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Impact of ^{18}F-FDG PET, PET/CT, and PET/MRI on Staging and Management as an Initial Staging Modality in Breast Cancer

A Systematic Review and Meta-analysis

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Objectives: We performed a systematic review and meta-analysis to evaluate the impact of ^{18}F-FDG PET, PET/CT, and PET/MRI on staging and management during the initial staging of breast cancer.

Methods: We searched the PubMed, Embase, Cochrane Library, and KoreaMed databases until March 2020 to identify studies that reported the proportion of breast cancer patients whose clinical stage or management were changed after PET scans. The proportion of changes was pooled using a random-effects model. Subgroup and metaregression analyses were performed to explore heterogeneity.

Results: We included 29 studies (4276 patients). The pooled proportions of changes in stage and management were 25% (95% confidence interval [CI], 21%–30%) and 18% (95% CI, 14%–23%), respectively. When stage changes were stratified according to initial stage, the pooled proportions were 11% (95% CI, 3%–22%) in stage I, 20% (95% CI, 16%–24%) in stage II, and 34% (95% CI, 27%–42%) in stage III. The relative proportions of intermodality and intention-to-treat changes were 74% and 70%, respectively. Using metaregression analyses, the mean age and the proportion of initial stage III to IV and histologic grade II to III were significant factors affecting the heterogeneity in changes in stage or management.

Conclusions: Currently available literature suggests that the use of ^{18}F-FDG PET, PET/CT, or PET/MRI leads to significant modification of staging and treatment in newly diagnosed breast cancer patients. Therefore, there may be a role for routine clinical use of PET imaging for the initial staging of breast cancer.

Key Words: breast neoplasms, ^{18}F-FDG, positron emission tomography, neoplasm staging, meta-analysis

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B reast cancer is the most common malignancy and the second leading cause of cancer-related deaths in women.[1] It is critical to accurately assess the extent of regional and distant disease in newly diagnosed breast cancer to optimize therapeutic decisions and clinical outcomes. Current oncologic practice guidelines do not systematically recommend ^{18}F-FDG PET/CT for the initial staging of breast cancer; the use of ^{18}F-FDG PET or PET/CT is not indicated in patients whose clinical stage is between I and operable III unless there is suspicion for metastatic disease, according to the National Comprehensive Cancer Network and the European Society for Medical Oncology guidelines.[2,3] The use of ^{18}F-FDG PET/CT is recommended in the setting of advanced breast cancer[2,4]; however, the European Society for Medical Oncology guideline states that PET/CT can be used instead of, but not in addition to, CT and bone scan.[4] The National Institute for Health and Clinical Excellence guideline recommends PET/CT only for the diagnosis of metastatic disease in patients with advanced breast cancer whose imaging is suspicious but not diagnostic of metastasis.[5] The Centers for Medicare and Medicaid Services in United States reimburses ^{18}F-FDG PET in breast cancer staging for distant metastasis except for axillary lymph nodes,[6] although the National Oncologic PET Registry, which supports the decision for PET coverage, has a limited database of breast cancer. In summary, the routine use of ^{18}F-FDG PET/CT in early breast cancer is not recommended, and the use of ^{18}F-FDG PET/CT in addition to other staging imaging modalities is not generally recommended even in advanced breast cancer unless standard imaging results are equivocal by currently available guidelines.

Nevertheless, a number of meta-analyses indicate that ^{18}F-FDG PET/CT has high diagnostic accuracy for the evaluation of regional and distant metastases,[7–9] as well as prognostic implications in newly diagnosed breast cancer patients.[10] Likewise, a recently published systematic review reported that the currently available literature suggests superior diagnostic efficacy of ^{18}F-FDG PET/CT compared with other staging modalities for the detection of regional and distant metastasis in newly diagnosed breast cancer.[11] In recent decades, a growing body of evidence has shown that additional findings on ^{18}F-FDG PET/CT produce a significant change in the initial staging and therapeutic management of breast cancer.[12–40] This literature suggests that the yield from PET/CT is considerable not only for high-risk patients (those with locally advanced or inflammatory breast cancer) but also for intermediate-risk patients who have clinical stage IIB disease or higher.[41] Some of the researches even indicate that ^{18}F-FDG PET/CT may have a substantial influence on early breast cancer.[16,22,24,30] The advent of PET/MRI, with its excellent diagnostic performance, may also impact clinical practice in breast cancer treatment,[42] and a comprehensive review of the role of ^{18}F-FDG PET scans including PET/MRI is required. Hence, we performed a systematic review and meta-analysis of the available literature on the impact of ^{18}F-FDG PET, PET/CT, and PET/MRI on clinical stage and management at initial staging in breast cancer patients.

PATIENTS AND METHODS

This meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.[43] The

protocol was registered to the International Prospective Register of Systematic Reviews network (registration number CRD42020168949).

Literature Search and Extraction

PubMed, Embase, Cochrane Library, and KoreaMed database were searched from inception to March 21, 2020. Search queries included the related terms "breast cancer," "initial staging," "^{18}F-FDG PET," and "impact," which are described in the supplementary materials (Supplemental Digital Content 1, http://links.lww.com/CNM/A302). There was no language restriction for the electronic search. The references of the extracted articles were examined to look for additional relevant articles.

The inclusion criteria were created based upon the Patient, Intervention, Comparator, Outcome, and Study design criteria.[43] We included studies that had (1) female "patients" with newly diagnosed breast cancer; (2) ^{18}F-FDG PET, PET/CT, or PET/MRI at initial staging as the "intervention"; (3) no "comparator"; (4) changes in staging or therapeutic plan after ^{18}F-FDG PET, PET/CT, or PET/MRI when compared with the initial stage or plan based on clinical, pathological, and conventional imaging results as the "outcome"; and (5) "study design" as original articles. The exclusion criteria included the following: (1) small sample size (<10 patients); (2) other publication types including conference abstracts, review articles, editorials, and letters; (3) articles irrelevant to the research question; (4) insufficient information provided in the study to calculate the proportion of changes in staging and management; and (5) overlapping study populations. We included studies in which PET scan was performed in the preoperative or early postoperative period but before any systemic treatment or radiation therapy (RT). When study populations may have overlapped, we selected the publication with the largest population for the meta-analysis.

Data Extraction and Quality Assessment

The outcomes, studies, and patient characteristics of each included study were extracted using a standardized form. The methodologic quality of the included studies was appraised using the Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS) tool.[44] Study selection, data extraction, and quality assessment were performed by 2 independent reviewers (S.H. and J.Y.C.). Disagreement, if present, was resolved via discussion.

Data Synthesis and Analysis

The primary outcome of this study was the impact of ^{18}F-FDG PET, PET/CT, or PET/MRI on staging and management, which was specifically measured using the proportion of patients whose disease stage or therapeutic plan changed due to imaging findings on ^{18}F-FDG PET, PET/CT, or PET/MRI. The change in stage included both up- and down-staging as reported on individual studies after ^{18}F-FDG PET compared with initial clinical stage based on conventional workup. The secondary outcomes were as follows: (1) exploration of heterogeneities via subgroup and metaregression analyses; (2) proportion of changes in stage after ^{18}F-FDG PET based on initial stage; and (3) proportion of intermodality and intention-to-treat changes in management. The metaregression analyses were performed using clinical variables, which allowed the number of the included studies to be more than
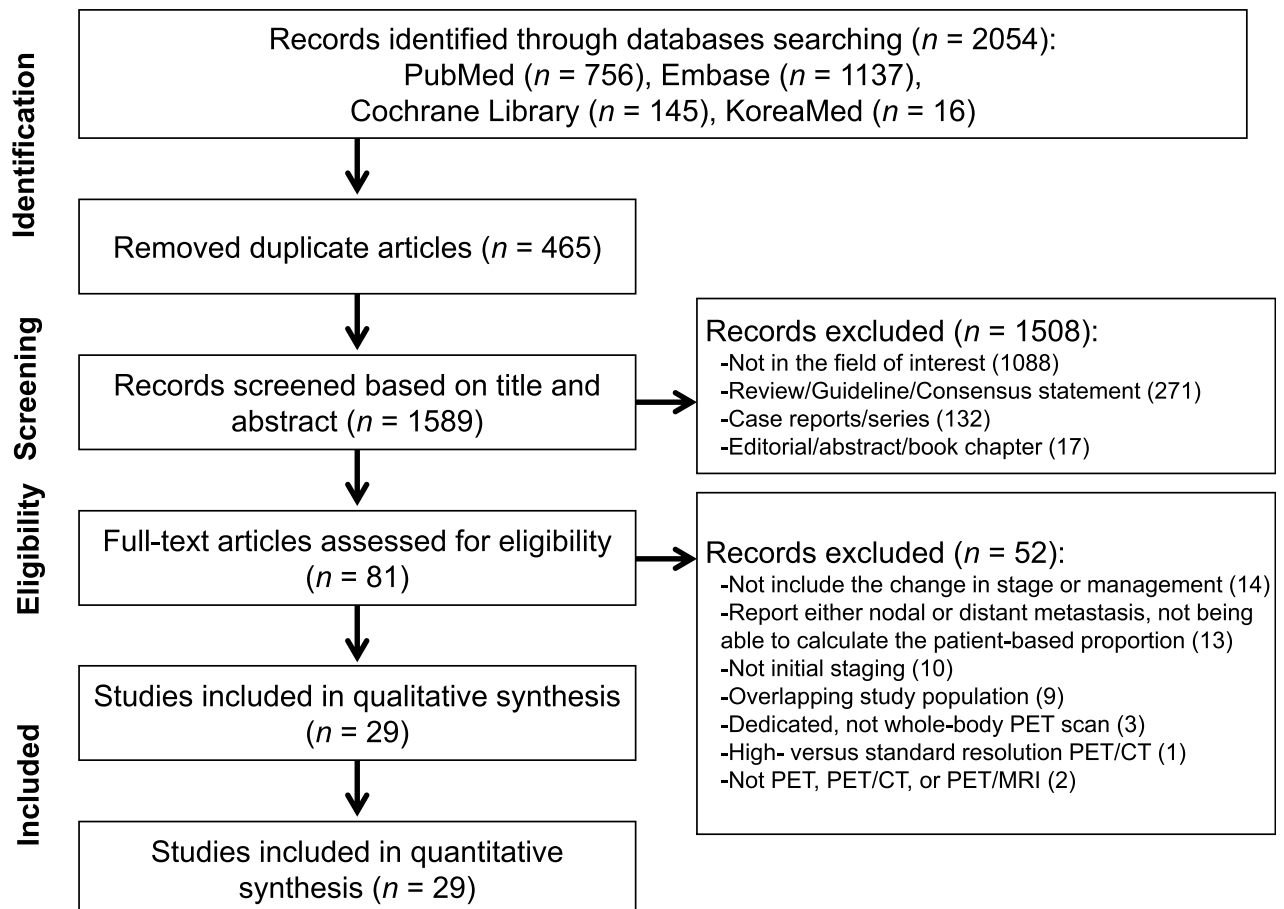

FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses flow chart showing the study selection process.

TABLE 1. Study Characteristics of the Included Studies

Author	Year	Design	Patients, n	Inclusion	Scanner	FDG Dose, MBq	Uptake Time, min	Confirmation of Lesions on PET
Bernsdorf et al[12]	2012	P	103	Operable tumor ≥2 cm with no suspicion of bilateral cancer, M1 or N3c	PET/CT	400	60	Histology, if not feasible, then imaging follow-up
Cermik et al[13]	2008	P	240	Not specified	PET	5.2/kg	45–110	Histology or imaging
Chandra et al[14]	2020	R	158	Stage I–II, T1–2/N0–1	PET/CT	6/kg	60	Histology or clinical follow-up
Cochet et al[15]	2014	P	142	≥T2	PET/CT	5/kg	60	Histology, imaging, and clinical follow-up
Evangelista et al[16]	2017	P	275	≥N1 or large tumor or HER2+ or TNBC or high grade; before NAC (n = 149); postoperative (n = 126)	PET/CT	3/kg	60	Histology, if not feasible, then imaging follow-up
Fuster et al[17]	2008	P	60	Noninflammatory, tumor >3 cm	PET/CT	740	60	Histology (imaging follow-up for multiple metastasis)
Gajjala et al[18]	2018	P	61	LABC (stage III)	PET/CT	370	60	Histology, if not feasible, then imaging follow-up
Garami et al[19]	2012	NR	115	Tumor <4 cm; no sign of M1 or N3	PET/CT	4.4–5.5/kg	60	Histology or imaging
Garg et al[20]	2016	P	79	LABC (stage III)	PET/CT	NR	NR	Typical lesions: considered positive; others: histology (imaging for bone foci)
Groheux et al[21]	2011	P	254	Stage II–III	PET/CT	5/kg	60	Histology or imaging
Gunalp et al[22]	2012	R	267	Grade II–III; preoperative (n = 141); postoperative (n = 126)	PET/CT	5/kg	60	Histology or clinical follow-up (MRI for bone foci)
Jeong et al[23]	2014	R	178	No clinical sign of N(+)	PET/CT	5.2/kg	60	Histology, if not feasible, then imaging follow-up
Klaeser et al[24]	2007	R	114	Intermediate or high risk; preoperative (n = 73); postoperative (n = 41)	PET	370	45–60	NR
Koolen et al[25]	2014	P	62	Neoadjuvant RT group: age ≥60 and tumor ≤3 cm; NAC group: T1 and ≥N1	PET/CT	180–240	60 ± 10	Histology or imaging
Krammer et al[26]	2015	P	101	≥T2 or ≥N1	PET/CT	199–350	60	Histology or imaging
Landheer et al[27]	2005	P	17	≥N1 at level 2 axillary node or with a high mitotic activity index	PET	200–220	60	Histology or imaging follow-up
Manohar et al[28]	2013	P	43	LABC	PET/CT	370–444	60	Typical lesions: considered positive; others: histology or imaging follow-up
Ng et al[29]	2015	P	154	LABC	PET/CT	NR	60	Histology or imaging
Nursal et al[30]	2016	R	419	Stage I–II	PET/CT	5/kg	60	NR
Piperkova et al[31]	2007	R	17	Not specified	PET/CT	370–555	<90	Histology or imaging
Reddy Akepati et al[32]	2018	R	171	Not specified	PET/CT	370–555	60	Histology
Riegger et al[33]	2012	R	106	Not specified	PET/CT	280 ± 40	60	Histology or imaging follow-up
Segaert et al[34]	2010	R	70	Stage IIB–III	PET/CT	4.5/kg	75	Histology or imaging follow-up
Sen et al[35]	2013	R	77	Not specified	PET/CT	370–555	60	Histology or imaging follow-up
Taneja et al[36]	2014	R	36	Not specified	PET/MRI	400 ± 56	48 ± 12	Histology, if not feasible, then imaging follow-up
Ulaner et al[37]	2016	R	232	Stage I–IIIC, TN	PET/CT	444–555	60	Histology, if not feasible, then imaging follow-up
Ulaner et al[38]	2017	R	483	Stage I–IIIC; ER+/HER2− (n = 238); HER2+ (n = 245)	PET/CT	444–555	60	Histology, if not feasible, then imaging follow-up
Walker et al[39]	2012	R	62	Inflammatory breast cancer	PET/CT	555–740	60–90	NR
Yararbas et al[40]	2018	R	234	Not specified	PET/CT	222–481	60	Typical lesions: considered positive; others: histology, if not feasible, imaging follow-up

LABC, locally advanced breast cancer; NAC, neoadjuvant chemotherapy; NR, not reported; P, prospective cohort study; R, retrospective cohort study; TNBC, triple-negative breast cancer.

TABLE 2. Patient Characteristics in the Included Studies

Author	Mean Age (Range)	Initial Stage, %	Histology‡ (Ductal/Lobular/Other, %)	Grade (I/II/III, %)	Receptor Phenotypes (ER+/PR+/HER2+, %)	Molecular Subtypes (Luminal A/B/HER2/TN)
Bernsdorf et al[12]	55 (24–81)	NR	80/14/6	11/52/36	72/55/21	NR/NR/NR/13
Cermik et al[13]	51† (24–80)	NR	NR	NR	NR	NR
Chandra et al[14]	56	I: 14; IIA/B: 60/26	NR	I–II/III: 44/56	NR	19/48/14/20
Cochet et al[15]	51 (25–85)	IIA/B: 15/40; IIIA/B/C: 8/13/11; IV: 12	90/8/2	I–II/III: 57/39	63/56/34	36/31/11/22
Evangelista et al[16] (preoperative)	53	I/II/III: 5/46/48	87/12/1	1/20/69	NR	11/50/9/28
Evangelista et al[16] (postoperative)	54	I/II/III: 21/35/44	83/9/6	3/22/75	NR	12/57/14/16
Fuster et al[17]	57	IIB: 65; IIIA/B/C: 11/6/5; IV: 13	87/13/0	NR	NR	NR
Gajjala et al[18]	51 (27–78)	IIIA/B/C: 23/68/9	98/0/2	NR	NR	13/49/12/26
Garami et al[19]	NR	I/II: 55/43	80/10/10	NR	77/NR/14	NR
Garg et al[20]	50† (18–80)	III: 100	98/0/2	NR	NR	NR
Groheux et al[21]	NR	IIA/B: 17/22; IIIA/B/C: 25/29/7	86/8/6	4/46/47	ER+/HER2−: 51; HER2+: 20	TN: 27
Gunalp et al[22] (preoperative)	47 (28–78)	I: 13; IIA/B: 36/35; IIIA/B: 9/1; IV: 6	NR	II–III: 100	NR	NR
Gunalp et al[22] (postoperative)	48 (25–75)	NR	NR	II–III: 100	NR	NR
Jeong et al[23]	55 (33–82)	T1/2/3: 61/36/3; N0: 100; M0: 100	82/6/12	NR	NR	NR
Klaeser et al[24]	59 (32–83)	I: 6; IIA/B: 36; IIIA/B/C: 15/20/13; IV: 10	61/5/34	NR	NR	NR
Koolen et al[25]	59 (26–75)	T1: 100; N0/1/2/3: 56/40/0/3; M0: 100	94/2/4	34/47/15	ER+/HER2−: 77; HER2+: 11	TN: 11
Krammer et al[26]	54	IIA/B: 51/23; IIIA/B/C: 9/5/1; IV: 11	77/14/9	5/46/43	64/54/54	NR
Landheer et al[27]	58 (29–80)	All N(+)	NR	NR	NR	NR
Manohar et al[28]	49 (28–80)	IIB: 7; IIIA/B/C: 35/56/2	NR	NR	NR	NR
Ng et al[29]	49 (26–70)	IIA/B: 13/53; IIIA/B/C: 28/5/2	NR	5/36/55	64/56/34	NR
Nursal et al[30]	52	I: 25; II: 75	73/7/20	NR	74/59/42	NR
Piperkova et al*[31]	55 (30–80)	NR	63/30/7	NR	NR	NR
Reddy Akepati et al[32]	54	IA: 5; IIA/B: 18/26; IIIA/B/C: 13/25/2; IV: 11	91/1/8	4/85/11	NR	NR
Riegger et al[33]	57 (25–84)	IA: 17; IIA/B: 36/18; IIIA/B/C: 5/4/2; IV: 15	79/16/5	10/57/35	NR	NR
Segaert et al[34]	56 (23–84)	IIB: 16; III: 84	90/10/0	NR	76/64/NR	NR
Sen et al[35]	52† (26–87)	I/II/III/IV: 25/49/23/3	80/4/16	NR	NR	NR
Taneja et al[36]	50 (34–75)	NR	100/0/0	6/64/14	NR	NR
Ulaner et al[37]	51† (25–93)	I: 10; IIA/B: 35/38; IIIA/C: 10/1	94/1/5	0/3/94	0/0/0	TN: 100
Ulaner et al[38] (ER+/HER2−)	55† (27–89)	I: 6; IIA/B: 30/40; IIIA/B/C: 10/11/3	79/14/7	2/16/77	100/85/0	NR
Ulaner et al[38] (HER2+)	50† (26–78)	I: 9; IIA/B: 29/38; IIIA/B/C: 13/9/2	92/3/5	0/7/89	67/53/100	NR
Walker et al[39]	49† (26–78)	T4d: 100; N0/1/2/3: 3/29/2/66; M0/1: 77/23	NR	0/37/52	48/39/45	NR
Yararbas et al[40]	53 (23–87)	IA–B: 1; IIA/B: 18/28; IIIA/B/C: 35/7/10	72/6/22	NR	NR	NR

*Patient characteristics were only available for the whole study population in whom PET/CT was performed for restaging as well as for staging.

†Median.

‡Other histologic types include mixed, papillary, mucinous, apocine, neuroendocrine, undifferentiated, atypical medullary, and adenosquamous carcinoma.

NR, not reported; PR, progesterone receptor; TN, triple-negative breast cancer.

or equal to 10.[45] Intermodality change was defined as an alteration in the type of management (eg, RT, surgery, systemic treatment, or multimodal treatment including a combination of RT, surgery, and systemic treatment).[46] Intention-to-treat change was defined as modification of treatment intent (eg, a change from curative to palliative approach).

The proportions were transformed using the Freeman-Tukey double arcsine method[47] and were then meta-analytically pooled using the DerSimonian-Liard method for calculating weights with the "meta" and "metafor" packages in R software (version 3.6.3; R Foundation for Statistical Computing, Vienna, Austria). Clopper-Pearson confidence intervals were used for individual studies. Higgins I^2 statistics were used to assess heterogeneity.[48] Funnel plots with Egger test were drawn to appraise the presence of publication bias.[49]

RESULTS

Study Characteristics

An electronic search retrieved 2054 articles (Fig. 1); of these, 81 articles were potentially eligible. After full-text review, we excluded 52 articles for the following reasons: no inclusion of changes in staging or management (n = 14), reports of either nodal or distant metastasis but without calculation of a patient-based proportion (n = 13), no initial staging (n = 10), overlapping study population (n = 9), dedicated breast PET scan (n = 3), comparison of high-resolution versus standard resolution PET/CT (n = 1), and not about PET, PET/CT, or PET/MRI (n = 2). Thus, 29 studies with 4276 patients were included in the meta-analysis.[12–40] Of note, there were 3 studies that included patients in whom PET/CT was performed in the preoperative and postoperative setting and patients with differential receptor phenotypes (estrogen receptor [ER]+/ human epidermal growth factor receptor 2 [HER2]− and HER2+) and separately evaluated each population[16,22,38]; these patients were considered as separate cohorts in the meta-analysis. Detailed study and patient characteristics are described in Tables 1 and 2. Table 3 summarizes the type of conventional staging procedures used in the included studies.

Quality Assessment

Study quality was considered moderate to good, with 25 of 29 studies satisfying at least 5 of the 8 RoBANS domains (Fig. 2). All studies were rated as having a low risk of bias in comparability of participants, incomplete outcome data, and selective outcome

TABLE 3. Conventional Staging Procedures in the Included Studies

Author	MG	Breast US	Breast MRI	CXR	BS	US Other Sites	CT	MRI Other Sites	Pathology
Bernsdorf et al[12]	+	+	−	+	−	−	−	−	−
Cermik et al[13]	−	−	−	−	−	−	−	−	+(Surgery)
Chandra et al[14]	+	−	−	−	−	−	−	−	+(Surgery/FNA)
Cochet et al[15]	+	+	±	+	+	−	+(C/AP); ±(brain)	±(Brain)	−
Evangelista et al[16]	+	+	−	−	±	−	±	±	±(Surgery)
Fuster et al[17]	−	−	+	−	+	+(Liver)	+	−	−
Gajjala et al[18]		+	−	−	+	+(AP)	+(C/A)	−	−
Garami et al[19]	+	+	−	+	+	+(A)	−	−	−
Garg et al[20]	−	−	−	+	+	+(A)	−	−	−
Groheux et al[21]	+	+	+	−	−	−	−	−	−
Gunalp et al[22]	+	+	+	Chest imaging (not specified)	±	±(AP)	±(AP)	±(AP)	−
Jeong et al[23]	+	+	±	+	−	+(AP)	−	−	−
Klaeser et al[24]	+	−	±	+	+	+(Liver)	±(C/AP)	±	−
Koolen et al[25]	±	+	+	±	±	−	−	−	−
Krammer et al[26]	+	+	±	+	+	+(A)	−	−	−
Landheer et al[27]	−	−	−	+	+	+(A)	−	−	−
Manohar et al[28]	−	−	−	+	+	+(A)	−	−	−
Ng et al[29]	+	+	−	−	+	−	+(C/AP)	−	+(CNB)
Nursal et al[30]	+	+	+	−	−	−	−	−	−
Piperkova et al[31]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Reddy Akepati et al[32]	−	+	−	+	+	+(A)	−	−	−
Riegger et al[33]	+	+	+	+	+	+(Liver)	+(C/A)	−	−
Segaert et al[34]	−	+	−	+	+	+(Liver)	−	−	−
Sen et al[35]	−	−	−	−	±	±(A)	±(C/A)	−	−
Taneja et al[36]	+	+	−	+	±	+(A)	−	−	−
Ulaner et al[37]	+	+	+	−	−	−	−	−	±(Surgery)
Ulaner et al[38]	+	+	+	−	−	−	−	−	±(Surgery)
Walker et al[39]	+	+	±	+	±	−	±(C/A)	−	−
Yararbas et al[40]	±	±	±	−	±	−	−	−	±

± indicates those performed in the selected patients.

A, abdominal; AP, abdominopelvic; BS, bone scan; C, chest; CNB, core-needle biopsy; CXR, chest x-ray; FNA, fine-needle aspiration; MG, mammography; NR, not reported; US, ultrasound.
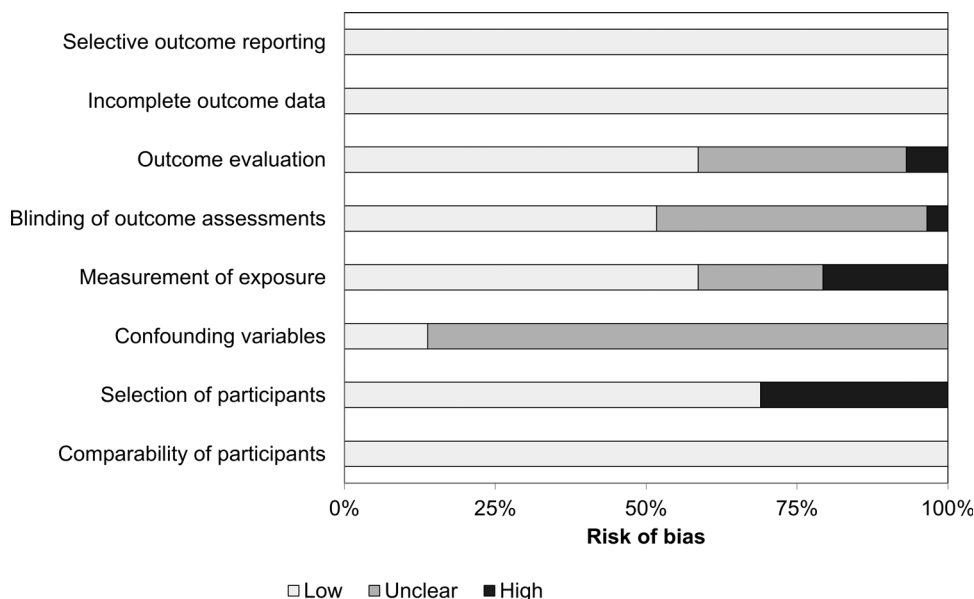
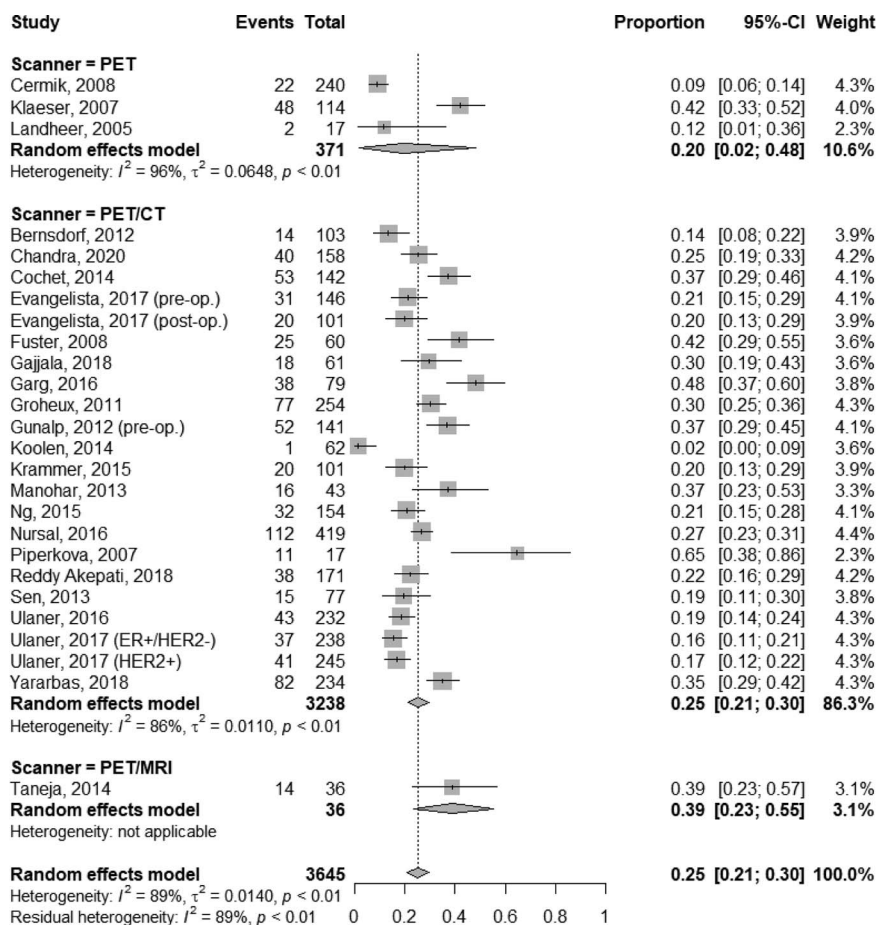**FIGURE 2.** Quality assessment using the RoBANS tool.

FIGURE 3. A forest plot shows the pooled proportion of changes in stage compared between ^{18}F-FDG PET, PET/CT, and PET/MRI versus conventional staging procedures.

reporting domains. Nine studies had a high risk of bias in the selection of participants because they were retrospective and did not report whether patients were consecutively enrolled.[23,30–32,35–38,40] Twenty-five studies were regarded as having an unclear risk of bias in confounding variables because the exact time interval between conventional staging procedures and PET scans was not reported.[12,14,16–27,29–32,34–40] For the measurement of exposure domain, 6 studies had a high risk of bias because a single reader interpreted PET images,[13,15,29,34,37,38] and 6 studies had an unclear risk of bias because they did not report the number of readers or their experience.[18,20,27,28,30,39] Regarding the blinding of outcome assessments domain, 13 studies had an unclear risk of bias as it was unclear whether PET interpretation was performed in a blinded

manner,[15,16,18,22–24,28–30,32,35,36,40] and 1 study had a high risk of bias because PET interpretation was not blinded to the findings of other tests.[19] For outcome evaluation, 10 studies showed an unclear risk of bias as the method for classifying stage was not explicitly mentioned,[12,14,17,25,27,28,30–32,36] and 2 studies had a high risk of bias as the method for confirmation of additional lesions on PET scan was reported.[24,39]

Impact of ^{18}F-FDG PET on Clinical Stage and Management

The changes in clinical stage and patient management after ^{18}F-FDG PET in all included studies stratified by scanner type are
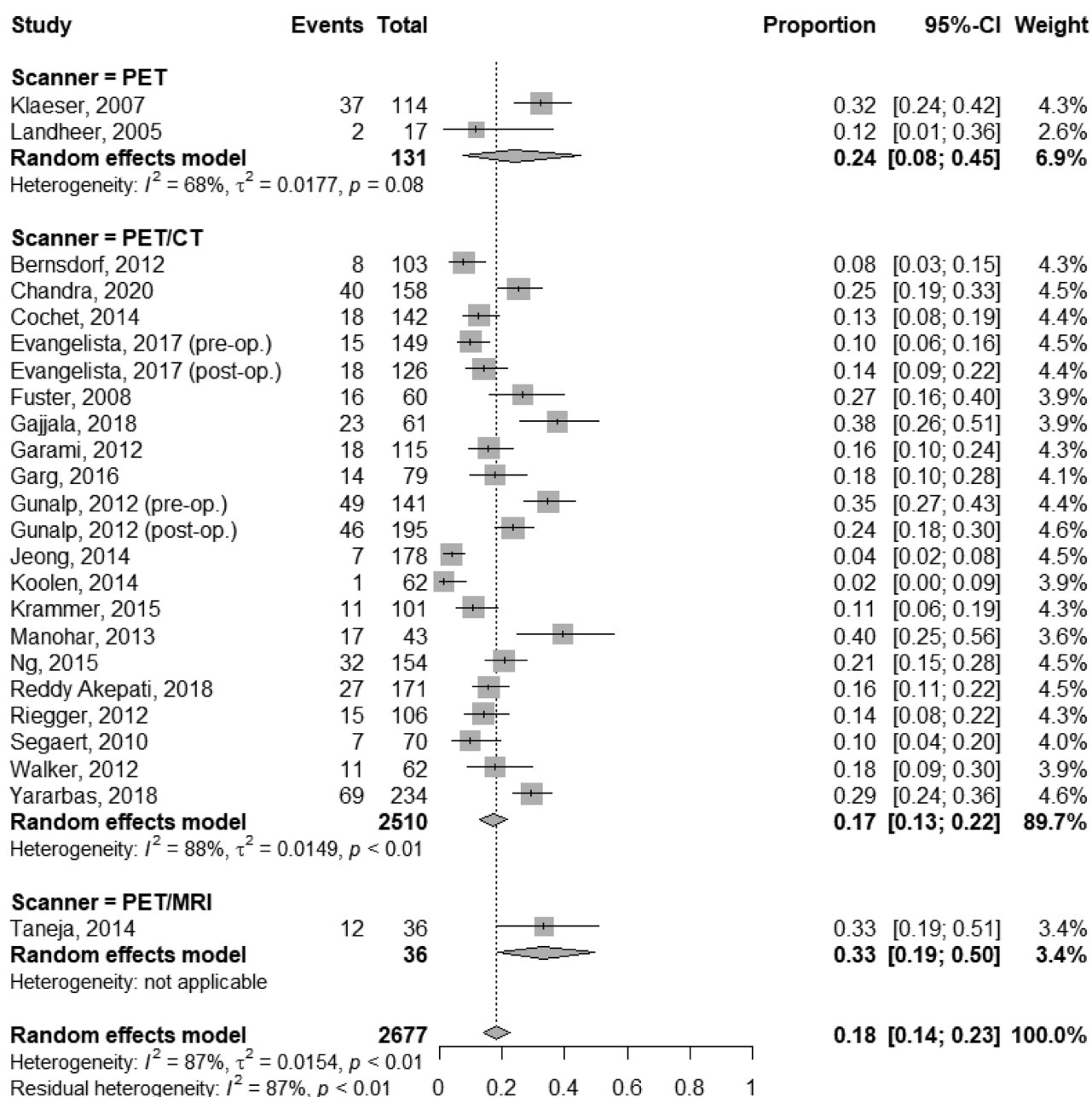

Study	Events	Total		Proportion	95%-CI	Weight
Scanner = PET						
Klaeser, 2007	37	114		0.32	[0.24; 0.42]	4.3%
Landheer, 2005	2	17		0.12	[0.01; 0.36]	2.6%
Random effects model		131		**0.24**	**[0.08; 0.45]**	**6.9%**
Heterogeneity: $I^2 = 68\%$, $\tau^2 = 0.0177$, $p = 0.08$						
Scanner = PET/CT						
Bernsdorf, 2012	8	103		0.08	[0.03; 0.15]	4.3%
Chandra, 2020	40	158		0.25	[0.19; 0.33]	4.5%
Cochet, 2014	18	142		0.13	[0.08; 0.19]	4.4%
Evangelista, 2017 (pre-op.)	15	149		0.10	[0.06; 0.16]	4.5%
Evangelista, 2017 (post-op.)	18	126		0.14	[0.09; 0.22]	4.4%
Fuster, 2008	16	60		0.27	[0.16; 0.40]	3.9%
Gajjala, 2018	23	61		0.38	[0.26; 0.51]	3.9%
Garami, 2012	18	115		0.16	[0.10; 0.24]	4.3%
Garg, 2016	14	79		0.18	[0.10; 0.28]	4.1%
Gunalp, 2012 (pre-op.)	49	141		0.35	[0.27; 0.43]	4.4%
Gunalp, 2012 (post-op.)	46	195		0.24	[0.18; 0.30]	4.6%
Jeong, 2014	7	178		0.04	[0.02; 0.08]	4.5%
Koolen, 2014	1	62		0.02	[0.00; 0.09]	3.9%
Krammer, 2015	11	101		0.11	[0.06; 0.19]	4.3%
Manohar, 2013	17	43		0.40	[0.25; 0.56]	3.6%
Ng, 2015	32	154		0.21	[0.15; 0.28]	4.5%
Reddy Akepati, 2018	27	171		0.16	[0.11; 0.22]	4.5%
Riegger, 2012	15	106		0.14	[0.08; 0.22]	4.3%
Segaert, 2010	7	70		0.10	[0.04; 0.20]	4.0%
Walker, 2012	11	62		0.18	[0.09; 0.30]	3.9%
Yararbas, 2018	69	234		0.29	[0.24; 0.36]	4.6%
Random effects model		2510		**0.17**	**[0.13; 0.22]**	**89.7%**
Heterogeneity: $I^2 = 88\%$, $\tau^2 = 0.0149$, $p < 0.01$						
Scanner = PET/MRI						
Taneja, 2014	12	36		0.33	[0.19; 0.51]	3.4%
Random effects model		36		**0.33**	**[0.19; 0.50]**	**3.4%**
Heterogeneity: not applicable						
Random effects model		2677		**0.18**	**[0.14; 0.23]**	**100.0%**
Heterogeneity: $I^2 = 87\%$, $\tau^2 = 0.0154$, $p < 0.01$						
Residual heterogeneity: $I^2 = 87\%$, $p < 0.01$						

FIGURE 4. A forest plot shows the pooled proportion of changes in management compared between ^{18}F-FDG PET, PET/CT, and PET/MRI versus conventional staging procedures.

illustrated in Figures 3 and 4, respectively. In individual studies, the proportion of alterations in staging and management ranged from 2% to 65% and from 2% to 40%, respectively.

For all the 24 studies (26 cohorts) combined, the pooled proportion of changes in stage was 25% (95% confidence interval [CI], 21%–30%). There was substantial heterogeneity based on Higgins I^2 statistics (I^2 = 89%). Publication bias was not present when we used the funnel plot and Egger test (Fig. 5A; P = 0.1079). Subgroup analysis according to scanner showed that there was an increasing trend in the proportion of stage changes from PET to PET/CT to PET/MRI (20% [95% CI, 2%–48%] to 25% [95% CI, 21%–30%] to 39% [95% CI, 23%–55%], respectively); however, no statistical significance was found (P = 0.2154). When we meta-analytically pooled studies reporting the proportion of changes stratified by initial stage, we noted different percentages of changes in staging: 11% (95% CI, 3%–22%) for stage I, 20% (95% CI, 16%–24%) for stage II, and 34% (95% CI, 27%–42%) for stage III (Supplementary Figs. 1–3, Supplemental Digital Contents 2–4, http://links.lww.com/CNM/A303, http://links.lww.com/CNM/A304, http://links.lww.com/CNM/A305; P = 0.0002).

Meta-analytic pooling of all 22 studies (24 cohorts) regarding changes in management indicated the pooled proportion was 18% (95% CI, 14%–23%). Higgins I^2 statistics demonstrated that there was substantial heterogeneity (I^2 = 87%). No publication bias was found (Fig. 5B; P = 0.5934). Subgroup analysis stratified by scanner indicated that the pooled proportions of modifications in management after PET, PET/CT, and PET/MRI were 24% (95% CI, 8%–45%), 17% (95% CI, 13%–22%), and 33% (95% CI, 19%–50%), respectively, with no statistical significance (P = 0.0843). Intermodality and intention-to-treat changes were available in 20 cohorts of 18 studies using PET/CT or PET/MRI (Fig. 6). The relative proportions of intermodality changes and intention-to-treat changes in terms of the summed total of each change divided by the sum of overall changes were 74% (284/386) and 70% (257/368), respectively.

Heterogeneity Exploration

We performed subgroup analyses, which were categorized according to the type of conventional staging modality other than local staging tools (eg, mammography, breast sonography, breast MRI) included in individual studies using PET/CT. There were no significant differences in the pooled proportions of modification in stage or management among studies that used surgical staging, those which included bone scan and sonography of the abdomen or liver, and those in which CT and/or MRI were performed, although the paucity of the included studies could limit their statistical significance (Table 4).

The results of metaregression analyses in studies using PET/CT are summarized in Table 5 and visualized in Supplementary Figure 4 (Supplemental Digital Content 5, http://links.lww.com/CNM/A306). The mean age, the proportion of advanced disease (initial stage III–IV), and the ratio of histologic grade II to III were significant factors contributing to heterogeneity. Specifically, metaregression analyses demonstrated that younger age was significantly correlated with an increased proportion of changes in staging and management after ^{18}F-FDG PET/CT. Increase in the percentage of patients with advanced disease was related to the increased rate of stage modification after ^{18}F-FDG PET/CT. Likewise, the proportion of grade II to III tumors was also a significant factor that increased the proportion of patient staging and management changes.

DISCUSSION

In this study, we found that the use of ^{18}F-FDG PET, PET/CT, or PET/MRI for initial staging of breast cancer led to changes in staging and management in 25% and 18% of patients, respectively, indicating that therapeutic approaches are altered due to PET imaging in approximately one fifth of patients. When assessing the type of management changes, intermodality and intention-to-treat changes consisted of approximately 70% of the overall changes in treatment. This indicates that additional findings on PET scans may have considerable impact on therapeutic plans such as omitting neoadjuvant chemotherapy followed by surgery and starting palliative chemotherapy as well as supporting an optimal plan for the extent and site of surgical resection or RT. This can allow timely treatment minimizing unnecessary delays and avoiding adverse effects of unwarranted neoadjuvant chemotherapy, surgery, or RT. In addition, as local ablative therapy such as metastatectomy or stereotactic body RT for oligometastatic lesions can provide a
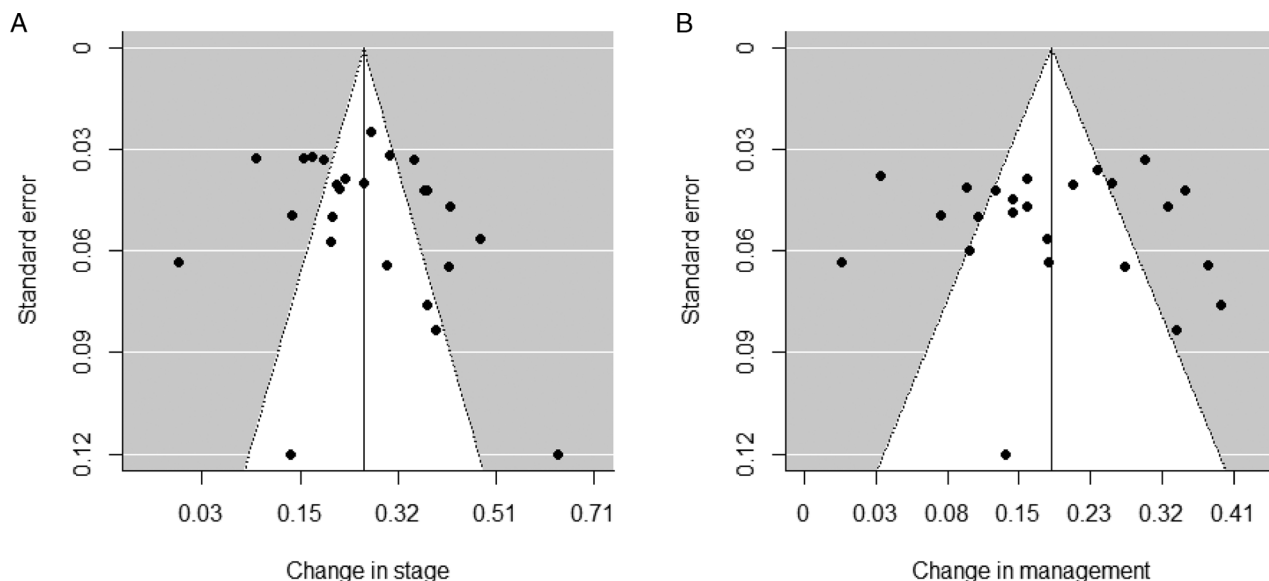

FIGURE 5. Funnel plots of studies assessing the proportion of changes in staging (**A**) and management (**B**).
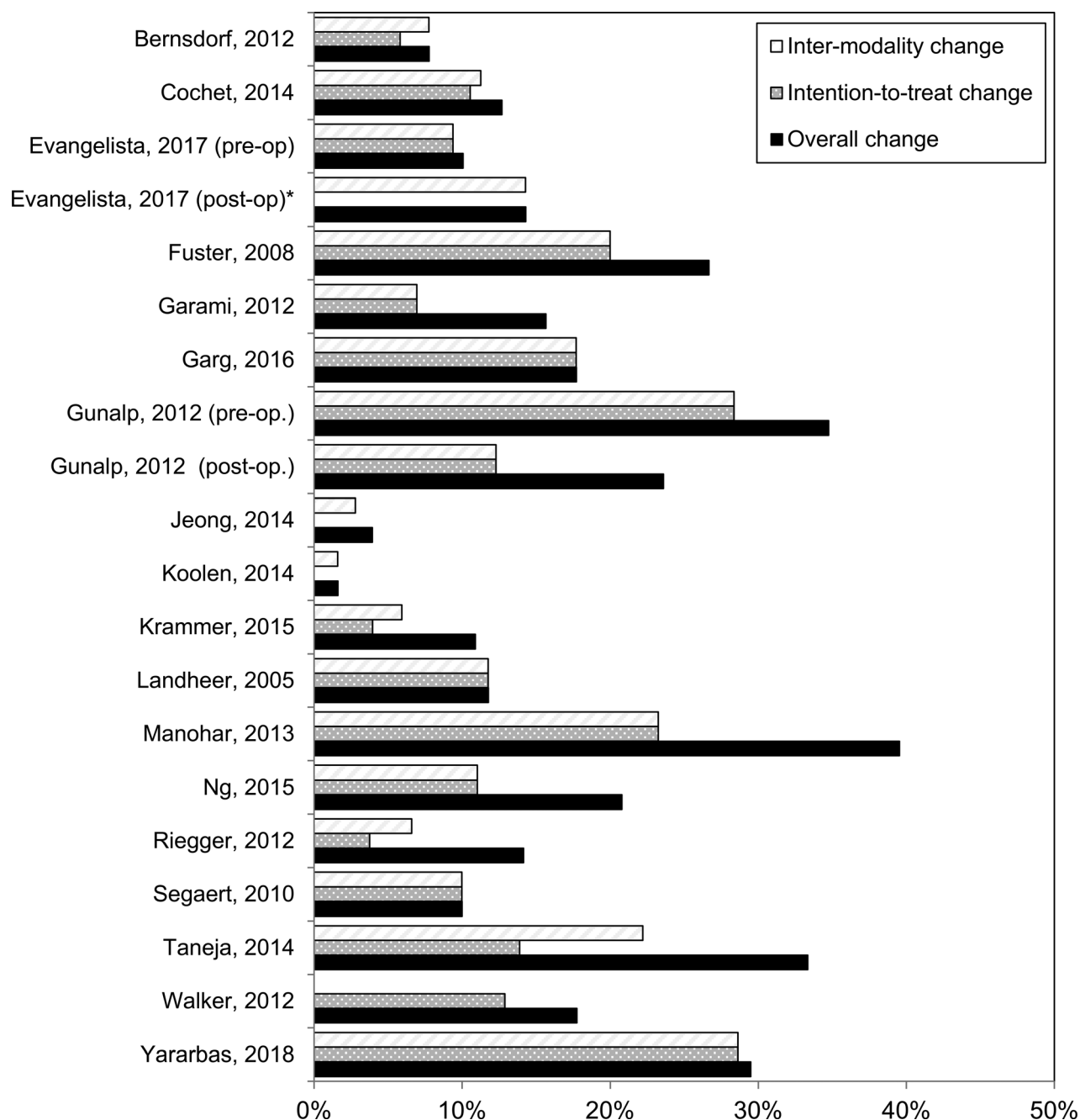
FIGURE 6. A grouped bar graph represents the proportion of changes in management categorized as intermodality and intention-to-treat changes. Information for intention-to-treat change was not available (asterisk).

potentially curative approach,[50] ^{18}F-FDG PET may identify a subset of patients who could benefit from these locally aggressive therapies and have prolonged survival. Therefore, it seems plausible that the use of ^{18}F-FDG PET scans can improve the management of breast cancer patients.

Notably, there was substantial heterogeneity across the included studies for changes in both staging and management. We found that clinical stage, tumor grade, and age were significant factors that affect heterogeneity. We have reported the differential pooled proportions of stage changes according to patient's initial stage. Our result is partly consistent with current clinical guidelines

in that the use of ^{18}F-FDG PET/CT is recommended in advanced stage breast cancer,[2–4] in that clinical stage changed in approximately one third of patients with stage III (34%) disease. However, our results also indicate that a nonnegligible proportion of patients in stage II (20%) and even in stage I (11%) can undergo stage changes and may benefit from the use of PET scans. These values are not significantly different from the reported proportions of stage migration from clinical stage I after ^{18}F-FDG PET/CT in the initial staging of non–small cell lung cancer[51,52] or head and neck squamous cell carcinoma,[53] for which ^{18}F-FDG PET/CT is recommended by guidelines[54,55] and covered by Medicare.[6] Well-designed

TABLE 4. Subgroup Analysis According to Conventional Staging Procedure in the Included Studies Using PET/CT

Outcomes	Conventional Modalities	Studies, n	Pooled Proportion	95% CI	I^2	P^*
Change in stage	CXR(−)/BS(−)/US(−)/CT(−)/MRI(−)	6	0.22	0.17–0.27	82%	0.3873
	BS(+)/US(+)/CT(−)/MRI(−)	4	0.31	0.19–0.44	86%	
	CT(+)/MRI(−)	4	0.27	0.18–0.37	73%	
	CT(+)/MRI(+)	4	0.29	0.20–0.38	83%	
Change in management	CXR(−)/BS(−)/US(−)/CT(−)/MRI(−)	1	0.25	0.19–0.32	NA	0.2638
	BS(+)/US(+)/CT(−)/MRI(−)	6	0.17	0.11–0.23	70%	
	CT(+)/MRI(−)	5	0.22	0.16–0.30	69%	
	CT(+)/MRI(+)	5	0.18	0.11–0.27	89%	

*P values of test for subgroup differences.
CXR, chest x-ray; NA, not applicable; US, ultrasound.

prospective studies (which could not be included in our meta-analysis because of overlapping study populations) reported that ^{18}F-FDG PET/CT changed the stage in 52% (61/117) of patients with locally advanced or inflammatory breast cancer[56] and in 17% (22/131) of patients with stage IIA to IIIA disease.[57] Invasive tumors with higher histologic grade exhibit higher ^{18}F-FDG uptake, which increased detectability of lesions.[58,59] Grade III tumors are more frequently associated with extra-axillary nodal metastasis,[21] for which PET scans show superior diagnostic efficacy compared with other conventional staging modalities; this may significantly influence planning fields for surgery or RT.[41] Of note, the clinical impact of ^{18}F-FDG PET can possibly be influenced by histologic types, as invasive ductal carcinoma usually exhibits higher FDG uptake than invasive lobular carcinoma.[41] Although the results of metaregression analyses with proportions of ductal or lobular histology were not statistically significant, we speculated that variable "other subtypes" across the included studies as shown in Table 2 may complicate the evaluation of the effect of histology by simple metaregression analysis. Breast cancer in younger women is associated with a greater tumor burden and an unfavorable biology.[60] We also speculated that heterogeneity among the studies is attributed to the differences in conventional staging modality and different practice patterns between institutions and study populations. Although we partly conducted subgroup analyses across different conventional staging modalities and found no statistical difference, we acknowledge that the limited number of studies and the heterogeneity within each subgroup may have limited the statistical significance of these

analyses. Moreover, practice patterns in breast cancer can vary widely because this cancer has a wide range of hormone receptors and molecular subtypes. Two retrospective studies by Ulaner et al[37,38] suggested that ^{18}F-FDG PET/CT may have a greater impact on staging and treatment in triple-negative breast cancer patients compared with ER+/HER2− or HER2+ breast cancer patients.

Our study has several limitations. First, approximately half of the studies (15/29) were retrospectively conducted. If the PET scans were performed to confirm suspected lesions on conventional imaging modalities, although this was not mentioned in any of the studies, we may have overestimated the potential impact of PET imaging on staging and/or management. Second, there was substantial heterogeneity among the studies, and therefore, caution is required when applying our pooled results in specific clinical circumstances. Although we found that age, stage, and grade were significant factors for heterogeneity, it remains unexplained to some extent. Third, the definition of changes in staging or management may vary across studies. Several studies performed a less specific classification of stage (ie, stage III, rather than substages IIIA–C) or treatment modality (ie, RT, without mention of extent and dose of radiation) that would cause an underestimation of our pooled proportions. If this detailed information had been provided, the impact of PET scans would have been greater. Fourth, there was a body of important studies that matched the scope of our review but not included in our meta-analysis. These studies reported either unsuspected nodal or distant metastasis; not being able to extract patient-based proportion would lead an underestimation of our pooled proportions of

TABLE 5. Metaregression Analysis of the Included Studies Using PET/CT

Outcomes	Variables	Studies, n	Slope Coefficient	95% CI	P	R^{2*}
Change in stage	Mean age, y	21	−0.0188	−0.0362 to −0.0015	0.0334	9%
	Initial stage III–IV, %	20	0.0024	0.0009 to 0.0040	0.0021	18%
	Ductal histology, %	18	−0.0033	−0.0099 to 0.0032	0.3184	0%
	Lobular histology, %	18	0.0065	−0.0025 to 0.0155	0.1596	0%
	Grade II–III, %	12	0.0101	0.0049 to 0.0153	0.0001	49%
	HER2+ phenotype, %	10	0.0007	−0.0018 to 0.0032	0.5810	0%
Change in management	Mean age, y	20	−0.0238	−0.0394 to −0.0081	0.0030	27%
	Initial stage III–IV, %	19	0.0016	−0.0002 to 0.0033	0.0824	5%
	Ductal histology, %	15	0.0007	−0.0083 to 0.0097	0.8816	0%
	Lobular histology, %	15	−0.0044	−0.0171 to 0.0084	0.5017	0%
	Grade II–III, %	11	0.0103	0.0054 to 0.0152	<0.0001	70%

*R^2 represents amount of heterogeneity that can be accounted for.
CXR, chest x-ray; NA, not applicable; US, ultrasound.

changes if included in our meta-analysis.[61–73] The number of currently available literature that supports the clinical importance of ^{18}F-FDG PET scans in staging or management of newly diagnosed breast cancer patients is even greater than that of included articles. Finally, it is not yet clear whether the considerable changes in staging and management after PET scans would directly translate to improved clinical outcomes. Further studies are warranted.

CONCLUSIONS

The use of ^{18}F-FDG PET, PET/CT, or PET/MRI substantially impacted clinical staging and management in newly diagnosed breast cancer. The pooled proportions of changes in staging and management were 25% and 18%, respectively. Intermodality and intention-to-treat changes constituted approximately 70% of the overall changes in treatment. Therefore, PET imaging may deserve routine clinical use for initial staging of breast cancer. Younger age and a higher proportion of patients with clinical stage III to IV and histologic grade II to III were significantly associated with a greater proportion of changes in stage or management after PET/CT.

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