Critical Reviews in Oncology / Hematology 151 (2020) 102943

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

[18F]FDG PET/CT in the staging of inflammatory breast cancer: A systematic review

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ARTICLE INFO

Keywords:
Positron emission tomography
Staging
Inflammatory breast cancer

ABSTRACT

Up to 78 % of patients with inflammatory breast cancer (IBC) present with axillary lymph node involvement and up to 40 % with distant metastases. Previous studies indicate that 2-deoxy-2-(^{18}F)fluoro-D-glucose ([^{18}F]FDG) positron emission tomography/computed tomography (PET/CT) might be used for initial staging in patients with inflammatory breast cancer (IBC). In other cancer types, [^{18}F]FDG PET/CT has been demonstrated to be a sensitive technique, providing complementary information on locoregional and distant disease to conventional imaging modalities. This systematic review showed that ^{18}F]FDG PET/CT detects additional locoregional lymph node metastases and distant metastases in 10.3 % of patients, that were not detected with standard staging imaging. Compared with conventional imaging procedures, [^{18}F]FDG PET/CT had better diagnostic performance for detection of locoregional and distant metastases and should standardly be used in the diagnostic work-up of IBC patients.

1. Introduction

At diagnosis, up to 78 % of patients with inflammatory breast cancer (IBC) have axillary lymph node involvement and up to 40 % present with distant metastases (stage IV).(van Uden DJP et al., 2017; Fouad et al., 2015; Dawood et al., 2014) Given this high rate of metastatic disease at presentation, patients with IBC routinely undergo extensive evaluations, including whole body bone scintigraphy, ultrasonography of the liver and a chest X-ray.(Dawood et al., 2011) The current standard of care in the management of local or locoregional IBC includes neo-adjuvant chemotherapy (NACT), followed by modified radical mastectomy, high-dose adjuvant radiation therapy to the chest wall and lymph nodes.(Dawood et al., 2011) Although this multimodal therapeutic approach has significantly improved survival, the 5-year overall survival rates (30–40 %) remain poor (van Uden DJP et al., 2017). In patients presenting with stage IV IBC, primary systemic therapy is used to achieve optimal local response, and patients should be evaluated for surgery and radiation therapy using a multidisciplinary approach (Ueno et al., 2018). Furthermore, identification of metastases might lead to change of management since these metastases might be treated by local therapy (including radiation therapy) or choice of systemic treatment might be changed based on metastatic load (Takiar et al., 2014; Akay et al., 2014).

Several studies have pointed out the added value of 2-deoxy-2-(^{18}F) fluoro-D-glucose [18 F]FDG PET/CT in patients with clinical stage II or III non-inflammatory breast cancer.(Groheux et al., 2016) Since IBC has a higher metastatic potential as compared to other breast cancer subtypes, implementation of [^{18}F]FDG PET/CT in the diagnostic workup might be of use. Probably [^{18}F]FDG PET/CT could replace other investigations for the detection of distant metastases. However, small lesions and PET-negative lesions are pitfalls as well as false-positive lesions; which both can lead to suboptimal patient management.

Inclusion of [^{18}F]FDG PET/CT might influence the diagnostic process for patients presenting with IBC, and may be supportive to the multidisciplinary discussion of which therapies are appropriate once distant disease has been diagnosed.

In the present study, we performed a systemic review of all available studies to address diagnostic performance of [^{18}F]FDG PET/CT in the

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https://doi.org/10.1016/j.critrevonc.2020.102943
Received 24 September 2019; Received in revised form 27 January 2020; Accepted 19 March 2020

staging of patients with inflammatory breast cancer and compared this to several conventional imaging modalities used for evaluation of the primary tumor, regional lymph nodes and distant metastases.

2. Materials and methods

Narrative research question: What is the diagnostic performance of [^{18}F]FDG PET/CT in the staging of patients with inflammatory breast cancer compared to conventional imaging modalities used for evaluation of the primary tumor, regional lymph nodes and distant metastases?

PICO question:

- Population: patients with inflammatory breast cancer
- Intervention: [^{18}F]FDG PET/CT
- Comparison: conventional imaging modalities (mammography, ultrasound of the breast/regional lymph nodes and abdomen), chest X-ray, whole body bone scintigraphy, CT of the chest/abdomen
- Outcomes: rates of additionally found disease in the breasts, locoregional lymph node metastases and distant metastases. Change of management based on [^{18}F]FDG PET/CT findings.

2.1. Search strategy

A systematic literature search was performed using the in the PUBMED, MEDLINE, EMBASE and COCHRANE Library from January 1990 to June 2019, on June 19th, 2019. The authors registered the protocol of the systematic review with PROSPERO (https://www.crd.york.ac.uk/prospero) on June 13th, 2019 (CRD42019138910).

1. PubMed using MESH terms: ((Breast[tiab] AND (neoplasm[tiab] OR neoplasms tiab OR cancer[tiab] OR carcinoma[tiab])) AND (inflammatory[tiab] OR "locally advanced")) OR ("Breast Neoplasms"[Mesh] AND (inflammatory[tiab]) OR ibc[tiab] OR "locally advanced"[tiab]) AND ("Tomography, Emission-Computed"[Mesh] OR "Fluorodeoxyglucose F18/diagnostic use"[Mesh] OR pet-ct OR PET/CT OR FDG PET) 2. Medline using free terms: (Tomography, emission-computed or positron emission tomography) AND inflammatory breast neoplasms 3. Embase using free terms: Positron emission tomography AND (inflammatory breast neoplasms or inflammatory breast cancer or inflammatory breast tumor). 4. Cochrane using free terms: Positron emission tomography AND (inflammatory breast neoplasms or inflammatory breast cancer or inflammatory breast tumor). 5. article-related references (manual cross-referencing).

2.2. Study selection and data extraction

Articles were collected in an Endnote library (Endnote X8, Thompson Reuters). From the initial search results, two investigators (DVU and MP) independently evaluated the abstracts and selected relevant articles matching the selection criteria of our study. Disagreements were resolved by discussion with a third party (EHJGA) until a consensus decision was reached. In case of duplicate publications, only the original publication was used with the original PET/CT data.

Studies were eligible for inclusion based on the following criteria: 1. Studies, in which [^{18}F]FDG PET/CT was used for staging of patients presenting with inflammatory breast cancer (with histological proof of malignancy) and compared to other types of imaging. 2. Studies based on a per-patient analysis 3. Data or subsets of data were presented in more than one article, the article with the most details or the most recent article was chosen. Exclusion criteria: 1. Abstracts presented at congresses, case reports, meta-analyses, reviews, letters, editorials and comments. 2. Duplicated studies with overlapping patient populations as well as studies with less than ten included patients. 3. Studies that involve patients with mixed population of histological subtypes of breast cancer, but not reporting subgroup analysis or individual data of inflammatory breast cancer patients 4. Animal studies or in vitro studies. 5. No full-text available in English. All articles were scoring using the QUADAS-2 system.(Whiting et al., 2011) Differences in opinion on either inclusion or exclusion were resolved by consensus procedure [by EHJGA as third reader].

2.3. Quality assessment of included studies

Two reviewers (DVU, MP) independently assessed the methodological quality of the studies using the quality assessment for studies of diagnostic accuracy (QUADAS-2) tool. Results were verified by a third reviewer (EHJGA). Any discrepancy was resolved by consensus. The QUADAS-2 tool is an evidence-based quality assessment tool for systematic reviews of diagnostic accuracy studies. A summary of the methodological quality is shown in

2.4. Content of the studies

From the selected publications, the following data were extracted: comparison of [^{18}F]FDG PET/CT with other diagnostic modalities with regard to the primary tumor, locoregional lymph nodes and/or distant metastases, change in management due to [^{18}F]FDG PET/CT results. Moreover, data on technical aspects such as SUV (standardized uptake value) were recovered as well as data on discovered lymph nodes and other modalities performed.

2.5. Data extraction

If available, data from individual studies were summarized in a 2×2 table classifying patients as true-positives, true-negatives, false-positives and false-negatives. The sensitivity and specificity of [^{18}F]FDG PET/CT in staging IBC (primary breast tumor, locoregional lymph nodes and distant metastases) were obtained from the individual studies (if adequate data was available) on a per-patient-based analysis.

A true positive test result is one that detects the condition when the condition is present. A true negative test result is one that does not detect the condition when the condition is absent. A false positive test result is one that detects the condition when the condition is absent. A false negative test result is one that does not detect the condition when the condition is present.

Sensitivity was determined according to the formula:TP/(TP + FN), and specificity was determined according to the TN/(TN + FP). Statistical analyses were performed using Graphpad Prism version 5.03 for Windows (GraphPad Software, San Diego California USA).

3. Results

3.1. Search results

The literature search generated a total of 1386 publications. Fig. 1 shows the flow chart of the search procedure for the publications. After removal of duplicate citations and addition of cross-referenced publications, publications were reviewed based on the abstract. 21 publications were considered eligible and were further analysed in full text.

Six publications were included in the analyses based on the QUADAS-2 criteria (Table 1). A summary of the methodological quality is shown in Table 2.

Of the six publications included in our analysis, one study was a prospective study and five studies were retrospective case series. A combined total of 271 patients with IBC were described in the included studies.

3.2. Primary breast tumors

Five studies (Alberini et al., 2009; Carkaci et al., 2009; Champion et al., 2013; Groheux et al., 2013; Yang et al., 2008) described the evaluation by [^{18}F]FDG PET/CT of primary breast tumors, with

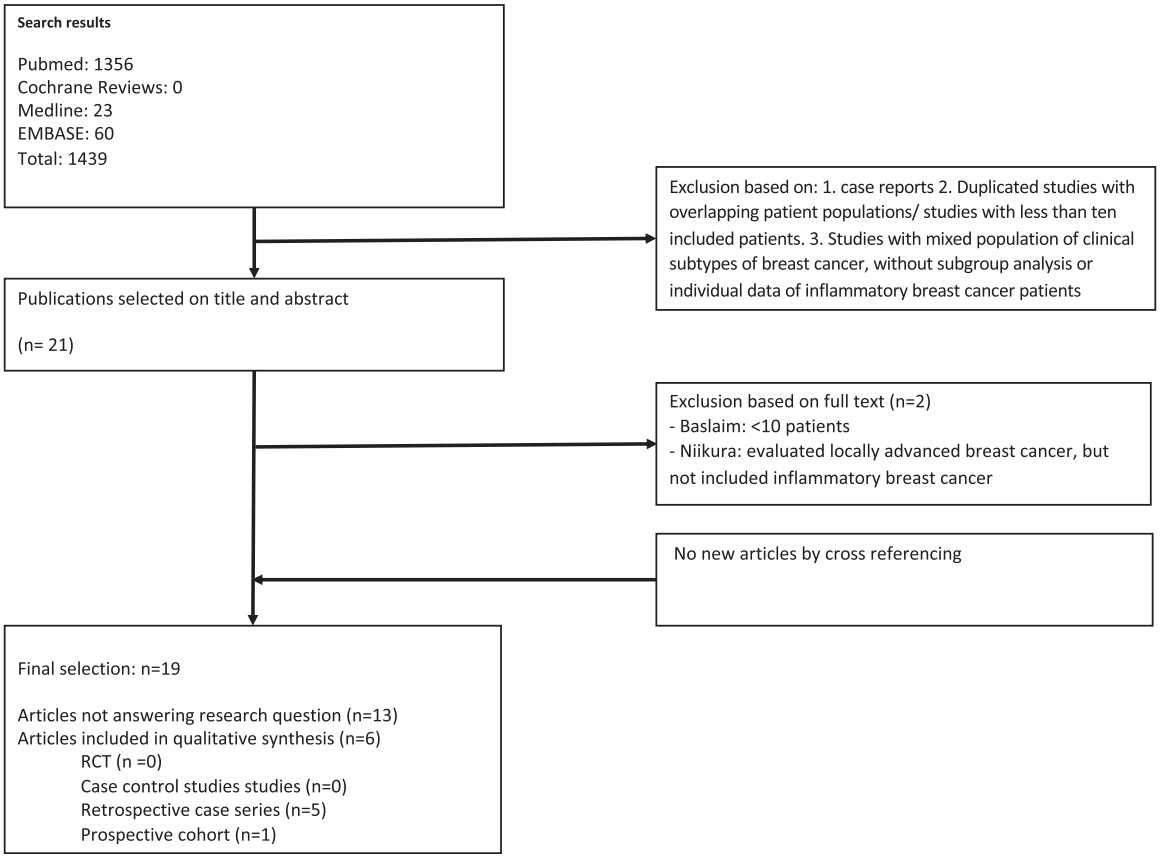

Fig. 1. Flow chart of the search for eligible studies on the diagnostic performance of [18F]FDG PET/CT in the staging of patients with infammatory breast cancer compared to conventional imaging modalities.

histopathologic examination as gold standard, with sensitivity ranging from 96 % to 100 %.(Alberini et al., 2009) included patients presenting with mastitis and showed that PET/CT scan was positive for primary malignant tumors in 100 % and also showed FDG uptake in two of three cases of benign mastitis. SUVmax values were measured at 9.0 ± 5.7 for IBC and at 12.0 and 22.0 in the two patients with false-positive PET results. An overlying skin-increased activity was found in 78 % of the IBC (46 of 59) patients, but was not observed in mastitis patients. (See Table 3) Carkaci found a mean SUV of 11.4 (range, 2.5–30.6). All patients had skin thickening that demonstrated hypermetabolic uptake and a mean SUV of 5.2 (range, 2.5–29.0). Champion displayed a mean SUVmax of 9 (range 3–26) and Groheux found that all primary tumors showed [^{18}F]-FDG uptake (mean maximal SUV, 8.7; range, 1.2–27.6). Walker did not describe ^{18}F-FDG uptake in the primary lesion. See Table 4 for diagnostic finding of [^{18}F]-FDG PET/CT on a per-patient based analysis in the staging of IBC.

3.3. Locoregional lymph nodes

(Alberini et al. (2009)) showed that, in 59 IBC patients, [^{18}F]FDG positive lymph nodes were detected in axillary (90 %; n = 53) and extra-axillary areas (56 %; n = 33) ipsilateral to the cancer. As compared with clinical examination, PET/CT upstaged the axillary lymph node status in 35 and downstaged the lymph node status in five patients. The nodal foci were compared with preoperative fine needle aspiration and/or pathological post-chemotherapy findings available in 44 patients which corresponded to 38 true positive, four false-negative, and two false-positive cases.(Champion et al. (2013)) showed that in 28 node-positive patients (of the 32 patients treated with mastectomy and axillary lymph node dissection), PET/CT had higher sensitivity and positive predictive value compared to contrast enhanced CT (sensitivity 93 % vs. 86 %, PPV 93 % vs. 89 %) to detect lymph node metastases on a per-patient base. (Carkaci et al. (2009)) reported that among 41 IBC patients, PET/CT detected metastases in the axillary lymph nodes in 90 %, and supraclavicular lymph nodes in 24 % of the patients. Furthermore, one false-negative axillary lymph node did not show increased [^{18}F]FDG uptake on PET/CT, but showed malignancy on ultrasonography-guided fine-needle aspiration biopsy of which no information was available regarding size of metastasis or whether it concerned for example isolated tumor cells.(Carkaci et al. (2009))

(Walker et al. (2012)) reported 14 additional locoregional lymph nodes as additional sites of disease in seven patients and this resulted in adaptation of radiation therapy planning with treatment of the additionally found lymph node sites.

3.4. Distant metastases

(Carkaci et al. (2009)) reported that among 41 patients with inflammatory breast cancer, seven of the 20 cases of distant metastases were not detected by other imaging modalities. (Alberini et al. (2009)) reported that among 62 patients with inflammatory breast cancer, six of 18 patients presenting with distant metastases were unsuspected before PET/CT was performed. In the study of (Groheux et al. (2013)), PET/CT outperformed conventional imaging for distant lymph nodes, bone metastases and liver metastases, whereas dedicated CT was more sensitive for lung metastases (100 % versus 85.7 %).(Yang et al. (2008)) showed that metastatic disease was diagnosed in 38 % of patients on PET/CT and was confirmed in all patients (44 % with histologic confirmation and 56 % with correlative conventional imaging). However, it was not described what conventional imaging was performed at baseline. Walker(Walker et al., 2012) reported six bone metastases and one non-breast second primary (gastrointestinal stromal tumor), in addition

Table 1
Basic study and patient characteristics of the included 6 publications. Study quality as measured by the QUADAS-tool (maximum score of 14 for the optimal study quality).

Author, year, Design,	Clinical criteria of IBC	Median FU (range)	Mean age (years)	QUADAS Score	Main findings of study			Upstaging and change of management
					Primary tumor	Axillary lymph nodes	Distant metastases	
Alberini, 2009 Prospective (59 patients)	Diffuse breast edema and erythema*, warmth, induration	44 months (5−59)	50.4	8	PET-scan was positive for the primary tumor in 100%	Nodal foci were compared in 44 patients compared with FNA/ pathological findings: 38 true positive	In 18/59 patients (31%), distant lesions were found on PET/CT 6 of these 18 patients (33 %) were unsuspected prior to PET/CT) No histological confirmation of metastatic sites	Upstaging: 12 patients upstaged to stage IV COM: 13/18 pts with metastasis found on PET/CT received only CT and RT
Carkaci, 2009 Retrospective 41 patients	erythema, edema involving more than two thirds of the breast*, or breast induration on palpation.	NA	50.0	8	PET-scan was positive for the primary tumor in 98 %	In 90 % of patients PET/CT detected axillary metastasis; 1 F N finding Biopsy findings available for 41 patients	In 20/41 patients (49 %), distant lesions were found; in 17 % PET/CT revealed distant metastases not known before PET/CT. Biopsy findings available for 7 patients: 2 false negative sites (pulmonary)	Upstaging: 7 patients upstaged to stage IV COM: NR
Champion, 2012 Retrospective 50 patients	diffuse erythema and edema involving more than one-third of the breast skin,	37 months (8−84)	51.0	9	PET-scan was positive for the primary tumor in 100%	28 node positive patients, of 32 treated by ALND: sensitivity 93%, PPV 93%	In 19/50 patients (38 %), distant lesions were found on PET/CT No histological confirmation of metastatic sites	Upstaging NR COM: NR
Groheux,2012 Retrospective 35 patients	diffuse erythema and edema, involving a third or more of the skin of the breast	NR	NR	9	PET-scan was positive for the primary tumor in 100 %	34 cN + patients histological confirmation NR for IBC	In 16/35 patients (45.7 %), distant lesions were found on PET/CT No histological confirmation of metastatic sites	Upstaging: 22/35 (63 %); 1 CRC, 1 TC COM: NR
Walker, 2011 Retrospective 62 patients	NR	40.9 months	49.3	9	NR	14 additional locoregional occurrences histological confirmation NR	PET/CT detected new areas of disease in 27/62 patients (44 %) histological confirmation of 1 metastatic site	Upstaging: 27 new disease areas (number of individual patients unknown)COM: 11 (17.7 %) change of radiation plan
Yang, 2007 Retrospective 24 patients	NR	NR	51	8	PET-scan was positive for the primary tumor in 95.8%	22 new node positive patients on PET/CT histological confirmation NR	In 9/24 patients (38 %), distant lesions were found on PET/CT histological confirmation of metastatic sites in 4 patients	Upstaging: 9 patients upstaged to stage IVCOM: NR

Abbreviations: IBC, inflammatory breast cancer; FU, follow up; LN, lymph node; CI, conventional imaging; cN+, clinical node positive; CRC, colorectal cancer; TC, thyroid cancer; PET, positron emission tomography; ALND, axillary lymph node dissection; NA, not available; COM, change of management; NR, not reported; * peau d'orange.

Table 2
Tabular presentation for QUADAS-2 results.

Item	Alberini	Carkaci	Champion	Groheux	Walker	Yang
1.Was the spectrum of patients representative of the patients who will receive the test in practice?	+	+	+	+	+	+
2.Were selection criteria clearly described?	+	+	+	+	+	+
3.Is the reference standard likely to correctly classify the target condition?	+	+	+	+	+	+
4.Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	+	–	+	+	?	–
5.Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?	+	+	+	+	+	+
6.Did patients receive the same reference standard regardless of the index test result?	+	+	+	–	+	–
7.Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	?	–	?	+	+	+
8.Was the execution of the index test described in sufficient detail to permit replication of the test?	+	+	+	+	+	+
9.Was the execution of the reference standard described in sufficient detail to permit its replication?	–	+	+	+	+	+
10.Were index test results interpreted without knowledge of results of the reference standard	–	+	–	–	–	–
11.Were the reference standard results interpreted without knowledge of the results of the index test?	–	–	–	–	–	–
12.Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	+	+	+	+	+	+
13.Were uninterpretable/ intermediate test results reported?	–	–	–	–	–	–
14.Were withdrawals from the study explained?	+	?	–	–	–	–
Risk of bias						
Patient selection	Low	High	High	High	High	High
Index test	High	Low	High	High	High	High
Reference standard	High	High	High	High	High	High
Flow and timing	Low	High	High	High	High	High

+ = yes; - = high risk,? = unclear.

to conventional imaging.

3.5. Upstaging and change of management

In all studies together, at least 28 out of 271 patients (10.3 %) were upstaged to stage IV disease based on additional PET/CT findings (Table 1). Walker described the number of additional areas of disease without corresponding number of patients. Therefore, the total number of upstaged patients in all publications is likely higher than 28.

Change of management was not included in all six studies;(Groheux et al. (2013)) described the finding of two additional malignancies (colorectal and thyroid cancer), as did Walker(Walker et al., 2012) (GIST), without clarification of the subsequent management. (Walker et al., 2012) described the effect of pre-treatment PET/CT on post-mastectomy radiation therapy. Based on PET/CT findings, radiation therapy was changed 17.7 % of patients (additional fields, adjustment of field size, and higher doses to the supraclavicular fossa and internal mammary chain. (Alberini et al. (2009)) treated 13 out of 18 patients with suspicion of metastases based on PET/CT, with chemotherapy and radiation therapy only. Other studies did not report additional data on follow-up of changes in locoregional treatment planning.

4. Discussion

This systematic review is the first to summarize the literature on the use of [^{18}F]FDG PET-CT in the initial staging in IBC. Our results indicate that [^{18}F]FDG PET/CT has additional value in the detection of locoregional lymph node metastasis and distant disease as compared to conventional imaging techniques. Additional findings on PET/CT during diagnostic workup provoked a change in treatment plan in estimated 10 % of patients. IBC has a higher tendency of lymph node metastases than other forms of breast cancer and indeed a high percentage of axillary lymph node involvement was noted in the analysed studies (up to 70 %).(Carkaci et al., 2009) Although the poor spatial resolution of PET/CT limits its detection rate for small sized lymph node metastases, detection of pre-treatment locoregional metastases in IBC resulted in adaptation of radiation therapy treatment fields and dose planning.(Walker et al., 2012)

Compared to conventional imaging (chest x-ray, bone scintigraphy, abdominal ultrasound), [^{18}F]FDG PET/CT shows unexpected distant metastases in up to 17 % of patients.(Alberini et al., 2009) Early detection of distant metastases is critical for correct staging and shared decision making when systemic treatment options are discussed. The sensitivity for conventional imaging to detect distant metastases in locally advanced breast cancer (LABC) ranges from 40 to 60%.(Manohar et al., 2013; Mahner et al., 2008) Previous research in non-inflammatory LABC has shown that the addition of [18 F]FDG PET/CT has led to the detection of unexpected stage IV disease in 8% of patients.(Van Der Hoeven JJM et al., 2004) Based on data presented in our review, > 10 % of IBC patients are upstaged to stage IV. According to the current NCCN guidelines, [^{18}F]FDG PET/CT is helpful in situations where standard imaging studies are equivocal.(Giordano et al., 2018) Given the high rate of metastases in IBC, [^{18}F]FDG PET/CT might have a more prominent role.(van Uden et al., 2015)

Inclusion of [^{18}F]FDG PET/CT in the diagnostic work up leads to changes in radiation therapy in nearly 18 % of IBC patients.(Walker et al., 2012) Furthermore, in one study, change of management regarding omitting surgery of the primary tumor was mentioned. In the series of Alberini,(Alberini et al., 2009) 13 of the 18 patients with suspicion of metastatic disease on [^{18}F]FDG PET/CT received chemotherapy followed by radiation therapy alone for the primary tumor. (Bourgier et al., 2012) In patients not willing or able to undergo surgery of locally advanced breast cancer, locoregional radiation therapy might be an alternative for local control and seems a reasonable alternative to be discussed with the individual patient to ensure patient tailored treatment.(Yee et al., 2018)

A previously performed meta-analysis in patients with non-inflammatory breast cancer showed that, compared with conventional imaging procedures, whole-body PET/PET-CT was found to have higher sensitivity (99 % vs. 57 %) for the detection of distant metastases.(Sun et al., 2015) Since IBC has a higher metastatic potential than early breast cancer and non-inflammatory LABC, PET/PET-CT theoretically is more valuable in IBC.(van Uden et al., 2015) We have previously shown that breast cancer subtypes in stage IV IBC are associated with distinct patterns of metastatic spread. Bone metastases were most commonly diagnosed in all stage IV IBC subtypes with a significant predominance in the HR + /HER2 − group. Liver metastases were more frequently observed in the HER2-enriched group and lung metastases in the HR − / HER2 − group.(Van Uden et al., 2019) By using [^{18}F]FDG PET/CT as diagnostic modality, the organs most at risk for metastatic spread could

Table 3
Technical aspects of 18 F-FGD-PET/CT in the included publications.

Author	No. of IBC	SUVmean			Correlative imaging	Test interval
		Primary breast tumor	Axillary Lymph nodes	Distant metastases		
Alberini	59	9.0 ± 5.7	6.4 ± 5.7	NR	CR, BS, AUS, AXUS + FNA (n = 34)	NR
Carkaci	41	11.4 (2.5–30.6)	11.7 (2.5–36.0)	- Bone (n = 9): 13.4 (5.8–24.6)- Liver (n = 6): 9 (4.9–12.7) - Pulmonary (n = 2): 12.4 (10.3–14.4)	BS, CR, AXUS, CCT, ACT	NR
Champion	50	9.0 (3 – 26)	7.9 ± 5.4	NR	DCE CT	5 ± 9 days (1 – 26)
Groheux	35	8.7 (1.2 – 27.6)	6.4 NR	NR	BS, CR, AXUS, CCT, ACT	NR
Walker	62	NR	NR	- Bone (n = 6): 7.9 (4.0–10.8) - Distant lymph nodes (n = 10): 5 (1.9–9.0)	BS, CR, AXUS, CCT, ACT	NR
Yang	24	NR	6.4 ± 5.7	NR (only SUVmax per lesion)	Breast US/ MRI, BS, ACT, CCT	NR

Abbreviations: SUV, standardized uptake value; ALN, axillary lymph nodes; NR, not reported; IBC, inflammatory breast cancer; FU, follow up; CR, chest radiography; BS, bone scintigraphy; AUS, abdominal ultrasound; AXUS, axillary ultrasound; DCE CT, dynamic contrast-enhanced computed tomography; CCT, chest CT, ACT, abdominal CT; MRI, magnetic resonance imaging.

be more closely evaluated than with conventional imaging. Special consideration should be given to cerebral metastases since [^{18}F]FDG PET/CT lacks sensitivity for cerebral metastases. Patients suspected for this should undergo dedicated cerebral imaging (MRI).(Groheux et al., 2016)

Some limitations regarding the present review have to be discussed. The systematic search excluded non-English studies from the analysis, thereby potentially missing relevant articles in other languages. We acknowledge the limited number of published studies, which predominantly describe the results from relatively small single-centre cohorts in a retrospective design. There are several other factors that might also influence the quality of study, such as the high number of items scored as “not documented”. We performed analyses according to the location of the disease, but lesion-based data was not available in all studies and this led to the high number of missing data. Furthermore, the interpretation of [^{18}F]FDG PET/CT scans was performed qualitatively in the majority of studies, and in the vast majority of these studies, no level of expertise of the person performing the interpretation was given as well as blinding for the results of other imaging modalities. In general, publication bias is of general concern in systematic reviews and this becomes particularly relevant for our limited number of included studies. Publication bias can influence the results of any systematic review since because small studies with favorable results might be published more easily than small studies with unfavorable results. However, a formal analysis of publication bias was not done. We did use the QUADAS-2 tool to identify sources of potential bias with the aim to ensure a minimal standard for included studies in a transparent manner (Whiting et al., 2011).

Finally, in the analysed studies, not every distant metastatic site detected by [^{18}F]FDG PET/CT was confirmed by histopathological analysis. Diagnostic biopsy of the metastatic site is the gold standard for diagnosing metastatic lesions, but also contains the risk of a false negative biopsy and in daily practice histologic evidence of metastatic disease is not always used in treatment decisions in case of a high radiological suspicion (Suh et al., 2016; Monfardini et al., 2014).

[^{18}F]FDG PET/CT might have a potential role in locoregional and systemic treatment planning in IBC, and potentially replacing conventional anatomical imaging techniques by increased sensitivity, at the cost of incidental findings. Incremental costs associated with additional procedures is commonly regarded a disadvantage of PET imaging early in the diagnostic workup (Caresia Aroztegui et al., 2017) Indeed, in a previous study in non-inflammatory metastatic breast cancer, upfront [^{18}F]FDG PET/CT introduced additional costs, however, the total number of tests decreased as compared with the standard work-up. Furthermore, the number of false positives decreased with PET/CT work-up. As opposed to costs associated with additional diagnostic procedures, omitting unnecessary surgery or invasive procedures could result in potential savings and a as a net result a more cost-efficient treatment strategy for IBC.(Koleva-Kolarova et al., 2015) The lack of appropriatedly sized studies on cost-effectiveness including both diagnostic and treatment procedures is a clear caveat.

Other directions for future studies on the role of PET imaging in IBC may be novel tracers, such as 16a-[^{18}F]fluoro-17b-oestradiol (FES), which can give insight in tumor ER expression in breast cancer. This might lead to a decrease of histological biopsies of metastatic locations which are normally advised to confirm findings and re-evaluate tumor receptor status of metastatic breast cancer.(Koleva-Kolarova et al., 2015) Furthermore, the role of [^{18}F]FDG PET/CT in assessment of response to neo-adjuvant systemic treatment should be evaluated. Early identification of non-responders to a particular chemotherapeutic regimen could theoretically lead to a change in treatment.(Alberini et al., 2009; Kolesnikov-Gauthier et al., 2012) The prognostic impact of early changes in [^{18}F]FDG PET/CT uptake in patients with locally advanced breast cancer who received NACT has been evaluated. The early change in [^{18}F]FDG PET/CT SUVmax after third-cycle NACT is an independent and good prognostic marker beyond pathologic response in patients

Table 4
diagnostic findings of 18 F-FDG PET/CT on a per-patient based analysis in the staging of IBC.

		Primary breast tumor								Locoregional lymph nodes								Distant metastases							
Author	No. of IBC	TP	FP	FN	TN	Se	Sp	PPV	NPV	TP	FP	FN	TN	Se	Sp	PPV	NPV	TP	FP	FN	TN	Se	Sp	PPV	NPV
Alberini	59	59	3[$]	0	0	100	NA	100	NA	38[#]	2	4	NA	90.5	NA	95	NA	3*	1*	3*	NA	NA	NA	NA	NA
Carkaci	41	40	0	1	0	97.6	NA	100	NA	37	1	5	NA	NA	NA	NA	NA	NA	2	4	NA	NA	NA	NA	NA
Champion	50	50	0	0	0	100	NA	100	NA	NA	NA	2	NA	93	NA	93	NA	NA	NA	NA	NA	NA	NA	NA	NA
Groheux	35	35	0	0	0	100	NA	100	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Walker	62	62	0	0	0	100	NA	100	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Yang	24	NA	NA	1	23	96	NA	NC	NA	NA	NA	NA	NA	95	100	100	33	NA	NA	NA	NA	NA	93	100	90

Abbreviations: IBC, inflammatory breast cancer; TP, true positive; FP, false positive; FN, false negative; TN, true negative; Se, sensitivity, in percent; Sp, specificity in percent; PPV, positive predictive value in percent; NPV, negative predictive, value in percent; NA, not available.
$: 3 patients had FP findings based on FDG-uptake in benign mastitis. All malign lesions (n = 59) were TP.
#: in 44 patients a comparison of PET results to preoperative FNA and/or postoperative results were available.
*: only reported for bone lesions.

with locally advanced breast cancer in general. Therefore, metabolic response as assessed by ^{18}F-FDG uptake can add information to pathologic response.(Bollineni et al., 2016; Liu et al., 2016) These results have also been found in a smaller group describing only IBC, in which PET/CT appeared to be useful to predict residual disease after NACT and survival in IBC.(Champion et al., 2013)

5. Conclusions

IBC is the most aggressive form of breast cancer with a high propensity of distant metastases. Accurate staging is of significant importance to guide locoregional and systemic treatment and to inform patients about their prognosis early in the course of their disease. [^{18}F]FDG PET/CT has a better diagnostic performance to assess both the extent of locoregional disease and presence of distant metastases compared to conventional imaging procedures. The considerable impact on patient management warrants replacement of conventional imaging by [^{18}F]FDG PET/CT in the diagnostic work-up of IBC patients.

Funding

The author(s) received no specific funding for this work.

Authors' contributions

All authors read and approved the final manuscript. All authors provided critical feedback and helped shape the research, analysis and manuscript.

Ethical approval for research

Not applicable.

External funding

No

Source of funding

Not applicable

Possible conflict of interest

The authors declare that they have no conflict of interest.

All the authors have made a significant contribution to this manuscript, have seen and approved the final manuscript, and have agreed to its submission to Critical Reviews in Oncology/Hematology.

Declaration of Competing Interest

The authors declare that they have no competing interests.

References

Akay, C.L., Ueno, N.T., Chisholm, G.B., Hortobagyi, G.N., Woodward, W.A., Alvarez, R.H., et al., 2014. Primary tumor resection as a component of multimodality treatment may improve local control and survival in patients with stage IV inflammatory breast cancer. Cancer. 120, 1319–1328.

Alberini, J.-L., Lerebours, F., Wartski, M., Fourme, E., Le Stanc, E., Gontier, E., et al., 2009. 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) imaging in the staging and prognosis of inflammatory breast cancer. Cancer [Internet] 115, 5038–5047. https://doi.org/10.1002/cncr.24534. Available from:.

Bollineni, V.R., Kramer, G.M., Jansma, E.P., Liu, Y., Oyen, W.J.G., 2016. A systematic review on [18F]FLT-PET uptake as a measure of treatment response in cancer patients. Eur J Cancer [Internet]. Elsevier Ltd 55, 81–97. https://doi.org/10.1016/j.ejca.2015.11.018. Available from:.

Bourgier, C., Pessoa, E.L., Dunant, A., Heymann, S., Spielmann, M., Uzan, C., et al., 2012. Exclusive alternating chemotherapy and radiotherapy in nonmetastatic inflammatory breast cancer: 20 years of follow-up. Int. J. Radiat. Oncol. Biol. Phys. 82, 690–695.

Caresia Aroztegui, A.P., García Vicente, A.M., Alvarez Ruiz, S., Delgado Bolton, R.C., Orcajo Rincon, J., Garcia Garzon, J.R., et al., 2017. 18F-FDG PET/CT in breast cancer: evidence-based recommendations in initial staging. J. Immunother. Emphasis Tumor Immunol. 39, 1–23.

Carkaci, S., Macapinlac, H.A., Cristofanilli, M., Mawlawi, O., Rohren, E., Gonzalez Angulo, A.M., et al., 2009. Retrospective study of 18F-FDG PET/CT in the diagnosis of inflammatory breast Cancer: preliminary data. J Nucl Med [Internet] 50, 231–238. https://doi.org/10.2967/jnumed.108.056010. Available from:.

Champion, L., Lerebours, F., Cherel, P., Edeline, V., Giraudet, A.L., Wartski, M., et al., 2013. 18F-FDG PET/CT imaging versus dynamic contrast-enhanced CT for staging and prognosis of inflammatory breast cancer. Eur. J. Nucl. Med. Mol. Imaging 40, 1206–1213.

Dawood, S., Merajver, S.D., Viens, P., Vermeulen, P.B., Swain, S.M., Buchholz, T.A., et al., 2011. International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment. Ann Oncol [Internet] 22, 515–523. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3105293&tool=pmcentrez&rendertype=abstract.

Dawood, S., Lei, X., Dent, R., Gupta, S., Sirohi, B., Cortes, J., et al., 2014. Survival of women with inflammatory breast cancer: a large population-based study. Ann. Oncol.

Fouad, T.M., Kogawa, T., Liu, D.D., Shen, Y., Masuda, H., El-Zein, R., et al., 2015. Overall survival differences between patients with inflammatory and noninflammatory breast cancer presenting with distant metastasis at diagnosis. Breast Cancer Res. Treat. 152.

Giordano, S.H., Elias, A.D., Gradishar, W.J., 2018. NCCN guidelines updates: breast cancer. JNCCN J Natl Compr Cancer Netw.

Groheux, D., Giacchetti, S., Delord, M., Hindie, E., Vercellino, L., Cuvier, C., et al., 2013. 18F-FDG PET/CT in Staging Patients with Locally Advanced or Inflammatory Breast Cancer: Comparison to Conventional Staging. J Nucl Med [Internet] 54, 5–11. https://doi.org/10.2967/jnumed.112.106864. Available from:.

Groheux, D., Cochet, A., Humbert, O., Alberini, J.-L., Hindie, E., Mankoff, D., 2016. 18F-FDG PET/CT for staging and restaging of breast Cancer. J Nucl Med [Internet] 57, 17S–26S. https://doi.org/10.2967/jnumed.115.157859. Available from:.

Kolesnikov-Gauthier, H., Vanlemmens, L., Baranzelli, M.C., Vennin, P., Servent, V., Fournier, C., et al., 2012. Predictive value of neoadjuvant chemotherapy failure in breast cancer using FDG-PET after the first course. Breast Cancer Res. Treat.

Koleva-Kolarova, R.G., Greuter, M.J.W., Van Kruchten, M., Vermeulen, K.M., Feenstra, T., Buskens, E., et al., 2015. The value of PET/CT with FES or FDG tracers in metastatic breast cancer: a computer simulation study in ER-positive patients. Br. J. Cancer.

Liu, Q., Wang, C., Li, P., Liu, J., Huang, G., Song, S., 2016. The role of (18)F-FDG PET/CT and MRI in assessing pathological complete response to neoadjuvant chemotherapy in patients with breast Cancer: a systematic review and meta-analysis. Biomed Res Int

[Internet]. Hindawi Publishing Corporation 2016, 3746232 Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4770138&tool=pmcentrez&rendertype=abstract.

Mahner, S., Schirrmacher, S., Brenner, W., Jenicke, L., Habermann, C.R., 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 [Internet] 19, 1249–1254. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18356138.

Manohar, K., Mittal, B.R., Bhoil, A., Bhattacharya, A., Singh, G., 2013. Role of 18F-FDG PET/CT in identifying distant metastatic disease missed by conventional imaging in patients with locally advanced breast cancer. Nucl. Med. Commun. 34, 557–561.

Monfardini, L., Preda, L., Aurilio, G., Rizzo, S., Bagnardi, V., Renne, G., et al., 2014. CT-guided bone biopsy in cancer patients with suspected bone metastases: retrospective review of 308 procedures. Radiol. Med.

Suh, Y.J., Lee, J.H., Hur, J., Hong, S.R., Im, D.J., Kim, Y.J., et al., 2016. Predictors of false-negative results from percutaneous transthoracic fine-needle aspiration biopsy: An observational study from a retrospective cohort. Yonsei Med. J.

Sun, Z., Yi, Y.L., Liu, Y., Xiong, J.P., He, C.Z., 2015. Comparison of whole-body PET/PET-CT and conventional imaging procedures for distant metastasis staging in patients with breast cancer: a meta-analysis. Eur. J. Gynaecol. Oncol.

Takiar, V., Akay, C.L., Stauder, M.C., Tereffe, W., Alvarez, R.H., Hoffman, K.E., et al., 2014. Predictors of durable no evidence of disease status in de novo metastatic inflammatory breast cancer patients treated with neoadjuvant chemotherapy and post-mastectomy radiation. Springerplus [Internet] 3, 166. Available from: http://springerplus.springeropen.com/articles/10.1186/2193-1801-3-166.

Ueno, N.T., Espinosa Fernandez, J.R., Cristofanilli, M., Overmoyer, B., Rea, D., Berdichevski, F., et al., 2018. International consensus on the clinical management of Inflammatory Breast Cancer from the Morgan Welch Inflammatory Breast Cancer research program 10th anniversary conference. J. Cancer 9 (8), 1437–1447.

Van Der Hoeven JJM, Krak N.C., Hoekstra, O.S., Comans, E.F.I., Boom, R.P.A., Van Geldere, D., et al., 2004. 18F-2-fluoro-2-deoxy-D-glucose positron emission tomography in staging of locally advanced breast cancer. J. Clin. Oncol. 22, 1253–1259.

van Uden, D.J.P., van Laarhoven, H.W.M., Westenberg, A.H., de Wilt, J.H.W., Blanken-Peeters, C.F.J.M., 2015. Inflammatory breast cancer: an overview. Crit. Rev. Oncol. Hematol. 116–126.

Van Uden, D.J.P., Van Maaren, M.C., Strobbe LJA, Bult P., Van Der Hoeven, J.J., Siesling, S., et al., 2019. Metastatic behavior and overall survival according to breast cancer subtypes in stage IV inflammatory breast cancer. Breast Cancer Res.

van Uden DJP, Bretveld R., Siesling, S., de Wilt, J.H.W., Blanken-Peeters, C.F.J.M., 2017. Inflammatory breast cancer in the Netherlands; improved survival over the last decades. Breast Cancer Res Treat [Internet]. Springer US 162, 365–374. Available from: http://link.springer.com/10.1007/s10549-017-4119-6.

Walker, G.V., Niikura, N., Yang, W., Rohren, E., Valero, V., Woodward, W.A., et al., 2012. Pretreatment staging positron emission tomography/computed tomography in patients with inflammatory breast cancer influences radiation treatment field designs. Int J Radiat Oncol Biol Phys [Internet]. Elsevier Inc 83, 1381–1386. https://doi.org/10.1016/j.ijrobp.2011.10.040. Available from:.

Whiting, P.F., Rutjes, A.W.S., Westwood, M.E., Mallett, S., Deeks, J.J., Reitsma, J.B., et al., 2011. Quadas-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann. Intern. Med.

Yang, W.T., Le-Petross, H.T., Macapinlac, H., Carkaci, S., Gonzalez-Angulo, A.M., Dawood, S., et al., 2008. Inflammatory breast cancer: PET/CT, MRI, mammography, and sonography findings. Breast Cancer Res. Treat. 109, 417–426.

Yee, C., Alayed, Y., Drost, L., Karam, I., Vesprini, D., McCann, C., et al., 2018. Radiotherapy for patients with unresected locally advanced breast cancer. Ann. Palliat. Med.