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Comparison of whole-body PET/PET-CT and conventional imaging procedures for distant metastasis staging in patients with breast cancer: a meta-analysis

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Summary

Aim: To compare the performance of whole-body PET/PET-CT with that of conventional imaging procedures for the overall assessment of distant metastasis in patients with breast cancer. *Materials and Methods:* The authors performed a meta-analysis of all available studies of whole-body PET/PET-CT compared with conventional imaging procedures. They calculated sensitivities, specificities, positive likelihood ratios, negative likelihood ratios, and constructed summary receiver operating characteristic (ROC) curves using bivariate regression models for whole-body PET/PET-CT and conventional imaging procedures, respectively. *Results:* Across six studies (609 patients), sensitivity, specificity, positive likelihood ratios, and negative likelihood ratios of whole-body PET/PET-CT were 0.99 (95% confidence interval [CI] = 0.88–1.00), 0.95 (95% CI = 0.89–0.98), 21.1 (95% CI = 8.2–55.5), and 0.02 (95% CI = 0.001–0.13), respectively, and of conventional imaging procedures they were 0.57 (95% CI = 0.37–0.74), 0.88 (95% CI = 0.78–0.94), 4.8 (95% CI = 2.8–8.2) and 0.49 (95% CI = 0.33–0.74), respectively. *Conclusion:* Compared with conventional imaging procedures, whole-body PET/PET-CT had excellent diagnostic performance for distant metastasis staging in patients with breast cancer.

Key words: PET; Breast cancer; Distant metastasis; Meta-analysis.

Introduction

Breast cancer is the most frequent malignant tumour in women worldwide, with an incidence of about 10% [1]. Approximately 40% of patients with locally advanced breast cancer will develop distant metastases within five years [2-4]. Early detection is essential for precise M staging, optimal management, and accurate comparison of protocol efficacies in patients with breast cancer.

To detect distant metastases, conventional imaging procedures with chest radiography, abdominal ultrasonography, and bone scan are commonly carried out as the standard of care in many cancer centers. Additional imaging procedures with CT and MRI were used to assess suspicious lesions. However, conventional imaging procedures have difficultly in distinguishing potential abnormalities from benign findings on the basis of morphological criteria, with only a sensitivity ranging from 32% to 43% for the detection of distant metastases [5-7]. ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}FDG PET) is a functional imaging modality that is based on the increased glucose metabolism of malignant cells. Because of its unique capability to image metabolically active lesions, ^{18}FDG PET has been reported to be more effective than conventional imaging procedures for the detection of distant metastases in patients with breast cancer [5-7]. However, anatomic information concerning distant lesions is limited on FDG PET images. The integration of PET and CT is expected to provide more anatomical details and allow better correlation of the PET images, which had become a standard modality for the detection of distant metastases in breast cancer patients [8]. Although many previous studies comparing whole-body PET/PET-CT with conventional imaging procedures have been done, results are controversial. Here, the authors undertook a meta-analysis of all available studies to compare the diagnostic performance of whole-body PET/PET-CT and conventional imaging procedures for the detection of distant metastases in patients with breast cancer.

Materials and Methods

Literature search

A comprehensive computer literature search of studies was performed to identify articles regarding the diagnostic performance of whole-body PET/PET-CT compared with conventional imaging procedures for the overall assessment of distant metastases in patients with breast cancer. MEDLINE, EMBASE, and EBM Review databases (last update July 15, 2012) were used

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Table 1. — *The clinical characteristics and study quality of included studies.*

Study	Origin	Design	Imaging system	No. of patients	Age (y)	Analysis method	Follow-up time	QUADAS
Schirrmeister *et al.* [6], 2001	Germany	Prosp	PET	89	28-86	QL+QN	NR	11
Mahner *et al.* [7], 2008	Germany	Retro	PET	119	28-89	QL	11(mean)	12
Fuster *et al.* [8], 2008	Spain	Prosp	PET-CT	60	40-82	QL+QN	≥12	11
Aukema *et al.* [16], 2010	Netherlands	Prosp	PET-CT	56	27-74	QL	13.4(mean)	11
Niikura *et al.* [17], 2011	USA	Retro	PET-CT	225	23-84	QL	≥24	12
Koolen *et al.* [18], 2011	Netherlands	Prosp	PET-CT	60	19-75	QL+QN	≥6	12

Prosp = prospective; Retro = retrospective; QL = qualitative; QN = quantitative; QUADAS = the number of items assessed as "yes" in the QUADAS tool.

for searching relevant articles with the following combination of search terms: (a) PET OR positron emission tomography, (b) breast cancer, and (c) staging OR distant metastases. References of the retrieved articles were also screened for additional studies. Reviewers of eligible studies were contacted and asked to supplement additional data when key information relevant to the meta-analysis was missing. The authors had no language restrictions for searching and identifying relevant studies.

Study selection

Studies were eligible for inclusion based on the following criteria: (1) whole-body PET/PET-CT and conventional imaging procedures evaluated breast cancer patients of all ages in any disease stage regardless of treatment status, (2) distant metastases findings were confirmed with histopathologic analysis and/or clinical and imaging follow-up, (3) the two imaging modalities (whole-body PET/PET-CT and conventional imaging procedures) were performed within three months of one another, (4) the studies were based on a per-patient analysis, (5) the studies including at least ten patients that were selected for inclusion in this meta-analysis, and (6) when 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. Studies were excluded based on the following criteria: (1) only whole-body PET/PET-CT or conventional imaging procedures was performed, (2) totals of true positives, false positives, true negatives, and false negatives were not provided, and (3) no data from a sub-analysis were provided.

Data extraction and quality assessment

Two reviewers (Y.K.L. and Q.Y.L) independently extracted the relevant data from each article and recorded these data on a standardized form and any difference was resolved by consensus. Data was extracted from the studies, including authors, year of publication, study design, sample size, imaging methods (whole-body PET/PET-CT or conventional imaging procedures) and imaging technical characteristics, reference standard, and totals of true positives, false positives, true negatives, and false negatives.

The authors assessed the methodological quality of the studies using the quality assessment for studies of diagnostic accuracy (QUADAS) tool [9]. It is the first systematically developed evidence-based quality assessment tool to be used in systematic reviews of diagnostic accuracy studies. The QUADAS tool includes 14 items, each of which is assessed as "yes", or "no".

Statistical analysis

The authors used bivariate regression models to obtain weighted overall estimates of the sensitivity and specificity as the main outcome measures, and to construct hierarchic summary receiver operating characteristic (HSROC) curves for whole-body PET/PET-CT and conventional imaging procedures, respectively [10-11]. Based on random-effects models, this bivariate approach accounts for potential between-study heterogeneity and incorporates the possible correlation between the sensitivity and the specificity. By using the pooled sensitivities and specificities, the authors also calculated diagnostic odds ratio (DOR), positive likelihood ratios (PLR), and negative likelihood ratios (NLR) for whole-body PET/PET-CT and conventional imaging procedures, respectively [11-12]. The discriminating ability is better with higher PLR and lower NLR. Although there is no absolute cutoff, a good diagnostic test may have PLR greater than 10.0 and NLR less than 0.1. All analyses were conducted with Stata version 11.0.

Results

Study selection and description

After independent review, ten articles dealing with the diagnostic performance of whole-body PET/PET-CT were compared with conventional imaging procedures for the detection of distant metastases in breast cancer patients. Of these publications, two articles [13, 14] were excluded because insufficient data were reported to enable construction of a 2×2 table of true-positive, false-negative, false-positive, and true-negative values. Two articles [5, 15] were excluded because the data was already reported in an included article [7]. Consequently, six articles [6-8, 16-18] were eligible for meta-analysis. A total of 609 patients were analyzed for the diagnostic accuracy of whole-body PET/PET-CT and conventional imaging procedures for the detection of distant metastases in the eligible articles. In four articles (66.7%), the study design was prospective (Table 1).

Study quality

The authors assessed the quality of the six articles according to the 14-item QUADAS assessment tool**.** Eleven of the 14 items were scored in all included articles. No study (0%) reported that all patients received the same reference test regardless of the index test result (item 6) and the reference standard was blinded to the index test results (item 11). Representative spectrum was present in 33.3% [7, 17] of the six articles (item 1).

When considering all six studies (609 patients) with data on a per-patient basis [6-8, 16-18], sensitivity, specificity, and DOR of whole-body PET/PET-CT were 0.99 (95% confidence interval [CI] = 0.88–1.00), 0.95 (95% CI = 0.89–0.98) and 1407 (95% CI = 82–24276), respec-

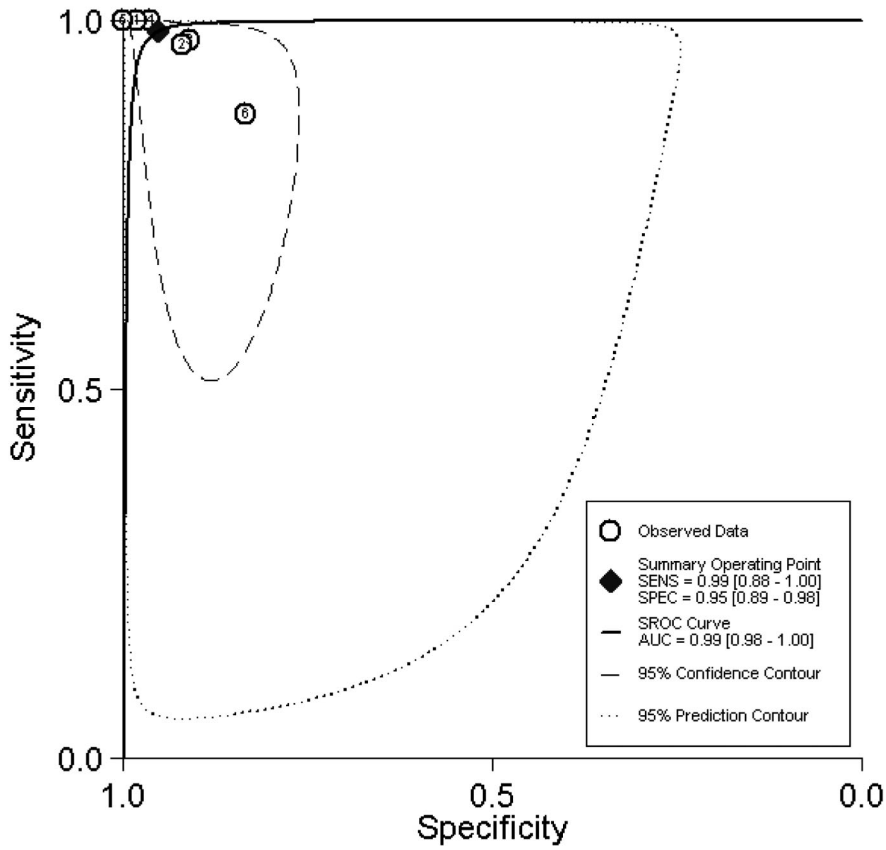

Figure 1. — HSROC curves of whole-body PET/PET-CT for the detection of distant metastases in breast cancer patients.

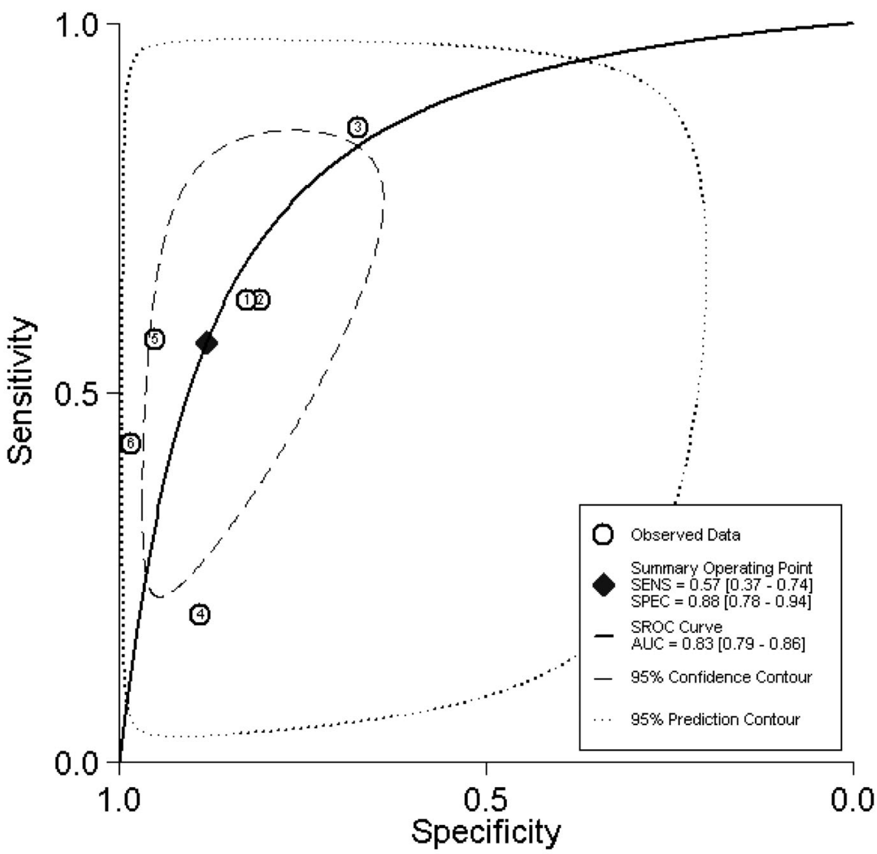

Figure 2. — HSROC curves of conventional imaging procedures for the detection of distant metastases in breast cancer patients.

tively, and of conventional imaging procedures were 0.57 (95% CI = 0.37–0.74), 0.88 (95% CI = 0.78–0.94), and 8.8 (95% CI = 4.8–19.8), respectively.

Likelihood ratio syntheses gave an overall PLR of 21.1 (95% CI = 8.2–55.5) and NLR of 0.02 (95% CI = 0.001–0.13) for whole-body PET/PET-CT on a per-patient basis. The respective figures for conventional imaging procedures were 4.8 (95% CI = 2.8–8.2) and 0.49 (95% CI = 0.33–0.74), respectively.

HSROC curves showed the overall good diagnostic performance of whole-body PET/PET-CT and conventional imaging procedures for all eligible studies (Figures 1-2). Overall weight area under the HSROC curves was 0.99 (95% CI = 0.98–1.00) and 0.83 (95% CI = 079–0.86), respectively.

Assuming a prevalence of distant malignancies of 10%, 20%, and 30% in cancer patients on a per-patient basis, NPVs for whole-body PET/PET-CT were 99.8%, 99.6%, and 99.3%, respectively, for conventional imaging procedures were 95%, 89%, and 83%, respectively.

Discussion

The presence of distant metastases is the most important predictor of survival in patients with breast cancer. A fast, accurate, and reliable diagnostic workup before treatment is of utmost importance because of its impact on treatment and prognosis. In this meta-analysis, the authors obtained summary estimates and summary ROC curves for the diagnostic accuracy of whole-body PET/PET-CT and conventional imaging procedures for the detection of distant metastases in patients with breast cancer. 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 in patients with breast cancer.

The DOR is a single indicator of test accuracy that combines the data from sensitivity and specificity into a single number [19]. It is the ratio of the odds of a positive test in a patient with disease relative to the odds of positive test in a patient without disease and has a value that ranges from 0 to infinity, with higher values indicating better discriminatory test performance [19]. This meta-analysis showed that the pooled patient-level DOR for whole-body PET/PET-CT and conventional imaging procedures was 1407 and 8.8, respectively, indicating that whole-body PET/PET-CT had higher accuracy than conventional imaging procedures for the detection of distant metastases in patients with breast cancer.

Since the HSROC curves are not easy to interpret and use in clinical practice, and since likelihood ratios are considered to be more clinically meaningful, both PLR and NLR were calculated and served as the present authors' measures of diagnostic accuracy [20, 21]. Likelihood ratios of >10 or < 0.1 indicated high accuracy. The patient-level PLR values of for whole-body PET/PET-CT and conventional imaging procedures were 21.1 and 4.8, respectively. Only the value (21.1) for whole-body PET/PET-CT was therefore high enough to diagnose distant metastases. On the other hand, the patient-level NLR values for whole-body PET/PET-CT and conventional imaging procedures were found to be 0.02 and 0.49, respectively. These data suggested that only a negative examination result of whole-body PET/PET-CT may be used alone as a justification to rule out distant metastases in patients with breast cancer.

Whole-body magnetic resonance imaging (WB-MRI), particularly with the introduction of moving patient platforms, improved integrated surface-coil technology, and ultrafast data acquisition, had become clinically feasible for the assessment of distant malignancies in patients with malignant tumors [22, 23]. One study [24] regarding the accuracy of 1.5 and 3.0T WB-MRI and ^{18}FDG-PET/CT for distant metastasis staging in patients with breast cancer also showed similar sensitivity (95% *vs.* 91%, $p > 0.05$), and specificity (92% *vs.* 86%, $p > 0.05$) on a per-lesion analysis. These results indicated that WB-MRI may be used as a first-line imaging technique for distant metastasis staging in patients with breast cancer.

The present meta-analysis had several limitations. First, the exclusion of conference abstracts, and letters to the editors may have led to publication bias. Although publication bias can be tested by using funnel plots, they were not performed in this meta-analysis because of the limited number of included studies. Second, there was no single clinical and imaging follow-up strategy, which may have affected the evaluation of whole-body PET/PET-CT and conventional imaging procedures. Actually, there is no well accepted gold standard, which is a common barrier to all studies assessing different imaging procedures for diagnostic accuracy in detection of distant metastases. Third, a wide variation in patient population, imaging techniques, study design, and quality in these selected studies may have affected the estimates of diagnostic accuracy of whole-body PET/ PET-CT and conventional imaging procedures. This was not analyzed because the number of included studies was small.

Compared with conventional imaging procedures, whole-body PET/PET-CT had excellent diagnostic performance for the detection of distant metastases in patients with breast cancer.

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