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The effectiveness of Positron Emission Tomography/Computed Tomography (PET/CT) for determining breast cancer stages: A Structured Literature Review

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Abstract: *Breast cancer is a common condition that affects millions of individuals every year across the globe. The accurate staging of breast cancer is fundamental to management decision-making, but there is some uncertainty as to the value of imaging modalities in this context. Specifically, the role of PET/CT has been questioned by some authors, but may represent an important advancement in the field. The aim of this systematic review was to evaluate the effectiveness of PET/CT in the staging of breast cancer. Fourteen eligible studies were included and analysis demonstrated that there is good evidence that PET/CT can identify metastases and lymph node involvements in breast cancer patients. This may impact on staging and treatment decisions in many patients, although the exact justification for PET/CT use remains unclear and further research is needed to clarify this issue. Recommendations for research and practice are provided following discussion of these findings.*

Key words: *Positron Emission Tomography/Computed Tomography*
Breast cancer stages

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I. Introduction

Breast cancer is one of the most common cancers worldwide and the most common overall in the UK, with almost 50,000 new diagnoses every year[1]. The condition will affect 1 in 8 women over the course of their lifetime and is most commonly diagnosed in women aged 50 years and over[2]. The incidence of breast cancer increases with age, and in women with a family history of breast cancer[2]. Genetic components, including the BRCA1 and BRCA2 genes are only seen in the minority of patients presenting with breast cancer and therefore lifestyle factors, including diet, excess alcohol consumption and obesity can also contribute to an increased risk of the condition[3].

Staging

In order to effectively guide the treatment of the cancer and determine the prognosis, it is necessary to stage the cancer accurately[4]. The tumour node metastasis (TNM) staging method is the most commonly used for breast cancer in the clinical setting, which relies on evaluating the size of the tumour and assessing the degree to which the cancer has spread[5]. Using the TNM system, tumour size is considered an important diagnostic aspect for breast cancer and the level of lymph node involvement is indicative of local spread of disease[6]. Tumours are classified using the TNM technique in order to guide therapeutic techniques and the system is reliant on accurate imaging techniques to assess tumour tissue in the breast, lymph nodes and more distant tissues[4]. For instance, the prognosis is generally poor where the tumour size is greater than 5 cm and where extensive lymph node involvement is noted and this may affect the severity and approach of treatment used by the clinical team[6].

Tumour Status		Status of the Lymph Nodes	
T0	No palpable tumour	N0	No palpable axillary nodes
T1	Tumour <2cm with no fixation to underlying muscle	N1a	Palpable nodes not thought to contain tumour
T2	Tumour >2cm but <5cm with no fixation	N1b	Palpable nodes thought to contain tumour
T3	Tumour maximum diameter >5cm	N2	Nodes >2cm or fixed to one another and deep structures
T4	Tumour of any size with fixation to the chest wall or ulceration of skin	N3	Supraclavicular or infraclavicular nodes
Metastases			
M0	No clinically apparent metastases		
M1	Distant metastases are present		

Figure One. Tumour, node, metastases classification system for breast cancer (Stanley, 2004: 410)

FDG-PET for breast cancer

As a result of these limitations to a multi-modal staging process in breast cancer, clinicians have sought a one-step imaging technique that can provide accurate staging information with minimal harm to the patient[7]. A potential technique that has been used in staging multiple types of tumours is positron emission tomography (PET) with the glucose analog 2-[18F] fluoro-2-deoxy-D-glucose (FDG-PET)[8]. This imaging technique provides detailed information on the metabolic activity of tissues, enabling metastases, both local and distant, to be identified with a large degree of accuracy, even in deep tissues due to their metabolism of glucose[8]. Indeed, the use of FDG-PET has been demonstrated in staging multiple tumour types, including breast cancer, as well as enabling monitoring of the treatment response and assessment of disease recurrence following theoretically effective treatment[7].

Although FDG-PET may be considered an optimal solution to the breast cancer staging problem, there are important limitations with the technology. Primarily, PET scans do not provide detailed anatomical information and while they provide detailed information on cancer activity and metabolism, there is the possibility that the cancer location could be misinterpreted and staging done incorrectly[9]. As a result of this significant limitation, the use of an accurate anatomical imaging modality in combination with PET is considered to be a promising way forward[4]. The combined use of PET and computerised tomography (CT) scanning has been seen in the clinical setting in recent years and has the potential to fulfil the needs of a one-stop breast cancer staging technique in practice[10]. In principle, CT scanning in combination with PET offers several advantages over using each of these technologies on their own, including the potential to localise FDG signals precisely, identify uptake of FDG in small lymph nodes, which may be missed on routine CT scanning protocols, and isolate metastases or recurrence of cancers in scar tissue[11].

However, despite the potential of this staging technique, current guidelines do not advise routine PET/CT scanning for breast cancer staging[11]. The Royal College of Physicians (2013) suggest that PET/CT should be used in multi-focal disease in patients with dense breasts, and in selected patients with disseminated breast cancer before treatment. A number of considerations underline these recommendations, including the elevated cost of PET/CT compared with other imaging techniques and a lack of clear information on the effectiveness of PET/CT in breast cancer staging compared with existing modalities and protocols[10]. There is an important need for this data to be collected and evaluated in order to inform contemporary practice and explore the potential of PET/CT staging to enhance survival in breast cancer patients.

The following literature review will consider the techniques and classification systems used to stage breast cancer in the UK and the technological aspects of PET and CT scanning that are suggestive of a role in breast cancer staging.

II. Methodology

Approach and rationale

In order to satisfy the aims and objectives of this paper, a systematic review of the literature was conducted using online journal databases. The systematic review methodology is considered a robust and methodological approach to the evaluation of published data, when answering a specific clinical question in a contemporary context[12].

Quantitative data was specifically utilised for the purposes of this systematic review in order to provide specific answers to the clinical questions posed. This form of data is compatible with the positivist philosophical approach, that suggests real world observations and data recording can be used to formulate and challenge

hypotheses, with a direct clinical application[13]. Hence, qualitative data was not included in this systematic review.

PICO criteria

In order to complete a systematic review it is necessary to define the patient population, intervention, comparison group, and the outcomes (PICO) within the context of the research question[14] (table 1). In this instance, the patient group was defined as patients with breast cancer, diagnosed prior to significant intervention, and the specific intervention was the use of combined PET/CT scanning. The comparison of PET/CT with other forms of staging protocols, including mammography, MRI, lymph node sampling, and either PET or CT used alone was used. These comparisons would either be on a head-to-head basis, or where these studies did not exist, data on sensitivity and specificity in relation to PET/CT would be compared to existing and comparable data for other protocols/techniques.

PICO criterion	Definition
Population	Patients diagnosed with breast cancer, prior to significant intervention
Intervention	Combined PET/CT
Comparisons	Other staging protocols for breast cancer: mammography, MRI, lymph node sampling
Outcomes	Sensitivity and specificity of PET/CT in staging breast cancer

Table 1. PICO criteria for the search process

III. Search process

Based on this definition, an accurate search strategy was devised for the online literature search. A number of databases were selected, based on their expanse and the inclusion of relevant journals relating to imaging studies and cancer research. These databases were: MEDLINE, Sciencedirect, and EMBASE. Google scholar was also used as a preliminary search tool, as this database has a large selection of grey literature available (i.e. non-peer reviewed literature, or unpublished data) that can maximise the availability of data for analysis[15]. The same search criteria were applied for all databases, including the use of the following search terms and relevant operators: 'PET/CT' AND 'breast cancer' AND 'staging'. These search terms were correlated with the key words identified in a number of articles following a cursory examination of the literature. In addition several key journals were identified and searched in order to allow for a wider identification of relevant papers, including: Radiology, the British Journal of Radiology and BMC Cancer.

IV. Exclusion and inclusion criteria

Exclusion and inclusion criteria were also applied to the literature search in order to exclude irrelevant data and refine the overall search process. Only papers published in the last ten years were considered suitable for inclusion, in order to maintain a contemporary perspective on the role of PET/CT in breast cancer staging. In addition all papers had to be published in the English language at some point, although they did not have to pertain to the UK directly. The content of papers was also important, with papers looking at specific patient groups excluded (e.g. male breast cancer) and papers exploring the role of PET/CT for purposes other than staging, including the detection of recurrences, and the evaluation of cancer in various bodily tissues.

The types of studies included were also important, according to the hierarchy of evidence[16]. These criteria note that systematic reviews, meta-analyses, and randomised controlled trials (RCTs) represent the most robust forms of clinical evidence for inclusion in systematic reviews[17]. This is due to the controlled nature of the group comparison and methodological rigour applied to these data. Following these studies, observational studies, including retrospective and prospective cohort studies are then considered the next highest form of evidence[16]. These studies were also considered eligible for inclusion, as there was an anticipated paucity of RCTs and higher-level analyses based on a cursory examination of the literature. Furthermore, RCTs may be limited due to the fact that established staging techniques have a high proven efficacy and therefore there would be a limited application of PET/CT in patients newly diagnosed with breast cancer in routine practice[17]. However, case studies, narrative literature reviews, and editorials were excluded from the search due to the fact that these are considered weak and unreliable forms of evidence[16].

All of these criteria were applied to paper identified during the initial search process, in order to refine the results systematically. Once the data set was available, the abstracts of all relevant papers were perused in order to scan for appropriateness in the review process. Following this stage of elimination, the remaining papers were read in totality in order to determine their value in the present discussion and to ensure the remained relevant to the aims of the study. The following section outlines the appraisal process applied in greater detail.

V. Critical appraisal and data analysis

Once the initial set of papers had been identified using the above search strategy, a process of systematic critical appraisal was performed in order to further explore the methodological strengths and weaknesses of the data. A number of tools can be used to perform critical appraisal and one of the most commonly used is the Critical Appraisal Skills Programme tool kit, which comprises a defined, validated set of questions for each study type aimed at assessing the rigour and value of the research in question (CASP, 1999). The CASP toolkit has been shown to provide a useful means of assessing papers for systematic review and therefore can be considered suitable in this context[18]. These tools were applied to each paper and those with significant weaknesses or flaws were identified and either excluded on that basis, or these flaws were further explored in the discussion of the article.

Following critical appraisal the main process of systematic analysis was performed in order to structure the review. For each paper, criteria were analysed according to the aims and objectives of the review, in order to provide a direct comparison of all relevant variables. Primarily, this process focused on analysing the data in order to determine the extent to which PET/CT was able to influence the staging of breast cancer and subsequent treatment decisions. Analysis was considered in terms of sensitivity and specificity of PET/CT, the ability to detect distant metastases, and head-to-head comparisons with other staging techniques, all of which were considered separately. Furthermore, where possible, treatment decisions and patient outcome data was used to inform the analysis in order to directly relate the use of PET/CT to clinical outcomes.

Following individual analyses of papers, a synthesis process was utilised in order to guide the composition of the review[13]. Each of the objectives of the study was answered directly, with reference to relevant data, and although meta-analysis was not performed, this process retained a quantitative component. Emerging concepts or ideas from the studies were also noted at this stage for broader discussion with the context of present and future practice.

IV. Results

Study identification

Based on the initial literature search a total of 131 eligible studies were identified. These studies were then reduced to 19 based on analysis of abstract content (figure 2), with exclusion of many studies due to a lack of relevance to the staging of breast cancer through PET/CT use (table 2). Finally, further analysis of paper contents and critical appraisal resulted in 14 papers eligible for inclusion due to a lack of significant methodological weaknesses or a failure to report quantitative data regarding key outcomes (table 2).

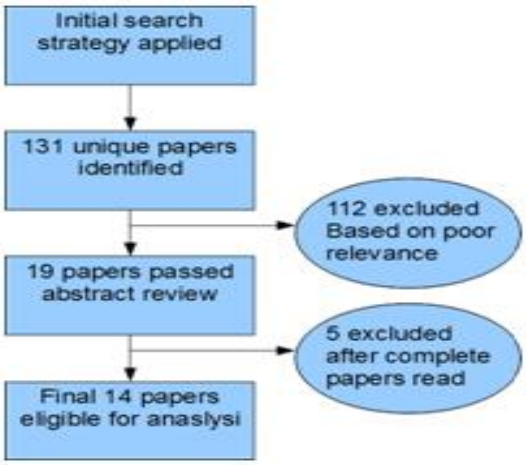

Figure 2. Flowchart of paper selection and inclusion/exclusion process. Exclusion criteria are further defined in table2.

Example of Studies	Reasons for exclusion
Koolen et al., 2013	Focus on receptor-specific breast cancer outcomes, not staging
Duch et al., 2013	Paper focused on response of cancer to neoadjuvant chemotherapy (NAC), not initial staging
Kumar et al., 2009	Paper focused on response to NAC

Schmidt et al., 2008	Focus on recurrence of breast cancer, not initial staging
Ueda et al., 2008	Paper utilised PET/CT combined with ultrasound for staging, not providing a staging comparison

Table 2. Excluded studies and reasons for exclusion.

Included studies

The characteristics of included papers are shown in tables (3, 4, and 5). These papers were considered eligible based on the inclusion and exclusion criteria noted in the previous section, as well as the fact that they had strong methodological qualities. Notable methodological weaknesses are shown for all studies (tables 3, 4,and 5), although further discussion of CASP scoring is shown in (Appendix 1).

A total of 14 papers were identified and analysed following the application of the search strategy described in the previous section. The main results of each paper are synthesised into an analysis focusing on sensitivity and specificity for primary tumours and metastases and comparisons of PET/CT with other modalities. Then the main results in terms of clinical utility during staging and treatment planning/prognosis are considered.

Table 3. Main characteristics of Studies that focus on Effectiveness of PET/CT: sensitivity and specific

Author/year	**Design**	**Patient no.**	**Patient characteristics**	**Outcome measures**	**Key findings**	**Quality issues**
Chae et al., 2009	Prospective cf. sonography and mammography	108	BC, -ve ALN (non-palpable)	Primary tumour detection	PET/CT: Sens 48%, Spec 82% Sonography: Sens 52%, spec 89% Mammography: Sens 33%, spec 96%	Only based on primary tumour
Fuster et al., 2008	Prospective cf. conventional	60	New BC >3cm, pre-operative	Staging and Distant Mets	PET/CT accurate staging 42% cases PET/CT: Sens 70%, Spec 100% (primary tumour) Distant Mets: Sens 100%, spec 98% cf. 80%, 83% standard imaging	Large breast tumours only, conventional imaging poorly defined
Niikura et al., 2011	Retrospective cf. standard	225	BC, -ve ALN	Sensitivity and specificity	PET/CT: Sens 97.4%, Spec 91.2% Standard: Sens 85.9%, Spec 76.3%	Single institution, poor patient selection criteria
Taira et al., 2009	Retrospective cf. SNB	90	BC, no chemotherapy	Sensitivity and specificity	PET/CT: Sens 48%, Spec 92%	Poorly defined patients, retrospective
Yang et al., 2009	Prospective cf. standard	80	Newly diagnosed BC	Accuracy and Distant Mets	MRI more accurate for primary tumour PET/CT identified distant mets 38% patients	Low level statistical analysis

Effectiveness of PET/CT: sensitivity and specificity

Sensitivity and Specificity of PET/CT

The overall results for sensitivity and specificity are shown in (figure 3). The sensitivity of PET/CT for the detection of additional distant lesions in patients with stage 2 or 3 breast cancer was 100% in one study, with a specificity of 96%, compared to conventional imaging with bone scintigraphy, liver ultrasound, and chest radiography[19]. A similar retrospective analysis of 225 patients with primary breast cancer staging suggested that the sensitivity for PET/CT imaging for distant metastases was 97.4%, compared to 85.9% for conventional imaging, with a specificity of 91.2% for PET/CT compared to 67.3% for conventional imaging[20]

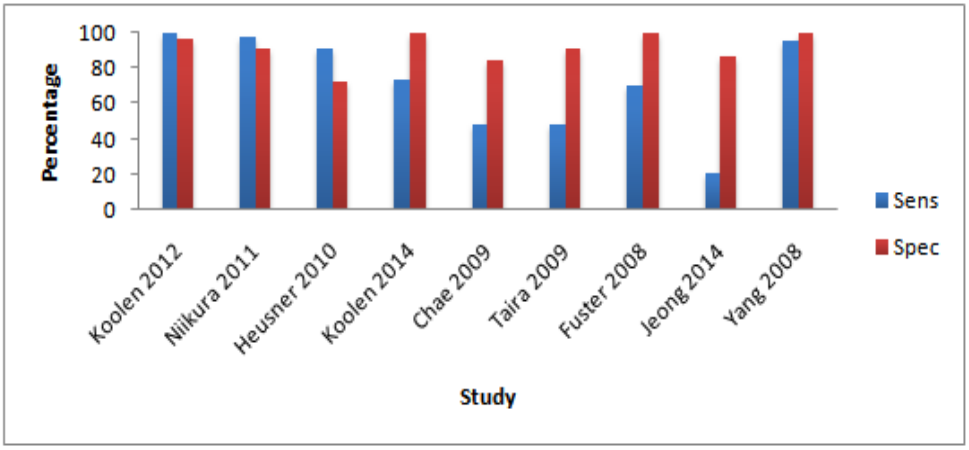

Figure 3. Sensitivity and specificity of PET/CT according to study

Heusner et al. 2010[21]compared PET/CT with diffusion-weighted MRI in 20 breast cancer patients and found that the sensitivity and specificity of PET/CT was 91% and 72%, respectively, with an overall accuracy of 76% for the detection of malignant lesions in local or distant tissue. The earlier staudy by Heunser et al. 2008[4] did not provide specific sensitivity or specificity values for the comparison of PET/CT with MRI or ultrasound, dueto the head-to-head comparative nature of the study, without a clear gold standard for the staging of disease.

Koolen et al., 2014[22] explored the role of PET/Ct in primary breast cancer staged as T1 based on initial evaluation in order to confirm the ability to accurately stage local and distant metastases and disease characteristics. The authors found that the sensitivity of PET/CT was 73%, with a specificity of 100% for axillary metastases, while 87% of primary tumours were detected by the technique. However, this was a size-dependent effect, with 59% of tumours under 1cm in size detectable with PET/CT and 98% detectable when tumours were greater than 1cm in size.

Axillary lymph node status

Axillary lymph node status was explored specifically in a number of studies Chae et al. 2009[23] compared the role of PET/CT to sonography and mammography in combination in a patient population of 108 women with diagnosed breast cancer but no clear metastases. The gold standard was axillary lymph node biopsy and sentinel node biopsy in this study. The sensitivity of PET/CT was 48% and the specificity was 84%, which was similar to the sensitivity and specificity of sonography (51.5% and 89.3%, respectively). Mammography was considered less sensitive (33%) but more specific (96%) compared to either approach, when used in isolation. In this study, PET/CT was less accurate overall with an accuracy of 73.2%, compared to 77.8% and 76.9% for sonography and mammography, respectively.

Taira et al., 2009[24] also explored the role of PET/CT in breast cancer detection compared to sentinel node biopsy and or axillary lymph node biopsy in 90 patients. The evaluation noted that the sensitivity of PET/CT was only 48%, while the specificity was 92%, suggesting that the approach was not sensitive enough to guide further evaluation of axillary disease in this patient group. However, Fuster et al. (2008) found that the sensitivity of PET/CT for correct staging of early stage breast cancer was significantly higher than noted in the previous two studies (70%), while the specificity of the technique was 100% compared with axillary lymph node biopsy as a gold standard. This study differed from those by Taira et al. 2009[24] and Chae et al. 2009[23] in that the aim was to evaluate the role of PET/CT in early staging of disease, where the tumour size was greater than 3cm, prior to surgery. This indicates that early use of PET/CT may be of greatest benefit to patients with breast cancer.

Jeong et al., 2014[25] evaluated 178 patients in whom standard imaging protocols had failed to detect any axillary lymph node metastases and applied PET/Ct to this group. The PET/CT techniques was able to detect the primary lesion in 156 patients, with a sensitivity of 87.6%, while the detection of axillary lymph node involvement was noted with PET/CT imaging. The sensitivity of PET/CT for axillary node staging was 20.8% and the specificity was 86.9%. Therefore, the role of PET/CT may be limited in patients with no clear axillary metastases on initial work-up.

Finally, the most encouraging results of PET/CT use in breast cancer staging have been noted in a study by Yang et al. 2008[26] who evaluated 24 patients with breast cancer and compared PET/CT with axillary lymph node biopsy to evaluate the use of PET/CT on staging specifically. The authors found that the sensitivity of PET/CT was 95% and the specificity 100%, suggesting that this imaging technique was clinically effective in determining the stage of disease in these patients.

Staging and prognostic impact

Detection of distant metastases

Heusner et al. 2008[4] performed a comprehensive study exploring the role of PET/CT mammography to MRI for detection of primary breast cancer tumours in forty women with suspected disease, in addition to comparing PET/CT to ultrasound for axillary lymph node staging and a comparison of PET/CT to a multimodal staging algorithm for distant metastases. The authors found that PET/CT mammography was no more effective than MRI at the detection of the primary breast lesion (PET/CT 95% versus MRI 100%, P=1.00). However, PET/CT scanning was better at detecting lesion focality compared to MRI (79% versus 73%, P<0.001). PET/CT imaging detected lymph node metastases in 80% of cases, compared with 70% in ultrasound examinations, although this was not a statistically significant difference (P=0.067).

Similarly, the detection of distant metastases by PET/CT was higher than for the multimodal algorithm (100% versus 70%), although this was not statistically significant (P=1.00). Although three patients with distant metastases were noted with PET/CT compared to other methods, and the technology resulted in management changes to 12.5% of patients, there is some conflicting data regarding the use of the PET/CT technique in TNM staging of the tumours. MRI imaging correctly identified the T stage of the tumour more frequently than PET/CT imaging (77% versus 54%, P=0.001), suggesting that the role of PET/CT in this context may be limited at present.

Koolen et al., 2014[22] also found that PET/CT was instrumental in the early stage of breast cancer detection, with eight additional patients diagnosed with disseminated disease based on PET/CT data alone, leading to a corresponding modification of treatment plans in this group. However, three additional lesions were found to be false positives in this whole-body evaluation of patients, which has the potential to cause more disruption to patients and result in unnecessary treatment escalation.

Bernsdorf et al.,2012[27] performed an evaluation of PET/CT in 103 consecutive patients who had been diagnosed with early stage breast cancer, defined as a tumour larger than 2cm in diameter, which was considered operable according to standard staging protocols. PET/CT was able to detect the primary tumour in 97% of cases, suggesting mild inferiority compared to standard protocols. However, PET/CT was instrumental in detecting distant and additional primary tumours in some patients: two patients were found to have additional primary tumours of the ovary and lung and six were found to have distant metastases in the bone, lung or ovaries. In addition, PET/CT alone detected an additional 12 cases of extra-axillary malignancy, with 14% of patients upgraded in the TNM staging process and modification of treatment in 8% (n=8) patients.

However, Jeong et al. 2014[25] found that PET/CT had a sensitivity of 87.6% for the primary tumour in patients with diagnosed breast cancer, while the sensitivity for the detection of axillary lymph nodes was very low (20.8%). Indeed, in this evaluation of 178 patients only two cases were seen where additional disease or metastases were noted, leading to a change in management in two patients. However, this must be balanced with the false positive rate noted in the study, which would have adversely affected 22 patients without axillary or distant lymph node metastases.

Author/year	Design	Patient no.	Patient characteristics	Outcome measures	Key findings	Quality issues
Bernsdorf et al., 2012	Prospective PET/CT vs standard imaging	103	Consecutive BC >2cm	Therapeutic value of PET/CT	PET/CT detected primary tumour in 97%, staging upgrade in 14%, change in treatment 8%	No Sens/Spec data, single institute
Groheux et al., 2012	Prospective cf. gold standard	254	Stage II and III BC	Stage and prognosis	Change in staging in 30.3% patients 3-year survival higher if M0 cf. M1 on PET/CT (88% vs 57%)	No comparison with existing imaging
Moon et al., 2013	Prospective supine vs breast PET/CT and PET/CT vs. MRI	40	BC, -ve ALN	Correlation with histopathology	Breast PET/CT better for staging (T) Correlations with pathology: PET/CT (72.5%), MRI (70.0%).	Small patient numbers, multiple modalities
Riegger et al., 2012	Retrospective cf. standard	106	Primary tumour BC	Staging and treatment	PET/CT more accurate for distant Mets and ALN (p<0.05) Change in treatment 14% patients	No Sens/Spec data, Retrospective

Table 4. Main characteristics of Studies that focus on Staging and prognostic impact

The use of PET/CT for the detection of distant metastases in patients with stage 2 or 3 breast cancer, prior to neoadjuvant chemotherapy, was associated with an improvement in metastasis detection compared to conventional imaging, including radiography, ultrasound and scintigraphy, with a low false positive rate (4%) and a change in clinical management noted in 13 out of 154 patients (8%)[19]. Similarly, Riegger et al. 2012[28] found that PET/CT was more accurate in the detection of axillary and distant metastases compared to conventional imaging (mammography, radiography, scintigraphy and ultrasound) (p=0.013), although the techniques did not differ in any other respects. In this study, clinical management of 14% of patients was altered as a direct result of FDG PET/CT findings compared with conventional imaging strategies.

Alteration of stage level

In the evaluation by Groheux et al. 2012[29] PET/CT results served to change the clinical stage of breast cancer in 77 out of 254 patients (30.3%), with additional distant and locoregional nodal disease detected in the majority of those cases. Prognostic data was also collected on these patients and it was shown that metastatic disease (M1) versus absence of metastatic disease (M0) on PET/CT was a significant predictor of poor survival , with a three-year survival of 57% versus 88% (p<0.001). Indeed, further analysis of patients evaluated through all imaging techniques suggested that only distal disease on PET/CT or triple-negative phenotypes were associated with prognosis.

Riegger et al.2012[28] found that PET/CT was more accurate for the detection of loco regional (axillary) metastases (p=0.013) and for distant metastases (p<0.005) when compared to a comprehensive combined imaging strategy. However, this was a retrospective study design and there was a lack of evaluation of the impact of selection bias and false-positive rates as a result of the study design, a significant limitation.

One study evaluated the potential use of diffusion-weighted whole body MRI compared to PET/CT for the staging of breast cancer[21]. The authors concluded that one of the major limitations of the DWI-MRI was poor specificity and inadequate differentiation of malignant and non-malignant lesions was more likely compared to PET/CT, favouring PET/CT as a whole body imaging technique in breast cancer staging.

Finally, Moon et al. 2013[30] performed a comparison of breast-specific PET/CT with supine PET/CT or MR-mammography in 40 women with diagnosed breast cancer. Interestingly the authors found that there were significant variations in the identified tumour characteristics based on the use of breast-specific or systemic PET/CT, with significant variations in tumour size (P<0.001), tumour to skin distance (P<0.001) and the volume of the axillary fossa (P=0.03). Definition of the tumour stage was more accurate with breast-specific PET/CT than with supine PET/CT (72.5% versus 67.5%), while both techniques were comparable in lymph node assessment. Furthermore, mammographic PET/CT was superior to MR-mammography in the detection of focal lesions (95% versus 90%) and in correlation of results with pathological findings. Therefore, mammography-PET/CT was the optimal imaging technique in this study and resulted in more accurate staging of disease than supine PET/CT and additional imaging techniques of the breast.

Author/year	Design	Patient no.	Patient characteristics	Outcome measures	Key findings	Quality issues
Heusner et al., 2008	Retrospective cf. standard imaging	40	Suspected BC	Treatment and staging	PET/CT 54% of staging accurate cf MRI 77% Change in treatment with PET/CT 12.5%	Single institution, retrospective
Heusner et al., 2010	Retrospective cf. DWI-MRI	20 (552 lesions)	BC diagnosed, preoperative	Sensitivity / specificity	PET/CT: Sens 94%, Sepc 99% MRI: Sens 91%, Spec 72% (82% false +ve)	Small patient no, retrospective
Jeong et al., 2014	Retrospective cf. standard imaging	178	BC, -ve ALN	Staging and treatment	PET/CT: Sens 87.6% (primary tumour) PET/CT: Sens 20.8%, spec 86.9% (ALN) Change in treatment In 3.9% patients	Retrospective, unclear standard protocol
Koolen et al., 2012	Prospective cf. standard	154	Stage II or III, to receive NAC	Distant Mets and clinical importance	42 new lesions in 25 patients with PET/CT Sens 100%, Spec 96% Change in treatment 8% patients	No comparable Sens/Spec data for standard
Koolen et al., 2014	Prospective cf. standard	62	T1 stage disease	Sensitivity	PET/CT detected primary in 87% patients Up to 98% in tumours >1cm	Single institution, limited patient group

Table 5. Main characteristics of Studies that include all previous aspects (Sensitivity, Specificity, Staging and Prognostic impact)

Cost and Ease of use

Of the studies included in the present review, there is little consideration given to cost effectiveness of PET/CT versus multimodal staging methods. However, it has been suggested by a number of authors that when PET/CT can be used in the place of several different technologies, the diagnostic and staging process would be associated with a reduced overall cost[28,30]. It should be noted that the majority of studies concluded that PET/CT was an adjunctive measure, to be used as part of the multiumodal staging process, and therefore this theoretical cost saving will not be applicable to practice[19,22]. Hence, the cost of PET/CT in terms of the ability of the technology to enhance patient care and reduce the need for expensive and ineffective interventions should be considered. This was not clearly addressed in the present review literature, although it can be assumed that the variable level of sensitivity or specificity of PET/CT would hinder the cost-effectiveness of the technique in practice, as the technology cannot be guaranteed to reduce future care costs[22].

\The ease of use of PET/CT is another issue that should be considered briefly, as several authors identified this as a potential obstacle or advantage to the staging process, depending on individual perspectives. Moon et al. (2013) provided an overview of this factor in their analysis of different forms of PET/CT, including breast-specific and whole body technology, and noted that both were technically challenging aspects to the staging process and would require additional operator training to ensure accuracy during staging. This contrasts with existing technology for the staging of breast cancer, where use of these technologies over decades has led to high operator reliability[28]. However, it is possible that PET/CT could be used affectively if training is optimised, although this remains a research interest of future studies.

V. Discussion

This section will provide an overview of the findings of the literature review and intends on placing these findings within the context of current research and practice. To specifically answer the research questions posed for this review, the following domains will be discussed in detail: sensitivity and specificity, clinical application of PET/CT, technical considerations of PET/CT use, and the limitations of studies included in this review.

Sensitivity and Specificity

Sensitivity and specificity for primary lesions

One of the most important means of assessing the effectiveness of imaging strategies in the identification of tumour characteristics is an evaluation of sensitivity and specificity characteristics[31]. Sensitivity is indicative of the false negative rate, whereby imaging studies can incorrectly miss the presence of either a tumour, or metastases in the axilla or more distant tissues[31]. The papers included in this review demonstrated a large degree of variability in the sensitivity value of PET/CT and often it is more suitable to compare this value to those achieved through comparison imaging techniques. The same is true for specificity results, which are indicative of false positive rates, and therefore a detailed discussion of the findings is required to understand the pooled data from included studies.

The sensitivity of PET/CT for the detection of the primary breast tumour was 48% in one study[23], compared to 52% for breast sonography and 33% for mammography, which was similar to the finding by Taira et al., where the sensitivity of PET/CT for primary lesions was 48%. However, a direct comparison of PET/CT against DWI-MRI showed sensitivities of 94% and 91%, respectively, for the primary lesions[21]. One of the reasons for this variability may be related to the size of the primary tumour, as Koolen et al., 2014 noted that sensitivity levels increased to 98% for PET/CT in tumours greater than 1cm in size. This may suggest that the technical limitations of PET/CT result in difficulties in imaging smaller lesion, resulting in an increased likelihood of missing these lesions in practice. However, of comfort is the fact that the specificity of PET/CT is almost uniformly high in all studies, ranging from 82-100%, suggesting that when lesions are identified in breast tissue they are very seldom false positive findings[21,23].

However, despite these findings, the use of PET/CT in defining the primary breast tumour in patients suspected of breast cancer may be limited, as this is a resource-intensive approach to cancer detection[32].

Impact of PET/CT on staging

Several studies in this paper assessed the potential of PET/CT to impact on patient staging as a specific outcome measure.In addition to the evaluation of sensitivity and specificity for lesions in various locations[27,29]. The staging process for breast cancer requires adequate identification and characterisation of the primary tumour, as well as the identification and characterisation of lymph node involvement and distant metastases[33]. Based on the ability of PET/CT to accurately define all of these tumour factors, particularly distant metastases, the technology would be assumed to have an impact on the staging process.

For all cases where PET/CT was employed, the alteration of staging was an upgrade rather than a downgrade, based on detection of additional tumour lesions in the body. This suggests that PET/CT may be an important adjunctive approach to enhancing existing staging protocols that may miss these lesions[34].

Which patients should receive PET/CT?

Defining the patient population that is most likely to benefit from this staging additional is complex due to the fact that even patients with low stage disease could have their stage enhanced by PET/CT imaging. Adding on this technology for all patients, regardless of their likely breast cancer stage following initial screening would be costly and raises the concern that contradictory results may emerge as more imaging techniques are used, which may complicate the staging process rather than enhance it[10,35]. The data presented in this paper is of limited use in defining the patient population where PET/CT may be of greatest benefit due to the complexity of this issue and the variability in defined patient populations in the included studies.

The value of TNM staging in breast cancer

An additional point that is worth considering prior to providing an overview of the clinical application of PET/CT based on the ability of the modality to enhance breast cancer staging, is whether or not the use of the TNM staging system remains the optimal approach to prognostication in breast cancer[25,29].

The role of TNM staging may be limited in determining true clinical outcomes for patients with breast cancer as a result of the biological activity profile of the tumour[36]. The fact that PET scanning in particular may be useful in assessing biological activity suggests that evaluations which are limited to detecting changes in TNM stages may be limited in assessing the true significance of PET/CT in practice[36]. Further studies would be needed to clarify the role of PET/CT in this way, but this remains an interesting area for future research.

VI. Conclusion

In summary, the aim of this paper was to evaluate the effectiveness of combined PET/CT for disease staging in breast cancer. A literature review was performed and analysis of the relevant studies suggested that there is a clear role for combined PET/CT in clinical practice. The role of PET/CT in cancer staging was a primary outcome in some published studies and the evidence suggests that this modality may be useful in influencing staging decisions in real life patients.

The benefits of PET/CT include the low false-positive rate for the detection of distant metastases, as well as the consistently high sensitivity for the detection of lymph node and metastatic disease. Some evidence also suggests that PET/CT imaging of the primary tumour can provide important prognostic information in some patients, although this is not consistent across studies. However, the role of PET/CT in comparison with a multi-modal imaging modality is largely difficult to determine, due to variable nature of these imaging strategies and the lack of clear RCT head-=to-head comparisons of these methods. Rather, the role of PET/CT seems to be as an adjunct to existing approaches routinely used in clinical practice.

However, despite the evidence in favour of the use of PET/CT in breast cancer staging and prognostication, there remain a number of unanswered questions and areas of uncertainty. For instance, the ideal patient selection criteria for the use of adjunctive PET/CT remains unclear and the value of PET/CT may be partially determined by the size of the primary tumour and the characteristics of the tumour. More research is needed to explore the value of PET/CT in the assessment of metabolic activity in tumours, which may enhance the use of this technology and provide further answers to these questions. Finally, there is a need to ensure that the full potential of PET/CT is explored in the literature, as this technology has the potential to revolutionise breast cancer imaging and imaging in a variety of cancers, influencing the staging and management of patients.

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