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 YCY designed the project, collected and analyzed the data and wrote the manuscript. JYL, YFX, BC, YJY, NNY and SLS were involved in selecting eligible patients. YML and YCY 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.

References
1. Wang D, Lu P, Zhang H, Luo M, Zhang X, Wei X, Gao J, Zhao Z and Liu C: Oct-4 and Nanog promote the epithelial-mesenchymal transition of breast cancer stem cells and are associated with poor prognosis in breast cancer patients. Oncotarget 5: 10803-10815, 2014.
2. Jemal A, Bray F, Center MM, Ferlay J, Ward E and Forman D: Global cancer statistics. CA Cancer J Clin 61: 69-90, 2011.
3. Suryanarayana Deo SV and Jha D: Role of Loco-regional surgery in metastatic breast cancer. J Cancer Res Ther 9: 181-186, 2013.
4. Berman AT, Thakral AD, Hwang WT, Solin LJ and Vapiwala N: Incidence and patterns of distant metastases for patients with early-stage breast cancer after breast conservation treatment. Clin Breast Cancer 13: 88-94, 2013.
5. Shanbhogue AK, Karnad AB and Prasad SR: Use of F-18 FDG PET/CT for detection of peritoneal carcinomatosis; a systematic review and meta-analysis. Br J Radiol 91: 20170519, 2018.
6. Wahl RL, Zasadny K, Helvie M, Specht JM, Tam SL, Kurland BF, Berman AT, Thukral AD, Hwang WT, Waikar S, Whitaker T, Ah-See AK, Eremin O, et al: Positron emission tomography using [(18)F]-fluorodeoxy-D-glucose to predict the pathologic response of breast cancer to primary chemotherapy. J Clin Oncol 18: 1676-1688, 2000.
7. Gebhart G, Gámez C, Holmes E, Robles J, García C, Cortés M, de Azambuja E, Fauria K, Van Dooren V, Aktan G, et al: [(18)F]-FDG PET/CT for early prediction of response to neoadjuvant lapatinib, trastuzumab, and their combination in HER2-positive breast cancer: Results from Neo-ALTTO. J Nucl Med 54: 1862-1868, 2013.
8. Coudert B, Piergy JA, Mouret-Reynier MA, Kerrou K, Ferrero JM, Petit T, Kerbrat P, Dupré PF, Bachelot T, Gabelle P, et al: Use of [(18)F]-FDG PET to predict response to neoadjuvant trastuzumab and doxetaxel in patients with HER2-positive breast cancer, and addition of bevacizumab to neoadjuvant trastuzumab and doxetaxel in [(18)F]-FDG PET-predicted non-responders (AVATAXHER): An open-label, randomised phase 2 trial. J Natl Cancer Inst 105: 1183-1192, 2013.
9. Koelen BB, Pengel KE, Wesseling J, Vogel WV, Vranken Peeters MJ, Vincent AD, Gillihsius KG, Rodenhuis S, Rutgers EJ and Valdés Olmos RA: FDG PET/CT during neoadjuvant chemotherapy may predict response in ER-positive/HER2-negative and triple negative, but not in HER2-positive breast cancer. Breast 22: 691-697, 2013.
10. Gennari A, Donati S, Salvadori B, Giorgetti A, Salvadori PA, Sorace O, Puccini G, Pisanì P, Poli M, Dani D, et al: Role of [(18)F]-fluorodeoxyglucose (FDG) positron emission tomography (PET) in the early assessment of response to chemotherapy in metastatic breast cancer patients. Clin Breast Cancer 1: 156-163, 2000.
11. Taitishi U, Gamez C, Dawood S, Yeung HW, Cristofanilli M and Macapinlac HA: Bone metastases in patients with metastatic breast cancer: Morphologic and metabolic monitoring of response to systemic therapy with integrated PET/CT. Radiology 247: 189-196, 2008.
12. Specht JM, Tam SL, Kurland BF, Gralow JR, Livingston BD, Hen HM, Ellis GK, Schubert EB, Dunwall LD and Mankoff DA: Serial 2-[(18)F] fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) to monitor treatment of bone-dominant metastatic breast cancer predicts time to progression (TTT). Breast Cancer Res Treat 105: 87-94, 2007.
13. Morris PG, Ulane GA, Eaton A, Fazio M, Jhaveri K, Patil S, Evangelista L, Park YJ, Serna-Tamayo C, Howard J, et al: Standardized uptake value by positron emission tomographic/computed tomographic as a prognostic variable in metastatic breast cancer. Cancer 118: 5454-5462, 2012.
30. Constantinidou A, Martin A, Sharma B and Johnston SR: Positron emission tomography/computed tomography in the management of recurrent/metastatic breast cancer: A large retrospective study from the Royal Marsden Hospital. Ann Oncol 22: 307-314, 2011.

31. Lee CI, Gold LS, Nelson HD, Chou R, Ramsey SD and Sullivan SD: Comparative effectiveness of imaging modalities to determine metastatic breast cancer treatment response. Breast 24: 3-11, 2015.

32. Pahk K, Rhee S, Cho J, Seo M, Lee S, Park T, Park S, Lee E, Park KH, Kim C, et al: The role of interim 18F-FDG PET/CT in predicting early response to neoadjuvant chemotherapy in breast cancer. Anticancer Res 34: 4447-4455, 2014.

33. Schelling M, Avril N, Nährig J, Kuhn W, Römer W, Sattler D, Werner M, Dose J, Jänicke F and Schwaiger M: Positron emission tomography using [(18)F]Fluorodeoxyglucose for monitoring primary chemotherapy in breast cancer. J Clin Oncol 18: 1689-1695, 2000.

34. Wahl RL, Jacene H, Kasamon Y and Lodge MA: From RECIST to PERCIST: Evolving considerations for PET response criteria in solid tumors. J Nucl Med 1 (50 Suppl): 122S-150S, 2009.

35. Kim MK, Ryu JS, Kim SB, Ahn JH, Kim SY, Park SI, Kim YH, Song HY, Shin JH, Jung HY, et al: Value of complete metabolic response by (18)F-fluorodeoxyglucose-positron emission tomography in oesophageal cancer for prediction of pathologic response and survival after preoperative chemoradiotherapy. Eur J Cancer 43: 1385-1391, 2007.

36. Ott K, Herrmann K, Lordick F, Wieder H, Weber WA, Becker K, Buck AK, Dobritz M, Fink U, Ulm K, et al: Early metabolic response evaluation by fluorine-18 fluorodeoxyglucose positron emission tomography allows in vivo testing of chemosensitivity in gastric cancer: Long-term results of a prospective study. Clin Cancer Res 14: 2012-2018, 2008.

37. Gayed I, Vu T, Iyer R, Johnson M, Macapinlac H, Swanston N and Podoloff D: The role of 18F-FDG PET in staging and early prediction of response to therapy of recurrent gastrointestinal stromal tumors. J Nucl Med 45: 17-21, 2004.

38. Dose Schwarz J, Bader M, Jenicke L, Hemminger G, Jänicke F and Avril N: Early prediction of response to chemotherapy in metastatic breast cancer using sequential 18F-FDG PET. J Nucl Med 46: 1144-1150, 2005.

39. Couturier O, Jerusalem G, Nguyen JM and Lustinx R: Sequential positron emission tomography using [(18)F]fluorodeoxyglucose for monitoring response to chemotherapy in metastatic breast cancer. Clin Cancer Res 12: 6437-6443, 2006.

40. Groheux D, Giacchetti S, Hatt M, Marty M, Vercellino L, de Roquancourt A, Cuvier C, Coussy F, Espié M and Hindié E: HER2-overexpressing breast cancer: FDG uptake after two cycles of chemotherapy predicts the outcome of neoadjuvant treatment. Br J Cancer 109: 1157-1164, 2013.