REVIEW ARTICLE

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18F-fluoroestradiol positron emission tomography in patients with breast cancer: a systematic review and meta-analysis

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INTRODUCTION

Breast cancer is a neoplasm that most commonly affects women worldwide, with an estimated 1.68 million new cases per year. According to the National Cancer Institute in Brazil, 73,610 new cases of breast cancer are estimated for the 3-year period from 2023 to 2025, which is the main cause of cancer mortality in females[1]. Despite the high 5-year survival rate of up to 89.5%[2], the potential for metastasis through the bloodstream and lymphatic vessels can lead to severe consequences if not detected and treated early.

The National Comprehensive Cancer Network guidelines highlight the estrogen receptor (ER) as a crucial prognostic indicator for breast cancer patients' disease-free survival and overall mortality[2]. The presence of ERs and progesterone receptors is an important factor influencing treatment strategies and patient prognosis[3]. Furthermore, hormone receptor-positive breast cancers exhibit higher survival rates and lower recurrence rates than hormone receptor-negative tumors[4].

Testing for hormone receptors is vital for breast cancer patients to determine their prognosis and treatment options. However, the invasive nature of the biopsy limits its effectiveness, and the variations in receptor status among primary and metastatic sites make it challenging to plan treatment for patients with recurrent and/or metastatic breast cancers[5,6].

Noninvasive tests like 18F-fluoroestradiol (FES) positron emission tomography-computed tomography (PET-CT) can evaluate estrogen distribution and binding in several sites and confirm metastasis simultaneously, making it an effective tool to predict treatment response in breast cancer patients[3,5,7]. To confirm the effectiveness of 18F-FES PET-CT in predicting treatment response, we conducted a pooled analysis of its diagnostic accuracy reported to date, despite predictions of previous studies.

METHODS

Bibliographic search

A systematic review was performed in accordance with Cochrane Collaboration and Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines[8,9].

We performed a comprehensive literature search of PubMed and the Cochrane Library without date restriction up to February 16, 2023, using the following MeSH vocabulary keywords and free text words: ((((((18F-FES) AND (PET-CT)) OR (FLUOROESTRADIOL F18)) OR (18f-FLUOROESTRADIOL)) OR (FES F18)) OR (FLUOROESTRADIOL)).

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Inclusion and exclusion criteria

Patients: Those diagnosed with breast cancer.

Index text: 18F-FES-PET.

Target condition: Diagnostic, staging, restaging.

Study design: Diagnostic accuracy cross-sectional study with prospective or retrospective recruitment.

Exclusion criteria: Case reports, animals, phantom, and radiopharmacokinetics.

No language or sample-size restrictions were used.

Reference standard

A composite standard including clinical follow-up and histopathological findings.

Outcome measures

The outcome measures included identification of predictors of 18F-FES-PET positivity, sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy.

Study selection

Titles and abstracts retrieved by the bibliographic search were independently screened by two authors (M.C.S. and R.P.C.). The full text of all relevant articles was acquired, and the study was further assessed for inclusion independently by the same two authors and studies not fulfilling the inclusion criteria were excluded.

Quality assessment

Studies were independently assessed by two authors (M.C.S. and R.P.C.) using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) checklist tool[10]. The QUADAS-2 tool assesses four domains: risk of bias in patient selection, index test, reference standard, and the timing of reference test. Each paper was scored independently by two evaluators (M.C.S. and R.P.C.) and discrepancies were resolved.

Data extraction

The following information was extracted from each study: sample size, age, indication for PET (diagnosis, primary staging, or recurrent disease staging), previous therapies, initial cancer stage, 18F-FES-PET characteristics, rates of positive PET, and histopathological correlation data. When histopathological correlation data were available, the numbers of true positives, false positives, true negatives, and false negatives were collected as appropriate. Using 18F-FES-PET for both primary staging and recurrent cancer staging, the extracted data were displayed separately when available.

Extracted data were collected using Excel 2007 (Microsoft Corporation, Redmond, CA, USA), and analysis was performed using Meta-Disc 1.4[11]. The detection rates were pooled using the generic inverse variance approach in the random-effects model[12]. Heterogeneity in the meta-analysis of detection rates was assessed using the X^2 statistic in the I^2 statistic[9]. The I^2 statistic indicates the percentage of the overall variability that can be attributed to between-study (or inter-study) variability, as opposed to within-study (or intrastudy) variability. An I^2 greater than 50% is considered to indicate substantial heterogeneity[9].

We explored the variability in diagnostic accuracy across studies by plotting the estimates of the observed sensitivities and specificities in forest plots and in receiver-operating characteristic (ROC) curve space. Whenever data for computing true-positive, false-negative, true-negative, and false-positive rates were available, we performed meta-analyses using the bivariate model to produce summary sensitivities and specificities[11]. The bivariate model jointly models sensitivity and specificity, specifying their logits as random study effects; a summary of the ROC curve can be derived from the model parameters. The significance level was set at p=0.05.

RESULTS

Identification of studies

Figure 1 summarizes the process of identification and selection of studies. A total of 248 studies were identified. The electronic search was complemented by manually checking the reference lists in review papers and all included studies. Overall, we included 24 studies comprising a total of 664 patients (range: 10–90 patients per study): 23 studies on diagnostic[6,13-28] and 1 study on staging[29]. Figure 2 shows the QUADAS-2 results.

A total of seven studies were reviewed for the diagnostic accuracy, in which the sensitivity ranged between 0.700 and 0.963 and the specificity ranged between 0.500 and 0.987. The pooled sensitivity and specificity of the method were 0.824 (95% confidence interval [CI] 0.763–0.874; i^2=0.1%) and 0.938 (95%CI 0.861–0.980; i^2=42.2%), respectively (Figure 3). The pooled-positive likelihood ratio was 4.13 (95%CI 1.61–10.62; i^2=62.9%) and the negative likelihood ratio was 0.25 (95%CI 0.18–0.35; i^2=0.0%).

The statistical correlation of 18F-FES PET-CT was analyzed in 11 studies with immunohistochemical essays, and it did not correlate significantly (r=0.76; p=0.12). Similar results were revealed in two articles that correlated the examinations with the tumor size (r=0.30; p=0.32).

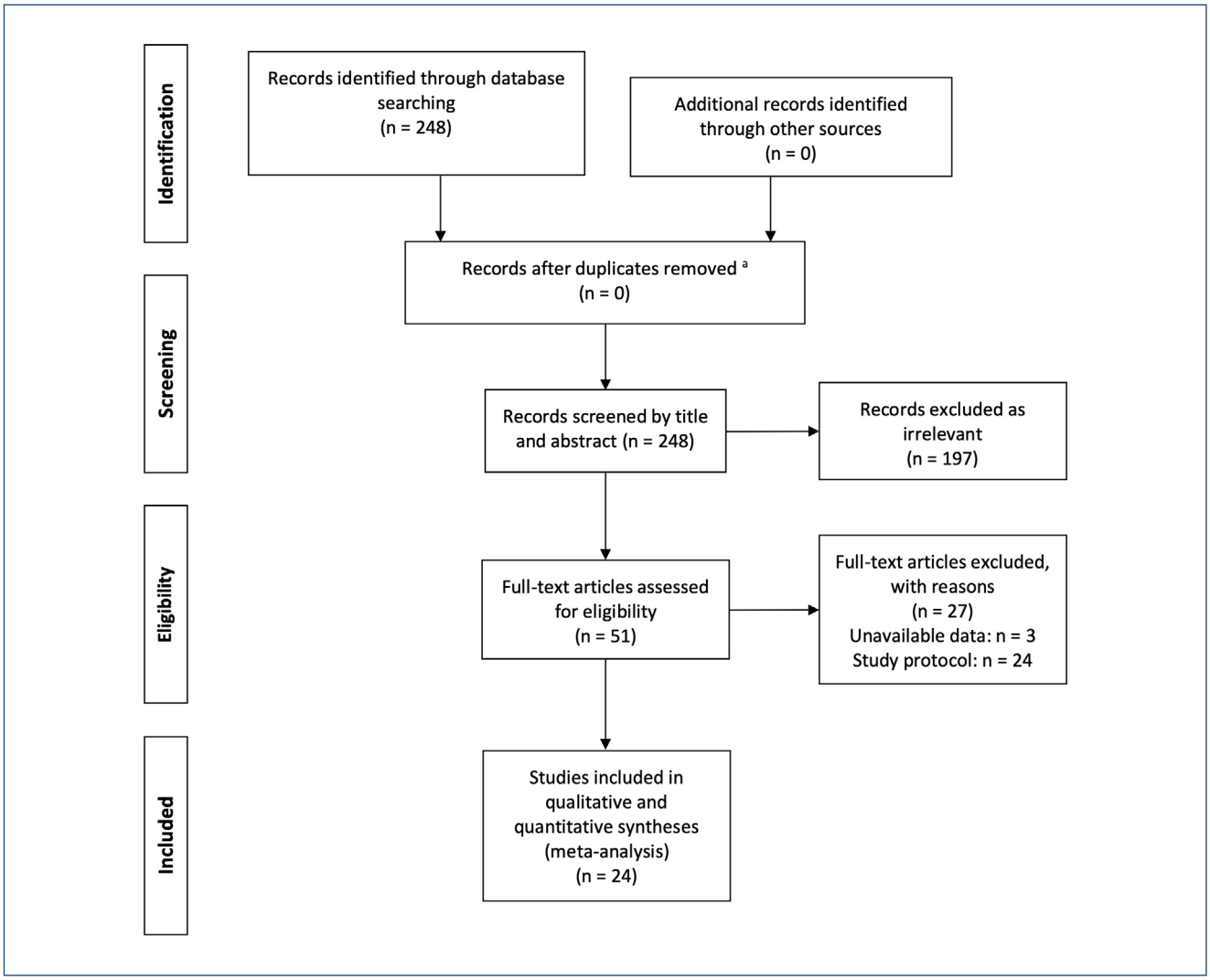

Figure 1. Preferred Reporting Items for Systematic Review and Meta-analysis flowchart, demonstrating the studies selection criteria.

One article compared the sensitivity of 18F-FES PET-CT and 18F-fluorodeoxyglucose (FDG) PET-CT in the evaluation of breast cancer recurrence[30]. A total of 40 patients were ER-positive. Using a threshold for positive interpretation, the sensitivity of 18F-FES was 71.1% and that of 18F-FDG was 80%, with no significant difference between the methods (p=0.48).

Initial staging was evaluated by two studies[29,31]. Liu et al., reported a sensitivity of 90.8% for 18F-FES and 82.8% for 18F-FDG in a retrospective study with 19 patients. 18F-FES PET-CT changed patient management in 26.3% of the cases. On the contrary, Gupta et al., in a prospective study with 10 patients, reported a sensitivity of 75.32% for 18F-FES and 92.21% for 18F-FDG (p=0.0004). Excluding liver lesions, the sensitivity of 18F-FES was 85.29% and that of 18F-FDG was 91.18% (p=0.2159). Management was changed for 20% of the patients.

DISCUSSION

18F-FDG PET imaging is a well-known and established diagnostic tool for staging/restaging patients. However, some breast tumors may have low FDG uptake, such as invasive lobular carcinoma (ILC). Other molecular imaging methods may be needed for the evaluation of this malignancy. ILC is nearly always (95%) ER-positive, thus ER-targeting PET tracers such as 18F-FES may have value[5]. 18F-FES is a recently available radiotracer in Brazil that can help to noninvasively assess whole-body ER protein expression and ligand binding function across multiple metastatic

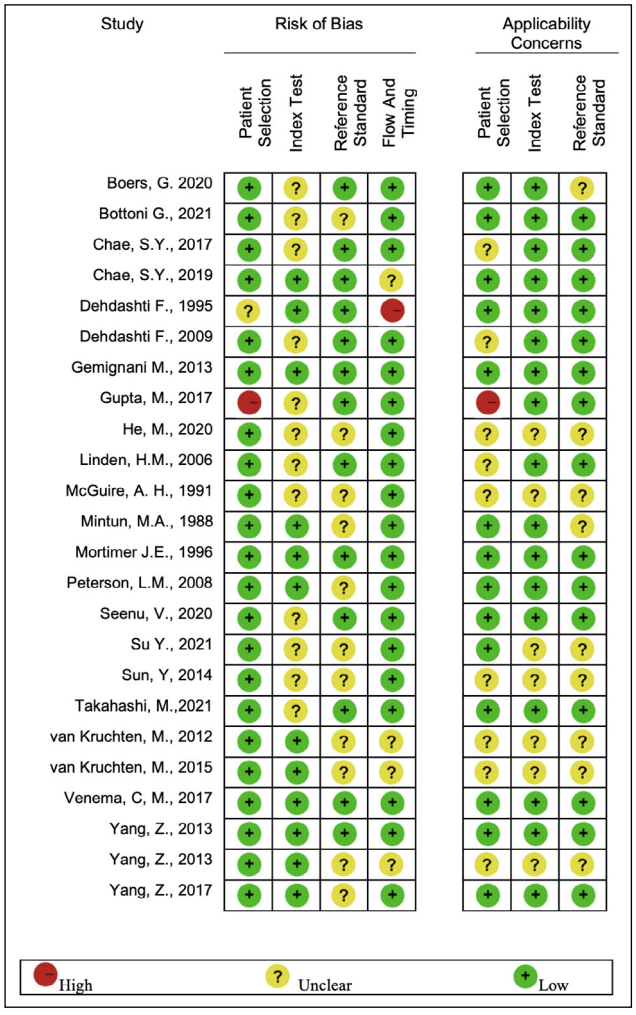

Figure 2. Quality Assessment of Diagnostic Accuracy Studies-2 results.

sites, demonstrate intertumoral and temporal heterogeneity of ER expression, quantify the pharmacodynamic effects of ER antagonist treatment, and predict endocrine therapy response.

With respect to the effectiveness of 18F-FES PET, diagnostic accuracy for the detection of lesions was evaluated in this pooled analysis, with a pooled sensitivity of 82% and a pooled specificity of 94%, resulting in a pooled AUC of 0.8899, thus demonstrating high diagnostic accuracy.

Immunohistochemistry sample analysis is the golden standard for the evaluation of ER expression. Amidst the included studies, eight perceived the correlation between the ER expression in immunohistochemistry and 18F-FES uptake, resulting in a pooled correlation of 0.76, with no significant heterogeneity, but not demonstrated statistical significance (Q=11.46, p=0.12, I^2=39%, despite a LFK index of -2.66, showing a major asymmetry).

The correlation between tumor size and 18F-FES uptake was only assessed in two studies, which differ largely in weight, with a positive correlation between size and uptake of 0.30, with no significant heterogeneity, but not demonstrated statistical significance (Q=0.95, p=0.33, I^2=0%). It is important to emphasize the small number of studies included in the analysis.

As the number of breast cancer patients seems to rise year by year, so does the drug options to treat the most variable cancer presentations[31]. For that, 18F-FES PET imaging might be a good option, allowing a correct evaluation of the ER status in vivo, noninvasively and painlessly, especially considering that the presence of metastases is one of the prognostic factors of the disease and the invasive biopsy in the bone, liver, and brain is often difficult. Furthermore, 18F-FES PET imaging can evaluate the whole body and show some heterogeneity in ER expression between the lesions (which is usually not assessed on a single lesion biopsy)[32].

A PET scan using 18F-FES may also be helpful for the interim therapy evaluation of patients under specific therapies, proving ER blockade, and then helping to choose more accurate therapies.

CONCLUSION

Current evidence suggests that 18F-FES PET for the detection of ER-positive lesions in breast cancer patients is sensible, with a pooled sensitivity of 82%, and highly specific, with a pooled specificity of 94%, demonstrating its high diagnostic accuracy, with a pooled AUC of 0.8899. This brings to light its potential to be added to the breast cancer toolbox as an imaging tool for therapy guiding and predicting the endocrine therapy response.

AUTHORS' CONTRIBUTIONS

CSM: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **FARFBC:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **PHRC:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **CESS:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration,

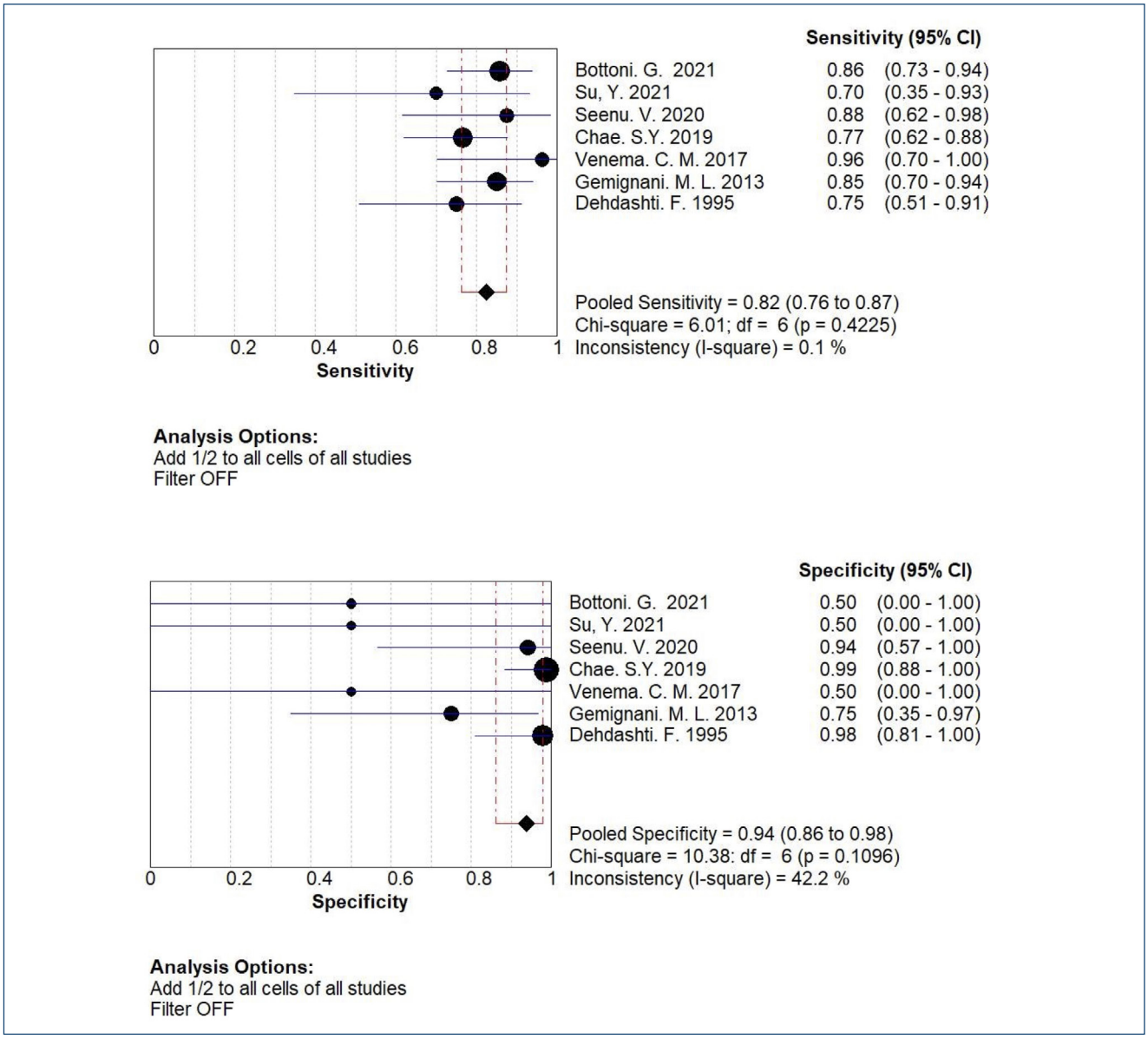

Figure 3. Pooled sensitivity and specificity.

Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **DFR:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **DBP:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **FDK:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **MMS:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **SALS:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **RWL:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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