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Review article

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Diagnostic performance of PET/computed tomography versus PET/MRI and diffusion-weighted imaging in the N- and M-staging of breast cancer patients

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Objective **To provide a systematic review regarding the diagnostic performance of 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography/magnetic resonance imaging (PET/MRI) and diffusion-weighted imaging (DWI) compared to 18F-FDG PET/computed tomography (CT) focused on nodal and distant staging in breast cancer patients.**

Methods **The *PubMed* and *Embase* databases were searched for relevant publications until April 2020. Two independent reviewers searched for eligible articles based on predefined in- and exclusion criteria, assessed quality and extracted data.**

Results **Eleven eligible studies were selected from 561 publications identified by the search. In seven studies, PET/CT was compared with PET/MRI, and in five, PET/CT with DWI. Significantly higher sensitivity for PET/MRI compared to PET/CT in a lesion-based analysis was reported for all lesions together (77% versus 89%) in one study, osseous metastases (69–99% versus 92–98%) in two studies and hepatic metastases (70–75% versus 80–100%) in one study. Moreover, PET/MRI revealed a significantly higher amount of osseous metastases (90 versus 141) than PET/CT. PET/CT is associated with a statistically higher specificity than PET/MRI in the lesion detection of all lesions together (98% versus 96%) and of osseous metastases (100% versus 95%), both in one study. None of the reviewed studies reported significant differences between PET/CT and DWI for any of the evaluated sites. There is a trend toward higher specificity for PET/CT.**

Conclusion **In general, there is a trend toward higher sensitivity and lower specificity of PET/MRI when compared to PET/CT. Results on the diagnostic performance of DWI are conflicting. Rather than evaluating it separate, it seems to have complementary value when combined with other MR sequences. *Nucl Med Commun* 41: 995–1004 Copyright © 2020 The Author(s). Published by Wolters Kluwer Health, Inc.**

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Introduction

Breast cancer is the most commonly diagnosed cancer in women worldwide with over two million new cases annually [1]. Despite decreasing mortality rates over the past few decades due to earlier diagnosis and improved treatment modalities, an estimated 600 000 women succumbed to breast cancer in 2018 [1]. Prognosis is mainly determined by the individual tumor burden reflected by the decrease of the 5-year survival rate from 99% in localized, 85% in regional, to 27% in metastasized breast cancer [2]. The median overall survival in patients with distant metastases is only 26 months and while the breast cancer subtype predisposes the site of distant metastases, bone structures are generally the most frequent location of metastatic dissemination followed by the lung and liver [3–5].

Accurate staging is of paramount importance because it determines the ideal treatment for each patient regarding surgery, (neo)adjuvant systemic therapy (NST), and radiotherapy. Breast cancer imaging for disease staging encompasses a wide range of modalities and includes, among others, MRI and PET with computed tomography (PET/CT) using 18F-fluorodeoxyglucose (18F-FDG) as a radioactive tracer [6]. Breast MRI is widely used to assess the

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locoregional extent of disease in patients as well as monitoring response to NST [7,8]. Complementary, whole-body 18F-FDG PET/CT has become an established imaging technique for the assessment of node positive, distant metastatic, and recurrent breast cancer [9].

Shortcomings of 18F-FDG PET/CT, like its inability of simultaneous acquisition and reduced soft tissue contrast, have recently led to the development of hybrid positron emission tomography/magnetic resonance imaging (PET/MRI) [10]. Theoretically, 18F-FDG PET/MRI could offer an attractive one-stop-shop solution for patients with locally advanced breast cancer with affected axillary lymph nodes who should undergo both breast MRI for locoregional staging and whole-body 18F-FDG PET/CT for nodal and distant staging. 18F-FDG PET/MRI could then subsequently be used to assess the response to NST [11,12]. Moreover, using 18F-FDG PET/MRI for breast cancer staging allows the possibility to perform diffusion-weighted imaging (DWI) as part of the MRI protocol.

DWI, an MRI sequence showing the restricted movement of water molecules in tumoral tissues, was recently introduced as a functional modality to evaluate microstructural characteristics in tumors [13]. DWI can visualize changes occurring at a cellular spatial scale making it an advantageous tool for evaluating changes in the tumor microenvironment, both before and after NST [14]. Since its recent introduction promising results have been reported on the value of DWI in the diagnostic work-up of breast cancer [15,16].

Several publications in recent literature have reported on the diagnostic performance of whole-body 18F-FDG PET/CT, 18F-FDG PET/MRI, and DWI in breast cancer patients. To investigate if 18F-FDG PET/MRI could safely replace 18F-FDG PET/CT, possibly with the addition of a DWI sequence to the MRI protocol, studies comparing these imaging modalities in the same cohort have to be evaluated. Therefore, the aim of the current study is to provide a systematic review summarizing the diagnostic performance of 18F-FDG PET/MRI and DWI compared to 18F-FDG PET/CT with a specific focus on nodal and distant staging in breast cancer patients.

Methods

Search strategy

For this systematic review, the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analysis for Diagnostic Test Accuracy Studies (PRISMA-DTA) were followed [17]. The *Embase* and *PubMed* databases were searched independently by two authors (C.M.d.M. and I.S.). The last search was run on 28 April 2020. Search terms used for the condition were breast or mamma combined with tumor, cancer, malignancy, and carcinoma. Terms for the imaging modalities were positron emission tomography computed tomography, positron emission tomography magnetic resonance imaging, diffusion weighted imaging, and their corresponding abbreviations (PET/CT, PET/MRI, and DWI). No specific terms were used to search for outcome. Detailed descriptions of the literature search strategies are provided in the Supplementary material, Supplemental digital content 1, *http://links.lww.com/NMC/A174*. A manual search of the reference lists of the retrieved articles was performed to identify any additional publications.

Eligibility criteria

All primary diagnostic test accuracy studies that evaluated the diagnostic performance regarding nodal and distant staging of breast cancer patients with 18F-FDG PET/CT versus 18F-FDG PET/MRI or 18F-FDG PET/CT versus DWI were considered eligible for inclusion. To avoid selection bias, in- and exclusion criteria were established prior to the literature search. Inclusion criteria were as follows: (1) staging of patients with primary or recurrent breast cancer; (2) reported accuracy of imaging modalities regarding nodal and distant staging; and (3) a comparison of the diagnostic performance of 18F-FDG PET/CT versus 18F-FDG PET/MRI or 18F-FDG PET/CT versus DWI. Exclusion criteria were as follows: (1) response evaluation to NST; (2) publication not available in English; and (3) editorials, conference publications, surveys, case reports, reviews, ex-vivo studies, and animal studies.

Study selection

Two independent reviewers (C.M.d.M. and I.S.) searched for eligible articles and excluded duplicates. After excluding irrelevant articles based on title and abstract, the full-text of the remaining articles were obtained and read thoroughly to check for eligibility. Any disagreements regarding eligibility were resolved by the intervention of a third reviewer (T.J.A.N.).

Data extraction and quality assessment

Data extraction was performed independently by two reviewers (C.M.d.M. and I.S.) using a standardized extraction form, and the final extraction was completed in a consensus meeting. The following data were extracted: first author, year of publication, country, study design (retrospective or prospective), index tests, reference standard, follow-up time, type of cancer (primary or recurrent; local, regional, or metastasized), pathology, magnetic field strength, acquired imaging sequences, contrast agent used, number of reviewers, blinding, and parameters of diagnostic performance such as sensitivity, specificity, and accuracy. The quality of the included studies was independently assessed by two reviewers (C.M.d.M. and I.S.) using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) [18].

Statistical analysis

Diagnostic performance as stated in the primary article was extracted using a standardized extraction form. Due to the high heterogeneity between and within studies and the inability to compute 2×2 contingency tables of

at least three studies for two or more imaging modalities regarding any of the anatomic locations, no meta-analysis was performed. Instead, descriptive tables were used to provide a clear overview of the diagnostic performance of the primary studies.

Results

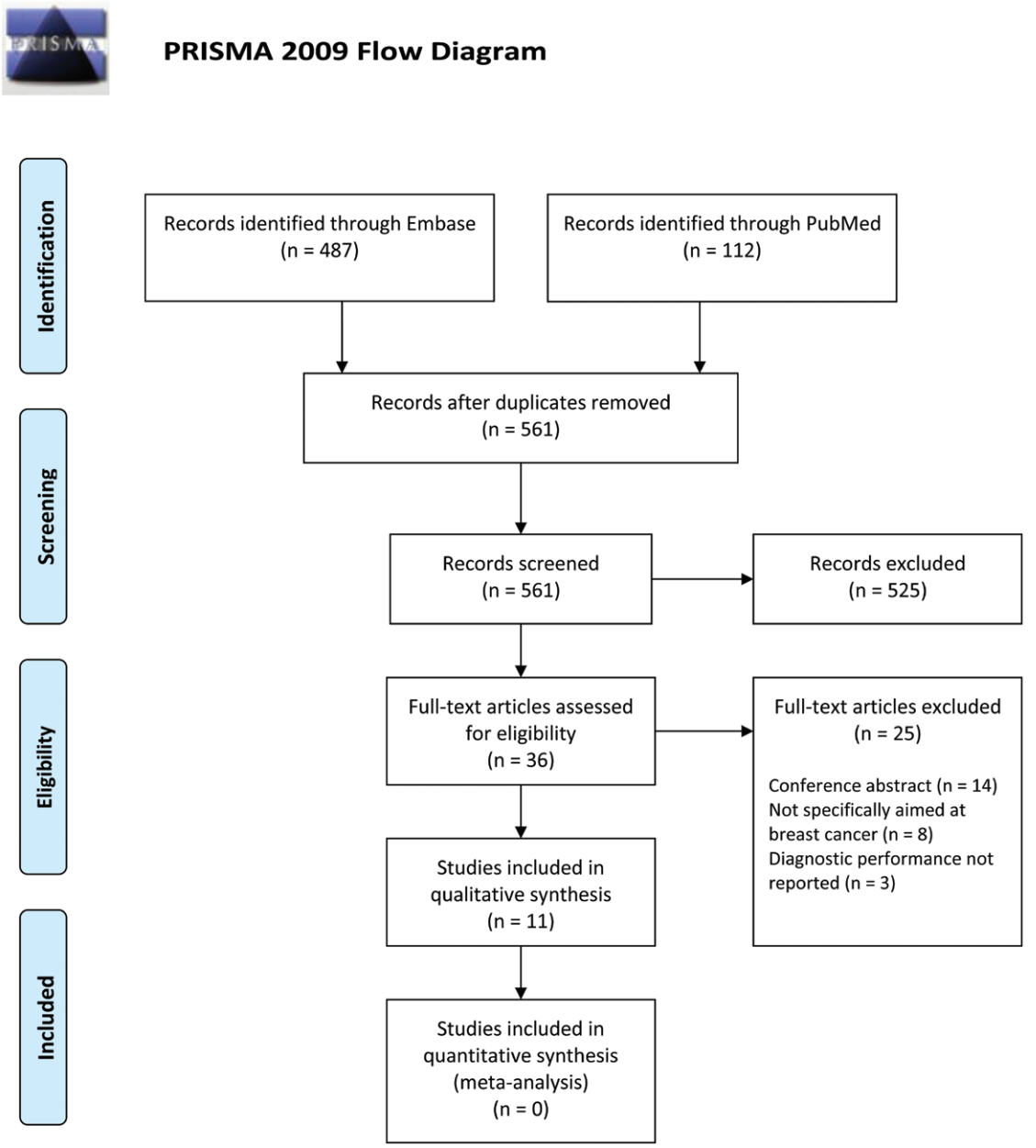
Study selection

After removing 38 duplicates, a total of 561 potentially eligible studies were identified in the primary search. Titles and abstracts of these 561 studies were read and in- and exclusion criteria were applied. Subsequently, 36 studies were reviewed based on full text. Finally, a total of 11 articles published between 2010 and 2020 were selected for this systematic review [19–29]. The search and selection processes are summarized in Fig. 1.

Characteristics of included studies

Eight of the 11 included studies (73%) had a prospective study design [19,22–26,28,29]. The included

Fig. 1



Flowchart of study selection process according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Table 1 Study characteristics

Author	Year	Country	Study design	*n*	Index tests	Reference standard	Follow-up time	Patients	Pathology
Grankvist *et al.* [23]	2010	Denmark	P	13	PET/CT, DWI	PET/CT	nr	Suspected or known metastasis, treated and untreated	nr
Heusner *et al.* [25]	2010	Germany	P	20	PET/CT, DWI	Pathology, concordant imaging findings, follow-up	nr	Initial and recurrent, untreated	IDC (12), ILC (4), others (4)
Ergul *et al.* [22]	2014	Turkey	P	24	PET/CT, DWI	Pathology	nr	Initial (stage I–II), untreated	IDC (19), ILC (1), others (4)
Catalano *et al.* [21]	2015	Italy	R	109	PET/CT, PET/MRI	Follow-up (109)	>11 months	Initial and recurrent, treated and untreated	IDC (109)
Grueneisen *et al.* [24]	2015	Germany	P	49	PET/CT, PET/MRI	Pathology (48), follow-up (1)	629 days	Initial, untreated	IDC (39), ILC (7), others (4)
Sawicki *et al.* [29]	2015	Germany	P	21	PET/CT, PET/MRI	Pathology (10), follow-up, prior imaging	16 months	Recurrent, untreated	IDC (12), ILC (4), unknown (5)
Melsaether *et al.* [26]	2016	USA	P	51	PET/CT, PET/MRI	Pathology (12), clinical follow-up (9), imaging follow-up (40), consensus (2)	19 months	Initial and recurrent, treated and untreated	nr
Pujara *et al.* [27]	2016	USA	R	35	PET/CT, PET/MRI	Follow-up (28), prior imaging (33), consensus	12 months	Suspected or known metastasis, untreated	IDC (15), ILC (2), unknown (4)
Catalano *et al.* [20]	2017	USA	R	51	PET/CT, PET/MRI, DWI	Pathology (42), follow-up (9)	>24 months	Initial, untreated	IDC (51)
Botsikas *et al.* [19]	2018	Switzerland	P	80	PET/CT, PET/MRI	Pathology (64), follow-up (16)	>12 months	Initial and recurrent, untreated	IDC (69), ILC (5), others (6)
Rezk *et al.* [28]	2019	Egypt	P	23	PET/CT, DWI	Pathology, follow-up	6–12 months	Recurrent	nr

CT, computed tomography; DWI, diffusion-weighted imaging; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; nr, not reported; P, prospective; R, retrospective.

studies contained a total of 476 patients (mean 43 per study, range 13–109). Six articles reported results comparing 18F-FDG PET/CT with 18F-FDG PET/MRI [19,21,24,26,27,29] four articles compared 18F-FDG PET/CT with DWI [22,23,25,28] and one article compared 18F-FDG PET/CT with both 18F-FDG PET/MRI and DWI [20]. Detailed information of the characteristics of the included studies is presented in Table 1.

Methodological quality assessment

Quality assessment of the included studies is summarized in Table 2. Significant risk of bias as well as significant applicability concerns were observed in all of the included studies except one [21]. Overall, the reference standard contained the highest risk of bias. This was mainly caused by no use of pathology, no use of an acceptable duration of follow-up, or the use of consensus between the imaging modalities to serve as a reference standard. Risk of bias regarding patient selection was mainly due the lack of blinding and the risk of recall bias. Concerns regarding applicability for the patient selection were due to the heterogeneous patient populations and the use of early stage breast cancer patients in whom the chances of having regional or distant metastases are generally lower.

Technical details

All included studies used 18F-FDG as a radiotracer. In six studies, the field strength was 3.0 T [19,23,24,26,27,29] in three 1.5 T [22,25,28] and in two it was not reported [20,21]. PET and MRI images were simultaneously acquired in all but one study evaluating PET/MRI, the exception being a sequential acquisition [19]. In five studies, reviewers assessed the images of the imaging modalities separately [22,23,25–27] while this was performed by the same reviewers in another five articles [19–21,24,29]. The remaining publication is unclear about image interpretation [28]. Intravenous contrast was administrated in all studies; however, only five studies used contrast in both techniques [20,21,24,25,29]. Detailed descriptions of the imaging sequences used for PET/MRI and DWI are depicted in Table 3.

PET/computed tomography versus PET/MRI

18F-FDG PET/CT was compared with 18F-FDG PET/MRI in seven studies comprising a total of 396 patients. Evaluated anatomic sites were all lesions, contralateral breast cancer, axillary, internal mammary, and mediastinal lymph nodes, bone, liver, lung, pleura, and brain. A tabular overview of the results is depicted in Table 4.

All lesions were evaluated in four primary studies [19,20,26,29]. In all four studies, the sensitivity of 18F-FDG PET/MRI was at least equal to that of 18F-FDG PET/CT, with only Botsikas *et al.* [19] reporting a statistically significant difference in favor of 18F-FDG PET/MRI (77% versus 89%, $P = 0.0013$). Catalano *et al.* found

Table 2 Quality assessment of the included articles based on Quality Assessment of Diagnostic Accuracy Studies 2

	Risk of bias				Applicability concerns		
Study	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Grankvist *et al.* [23]	Low	Low	High	Low	High	High	High
Heusner *et al.* [25]	Low	Low	High	Low	Low	Low	Low
Ergul *et al.* [22]	Low	High	Low	Low	High	Low	Low
Catalano *et al.* [21]	Low	Low	Low	Low	Low	Low	Low
Grueneisen *et al.* [24]	Low	High	Low	Low	Low	Low	Low
Sawicki *et al.* [29]	Low	Low	High	High	Low	Low	Low
Melsaether *et al.* [26]	Low	Low	High	Low	High	Unclear	Low
Pujara *et al.* [27]	Low	Low	High	Low	Low	Unclear	Low
Catalano *et al.* [20]	High	Low	Low	Low	Low	Low	Low
Botsikas *et al.* [19]	Low	Low	Low	Low	Low	High	Low
Rezk *et al.* [28]	High	High	Unclear	Low	Low	Low	High

a significantly higher accuracy for staging of breast cancer patients in favor of 18F-FDG PET/MRI (75% versus 98%, $P = 0.005$). Contrasting results were found regarding specificity, for which only Botsikas *et al.* reported a statistically significant difference in favor of 18F-FDG PET/CT (98% versus 96%, $P = 0.0075$). Three studies reported on the diagnostic performance regarding axillary lymph node staging and none of these studies reported a statistical difference between 18F-FDG PET/CT and 18F-FDG PET/MRI [19,24,26]. In general, there is a trend toward a higher sensitivity for 18F-FDG PET/MRI and a higher specificity for 18F-FDG PET/CT. Four studies compared the diagnostic performance for the detection of bone metastases between 18F-FDG PET/CT and 18F-FDG PET/MRI [19,21,26,27]. Botsikas *et al.* found a higher sensitivity for 18F-FDG PET/MRI (69% versus 92%, $P = 0.0034$) and a higher specificity for 18F-FDG PET/CT (100% versus 95%, $P = 0.0081$) in the lesion detection of bone metastases. Melsaether *et al.* [26] demonstrated higher sensitivity in a lesion-based analysis in favor of 18F-FDG PET/MRI (99% for reader 3 and 87% for reader 4 versus 98% for reader 1 and 95% for reader 2, $P = 0.012$). However, the patient-based analysis in this same publication did not reveal a statistically significant difference. Moreover, Catalano *et al.* demonstrated that 18F-FDG PET/CT revealed a statistically lower amount of osseous lesions compared to 18F-FDG PET/MRI (90 versus 141, $P < 0.001$). Regarding the detection of metastases in distant lymph nodes, two studies reported similar diagnostic performance between 18F-FDG PET/CT and 18F-FDG PET/MRI [26,27]. Regarding hepatic metastases, Melsaether *et al.* reported higher sensitivity in favor of 18F-FDG PET/MRI on a lesion-based analysis (75% for reader 3 and 70% for reader 4 versus 100% for reader 1 and 80% for reader 2, $P < 0.001$), but similar performance in a patient-based analysis (73% for readers 3 and 4 versus 100% for reader 1 and 91% for reader 2, $P = 0.095$). Pujara *et al.* [27] found lower sensitivity for PET/CT in a patient-based analysis (86% versus 100%) but did not review the data statistically. Only Melsaether *et al.* compared the diagnostic accuracy of 18F-FDG PET/CT and 18F-FDG PET/MRI for the detection of lung metastases and did so both lesion- and patient-based. While there was a trend toward superiority for 18F-FDG PET/CT, no statistically significant difference was found regarding sensitivity both in a lesion-based (100% for reader 3 and 96% for reader 4 versus 87% for reader 1 and 74% for reader 2, $P = 0.065$) and in a patient-based analysis (100% for readers 3 and 4 versus 100% for reader 1 and 83% for reader 2, $P > 0.99$). Contrarily, 18F-FDG PET/MRI was significantly superior regarding patient-based specificity (80% for reader 3 and 82% for reader 4 versus 89% for reader 1 and 99% for reader 2, $P = 0.008$).

Contralateral breast cancer, internal mammary lymph nodes, mediastinal lymph nodes, pleural metastases, and brain metastases were compared in one study each [19,26].

PET/computed tomography versus diffusion-weighted imaging

18F-FDG PET/CT was compared with DWI in four studies comprising a total of 131 patients [20,22,25,28]. DWI was also compared to 18F-FDG PET/CT as part of the MRI protocol in all seven studies evaluating the diagnostic performance of 18F-FDG PET/MRI [19–21,24,26,27,29]. Evaluated sites were all lesions, locoregional and distant lymph nodes, bone, lung, liver, and other sites not specified. None of the reviewed studies reported a significant difference between 18F-FDG PET/CT and DWI for any of the evaluated sites. A tabular overview of the results is depicted in Table 5.

Three studies evaluated the diagnostic performance regarding all metastases [20,25,28]. In the study by Heusner *et al.*, higher accuracy for PET/CT was found both in a lesion-based analysis (98% versus 71%) as well as in a compartment-based analysis (98% versus 76%), and Rezk *et al.* found similar results in a lesion-based analysis (85% versus 81%, $P = 0.66$) [25,28]. On the contrary, in the study by Catalano *et al.*, DWI achieved higher accuracy in a patient-based analysis (75% versus 84%, $P = 0.27$) [20]. Three studies investigated (loco)regional lymph nodes and all studies showed that better diagnostic performance was achieved with 18F-FDG PET/CT [22,25,28]. In a study by Heusner *et al.*, similar sensitivity for the

Table 3 Technical details of imaging

First author	Index tests	Field strength	PET/MRI acquisition	Intravenous contrast	Imaging sequences [(PET)-MRI]	Reviewers	Blinding	Delay a
Grankvist *et al.* [23]	PET/CT, DWI	3.0T	na	Yes, no	Neck-thorax, lumbar and pelvic: T1, STIR, T2 fat suppressed. Whole-body: DWI (b-value nr)	2+2	Yes	na
Heusner *et al.* [25]	PET/CT, DWI	1.5T	na	Yes, yes	Whole-body: DWI (b-value 50/600/800), T2 HASTE, DWI (spine), T2 SPAIR, T1w FLASH, T2 HASTE, contrast-enhanced T1 VIBE.	2+2	nr	na
Ergul *et al.* [22]	PET/CT, DWI	1.5T	na	No, yes	Breast: T1, T2, TIRM, DWI (b-value 50/400/ 800), contrast-enhanced 3D T1 fat suppressed.	2+1	No	na
Catalano *et al.* [21]	PET/CT, DWI	nr	Simultaneous	Yes, yes	Whole-body: DWI (b-value 50/400/800), STIR, T1 Dixon, T2 HASTE, contrast-enhanced T1 fat suppressed VIBE.	2	nr	6 weeks
Grueneisen *et al.* [24]	PET/CT, PET/MRI	3.0T	Simultaneous	Yes, yes	Whole-body (prone): T2 TIRM, T2 FSE, DWI (b-value 0/500/1000), contrast-enhanced T1 FLASH.	2	Yes	2 weeks
Sawicki *et al.* [29]	PET/CT, PET/MRI	3.0T	Simultaneous	Yes, yes	Whole-body: 3D Dixon VIBE, T2 HASTE, DWI (b-value 0/500/1000), T2 TIRM, contrast-enhanced T1 fat suppressed VIBE.	2	Yes	4 weeks
Melsaether *et al.* [26]	PET/CT, PET/MRI	3.0T	Simultaneous	No, yes	Whole-body (supine): Dixon, contrast-enhanced 3D T1, DWI (b-value 0/350/700).	2+2	Yes	na
Pujara *et al.* [27]	PET/CT, PET/MRI	3.0T	Simultaneous	No, yes	Whole-body (prone): 3D VIBE for MRAC, 3D T1 VIBE, DWI (b-value 0/350/700).	1+1	nr	na
Catalano *et al.* [20]	PET/CT, PET/MRI, DWI	nr	Simultaneous	Yes, yes	Whole-body: DWI (b-value 50/400/800), STIR, T1 Dixon, T2 HASTE, contrast-enhanced T1 fat suppressed VIBE.	2	Yes	6 weeks
Botsikas *et al.* [19]	PET/CT, PET/MRI	3.0T	Sequential	No, yes	Whole-body (supine): T2 FSE, DWI (b-value 0/1000), 3D T1 Dixon, 3D T1 FFE. Breast (prone): T2 FSE, DWI (b-value 0/1000), contrast-enhanced 3D T1 Dixon, 3D T1 FFE.	2	Yes	3 months
Rezk *et al.* [28]	PET/CT, DWI	1.5T	na	Yes, no	Whole-body: T1 TSE, STIR, DWI (b-value 0/1000).	1	nr	na

a, delay in the case of same reviewer of both imaging modalities; b-value (s/mm^2); DWI, diffusion-weighted imaging; FFE, fast-field echo; FLASH, fast low-angle shot; FSE, fast spin echo; HASTE, half-Fourier acquisition single-shot turbo-spin echo; MRAC, MRI-based attenuation correction; na, not applicable, nr, not reported; SPAIR, spectral selection attenuated inversion recovery; STIR, short tau inversion recovery TIRM, turbo inversion recovery magnitude; VIBE, volumetric interpolated breath-hold examination.

detection of regional lymph node metastases was found (75% versus 75%), while a higher specificity was achieved by 18F-FDG PET/CT (100% versus 64%) [25]. Rezk *et al.* found better diagnostic performance for 18F-FDG PET/CT regarding sensitivity (90% versus 84%, $P = 0.59$) and specificity (82% versus 73%, $P = 0.47$) in a similar analysis [28]. Regarding axillary lymph node metastases, higher accuracy was achieved by 18F-FDG PET/CT (75% versus 63%) in one study [22]. Two studies evaluated metastases in the bone and two in distant lymph nodes; for all analyses, 18F-FDG PET/CT achieved better diagnostic performance than DWI [25,28]. The lung, liver, distant lesions, other organs not specified, and lymphatic system were evaluated by one study each [25,28].

Discussion

Based on the results summarized in this systematic review, 18F-FDG PET/MRI has demonstrated to achieve similar diagnostic performance to 18F-FDG PET/CT with no statistically significant differences in nodal staging and an even higher accuracy in overall distant staging of breast cancer patients. In general, there is a trend toward higher sensitivity and lower specificity for 18F-FDG PET/MRI when compared to 18F-FDG PET/CT. Results on the diagnostic performance of DWI only are conflicting if used separately. It tends to have a complementary value when combined with other MR sequences.

Combining the evidence from the primary studies, it can be concluded that 18F-FDG PET/MRI and 18F-FDG PET/CT have similar diagnostic performance regarding lesion detection with a slight tendency to improved sensitivity for 18F-FDG PET/MRI and higher specificity for 18F-FDG PET/CT [19,20,26,29]. Pace *et al.* [30] previously concluded that 18F-FDG PET/MR performs equally to 18F-FDG PET/CT in the anatomic allocation and multiple studies show a strong correlation between the standardized uptake values (SUVs) derived from these two hybrid techniques [27]. In line with these findings, the main reason for the higher sensitivity of 18F-FDG PET/MR comes from non-FDG-avid lesions such as permeative osseous metastases and subcentimeter hepatic metastases that are visible on MRI but not on CT [20,29]. Based on the primary articles included in this review, the diagnostic performance of DWI for lesion detection and staging is inconclusive. Of 283 lesions for which a standard of reference was available and that were only seen on DWI and not on 18F-FDG PET/CT in a study by Heusner *et al.*, 231 (82%) were false-positives mainly in the bone and distant lymph nodes [25]. They agree with previous publications stating that DWI only causes false alarm [31].

The determination of the correct clinical nodal status is essential to provide the patient with the appropriate oncological treatment and strongly influences patients' prognosis [2]. Compared to a sensitivity of 60% and specificity

Table 4 PET/computed tomography versus PET/MRI

			PET/CT			PET/MRI		
First author	Site	Analysis	Sensitivity (%; 95 CIs)	Specificity (%; 95 CIs)	Accuracy (%; 95 CIs)	Sensitivity (%; 95 CIs)	Specificity (%; 95 CIs)	Accuracy (%; 95 CIs)
Sawicki	All	L	96	89	95	100	89	99
Sawicki	All	P	100	–	–	100	–	–
Melsaether	All	P	97A,B (88–99)	77A–82B (64–91)	–	100A,B (92–100)	86C–90D (76–95)	–
Catalano	All[a]	P	–	–	75	–	–	98[b]
Botsikas	All	L	77 (67–85)	98 (97–99)[c]	–	89 (81–94)[d]	96 (94–98)	–
Botsikas	All[e]	P	69 (39–90)	100 (93–100)	–	85 (54–97)	97 (89–99)	
Grueneisen	Axillary LNs	P	78 (52–94)	94 (79–99)	88	78 (52–94)	90 (74–98)	86
Melsaether	Axillary LNs	P	88A,B (64–99)	95A,B (88–98)	–	88D–100C (69–97)	95C,D (88–98)	–
Botsikas	Axillary LNs	L	81 (67–90)	92 (85–96)	–	85 (72–93)	89 (82–94)	–
Botsikas	Axillary LNs	P	83 (68–91)	76 (58–89)	–	87 (73–95)	68 (49–82)	–
Botsikas	Internal mammary LNs	L	90 (54–99)	100 (97–100)	–	90 (54–99)	100 (97–100)	–
Botsikas	Internal mammary LNs	P	89 (51–99)	100 (94–100)	–	89 (51–99)	100 (94–100)	–
Botsikas	Mediastinal LNs	L	100 (52–100)	100 (94–100)	–	100 (52–100)	100 (94–100)	–
Botsikas	Mediastinal LNs	P	100 (52–100)	100 (94–100)	–	100 (52–100)	100 (94–100)	–
Catalano	Bone	P	85 (70–96)	–	–	96 (87–100)	99 (96–100)	–
Melsaether	Bone	L	87B–99A (79–100)	–	–	95D–98C (90–100) †	–	–
Melsaether	Bone	P	96A,B (84–100)	97A–100B (90–100)	–	100C,D (91–100)	100C,D (93–100)	–
Pujara	Bone	P	94	–	–	100	–	–
Botsikas	Bone	L	69 (48–85)	100 (97–100) ‡	–	92 (73–99) †	95 (90–98)	–
Botsikas	Bone	P	67 (31–91)	100 (94–100)	–	89 (51–99)	97 (89–99)	–
Melsaether	Liver	L	70B–75A (54–87)	–	–	80D–100C (66–100) †	–	–
Melsaether	Liver	P	73A,B (50–88)	100A,B (95–100)	–	91D–100C (78–100)	98C–100D (92–100)	–
Pujara	Liver	P	86	–	–	100	–	–
Melsaether	Distant LNs	L	85B–95A (72–99)	–	–	92D–95C (80–99)	–	–
Melsaether	Distant LNs	P	82A–91B (66–95)	95B–98A (88–100)	–	91D–100C (78–100)	98C,D (90–100)	–
Pujara	Distant LNs	P	100	–	–	100	–	–
Botsikas	Contralateral BC	L	25 (1–78)	99 (92–100)		100 (40–100)	99 (92–100)	
Botsikas	Contralateral BC	P	33 (2–87)	99 (92–100)		100 (31–100)	99 (92–100)	
Melsaether	Lung	L	96B–100A (79–100)	–	–	74D–87C (53–96)	–	–
Melsaether	Lung	P	100A,B (74–100)	80A–82B (71–90)	–	83D–100C (62–100)	89C–91D (81–96) ‡	–
Melsaether	Pleura	L	100A,B (80–100)	–	–	100A,B (80–100)	–	–
Melsaether	Pleura	P	100A,B (74–100)	100A,B (95–100)	–	100C,D (74–100)	100C,D (95–100)	–
Melsaether	Brain	L	–	–	–	93D–100C (70–100)	–	–

A, reader 3 (PET/CT); B, reader 4 (PET/CT); C, reader 1 (PET/MRI); CI, confidence interval; CT, computed tomography; D, reader 2 (PET/MRI); L, lesion level; LNs, lymph nodes; P, patient level.
[a]Staging performance.
[b]Significantly higher accuracy.
[c]Significantly higher specificity.
[d]Significantly higher sensitivity.
[e]Patients with bone, liver, pulmonary, mediastinal, pleural and thoracic wall metastases.

of 97% of 18F-FDG PET/CT reported in a systematic review by Robertson *et al.* [32], the primary studies in this review achieve on average a higher sensitivity and lower specificity. From another systematic review by Liang *et al.* [33], it can be concluded that MRI shows superiority over 18F-FDG PET/CT in assessing nodal status with fewer false positive and false negative results. In addition, a recent prospective study by Bruckmann *et al.* [34] showed that the diagnostic accuracy is further improved by combining 18F-FDG PET with MRI, with a significantly higher diagnostic confidence in lesion characterization. The findings summarized in the current systematic review show that 18F-FDG PET/MRI tends to be noninferior to 18F-FDG PET/CT. Moreover, the addition of an axillary dedicated hybrid protocol as investigated by Van Nijnatten *et al.* [35] could even further improve the diagnostic performance of 18F-FDG PET/MRI in determining the clinical nodal status. Opposite to the results found by Chung *et al.* [15], Ergul *et al.* [22] found a strikingly low sensitivity and high specificity for DWI compared to 18F-FDG PET/CT in early stage breast cancer patients. They state that the low tumor cell burden in their cohort likely rendered DWI-mediated detection difficult [22]. In summary, regarding nodal staging, 18F-FDG PET/CT could safely be replaced by 18F-FDG PET/MRI, while DWI alone shows conflicting results.

The bone is the predominant site of metastatic dissemination in breast cancer patients and occurs in 69% of patients with advanced disease [36–38]. Remarkably more osseous lesions are detected by 18F-FDG PET/MRI compared to 18F-FDG PET/CT and it seems that the majority of the missed lesions on 18F-FDG PET/CT are permeative in nature and lack FDG avidity [19,21,26,39]. Bone marrow replacement in non-FDG-avid lesions revealed by T1-weighted MRI sequences can lead to a positive lesion on PET/MRI, while the low conspicuity due to low-intrinsic tissue contrast on CT would render these lesions negative [19,21]. Moreover,

Table 5 PET/computed tomography versus diffusion-weighted imaging

			PET/CT			DWI		
First author	Site	Analysis	Sensitivity (%; 95 CIs)	Specificity (%; 95 CIs)	Accuracy (%; 95 CIs)	Sensitivity (%; 95 CIs)	Specificity (%; 95 CIs)	Accuracy (%; 95 CIs)
Heusner	All	L	95	99	98	86	67	71
Heusner	All	C	94	99	98	91	72	76
Catalano	All	P	–	–	75	–	–	84
Rezk	All	L	85	86	85	82	78	81
Ergul	Axillary LNs	P	67	89	75	40	100	63
Heusner	Regional LNs	P	75	100	93	75	64	67
Rezk	Regional LNs	L	90	82	–	84	73	–
Grankvist	Bone	L	100	100	–	67A–70B	40B–95A	–
Heusner	Bone	P	100	100	100	86	8	35
Heusner	Distant LNs	P	100	100	100	100	0	30
Rezk	Distant LNs	L	86	92	–	83	80	–
Heusner	Lung	P	100	100	100	100	100	100
Heusner	Liver	P	100	100	100	100	82	85
Rezk	Distant lesions	L	84	84	–	80	81	–
Heusner	Other organs	P	100	94	95	66	94	89
Heusner	Organs	C	100	98	99	87	75	77

A, STIR and DWI with and without T1; B, DWI only; C, compartment level; CI, confidence interval; CT, computed tomography; DWI, diffusion-weighted imaging; L, lesion level; LNs, lymph nodes; P, patient level; STIR, short tau inversion recovery.

enhancement after gadolinium administration could further increase the diagnostic confidence [21]. The results summarized in this review show a lesion-level preference for 18F-FDG PET/MRI with at least noninferiority on a patient-level [19,21,26,27]. While Grankvist *et al*. [23] demonstrated that DWI combined with other sequences yields a high specificity and improves diagnostic efficacy, many of the lesions suspicious on DWI were false-positive and Heusner *et al*. [25] clearly stated that DWI alone generates a lot of discordant and false-positive findings and in its current form it is unsuitable for the detection of osseous metastases [23].

A widespread concern that has kept clinicians hesitant to the use of 18F-FDG PET/MRI as an alternative for 18F-FDG PET/CT for whole-body staging in breast cancer is the diagnostic performance of MRI in the detection of small non-FDG-avid pulmonary lesions [40–43]. Similar to another publication, Melsaether *et al*. found a higher sensitivity for 18F-FDG PET/CT in pulmonary lesion detection, while this difference could not be established on a patient-level [26,44]. However, a recent study by Martin *et al*. in a cohort of 1003 cancer patients found that the amount of missed malignant lung lesions was negligibly low (0.8%), and other publications state that the vast majority of small non-FDG-avid pulmonary lesions missed on 18F-FDG PET/MRI remain stable on follow-up and are likely to be benign [41,45,46]. Moreover, 18F-FDG PET/MRI is associated with higher diagnostic confidence likely due to the high soft-tissue contrast of MR compared with CT and especially in large lung lesions the higher intrinsic contrast of MR imaging may provide better conspicuity [40]. These recent findings combined with promising new MRI sequences, such as the ultrashort echo time sequence that is expected to improve pulmonary lesion detection, suggest that 18F-FDG PET/MRI can safely replace 18F-FDG PET/CT regarding the detection of pulmonary lesions [47].

Together with bone and lung, the liver is the most common site of metastatic disease in breast cancer patients. A recent systematic review and meta-analysis by Hong *et al*. investigated the diagnostic performance of 18F-FDG PET/MRI for hepatic metastases in a diverse group of patients with primary malignancy. Similar to the results in this systematic review, they found very good diagnostic accuracy for the detection of hepatic metastases with a patient-level meta-analytic summery sensitivity of 99.2% and specificity of 98.6% [11,26,48]. Especially in subcentimeter hepatic metastases, the reported sensitivity of 18F-FDG PET/MRI outperforms that achieved by 18F-FDG PET/CT [48]. Because two early publications reported on the usefulness of DWI for the detection of small (≤10 mm) hepatic lesions, the presence of a DWI sequence in MRI protocols could have contributed to the high sensitivity achieved by 18F-FDG PET/MRI [49,50].

The results summarized in this publication should be taken with caution and the large degree of heterogeneity between and within studies causes several limitations. First, a heterogeneous cohort of patients was used varying from primary staging to restaging of patients suspicious for recurrence. Second, different imaging sequences and radiofrequency coils were used. Third, in the majority of studies, 18F-FDG PET/MRI and 18F-FDG PET/CT were performed on the same day on the same dose of 18F-FDG. Differences in acquisition time influence the tumor-to-background ratio and tumor-to-nontumor ratios which have an effect on tumor visibility and possibly on diagnostic performance [51,52]. Multiple studies suggest that delayed acquisition could have a beneficial effect on the sensitivity; therefore, the order of imaging should be taken into account when comparing the diagnostic performance of 18F-FDG PET/CT with 18F-FDG PET/MRI [51–54]. Fourth, in some studies, intravenous contrast was not used in both techniques. For example, in three of the included studies, patients underwent unenhanced

whole-body 18F-FDG PET/CT and they were compared with enhanced 18F-FDG PET/MRI, so the results should be interpreted with this important limitation in mind [19,26,27]. Last, due to the high heterogeneity between and within studies and the inability to compute 2×2 contingency tables of at least three studies for two or more imaging modalities, no meta-analysis was performed.

18F-FDG PET/MRI is a promising imaging tool for performing accurate nodal and distant staging of breast cancer patients with lower radiation exposure compared to 18F-FDG PET/CT. Melsaether *et al*. reported an average dose reduction of 50% when using 18F-FDG PET/MRI instead of 18F-FDG PET/CT [26]. Other advantages of 18F-FDG PET/MRI compared to 18F-FDG PET/CT are the soft tissue contrast and motion correction possibilities [55]. SUVs could be valuable in determining prognosis of breast cancer patients and it has been evaluated in both imaging modalities by Pujara *et al*. who found a strong correlation of the maximum SUV acquired by 18F-FDG PET/MRI compared to 18F-FDG PET/CT [27,56]. Pace *et al*. compared SUVs for nodal and distant metastases and found that both the maximum SUV and mean SUV were significantly higher on 18F-FDG PET/MRI than on 18F-FDG PET/CT [57]. Van Nijnatten *et al*. [35] reported comparable values achieved on hybrid PET/MRI for the primary tumor and the most FDG-avid lymph node. PET/MRI, a multimodal and multiparametric technique, may provide more quantitative information than PET/CT [58]. Even though the per-examination cost of 18F-FDG PET/MRI is approximately 50% higher, the possibility of a one-stop-shop solution for, for example, node-positive breast cancer patients could not only reduce costs in initial staging but could also reduce the burden on the patient [59].

To conclude, the relatively new imaging modality 18F-FDG PET/MRI has demonstrated to be noninferior to 18F-FDG PET/CT regarding nodal staging. For distant staging, a trend toward a higher sensitivity in lesion detection for 18F-FDG PET/MRI and a higher specificity for 18F-FDG PET/CT can be observed with the former detecting a significantly higher amount of osseous metastases, which are the most common type of distant metastases in breast cancer. Results on the diagnostic performance of DWI are conflicting, and it tends to have a complementary value when combined with other MR sequences rather than evaluating it separately. We deem 18F-FDG PET/MRI to be accurate enough in nodal staging and distant staging to be able to replace 18F-FDG PET/CT in breast cancer staging, hereby forming an attractive one-stop-shop solution for breast cancer patients for whom both an MRI as well as a PET-CT is indicated.

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Conflicts of interest

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