Diagnostic value of whole-body diffusion-weighted magnetic resonance imaging for detection of primary and metastatic malignancies: A meta-analysis

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ABSTRACT

Purpose: To perform a meta-analysis to evaluate the diagnostic performance of whole-body diffusion-weighted magnetic resonance imaging (WB-DWI) technique in detection of primary and metastatic malignancies compared with that of whole-body positron emission tomography/computed tomography (WB-PET/CT).

Materials and methods: Search Pubmed, MEDLINE, EMBASE and Cochrane Library database from January 1984 to July 2013 for studies comparing WB-DWI with WB-PET/CT for detection of primary and metastatic malignancies. Methodological quality was assessed by the quality assessment of diagnostic studies (QUADAS) instrument. Sensitivities, specificities, predictive values, diagnostic odds ratio (DOR) and areas under the summary receiver operator characteristic curve (AUC) were calculated. Potential threshold effect, heterogeneity and publication bias were investigated.

Result: Thirteen eligible studies were included, with a total of 1067 patients. There was no significant threshold effect. WB-DWI had a similar AUC (0.966 (95% CI, 0.940–0.992) versus 0.984 (95% CI, 0.965–0.999)) with WB-PET/CT. No significant difference was detected between AUC of WB-DWI and WB-PET/CT. WB-DWI had a pooled sensitivity of 0.897 (95% CI, 0.876–0.916) and a pooled specificity of 0.954 (95% CI, 0.944–0.962). WB-PET/CT had a pooled sensitivity of 0.895 (95% CI, 0.865–0.920) and a pooled specificity of 0.975 (95% CI, 0.966–0.981). Heterogeneity was found to stem primarily from data type (per lesion versus per patient), MR sequence (DWIBS only and DWIBS with other sequence), and primary lesion type (single type and multiple type). The Deeks’s funnel plots suggested the absence of publication bias.

Conclusion: WB-DWI has similar, good diagnostic performance for the detection of primary and metastatic malignancies compared with WB-PET/CT. DWIBS with other MR sequences could further improve the diagnostic performance. More high-quality studies regarding comparison of WB-DWI and WB-PET/CT and combination of them in detecting malignancies are still needed to be conducted.

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1. Introduction

In oncology, detection and staging of primary and metastatic malignancies are of importance. Both presence and extent of malignancies are crucial factors for the survival of patients. As tumor spread may involve different anatomical regions, accurate detection of distant malignancies is a fundamental precondition for guiding subsequent staging and optimal management.

Whole-body detection and evaluation require combined imaging protocols that are tailored individually to the given disease entity and region of interest. Past clinical practice has shown that fluorine 18 fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) possesses substantially higher sensitivity and specificity in detection and staging for some malignancies compared with CT or PET alone, although expensive and radioactive ions such as fluorine-18-2-fluoro-2-deoxy-D-glucose are its disadvantages [1]. In recent years, whole-body magnetic resonance imaging (WB-MRI), with its lack of ionizing radiation but high contrast and spatial resolution, has been put forward as another promising whole-body technique for the assessment of distant metastases in patients with malignant tumor [2,3]. Up to date, WB-MRI provides mainly morphological information on tumor spread; however, the lack of functional information has been overcome.

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by the introduction of whole-body diffusion-weighted magnetic resonance imaging (WB-DWI) in clinical practice [4]. With the introduction of diffusion-weighted whole-body MRI with background body signal suppression (DWIBS) technique [5], WB-DWI has become clinically feasible. It has been applied to detect primary and metastatic malignancies in patients with suspicious tumors [6-9].

Although the role of WB-DWI has been well assessed in the literature, there remain some controversial results. With DWIBS, tumor sites may be detected throughout the entire body with high contrast resolution; however, exact localization of lesions with DWIBS may be less accurate due to lack of anatomical reference because most normal anatomic structures signal is suppressed. DWIBS provides complementary value to morphological imaging studies. So we performed a meta-analysis to assess the overall diagnostic value of DWIBS as a reliable WB-DWI protocol in detection of primary and metastatic malignancies compared with that of WB-PET/CT, which, to our knowledge, has not previously been studied.

2. Methods

2.1. Publication search

Pubmed, MEDLINE, EMBASE, Cochrane Library database were all searched (Last search was updated on July, 2013). The following terms were used in searching: (DWIBS OR diffusion weighted imaging with background signal suppression OR whole-body diffusion-weighted imaging OR whole-body DWI) and (neoplasm OR malignancy OR tumor OR cancer). All the searched studies were retrieved, and their references were checked as well for other relevant publications. We also review articles to find additional eligible studies.

2.2. Inclusion and exclusion criteria

Studies meeting the following selection criteria were included in this meta-analysis: (1) whole-body DWI or DWIBS and 2-fluoro-2-deoxy-d-glucose (FDG) WB-PET/CT detected or evaluated primary or metastatic lesion in patients of all ages regardless of the location of primary tumors (2) for per-patient or per-lesion statistics, sufficient data were presented to calculate true-positive (TP), false-positive (FP), true-negative (TN) and false-negative (FN) in the original published study, (3) articles were published in English, (4) lesions were confirmed with histopathologic analysis and/or clinical and imaging follow-up, (5) the two imaging modalities (WB-DWI and WB-PET/CT) were performed within 1 month of one another (6) ten or more patients were included. (7) 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 WB-PET/CT or WB-DWI was performed. (2) Totals of true positives, false positives, true negatives, and false negatives were not provided.

2.3. Data extraction and quality assessment

Relevant studies were examined by two independent observers with the Quality Assessment of Diagnostic Studies (QUADAS) [10] tool specifically developed for systematic reviews of diagnostic test accuracy. Data extraction including characteristics of the study design, types of primary and metastatic lesion, methodological details for whole-body DWI, and outcome data was performed independently and discrepancies were resolved by discussion by 2 reviewers. The relevant data (TP, FP, TN, FN) were extracted into designed data collection forms.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>The characteristics of the each study included.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author</td>
<td>Year</td>
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<tr>
<td>----------</td>
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</tr>
<tr>
<td>Chen1</td>
<td>2010</td>
</tr>
<tr>
<td>Chen2</td>
<td>2009</td>
</tr>
<tr>
<td>Fisher1</td>
<td>2008</td>
</tr>
<tr>
<td>Fisher2</td>
<td>2008</td>
</tr>
<tr>
<td>Takenaka1</td>
<td>2011</td>
</tr>
<tr>
<td>Takenaka2</td>
<td>2011</td>
</tr>
<tr>
<td>Moaziz</td>
<td>2011</td>
</tr>
</tbody>
</table>

DWIBS: diffusion weighted imaging with background signal suppression.
2.4. Meta analysis

Diagnostic performance estimates for detecting primary and metastatic lesion, such as sensitivity, specificity and likelihood ratio were calculated and pooled on a per-lesion or per-patient basis. Using random-effects or fixed-effects model depends on the presence of statistical heterogeneity. Heterogeneity was explored by likelihood Chi-square Value ($\chi^2$) test and the inconsistency index ($I^2$). P-value < 0.05 or $I^2 > 50\%$ suggested heterogeneity; a random effects model was for the meta-analysis to obtain a summary accuracy parameter if heterogeneity was identified; otherwise a fixed effects model was used.

One of main causes of heterogeneity is the threshold effect in test accuracy studies. The threshold effect arises owing to different thresholds or cut-offs used in different studies to define a positive (or negative) test result. If the threshold effect exists, which was assessed by computing Spearman correlation between the logit of sensitivity and logit of (1-specificity), there is a positive correlation between sensitivities and 1-specificities (or a negative correlation between sensitivities and specificities). A positive correlation ($P < 0.05$) suggested the threshold effect. If heterogeneity due to threshold effect was present, the accuracy data should be pooled by fitting a SROC curve and calculating the area under the curve (AUC). Apart from the threshold effect, in test accuracy studies, several other factors can contribute to heterogeneity. If there was no threshold effect but significant heterogeneity, a regression meta-analysis and subgroup analysis was performed because assessment should only be attempted within homogeneous subgroup.

Publication biases were assessed by Deeks’s funnel plots.

All the statistical computations were performed using the MetaDisc software [11] version 1.4 and the Stata/SE statistical software version 12.1 (StataCorp LP, Texas, USA). P values of less than 0.05 were considered to be statistically significant.

3. Result

3.1. Eligible studies

Our search strategy identified 117 primary studies. After ruling out the obviously irrelevant abstracts and articles, 24 articles were left and their full texts were obtained. Fig. 1 outlines our study selection process. Finally there were 13 studies in 8 articles [7,12–18] included in the meta-analysis. Main reasons for exclusion were as follows: (1) Irrelevant to WB-DWI or DWIBS compared with PET/CT for detecting primary or metastatic lesion. (2) Totals of true positives, false positives, true negatives, and false negatives were not provided. The characteristics of the each study included are presented in Table 1.

3.2. Threshold effect analyze

Spearman correlation coefficient was determined to be $-0.063 (P=0.837)$ and $-0.217 (P=0.576)$ for WB-DWI and WB-PET/CT respectively, which indicated absence of threshold effect in WB-DWI and PET/CT studies included.

3.3. Diagnostic performance of WB-DWI and WB-PET/CT

Figs. 2 and 3 shows the SROC curves of the performance of WB-DWI and WB-PET/CT. Using the fitted summary ROC curve, overall AUC for WB-DWI and WB-PET/CT was 0.966 and 0.984 respectively, indicating good diagnostic accuracy. Pair-wise comparisons confirmed no statistical difference between WB-DWI and WB-PET/CT performance. For each technique, the weighted summary of sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, DOR, value for heterogeneity, and $P$ value are summarized in Table 2. No 95% CIs of OR included 1, confirming the diagnostic value of all modalities.

3.4. Heterogeneity and meta-regression analysis

The heterogeneity in sensitivity tests and specificity tests was highly significant ($p < 0.05$ and $I^2 > 50\%$) for both WB-DWI and PEC/CT studies. It is confirmed that there was strong evidence of between-study heterogeneity. To explore possible explanations for the heterogeneity, we firstly applied meta-regression analysis by adding the number of patients, number of lesions, year of publication, data type, MR strength, MR sequence, primary lesion type, detected lesion type, and study design. Meta regression analysis showed data type (per lesion and per patient), MR sequence (DWIBS only and DWIBS with other sequence), primary lesion type (single type and multiple type) were the most important variable sources of heterogeneity for sensitivity and specificity (Table 3).

3.5. Subgroup analysis

Subgroup analyses were then conducted based on the data type (per lesion versus per patient), MR sequence (DWIBS only and DWIBS with other sequence), primary lesion type (single type and
Fig. 2. Summary ROC (SROC) curves for WB-DWI. AUC: area under ROC curve; SE (AUC), standard error of area under the ROC curve; Q*, the maximum joint sensitivity and specificity on a symmetric ROC curve; SE (Q*), standard error of Q*. The middle line was the summary ROC curve and the two beside are 95% confidence intervals. Each black circle represents an individual research study in the WB-DWI meta-analysis, with the size of the circle directly proportional to the sample size of the study.

Fig. 3. Summary ROC (SROC) curves for WB-PET/CT. AUC: area under ROC curve; SE (AUC), standard error of area under the ROC curve; Q*, the maximum joint sensitivity and specificity on a symmetric ROC curve; SE (Q*), standard error of Q*. The middle line was the summary ROC curve and the two beside are 95% confidence intervals. Each black circle represents an individual research study in the WB-PET/CT meta-analysis, with the size of the circle directly proportional to the sample size of the study.

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PLR</th>
<th>NLR</th>
<th>DOR</th>
<th>AUC</th>
<th>Threshold effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>WB-DWI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooled estimates</td>
<td>0.897</td>
<td>0.954</td>
<td>11.888</td>
<td>0.12</td>
<td>120.84</td>
<td>AUC = 0.9657</td>
<td>$P = 0.817$</td>
</tr>
<tr>
<td>95%CI</td>
<td>0.876–0.916</td>
<td>0.944–0.962</td>
<td>5.965–23.694</td>
<td>0.071–0.203</td>
<td>43.978–332.05</td>
<td>SE (AUC) = 0.0133</td>
<td></td>
</tr>
<tr>
<td>$P$ value*</td>
<td>$P = 0.000$</td>
<td>$P = 0.000$</td>
<td>$P = 0.000$</td>
<td>$P = 0.000$</td>
<td>$P = 0.000$</td>
<td>Q* = 0.9131</td>
<td></td>
</tr>
<tr>
<td>$I^2$</td>
<td>85.60%</td>
<td>91.40%</td>
<td>91.30%</td>
<td>84.70%</td>
<td>86.00%</td>
<td>$P = 0.000$</td>
<td></td>
</tr>
<tr>
<td>WB-PET/CT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooled estimates</td>
<td>0.895</td>
<td>0.975</td>
<td>26.889</td>
<td>0.071</td>
<td>448.2</td>
<td>AUC = 0.9845</td>
<td>$P = 0.576$</td>
</tr>
<tr>
<td>95%CI</td>
<td>0.865–0.920</td>
<td>0.966–0.981</td>
<td>10.473–69.038</td>
<td>0.031–0.162</td>
<td>124.58–1612.4</td>
<td>SE (AUC) = 0.0101</td>
<td></td>
</tr>
<tr>
<td>$P$ value*</td>
<td>$P = 0.000$</td>
<td>$P = 0.000$</td>
<td>$P = 0.000$</td>
<td>$P = 0.000$</td>
<td>$P = 0.000$</td>
<td>Q* = 0.9461</td>
<td></td>
</tr>
<tr>
<td>$I^2$</td>
<td>90.40%</td>
<td>83.40%</td>
<td>95.20%</td>
<td>87.60%</td>
<td>79.20%</td>
<td>$P = 0.000$</td>
<td></td>
</tr>
</tbody>
</table>

WB-DWI: whole-body diffusion-weighted magnetic resonance imaging (WB-DWI); WB-PET/CT: whole-body positron emission tomography/computed tomography (WB-PET/CT); PLR: positive likelihood ratio; NLR: negative likelihood ratio; DOR: diagnostic odds ratio; AUC: area under SROC curve.
multiple type) for WB-DWI studies. The results of subgroup analysis are presented in Table 4.

3.6. Publication bias

The results of Deek's funnel plot asymmetry test showed absence of publication bias for included studies for WB-DWI (P=0.210) and WB-WB-PET/CT (P=0.801). (Figs. 4 and 5)

4. Discussion

An accurate, cost-effective, time-saving whole-body diagnostic workup is considerably important for patients with malignancies in clinical practice because of its impact on treatment strategy and prognosis. DWIBS introduced by Takahara [5] provides the possibility of whole-body screening in recent years. WB-DWI is same as DWIBS that may look similar to PET, but the sensitivity and specificity of WB-DWI images for tumor detection are still under investigation. This present meta-analysis mainly focused on the diagnostic performance of WB-DWI compared with WB-PET/CT in detecting primary and metastatic lesions in patients with tumor, which to our knowledge had not previously been studied. Summary estimates and summary ROC curves obtained from data of 1067 patients in 13 studies demonstrated high sensitivity, specificity and the area under SROC curves (AUC) for both WB-DWI and WB-PET/CT for detection of primary and metastatic malignancies. AUC of WB-PET/CT was slightly higher than that of WB-DWI; however, the difference was not statistically significant (p = 0.13).

Since likelihood ratios (LR) are considered to be easier to interpret and more meaningful than sensitivity, specificity and AUC in clinical practice, both positive LR (PLR) and negative LR (NLR) were calculated and served as our measures of diagnostic accuracy. The LR indicates how much a given test would raise or lower the probability of having disease. A diagnostic test to be highly useful should have a high PLR > 10 and a low NLR < 0.1; to be moderately useful it should have a PLR of 5–10 and NLR of 0.1–0.2, suggested by a rule of thumb for interpretation of the LR [19–21]. Based on this rule of thumb, PLR values of WB-DWI and WB-PET/CT were 11.888 and 26.889, respectively, which were therefore good at ruling in malignancies. On the other hand, since NLR values of WB-DWI and WB-PET/CT were 0.12 and 0.071, respectively. These data indicate that WB-DWI should not be used alone as a justification to rule out malignancies.

The results of meta-regression analysis indicated that data type (per lesion versus per patient), MR sequence (DWIBS only and DWIBS with other sequence) and primary lesion type (single type and multiple types) were important variable sources of heterogeneity. Sensitivity and specificity used in this meta-analysis were based on “per lesion” or “per patient” level. Different kinds of data type might influence diagnostic accuracy and cause the between-study heterogeneity. Possible explanations for impact of primary lesion type on the diagnostic accuracy of WB-DWI are that different kinds of diseases have different histopathologic changes and biological nature. WB-DWI evaluation would be affected by the heterogeneous composition of organs or tumors compared with the evaluation of only one organ or tumor. MR signals in DWI might be heterogeneous between different tumors showing different water diffusion signals. Subgroup analysis indicated that sensitivity and specificity for WB-DWI in group including multiple type of primary tumor were higher than that of group including single type of primary tumor; the difference was statistically significant. In subgroup analysis, we also found that DWIBS with other sequences (TIW, T2W, and STIR) could improve the sensitivity compared with DWIBS only. Ohno et al. [16] compared the sensitivity and specificity of three MR protocols. The sensitivity of whole-body DLI imaging, WB-MRI without DWI imaging and WB-MRI with DWI imaging was 52.7%, 60.0% and 70.0%, respectively. The specificity of these MR protocols mentioned above was 87.7%, 92.0% and 92.0%, respectively. They suggested that the combination of WB-DWI and other sequences may improve the sensitivity of WB-MRI. According to our data, the subgroup of DWIBS with other sequences had higher pooled sensitivity 0.913 (0.877–0.941) than the subgroup of DWIBS only 0.889 (0.861–0.913), but the difference was not significant statistically. Further studies with large sample size should be conducted to explore the effect.

Functional or metabolic pathologic changes can occur in the absence of any corresponding anatomical changes, and are not visualized by anatomical imaging. WB-DWI, which allows visualization and quantification of the mobility of water molecules, can provide functional information. There is a certain degree of resemblance of WB-DWI to PET [22]. WB-PET/CT is also able to acquire functional information. Both WB-DWI and WB-PET/CT could be powerful tools for detecting subtle lesions and pathologic changes in normal sized structures [23].

These two imaging modalities have some different advantages across different sites when used for the detection of malignancies. WB-DWI has better performance than WB-PET/CT for detecting brain metastases because of obscuring some lesions by high physiological FDG uptake of these organs [24]. In contrast, WB-PET/CT may perform better than WB-DWI for the detection of distant nodes [25]. Previous studies also seem to indicate that WB-DWI is less specific in the thorax than in other sites and less sensitive for

<table>
<thead>
<tr>
<th>Variable</th>
<th>Data type</th>
<th>MR strength</th>
<th>MR Sequence</th>
<th>Primary lesion type</th>
<th>Detected lesion type</th>
<th>Study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of studies</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Coefficient</td>
<td>−2.576</td>
<td>−1.187</td>
<td>1.208</td>
<td>1.198</td>
<td>−0.93</td>
<td>2.282</td>
</tr>
<tr>
<td>Standard error</td>
<td>0.3792</td>
<td>1.3041</td>
<td>0.4058</td>
<td>0.3948</td>
<td>0.6722</td>
<td>1.234</td>
</tr>
<tr>
<td>P</td>
<td>0.0001</td>
<td>0.3979</td>
<td>0.0155</td>
<td>0.0141</td>
<td>0.2091</td>
<td>0.1015</td>
</tr>
</tbody>
</table>

DOR: diagnostic odds ratio; Q*, the maximum joint sensitivity and specificity on a symmetric ROC curve.

Table 3
Result of regression meta-analysis.

Table 4
Summary estimates of sensitivity, specificity, and diagnostic odds ratio of subgroup.
abdominal and pelvic sites [13]. Thus, the combined use of WB-DWI and WB-PET/CT may be complementary and improve the diagnostic performance of WB-DWI and WB-PET/CT alone. In the future, more studies to explore the combined use of WB-PET/CT and WB-DWI would be needed to be conducted.

Factors, such as radiation, contraindications, examination time, cost and availability, may affect the clinical routine application of WB-DWI and WB-PET/CT. The choice of whole body imaging modality (WB-DWI or WB-PET/CT) may depend on comprehensive considerations of these aspects.

WB-PET/CT has the risk of radiation exposure for patients in clinical scenario. On the contrary, WB-DWI is nonradiative. There are different contraindications for these two techniques. The pregnant, children should be suggested to avoid WB-PET/CT examine because PET/CT examine exposes the patient to ionizing radiation. The presence of claustrophobia, pacemaker, and magnetized metal in patients are limited in MR scanner.

As far as the examination time which includes mean preparation time and scan/acquisition time, examination time for WB-DWIBS only is shorter than that for WB-PET/CT. WB-DWIBS does not need preparation time. Total acquisition time for WB-DWIBS ranges from 5.5 min to 24 min in our included studies. Nevertheless, total acquisition time for WB-MRI including DWIBS and other sequences may depend on the sequences. In our included studies, it ranges from 12 min to 90 min. By contrast, WB-PET/CT acquisition is started 50–60 min after completion of injection. Total acquisition time for WB-PET/CT ranges from 22 min to 60 min in our included studies.

The cost is a challenging issue, as it heavily depends on local policies for reimbursement in different countries and regions. Overall, the basic cost is not so different. Whether the benefits and quality-of-life improvements outweigh the costs should, of course, be addressed in a formal cost-effectiveness study.

The availability of the technique is probably the best guide for indication of clinical choice and application. Compared with
WB-PET/CT, WB-DWI may have better procurability and reproducibility of imaging process. WB-DWI can be implemented on most modern MRI scanners without radiation exposure. Moreover, unlike PET/CT, anatomical whole-body MRI and whole-body DWI can be performed in the same scanner without patient repositioning, which result in a perfect match between anatomical and functional datasets.

The choice of these two whole body evaluation techniques must always be balanced versus the purpose and outcome of an investigation.

One major bias of the study was the heterogeneity of the different tumors and the inclusion of patients with different disease stage. The series included were dealing with many different tumors. From the standpoint of clinical practice, this group of series was not considered as a homogeneous material. The type and location of tumors were an important source of heterogeneity, which was suggested with comparison and subgroup analyses. Another bias should be commented was that almost all papers were published in the “radiological” literature and not in the nuclear medicine journals. However, Deeks's funnel plots did not show any publication bias. A possible explanation for this recessive publication bias was that the number of nuclear medicine journals was less than radiological journals. Another explanation was that studies included in our meta-analysis might mainly focus on WB-DWI and WB-PET/CT was used as a reference comparison.

Other limitations of this meta-analysis should be addressed. Firstly, the number of studies available that could be included in this meta-analysis was small, and therefore subgroup analyses according to every location of the primary tumors, which is likely to influence the diagnostic accuracy of WB-PET/CT and WB-DWI, were not performed. Secondly, there was no well-accepted reference standard. The reference standard of each individual studies included in this meta-analysis ranged from histopathological analysis to clinical or imaging follow-up. Finally, although the funnel plot did not show any publication bias, the influence of bias in the present analysis could not be completely excluded. Only studies published in English were included, which might induce the “Tower of Babel” bias that refers to the fact that investigators working in a language other than English could be sending only studies with positive results to international journals.

In conclusion, WB-DWI has a similar, good accuracy compared with WB-PET/CT. DWIBS with other MR sequences can improve the diagnostic performance. More high-quality studies regarding comparison of WB-DWI and WB-PET/CT and combination of them in detecting malignancies are still needed to be conducted.

Conflicts of interest

The authors have declared no conflicts of interest.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejrad.2013.11.017.

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