Review

Current role and future prospects of Positron Emission Tomography (PET)/Computed Tomography (CT) in Management of Breast Cancer

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Review

Current Role and Future Prospects of Positron Emission Tomography (PET)/Computed Tomography (CT) in Management of Breast Cancer

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Abstract: Breast cancer has become the most diagnosed cancer in women globally with 2.3 million new diagnosis each year. Accurate early staging is essential for improving survival rates with metastatic spread from loco regional to distant metastasis decreasing rates by 50%. Current guidelines do not advice the routine use of Positron Emission Tomography (PET)-Computed Tomography (CT) in staging of early breast cancer in the absence of symptoms. However, there is a growing body of evidence to suggest that PET-CT used in this early stage can benefit the patient by improving staging and as a result treatment and outcome as well as psychological burden without increasing costs to the health service. Ongoing research in PET radiomics and artificial intelligence is showing promising future prospects in its use in diagnosis, staging, prognosticatication and assessing response to treatment in breast cancer. Furthermore ongoing research to address current limitations of PET-CT by improving techniques and tracers is encouraging.

Keywords: Breast Cancer; Staging; PET CT; FDG PET; Radiomics; Artificial intelligence

Introduction

Breast cancer is the most diagnosed cancer in women worldwide[1]. Furthermore, there are 685,000 deaths yearly making it the fifth leading cause of mortality worldwide[1]. The heterogeneous nature of the disease with differing sub types increases the complexity of the disease; however, the combination of early detection programmes, improvement in the accuracy of staging and imaging techniques has increased the survival rates for breast cancer patients by enabling improved planning and treatment options compared to when surgery was the primary method of treatment[2]. At present, the five-year survival rate for women diagnosed within the UK is 85% when diagnosed at an early stage however this decreases to 26.6% when diagnosed at stage IV [3]. Thus it is important to stage the patients accurately to ensure the best possible patient outcomes. Literature suggest that approximately 2-10% of breast cancers will be metastatic in nature at the time of diagnosis, with clear signs and symptoms permitting accurate diagnosis and treatment [4]. It is suggested that that only 5-7% newly diagnosed breast cancer have occult metastasis [5–7]. In early breast cancer (T1 to T2) the incidence of distant metastases is <2% in comparison to more advanced tumours (T3 and T4) where it is as high as 15-20% [8–10]. Hence the general consensus in most of the national and international guidelines such as National Institute for Care Excellence, National Comprehensive Cancer Network (NCCN 2023) and European Society for Medical Oncology (ESMO2023) is not to use routine staging to diagnose occult distant metastasis in early breast cancer patients without any specific symptoms[11–13]. There is lack of generalised consensus on indications as well as the type of staging investigations used in breast cancer management. Most centres uses Computed Tomography (CT) of Thorax, abdomen and pelvis with combination of other modalities such as Magnetic Resonance Imaging (MRI) or bone scan. Currently there is limited data on usefulness of functional imaging modalities such as PET-CT scan as a staging investigation in early and locally advanced breast cancer

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[14]. Current NCCN guidelines suggests that PET/CT may be helpful when standard imaging is equivocal and also suggests that it may also be helpful in identifying unsuspected regional nodal disease or distant metastases when used in addition to standard tests. However the guideline is advising its use in stage I, II and operable Stage III breast cancer as there is high false negative rate for detection of sub centimetre lesions and low grade disease and false positive in patients without locally advanced disease [12]. Its use in patients with stage III disease or when standard staging presents suspicious results suggesting its main benefits lie in identifying unsuspected regional nodal disease and distant metastasis in locally advanced disease alongside standard staging[12]. However, there is increasing evidence for usefulness of PET-CT in early stage breast cancer [15,16]. Survival rates demonstrate 76-99% for loco regional metastases versus 20-28% for distant metastases showing a decrease of 50% therefore proving the importance for accurate and early detection of cancer to increase treatment options [1].

In this review, we aim to evaluate the current evidence of usefulness of PET-CT in staging breast cancer in different setting along with its future prospects.

Materials and Methods

Authors searched in the MEDLINE database for published peer reviewed literature using the relevant MeSH terms for "PET-CT" OR "FDG-PET" AND "breast cancer" OR "breast" AND "radiomics" OR "artificial intelligence". All levels of evidences were considered and only articles published in English were reviewed.

Results and Discussions

PET-CT in primary cancer diagnosis

PET-CT is not generally used in primary breast cancer detection. This is due to high false negative results especially with lesions less than 1cm in size and with low grade tumours [17]. Other major limiting factor is the higher cost involved with PET CT. The sensitivity and specificity of PET CT for the diagnosis of breast cancer is variable and different studies and ranges from 48-96 and 73-100% respectively [18]. Grueneisen et al showed in a study comparing MRI, PET-CT and PET-MRI in breast cancer patient, PET-MRI and MRI showed higher accuracy in identifying the tumour size than the PET-CT (82%, 82% and 68% respectively). This study also shown that both PET-MRI and MRI showed higher accuracy in detecting multifocal and multi centric breast cancer than PET-CT (89%,89% and 56% respectively)[19].

In spite of limited role for PET-CT in establishing diagnosis of breast cancer, studies have suggested that PET-CT can provide useful histopathological features of cancer which may have some important influence on planned treatment. Some studies have suggested positive correlation with FDG uptake and Ki 67 level, Oestrogen Receptor (ER) and Progesterone Receptor (PR) status[20]. In a retrospective study of 548 patients by Koo et al, it was identified that triple-negative and HER2-positive tumours had 1.67-fold ($P < 0.001$) and 1.27-fold ($P = 0.009$) higher SUVmax values, respectively, than luminal A tumours after adjustment for invasive tumour size, lymph node involvement status and histologic grade on multivariate analysis[21]. Hogan et al evaluated the usefulness of PETCT in invasive lobular cancers (ILC) as these cancers are more difficult than invasive ductal cancers (IDC) on imaging with mammogram, ultrasound and MRI [22,23]. Furthermore many studies have shown that the ILC have lower standardised uptake values in comparison with IDC [24,25]. Hence metastasis from ILC may be less appreciable in comparison to metastasis from IDC [26]. Hogan et al in a study of 146 ILC patients, showed that FDG PET is more likely to identify asymptomatic, clinically occult distant metastasis in stage III IDC than in stage III ILC [22].

PET-CT in Breast Cancer Staging

Current literature has very limited evidence in assessing the clinical usefulness of PETCT in breast cancer staging and most of the studies evaluating the role of PET is retrospective in nature with limited number of patients.

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As many studies have shown that the yield of any staging investigation to diagnose asymptomatic distal metastasis in early stage breast cancer is very low, current consensus is mainly advising the use of PET-CT only when conventional imaging is equivocal and in stage IIIB breast cancer [12]. However, in a study of 225 patients Niikura et al showed PET-CT has 97.4% sensitivity and 91.2% specificity compared with 85.9% sensitivity and 67.3% specificity of conventional techniques including CT, US and bone scan in detecting distant metastases [27]. It is important to note that this study a good proportion of patients were found to have stage I to stage IIIB breast cancer (41.3%). In another study by Riedl et al 134 patients under the age of 40 who had PET-CT for staging were reviewed and found that PET-CT identified unexpected extra axillary regional nodal and distant metastases in 21% of patients, including 15 patients (11%) showing extra axillary lymph nodal disease and 20(15%) showing distant metastases and with 7 cases showing both [28]. Again, it is interesting to see that a significant proportion of these patients were having disease stage outside the current guideline recommendations (15% with Stage I,33% with Stage IIA,35% with Stage IIB and 17% with Stage III) [28].

Bone metastasis is one of the most common sites of metastasis in breast cancer. Bone metastasis can be lytic, sclerotic, mixed or intramedullary without obvious bone changes [29,30]. FDG-PET is better than bone scan in identifying lytic and intramedullary metastases. Though FDG-PET is less efficient in identifying sclerotic bone metastases, these non-avid lesions are usually identified on the CT component of FDG-PET Scans [31,32].

PET CT had sensitivity and negative predictive value of 100% in comparison to a sensitivity of 92% and negative predictive value of 83% with conventional imaging to exclude local recurrence or distant metastases in a study of 77 PET CT scans in 39 breast cancer patients [32]. Same study showed that PET CT had a specificity of 76.9% and positive predictive value of 89% which was comparable to conventional CT, with a specificity of 76.9% and positive predictive value of 88% [32].

PET-CT and Lymph Node metastases

Currently the most common image modality used to assess lymph nodes remain US of axilla with biopsy of abnormal looking lymph nodes in the preoperative work up of early breast cancer patients. In clinically node negative patients, sentinel lymph node biopsy remain as the gold standard to stage axilla accurately. Meta-analysis done by Peare et al reviewed 25 studies comparing FDG-PET and sentinel lymph node biopsy to stage axillary lymph nodes. This meta-analysis showed that PET-CT was inferior to sentinel lymph node biopsy in accurately staging axilla. Even though the PET-CT had very high specificity of 94% the sensitivity was low which limits its use in preoperative staging at present [33]. Another study by Wahl et al evaluated 360 patients with new breast cancer diagnosis who had PET-CT to assess the axillary lymph nodes before surgery. FDG-PET was 61% sensitive and 80% specific for axillary node metastases. Positive predictive value was 62% and negative predictive value was 79%. They concluded that at present the performance of FDG-PET is inferior to sentinel lymph node biopsy for consideration of replacing the surgical technique to accurately stage the axilla [34]. The commonly cited reasons for suboptimal performance of PET CT to identify nodal metastases is the inability to detect small metastatic deposits and the degree of avidity of the primary breast cancer may also have a role to play[35,36]. Another postulated factor for poor performance of PET CT was obesity as these patients produced images of inferior quality [34]. Schirrmeister et al used PET CT in a subset of patients who had chemotherapy and concluded that there is higher incidence of false negative results after systemic chemotherapy [37]. Other suggested reasons for false positive results on PET CT are previous biopsy, other tumours such as lymphoma, infective and inflammatory conditions and vaccines [38–41]. Meta-analysis by Peare et al also concluded that the limited studies done to comparing the sensitivity and specificity of various imaging modalities such as US and MRI shown similar specificity and sensitivity to PET-CT [33,42]. Considering the expense and radiation dose associated with PET-CT, US remains the modality of choice at present to assess axillary lymph nodes.

Another recent study by Yararbas et al showed a significant rate of upstaging based on identification of extra axillary regional lymph nodes and distant metastases and shown that 18.6% of

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patients with stage IIA, 30% with stage II B and 46.3% with stage IIIA breast cancer had upstaging after PET-CT[43]. Ko et al in another study of 195 breast cancer patients with stage II A to stage IIIC disease showed an overall upstaging rate for regional nodal metastases and/or distant metastases was 37% after PET CT. This includes an upstaging of 24% in stage II A, 39% in stage II B, 54% in stage IIIA, 27% in stage IIIB and 37% in stage IIIC [44].]. Seo et al showed in a retrospective study of 249 patients, PET CT had a higher positive predictive value (PPV) of 87.1% in diagnosing internal mammary chain lymph node metastasis in stage III cancer [45].

PET-CT and Distant metastases

Meta-analysis by Hong et al of 8 PET CT studies with a total of 748 patients has reported a sensitivity of 0.96 and specificity of 0.95 for detection of distant metastasis for PETCT and across 6 comparative studies with 664 patients sensitivity and specificity of PET CT were 0.97 and 0.95 whilst that of conventional imaging were 0.56 and 0.91 confirming higher sensitivity of PET CT for diagnosis of distant metastases [46]. Bone metastases is one of the common sites for distant metastases in breast cancer. PET CT may help to identify focal areas of FDG uptake much earlier than bone scintigraphy. Hansen et al analysed lesion based sensitivity of FDG PET-CT, low dose CT and bone scintigraphy and showed that lesion based sensitivity was 98.2% and 98.8% for early and delayed FDG PET CT respectively compared with 79.9% for low dose CT and 76% for Bone scan and 98.6% for combined low dose CT and Bone scan[47]. In this study, only 51.2% of osteolytic metastases were detected by bone scan. Another retrospective study of 198 patients, PET-CT showed higher accuracy than CT for detection of bone metastases demonstrating increased metabolic activity prior to structural changes [48]. Another meta-analysis by Rong et al consisting of 668 patients in 7 studies shown that PET CT has a sensitivity of 0.93 and specificity of 0.99 in detecting bone metastases in comparison to a sensitivity of 0.81 and specificity of 0.98 for bone scintigraphy[49].

PET-CT and Prognosis

With the current era of personalised and tailored treatment, prognostic evaluation of breast cancer is important in planning the appropriate treatment. Many studies have shown that FDG uptake positively correlate with aggressive tumour behaviour and poor prognosis [42,50,51]. Baba S et al showed that higher uptake was associated with larger tumour, higher nuclear grade and triple negative receptor status [50]. Meta-analysis by Diao et al 3574 patients in 15 studies for event free survival, patients with higher primary standardised uptake values (SUVmax) showed a poorer survival prognosis with pooled HR of 1.96[52]. Kitajima et al assessed relationship between FDG-PET findings and immune microenvironment in breast cancer in a series of 502 patients and found that high SUVmax was significantly related to high tumour infiltration lymphocytes (TIL) had a significantly shorter recurrence free survival (RFS) than those with low SUVmax [53].

PET-CT and treatment response

Ability to predict response to neo adjuvant therapy and to identify non responders early in the treatment would be of great clinical utility in breast cancer management. Currently there is no single gold standard tool available in our clinical practice. However a number of studies have shown encouraging result of PET- CT in predicting the response to neo adjuvant systemic therapy. Factors such as higher base line glycolytic activity and bigger reduction in SUVmax after initial cycles of chemotherapy suggest pathological response after neo adjuvant chemotherapy [54]. Han S et al in a recent meta-analysis of 1630 patients in 21 studies showed that a pooled hazard ratio of metabolic responses on Disease Free Survival was 0.21 for interim PET scans and 0.31 for post treatment PET scan [55]. The same meta-analysis demonstrated that pooled HRs for interim and post treatment PET regarding the influence of metabolic responses on Overall Survival were 0.20 and 0.26 respectively. This suggest that use of PET CT for evaluation of response to NAC provides significant predictive value for disease recurrence and survival [55].

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PET-CT and Disease Recurrence

Meta-analysis by Xiao et al of 1752 patients in 26 studies with suspicious recurrence of breast cancer, showed that the pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio and diagnostic odds ratio of PET CT were 0.90, 0.81, 4.64, 0.12 and 46.52 respectively and concluded that FDG PET-CT is valuable in detecting cancer relapse. In this meta-analysis, recurrence was suspected because of elevation of tumour markers (56.8%), suspicion on conventional imaging modalities (33.9%), and suggestive clinical symptoms or physical examinations (9.4%)[56]. Another study by Hildebrandt et al showed that in 100 patients with suspected recurrence, the area under the receiver operating curve for distant recurrence was 0.99 for FDG PET-CT, 0.84 for contrast enhanced CT and 0.86 for combination of contrast enhanced CT and Bone scintigraphy[57]. Vogsen et al, in a prospective study of 225 patients with suspected breast cancer recurrence, showed that Sensitivity, specificity, and AUC-ROC for diagnosing distant metastases by PET CT were 1.00, 0.88, and 0.98, respectively [58].

Rising tumours during post treatment surveillance is challenging situation to identify breast cancer recurrence. Dong Y et al in a retrospective study shown that PET/CT was more sensitive to detect the malignant foci and had better patient-based sensitivity and specificity(95% and 71.4% respectively) when compared with sensitivity and specificity of conventional imaging techniques (78.9% and 57.1%) in this setting[59]. Corso et al retrospectively reviewed 561 breast cancer patients who underwent surgery with curative intent and had raised tumour markers and they found that increased tumour marker levels detected in asymptomatic patients during adjuvant therapies and follow up significantly predictive of distant metastases identified on FDG PET-CT [60].

Impact of indeterminate lesions on PET-CT

Even though accurate staging of breast cancer helps to plan and tailor treatment appropriately, there is variation in diagnostic accuracy for different imaging modalities. FDG PET- CT may have higher accuracy to diagnose distant metastases than conventional imaging modalities, but it is not completely from false results. Incidental findings may generate additional tests, potential delay in treatment and more importantly anxiety in patients [58]. Vogsen et al reviewed 225 eligible patients with suspicious cancer recurrence where FDG PET CT was carried out. In this study, indications for PET-CT was local recurrence in 20% of which patients and clinical symptoms in 80% patients. FDG PET-CT was positive for metastases in 32% and negative in 68% patients. A biopsy confirmed metastases in 72.2% of patients with positive FDG PET CT. Interestingly 18/225(8%) patients had non breast malignancy on FDG PET-CT [58]. This is similar to the rates of non-breast malignancies identified in other studies [61–65]. FDG-PET/CT provided a high posterior probability of positive test, and a negative test was able to rule out distant metastases in women with clinically suspected recurrent breast cancer. Furthermore, one-fifth of patients examined for incidental findings detected at FDG-PET/CT were diagnosed with clinically relevant conditions. Further examinations of false-positive incidental findings in one of six women should be weighed against the high accuracy for diagnosing metastatic breast cancer [58].

PET-CT and cost effectiveness

Ko et al in their study of 195 patients with stage IIA-IIIC breast cancer, compared the cost implications and radiation exposure associated with PET-CT against those with CT of Chest, Abdomen and Pelvis with Bone scan. They found that the costs for both are comparable and with reduced radiation exposure associated with PET-CT [44]. Another recent study by Hyland et al, 564 patients with stage II-III breast cancer data were reviewed to compare the cost implications of staging procedures and concluded that PET/CT reduced false positive risk by half (22.1% vs 11.1%) and decreased workup of incidental findings, allowing for earlier treatment start and also found that PET-CT is cost effective and may be cost saving in some settings [66].

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PET-CT and future prospects

Usefulness of PET-CT in breast cancer is mainly limited due to lower sensitivity to identify smaller tumours of less than 1cm and low uptake in lower grade cancers. Studies are evaluating various techniques as well as testing a range of tracers to improve the limitations associated with PET-CT. One of the improved techniques is Total Body PET scanners which come with ultrahigh sensitivity and allows it to provide comparable images with significantly lower activity which is due to higher signal-to-noise (SNR) ratio. Total Body PET will enable higher sensitivity (up to 68 times higher than PET-CT) and will yield a higher SNR value and allow for a 40 fold reduction in radioactivity dose [67]. It is also reported that Total Body PET scan reduces the imaging time by a factor of 24[67]. Shorter acquisition time also results in less movement-induced blurring. Total Body scanners also addresses another limitation of PET-CT in identifying smaller lesions as it is associated with ultrahigh sensitivity, good spatial resolution and long scan range. Furthermore, novel, four dimensional (4D) dynamic whole body PET acquisition method improves tumour characterisation [68]. Another advantage of Total-body scanner is the 10 fold reduction in file size of raw PET data permitting faster data processing, reconstruction and transport [69]. Longer acquisition delay permits to carry out scans at later time points after tracer injection and this may be helpful in identifying smaller lesions and cancers with low avidity. Another major advantage of total body scanner is its ability to differentiate between residual disease and post therapy changes. Another important development to address limitations of PET based imaging is to implement Multi-tracer PET studies using cocktail injections where two radiopharmaceuticals are injected prior to a single PET acquisition [70]. Sodium fluoride (NaF) reflects osteoblastic activity with high potential for detecting osteoblastic metastases when combined with FDG. New PET Tracers such as 89Zr-trastuzumab and 89Zr-pertuzumab were developed for measuring Her2 expression in the primary and metastatic lesions non-invasively [71].

With the paradigm shift towards personalised medicine, identification of reliable and non-invasive biomarkers able to predict tumour heterogeneity is pivotal in improving patient treatment. At present, tumour biology is deciphered using invasive procedures such as biopsy with its limitations. Biopsy from one lesion or one part of the lesion may necessarily represent the whole tumour heterogeneity [72,73]. Another limitation of invasive biopsy to identify tumour biology is the inability to sample all suspicious distant metastatic lesions to identify any clonal difference. Radiomics is an emerging technique in the field of medical image analysis to assess tumour biology non-invasively by identifying mineable variables hidden in the pixels of images routinely not visualised by human eye. This helps to avoid the requirement multiple and repeated biopsies to aid treatment planning in breast cancer [74–76]. With the current development of artificial intelligence, the development of algorithms, tools and applications is rapidly evolving in the field of nuclear medicine [77]. A study by Yoon et al carried out a texture based analysis of intra tumoural metabolic heterogeneity to identify the presence of invasive components in a retrospective analysis of 65 patients with ductal carcinoma in situ (DCIS) who underwent PET-CT. They found that a lower area under curve (AUC) of cumulative SUV histograms, a parameter reflecting higher intra tumoural heterogeneity, was associated with underestimation of invasive disease and suggested sentinel lymph node biopsy in this subset of patients [78]. Currently a number studies have analysed a range of radiomic parameters to predict tumour biology with variable results [79–84]. A number of studies have evaluated the potential use of PET generated radiomic features and artificial intelligence in predicting the response to neo adjuvant chemotherapy with varying degree of success [80,82,85]. Song and colleagues proposed a machine learning (ML) based radiomic model developed analysing FDG PET-CT with a view to predict axillary lymph node metastases in a study of 100 patients with invasive ductal breast cancer and demonstrated that the model showed 90.9% sensitivity, 71.4% specificity and 80% accuracy in preoperative detection of axillary lymph node metastases [86]. Another potential area where AI and PET radiomics will be useful is in assessing treatment response especially in patients with multiple metastases. Manual segmentation of all metastatic lesions is time consuming. Moreau and colleagues shown very promising result in this field by training two deep learning models to automatically segment metastatic lesions on the baseline and follow up PET-CT

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in 60 patients with 87% sensitivity and 87% specificity to assess treatment response [87]. Huang et al and Ha et al applied AI on FDG PET to obtain prognostic data and showed good correlation of radiomic variables and tumour molecular subtypes, immunohistochemistry and relapse free survival [80,88].

Dedicated breast PET (dbPET) provide high resolution molecular imaging acquired on uncompressed breast, using a high resolution full ring dedicated breast tomograph and study by Satoh et al showed that the deep learning model trained had 93% sensitivity and specificity in comprehending breast cancer and non-breast cancer in 160 breasts, compared with 77-89% sensitivity and 79-100% specificity obtained from two expert radiologists [89]. PET radiomics has the potential to improve diagnosis, staging, pathological characterisation, treatment response assessment and prognostication in breast cancer patients.

Conclusion

There is growing body of evidence to support clinical usefulness of PET-CT as a staging tool in early and locally advanced breast cancer with significant rate of upstaging of the disease. This information is useful in tailoring appropriate treatment for breast cancer patients. Limited studies assessing the cost evaluation suggest that PET-CT is cost effective as a staging modality. Furthermore, ongoing research in PET imaging techniques and tracers to address the current limitations of PET CT are encouraging. Ongoing research in the field of PET derived radiomics and artificial intelligence is very promising especially in tumour characterisation, evaluating lymph node status and predicting response to neo adjuvant chemotherapy. At present PET radiomic studies are still non standardised and lack reproducibility and needs further validation. Larger prospective studies are needed to confirm the clinical utility and effectiveness of PET imaging in diagnosis, staging, pathological characterisation, prognostication as well as treatment response assessment in future.

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