Comparison of FDG whole-body PET/CT and gadolinium-enhanced whole-body MRI for distant malignancies in patients with malignant tumors: a meta-analysis

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Background: We performed a meta-analysis to compare the performance of whole-body positron emission tomography/computed tomography (WB-PET/CT) with that of whole-body magnetic resonance imaging (WB-MRI) for the overall assessment of distant malignancies in patients with malignant tumors.

Methods: We performed a meta-analysis of 13 available articles (1239 patients). We calculated sensitivities, specificities, positive likelihood ratios, and negative likelihood ratios, and constructed summary receiver operating characteristic curves using bivariate regression models for WB-PET/CT and WB-MRI, respectively.

Results: Across nine studies (1070 patients), WB-PET/CT have similar patient-based sensitivity (0.85 versus 0.85) and specificity (0.96 versus 0.97) with WB-MRI. Across 5 studies (210 patients), WB-PET/CT have similar lesion-based sensitivity (0.85 vs 0.88) and specificity (0.90 vs 0.89) with WB-MRI. Across four studies (511 patients), the combined use may have higher patient-based sensitivity (0.89) than WB-PET/CT (0.82) and WB-MRI (0.81) alone.

Conclusion: Both WB-PET/CT and WB-MRI have good diagnostic performance for the overall assessment of distant malignancies in patients with malignant tumors. The combined use may provide more added value than WB-PET/CT and WB-MRI alone.
**Key words:** computed tomography, distant metastasis, magnetic resonance, neoplasms, positron emission tomography

**introduction**

The presence of distant malignancies is an important prognostic factor for patients with cancers. Precise detection of distant malignancies is a fundamental precondition for guiding subsequent staging procedures and optimal management.

Conventional imaging procedures (the combination of chest radiography, computed tomography, ultrasonography, bone scan, etc.) are commonly used to detect distant metastases with or without second primary cancers in patients with cancers, with suboptimal sensitivities and specificities [1–4]. The introduction of combined positron emission tomography (PET)/computed tomography (CT) scanners has made a new modality for whole-body imaging, which combined the functional data of PET with the detailed anatomic information of CT scanners in a single examination. Whole-body PET or whole-body PET/CT (WB-PET/CT) was used successfully for the detection of distant malignancies in several malignant tumors, with greater sensitivity compared with conventional imaging modalities [1–4].

Whole-body magnetic resonance imaging (WB-MRI), particularly with the introduction of improved integrated surface-coil technology and ultrafast data acquisition, had become clinically feasible for the assessment of distant malignancies in patients with malignant tumors [5–7]. Although many previous studies comparing WB-MRI with WB-PET/CT for detecting distant malignancies have been done, results are controversial. Here, we undertook a meta-analysis of all available studies to compare the diagnostic performance of WB-PET/CT and WB-MRI in evaluating distant malignancies in patients with malignant tumors.

**methods**

**literature search**

A comprehensive online literature search of studies was performed to identify articles about the diagnostic performance of WB-PET/CT compared with WB-MRI for the overall assessment of distant metastases with or without second primary cancers in patients with malignant tumors. The MEDLINE, EMBASE, and EBM Review databases (last update 20 October 2011) were used for searching relevant articles with the following combination of search terms: (i) PET; (ii) MRI; and (iii) staging or distant metastases. References of the retrieved articles were also screened for additional studies. Authors of eligible studies were contacted and asked to supplement additional data when key information relevant to the meta-analysis was missing. We had no language restrictions for searching and identification of relevant studies.

**study selection**

Studies were eligible for inclusion based on the following criteria: (i) 2-Fluoro-2-deoxy-D-glucose (FDG) WB-PET/CT and gadolinium-enhanced WB-MRI evaluated malignant tumor patients of all ages in any disease stage regardless of the location of primary tumors. (ii) Distant metastases and second primary cancers findings were confirmed with histopathologic analysis and/or clinical and imaging follow-up. (iii) The two imaging modalities (WB-PET/CT and WB-MRI) were performed within 1 month of one another. (iv) The studies were based on a per-patient or per-lesion analysis. (v) The studies including at least 10 patients were selected for inclusion in this meta-analysis. (vi) 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. (vii) WB-MRI must include basic sequences of T1, T2, and contrast-enhanced T1. Short-time inversion recovery (STIR) may be used as a selective sequence. Studies were excluded based on the following criteria: (i) only WB-PET/CT or WB-MRI was performed. (ii) Totals of true positives, false positives, true negatives, and false negatives were not provided. (iii) The diffusion-weighted imaging (DWI) sequence was used for WB-MRI.

**data extraction and quality assessment**

Two reviewers (G.Z.X. and C.Y.L) independently extracted the relevant data from each article and recorded these data on a standardized form. Any difference was resolved by consensus. Data were extracted from the studies, including authors, year of publication, study design, sample size, imaging methods (WB-PET/CT or WB-MRI) and imaging technical characteristics, reference standard, and totals of true positives, false positives, true negatives, and false negatives.

We assessed the methodological quality of the studies using the quality assessment for studies of diagnostic accuracy (QUADAS) tool [8]. The QUADAS tool includes 14 items: representative spectrum (item 1), the clear selection criteria (item 2), acceptable reference standard (item 3), acceptable delay between tests (item 4), partial verification (item 5), the same reference test regardless of the index test result (item 6), incorporation bias (item 7), the execution of the index test in detail (item 8), the reference standard (item 9) in detail, blinding to reference test results (item 10), the reference standard was blinded to the index test results (item 11), the availability of clinical data that would be available in clinical practice when using the index test (item 12), reporting of uninterpretable results (item 13), and explanation of withdrawals from the study (item 14). The 14 items were scored in all included articles, each of which is assessed as ‘yes’, or ‘no’.

**statistical analysis**

We used a bivariate regression model 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 WB-PET/CT and WB-MRI, respectively [9, 10]. By using the pooled sensitivities and specificities, we also calculated diagnostic odds ratio (DOR), positive likelihood ratios (PLR) and negative likelihood ratios (NLR) for WB-PET/CT and WB-MRI, respectively [10, 11]. Per-patient and per-lesion data were calculated for WB-PET/CT and WB-MRI, respectively.

We also used the pooled patient-level sensitivities and specificities obtained in this meta-analysis to calculate the negative predictive values (NPVs, i.e. the probability that a patient does not have distant malignancies when the test is negative) of WB-PET/CT and WB-MRI when the prevalence of distant malignancies in the population was assumed to be 10%, 20%, and 30%, respectively.

All analyses were conducted with Stata version 11.0 (Stata Corporation, College Station, TX).
results

study selection and description
After independent review, 17 articles dealing with the diagnostic performance of WB-PET/CT compared with WB-MRI for the overall assessment of distant malignancies in patients with malignant tumors. Of these publications, two articles [12, 13] were excluded because too little data were reported to permit construction of a 2 × 2 table of true-positive, false-negative, false-positive, and true-negative values. Two articles [14, 15] were excluded because only the DWI sequence was used. Consequently, 13 articles (1239 patients) [7, 16–27] were eligible for this meta-analysis (supplementary Table S1, available at Annals of Oncology online). Eight articles (1029 patients) were analyzed on a patient-level, four articles (169 patients) were analyzed on a lesion-level, one article (41 patients) was analyzed on both a patient-level and a lesion-level [16]. In all articles, the study design was prospective.

study quality
We assessed the quality of the 13 articles according to the 14-item QUADAS assessment tool. Eleven of the 14 items could be 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 (item 1) was present in 84.6% of the 13 articles [7, 16–23, 25–26].

diagnostic accuracy of WB-PET/CT and WB-MRI alone

patient-level data
When considering all nine studies (1070 patients) with data on a per-patient basis [7, 16, 18–20, 22, 24, 26, 27], sensitivity, specificity and DOR of WB-PET/CT were 0.85 (95% confidence interval [CI] 0.68–0.94), 0.96 (95% CI 0.95–0.97) and 145 (95% CI 47–446), respectively, and of WB-MRI were 0.86 (95% CI 0.70–0.94), 0.97 (95% CI 0.94–0.99) and 218 (95% CI 46–1024), respectively (Table 1).

Likelihood ratio syntheses gave an overall PLR of 22.7 (95% CI 14.6–35.4) and NLR of 0.16 (95% CI 0.07–0.36) for WB-PET/CT on a per-patient basis. The respective figures for WB-MRI were 32.3 (95% CI 13.7–76.0) and 0.15 (95% CI 0.07–0.34). HSROC curves showed the overall good diagnostic performance of WB-PET/CT and WB-MRI for all eligible studies on a per-patient basis (Figures 1 and 2).

Assuming a prevalence of distant malignancies of 10%, 20%, and 30% in cancer patients on a per-patient basis, NPPs for WB-PET/CT were 0.98, 0.96, and 0.94, respectively, for WB-MRI were 0.98, 0.96, and 0.94, respectively.

lesion-level data
When considering all 5 studies (210 patients) with data on a per-lesion basis [16, 17, 21, 23, 25], sensitivity, specificity and DOR of WB-PET/CT were 0.85 (95% confidence interval [CI] = 0.79–0.90), 0.90 (95% CI 0.82–0.94) and 49 (95% CI 30–83), respectively, and of WB-MRI were 0.88 (95% CI 0.80–0.94), 0.89 (95% CI 0.81–0.94) and 63 (95% CI 21–184), respectively (Table 1).

Likelihood ratio syntheses gave an overall PLR of 8.2 (95% CI 4.9–13.8) and NLR of 0.17 (95% CI 0.12–0.23) for WB-PET/CT on a per-lesion basis. The respective figures for WB-MRI were 8.2 (95% CI 4.4–15.0) and 0.13 (95% CI 0.07–0.24). HSROC curves showed the relatively good diagnostic performance of WB-PET/CT and WB-MRI for all eligible studies on a per-lesion basis (supplementary Figures S1 and 2, available at Annals of Oncology online).

diagnostic accuracy of the combined use of whole-body PET-CT and whole-body MRI

When considering all four studies (511 patients) with data on the combined use of WB-PET/CT and WB-MRI [22, 24, 26, 27], sensitivity, specificity and DOR of the combined use of WB-PET/CT and WB-MRI on a per-patient basis were 0.89 (95% CI 0.86–0.96), 0.98 (95% CI 0.97–0.99) and 510 (95% CI 36–1911), respectively, and of WB-PET/CT were 0.82 (95% CI 0.69–0.90), 0.97 (95% CI 0.94–0.98) and 126 (95% CI 51–312), respectively, and of WB-MRI were 0.81 (95% CI 0.64–0.90), 0.98 (95% CI 0.95–0.99) and 84 (95% CI 42–811), respectively (Table 1).

Likelihood ratio syntheses gave an overall PLR of 55.4 (95% CI 25.4–121) and NLR of 0.11 (95% CI 0.05–0.26) for the combined use of WB-PET/CT and WB-MRI on a per-lesion basis. The respective figures for WB-PET/CT were 23.9 (95% CI 14.1–40.6) and 0.19 (95% CI 0.11–0.34), respectively. The

Table 1. Diagnostic accuracy of whole-body PET/CT and whole-body MRI

<table>
<thead>
<tr>
<th>Study characteristics</th>
<th>System</th>
<th>No. of studies (no. of patients)</th>
<th>Independent estimates (95% CI)</th>
<th>DOR (95% CI)</th>
<th>Likelihood ratio (95% CI)</th>
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<tr>
<td></td>
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<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>PLR</td>
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<tr>
<td>The use of WB-PET/CT and WB-MRI alone</td>
<td>Per-patient level</td>
<td>WB-PET/CT</td>
<td>9 (1070)</td>
<td>0.85 (0.68–0.94)</td>
<td>0.96 (0.95–0.97)</td>
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<td></td>
<td></td>
<td>WB-MRI</td>
<td>9 (1070)</td>
<td>0.86 (0.70–0.94)</td>
<td>0.97 (0.94–0.99)</td>
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<tr>
<td></td>
<td>Per-lesion level</td>
<td>WB-PET/CT</td>
<td>5 (210)</td>
<td>0.85 (0.79–0.90)</td>
<td>0.90 (0.82–0.94)</td>
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<tr>
<td></td>
<td></td>
<td>WB-MRI</td>
<td>5 (210)</td>
<td>0.89 (0.81–0.94)</td>
<td>0.89 (0.81–0.94)</td>
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<tr>
<td>The combined use of WB-PET/CT and WB-MRI</td>
<td>Per-patient level</td>
<td>The combined use</td>
<td>4 (511)</td>
<td>0.89 (0.86–0.96)</td>
<td>0.98 (0.97–0.99)</td>
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<td></td>
<td></td>
<td>WB-PET/CT</td>
<td>4 (511)</td>
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<td>WB-MRI</td>
<td>4 (511)</td>
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<td>0.98 (0.95–0.99)</td>
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</table>

WB-PET/CT, whole-body PET/CT; WB-MRI, whole-body MRI.
and prognosis. In this meta-analysis, we obtained summary estimates and summary ROC curves for the diagnostic accuracy of WB-PET/CT and WB-MRI in the detection of distant malignancies in cancer patients. Both WB-PET/CT and WB-MRI were found to have high sensitivity and specificity for detecting distant malignancies in patients with 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 our measures of diagnostic accuracy [28, 29]. Likelihood ratios of >10 or <0.1 indicate high accuracy. The patient-level PLR values for WB-PET/CT and WB-MRI were 22.7 and 33.3, respectively, which were therefore high enough to diagnose distant malignancies. On the other hand, the patient-level NLR values for WB-PET/CT and WB-MRI were found to be 0.16 and 0.15. These data suggest that a negative examination result of WB-PET/CT and WB-MRI could not be used alone as a justification to rule out distant malignancies.

The DOR is a single indicator of test accuracy that combines the data from sensitivity and specificity into a single number [30]. 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 [30]. This meta-analysis showed that the pooled patient-level DOR for WB-PET/CT and WB-MRI was 145 and 218, respectively, indicating a high level of accuracy for WB-PET/CT and WB-MRI on a patient-level analysis. But the pooled lesion-level DOR for WB-PET/CT and WB-MRI was 46 and 70, respectively, indicating that the accuracy for WB-PET/CT and WB-MRI on a lesion-level analysis was not high.

Both WB-PET/CT and WB-MRI can be interpreted in a qualitative manner. Because of the lack of evidence to support the use of SUV in determining positivity [31], no SUV cutoff value was used in most studies while reviewing PET/CT images [14, 18, 19, 21–22]. WB-PET/CT imaging is easy to be interpreted by both nuclear medicine physicians and clinical oncology physicians. As a comparison, WB-MRI is often more operator dependent than WB-PET/CT, which may affect the clinical routine application of WB-MRI. Compared with WB-MRI, WB-PET/CT may have better reproducibility of imaging process. Moreover, the mean scan time for WB-MRI is longer than that for WB-PET/CT. These factors may also affect the clinical routine application of WB-MRI.

We included all studies with basic sequences of $T_1$, $T_2$, and contrast-enhanced $T_1$ for WB-MRI imaging. We also excluded two studies [14, 15] with the DWI sequence for WB-MRI because the use of DWI may affect sensitivities and specificities of WB-MRI for distant staging in cancer patients. Ohno et al. [20] reported that sensitivity and specificity of whole-body DWI imaging were 52.7% and 87.7%, of WB-MRI without DWI imaging were 60.0% and 92.0%, of WB-MRI with DWI imaging were 70.0% and 92.0%. The added use of DWI may improve the sensitivity of WB-MRI.

WB-PET/CT and WB-MRI have some different advantages across different sites when used for the detection of distant malignancies. WB-MRI showed better performance than WB-PET/CT for detecting brain metastases, because high

**discussion**

A fast, accurate, reliable diagnostic workup for cancer patients is of utmost importance because of its impact on treatment

![Figure 1. Hierarchical summary receiver operating characteristic curve for the diagnostic performance of whole-body MRI on a patient-level analysis.](https://example.com/image1.png)

Figure 1. Hierarchical summary receiver operating characteristic curve for the diagnostic performance of whole-body MRI on a patient-level analysis.

![Figure 2. Hierarchical summary receiver operating characteristic curve for the diagnostic performance of whole-body PET/CT on a patient-level analysis.](https://example.com/image2.png)

Figure 2. Hierarchical summary receiver operating characteristic curve for the diagnostic performance of whole-body PET/CT on a patient-level analysis.
physiological FDG uptake of these organs may obscure some lesions [16, 19, 22]. Previous studies also showed that WB-MRI had higher sensitivity than WB-PET/CT for detecting bone metastases [7, 17, 21, 23]. In contrast, WB-PET/CT had been found to perform better than WB-MRI for the detection of distant nodes [7, 17, 19]. Thus, the combined use of WB-PET/CT and WB-MRI may correct more diagnostic errors and enhance the diagnostic accuracy of WB-PET/CT and WB-MRI alone. This meta-analysis documented that the comparison of the combined use of WB-PET/CT and WB-MRI performance with that of WB-PET/CT and WB-MRI alone in four studies (511 patients) suggested a major difference for sensitivity by 7–8% using the combined use over WB-PET/CT or WB-MRI alone.

Our meta-analysis had several limitations. First, the exclusion of conference abstracts and letters to the editors may have led to publication bias. Publication bias can be tested by using funnel plots. In this meta-analysis, funnel plot analysis was not performed because of the limited number of included studies. Secondly, there was no single clinical and imaging follow-up strategy, which may have affected the evaluation of WB-PET/CT and WB-MRI. 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 malignancies. Thirdly, we did not perform subgroup analyses according to every location of the primary tumors because of the limited number of included studies in this meta-analysis. The location of the primary tumor might influence the difference of distant sites, which is likely to affect the diagnostic accuracy of WB-PET/CT and WB-MRI.

In conclusion, both WB-PET/CT and WB-MRI have excellent diagnostic performance for the overall assessment of distant malignancies in cancer patients. The combined use may provide more added value than WB-PET/CT and WB-MRI alone.

disclosure
The authors have declared no conflicts of interest.

references
Discordance in receptor status between primary and recurrent breast cancer has a prognostic impact: a single-Institution analysis

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Background: Tumor phenotype may change during breast cancer progression. This study evaluates the prognostic impact of receptor discordance between paired primaries and recurrences.

Patients and methods: One hundred and thirty-nine patients underwent histological sampling of suspected breast cancer recurrence. All the pathology assessments [ER, PgR and human epidermal growth factor receptor 2 (HER2)] on both primaries and confirmed recurrences were performed at the same laboratory.

Results: A breast cancer recurrence was confirmed in 119 cases. Rates of discordance were 13.4%, 39% and 11.8% for ER, PgR and HER2, respectively. Ninety-two patients maintained the same tumor phenotype [i.e. the same hormone receptors (HR) and HER2 status], whereas 27 (22.7%) changed during progression. The loss of HR positivity and the loss of HER2 positivity resulted in a worse post-recurrence survival (P = 0.01 and P = 0.008, respectively) and overall survival (OS; P = 0.06 and P = 0.0002, respectively), compared with the corresponding concordant-positive cases. Tumor phenotype discordance was associated with worse post-recurrence and OS (P = 0.006 and P = 0.002, respectively); those cases who turned into triple-negative experienced the poorest outcome, respect to the concordant group (P = 0.001, OS).

Conclusions: We demonstrated for the first time an impact on OS of phenotype discordance between primary breast cancer and relapse. Among discordant cases, receptor loss resulted in the main determinant of poorer outcome.

Key words: breast cancer, HER2, hormone receptors, discordance, survival

introduction

Breast cancer is a heterogeneous disease, encompassing at least three major subtypes: the hormone receptor (HR) positive, the human epidermal growth factor receptor 2 (HER2) positive and the triple-negative (TN) subtype [1, 2]. Adjuvant treatments are selected according to the molecular subtype of breast cancer; however, in spite of more effective therapies, 20% to 30% of the patients with early breast cancer will eventually relapse [3, 4]. At the time of relapse, treatment decisions are still based on the biological features of primary tumor, although a growing body of evidence indicates a lack of concordance in receptor status between primary and recurrent tumors in up to 40% of the cases [5–14]. We have previously reported a discordance of 21% for HR expression and of 16%