Diagnostic Performance of Magnetic Resonance Imaging for the Detection of Bone Metastasis in Prostate Cancer: A Systematic Review and Meta-analysis

Sungmin Woo\textsuperscript{a,1}, Chong Hyun Suh\textsuperscript{b,c,1}, Sang Youn Kim\textsuperscript{a,*}, Jeong Yeon Cho\textsuperscript{a,d}, Seung Hyup Kim\textsuperscript{a,d}

\textsuperscript{a}Department of Radiology, Seoul National University College of Medicine, Seoul, Korea; \textsuperscript{b}Department of Radiology and Research Institute of Radiology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Republic of Korea; \textsuperscript{c}Department of Radiology, Namwon Medical Center, Jeollabuk-do, Republic of Korea; \textsuperscript{d}Institute of Radiation Medicine and Kidney Research Institute, Seoul National University Medical Research Center, Seoul, Korea

\textbf{Abstract}

\textbf{Context:} Magnetic resonance imaging (MRI) has been tested for detecting bone metastasis and has shown promising results. Yet, consensus has not been reached regarding whether it can replace the role of bone scintigraphy in this clinical setting or not.

\textbf{Objective:} To review the diagnostic performance of contemporary (\textgreater{}1.5 T) MRI for the detection of bone metastasis in patients with prostate cancer.

\textbf{Evidence acquisition:} MEDLINE and EMBASE were searched up to January 22, 2017. We included studies that used MRI using \textgreater{}1.5-T scanners for the detection of bone metastasis in patients with prostate cancer, using histopathology or best value comparator as the reference standard. Two independent reviewers assessed the methodological quality using the Quality Assessment of Diagnostic Accuracy Studies-2 tool. Per-patient sensitivity and specificity of included studies were calculated, and pooled and plotted in a hierarchical summary receiver operating characteristic plot. Meta-regression and sensitivity analyses were performed.

\textbf{Evidence synthesis:} Ten studies (1031 patients) were included. Pooled sensitivity was 0.96 (95% confidence interval [CI] 0.87–0.99) with a specificity of 0.98 (95% CI 0.93–0.99). At meta-regression analysis, only the number of imaging planes (\textgreater{}2 vs 1) was a significant factor affecting heterogeneity (\textit{p} < 0.01). Sensitivity analyses showed that specificity estimates were comparable and consistently high across all subgroups, but sensitivity estimates demonstrated some differences. Studies using two or more planes (\textit{n} = 4) had the highest sensitivity (0.99 [95% CI 0.98–1.00]).

\textbf{Conclusions:} Contemporary MRI shows excellent sensitivity and specificity for detection of bone metastasis in patients with prostate cancer. Using two or more imaging planes may further improve sensitivity. However, caution is needed in applying our results due to the heterogeneity among the included studies.

\textbf{Patient summary:} We reviewed studies using contemporary magnetic resonance imaging (MRI) for the detection of bone metastasis in prostate cancer patients. MRI shows excellent diagnostic performance in finding patients with bone metastasis.

\textcopyright{} 2017 European Association of Urology. Published by Elsevier B.V. All rights reserved.

\textsuperscript{1} These authors contributed equally.

* Corresponding author. Department of Radiology, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 110-744, Korea. Tel. +82 2 2072 4897; Fax: +82 2 743 6385. E-mail address: iwishluv@empas.com (S.Y. Kim).

http://dx.doi.org/10.1016/j.eururo.2017.03.042

0302-2838/\textcopyright{} 2017 European Association of Urology. Published by Elsevier B.V. All rights reserved.
1. Introduction

Determining the presence of bone metastasis is important in the management of prostate cancer. It not only represents the most common site of initial metastases, but also is a major cause of morbidity and mortality in patients with prostate cancer. Therefore, it is crucial to accurately detect bone metastasis in order to plan the most optimal management for patients with prostate cancer [1]. Currently, Tc 99m bone scintigraphy (BS) is recommended by guidelines as the initial work-up modality for bone metastasis despite its poor accuracy, because it is widely available compared with more advance modalities [2]. However, magnetic resonance imaging (MRI) has continuously been tested for the purpose of detecting bone metastasis during the past 3 decades and has shown promising results [3]. Recent studies have shown that axial skeleton MRI, whole-body MRI, and even routine prostate MRI are excellent in determining bone metastasis in patients with prostate cancer [4–6]. Yet, consensus has not been reached regarding whether it can replace the role of BS in this clinical setting or not.

Therefore, we performed a systematic review and meta-analysis to evaluate the diagnostic performance of contemporary MRI for the detection of bone metastasis in patients with prostate cancer.

2. Evidence acquisition

The present meta-analysis was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The research question for the purpose of this meta-analysis was formulated based on the following Patient Index Data Set Comparator Outcomes Study design (PICOS) criteria [7]: What is the diagnostic performance of contemporary MRI (magnetic field strength ≥1.5 T) for the detection of bone metastasis in patients with prostate cancer, as compared with histopathological results or best value comparator (BVC; a combination of imaging/clinical/biological studies and at least 6 mo of follow-up)?

2.1. Literature search

A computerized search of MEDLINE and EMBASE databases up to January 22, 2017 was performed to identify studies that were relevant to our research question. The search query combined synonyms for prostate cancer, MRI, bone, and diagnostic accuracy as follows: (“prostate cancer” OR “prostatocarcinoma” OR “prostate neoplasm” OR “prostate tumor”) AND ([bone] OR [skeletal]) AND (“magnetic resonance imaging” OR “MR imaging” OR [MRI] OR [MR]) AND ([detection] OR [detectability] OR [positivity] OR [sensitivity] OR [specificity] OR [diagnosis] OR [diagnostic OR [accuracy] OR [performance]). Bibliographies of identified articles were screened to identify additional relevant studies. The search was limited to studies on “humans” using the “English” language.

2.2. Study selection

2.2.1. Inclusion criteria

We included studies that met the following PICOS criteria (10): (1) patients diagnosed with prostate cancer, (2) MRI used as the index test for detection of bone metastasis, (3) histopathology or BVC as the reference standard for comparison, (4) sufficient information to reconstruct 2 × 2 contingency tables regarding sensitivity and specificity, and (5) publication type of original articles.

2.2.2. Exclusion criteria

The exclusion criteria were as follows: (1) study population of <10 patients; (2) study population comprising patients with tumors other than prostate cancer; however, studies were included if the diagnostic performance was separately provided for each type of tumor; (3) review articles, guidelines, consensus statements, letters, editorials, and conference abstracts; (4) MRI with a magnetic field strength of <1.5 T; (5) MRI used for the detection of bone metastasis in prostate tumor, but focusing on topics rather than on diagnostic accuracy; (6) overlapping patient population; and (7) insufficient data for the reconstruction of 2 × 2 tables. In case of an overlapping study population, the study with the largest study population was included. Authors of the studies were contacted for provision of further information when 2 × 2 tables could not be reconstructed.

The literature search and study selection process was independently performed by two reviewers (S.W. and C.H.S., with 4 yr of experience in performing systematic reviews and meta-analyses) with consultation from a third reviewer (S.Y.K.) for reaching a consensus when disagreement was present.

2.3. Data extraction and quality assessment

The following data were extracted from the selected studies using a standardized form: (1) patient characteristics—number of patients, number of patients with bone metastasis, clinical setting (newly diagnosed vs treated and risk stratification of bone metastasis according to clinical criteria), median age and range of patients, prostate-specific antigen (PSA) level, PSA doubling time, Gleason score (based on biopsy and radical prostatectomy [RP] specimens in primary and treated prostate cancer, respectively), and clinical T stage (pathological T stage in post-RP patients); (2) study characteristics—origin of study (authors, institution, and duration of patient recruitment), publication year, study design (prospective vs retrospective, multicenter vs single center, and consecutive vs nonconsecutive enrollment), reference standard, interval between MRI and reference standard, blinding to reference standard, and characteristics of readers (number and experience); and (3) MRI characteristics—magnet field strength; scanner model and manufacturer; coverage of MRI (whole body, axial skeleton or pelvis [as included in routine prostate multiparametric MRI]); type of MRI sequences used among diffusion-weighted imaging (DWI), contrast-enhanced (CE)
MRI, T1-weighted imaging (T1WI), T2-weighted imaging (T2WI), or short tau inversion recovery (STIR), and their corresponding technical parameters; and criteria for bone metastasis.

The methodological quality of the included studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool [8]. Data extraction and quality assessment were performed independently by two reviewers (S.W. and C.H.S.), and consensus was reached via discussion with a third reviewer (S.Y.K.).

2.4 Data synthesis and analysis

The primary outcome of this meta-analysis was the per-patient diagnostic performance of MRI for the detection of bone metastasis in patients with prostate cancer. As a secondary outcome, we aimed to assess the presence of heterogeneity among the included studies and explore potential causes.

Two by two tables were tabulated for the included studies to calculate their sensitivity and specificity. If diagnostic performance of several MRI sequences were separately assessed, we selected the results using the most advanced MRI sequence or most comprehensive MRI protocol (ie, DWI + conventional sequences > DWI > conventional sequences). When results from multiple independent readers were given, the result with the highest accuracy was used. Of note, although one study included in our meta-analysis [9] assessed bone metastasis on a per-lesion basis, it was analyzed as per-patient for the following reasons: (1) this was the only study not providing per-patient diagnostic performance and (2) the mean number of lesions per patient in this study was 1.1 (26/24).

Summary estimates of sensitivity and specificity were calculated using hierarchical logistic regression modeling including bivariate and hierarchical summary receiver operating characteristic (HSROC) modeling [10–12]. These results were plotted using HSROC curves with 95% confidence and prediction regions. Publication bias was evaluated using visual analysis of the Deeks et al’s funnel plot and calculating the p value using Deeks et al’s asymmetry test [13].

Heterogeneity was determined using the following: (1) Cochran’s Q test with p < 0.05 indicating the presence of heterogeneity; (2) Higgins I² test with the following criteria for the interpretation of the degree of heterogeneity: inconsistency index (I²) = 0–40%, heterogeneity might not be important; 30–60%, moderate heterogeneity may be present; 50–90%, substantial heterogeneity may be present; and 75–100%, considerable heterogeneity [14]; and (3) testing for the presence of a threshold effect (a positive correlation between sensitivity and false positive rate) among the selected studies.

Meta-regression analyses using several covariates were performed to explore the cause of heterogeneity as follows: (1) clinical setting (newly diagnosed vs treated), (2) reference standard (BVC only vs inclusion of histopathology), (3) magnet field strength (1.5 vs 3 T), (4) MRI coverage (pelvis vs axial skeleton/whole body), (5) MRI sequence (only conventional sequences vs DWI included), (6) number of imaging planes (1 vs ≥2), and (7) minimum slice thickness among sequences used (≤4 vs >4 mm). In addition, sensitivity analyses for the various settings stratified to the covariates described above were performed.

The “midas” module in Stata 10.0 (StataCorp LP, College Station, TX, USA) and “mada” package in R software version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analyses, with p < 0.05 indicating statistical significance.

3. Evidence synthesis

3.1 Literature search

The systematic literature search initially yielded 1689 articles. After removing 697 duplicates, screening of the 992 titles and abstracts yielded 46 potentially eligible original articles. Full-text reviews were considered and 36 studies were excluded due to the following reasons: not in the field of interest (n = 21), insufficient data to reconstruct 2 × 2 tables (n = 9), <10 patients (n = 2), study population shared with other studies (n = 3), and non-English publication (n = 1). Ultimately, 10 studies including 1031 patients evaluating the diagnostic performance of MRI for the detection of bone metastasis in patients with prostate cancer were included in this meta-analysis [4–6, 9, 15–20]. The study selection process is summarized in Figure 1.

3.2 Characteristics of included studies

The patient characteristics are described in Table 1. The size of the study population ranged from 21 to 308 patients, with the percentage of patients with bone metastasis ranging from 6.8% to 71.4%. Four studies included only patients with newly diagnosed prostate cancer, three included only those with treated prostate cancer, and three included a mixed population of newly diagnosed and treated prostate cancer. The patients had a median age of 63–78 yr. Six studies were based on patients with a clinically “high risk” of bone metastasis, two studies included patients with any risk, and two studies were unclear regarding this risk. The median PSA and Gleason scores were 2.7–31 ng/ml and 7–9, respectively.

The study characteristics are summarized in Table 2. The study design was prospective in six studies and retrospective in four. All but two studies were single-center studies. Patient recruitment was consecutive in all but two studies (nonconsecutive 1:3 matching for normal and metastasis in one study and not explicit in another). Four studies used either histopathology or BVC as the reference standard; while the other six used only BVC. The imaging modalities used in the included studies for BVC included BS, targeted x-ray, computed tomography (CT), MRI, and positron emission tomography/CT. The interval between MRI and the reference standard was not provided in three studies. MRI was interpreted blinded to the reference standard in all but one study, which was not explicit.
The MRI characteristics are shown in Table 3. Six studies used 3-T scanners, two used 1.5-T scanners, and two used 1.5- or 3-T scanners. Regarding coverage of MRI, four studies used whole-body MRI, two assessed the axial skeleton, and four covered only the pelvis using a routine prostate MRI protocol. A combination of DWI and conventional sequences (T1WI, T2WI, and/or STIR) was used in five studies, only DWI in one study, and only conventional sequences in four studies. The criteria for bone metastasis were explicit in seven studies; however, three studies were not clear on this issue as one study was not explicit regarding the role of T1WI and STIR, another study did not provide any criteria, and the other simply stated the use of a five-point Likert scale.

3.3. Quality assessment

Overall, the quality of the studies was considered moderate, with eight of the 10 studies satisfying at least four of the seven QUADAS-2 domains (Fig. 2). Regarding the patient selection domain, one study was considered to have a high risk of bias due to a nonconsecutive case/control design [19]. In addition, one study was considered to have an unclear risk of bias, as it did not explicitly mention whether patient enrollment was consecutive or not [9]. There was high concern for applicability in one study, as it included patients with no metastasis or oligometastasis (<5 metastases) based on conventional imaging and excluding those with polimetastasis [15]. Regarding the index test domain, there was an unclear risk of bias in four studies, as it was unclear whether MRI was evaluated blinded to the reference standard in one study [9] and whether a prespecified threshold was used in three studies [15,16,19]. There was low concern for applicability in all 10 studies. Regarding the reference standard domain, all the studies had an unclear risk of bias, as it was unclear whether the derivation of the reference standard was blinded to MRI. There was unclear concern for applicability in three studies, as they did not explicitly mention whether MRI–reference standard interval was at least 6 mo when BVC was used as the reference standard [6,15,20]. Regarding the flow and timing domain, three studies had a high risk of bias as different reference standards were applied within the study [4,6,16,19]. Two studies were considered to have an unclear risk of bias as the MRI–reference standard interval was not provided [15,20].

3.4. Diagnostic accuracy

The sensitivity and specificity of the 10 individual studies were 72–100% and 70–100%, respectively. Although the Cochran’s Q test suggested that heterogeneity was not present ($Q = 2.970, \ p = 0.113$), the Higgins $I^2$ statistics demonstrated substantial heterogeneity with regard to both sensitivity ($I^2 = 81.44\%$) and specificity ($I^2 = 85.85\%$). No threshold effect was shown upon visualization of the coupled forest plot of sensitivity and specificity (Fig. 3), with a correlation coefficient between sensitivity and false positive rate of $–0.581$ (95% confidence interval [CI] $–0.886$ to $0.077$).

For all 10 studies combined, the pooled sensitivity and specificity were 0.96 (95% CI 0.87–0.99) and 0.98 (95% CI 0.93–0.99), respectively. In the HSROC curve, there was a large difference between the 95% confidence and prediction regions, additionally indicating that heterogeneity was present between the studies (Fig. 4). The area under the HSROC curve was 0.99 (95% CI 0.98–1.00). According to the Deeks et al’s [13] funnel plot, the likelihood of publication...
bias was low, with a p value of 0.23 for slope coefficient (Fig. 5).

3.5. Exploration of heterogeneity

The results of meta-regression analyses are shown in Table 4. Only the number of imaging planes used was shown to be a significant factor affecting heterogeneity (p < 0.01). Specifically, sensitivity was significantly higher when using two or more imaging planes (0.99 [95% CI 0.98–1.00]) compared with when using only one plane (0.87 [95% CI 0.80–0.94], p < 0.01). Although specificity also showed “statistically” higher values when using two or more planes, the difference was not considered meaningful: 0.95 (95% CI 0.98–1.00) versus 0.95 (95% CI 0.90–1.00; p = 0.01). Otherwise, clinical setting, reference standard, magnet field strength, MRI coverage, type of MRI sequences used, and minimum slice thickness were not shown to be significant factors affecting the heterogeneity.

The results of sensitivity analyses are shown in Figure 6. The specificity estimates were comparable with consistently high values across all subgroup (0.91–0.99). In general, the sensitivity estimates were also comparable across most subgroups with pooled sensitivity ranging from 0.93 to 1.00; however, a few subgroups showed slightly lower pooled sensitivity. Specifically, studies that included only patients with treated prostate cancer (0.89 [95% CI 0.74–1.00]), used both 1.5- or 3-T scanners (0.89 [95% CI 0.80–0.94]), and used only one imaging plane for analysis (0.87 [95% CI 0.80–0.94]) tended to show lower sensitivity. However, pooling the results for studies including patients with any risk and those using both 1.5- or 3-T scanners were considered unstable as only two studies were included in these subgroups. In addition, when a sensitivity analysis was performed using nine studies, excluding a single study [15] that (1) was considered to have high concern for applicability regarding patient selection and (2) showed particularly inferior diagnostic performance in terms of both sensitivity and specificity, the degree of heterogeneity was substantially decreased (I^2 = 57.14 and 75.64 for sensitivity and specificity, respectively) with sensitivity of 0.97 (95% CI 0.89–0.99) and 0.98 (95% CI 0.95–0.99).

3.6. Discussion

In the current meta-analysis, we evaluated the diagnostic accuracy of contemporary MRI (using scanners with a magnetic field strength of 1.5 T or higher) for the detection of bone metastasis in patients with prostate cancer. Our results show that the pooled per-patient sensitivity and specificity of the 10 included studies were 0.96 (95% CI 0.87–0.99) and 0.98 (95% CI 0.93–0.99), respectively. Based on this excellent diagnostic performance of MRI for the detection of bone metastasis, MRI could be used as one of the primary modalities for triaging patients with newly diagnosed or treated prostate cancer and to help decide on the most optimal management. Although we did not directly compare the performance between MRI and BS, which would be best addressed by well-designed randomized controlled trials,
Table 2 – Study characteristics

<table>
<thead>
<tr>
<th>First author</th>
<th>Publication year</th>
<th>Origin of study</th>
<th>Study design</th>
<th>Institution</th>
<th>Prospective</th>
<th>Multicenter</th>
<th>Consecutive enrollment</th>
<th>Reference standard</th>
<th>MRI-reference standard interval</th>
<th>Blinding</th>
<th>Reader characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conde-Moreno [15]</td>
<td>2016</td>
<td>10.2014–3.2015</td>
<td>Conceptor Hospitalario Provincial de Castellón</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>BVC</td>
<td>All imaging studies (BS, CT, WB-DW-MRI, choline-PET/CT) by a multidisciplinary team</td>
<td>NR</td>
<td>Yes</td>
<td>NR</td>
</tr>
<tr>
<td>Kitajima [16]</td>
<td>2014</td>
<td></td>
<td>Mayo Clinic</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>BVC or histopathology</td>
<td>Dedicated CT, MRI, or PET–CT and follow-up after 6 mo</td>
<td>NR</td>
<td>Yes</td>
<td>2</td>
</tr>
<tr>
<td>Lecouvet [4]</td>
<td>2007</td>
<td>NR</td>
<td>Cliniques universitaires Saint Luc</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>BVC or histopathology</td>
<td>CT correlation for equivocal MRI findings or imaging (BS, MRI), clinical, and biological follow-up at 6 mo by specialists for each modality</td>
<td>NR</td>
<td>Yes</td>
<td>2</td>
</tr>
<tr>
<td>Lecouvet [5]</td>
<td>2012</td>
<td>3.2007–3.2010</td>
<td>Cliniques universitaires Saint Luc</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>BVC</td>
<td>All available imaging tests (BS/TXR, WB-MRI) and clinical/biological follow-up after 6 mo by specialists for each modality</td>
<td>NR</td>
<td>Yes</td>
<td>2</td>
</tr>
<tr>
<td>Mosavi [17]</td>
<td>2012</td>
<td>10.2009–3.2011</td>
<td>Uppsala University Hospital Cliniques universitaires Saint Luc, Centre Hospitalier Universitaire Vaudois</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>BVC</td>
<td>BS, MRI (T1WI, STIR), and follow-up using 18F-NaF PET/CT and DWI ≥7 mo</td>
<td>Yes</td>
<td>2</td>
<td>Consensus</td>
</tr>
<tr>
<td>Pasoglou [18]</td>
<td>2015</td>
<td>2.2012–12.2012</td>
<td>Cliniques universitaires Saint Luc, Centre Hospitalier Universitaire Vaudois</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>BVC</td>
<td>Consensus session of all available MRI by radiologists, prospective clinical and biological follow-up by uro-oncologist, and imaging follow-up at 6 mo</td>
<td>NR</td>
<td>Yes</td>
<td>NR</td>
</tr>
<tr>
<td>Piccardo [9]</td>
<td>2014</td>
<td>NR</td>
<td>E.O. Galliera Hospital, Azienda Sanitaria dell’Alto Adige</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>BVC</td>
<td>Contrast-enhanced CT and multiparametric MRI at 12 mo follow-up, and response to treatment, lab tests, other imaging studies (x-ray, BS) At least 1 yr or imaging/clinical follow-up</td>
<td>12–18 mo</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Vargas [19]</td>
<td>2016</td>
<td>1.2000–6.2014</td>
<td>Memorial Sloan Kettering Cancer Center</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>BVC or histopathology</td>
<td>Comprehensive review of initial and follow-up BS, MRI, CT, TXR, PET, and clinical/laboratory follow-up at a multidisciplinary urological-oncological conference</td>
<td>&gt;1 yr</td>
<td>Yes</td>
<td>2</td>
</tr>
<tr>
<td>Venkitaraman [20]</td>
<td>2009</td>
<td>1.2001–10.2005</td>
<td>Royal Marsden Hospital</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>BVC</td>
<td>MRI, BS, or other imaging (TXR, CT) and follow-up studies (BS or MRI) assessing treatment response</td>
<td>NR</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>Woo [6]</td>
<td>2016</td>
<td>1.2013–12.2013</td>
<td>Seoul National University Hospital</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>BVC or histopathology</td>
<td>Comprehensive review of initial and follow-up BS, MRI, CT, TXR, and PET, and clinical/laboratory follow-up at a multidisciplinary urological-oncological conference</td>
<td>NR</td>
<td>Yes</td>
<td>2</td>
</tr>
</tbody>
</table>

BS = bone scintigraphy; BVC = best value comparator; CT = computed tomography; DW = diffusion weighted; DWI = diffusion-weighted imaging; MRI = magnetic resonance imaging; MSK = musculoskeletal; NR = not reported; PET = positron emission tomography; STIR = short tau inversion recovery; TXR = targeted x-ray; T1WI = T1-weighted imaging; WB = whole body.

we speculate that MRI is a more superior modality in terms of the sensitivity and specificity for detecting bone metastasis in patients with prostate cancer, given the well-known limited diagnostic performance of B5 in the literature (ie, pooled sensitivity and specificity of 0.71 and 0.91, respectively) [21]. However, as our meta-analysis was based on a per-patient basis and we did not assess the per-lesion diagnostic performance of MRI, whether MRI can be used to identify the metastatic burden or as a modality for assessing global treatment response cannot be answered from the results of our study.

There was significant heterogeneity among the included studies. Based on meta-regression analysis, the only statistically significant factor that may be attributable to this heterogeneity was the number of imaging planes used for the determination of bone metastasis. Specifically, studies that used two or more planes (0.99) showed significantly greater sensitivity compared with those using only one plane (0.87). Regarding MRI technology, use of DWI or slice thickness (≤4 or >4 mm) was not shown to affect the heterogeneity. Regarding slice thickness, the cutoff value of 4 mm was based on practical guidelines and may not have been a significant factor as all but two of the included studies had a minimum slice thickness of 5 or less [17,20,22,23]. However, it is unclear why the addition of DWI did not result in superior results compared with using only conventional sequences of T1WI, T2WI, or STIR. Of note, CE MRI was not separately analyzed as a covariate in the current meta-analysis, as it was used in only two studies, where it was not a dominant sequence but rather one among several MRI sequences included in their multiparametric prostate MRI protocol [6,16]. Further studies may be needed to verify the added value of DWI and CE MRI in determining bone metastasis. Collectively, based on these results with regard to technical aspects of MRI, guidelines should recommend that at least two different planes be used when assessing bone metastasis from prostate cancer.

The current study highlights that regardless of the coverage of MRI—that is, whether it covered only the pelvis in routine prostate MRI, or whether a dedicated axial skeleton or whole-body MRI was utilized—there was consistently high per-patient sensitivity (0.94, 0.95, and 0.97, respectively) and specificity (0.99, 0.94, and 0.97, respectively). This is substantiated by the literature in that although the use of axial skeleton or whole-body MRI may allow identification of a greater number of metastatic bone lesions, the probability of missing a patient with metastasis is negligible due to the fact that isolated peripheral metastasis is highly uncommon as prostate cancer primarily metastasizes to the lower spine and pelvis before spreading throughout the whole body [4,6,24]. The decision to simply use routine prostate MRI, or perform additional axial skeleton or whole-body MRI should be based on further studies assessing cost effectiveness, where the latter two would be more effective in terms of per-lesion detection, but would increase cost in terms of MRI acquisition time and medical costs.

Table 3 – MRI characteristics

<table>
<thead>
<tr>
<th>First author</th>
<th>Magnetic strength (T)</th>
<th>Vendor</th>
<th>Sequence used</th>
<th>Coverage</th>
<th>Minimum ST (mm)</th>
<th>Slice thickness criteria</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Sensitivity per-lesion (95% CI)</th>
<th>Specificity per-lesion (95% CI)</th>
<th>Sensitivity per-lesion (95% CI)</th>
<th>Specificity per-lesion (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cooke-Morrocco [5]</td>
<td>1.5</td>
<td>Siemens</td>
<td>Magnetom Avanto</td>
<td>Whole body</td>
<td>No</td>
<td>5</td>
<td>±0.5, 10, 15</td>
<td>A</td>
<td>0.95</td>
<td>0.89</td>
<td>0.87</td>
<td>0.71</td>
</tr>
<tr>
<td>LeCouteur [9]</td>
<td>1.5</td>
<td>Philips</td>
<td>Achieva</td>
<td>Axial plane</td>
<td>Yes</td>
<td>S</td>
<td>±0.5, 10, 15</td>
<td>A</td>
<td>0.95</td>
<td>0.89</td>
<td>0.87</td>
<td>0.71</td>
</tr>
<tr>
<td>Mosavi [17]</td>
<td>1.5</td>
<td>Philips</td>
<td>Achieva</td>
<td>Axial plane</td>
<td>Yes</td>
<td>S</td>
<td>±0.5, 10, 15</td>
<td>A</td>
<td>0.95</td>
<td>0.89</td>
<td>0.87</td>
<td>0.71</td>
</tr>
<tr>
<td>Venkataraman [20]</td>
<td>1.5</td>
<td>GE</td>
<td>HD</td>
<td>Axial plane</td>
<td>Yes</td>
<td>S</td>
<td>±0.5, 10, 15</td>
<td>A</td>
<td>0.95</td>
<td>0.89</td>
<td>0.87</td>
<td>0.71</td>
</tr>
<tr>
<td>Woo [6]</td>
<td>3</td>
<td>Philips</td>
<td>Ingenia</td>
<td>Axial plane</td>
<td>Yes</td>
<td>S</td>
<td>±0.5, 10, 15</td>
<td>A</td>
<td>0.95</td>
<td>0.89</td>
<td>0.87</td>
<td>0.71</td>
</tr>
</tbody>
</table>

A = axial; C = coronal; DCE = dynamic contrast enhanced; DWI = diffusion-weighted imaging; MRI = magnetic resonance imaging; NR = not reported; ST = slice thickness; T1WI = T1-weighted imaging; T2WI = T2-weighted imaging; S = sagittal; STIR = short tau inversion recovery.
Fig. 2 – Grouped bar charts showing risk of bias (left) and concerns for applicability (right) of 10 included studies using QUADAS-2. QUADAS-2 = Quality Assessment of Diagnostic Accuracy Studies-2.

Fig. 3 – Coupled forest plots of pooled sensitivity and specificity. Numbers are pooled estimates with 95% CIs in parentheses. Corresponding heterogeneity statistics are provided at bottom right corners. Horizontal lines indicate 95% CIs. CI = confidence interval.
The clinical setting (newly diagnosed or treated prostate cancer) is a major factor when determining bone metastasis in prostate cancer patients. Although not significant at meta-regression analysis, sensitivity analysis showed that studies including only treated prostate cancer patients showed a tendency for lower sensitivity compared with those including only patients with newly diagnosed prostate cancer (0.89 vs 0.93). We speculate that in patients who have already received systemic treatment (ie, androgen deprivation therapy), the imaging characteristics of metastatic bone lesions may have changed compared with the original (or pretreatment) appearance, thereby hindering accurate detection [25,26]. This may not be applicable for patients treated with local therapy such as RP; however, we were unable to perform separate analyses according to the type of treatment as the included studies did not provide separate diagnostic performance values. Another aspect of clinical setting is the risk stratification for possibility of bone metastasis. Guidelines recommend that screening for bone metastasis be performed in high-risk patients [2]. Based on sensitivity analysis, the pooled sensitivity and specificity were comparable in studies including only high-risk patients (0.95 and 0.93, respectively), in studies on patients with any risk (0.91 and 0.99, respectively), and for all 10 studies (0.96 and 0.98, respectively). However, one study included only patients with no or less than five metastatic bone lesions based on conventional imaging, and reported distinctively inferior diagnostic performance compared with the other nine studies (sensitivity of 0.72 and specificity of 0.70). This study was considered to have high concern for applicability as in real-life clinical practice; metastatic screening would not be employed for patients with low or

**Table 4 - Results of meta-regression analysis of MRI for the detection of bone metastasis in patients with prostate cancer**

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Subgroup</th>
<th>Meta-analytic summary estimates</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Sensitivity (95% CI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Specificity (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Clinical setting</td>
<td>Newly diagnosed</td>
<td>0.97 (0.93–1.00)</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>Treated</td>
<td>0.93 (0.83–1.00)</td>
<td></td>
</tr>
<tr>
<td>Reference standard</td>
<td>BVC only</td>
<td>0.96 (0.87–1.00)</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td>BVC or histopathology</td>
<td>0.95 (0.88–1.00)</td>
<td></td>
</tr>
<tr>
<td>Magnetic field strength</td>
<td>3 T used</td>
<td>0.95 (0.87–1.00)</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>1.5 T only</td>
<td>0.96 (0.91–1.00)</td>
<td></td>
</tr>
<tr>
<td>MRI coverage</td>
<td>Pelvis</td>
<td>0.94 (0.86–1.00)</td>
<td>0.34</td>
</tr>
<tr>
<td></td>
<td>Axial skeleton or whole body</td>
<td>0.97 (0.92–1.00)</td>
<td></td>
</tr>
<tr>
<td>MRI sequence</td>
<td>DWI used</td>
<td>0.96 (0.89–1.00)</td>
<td>0.68</td>
</tr>
<tr>
<td></td>
<td>Conventional sequences only</td>
<td>0.95 (0.89–1.00)</td>
<td></td>
</tr>
<tr>
<td>Number of imaging planes</td>
<td>≥2</td>
<td>0.99 (0.98–1.00)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0.87 (0.80–0.94)</td>
<td></td>
</tr>
<tr>
<td>Minimum slice thickness</td>
<td>≤4 mm</td>
<td>0.96 (0.88–1.00)</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>&gt;4 mm</td>
<td>0.96 (0.90–1.00)</td>
<td></td>
</tr>
</tbody>
</table>

BVC = best value comparator; CI = confidence interval; DWI = diffusion-weighted imaging; MRI = magnetic resonance imaging.
intermediate risk of bone metastasis only. Therefore, we performed sensitivity analysis excluding this single study, and yielded consistent diagnostic performance with a substantially lower degree of heterogeneity: sensitivity and specificity of 0.97 (95% CI 0.89–0.99) and 0.98 (95% CI 0.95–0.99), respectively; $I^2 = 57.4$ and 75.64, respectively.

One of the major limitations of our meta-analysis is that all included studies used BVC or predominantly BVC as the reference standard. As BVC is based on a combination of clinical, laboratory, imaging, and follow-up studies, this inherently imposes a significant risk for differential verification biases among all included patients. However, it is unlikely that any further study will solely use biopsy or surgery to obtain histopathological results for the reference standard when determining bone metastasis, as this would not be feasible in clinical practice and would be ethically unjustifiable. Another limitation of this meta-analysis is that we were unable to assess the per-lesion diagnostic performance of MRI, as only two studies provided such information. Future studies may be needed to elucidate the per-lesion sensitivity and specificity of MRI for the detection of bone metastasis in patients with prostate cancer. Furthermore, caution is needed in applying our results to routine clinical practice, as there was substantial heterogeneity among the included studies and we used the results with the highest accuracy when diagnostic performance from multiple independent readers were provided in the included studies.

4. Conclusions

MRI shows excellent sensitivity and specificity for the detection of bone metastasis in patients with prostate cancer. Studies using two or more planes for assessment showed the highest sensitivity and specificity, while diagnostic performance was consistently high across multiple subgroups.

**Author contributions:** Sang Youn Kim had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Woo, Suh, S.Y. Kim.

**Acquisition of data:** Woo, Suh, S.Y. Kim.

**Analysis and interpretation of data:** Woo, Suh, S.Y. Kim.

**Drafting of the manuscript:** Woo.

**Critical revision of the manuscript for important intellectual content:** Suh, S.Y. Kim, Cho, S.H. Kim.

**Statistical analysis:** Suh.

**Obtaining funding:** None.

**Administrative, technical, or material support:** None.

**Supervision:** S.Y. Kim, Cho, S.H. Kim.

**Other:** None.

**Financial disclosures:** Sang Youn Kim certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

**Funding/Support and role of the sponsor:** None.

**References**


