Comparison of whole-body bone scintigraphy with axial skeleton magnetic resonance imaging in the skeletal evaluation of carcinoma prostate

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INTRODUCTION

Whole-body bone scintigraphy (WBBS) is considered to be the standard of care in the initial skeletal evaluation of patients with carcinoma prostate. Magnetic resonance imaging (MRI) is a potential alternative technique for detecting bone metastasis. The objective of this study was to compare the diagnostic performance of WBBS with a single-photon emission computed tomography–computed tomography (SPECT-CT) correlation of the suspicious WBBS lesions to the axial skeleton (AS)-MRI in diagnosing bone metastasis in patients with carcinoma prostate.

METHODS: WBBS and AS-MRI were both performed during the initial skeletal evaluation in 35 patients of carcinoma prostate with the prostate-specific antigen (PSA) in the range of 10–50 ng/ml. Suspicious lesions on the WBBS were correlated on SPECT CT. The presence or absence of metastasis was determined by best valuable comparator. The validity parameters of WBBS and AS-MRI were computed and compared.

RESULTS: The sensitivity, specificity, positive predictive value, and negative predictive value of WBBS and AS-MRI for detecting patients with bone metastasis were 55.6%, 88.5%, 62.5%, 85.2% and 100.0%, 96.2%, 90.0%, 100%, respectively. The kappa value and the accuracy of WBBS were 0.457 and 80.0%, respectively. The kappa value and accuracy of AS-MRI were 0.928 and 97.1%, respectively.

CONCLUSIONS: The diagnostic performance of AS-MRI in detecting patients with bone metastasis due to carcinoma prostate is superior to that of WBBS with SPECT-CT correlation of the suspicious lesions in the PSA range of 10–50 ng/ml.

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metastasis at an earlier stage, before the osteoblastic reaction is detectable on WBBS.[7] While the WBBS images the entire skeleton, MRI surveys for the bone metastasis can be limited to the spine, the pelvic bones, and the proximal femur [axial skeleton (AS)].[6,8] The rationale for targeting the AS is based on the typical preferential distribution of the metastasis from the prostate to this region.

Even though the advantages of adding a SPECT-CT correlation to the suspicious WBBS findings are well known,[5] the comparative study by Lecouvet et al. between WBBS and AS-MRI did not employ SPECT-CT correlation of the suspicious WBBS findings.[6] In this study, we have tried to address this issue. The objective of this study was to compare the diagnostic performance of WBBS with a SPECT-CT correlation of the suspicious lesions to AS-MRI in diagnosing skeletal metastasis in patients with carcinoma prostate.

METHODS

Between July 2015 and June 2017, patients with biopsy-proven clinically nonmetastatic carcinoma prostate with prostate-specific antigen (PSA) in the range of 10–50 ng/ml were included in this prospective study. Patients with severe bone pain suggestive of metastasis, clinically evident metastasis, and history of other malignancies were excluded. Furthermore, the patients who had received prior treatment with agents that can affect testosterone levels directly or indirectly were excluded from the study. Patients with contraindications to MRI were also excluded. A minimum of 27 patients were planned to be enrolled in the study. However, 35 patients were included as a greater number of patients were available and willing to participate in the study during the specified study period.

The study protocol was presented to the hospital ethical committee, and the ethical clearance was obtained before beginning the study. The study was approved by the ethics committee of the institution with the approval number of Dissertation Review/DM/MCH/2014/21 on July 30, 2015. Patients were explained about the additional MRI sequences that may have to be acquired in addition to the prostate protocol MRI. Prior informed written consent was obtained from all the patients before including them in the study. All the procedures in the study adhered to the ethical guidelines of the Declaration of Helsinki and its amendments. In all the patients, AS-MRI was performed at least 4 weeks after the prostate biopsy as the postbiopsy hemorrhage might have affected the interpretation of MRI of the prostate.[9] WBBS was performed one day before or after the AS-MRI study.

Whole-body bone scintigraphy procedure
Fifteen millicuries of$^{99m}$technetium-MDP was injected intravenously. After 3 h, whole-body images were acquired using a high-resolution collimator on a dual-head, variable-angle gamma camera. Scanning was performed in whole-body mode in the anterior and posterior projections. Additional spot views were performed when appropriate. Targeted SPECT-CT correlation was obtained in the case of a suspicious hotspot at the discretion of the nuclear physician. WBBS was read in conjunction with the SPECT-CT correlation of the suspected areas by a panel of three nuclear medicine physicians and was reported as one of the following three categories – normal/benign: absence of uptake or focal increased uptake typical of benign origin (fracture, degenerative joint disease, Paget’s disease of bone, etc.): positive: bone metastases; and equivocal: image could not be confidently categorized as one of the former two subgroups.[6]

Magnetic resonance imaging procedure
MRI systems used in our series were GE Signa HDxt 1.5T and GE discovery MR750w 3T. Both machines were randomly used on the basis of availability. AS-MRI was performed with the following sequences. For imaging the pelvis and the proximal femur, axial spin-echo T1 and short-tau inversion recovery (STIR) sequences were used. For imaging the spine, sagittal STIR sequences of the whole spine were used. Dedicated phased array coils were used, and no intravenous contrast was given. Patients were categorized and reported by a panel of three musculoskeletal radiologists (who were not involved in the reporting of the MRI of the prostate) into one of the following three categories: normal or benign, metastatic, and equivocal when only one nonspecific small lesion (10 mm) had been detected.[4,6,8] The MRI protocol also included screening of the abdomen for assessment of the solid organs.

The readers of AS-MRI were blinded to the patient’s clinical status and the WBBS findings. Similarly, the readers of WBBS were blinded to the AS-MRI findings and the clinical status. In reporting of both the WBBS and AS-MRI, the disagreements were settled with mutual consensus. These WBBS and AS-MRI reports were used in the calculation of validity parameters and for the comparison of the diagnostic performance.

Final diagnosis was arrived, and all the patients were treated and followed up according to the EAU prostate cancer guidelines.[2,10–12] After discussion in a multidisciplinary tumor board, the treatment plan was individualized according to the clinical profile, performance status, and the evidence available at that time. Patients were followed up clinically (symptomatic assessment and digital rectal examination). PSA follow-up, alkaline phosphatase measurements, and prospective follow-up imagings were performed according to the indication. The frequency of clinical visits and frequency and choice of the follow-up imaging were individualized according to the clinical profile of the patient. Various imaging modalities used in the follow-up included WBBS, CT, MRI, and $^{68}$gallium.
prostate-specific membrane antigen positron emission tomography-CT.

The final conclusion of the initial metastatic status was arrived at the end of the follow-up period by a multidisciplinary panel comprising of uro-oncologist, nuclear physician, and musculoskeletal radiologist after evaluating the initial WBBS and MRI, imaging performed during the follow-up period, PSA values, and the clinical status. The systematic use of initial imaging, prospective follow-up imaging, clinical status, and PSA to arrive at a final conclusion of the initial metastatic status is known as the best valuable comparator (BVC). In our study, BVC was used as the reference standard to determine the presence or the absence of metastasis.

The numerical variables were expressed as mean and standard deviation. The categorical variables were expressed as frequency and percentage. The validity parameters (sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV], and accuracy) of WBBS and AS-MRI were computed. To obtain the association of WBBS reports and AS-MRI reports with metastasis as calculated by the reference method, Fisher’s exact test and Cohen’s kappa were used. Analysis was performed by Statistical Package for Social Sciences (SPSS for Windows, version 20.0; IBM Corp., New York, USA). The value of $P < 0.05$ was considered as statistically significant.

For calculation of validity parameters, the results were analyzed categorizing the equivocal reports from WBBS and AS-MRI as positive for metastasis in patients with no metastasis by BVC. In patients with the presence of metastasis by BVC, the equivocal WBBS and AS-MRI reports were characterized as negative for metastasis. This pessimistic approach was chosen to obtain threshold sensitivities and specificities of the techniques for an effective comparison. The authors confirm the availability of, and access to, all the original data reported in this study.

**RESULTS**

The mean age of the study population was 67.20 ± 6.851 years (50-79 years). The mean PSA value was 23.58 ± 9.796 ng/ml (12.62 – 47.65 ng/ml). The patient characteristics according to the age, PSA, Gleason score, and T stage are shown in Table 1. Thirty patients (94.3%) were in the high-risk category and 2 patients (5.7%) were in the intermediate-risk category of the prostate cancer. The MRI nodal staging was N0 in 21 cases (60%) and N1 in 14 cases (40%).

| Table 1: Patient characteristics (n=35) |
|---------------------------------------|
| **Patient characteristics**           | **Number of patients (%)** |
| **Age (years)**                       |                            |
| 50-59                                 | 5 (14.3)                   |
| 60-69                                 | 17 (48.6)                  |
| 70-79                                 | 13 (37.1)                  |
| **PSA (ng/ml)**                       |                            |
| 10.00-19.99                           | 16 (45.7)                  |
| 20.00-29.99                           | 11 (31.4)                  |
| 30.00-39.99                           | 5 (14.3)                   |
| 40.00-49.99                           | 3 (8.6)                    |
| **Gleason score**                     |                            |
| ≤6                                    | 2 (5.7)                    |
| 3+4/4+3                              | 15 (42.9)                  |
| 8                                    | 11 (31.4)                  |
| 9/10                                 | 7 (20.0)                   |
| **T-stage**                           |                            |
| T2a                                   | 1 (2.9)                    |
| T2b-T2c                              | 8 (22.9)                   |
| T3a                                   | 12 (34.3)                  |
| T3b-T4                               | 14 (40.0)                  |

PSA=Prostate-specific antigen

In our series, SPECT-CT correlation of the suspicious WBBS lesions was obtained in 15 patients (42.9%) and was not considered necessary in the rest (20 patients (57.1%)). Initial WBBS and AS-MRI had similar reports in 29 patients. Both AS-MRI and WBBS were reported as negative for metastasis in 23 patients (SPECT-CT correlation of the suspicious WBBS lesions was obtained in seven of these patients). Both were reported as positive for metastasis in five patients (SPECT-CT correlation of suspicious WBBS lesions was performed in all the five patients). Both had equivocal finding in one patient (SPECT-CT correlation of the suspicious WBBS lesions was performed in this patient). Initial AS-MRI and WBBS reports were different in 6 patients. AS-MRI was reported as negative for metastasis, and WBBS was reported as equivocal in two patients (SPECT-CT correlation of suspicious WBBS lesions was obtained in both these patients). AS-MRI was reported as positive for metastasis, whereas WBBS was reported as negative for metastasis in four patients (SPECT-CT correlation was not performed in any of these four patients as the WBBS had not picked up any suspicious lesions).

By BVC, bone metastasis was found in 9 patients (25.7%) and no metastasis was found in 26 patients (74.3%). The sensitivity, specificity, PPV, NPV, and accuracy of WBBS for detecting patients with skeletal metastasis are depicted in Table 2. Kappa value was 0.457 which indicated moderate agreement between the WBBS findings and the metastasis as detected by the BVC. Three patients had equivocal reports on WBBS. By BVC, all the three patients were not found to have bone metastasis. The WBBS findings were considered as positive for metastasis for calculation of validity parameters.

The sensitivity, specificity, PPV, NPV, and accuracy of AS-MRI for detecting skeletal metastasis are depicted in Table 2. Kappa value was 0.928 which indicated an almost perfect agreement between the AS-MRI findings and the metastasis as detected by the BVC. One patient had an equivocal report on AS-MRI. By BVC, he was not found to have bone metastasis. His AS-MRI finding was considered as positive for metastasis for calculation of validity parameters.
A total of 15 bone metastatic lesions were found in 9 patients as detected positive for metastasis by BVC. The mean long-axis dimension of the bone metastasis was 2.01 ± 0.591 cm. The mean short-axis dimension of the bone metastasis was 0.95 ± 0.200 cm. The metastatic bone lesions (according to the location) as were diagnosed with WBBS and AS-MRI are described in Table 3. All the lesions picked by WBBS had SPECT-CT correlation. None of the patients had metastatic lesions in the extra AS. None of the patients in our study had visceral metastasis.

Out of the 9 patients diagnosed with metastasis, the primary treatment was androgen deprivation therapy (ADT) alone in 5 patients and ADT + docetaxel[13,14] in 4 patients. Out of the 26 patients not diagnosed with metastasis, the primary treatment was radical prostatectomy in 11 patients, definitive radiotherapy in 13 patients, and ADT alone in 2 patients.

### DISCUSSION

Prostate cancer is globally the second most common type of cancer in men.[15] Prostate cancer cells have an exquisite tropism for bone, which clinically translates into a high rate of bone metastasis. Bone marrow is the initial metastatic site in 80% of the carcinoma prostate patients who develop metastasis.[16] It is mandatory to precisely rule out the presence of metastasis as it represents the tipping point for excluding definitive local therapy.

Our objective was to compare WBBS with an investigation which is effective and which does not require a lot of additional cost and time. Accordingly, MRI protocol in our study targets only the AS, thereby saving cost and time. At the authors’ institution, the cost of AS-MRI and WBBS are similar. In addition to the recommended MRI prostate for the local staging, we had to perform few additional MRI sequences of the spine which took an additional time of approximately 10 min.

In limiting the MRI study to the AS, we have not compromised on the diagnostic performance in detecting the number of patients with metastasis. The limited sensitivity of MRI in detecting the metastasis in the skull, ribs, and scapulae has been well documented.[17] In ribs, the respiratory artifacts make MRI a less ideal tool to pick up metastasis.[17] The available evidence comparing the whole-body MRI to the AS-MRI has shown their equivalent effectiveness in determining the bone metastatic status in the patients with carcinoma prostate.[17] Furthermore, the objective of the study was to compare the diagnostic performance of the two modalities in diagnosing the number of patients with skeletal metastasis, not the number of metastatic lesions. A comparison of the two imaging modalities covering the anatomical areas of varying extent (whole body in bone scintigraphy and AS in MRI) is plausible.

A study of 66 patients with high-risk prostate cancer did not show any case of isolated peripheral metastasis without the presence of metastasis in AS.[6] In a study of 200 patients with breast and prostate cancer, MRI limited to AS did not result in any significant loss of accuracy for staging when compared with WBBS, as isolated peripheral skeletal metastasis was observed in only 2% of the patients.[18] In our series also, we did not find any peripheral bone metastasis outside the AS.

The probability of detecting skeletal metastasis by WBBS is very low if the PSA is <10 ng/ml.[19] The probability of detecting metastasis by WBBS is much higher at a cutoff

### Table 2: Validity parameters of whole-body bone scintigraphy and axial skeleton magnetic resonance imaging in detecting patients with metastasis (n=35)

| Bone metastasis (BVC) | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Accuracy (%) | P |
|-----------------------|----------------|----------------|--------|--------|--------------|---|
| WBBS                  |                |                |        |        |              |   |
| Positive (n=9)        | 5              | 3              | 55.6   | 88.5   | 62.5         | 85.2 | 80.0 | 0.015 |
| Negative (n=26)       |                |                |        |        |              |   |
| Positive (n=8)        | 4              | 23             | 96.2   | 100.0  | 90.0         | 97.1 | 0.000 |
| Negative (n=17)       |                |                |        |        |              |   |
| Positive (n=10)       | 0              | 25             | 100.0  | 90.0   | 100.0        | 97.1 | 0.000 |

P<0.05 is significant. WBBS=Whole-body bone scintigraphy, AS-MRI=Axial skeleton magnetic resonance imaging, BVC=Best valuable comparator, PPV=Positive predictive value, NPV=Negative predictive value

### Table 3: Metastatic bone lesions detected by axial skeleton magnetic resonance imaging and whole-body bone scintigraphy at different anatomical regions

| Anatomical regions             | Metastatic bone lesions as detected by BVC (reference method) | AS-MRI detected metastatic bone lesions | WBBS detected metastatic bone lesions |
|-------------------------------|---------------------------------------------------------------|----------------------------------------|--------------------------------------|
| Hip bone (ilium, ischium, pubis) | 6                                                             | 6                                      | 5                                    |
| Acetabulum and proximal femur | 4                                                             | 4                                      | 4                                    |
| Pelvic part of spine (sacrum and coccyx) | 3                                                              | 3                                      | 1                                    |
| Cervical and dorsolumbar spine | 2                                                             | 2                                      | 1                                    |
| Extra axial skeleton           | Nil                                                           | NA                                     | Nil                                  |

WBBS=Whole-body bone scintigraphy, AS-MRI=Axial skeleton magnetic resonance imaging, BVC=Best valuable comparator
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PSA of >50 ng/ml. Confusion in the clinical practice in detecting skeletal metastasis is frequent in the group with PSA between 10 and 50 ng/ml. Accordingly, our study design was to include the patients in the above critical PSA range. We believe that patient selection based on the above PSA range in our study provides an ideal ground for head-to-head comparison of the two imaging modalities.

The proposed confirmatory method to diagnose skeletal metastasis is said to be biopsy from the lesion. However, open bone biopsy is associated with significant complication rates in the vertebral and the deeply seated pelvic bone lesions. The diagnostic accuracy of CT-guided biopsy of the spine is poor. Hence, we did not obtain histological diagnosis which would have been clinically impractical and ethically unjustifiable. Most of the recent studies had determined the presence or absence of metastasis by BVC which is based on arriving at the final conclusion on the initial metastatic status based on a comprehensive review of available images and clinical follow-up. In a recent systematic review and meta-analysis also, the BVC has been accepted as the reference method. We feel that BVC is a very useful tool in arriving at a conclusion on the presence or absence of bone metastasis, particularly in the patients with equivocal reports and contradicting reports by WBBS and AS-MRI, as the follow-up imaging and clinical follow-up make the diagnosis more accurate.

By BVC, 9 patients in our study were found to have bone metastasis. WBBS diagnosed bone metastasis in 5 of these 9 patients. Of the 4 patients not diagnosed by WBBS, 2 had solitary metastasis in the sacral vertebra. We feel radiotracer accumulation in the urinary bladder made it difficult to interpret the sacral bone metastasis in these patients. As the lesion was masked and there was no suspicion from WBBS, SPECT-CT correlation was also not performed. All the four patients in whom WBBS had not detected metastasis had a single bone metastatic lesion by the BVC.

In the study by Leucovet et al., the specificity of the WBBS with a targeted X-ray correlation was 64%. The specificity of WBBS with a targeted SPECT-CT correlation in our series was 88.5%. SPECT-CT correlation effectively ruled out metastasis in 7 patients with suspicious lesions on WBBS, thereby contributing to the increased specificity [Figure 2]. In the case of equivocal WBBS or AS-MRI findings, we have employed a pessimistic approach while calculating the validity parameters. Leucovet et al. had used a similar pessimistic approach to obtain the threshold sensitivity and specificity for the effective comparison of the two imaging modalities.

Based on the validity parameters, kappa value, and accuracy in our study, the diagnostic performance of AS-MRI was better than the WBBS in detecting skeletal metastasis in the patients with carcinoma prostate. Despite adding SPECT-CT correlation of the suspicious WBBS findings, the diagnostic performance of WBBS could not match to that of AS-MRI. Restricting the MRI survey to AS had not affected the diagnostic superiority of MRI. Furthermore, AS-MRI performed with both 1.5T and 3T systems yielded results superior to WBBS.

Our sample size is limited. Our findings should be validated in a larger population of patients by a multicentric study. Recent evidence supports multiparametric MRI before the prostate biopsy. The cost and time benefits are best served when MRI prostate and MRI spine are performed simultaneously. Our study protocol was established prior to the recent change in guidelines, and the clinical utility of additional AS MRI along with MRI prostate before the biopsy should be evaluated in the future prospective studies. Recently, there have been emerging evidences on individualizing the therapy according to the metastatic burden in hormone-naïve metastatic prostate cancer. The skeletal MRI protocol in our study is limited to AS, and if the entire metastatic burden needs to be assessed, additional sequences might be required. Again, our study protocol was designed before the establishment of this concept, and hence, due consideration was not given to a scenario that may require exact measurement of the metastatic burden. The clinical course of the patients in the follow-up period has not been discussed elaborately in this article as it was broadly heterogeneous and was beyond the scope of this article.

**CONCLUSIONS**

The diagnostic performance of AS-MRI in detecting the patients with bone metastasis due to carcinoma prostate is superior to that of WBBS with SPECT-CT correlation of the suspicious WBBS lesions in the PSA range of 10–50 ng/ml. A large multicentric study with larger sample size is required to clearly define the role of AS-MRI in the initial skeletal evaluation of the patients with carcinoma prostate.
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