Role of Positron Emission Tomography-Computed Tomography in Locally Advanced Breast Cancer

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Abstract Breast cancer is the commonest cancer among women and leading cause of cancer related mortality worldwide. Locally advanced breast cancer is the common subgroup of breast cancer encountered in developing countries. The last decade witnessed the voluminous upsurge in the use of positron emission tomography-computed tomography. Its role has been evaluated in different aspects of breast cancer - diagnosing and staging the disease, assessing the therapeutic response to chemotherapy, and restaging the recurrent disease. The present review aims to delineate the current role of positron emission tomography-computed tomography in the management of locally advanced breast cancer, based on available literature.

Keywords Breast neoplasms · Positron emission tomography · Diagnostic Imaging · Neoplasm staging

Introduction

According to GLOBOCAN 2012 estimates, breast cancer is the second most common cancer in the world, and is the most

frequent cancer among women with an estimated 1.67 million new cancer cases diagnosed in 2012 (25 % of all cancers). It is a rising menace in both developing and developed countries [1]. Locally advanced breast cancer (LABC) constitutes majority of the breast cancer cases in developing countries unlike developed countries where early disease predominates in view of widespread screening and educational programs. The definition of LABC is not uniform across the centers globally considering the wide spectrum of presentation. National comprehensive cancer guidelines [2] describe LABC as AJCC stage III breast cancer; it includes breast cancer which fulfills any of the following criteria in the absence of distant metastasis: tumor of more than 5 cm size with regional lymphadenopathy (N1 to N3); tumors of any size with direct extension to chest wall and/or skin (including ulcer or satellite nodules) irrespective of regional lymphadenopathy; or regional lymphadenopathy (clinically fixed or matted axillary lymph nodes, infraclavicular, supraclavicular or internal mammary lymphadenopathy) irrespective of tumor stage. Overall LABC comprises a heterogeneous disease spectrum with a risk of distant metastases in 15 to 20 % of clinically stage III patients. Conventional staging workup recommended for LABC include a chest X-ray/CT chest, bone scintigraphy, and abdominal ultrasound / CT scan.

The last decade witnessed the voluminous upsurge in the use of 8-fluorodeoxyglucose (18-FDG) Positron Emission Tomography (PET) in the field of oncology including breast cancer. It is a unique form of diagnostic functional imaging that is aimed at detecting increased glucose metabolism in tumor cells (owing to enhanced expression of glucose transporters and Hexokinase enzyme) in vivo using radiolabeled tracers [3–5]. Fusion of PET to CT (PET-CT) can, therefore, provide metabolic information, complementary and additive to the morphologic imaging data; this increases the sensitivity and specificity in evaluating potential disease sites [6]. The

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role of PET-CT has been evaluated in different aspects of breast cancer - diagnosing and staging the disease, assessing the therapeutic response to chemotherapy, and restaging the recurrent disease. The present review aims to delineate the current role of PET-CT in the management of LABC, based on available literature.

Primary Staging of Locally Advanced Breast Cancer

Initial accurate cancer staging is critical because of number of reasons: (a) it helps in deciding optimal management plan for the patients based on the cancer stage; (b) it helps in predicting the prognosis of the disease; (c) it provides oncologists and researchers a common terminology to exchange information about their patients across the centers, and to evaluate and compare the results of various studies including trials; (d) it further helps them in identifying the trials which may be suitable for their patients [2].

Breast cancer staging incorporates assessment of primary tumor, regional lymph nodes and distant sites. Being a whole-body procedure, PET/CT is able to assess all these data in a single test, providing morphological information and also evaluating the metabolic activity of the disease.

Primary Tumor Staging

Locally advanced breast cancer is a clinical diagnosis; radiological assessment of the primary tumor is rarely required. Mastectomy is done in majority of the patients either upfront if suitable or following neoadjuvant chemotherapy. Though breast conservation surgery (BCS) has established itself as a standard of care in early breast cancer in last three decades, it is rarely contemplated in LABC [7]. The scenario is grimmer in developing countries where majority of LABC is a full blown T4 disease with extensive skin and/or chest wall involvement, and is not suitable for BCS. However, in a select group of patients with T3 tumors or T4 tumors with small skin involvement, BCS may be contemplated following neoadjuvant chemotherapy in specialized centers. This select group of patients merits radiological assessment of the index breast to exclude tumor multicentricity. PET-CT has good sensitivity (90 %) of identifying large tumors of more than 2 cm in size; however, PET-CT tends to miss additional small foci of breast cancer due to its limited spatial resolution and the low FDG avidity of well differentiated tumors [8, 9]. Choi et al. [10] reported that the sensitivity of 18 F-FDG PET/CT in the detection of multiple additional lesions was lowest as compared to USG and MRI breast (PET-CT vs. USG vs. MRI, 12.5 vs. 80 vs. 81.1 %); though PET-CT was shown to have highest specificity (PET-CT vs. USG vs. MRI, 95.8 vs. 93.7 vs. 87.6 %). The authors concluded that they did not find a diagnostic role of 18 F-FDG PET/CT in differentiating

multiple tumors from a single tumor, with its low sensitivity of 12.5 %. Currently, available literature does not support role of PET-CT in the primary tumor staging (T staging) in LABC. PET-CT may be of ancillary value, due to its high specificity, in suspicious additional breast lesions detected on either USG or MR [11].

Lymph Nodal Staging

Axillary Lymph Nodes

Undoubtedly, axillary lymph nodal status is the most important prognostic variable in breast cancer. In majority of the patients, lymph nodes are clinically palpable in axilla, and axillary lymphadenectomy (ALND) is the standard of care to assess the axilla pathologically. However, a few patients who have clinically N0 axilla (i.e., no lymph nodes are palpable in axilla), are potential candidates for sentinel lymph node biopsy (SLNB) as a negative SLNB may omit obligation of ALND and its associated postoperative morbidity. The caveats associated with SLNB in LABC are two folds: firstly, false negativity of SLNB, and secondly, requirement of second surgical procedure if results of SLNB are not immediately available. False negativity of SLNB is reported to be 5–10 %, though it varies from centre to centre [8]. This false negativity is pronounced in LABC where chances of positive axilla are quite high (80–85 %) One of the reasons for false negative axilla in LABC may be massive invasion of the metastatic nodes which have lost capacity of phagocytosis. Can we replace SLNB with other investigations? USG axilla with guided cytology from suspicious axillary nodes has been the standard approach in clinically N0 axilla to triage the patients for SLNB; positive cytology can direct the patients for straight ALND. In a study of 502 patients of invasive breast cancer, Baruah et al. reported that pre-operative axillary ultrasonography and guided cytology avoided unnecessary SLNB in 28.5 % of node-positive patients and in 7.8 % of overall patients [12]. Other studies also confirmed these findings and concluded that axillary ultrasonography and guided cytology can spare SLNB in 20–30 % node positive patients [13–15]. PET-CT has not shown to be of sufficient sensitivity to replace SLNB [16]. Cooper et al. [17] did a meta-analysis of 26 studies (total patients=2591) evaluating diagnostic accuracy of PET or PET-CT for the assessment of axilla; they reported that mean sensitivity was 63 % (95 % CI: 52–74 %; range 20–100 %) and mean specificity 94 % (95 % CI: 91–96 %; range 75–100 %). The authors concluded that present literature does not support the routine use of PET-CT to assess clinically N0 axilla. However, this is also worthwhile to note the high specificity of 94 % of PET-CT in evaluating axilla. Unlike early breast cancer, LABC is marked by high axillary nodal disease. These two facts

may translate into reasonable strategy of applying PET-CT before SLNB in LABC as it would identify 50–60 % cases of clinically occult lymph node disease in axilla and would spare SLNB in these patients, and also reduce the risk linked to false negative SLNB [6, 8, 18]. Axillary assessment following NACT is another controversial area and role of SLNB in this scenario is still questionable. There is scope for PET-CT in this condition; a negative axilla on PET-CT prior to NACT would inspire confidence in surgeons to perform SLNB following NACT [8].

Extra-Axillary Regional Lymph Node Staging

PET-CT has been shown to perform better in delineating extra-axillary regional lymphadenopathy including supraclavicular and internal mammary nodes in comparison to conventional imaging (CI). In a study of 43 LABC patients who had no evidence of distant metastasis following CI, Manohar et al. [4] reported that PET-CT detected additional regional lymphadenopathy in 16 of 43 (37.2 %) patients. Groheux et al. [19] also reported that PET-CT revealed additional N3 nodal disease (infra or supra clavicular and internal mammary nodes) in 32 of 117 (27.3 %) patients. Identification of N3 disease not only upstages the disease while also leads to change in therapeutic decisions related to extent of surgery or placement of radiation portals. Figure 1 displays PET-CT images showing internal mammary lymphadenopathy and supraclavicular lymphadenopathy.

Distant Metastasis

Imaging plays an important role in identification of clinically occult distant metastasis. Literature suggests 25–30 % upstaging in LABC where identification of distant metastasis changes the disease stage from III to IV. Inability of identify these cases would not only dilute the survival rates of stage III patients (Will Roger phenomenon) but also have other serious implications: firstly, selection of incorrect treatment for the patients; and secondly, delay in the surgical treatment of other potentially curable stage III patient.

Table 1 [10, 19–22] displays the previously published studies which compared conventional imaging (CI) with PET-CT for the detection of distant metastasis in breast cancer. Almost all studies have revealed high sensitivity and specificity of PET-CT as compared to CI in diagnosing distant metastasis. Obvious advantages of PET-CT in this scenario are (a) it's a one-stop investigation which can screen the whole body in one sitting, and (b) metastatic lesions glow in PET-CT due to FDG avidity and so can be identified easily.

Till recently, NCCN recommended Chest X-ray, USG abdomen and bone scintigraphy for the detection of distant metastasis in LABC. However, the recommendation has been updated to include CT chest and CT abdomen considering the low sensitivity of USG abdomen and chest X-ray to detect lung and liver metastasis [23]. Though the inclusion of CT in the conventional imaging protocols improved overall sensitivity of CI from 50–60 to 90–100 %, PET-CT continues to score over CI due to better sensitivity for diagnosing pleural

Fig. 1 (a & b) displays FDG avid left internal mammary lymphadenopathy, (c & d) displays FDG avid left supraclavicular lymphadenopathy

Table 1 Previous published studies comparing Positron Emission Tomography-Computed Tomography with conventional imaging in locally advanced breast Cancer

Study	Sample size	Patient profile	Conventional imaging protocols	Conventional imaging		PET-CT	
				Sensitivity	Specificity	Sensitivity	Specificity
Choi et al. [10]	154	All stages	Chest radiograph, USG of abdomen and pelvis, Bone scan	61.5 %	99.2 %	100 %	96.4 %
Fuster et al. [20]	60	large (>3 cm) primary breast cancer	Chest CT, USG liver, Bone scan	60 %	83 %	100 %	98 %
Mahner et al. [21]	119	LABC	Chest radiograph, USG of abdomen and pelvis, Bone scan	43 %	98 %	87 %	83 %
Groheux et al. [19]	117	LABC	Chest radiography/CT, Abdominal USG/CT, Bone scan	63.6 %	100 %	97.7 %	100 %
Niikura et al. [22]	134	LABC	Chest radiography/CT, Abdominal CT, Bone scan	83 %	85 %	98 %	90 %

metastasis 100 vs. 50 % and obviously for being one-stop imaging modality for other organs as well [10, 19, 21, 22]. CT part of the PET-CT definitely improves the sensitivity of PET-CT for parenchymal nodules, it is worthwhile to note that free breathing CT is less efficient than standard diagnostic thoracic CT for diagnosing sub-centimetric nodules and lymphangitis [19].

Skeleton is the most common site of metastasis in breast cancer; skeletal metastasis accounts for almost 90 % of all metastatic sites in breast cancer [24]. Breast cancer related skeletal metastasis can be of three types: osteoblastic, osteolytic and with marrow involvement; a combination of these skeletal metastatic types is recognized in many patients. Though bone scintigraphy has been the standard investigation modality to diagnose skeletal metastasis, it has its own pitfalls. Bone scintigraphy detects lesions when the reparative process in the cortex sets in. Metastatic lytic lesions may not show significant reactive bone formation and escape detection in bone scintigraphy; same holds true for metastatic bone marrow involvement. Groheux et al. [19] reported low sensitivity of bone scintigraphy (76.7 %) in comparison to PET-CT (100 %). This indicates that all the lesions which were detected by bone scintigraphy were also revealed by PET-CT; however, the reverse was not true in view of presence of osteolytic and marrow lesion in some patients (7/30, 23.3 % cases of skeletal metastasis). In another study by Manohar et al. [4], 5 of the 42 bone scintigraphy negative patients had evidence of skeletal metastasis on PET-CT; three patients had marrow metastases while other two had osteolytic lesions. Other studies have also confirmed the similar trends of high sensitivity of PET-CT over skeletal scintigraphy. It can be argued that osteoblastic lesions may not be FDG avid and may escape detection; however, these osteoblastic metastasis are usually identified on the CT part of the PET-CT [25]. Figure 2 displays PET-CT images showing osteolytic and bone marrow metastasis.

It also needs to be highlighted that bone scintigraphy is truly a whole-body imaging in comparison to PET-CT which

captures images from the mid-thigh level to the base of the skull. Most of the skull, distal upper and lower extremities are not included in the imaged field of the PET-CT; however, presence of these atypical skeletal metastasis involving distal extremities is rare and its true clinical significance is doubtful.

PET-CT helps in identifying non-regional distant lymphadenopathy, both supra-diaphragmatic (cervical, mediastinal, hilar and/or contralateral axillary) and infra-diaphragmatic (para-aortic, pelvic, and/or inguinal) in LABC. In a study of 225 patients of breast cancer (LABC, $n=88$) Niikura et al. [22] identified metastatic mediastinal nodes in 25 patients with high sensitivity and specificity (96 and 99 %). In another study of 119 patients of LABC, Mahner et al. [21] reported metastatic mediastinal nodes in 50 patients with high sensitivity and specificity (94 % each); the authors also reported, low sensitivity (31 %) of CI, though with high specificity (94 %) in the detection of these metastatic mediastinal nodes. Groheux et al. [19] identified 19 on PET-CT as compared to ten distant lymphadenopathy following CI. This fact merits to be highlighted that most of the PET-CT detected distant lymphadenopathy was not confirmed pathologically in any of these studies. When these non-regional distant lymphadenopathy is identified in addition to other sites of distant organ metastasis on PET-CT, it does not confound the clinical picture and does not lead to change in management per se. Finding of isolated non-regional distant lymphadenopathy, when easily accessible for biopsy (contra-lateral axillary, contra-lateral supraclavicular, cervical or inguinal) also does not create much of a clinical perplexity. The dilemma occurs when additionally identified non-regional distant lymphadenopathy is not accompanied by other sites of distant metastasis and is also not easily accessible for biopsy as well (mediastinal, para-aortic and pelvic). In a study of 52 patients of LABC with negative CI for distant metastasis, vander Hoeven et al. [26] reported one case of proven false positive mediastinal node on PET-CT; mediastinoscopy directed biopsy confirmed Sarcoidosis in this patient. In another study of 154 patients of all stages of breast cancer, Choi et al. [10] identified five cases of non-regional distant

Fig. 2 (a & b) displays FDG avid lytic lesion in the vertebra, (c & d) displays diffuse uptake of FDG in sternum without any concomitant bony lesion on CT suggestive of marrow involvement

lymphadenopathy - mediastinal in three, cervical in one, para-aortic in one, inguinal and pelvic in one. Pathological evaluation was done in only one patient with inguinal lymphadenopathy which came out to be reactive. It can be inferred for the available literature that distant metastatic lymphadenopathy is identified in a sizeable number of LABC patients; should these patients be really labeled as metastatic based on these PET-CT detected lymphnodes in the absence of pathological confirmation is an open question which necessitates further studies to be answered.

Overall, various studies have showed that PET-CT leads to upstaging - both inter-stage i.e., Stage III to IV due to identification of distant metastasis, and intra-stage i.e., within stage III due to identification of additional regional lymph nodes. This upstaging can result in change in management in a significant number of patients. Manohar et al. [4] reported that PET-CT resulted in upstaging in 17/43 (39.5 %) of LABC patients when compared to CI. Almost similar results were reported by Fuster et al. [20] and Groheux et al. [19]; they found upstaging of LABC in 42 and 52 % patients respectively with PET-CT as compared to CI.

Assessment of Response to Neoadjuvant Chemotherapy

Role of neoadjuvant chemotherapy (NACT) in LABC comes into play in two scenarios: firstly, when the patient is not operable

upfront due to extensive skin and/or chest wall involvement, and secondly, when breast conservation therapy is contemplated. NACT is advised in these patients for tumor shrinkage or down-staging. Previously published randomized controlled trial to compare neo-adjuvant vs. adjuvant chemotherapy in LABC concluded that timing of chemotherapy to surgery does not influence overall survival [27].

Clinical response to NACT is seen in 60–70 % of the patients. Response to NACT may be assessed either clinically or radiologically using ultrasonography or MRI; however, measurable morphological shrinkage takes almost 2 to 4 cycles. This long lag-period result in continuation of ineffective chemotherapy in non-responders, and the tumor may, instead, progress. Moreover, these morphologically based radiological investigations largely fail to differentiate tumor from fibrotic tissue. Functional imaging with PET-CT scan seems to score over these morphologically based radiological investigations as metabolic response happens earlier than morphological response.

Previous studies have reported that sensitivity of PET-CT for the evaluation of response to chemotherapy varies from 39 to 100 % while specificity varies from 74 to 100 % [28]. This marked heterogeneity in the results of various studies may be elucidated by - heterogeneous patient population, different PET scan protocols, timing of follow-up scan in relation to number of chemotherapy cycles, different SUV cut-offs to categorize response and different pathological criteria. In a

Table 2 Grade practice recommendation for the role of PET-CT in locally advanced breast cancer

Clinical scenario	Grade of recommendation ^a	Implications for practice
Assessment of primary tumor	+/-	Current literature does not support PET-CT in the assessment of primary tumor.
Assessment of axillary lymph nodes	+	Though sensitivity of PET-CT is low in identifying axillary lymph node metastasis, it's high specificity may help to omit sentinel lymph node biopsy in PET-CT positive axilla.
Assessment of extra-axillary regional lymph nodes	++	PET-CT is a good modality in assessing extra-axillary lymphadenopathy.
Assessment of distant metastasis	+++	PET-CT scores over conventional imaging in assessing distant metastasis in view of its high sensitivity and specificity, and being the one-stop investigation.
Assessment of response to chemotherapy	++	PET-CT is a good modality in assessing early metabolic response to chemotherapy.

^a +/- No definitive role, +Rising role, ++ Promising role, +++ Definite role

study of 64 patients, Rousseau et al. [29] compared PET-CT scan done after the first, second, third, and sixth course of NACT; they concluded pathologic response to neoadjuvant chemotherapy in stage II and III breast cancer can be predicted accurately after two cycles of NACT with a sensitivity, specificity, and negative predictive value of 89, 95, and 85 % when using 60 % of SUV at baseline as the cutoff value. In a study of 23 LABC patients, Kumar et al. [30] concluded that sensitivity, specificity, and accuracy of PET/CT in detecting responders were 93, 75, and 87 %, respectively. The authors conducted the follow-up scan after two cycles of chemotherapy to assess response; they considered 50 % reduction in SUV as the cut-off value to differentiate between responders and non-responders. What can be inferred from the currently available literature is - (a) gradual reduction in tumor FDG uptake (SUV) suggests response to NACT, (b) PET performed after two cycles of NACT can differentiate responders from non-responders, and (c) changes in FDG metabolism often precede morphologic changes in tumor and therefore PET-CT can demonstrate response sooner than conventional imaging techniques [24].

Table 2 summarizes the role of PET-CT in different aspects of management of locally breast cancer based on available literature.

Conclusion

Current evidence suggests that FDG PET-CT is more accurate than conventional imaging in upstaging both lymph-nodal disease and distant metastasis in LABC. PET-CT is a promising tool to assess early response to neoadjuvant chemotherapy as metabolic response precedes anatomical response. In addition PET-CT has an advantage of being a single one time investigation modality in comparison to multiple organ directed investigative modalities

currently being used for staging LABC. However, as most of the published studies are retrospective in nature, more prospective studies with larger sample size are needed in future to define the role of PET-CT in the management of LABC.

Conflict of Interest The author's declares that they have no conflict of interest.

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M et al (2015) Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 136:E359–86
2. Cancer Staging [Internet]. National Cancer Institute. [cited 2015 Apr 12]. Available from: <http://www.cancer.gov/cancertopics/diagnosis-staging/staging-staging-fact-sheet>
3. Smith JA, Andreopoulou E (2004) An overview of the status of imaging screening technology for breast cancer. *Ann Oncol* 15:i18–26
4. Manohar K, Mittal BR, Bhoil A, Bhattacharya A, Singh G (2013) Role of 18 F-FDG PET/CT in identifying distant metastatic disease missed by conventional imaging in patients with locally advanced breast cancer. *Nucl Med Commun* 34:557–61
5. Garg PK (2014) Preoperative fluorodeoxyglucose positron emission tomography-computed tomography in papillary thyroid cancer: a futile exercise. *J Int Med Res* 42:243–4
6. Challa VR, Srivastava A, Dhar A, Parshad R, Bal C, Mohan Reddy Gona R et al (2013) Role of fluorine-18-labeled 2-fluoro-2-deoxy-D-glucose positron emission tomography-computed tomography in the evaluation of axillary lymph node involvement in operable breast cancer in comparison with sentinel lymph node biopsy. *Indian J Nucl Med* 28:138–43
7. Deo SVS, Varma MC, Shukla NK (2008) Management of patients with breast cancer: are we ready in India for sentinel lymph node biopsy? *Natl Med J India* 21:27–30
8. Groheux D, Hindié E, Rubello D, Espié M, Baillet G, Giacchetti S et al (2009) Should FDG PET/CT be used for the initial staging of breast cancer? *Eur J Nucl Med Mol Imaging* 36:1539–42
9. Heusner TA, Kuemmel S, Umutlu L, Koeninger A, Freudenberg LS, Hauth EAM et al (2008) Breast cancer staging in a single

- session: whole-body PET/CT mammography. *J Nucl Med* 49: 1215–22
10. Choi YJ, Shin YD, Kang YH, Lee MS, Lee MK, Cho BS et al (2012) The effects of preoperative (18)F-FDG PET/CT in breast cancer patients in comparison to the conventional imaging study. *J Breast Cancer* 15:441–8
 11. Jung NY, Kim SH, Kim SH, Seo YY, Oh JK, Choi HS et al (2015) Effectiveness of breast MRI and 18 F-FDG PET/CT for the preoperative staging of invasive lobular carcinoma versus ductal carcinoma. *J Breast Cancer* 18:63–72
 12. Baruah BP, Goyal A, Young P, Douglas-Jones AG, Mansel RE (2010) Axillary node staging by ultrasonography and fine-needle aspiration cytology in patients with breast cancer. *Br J Surg* 97:680–3
 13. Sianesi M, Ceci G, Ghirarduzzi A, Del Rio P, Guazzi A, Pisanelli B et al (2009) Use of axillary ultrasonography in breast cancer: a useful tool to reduce sentinel node procedures. *Ann Ital Chir* 80: 315–8
 14. Van Rijk MC, Deurloo EE, Nieweg OE, Gilhuijs KGA, Peterse JL, Rutgers EJT et al (2006) Ultrasonography and fine-needle aspiration cytology can spare breast cancer patients unnecessary sentinel lymph node biopsy. *Ann Surg Oncol* 13:31–5
 15. Leenders MWH, Broeders M, Croese C, Richir MC, Go HLS, Langenhorst BLM et al (2012) Ultrasound and fine needle aspiration cytology of axillary lymph nodes in breast cancer. To do or not to do? *Breast Edinb Scotl* 21:578–83
 16. Pritchard KI, Julian JA, Holloway CMB, McCready D, Gulenchyn KY, George R et al (2012) Prospective study of 2-[¹⁸F]fluorodeoxyglucose positron emission tomography in the assessment of regional nodal spread of disease in patients with breast cancer: an Ontario clinical oncology group study. *J Clin Oncol* 30:1274–9
 17. Cooper KL, Harnan S, Meng Y, Ward SE, Fitzgerald P, Papaioannou D et al (2011) Positron emission tomography (PET) for assessment of axillary lymph node status in early breast cancer: a systematic review and meta-analysis. *Eur J Surg Oncol* 37:187–98
 18. Robertson IJ, Hand F, Kell MR (2011) FDG-PET/CT in the staging of local/regional metastases in breast cancer. *Breast Edinb Scotl* 20: 491–4
 19. Groheux D, Giacchetti S, Delord M, Hindié E, Vercellino L, Cuvier C et al (2013) 18 F-FDG PET/CT in staging patients with locally advanced or inflammatory breast cancer: comparison to conventional staging. *J Nucl Med* 54:5–11
 20. Fuster D, Duch J, Paredes P, Velasco M, Muñoz M, Santamaría G et al (2008) Preoperative staging of large primary breast cancer with [18 F]fluorodeoxyglucose positron emission tomography/computed tomography compared with conventional imaging procedures. *J Clin Oncol* 26:4746–51
 21. 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* 19:1249–54
 22. Niikura N, Costelloe CM, Madewell JE, Hayashi N, Yu T-K, Liu J et al (2011) FDG-PET/CT compared with conventional imaging in the detection of distant metastases of primary breast cancer. *Oncologist* 16:1111–9
 23. NCCN clinical practice guidelines in oncology (NCCN guidelines®) Breast Cancer, Version 2.2015 [Internet]. [cited 2015 May 10]. Available from: http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
 24. Rosen EL, Eubank WB, Mankoff DA (2007) FDG PET, PET/CT, and breast cancer imaging. *RadioGraphics* 27:S215–29
 25. Morris PG, Lynch C, Feeney JN, Patil S, Howard J, Larson SM et al (2010) Integrated positron emission tomography/computed tomography may render bone scintigraphy unnecessary to investigate suspected metastatic breast cancer. *J Clin Oncol* 28:3154–9
 26. Van der Hoeven JJM, Krak NC, Hoekstra OS, Comans EFI, Boom RPA, van Geldere D et al (2004) 18 F-2-fluoro-2-deoxy-d-glucose positron emission tomography in staging of locally advanced breast cancer. *J Clin Oncol* 22:1253–9
 27. Deo SVS, Bhutani M, Shukla NK, Raina V, Rath GK, Purkayasth J (2003) Randomized trial comparing neo-adjuvant versus adjuvant chemotherapy in operable locally advanced breast cancer (T4b N0–2 M0). *J Surg Oncol* 84:192–7
 28. Ozkan E (2013) Positron emission tomography/computed tomography in locally advanced breast cancer. *Exp Oncol* 35:253–7
 29. 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 [18 F]fluorodeoxyglucose positron emission tomography. *J Clin Oncol* 24:5366–72
 30. Kumar A, Kumar R, Seenu V, Gupta SD, Chawla M, Malhotra A et al (2009) The role of 18 F-FDG PET/CT in evaluation of early response to neoadjuvant chemotherapy in patients with locally advanced breast cancer. *Eur Radiol* 19:1347–57