Utility of [18F] Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography (FDG PET/CT) in the Initial Staging and Response Assessment of Locally Advanced Breast Cancer Patients Receiving Neoadjuvant Chemotherapy

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Received: 6 October 2014 / Accepted: 19 May 2015 / Published online: 22 July 2015
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Abstract In India up to 50 % of breast cancer patients still present as locally advanced breast cancer (LABC). The conventional methods of metastatic work up include physical examination, bone scan, chest & abdominal imaging, and biochemical tests. It is likely that the conventional staging underestimates the extent of initial spread and there is a need for more sophisticated staging procedure. The PET/CT can detect extra-axillary and occult distant metastases and also aid in predicting response to chemotherapy at an early point in time. To evaluate the utility of FDG PET/CT in initial staging and response assessment of patients with LABC receiving NACT. A prospective study of all biopsy confirmed female patients diagnosed with LABC receiving NACT from April 2013 to May 2014. The conventional work up included serum chemistry, CECT chest and abdomen and bone scan. A baseline whole body PET/CT was done in all patients. A repeat staging evaluation and a whole body PET/CT was done after 2/3rd cycle of NACT in non-responders and after 3/4 cycles in clinical responders. The histopathology report of the operative specimen was used to document the pathological response.

The FDG PET/CT reported distant metastases in 11 of 38 patients, where as conventional imaging revealed metastases in only 6. Almost all the distant lesions detected by conventional imaging were detected with PET/CT, which showed additional sites of metastasis in 3 patients. In 2 patients, PET/CT detected osteolytic bone metastasis which were not detected by bone scan. In 5 patients PET CT detected N3 disease which were missed on conventional imaging. A total of 14 patients had second PET/CT done to assess the response to NACT and 11 patients underwent surgery. Two patients had complete pathological response. Of these 1 patient had complete metabolic and morphologic response and other had complete metabolic and partial morphologic response on second PET/CT scan. The 18 FDG PET/CT can detect more number of metastasis as well as additional sites of metastasis compared to conventional methods. The response assessment resulted in change of treatment regimen in 14 % of patients.

Keywords Locally advanced breast cancer · 18F FDG PET/CT for staging · Neoadjuvant chemotherapy response assessment

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Introduction

The breast cancer has become the most common cancer of urban women and the second among rural women in India. The age standardized incidence rates range from 6.2 to 39.5 per 100,000 women. The majority of the women still present at an advanced stage particularly in public sector hospitals. The reasons attributed include lack of awareness, socioeconomic factors and the absence of a screening program.

Almost 30 to 50 % of these patients present with a locally advanced disease at presentation [1]. The term locally advanced breast cancer (LABC) is used to describe a breast cancer that has progressed locally but has not yet spread beyond the regional lymph nodes. It encompasses patients with the stage III disease according to AJCC/TNM, 7th edition, 2010 [2]. The stage III has been subdivided into A, B and C depending on the presence of N2 (A), T4 (B) or N3 (C) disease. As of today, the standard treatment is multimodal consisting of neo-adjuvant chemotherapy (NACT) followed by definitive surgery, adjuvant chemotherapy (if not completed before) and radiation therapy with or without hormonal treatment. The LABC is associated with substantial risk of occult metastases in about 20 % of patients [3]. Hence these patients need extensive workup for distant metastases prior to initiation of therapy. The conventional or standard methods of staging include physical examination, serum chemistry (blood count, liver function tests) mammogram, ultrasound of breast, magnetic resonance imaging (MRI) of breast, skeletal scintigraphy, chest imaging (chest x-ray or contrast enhanced computerized tomography (CECT) of the chest) and abdominal ultrasound or CECT [4]. The problem with these conventional tools is that they are multiple tests, less reliable as they rely on morphological characteristics of the target lesions (size, border, irregularity etc.) and lack the ability to detect extra axillary nodes such as internal mammary nodes leading to error in staging and treatment. The LABC patients have a high rate of systemic relapse, so current conventional evaluations are likely to underestimate the extent of disease [5]. Consequently, there is a need for more sophisticated staging procedures to exclude patients with metastatic disease from the aggressive treatment strategy in LABC. Several studies have reported the better ability of PET and PET/CT in detection of extra-axillary nodes and distant metastases compared to conventional staging methods [4–9]. In contrast to conventional tools, the 18F FDG PET/CT co-registers anatomical CT images and the functional PET images in a single study. Furthermore, the cost of performing multiple studies in the conventional staging may add up to that of a single PET/CT study.

Another area where PET/CT could have a role in the management of LABC patients is in assessing the treatment response. It has been reported that early response after two or three cycles of chemotherapy can be a predictor of pathologic complete remission and may therefore serve as a predictor for long-term outcome [10–12]. Around 70 % of patients demonstrate clinical response to NACT, but only about 20 % achieve complete pathologic response [13–15]. In comparison with non-responders, patients with complete pathologic response or minimal residual disease have longer disease-free and overall survival rates [13, 16]. Therefore, methods that allow prediction of therapeutic effectiveness at an early time point could help to individualize treatment, switch over to non-

cross resistant chemotherapeutic agents and to avoid potentially ineffective chemotherapies. Again the conventional anatomical methods such as mammogram, MRI and CECT record the morphological response which takes some time to manifest (at least 4–6 weeks) whereas the PET/CT records the biological response of the tumour in addition to morphologic response. The distinction between post chemotherapy fibrosis and the residual viable tumour tissue is also a problem with the conventional tools. The metabolic response to chemotherapy occurs much earlier to the tumor size reduction; hence by employing PET/CT at the completion of 2 or 3 cycles of chemotherapy, one can predict the effectiveness of the chemotherapy regimen. This early detection of non-responders aids in change of the therapeutic plan. In complete responders a breast conservation strategy could be employed. Hence the present study was designed to evaluate the utility of 18F- FDG PET/CT in initial staging and response assessment of patients with LABC receiving NACT with specific objective to compare 18F- FDG PET/CT with conventional methods in staging of LABC and to evaluate its role in predicting pathological response to NACT.

Materials and Methods

This is a prospective study of all willing, biopsy confirmed female patients diagnosed with LABC by conventional tools receiving initial NACT, at Sri Venkateswara Institute of Medical Sciences (SVIMS), from April 2013 to May 2014.

Inclusion and Exclusion Criteria

All consenting female patients with the biopsy proven, unilateral, newly diagnosed locally advanced breast cancer (defined as those belonging to stage III, AJCC/TNM, 7th edition, 2010 after conventional work up) presenting to surgical, medical or radiation oncology departments of SVIMS during the study period were included. The patients with early breast cancer, pregnancy, uncontrolled diabetes, male breast cancer and those who have already received treatment elsewhere were excluded. The institutional ethical committee clearance was obtained and all the investigations were done free of cost through funding by the Institute.

Methods

All consenting, eligible patients presenting with clinical suspicion of LABC were thoroughly evaluated with detailed history, physical examination, serum chemistry (complete blood count, liver function tests), bilateral mammosonogram followed by a confirmatory biopsy (tru-cut/incisional/excisional biopsy) for histological diagnosis and immunohistochemistry for hormone receptor status, Her 2 *nu* amplification and Ki

Table 1 Patient and tumour characteristics

Age range: 27 to 73 years		
Staging:		Percent
IIIA	10	26
IIIB	25	65
IIIC	03	09
Histology:		
IDC	37	
Metaplastic	01	
ER/PR		
Positive	23	60
Negative	15	40
Her 2 Nu		
Not amplified	26	68
Amplified	09	23
Equivocal	03	

67 expression. As a part of conventional staging they were evaluated with 99 m Tc MDP bone scan, CECT chest and abdomen. The ipsilateral mammogram was omitted for patients with ulcerated and/or painful lesions. All these patients underwent a baseline whole body 18F FDG PET/CT, according to the standard protocol practiced in the department of Nuclear Medicine, SVIMS. Those patients who harboured metastasis on the conventional or PET/CT imaging unequivocally received palliative chemotherapy. All other patients received NACT as per the protocols of department of Medical oncology. The response to NACT was determined clinically before each cycle and recorded. A restaging whole body PET/CT was done after 2nd or 3rd cycle in non-responders and after 3rd or 4th cycle in responders. The decision to change chemotherapy regimen or to perform surgery or irradiate in non-responders was

made after discussion in the institutional multidisciplinary tumour board. In responders, a symptom directed restaging work-up was done and the surgery was scheduled after 2–3 weeks of the last chemotherapy and once all the blood parameters are normalized. The pathological response was assessed by histopathological analysis of the operative specimen and was compared with the restaging PET/CT report.

Results

During the study period, a total of 123 patients with breast cancer presented out of whom, 38 patients met the inclusion criteria for the study. A total of 10 (26 %) patients found to have metastasis and referred for palliative chemotherapy and 28 patients received NACT. Finally 14 of 28 patients underwent restaging PET/CT and 11 of these underwent surgery. The patient and tumour characteristics are given in the Table 1.

Staging

The conventional staging work up detected metastatic disease in 6 (15 %) patients whereas the whole body PET/CT reported metastasis in 11 (26 %) patients, out of which one patient was found to have abscess in the lung (false positive) on biopsy. The PET/CT not only detected metastasis in 4 additional patients apart from all the 6 patients reported so by the conventional tools, it also picked up additional sites of metastasis in these patients. The conventional tools picked up a total of 8 metastatic sites in 6 patients, whereas PET/CT reported 15 metastatic sites in 11 patients. The comparison of PET/CT with CECT and Bone scan are shown in Figs. 1 and 2. The PET/CT detected 3 osteolytic skeletal metastasis which were not picked by the

Fig. 1 PET/CT Vs CECT -Sites of metastasis

Fig. 2 18F- FDG PET/CT Vs Bone scan metastatic sites

conventional bone scan. One mixed lesion was picked by both where as one osteoblastic metastasis was missed by PET/CT.

All the primary tumours showed FDG uptake, the baseline mean maximum standardized uptake value (SUVmax) for the primary lesion was 13.91 (range 5–42.6) and baseline mean SUVmax in axilla was 9.06 (range 1–18.4). In 5 (13 %) patients of all the 38, PET/CT detected N3 disease which was missed by conventional imaging, of which 3 patients also had systemic metastasis (Fig. 3). The extra axillary sites of nodal disease detected were internal mammary node in 2 patients, infraclavicular nodes in 2 patients and supraclavicular nodes in 4 patients. Of the 28 LABC patients, PET/CT changed staging from IIIA to IIIC in 2 patients (7 %). In comparison to conventional imaging the PET/CT upstaged the disease in 33 % of the patients.

Response Assessment

A total of 14 patients underwent restaging PET/CT of whom 11 underwent modified radical mastectomy. On restaging PET/CT, 9 (64 %) patients had response and 5 (36 %) patients had stable disease. In 2 (14 %) patients with stable disease, chemotherapy regimen was changed and 3 patients underwent surgery. One patient among the responder group did not turn up for surgery.

Fig. 3 PET/CT image of a patient showing a large primary with axillary, supraclavicular, internal mammary nodes and metastasis in liver and lung

The mean post treatment SUVmax of the primary lesion was 5.06 (range 0–13.65), a 64 % reduction compared to the baseline SUVmax of the primary tumor (Fig. 4). The comparison between restaging PET/CT report and final histopathology is given in Table 2. The response assessment correlated with the pathologic response in 9 of 11 (80 %) patients. Overall, the PET/CT provided information which had impact on the treatment plan in 36 % of the patients (10 metastatic, 2 N3 disease, 2 received 2nd line chemotherapy, 14 of 38 patients) (Fig. 5).

Discussion

The recommendations of the international guidelines for the work up of a patient with locally advanced breast cancer vary from one another. The more commonly followed National comprehensive cancer network clinical practice guidelines in oncology in its latest version (available at the time of writing the article) recommends PET/CT as category 2B option. The panel also advocates the performance of PET/CT particularly in patients with equivocal or suspicious findings on standard staging studies [17]. One of the reasons for not advocating the PET/CT is the lack of data showing clinical benefit. The majority of available evidence comes from the earlier studies which have used only PET. The superiority of combined PET/CT over PET is well documented. The emerging data on combined PET/CT can change the future guidelines. The problem with the standard staging studies have been mentioned earlier. In comparison, the PET/CT being a single and sensitive study and has several advantages. The reported advantages include detection of multicentric disease, occult metastasis, extra axillary nodal disease and incidental second primaries [9].

In the present study PET/CT was superior to conventional staging methods in identifying more number of

Fig. 4 The chart comparing T SUVmax pre and post treatment

patients with metastasis (26 vs 15 %). It also picked additional sites of metastasis in patients who were harbouring metastasis. This has therapeutic implications particularly when the role of surgery, radiofrequency ablation or cyberknife in patients with oligometastasis is being seriously contemplated. The PET/CT also detected disease in internal mammary and infraclavicular nodes in 7 % of patients. Again this has implications for the target volume planning of post-surgery radiation fields and radiation boost in the era of conformal radiotherapy. In a study of 119 patients, of which 69 were newly diagnosed LABC reported by Mahner et al., conventional imaging detected metastasis in 8 patients (11 %) compared to 18F FDGPET which detected metastasis in 18 patients (26 %) [4].

In the present study, in comparison to the bone scan, PET/CT picked up more osteolytic lesions and missed one osteoblastic lesion. It has been suggested that with careful examination, the osteoblastic lesions can be detected on the CT component of the PET/CT even without the tracer uptake [18]. The one area where the bone scan scores over the PET/CT is that it is a whole body scan in the truest sense compared to PET/CT where images are usually acquired from the skull base to mid thigh with arms raised. Hence most of the skull bones, upper and lower limb bones are not included in the study with PET/CT. In a recently published study of 117 LABC patients out of which 82 were non Inflammatory LABC, from France, Groheux et al., reported modification of the clinical stage in

48 % of patients with non-inflammatory LABC. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy for the diagnosis of bone lesions were all superior with the PET/CT than the bone scan. In contrast the same parameters were relatively better for a dedicated CECT chest for the detection of lung metastasis. The main reason for the inferior results with the PET/CT in the evaluation of lung metastasis is the lack of breath holding and no contrast being used. This limitation of PET/CT can be overcome by performing the diagnostic CT with contrast along with the PET [18]. In the present study the PET/CT, though did not miss any lung metastasis detected on CECT chest; it reported one false positive metastasis and it also picked 2 additional lesions. In the abdominal imaging also the PET/CT detected 4 lesions compared to only one with the CECT. The detection of brain metastases with PET/CT is difficult owing to the normal background uptake in brain. This is important particularly in patients with Her 2 Nu amplified tumors and triple negative breast cancer. Future advances in the PET imaging with newer tracers or combined PET/MR imaging can address this issue.

Another area which the present study focused was assessing treatment response. The time lag between chemotherapy and the morphologic response (identifiable tumor size reduction) ranges anywhere between 4 and 6 weeks, which is too long. Furthermore, with the morphological imaging it is difficult to distinguish fibrosis with the viable tumor residue

Table 2 The comparison between PET/CT response and the final HPE

		Pathological response		Prediction of response				
		Responders	Non responders	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
PET/CT response	Responders	8	1	88	50	88	50	82
	Non responders	1	1					

Fig. 5 Pre and post treatment PET/CT images of complete response **a** baseline PET/CT **b** Post treatment complete response

and the presence of scarring, oedema and inflammatory reaction in the post chemotherapy setting can lead to misclassification of a chemo-sensitive tumour into a non-responder [19]. The use of PET/CT can avoid all these problems. The PET/CT can detect response of the tumour as early as following 1st or 2nd cycle of chemotherapy by documenting the reduction in the metabolic activity. The implications of this approach is the early discontinuation of the ineffective and potentially toxic chemotherapy and institution of the new non cross resistant therapy. If possible even surgery or irradiation can be considered. The cutoff percent reduction in metabolic activity is debatable and studies vary in choosing from 20 to 60 % after 1st or 2nd cycle of chemotherapy [20–27]. In responders, the PET/CT can identify a subset of patients such as those with complete response or minimal residual disease who are eligible for the breast conservation.

To conclude, the PET/CT upstaged disease in 33 % of the patients and influenced treatment decision in 36 % of the patients, which is comparable to the studies, reported earlier [9, 18, 23, 26, 28]. The major criticism against the wider use of

PET/CT includes detection of indeterminate nodules in the lung, which could be granulomatous or infective aetiology which we did not encounter in our study. Another concern is the cost vs benefit issue. But, when the cost of performing multiple tests is added together, the total cost may come up to that of a single PET/CT study. Since being a smaller study, the conclusions drawn needs to be verified by a larger study.

Conflict of Interest None of the Authors have any conflict of interest

References

1. Agarwal G, Ramakant P (2008) Breast cancer care in India: the current scenario and the challenges for the future. *Breast Care* 3: 21–27
2. AJCC (American Joint Committee on Cancer) (2010) In: Edge SB, Byrd DR, Compton CC et al (eds) *Cancer staging manual*, 7th edn. Springer, New York, p 347

3. Tham YL, Kramer R, Osborne CK (2010) Evaluation of patients for metastasis prior to primary therapy. In: Harris JR, Lippman ME, Morrow M, Osborne CK (eds) *Diseases of the breast*, 4th edn. Lippincott Williams & Wilkins, Philadelphia, p 483
4. Mahner S, Schirmacher S, Brenner W, Jenicke L, Habermann CR, Avril N et al (2008) Comparison between positron emission tomography using 2-[fluorine-18] fluoro-2-deoxy-D-glucose, conventional imaging and computed tomography for staging of breast cancer. *Ann Oncol* 19:1249–1254
5. Al-Husaini H, Amir E, Fitzgerald B, Wright F, Dent R, Fralick J et al (2008) Prevalence of overt metastases in locally advanced breast cancer. *Clin Oncol (R Coll Radiol)* 20(5):340–344
6. Schirmmeister H, Kühn T, Guhlmann A, Santjohanser C, Hörster T, Nüssle K et al (2001) Fluorine-18 2-deoxy-2-fluoro-D-glucose PET in the preoperative staging of breast cancer: comparison with the standard staging procedures. *Eur J Nucl Med* 28:351–358
7. Groheux D, Moretti JL, Baillet G, Espie M, Giacchetti S, Hindie E et al (2008) Effect of (18) F-FDG PET/CT imaging in patients with clinical stage II and III breast cancer. *Int J Radiat Oncol Biol Phys* 71:695–704
8. Fuster D, Duch J, Paredes P, Velasco M, Muñoz M, Santamaría G et al (2008) Preoperative staging of large primary breast cancer with [18F] fluorodeoxyglucose positron emission tomography/computed tomography compared with conventional imaging procedures. *J Clin Oncol* 26:4746–4751
9. Van der Hoeven JJ, Krak NC, Hoekstra OS, Comans EF, Boom RP, Van Geldere D et al (2004) 18F-2-fluoro-2-deoxy-d-glucose positron emission tomography in staging of locally advanced breast cancer. *J Clin Oncol* 22:1253–1259
10. Von Minckwitz G, Sinn HP, Raab G, Loibl S, Blohmer JU, Eidtmann H, German Breast Group et al (2008) Clinical response after two cycles compared to HER2, Ki-67, p53, and bcl-2 in independently predicting a pathological complete response after preoperative chemotherapy in patients with operable carcinoma of the breast. *Breast Cancer Res* 10:R30
11. De Boer RH, Saini A, Johnston SR, O'Brien ME, Ellis PA, Verrill MW et al (2000) Continuous infusion combination chemotherapy in inflammatory breast cancer: a phase II study. *Breast* 9:149–155
12. Auclerc G, Borel C, Khayat D, Soubrane C (1992) Weil M [Primary chemotherapy in the treatment of breast cancer]. *Ann Chir Plast Esthet* 37:663–669
13. Fisher ER, Wang J, Bryant J, Fisher B, Mamounas E, Wolmark N (2002) Pathobiology of preoperative chemotherapy: findings from the national surgical adjuvant breast and bowel (NSABP) protocol B-18. *Cancer* 95:681–695
14. Van der Hage JA, Van de Velde CJ, Julien JP, Tubiana-Hulin M, Vandervelden C, Duchateau L (2001) Preoperative chemotherapy in primary operable breast cancer: results from the European organization for research and treatment of cancer trial 10902. *J Clin Oncol* 19:4224–4237
15. Bonadonna G, Valagussa P, Brambilla C, Ferrari L, Moliterni A, Terenziani M et al (1998) Primary chemotherapy in operable breast cancer: eight-year experience at the Milan cancer institute. *J Clin Oncol* 16:93–100
16. Feldman LD, Hortobagyi GN, Buzdar AU, Ames FC, Blumenschein GR (1986) Pathological assessment of response to induction chemotherapy in breast cancer. *Cancer Res* 46:2578–2581
17. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. V 3.2014. National Comprehensive Cancer Network. Available at <http://bit.ly/jOuSuf>. Accessed October 2, 2014.
18. Groheux D, Giacchetti S, Delord M, Hindie E, Vercellino L, Cuvier C et al (2013) 18F FDG PET/CT in patients with locally advanced or inflammatory breast cancer: comparison to conventional staging. *J Nucl Med* 54:5–11
19. Wolfgang A (2009) Weber. Use of PET for monitoring cancer therapy and for predicting outcome. *J Nucl Med* 46:963–995
20. Wahl RL, Zasadny K, Helvie M, Hutchins GD, Weber B, Cody R (1993) Metabolic monitoring of breast cancer chemotherapy using positron emission tomography-initial evaluation. *J Clin Oncol* 11: 2101–2111
21. Schelling M, Avril N, Nāhrig J, Kuhn W, Römer W, Sattler D et al (2000) Positron emission tomography using [(18) F] Fluorodeoxyglucose for monitoring primary chemotherapy in breast cancer. *J Clin Oncol* 18:1689–1695
22. Smith IC, Welch AE, Hutcheon AW, Miller ID, Payne S, Chilcott F et al (2000) 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
23. Rousseau C, Devillers A, Sagan C, Ferrer L, Bridji B, Campion L et al (2006) Monitoring of early response to neoadjuvant chemotherapy in stage II and III breast cancer by [18F] fluorodeoxyglucose positron emission tomography. *J Clin Oncol* 24:5366–5372
24. McDermott GM, Welch A, Staff RT, Gilbert FJ, Schweiger L, Semple SI et al (2007) Monitoring primary breast cancer throughout chemotherapy using FDG-PET. *Breast Cancer Res Treat* 102: 75–84
25. Schwarz-Dose J, Untch M, Tiling R, Sassen S, Mahner S, Kahlert S et al (2009) Monitoring primary systemic therapy of large and locally advanced breast cancer by using sequential positron emission tomography imaging with [18F] fluorodeoxyglucose. *J Clin Oncol* 27:535–541
26. Dunnwald LK, Gralow JR, Ellis GK (2008) Tumor metabolism and blood flow changes by positron emission tomography: relation to survival in patients treated with neoadjuvant chemotherapy for locally advanced breast cancer. *J Clin Oncol* 26:4449–4457
27. Groheux D, Hindie E, Giacchetti S, Delord M, Hamy AS, Roquancourt AD et al (2012) Triple negative breast cancer: early assessment with 18F-FDG PET/CT during neoadjuvant chemotherapy identifies patients who are unlikely to achieve a pathologic complete response and are at high risk of early relapse. *J Nucl Med* 53:249–254
28. Skoura EV, Datsis IE (2007) PET imaging in breast cancer. *Hosp Chronicles* 2:12–18